BVSC & AH STUDY BOOK 2 OF 7

Systemic Pharmacology: Drugs by Body System

Thirty-three chapters on the drugs that act on the autonomic nervous system, brain, inflammation, heart, blood, kidney, lungs, gut and hormones. Each chapter explains the mechanism, the clinical meaning and the species cautions, and ends with a 10-question self-test.

33 chapters | **330** practice questions | **No** dose tables

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Start here

Pick a chapter from the list on the left (or the top bar on a phone). The chapters follow seven parts: autonomic and neuromuscular drugs, central nervous system, inflammation and joint drugs, cardiovascular, blood and renal drugs, respiratory and digestive drugs, and endocrine and reproductive drugs. Each chapter has six parts: Learn, Concepts, Compare, Species, Quiz and Revise. Your quiz progress is saved on this device only.

CHAPTER 1 OF 33

Autonomic nervous system and neurotransmission

The autonomic nervous system controls involuntary functions through two divisions that use acetylcholine and noradrenaline. This chapter explains how the two systems are organised, how each transmitter is made, released and removed, and which receptor subtypes sit on which organs.

After this chapter you can

- Compare the anatomical organisation of the sympathetic and parasympathetic divisions

- Describe synthesis, storage, release and removal of acetylcholine
- Describe synthesis, storage, release and removal of noradrenaline
- Match muscarinic, nicotinic and adrenergic receptor subtypes to their main organ effects
- Explain why knowing the transmitter and receptor predicts drug effects and side effects

Why the autonomic system matters in pharmacology

The autonomic nervous system (ANS) runs the body's involuntary functions: heart rate, blood pressure, gut motility, glandular secretion, pupil size, bronchial tone and bladder emptying. A very large number of veterinary drugs work by copying, blocking or prolonging the action of its two main transmitters, **acetylcholine (ACh)** and **noradrenaline (NA, norepinephrine)**.

If you understand the pathway, you can predict both the intended effect and the side effects of drugs such as atropine, xylazine, neostigmine, phenylephrine and propranolol without memorising them one by one.

Sympathetic and parasympathetic organisation

Both divisions use a **two-neuron chain**: a preganglionic neuron from the central nervous system synapses in a ganglion with a postganglionic neuron, which then reaches the effector organ. The divisions differ in where they leave the cord and where the ganglia lie.

- **Sympathetic (thoracolumbar outflow).** Preganglionic fibres leave the thoracic and anterior lumbar cord. Ganglia lie close to the spinal cord (paravertebral chain and prevertebral ganglia), so preganglionic fibres are short and postganglionic fibres long. One preganglionic fibre contacts many postganglionic neurons, so the response is widespread, the so-called fight or flight pattern.
- **Parasympathetic (craniosacral outflow).** Fibres leave with cranial nerves III, VII, IX and X and with the sacral segments. Ganglia lie near or within the target organ, so preganglionic fibres are long and postganglionic fibres short. The response is more discrete, the rest and digest pattern. The vagus carries most of the parasympathetic supply to the thorax and abdomen.

Two exceptions are worth remembering. The **adrenal medulla** behaves like a modified sympathetic ganglion: preganglionic fibres act directly on it and it releases mainly adrenaline into the blood. **Sweat glands** in many species receive sympathetic fibres that release ACh rather than NA. Sweating is prominent in the horse, but in that species it is driven largely by circulating adrenaline acting on the glands, so do not over-generalise.

Most organs receive both supplies and the two usually oppose each other, which is why a drug that blocks one division unmasks the other.

Acetylcholine: synthesis, release and removal

ACh is the transmitter at all autonomic ganglia, at parasympathetic postganglionic endings, at the skeletal neuromuscular junction, and at sympathetic endings to sweat glands.

1. **Synthesis.** Choline is taken up into the nerve terminal by a transporter (the rate-limiting step) and combined with acetyl-CoA by *choline acetyltransferase*.
2. **Storage.** ACh is packed into synaptic vesicles.
3. **Release.** An action potential opens voltage-gated calcium channels. Calcium entry triggers vesicle fusion and exocytosis. Botulinum toxin acts here by preventing release.
4. **Receptor action.** ACh binds nicotinic or muscarinic receptors on the target cell.
5. **Removal.** *Acetylcholinesterase* splits ACh into choline and acetate within milliseconds. Much of the choline is recycled into the terminal. There is no significant reuptake of intact ACh.

Because removal is by enzyme and not by reuptake, **anticholinesterase drugs** and organophosphate insecticides cause ACh to accumulate, which is the basis of cholinergic poisoning (see the next chapter).

Noradrenaline: synthesis, release and removal

NA is the transmitter at most sympathetic postganglionic endings. The adrenal medulla also releases adrenaline and some NA.

1. **Synthesis.** Tyrosine is converted to DOPA by *tyrosine hydroxylase* (the rate-limiting step), then to dopamine. Dopamine is taken into vesicles and converted

to NA by *dopamine beta-hydroxylase*. In the adrenal medulla NA is further methylated to adrenaline.

2. **Storage.** NA is held in vesicles together with ATP.
3. **Release.** As with ACh, calcium-dependent exocytosis follows the action potential.
4. **Feedback.** NA acts on presynaptic alpha-2 receptors on the same terminal and reduces further release. This is why alpha-2 agonists such as xylazine and dexmedetomidine lower sympathetic outflow and cause sedation and bradycardia.
5. **Removal.** The main route is **reuptake into the nerve terminal** by the noradrenaline transporter (uptake-1). Smaller roles are played by uptake into other tissues, diffusion away, and breakdown by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT).

A common confusion: ACh is destroyed at the synapse, whereas NA is mostly *recycled*. Drugs that block reuptake therefore potentiate NA but not ACh.

Receptor subtypes and organ effects

The transmitter does not decide the response; the **receptor on the organ** does.

Cholinergic receptors

- **Nicotinic.** Ligand-gated ion channels. Muscle type (N_M) at the neuromuscular junction; neuronal type (N_N) in autonomic ganglia and the adrenal medulla.
- **Muscarinic (M_1 to M_5).** G-protein-coupled receptors on effector organs. M_2 in the heart slows the rate and conduction. M_3 in smooth muscle and glands causes contraction, secretion, bronchoconstriction, increased gut motility, bladder emptying and miosis. M_1 is found in ganglia and the CNS.

Adrenergic receptors

- **Alpha-1.** Vascular smooth muscle constriction (raises blood pressure), contraction of sphincters, dilation of the pupil.
- **Alpha-2.** Mostly presynaptic inhibition of transmitter release; also central sedation and some vasoconstriction.
- **Beta-1.** Heart: faster rate, stronger contraction, faster conduction; renin release from the kidney.

- **Beta-2.** Bronchodilation, vasodilation in skeletal muscle, relaxation of uterus and gut smooth muscle.
- **Beta-3.** Lipolysis; some role in bladder relaxation.

Clinical link: a bronchodilator such as salbutamol is chosen for its beta-2 selectivity so that heart rate is affected less, and a non-selective beta blocker can worsen airway narrowing for the same reason.

Putting it together and common confusions

To predict a drug's action, ask three questions: which transmitter pathway does it touch, at which step (synthesis, release, receptor, removal), and which receptor subtype is involved.

- Ganglionic drugs affect both divisions because ACh at ganglia is nicotinic in both.
- Nicotinic receptors in muscle and ganglia are different subtypes, which is why neuromuscular blockers do not usually cause autonomic effects at clinical concentrations.
- Most vascular beds are controlled by sympathetic tone alone; there is little parasympathetic supply to them, so vessel diameter is changed mainly by altering sympathetic activity.
- Receptor effects can vary by species and organ, so always check the actual response in the animal in front of you.

Concept cleared

Two-neuron chain
Both divisions have a preganglionic and a postganglionic neuron joined at a ganglion. ACh is the ganglionic transmitter in both.

Transmitter versus receptor
Effects depend on the receptor subtype in the organ. ACh excites the gut through muscarinic receptors but slows the heart through the same family acting on M2.

Removal differs

ACh is hydrolysed by acetylcholinesterase; NA is mainly taken back up by the nerve terminal. This explains why anticholinesterases and reuptake blockers behave differently.

Presynaptic alpha-2 brake

Alpha-2 receptors on sympathetic terminals reduce NA release. Alpha-2 agonists exploit this for sedation and analgesia.

Memory aid: Remembering the outflows

Sympathetic = Thoracolumbar (T before P in the alphabet pairs with S: 'SympaTHetic = THoracic'). Parasympathetic = Craniosacral ('Para = cranial and sacral, the two ends'). Receptor shortcut: alpha-1 constricts, beta-1 speeds the heart, beta-2 relaxes airways.

Compare and contrast

Sympathetic versus parasympathetic

Feature	Sympathetic	Parasympathetic
Outflow	Thoracolumbar	Craniosacral
Ganglia	Near spinal cord	Near or in target organ
Preganglionic fibre	Short	Long
Postganglionic transmitter	Mostly NA	ACh
Typical effect	Fight or flight, widespread	Rest and digest, discrete

ACh versus NA handling

Step	Acetylcholine	Noradrenaline
Precursor	Choline + acetyl-CoA	Tyrosine
Rate-limiting step	Choline uptake	Tyrosine hydroxylase
Release trigger	Calcium-dependent exocytosis	Calcium-dependent exocytosis
Main removal	Acetylcholinesterase	Neuronal reuptake
Receptors	Nicotinic, muscarinic	Alpha and beta

Species notes

Dog and cat

Vagal tone at rest is high, especially in athletic dogs, so sinus arrhythmia and slow resting rates can be normal. Cats are sensitive to the effects of alpha-2 agonists on heart rate and vomiting.

Horse

The gut is very sensitive to autonomic balance; drugs that reduce parasympathetic activity can slow motility and predispose to colic. Sweating is mainly under adrenaline influence.

Ruminants

Rumen motility depends on vagal activity, so drugs that block or mimic the parasympathetic system have marked effects on rumen function. Ruminants are very sensitive to alpha-2 agonists.

Pig and poultry

Autonomic principles are the same, but drug responses and sensitivity differ; avoid extrapolating dose or response from other species and use the label or data sheet.

Clinical pearls

Self-test: 10 questions

1. Which statement correctly describes the parasympathetic division?

Parasympathetic outflow is craniosacral, with ganglia close to the effector so postganglionic fibres are short.

2. The rate-limiting step in noradrenaline synthesis is catalysed by:

Tyrosine hydroxylase converts tyrosine to DOPA and limits the pathway.

3. The main mechanism terminating the synaptic action of noradrenaline is:

Neuronal reuptake (uptake-1) is the principal route; MAO and COMT are minor.

4. Acetylcholine at the synapse is removed mainly by:

Acetylcholinesterase splits ACh into choline and acetate, and choline is recycled.

5. Which receptor mediates slowing of the heart by the vagus?

Cardiac M2 receptors reduce rate and AV conduction.

6. Bronchodilation is mainly produced by stimulation of:

Beta-2 receptors relax airway smooth muscle, while M3 causes bronchoconstriction.

7. Presynaptic alpha-2 receptors on sympathetic terminals:

They provide negative feedback, which is exploited by alpha-2 agonists.

8. The adrenal medulla is best described as:

It is innervated by preganglionic sympathetic fibres and releases adrenaline into the blood.

9. The transmitter in all autonomic ganglia is:

Both divisions use ACh at the ganglion, acting on neuronal nicotinic receptors.

10. Alpha-1 stimulation in vascular smooth muscle causes:

Alpha-1 receptors constrict vessels and raise blood pressure.

Key points to revise

1. The ANS uses a two-neuron chain with a ganglion between neurons.
2. Sympathetic outflow is thoracolumbar; parasympathetic is craniosacral.
3. ACh is made from choline and acetyl-CoA by choline acetyltransferase.
4. Acetylcholinesterase removes ACh at the synapse.
5. NA is made from tyrosine; tyrosine hydroxylase is rate-limiting.
6. NA is removed mainly by neuronal reuptake, with MAO and COMT playing minor roles.
7. Muscarinic M2 slows the heart; M3 causes secretion and smooth muscle contraction.
8. Beta-1 acts on the heart and beta-2 on airways and some vessels.

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- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Lecture notes: Drugs acting on the autonomic nervous system (BASU)
- Merck Manual Consumer Version: Overview of the Autonomic Nervous System
- Vetscraft: Cholinergic drugs

CHAPTER 2 OF 33

Cholinergic drugs

Drugs that mimic or prolong the action of acetylcholine: direct agonists, reversible and irreversible anticholinesterases, their place in ruminant and equine practice, and how cholinergic toxicity (organophosphate and carbamate poisoning) is recognised and understood.

After this chapter you can

- Distinguish direct-acting cholinergic agonists from anticholinesterases
- Explain why bethanechol, pilocarpine and carbachol act where they do, using muscarinic receptor distribution
- Compare reversible and irreversible anticholinesterases, including the idea of enzyme aging
- Describe uses of cholinergic drugs in ruminant, equine and small animal practice and the cautions that go with them
- Recognise the muscarinic, nicotinic and central signs of cholinergic toxicity and the logic of treatment

The cholinergic synapse in brief

Acetylcholine (ACh) is released by all preganglionic autonomic neurons, by postganglionic parasympathetic neurons, by motor neurons at the neuromuscular junction, and by some neurons in the brain. It acts on two receptor types. **Muscarinic** receptors (M1 to M5) are G-protein-coupled and sit on effector organs: heart, smooth muscle, glands and eye. **Nicotinic** receptors are ligand-gated ion channels found in autonomic ganglia and at the skeletal muscle end plate.

ACh is destroyed within milliseconds by **acetylcholinesterase** (AChE) at the synapse. A cholinergic drug therefore has two ways to raise cholinergic activity: copy ACh at the receptor (a *direct agonist*) or stop the enzyme from destroying it (an *anticholinesterase*). The anticholinesterase is an indirect agonist, because it only works where ACh is already being released.

A common confusion is to treat cholinergic and parasympathomimetic as the same thing. They overlap, but nicotinic effects at ganglia and muscle are cholinergic and

are not parasympathetic.

Direct-acting agonists

Natural ACh is useless as a drug because AChE and plasma cholinesterases destroy it almost at once and it acts on every cholinergic receptor. Useful agonists are made resistant to these enzymes and are more selective.

- **Bethanechol** is an ester of choline that resists breakdown and acts almost only on muscarinic receptors. Its main target is the detrusor muscle of the bladder and gastrointestinal smooth muscle. It is used for bladder atony and detrusor hyporeflexia, and has been suggested in horses with urine retention from neurological disease. Current veterinary references describe it as promoting detrusor contraction, so it should only be used when the outflow is not obstructed. Giving it against a blocked urethra raises bladder pressure and risks rupture.
- **Carbachol** acts on both muscarinic and nicotinic receptors and resists hydrolysis. It is used as an intraocular miotic in surgery. Its systemic use is limited by widespread effects, and in horses it can provoke colic.
- **Pilocarpine** is a plant alkaloid with muscarinic action. Its classical uses are as a miotic in glaucoma and as a sialogogue. Because it is a tertiary amine, it enters the brain, and systemic overdose causes central effects.

The expected effects of a muscarinic agonist are easy to predict: slow heart rate, bronchoconstriction, salivation, lacrimation, sweating, increased gut motility and secretion, bladder contraction and miosis. Every contraindication follows from these effects: asthma-like airway disease, bradycardia, intestinal or urinary obstruction and peptic ulcer.

Reversible anticholinesterases

These drugs bind AChE and temporarily block it, so ACh survives longer and its effects are amplified at every site where it is released. Three drugs are used often enough to be worth separating by how they bind.

- **Edrophonium** binds by weak, purely reversible forces. Its effect lasts only minutes. It is used for the diagnostic test for myasthenia gravis and for brief reversal of neuromuscular block.

- **Neostigmine** and **pyridostigmine** transfer a carbamyl group to the enzyme. This carbamylated enzyme recovers slowly (minutes to hours), so the effect lasts longer. Both are quaternary ammonium compounds, so they do not enter the brain well. Pyridostigmine is the usual long-term treatment for acquired myasthenia gravis in dogs.
- **Physostigmine** is a tertiary amine. It crosses the blood-brain barrier, which is why it is used to reverse central anticholinergic poisoning in some situations.

Neostigmine also has a small direct effect at the skeletal muscle end plate, and it is the standard reversal agent for non-depolarising muscle relaxants. Because it enhances muscarinic effects everywhere, an anticholinergic such as atropine or glycopyrrolate is given with it to stop bradycardia, salivation and bronchospasm.

Irreversible anticholinesterases and enzyme aging

Organophosphates (OPs) phosphorylate the serine in the active site of AChE. The bond is so stable that the enzyme is effectively lost until new enzyme is made. Some OP compounds are also used as ectoparasiticides and as insecticides, which is where most clinical cases come from. Carbamate insecticides, in contrast, inhibit AChE by carbamylation, which is reversible. Carbamates generally give a shorter and less severe illness for that reason, though poisoning can still be fatal.

The key concept is **aging**. After a time that depends on the compound, the phosphorylated enzyme loses a chemical group and becomes resistant to oxime reactivators such as pralidoxime. Oximes work only on non-aged enzyme, so they are most useful early after exposure.

Beyond the acute cholinergic crisis, veterinary references describe an **intermediate syndrome** in dogs and cats, appearing one to four days after a large exposure, with weakness of neck, limb and respiratory muscles and without the salivation and fasciculations of the acute phase. Delayed neuropathy is a separate entity described for some OPs. Details are in the sources listed below.

Ecothiopate and similar long-acting agents have been used as eye drops in glaucoma in humans, but have little place in Indian veterinary practice.

Uses in ruminant, equine and small animal practice

Clinical use of cholinergic stimulants is narrower than the pharmacology suggests, because the side effects are widespread and the conditions treated usually have a cause that should be corrected first.

- **Ruminants.** Neostigmine has traditionally been used to stimulate forestomach motility in atony, but only after the underlying cause (metabolic disease, indigestion, hypocalcaemia and similar) is dealt with. Stimulating a paralysed gut against a mechanical obstruction is harmful. Ruminants are also very sensitive to cholinergic drugs and to organophosphate poisoning through sprayed forage, dips and misused pesticides.
- **Horses.** The equine gut is prone to colic when stimulated. Neostigmine and other cholinomimetics can cause abdominal pain, and a primary use of neostigmine in horses is therefore reversal of neuromuscular block under anaesthesia, with an anticholinergic to guard against bradycardia. Bethanechol may be considered for bladder atony, with the injectable form only available through compounding in some countries.
- **Dogs and cats.** Bethanechol for detrusor atony after the outflow has been confirmed open; pyridostigmine for myasthenia gravis; edrophonium for diagnosis of myasthenia.

The theme to teach students is simple: first find out whether the gut or bladder is obstructed, then decide whether a stimulant is safe.

Cholinergic toxicity

Cholinergic toxicity can come from overdose of a cholinomimetic, from anticholinesterase drugs, or most often from organophosphate and carbamate insecticide exposure. The signs can be grouped by receptor.

- **Muscarinic:** salivation, lacrimation, urination, diarrhoea (the SLUD group), vomiting, colic, sweating, miosis, bronchoconstriction with excess bronchial secretion, and slow heart rate.
- **Nicotinic:** muscle fasciculations, then weakness and paralysis. Respiratory muscle failure is a main cause of death.
- **Central:** restlessness, ataxia and seizures. Cattle and sheep more often show depression, while dogs and cats more often show convulsions.

Treatment logic. Atropine blocks the muscarinic effects, and is given to effect and repeated. It does not touch nicotinic signs such as fasciculations and muscle paralysis, which is why large OP exposures can still kill an animal whose secretions are dry. Pralidoxime reactivates non-aged enzyme and is therefore most helpful early and in organophosphate poisoning; veterinary references advise against using it alone in carbamate poisoning. Decontamination of skin and gut and supportive ventilation matter as much as the antidotes. Morphine, barbiturates and phenothiazines are listed as contraindicated in these references.

A common trap: with carbamates, blood cholinesterase may look near normal in the laboratory because the inhibition reverses quickly. Treat the animal, not the test.

For any local rules on withdrawal periods or banned pesticides in India, check the current notification.

Concept cleared

Concept cleared: Direct versus indirect
A direct agonist is like a person who walks in and sits on the chair. An anticholinesterase is like someone who stops the cleaners from removing the chairs. The second only works when chairs (ACh) are already being put out, so its effect follows the natural pattern of nerve activity.

Concept cleared: Why bethanechol is selective
Bethanechol carries a chemical group that protects it from cholinesterase and also makes it fit muscarinic sites far better than nicotinic ones. That is why it can empty a bladder without producing muscle twitching.

Concept cleared: Enzyme aging
Think of an organophosphate as glue holding a door shut. For a short time a solvent (pralidoxime) can dissolve the glue. After aging the glue has set hard and the solvent no longer works, so the enzyme is lost until the body makes more.

Concept cleared: Atropine and the nicotinic gap

Atropine is a muscarinic blocker only. In organophosphate poisoning it dries secretions and corrects slow heart rate, but muscle weakness and paralysis are nicotinic, so an animal can still stop breathing even with a dry mouth and dilated pupils.

Memory aid: SLUD and the nicotinic extras

SLUD = Salivation, Lacrimation, Urination, Diarrhoea (muscarinic). Add miosis, bradycardia, bronchospasm. Then Nicotinic = muscle twitch, then paralysis. Atropine fixes SLUD but not the twitch.

Compare and contrast

Direct agonists

Drug	Receptors	Resists cholinesterase	Main use
Bethanechol	Muscarinic	Yes	Bladder atony, detrusor hyporeflexia
Carbachol	Muscarinic and nicotinic	Yes	Intraocular miosis in surgery; limited systemic use
Pilocarpine	Muscarinic	Not an ester, not hydrolysed	Miotic in glaucoma, sialogogue
Acetylcholine	Both	No	Not used clinically

Anticholinesterases

Drug	Binding	Duration	Notes
Edrophonium	Reversible, non-covalent	Minutes	Myasthenia test; brief reversal
Neostigmine, pyridostigmine	Carbamylation, reversible	Hours	Reversal of relaxants; myasthenia; quaternary, poor brain entry
Physostigmine	Carbamylation, reversible	Hours	Tertiary, enters brain
Organophosphates	Phosphorylation, aging	Days or longer	Poisoning; oxime reactivation early only
Carbamate insecticides	Carbamylation, reversible	Shorter	Poisoning; atropine main antidote

Species notes

Cattle and sheep

Often show depression rather than convulsions in OP poisoning; rumen contents can prolong absorption, so activated charcoal is especially recommended in cattle. Poisoning is usually accidental, for example from sprayed forage or dips.

Horse

Cholinomimetics can provoke colic, so neostigmine is used mainly to reverse relaxants, together with an anticholinergic. Bethanechol has been suggested for bladder atony after neurological disease.

Dog

Pyridostigmine is used for acquired myasthenia gravis; bethanechol for detrusor atony once obstruction is excluded. Intermediate syndrome after massive OP exposure is reported mainly in dogs and cats.

Cat

Cats are sensitive to organophosphates, and the low end of the atropine range is used in treatment. Dichlorvos collars have been linked to an ataxia and depression syndrome.

Pig

Pigs can be poisoned by contaminated drinking water; treatment follows the same atropine-first logic as other species.

Clinical pearls

Self-test: 10 questions

1. Which drug is a direct-acting, muscarinic-selective agonist used for bladder atony?

Bethanechol resists cholinesterase and acts on muscarinic receptors in the detrusor. The others are anticholinesterases.

2. Why is acetylcholine not used as a drug?

AChE and plasma cholinesterases destroy it within moments, and it has no receptor selectivity.

3. Which anticholinesterase has the shortest duration of action?

Edrophonium binds by weak reversible forces and acts for minutes.

4. Which anticholinesterase can enter the brain?

Physostigmine is a tertiary amine. Neostigmine and pyridostigmine are quaternary and poorly cross the blood-brain barrier.

5. Enzyme aging in organophosphate poisoning means that

After aging, the phosphorylated enzyme is resistant to oximes, so they are most useful early.

6. Which sign of OP poisoning is NOT corrected by atropine?

Fasciculations and paralysis are nicotinic effects; atropine blocks only muscarinic receptors.

7. Why is an anticholinergic given with neostigmine when reversing a muscle relaxant?

Neostigmine raises ACh at muscarinic sites too; the anticholinergic blocks those unwanted effects.

8. Why should bethanechol be used cautiously in a urinary retention case?

It stimulates the detrusor, so the outflow must be open first.

9. Which statement about carbamate poisoning is correct?

Reversible inhibition may recover during sampling or transport; atropine is the mainstay, and oximes alone are not advised.

10. In horses, the main caution with neostigmine is

Equine gut is sensitive to cholinergic stimulation; this limits clinical use other than relaxant reversal.

Key points to revise

1. Cholinergic drugs act directly on receptors or indirectly by inhibiting acetylcholinesterase.
2. Bethanechol is muscarinic selective and acts on bladder and gut smooth muscle.

3. Neostigmine and pyridostigmine are quaternary and act peripherally; physostigmine is tertiary and acts centrally.
4. Edrophonium is the shortest acting anticholinesterase.
5. Organophosphates bind irreversibly; aging makes the enzyme resistant to oximes.
6. Carbamates inhibit reversibly and cause shorter illness.
7. Cholinergic toxicity has muscarinic, nicotinic and central signs.
8. Atropine is the antidote for muscarinic signs; pralidoxime reactivates enzyme early in OP poisoning.

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Sources

- Merck Veterinary Manual: Organophosphate toxicosis in animals
- Merck Veterinary Manual: Carbamate insecticides toxicity
- Merck Veterinary Manual: Pharmacotherapeutics in urine retention in animals

CHAPTER 3 OF 33

Anticholinergic drugs

Muscarinic antagonists: how atropine, glycopyrrolate and hyoscine block parasympathetic effects, their use in premedication, bradycardia and smooth muscle spasm, and the cautions that differ between species.

After this chapter you can

- Explain the mechanism of muscarinic receptor blockade and predict the organ effects
- Compare atropine, glycopyrrolate and hyoscine by structure, brain entry and duration

- Describe indications in premedication, vagal bradycardia, spasm and organophosphate poisoning
- Recognise atropine toxicity and its management in principle
- State species-specific cautions for ruminants, horses, rabbits, cats and dogs

Mechanism and the effects you can predict

Anticholinergic drugs in this chapter are **competitive muscarinic antagonists**. They occupy the receptor so acetylcholine cannot act. They do not stop release of acetylcholine, and they do not block nicotinic receptors at the neuromuscular junction in ordinary doses.

Since muscarinic receptors are on the heart, glands, smooth muscle and eye, the effects can be worked out from the parasympathetic system in reverse:

- **Heart:** block of M2 receptors at the sinoatrial node raises heart rate and speeds atrioventricular conduction.
- **Glands:** less saliva, bronchial, and sweat secretion. Gastric acid falls only a little.
- **Smooth muscle:** bronchodilation, reduced gut motility and tone, and relaxation of the bladder detrusor.
- **Eye:** mydriasis and loss of accommodation (cycloplegia).
- **Brain:** tertiary amines such as atropine and hyoscine enter the central nervous system and can cause sedation or, at higher doses, excitement.

Every cautionary statement about these drugs is a result of one of these effects. Glaucoma, tachycardia, intestinal ileus and urinary retention all worsen.

Atropine

Atropine is a plant alkaloid (from Atropa belladonna and related plants). It is a tertiary amine, so it is well absorbed and crosses the blood-brain and placental barriers. Veterinary notes put its vagal-blocking action at roughly an hour to an hour and a half, which is shorter than glycopyrrolate.

A well-known point is the **initial slowing of heart rate** that can occur after rapid intravenous injection, before the rise in heart rate. This is attributed to a brief central vagal effect. It is a reason to give the drug slowly and not to panic when the first change is a lower rate.

Atropine is also the antidote for muscarinic signs of cholinesterase-inhibitor poisoning and for overdose of neostigmine or edrophonium. In that use it is given to effect, and the endpoint is not a fixed amount but dry secretions, a clear chest and a heart rate that has recovered.

Atropine causes mydriasis, so it is avoided in glaucoma and when the iris is stuck to the lens. Used in the eye, it is a long-acting mydriatic and cycloplegic, helpful in uveitis to relieve ciliary spasm.

Glycopyrrolate and hyoscine

Glycopyrrolate is a synthetic quaternary ammonium compound. Because it carries a permanent charge, it passes poorly across the blood-brain barrier and the placenta. Compared with atropine it has little central effect, produces less tachycardia, and its action lasts longer, around two to three hours in the teaching material used here. It is often chosen for patients with central nervous system disease and for pregnant animals, and it is the standard partner for neostigmine. It is usually more expensive than atropine, which matters in many Indian practices.

Hyoscine (scopolamine) is another belladonna alkaloid. The two forms behave very differently:

- **Hyoscine hydrobromide** is a tertiary amine with prominent central effects: sedation, amnesia and antiemetic action, which is why it is used for motion sickness in people.
- **Hyoscine butylbromide** is quaternary. It does not enter the brain much, and its main use is as a **spasmolytic** for smooth muscle cramps in gut, bile and urinary tracts. It is used in horses with spasmodic colic and to relax the rectum for examination, and in other species for colic or spasm. Check the product label for the species it is registered for in India.

Other synthetic muscarinic antagonists include ipratropium for airways and tropicamide for eye examination. Their selection depends on route and desired site of action, not on a new mechanism.

Uses: premedication, bradycardia and spasm

Premedication. In the past anticholinergics were given routinely before anaesthesia to dry secretions and to prevent vagal reflexes. Current teaching is that routine use

is not advised. They are used when there is a reason, such as procedures that provoke vagal stimulation (for example, traction on the eye) or when a drug that slows the heart is given. A rise in heart rate also raises myocardial oxygen demand, so a healthy animal with a normal heart rate gains little.

Bradycardia. Anticholinergics treat bradycardia that is due to vagal tone, for instance with opioids, with surgical traction, or during reversal of neuromuscular block with neostigmine. They do not treat every slow heart rate. For example, the slow rate after an alpha-2 agonist comes with raised vascular tone and is a response to hypertension. Whether to give an anticholinergic in that case is debated, and many clinicians prefer reversing the alpha-2 drug.

Spasm. Hyoscine butylbromide and atropine relax smooth muscle in gut and urinary spasm. Spasmolytic action is only symptomatic, and the cause of pain still has to be found.

Poisoning. Atropine is the principal antidote for the muscarinic signs of organophosphate and carbamate poisoning. It is repeated as needed and does not reverse nicotinic muscle effects.

Atropine toxicity

Overdose or plant poisoning produces the opposite picture to cholinergic toxicity: dry mouth, dilated unresponsive pupils, fast heart rate, hot dry skin with raised body temperature, restlessness or delirium, urinary retention and ileus. The old human saying is dry as a bone, red as a beet, mad as a hatter, blind as a bat.

In animals, management is supportive: cooling, sedation of agitation, fluids and watching for gut stasis and urinary retention. Physostigmine can reverse the central and peripheral effects of anticholinergics in selected cases, but it carries its own risks and should be used on professional guidance.

Atropine used to treat organophosphate poisoning can also be overdone. The aim is to dry secretions and restore heart rate, not to produce full atropinisation with a fast heart rate and ileus. Veterinary references advise avoiding overtreatment.

Cautions by species

- **Horses.** Atropine is not routinely used in anaesthesia. It can cause ileus and colic, and a long-lasting depression of gut motility is dangerous in a species with a sensitive gut. If it is needed for a slow heart rate, some practitioners give mineral oil or take other precautions. Glycopyrrolate is seen as the more suitable drug in some situations. Heavy sweating is part of equine thermoregulation, so reduced sweating matters in hot climates.
- **Ruminants.** Atropine is not very good at drying oral secretions in ruminants and some authors say it makes saliva thicker, which impairs clearance and may raise the risk of bloat. Rumen motility is also reduced. Low doses and careful monitoring of the rumen are advised.
- **Rabbits and rats.** Many rabbits have an enzyme, atropinesterase, in the liver that destroys atropine, so doses that work in dogs may fail. Veterinary notes say they need higher doses, and glycopyrrolate is often preferred in practice.
- **Cats.** Cats are sensitive to the effects of xylazine, and atropine may be given with alpha-2 drugs by some practitioners. Check for cardiopulmonary disease before using any combination.
- **Dogs.** Avoid anticholinergics in animals that already have a fast heart rate, and in those with glaucoma. In brachycephalic dogs, the thickened secretions can obstruct the airway.

Concept cleared

Concept cleared: Tertiary versus quaternary
A quaternary drug carries a permanent charge, so it cannot easily slip through the lipid wall of the brain capillary. Glycopyrrolate and hyoscine butylbromide are quaternary and stay in the body. Atropine and hyoscine hydrobromide are tertiary and walk into the brain.

Concept cleared: Competitive block
Atropine sits on the receptor like a person holding a seat. If acetylcholine rises a lot, as in organophosphate poisoning, it can push the blocker away, so large amounts of atropine may be needed to maintain the block.

Concept cleared: Why heart rate first falls

Fast intravenous atropine can briefly stimulate vagal centres or act on some receptors before blocking the heart. It is a short effect, and slow injection reduces it.

Concept cleared: Not all bradycardia is vagal

Atropine corrects bradycardia caused by high vagal tone. A slow heart rate caused by an alpha-2 agonist is a baroreflex response to raised vascular resistance, so blocking the vagus may add workload to the heart.

Memory aid: Atropine in reverse

Cholinergic is SLUD (wet). Anticholinergic is the opposite: dry mouth, big pupils, fast heart, hot skin, slow gut, no urine. If you know SLUD, say the opposite for atropine.

Compare and contrast

Atropine, glycopyrrolate and hyoscine

Drug	Structure	Brain entry	Duration (teaching notes)	Main points
Atropine	Tertiary	Yes	About 1 hour or somewhat more	Antidote; mydriasis; first dip in heart rate if given fast
Glycopyrrolate	Quaternary	Poor	About 2 to 3 hours	Less tachycardia; suits CNS disease and pregnancy
Hyoscine hydrobromide	Tertiary	Yes	Variable	Sedative and antiemetic effects
Hyoscine butylbromide	Quaternary	Poor	Variable	Spasmolytic for gut and urinary tract

Anticholinergic versus cholinergic toxicity

Feature	Anticholinergic toxicity	Cholinergic toxicity
Pupils	Dilated	Constricted
Secretions	Dry	Excessive
Heart rate	Fast	Slow
Gut	Ileus	Hypermotility, diarrhoea
Skin	Hot, dry	Sweating
Antidote	Supportive; physostigmine in selected cases	Atropine, and an oxime for OP

Species notes

Horse

Atropine can cause ileus and colic, so it is not used routinely; glycopyrrolate is considered when an anticholinergic is needed. Hyoscine butylbromide is used for spasmodic colic.

Cattle and sheep

Atropine is poor at drying secretions in ruminants and may thicken saliva; watch for bloat and impaired rumen function. Drug doses are lower per body weight than in small animals.

Rabbit

Atropinesterase in the liver destroys atropine in many rabbits, so the response is unreliable. Glycopyrrolate is often used instead.

Cat

Atropine is used for vagal bradycardia and as the OP antidote at the low end of the range. Cats given xylazine often vomit; check heart and lung health first.

Dog

Use only when indicated; avoid in tachycardia and glaucoma. Glycopyrrolate gives longer action and less heart rate increase than atropine.

Clinical pearls

Self-test: 10 questions

1. Which drug is a quaternary ammonium compound with little CNS effect?

Glycopyrrolate carries a permanent charge and passes poorly across the blood-brain barrier.

2. Atropine acts by

It competes with acetylcholine at muscarinic receptors.

3. Which effect is NOT expected from atropine?

Atropine causes mydriasis; miosis is a cholinergic effect.

4. The main reason atropine is not routinely used in horses is

Reduced gut motility is dangerous in horses.

5. Why may atropine fail in some rabbits?

Hepatic atropinase breaks down atropine in many rabbits.

6. Hyoscine butylbromide is mainly used as

It is quaternary and acts peripherally on smooth muscle.

7. In organophosphate poisoning, atropine does NOT treat

Those are nicotinic effects.

8. Why give glycopyrrolate with neostigmine?

Neostigmine raises acetylcholine at muscarinic sites; the anticholinergic blocks those effects.

9. Which sign suggests anticholinergic toxicity?

Anticholinergic toxicity is the reverse of cholinergic toxicity.

10. Why is atropine avoided in glaucoma?

Pupil dilation may worsen drainage and raise intraocular pressure.

Key points to revise

1. Anticholinergics are competitive muscarinic antagonists.
2. Effects: tachycardia, dry secretions, bronchodilation, reduced gut motility, mydriasis.
3. Atropine is tertiary and enters the brain; glycopyrrolate is quaternary and does not.
4. Glycopyrrolate acts longer than atropine and gives less tachycardia.
5. Hyoscine butylbromide is used for smooth muscle spasm.
6. Atropine is the antidote for muscarinic signs of OP and carbamate poisoning, but not nicotinic signs.
7. Atropine toxicity is the reverse of SLUD.
8. Species cautions: ileus in horses, thick secretions in ruminants, atropinesterase in rabbits.

Go deeper on this site

- Ch 4. Adrenergic agonists and antagonists (in this book)
- Ch 2. Cholinergic drugs (in this book)

- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Hill Agricultural / COVAS teaching material: Preanaesthetics
- Western University of Health Sciences: Pharmacology of premedication
- Merck Veterinary Manual: Organophosphate toxicosis in animals

CHAPTER 4 OF 33

Adrenergic agonists and antagonists

Adrenergic drugs mimic or block noradrenaline and adrenaline at alpha and beta receptors. This chapter links receptor selectivity to the effects you see in shock, cardiac arrest, anaphylaxis, sedation, asthma and heart disease.

After this chapter you can

- Name the adrenergic receptor subtypes and the main effect of each
- Compare the catecholamines (adrenaline, noradrenaline, dopamine, dobutamine, isoprenaline) by receptor selectivity
- Explain why adrenaline is the drug of choice in anaphylaxis and cardiac arrest
- Distinguish selective and non-selective alpha and beta blockers and their clinical uses
- Predict adverse effects and cautions from receptor pharmacology

Adrenergic receptors in brief

Sympathetic nerves release **noradrenaline**, and the adrenal medulla releases mainly **adrenaline**. Both act on G-protein-coupled receptors. Almost every adrenergic drug effect can be predicted if you remember four receptor types.

Selectivity is the key idea of this chapter. A drug that is selective for one receptor gives a narrower, more predictable effect. A drug that acts on several gives a broad effect, which can be useful in an emergency but causes more side effects.

- **Alpha-1**: smooth muscle contraction. Vasoconstriction (raises blood pressure), mydriasis, contraction of the bladder neck and urethral sphincter.
- **Alpha-2**: mostly presynaptic and central. Reduce noradrenaline release and sympathetic outflow, causing sedation, analgesia and muscle relaxation. Peripherally they can cause vasoconstriction.
- **Beta-1**: heart. Raise heart rate and force of contraction and speed conduction. Also stimulate renin release.
- **Beta-2**: bronchodilation, vasodilation in skeletal muscle, uterine relaxation, and glycogenolysis.

Catecholamines and their selectivity

Catecholamines have a catechol ring and act quickly. They are destroyed in the gut and by enzymes (MAO and COMT), so they are given by injection or infusion and last only minutes. This is useful because the effect can be titrated and stopped quickly.

- **Adrenaline (epinephrine)**: acts on alpha-1, beta-1 and beta-2. The result depends on dose and tissue. It strongly increases cardiac work and oxygen demand.
- **Noradrenaline (norepinephrine)**: mainly alpha-1 and beta-1, with little beta-2. It is a potent vasopressor, used when the problem is low vascular tone.
- **Dopamine**: the precursor of noradrenaline. Acts on dopamine receptors, beta-1, and at higher rates alpha-1, partly by releasing noradrenaline.
- **Dobutamine**: synthetic, mainly beta-1. It increases contractility more than heart rate and does not release noradrenaline.
- **Isoprenaline**: non-selective beta agonist with no alpha action. It causes tachycardia and arrhythmias, so its use is limited, for example in short-term treatment of bradyarrhythmias.

A common confusion: dopamine is often called the 'renal dose' drug. Low rates act on renal dopamine receptors and increase renal blood flow and urine output, but this has not been shown to protect kidneys, so do not treat it as a kidney-saving drug.

Uses in shock, cardiac arrest and anaphylaxis

In **shock** the aim is to restore tissue perfusion. First correct the cause and the fluid deficit. Adrenergic drugs are added when blood pressure or cardiac output remain poor after fluids. Match the drug to the problem: a weak pump (cardiogenic shock) responds to beta-1 agents such as dobutamine or dopamine. Vasodilatory shock (for example sepsis) needs a vasopressor such as noradrenaline. Using a pure inotrope in a vasodilated patient will not fix pressure.

In **cardiac arrest**, adrenaline is the standard drug. Its alpha-1 action raises aortic diastolic pressure and so coronary and cerebral perfusion during compressions. Beta effects add little and may increase myocardial oxygen demand.

In **anaphylaxis**, adrenaline is the first-line drug. It is a physiological antagonist of the mediators released: alpha-1 reverses vasodilation and oedema, beta-1 supports the heart, and beta-2 relaxes bronchial muscle and reduces further mediator release from mast cells. Antihistamines and corticosteroids act too slowly and do not replace it.

Caution: adrenaline can cause ventricular arrhythmias, particularly when the myocardium is already sensitised, for example by some inhalant anaesthetics. Extravasation of vasoconstrictor infusions can cause local tissue necrosis, so give them through a secure intravenous line.

Other agonists: alpha-2 and beta-2 drugs

Alpha-2 agonists (xylazine, medetomidine, dexmedetomidine, detomidine, romifidine) are widely used as sedative-analgesics in animals. Their cardiovascular effects follow from the receptor: initial vasoconstriction and hypertension, then bradycardia and reduced cardiac output. Ruminants are very sensitive to xylazine. These effects can be reversed by an alpha-2 antagonist such as atipamezole or yohimbine.

Beta-2 agonists (salbutamol, terbutaline, clenbuterol) relax bronchial and uterine smooth muscle. They are used for airway disease and, in some species, for tocolysis. Higher doses lose selectivity, causing tachycardia and tremor.

Alpha-1 agonists such as phenylephrine are vasopressors and nasal or ocular decongestants. Phenylpropanolamine and pseudoephedrine act mainly by releasing noradrenaline and have been used to raise urethral tone in urinary incontinence in dogs.

Regulation: beta-2 agonists have been misused as growth promoters in food animals. Check the current notification on the status of such use in India.

Alpha and beta blockers

Blockers occupy the receptor without activating it, so their effect depends on how much sympathetic tone is present.

- **Alpha-1 blockers** (prazosin, phenoxybenzamine): cause vasodilation and relax the urethral sphincter. Phenoxybenzamine binds irreversibly and is used to prepare patients with phaeochromocytoma and sometimes for urethral spasm. Main adverse effect is hypotension.
- **Alpha-2 antagonists** (atipamezole, yohimbine): reverse sedation from alpha-2 agonists.
- **Non-selective beta blockers** (propranolol): block beta-1 and beta-2. They slow the heart and reduce arrhythmias, but beta-2 blockade can cause bronchospasm, so they are risky in asthmatic or feline airway disease.
- **Beta-1 selective blockers** (atenolol, metoprolol, esmolol): preferred when the airways matter. Esmolol is very short acting and is given by infusion for supraventricular tachyarrhythmias.
- **Carvedilol** blocks beta and alpha-1 receptors and is used in some cardiac patients.

Cautions for beta blockers: they can precipitate decompensation in animals with severe heart failure that depend on sympathetic drive, they can mask signs of hypoglycaemia, and stopping them abruptly can cause rebound tachycardia. Selectivity is relative and is lost at higher doses.

Putting it together: predicting effects

When you meet an adrenergic drug, ask three questions. Which receptors does it act on? Is it an agonist or a blocker? How fast is it removed? From these answers you can predict heart rate, blood pressure, airway tone and likely adverse effects without memorising lists.

Examples: a beta-1 selective agonist should raise contractility with less effect on the airways. A pure alpha-1 agonist should raise pressure and may cause a reflex

slowing of the heart. A non-selective beta blocker should slow the heart and tighten the airways.

Drug interactions follow the same logic. Monoamine oxidase inhibitors increase the effect of indirectly acting amines and of dopamine. Alpha-2 agonists combined with other sedatives deepen cardiovascular depression. Alpha blockers given with a beta agonist can leave beta-2 vasodilation unopposed, causing hypotension, which is the reason adrenaline's pressor effect can reverse in the presence of an alpha blocker.

Concept cleared

Selectivity is relative
Receptor selectivity falls as dose rises. A beta-1 selective drug at a high dose also acts on beta-2.

Dose-dependent adrenaline effects
Adrenaline has alpha and beta actions at once. Which one dominates depends on dose, route and the tissue involved.

Match drug to the haemodynamic problem
Pump failure needs an inotrope, vasodilatory shock needs a vasopressor, and both need volume and the underlying cause treated.

Physiological antagonism
Adrenaline reverses anaphylaxis by producing opposite effects to the mediators, not by blocking them.

Memory aid: Receptors: 1, 2, 1, 2
Alpha-1 constricts, alpha-2 calms. Beta-1 beats the heart, beta-2 breathes (opens the airways).

Compare and contrast

Catecholamines at a glance

Drug	Main receptors	Main effect	Typical use
Adrenaline	Alpha-1, beta-1, beta-2	Vasoconstriction, cardiac stimulation, bronchodilation	Cardiac arrest, anaphylaxis
Noradrenaline	Alpha-1, beta-1	Strong vasoconstriction	Vasodilatory shock
Dopamine	Dopamine, beta-1, alpha-1 at higher rate	Inotropy, then pressor effect	Cardiogenic or endotoxic shock
Dobutamine	Beta-1	Increased contractility	Low output heart failure
Isoprenaline	Beta-1, beta-2	Tachycardia, vasodilation	Short-term bradyarrhythmia

Adrenergic blockers

Drug	Selectivity	Main effect	Key caution
Prazosin	Alpha-1	Vasodilation, lower urethral tone	Hypotension
Phenoxybenzamine	Alpha, irreversible	Prolonged alpha block	Hypotension, slow offset
Atipamezole	Alpha-2	Reverses sedation	Sudden arousal, vasodilation
Propranolol	Beta-1 and beta-2	Slows heart, reduces arrhythmia	Bronchospasm
Atenolol	Beta-1	Slows heart	Decompensated heart failure

Species notes

Dogs

Dobutamine and dopamine are used by infusion in low output states. Phenylpropanolamine is used for urethral sphincter incompetence.

Cats

Cats are sensitive to beta-2 blockade of airways. Dobutamine has a longer half-life and can stimulate the central

Atenolol and similar drugs are used in selected cardiac cases.

nervous system, so it is used cautiously and rarely.

Horses

Clenbuterol is used for airway disease, and detomidine and romifidine are common alpha-2 sedatives. Check competition rules on prohibited substances.

Ruminants

Cattle are highly sensitive to xylazine, and sedation can come with salivation, bloat risk and, in pregnancy, uterine effects. Use of adrenergic drugs in food animals needs a withdrawal and regulatory check.

Birds and exotics

Alpha-2 agonists are used with care because of cardiovascular depression. Atipamezole reversal is common.

Clinical pearls

Self-test: 10 questions

1. Which receptor mainly mediates bronchodilation?

Beta-2 receptors relax bronchial smooth muscle, which is why beta-2 agonists are used for airway disease.

2. First-line drug for anaphylaxis is

Adrenaline reverses vasodilation, oedema and bronchospasm quickly. Antihistamines and steroids are slower and adjunctive.

3. Which catecholamine is mainly a beta-1 agonist that raises contractility with little noradrenaline release?

Dobutamine acts mainly on beta-1 receptors and does not release noradrenaline.

4. Why is adrenaline given in cardiac arrest?

The alpha-1 effect increases aortic diastolic pressure and hence coronary and cerebral perfusion during compressions.

5. Atipamezole reverses the effects of

Atipamezole is an alpha-2 antagonist and reverses alpha-2 agonist sedation.

6. A non-selective beta blocker is most hazardous in an animal with

Beta-2 blockade can tighten the airways and worsen bronchospasm.

7. Phenoxybenzamine differs from prazosin because it

Phenoxybenzamine binds alpha receptors irreversibly, so its effect is prolonged.

8. A patient in vasodilatory shock after adequate fluids most needs

The problem is low vascular tone, so an alpha-1 vasopressor is appropriate.

9. Common early effect of alpha-2 agonists on the cardiovascular system is

Peripheral vasoconstriction raises pressure initially, then reflex bradycardia and reduced output follow.

10. Which statement about selectivity is correct?

At higher doses selective drugs act on other receptor subtypes too.

Key points to revise

1. Four receptor types: alpha-1, alpha-2, beta-1, beta-2.
2. Catecholamines are short acting and given by infusion or injection.
3. Adrenaline acts on alpha-1, beta-1 and beta-2.
4. Noradrenaline is mainly a vasopressor.
5. Dobutamine is mainly beta-1 and increases contractility.
6. Adrenaline treats anaphylaxis by reversing its effects physiologically.
7. Alpha-2 agonists sedate and are reversed by atipamezole or yohimbine.
8. Selectivity is lost at higher doses.

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- Ch 5. Ganglion and neuromuscular blocking drugs (in this book)
- Ch 3. Anticholinergic drugs (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Positive Inotropes for Use in Animals

CHAPTER 5 OF 33

Ganglion and neuromuscular blocking drugs

Drugs that block nicotinic transmission at autonomic ganglia and at the skeletal muscle end plate. The chapter covers depolarising and non-depolarising relaxants, reversal, monitoring and the drug interactions that matter during anaesthesia.

After this chapter you can

- Explain why ganglion blockers have almost no clinical use while neuromuscular blockers are important in anaesthesia
- Compare depolarising and non-depolarising block in mechanism, early signs and reversibility
- Describe how neostigmine, anticholinergics and sugammadex reverse block
- State what must be monitored when a relaxant is used and why
- List drugs and conditions that prolong neuromuscular block

Two nicotinic targets, two very different outcomes

The nicotinic acetylcholine receptor is a ligand-gated ion channel. There are different subtypes: one in autonomic ganglia (neuronal type) and one at the skeletal muscle end plate (muscle type). Drugs that block them are therefore separated into **ganglion blockers** and **neuromuscular blockers**.

Neuromuscular blockers paralyse skeletal muscle so that surgery, intubation and controlled ventilation are easier. They are used only in animals that are already unconscious, because they have **no sedative, analgesic or anaesthetic action**. An animal that is paralysed but not anaesthetised is fully aware and in pain, and cannot show it.

A common confusion is to think that a relaxant makes the animal unconscious or pain free. It does not. Another is to treat the loss of movement as proof of adequate anaesthesia. After a relaxant, a rise in heart rate or blood pressure to a surgical stimulus may be the only warning that depth is too light, so cardiovascular trends must be watched closely.

Ganglion blocking drugs

Ganglion blockers such as hexamethonium, mecamylamine and the older trimetaphan occupy neuronal nicotinic receptors, or the channel they form, in both sympathetic and parasympathetic ganglia. They block all autonomic outflow at once.

The effect in a given organ depends on which branch dominates at rest. This is the key idea. In blood vessels, sympathetic tone dominates, so the result is vasodilation and a fall in blood pressure, with orthostatic hypotension. In the heart, vagal tone

dominates, so heart rate rises. In the gut and bladder, parasympathetic tone dominates, so there is constipation, ileus and urinary retention. In the eye, the pupil dilates and accommodation is lost. Salivation is reduced.

Because they affect everything, are hard to control and give rise to these effects, ganglion blockers are not used in routine veterinary practice. They remain important in teaching because they illustrate how organs are under dual control, and because some drugs have ganglion-blocking effects as a side action. The details of any use in a specific species should be checked in a current formulary.

Non-depolarising (competitive) blockers

Atracurium, cisatracurium, rocuronium, vecuronium and pancuronium bind to the nicotinic receptor at the end plate without opening it. They compete with acetylcholine, and when enough receptors are blocked the end plate cannot reach threshold, so the muscle relaxes. Because the block is competitive, it can be overcome by raising acetylcholine, which is the basis of reversal.

Muscles go weak in a progressive way and then become flaccid. Small, fast muscles of the eye and face are affected earliest, then limbs and trunk, and the diaphragm last. Recovery happens in reverse, with the diaphragm returning first. Good breathing does not prove that the muscles of the larynx and pharynx are safe, so swallowing and airway protection may still be impaired.

The agents differ in how they are cleared. Steroidal agents (rocuronium, vecuronium, pancuronium) depend on organ function. Atracurium and cisatracurium are broken down by enzymatic hydrolysis and by Hofmann elimination in plasma, so they are less affected by liver and kidney disease and are often chosen in sick animals. Atracurium can release histamine at higher doses, and slow injection reduces this. Pancuronium can raise heart rate through muscarinic blocking effects.

Depolarising blocker: succinylcholine

Succinylcholine (suxamethonium) is the only depolarising relaxant in common use. It attaches to the nicotinic receptor and opens it, like acetylcholine does, but it is not removed quickly by acetylcholinesterase. The end plate stays depolarised and

cannot respond to further stimulation. The first sign is **fasciculation**, followed by flaccid paralysis.

Its action is ended by plasma pseudocholinesterase (butyrylcholinesterase), which breaks it down before it reaches the junction, and by diffusion away from the end plate. Anything that lowers pseudocholinesterase, including liver disease, malnutrition, pregnancy and some drugs, prolongs the effect.

The block has two phases. **Phase I** is the depolarising block just described. With large, repeated or infused doses it may change to **phase II**, which resembles a non-depolarising block.

Succinylcholine is rarely used in current veterinary practice. Reasons listed by current references include arrhythmias, potassium release that can be dangerous in animals with muscle disease, myoglobinuria after recovery, a possible link with malignant hyperthermia, and the absence of a specific antagonist. In the past it was used for restraint of large animals and wildlife, but because it paralyses without analgesia or sedation, this is now considered unacceptable.

Reversal and monitoring

Reversal of non-depolarising block. Anticholinesterases such as neostigmine, pyridostigmine and edrophonium raise acetylcholine at the junction so it can win the competition. Because they raise acetylcholine at muscarinic receptors too, they cause bradycardia, bronchospasm, salivation and hypermotility, so atropine or glycopyrrolate is given with them. Neostigmine takes several minutes and cannot reverse a very deep block. Reversal should be started only when some recovery is already present.

Sugammadex is a different kind of drug. It is a cyclodextrin that wraps around rocuronium and vecuronium, removing them from the junction. It acts quickly, has no muscarinic effects and can reverse a deep block, but it does not work for atracurium and cisatracurium.

Succinylcholine. Phase I block should not be reversed with an anticholinesterase, because it will deepen the block. Phase II block may respond, so the type of block must be known.

Monitoring. Because paralysis removes the usual signs of anaesthetic depth (jaw tone, palpebral reflex, movement), depth has to be judged from cardiovascular responses and other monitors. Ventilation must be supported until function returns. A peripheral nerve stimulator is used to judge the degree of block and its recovery, and full recovery should be confirmed before extubation to avoid hypoventilation, hypoxia and aspiration.

Drug interactions and patient factors

A relaxant rarely acts alone, and its duration depends on what else the patient receives and on the patient's condition.

- **Inhalant anaesthetics** (isoflurane, sevoflurane) increase the potency of non-depolarising blockers, so less drug is needed.
- **Antibiotics:** aminoglycosides, polymyxins, tetracyclines and lincosamides can enhance block. A dog given gentamicin and a relaxant may recover slowly.
- **Other drugs:** quinidine, procaine, lidocaine, diazepam and barbiturates can enhance block in some circumstances.
- **Physiological factors:** hypermagnesaemia, hypokalaemia, acidosis and hypothermia prolong block. Correct these before reversing.
- **Disease:** myasthenia gravis makes animals very sensitive to non-depolarising agents. Liver, kidney and low pseudocholinesterase states change how long certain agents last.
- **Anticholinesterase drugs and organophosphates** prolong succinylcholine, since they inhibit cholinesterase.

The practical rule is to review every drug the patient has received, including recent dips or pesticide exposure, before using a relaxant, and to use a nerve stimulator where possible.

Concept cleared

Concept cleared: Ganglion block depends on tone
A ganglion blocker removes both autonomic brakes and accelerators. What you see is whichever branch was winning at rest: vessels lose sympathetic tone and dilate, while the heart loses vagal tone and speeds up.

Concept cleared: Competitive versus depolarising

A competitive blocker is a key stuck in the lock that does not turn: the door cannot open. Succinylcholine is a key that turns and then jams: the door opens once, then stays unresponsive. More acetylcholine can push out the first key, but it only worsens the jam.

Concept cleared: Why reversal needs an anticholinergic

Neostigmine does not know where the acetylcholine is. It protects it at muscle and also at heart, gut and glands. The anticholinergic protects those other sites.

Concept cleared: Sugammadex is a chemical trap

It does not act on receptors. It captures rocuronium or vecuronium molecules like a cup, so the relaxant leaves the junction and the muscle recovers. That is why it does not work for drugs that do not fit the cup.

Memory aid: Which block to reverse

Competitive block: Compete back with neostigmine (plus atropine or glycopyrrolate). Depolarising phase I: Do not reverse, wait. Rocuronium and vecuronium only: Sugammadex.

Compare and contrast

Depolarising and non-depolarising block

Feature	Succinylcholine (depolarising)	Atracurium, rocuronium, vecuronium (non-depolarising)
Action at receptor	Activates, holds end plate depolarised	Occupies without activating
Early sign	Fasciculations	Progressive weakness
Termination	Plasma pseudocholinesterase and diffusion	Redistribution, metabolism or excretion depending on drug
Effect of anticholinesterase	Phase I prolonged; phase II may be reversed	Reversed
Veterinary use	Rare; important adverse effects	Standard choice with ventilation

Reversal agents

Agent	Mechanism	Works on	Notes
Neostigmine	Anticholinesterase	Non-depolarising block	Slow; muscarinic effects; give with anticholinergic
Edrophonium	Short anticholinesterase	Non-depolarising block	Brief; also an anticholinergic beforehand
Pyridostigmine	Anticholinesterase	Non-depolarising block	Longer acting
Sugammadex	Encapsulates drug	Rocuronium, vecuronium	Fast; no muscarinic effects; not for atracurium or cisatracurium

Species notes

Dog

Succinylcholine lasts longer in dogs than in cats according to veterinary references. Atracurium and

Cat

Succinylcholine action is shorter than in dogs. Intubation and laryngospasm have been studied

cisatracurium are useful in animals with liver or kidney disease.

with rocuronium and sugammadex in cats.

Horse
Atracurium and rocuronium are used with ventilation. Anticholinesterases can cause bradycardia, hypotension and colic, so an anticholinergic may be needed.

Cattle
Succinylcholine was historically used for restraint. Paralysis without analgesia is unacceptable, and reliable airway and ventilation support is needed.

Pig
Pigs of some breeds are susceptible to malignant hyperthermia triggered by succinylcholine and some inhalants; avoid known triggers.

Clinical pearls

Self-test: 10 questions

1. Why can ganglion blockers cause hypotension?

Blood vessels are mainly under sympathetic tone, so ganglion block causes vasodilation.

2. A neuromuscular blocker used alone in a conscious animal would

These drugs act at the end plate and have no central effect.

3. The first sign after succinylcholine is

Initial depolarisation causes muscle twitching before paralysis.

4. Which drug terminates succinylcholine action?

It is broken down by plasma cholinesterase before reaching the junction.

5. Which relaxant is cleared mainly by Hofmann elimination and ester hydrolysis?

Atracurium and cisatracurium do not depend much on liver or kidney function.

6. Sugammadex will NOT reverse

It encapsulates steroidal agents only.

7. Why is glycopyrrolate or atropine given with neostigmine?

Neostigmine raises ACh at muscarinic sites and causes bradycardia and secretions.

8. Which muscle usually recovers first from non-depolarising block?

The diaphragm is relatively resistant, but airway protection may still be impaired.

9. Which of these prolongs non-depolarising block?

Aminoglycosides, hypothermia, acidosis, hypermagnesaemia and hypokalaemia prolong block.

10. A phase I succinylcholine block should be

Anticholinesterases prolong phase I block.

Key points to revise

1. Ganglion blockers affect all autonomic outflow and are not used clinically; effects depend on dominant tone.
2. Neuromuscular blockers act at the muscle-type nicotinic receptor and give no sedation or analgesia.
3. Non-depolarising agents compete with acetylcholine and can be reversed.
4. Succinylcholine depolarises the end plate and causes fasciculations first.
5. Succinylcholine is ended by pseudocholinesterase and has no antagonist.
6. Neostigmine reversal needs an anticholinergic.
7. Sugammadex encapsulates rocuronium and vecuronium.
8. Monitoring with a nerve stimulator and ventilation support are essential.

Go deeper on this site

- Ch 6. Anticonvulsants and drugs for epilepsy (in this book)
- Ch 4. Adrenergic agonists and antagonists (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

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- Merck Veterinary Manual: Competitive nondepolarizing agents and antagonists

CHAPTER 6 OF 33

Anticonvulsants and drugs for epilepsy

How anticonvulsant drugs calm an over-excitable brain, with the concepts behind phenobarbital, bromide, levetiracetam and other drugs, a stepwise approach to status epilepticus, and the species cautions that matter in practice.

> **After this chapter you can**

- Explain the three broad mechanisms by which anticonvulsants reduce seizure activity
- Describe why phenobarbital needs monitoring and causes drug interactions
- Explain why bromide has a very long half-life and why it is avoided in cats
- State the role of levetiracetam and other add-on drugs
- Outline the stepwise approach to status epilepticus and the main species cautions

Seizures, epilepsy and the aim of treatment

A **seizure** is a sudden, abnormal and excessive electrical discharge of brain neurons that shows as a change in behaviour, movement or consciousness. **Epilepsy** means recurrent seizures that arise from the brain itself. A seizure can also be a symptom of another problem, such as hypoglycaemia, hypocalcaemia, a liver shunt, toxins or a brain tumour. These are called reactive or structural causes, and treating the cause matters more than giving an anticonvulsant.

Anticonvulsants do not cure epilepsy. They raise the seizure threshold so that fewer and milder seizures occur. The usual goal is fewer seizures with acceptable side effects, not zero seizures at any cost. Treatment is usually started when seizures are frequent, are in clusters, last long, or cause severe post-ictal signs, and the owner must understand that it is lifelong in most dogs.

Most drugs work in one or more of three ways. They **enhance inhibition** (more GABA effect), they **block excitation** (block sodium or calcium channels, or reduce glutamate), or they **change neurotransmitter release** at the nerve terminal.

Phenobarbital

Phenobarbital is a barbiturate and remains a first-choice drug in dogs and an option in cats and horses. It binds the $GABA_A$ receptor and prolongs the opening of the chloride channel, so the neuron becomes harder to fire. It also reduces excitatory glutamate effects at higher concentrations.

Three ideas make it easy to understand.

- **Slow onset.** A steady blood level takes some days to build up, because the half-life is long. It is therefore not a drug for stopping a seizure that is happening now.

- **Enzyme induction.** Phenobarbital induces liver microsomal enzymes. Over weeks it speeds up its own breakdown (so the blood level can fall on the same dose) and the breakdown of other drugs such as some other anticonvulsants, corticosteroids and many others. Stopping it reverses this and can make other drugs suddenly stronger.
- **Liver effects.** Mild enzyme rises are common and often harmless, but long use at high blood levels can cause real liver injury. Serum levels and liver tests are therefore checked from time to time.

Common early side effects are sedation, ataxia, increased appetite, thirst and urination. These often fade over a few weeks. Rarely, blood cell changes occur. Doses are never stopped suddenly, because withdrawal can provoke seizures, including status epilepticus.

Bromide

Potassium or sodium bromide is an old drug that is still very useful. Bromide ions compete with chloride ions and enter neurons through chloride channels, which makes the cell membrane hyperpolarised and harder to excite.

The key concept is the **very long half-life**, measured in weeks. Because of this, a steady-state level takes several months to reach, and the drug is cleared by the kidney, not the liver. This is why it is a good partner for phenobarbital in dogs with liver trouble or when phenobarbital alone is not enough, and why a missed dose matters little once at steady state.

Bromide handling follows chloride handling by the kidney. If the dog eats a high-salt (high-chloride) diet, bromide is excreted faster and the level falls. If salt intake is cut, the level rises. A sudden change in diet can therefore cause breakthrough seizures or toxicity. Typical side effects are sedation, ataxia, thirst, appetite increase and sometimes pancreatitis or skin reactions.

Cats are different. A good proportion of cats given bromide develop a cough or an asthma-like airway disease, so it is generally avoided in this species.

Levetiracetam, imepitoin and other drugs

Levetiracetam binds synaptic vesicle protein SV2A and reduces abnormal neurotransmitter release. It has few drug interactions and little liver metabolism, and

it is generally well tolerated, with mild sedation or ataxia the commonest effects. Its weakness in dogs is a short half-life, so it needs frequent dosing or an extended-release form. It is used as an add-on in dogs with poor control, and in cats and horses. It is also a useful drug in animals with liver disease because it is not heavily metabolised there.

Zonisamide blocks sodium and calcium channels and is used as an add-on in dogs. **Imepitoin** is a partial agonist at the benzodiazepine site of the $GABA_A$ receptor. It is licensed for idiopathic epilepsy in dogs in some countries; check whether it is marketed in India. **Gabapentin** and **pregabalin** act on calcium channels and are used as add-ons, and gabapentin is also an analgesic. **Phenytoin** is a sodium channel blocker that is poorly suited to dogs because it is cleared quickly there.

The general rule: start with one drug, give it time and measure the blood level when possible, then add a second drug with a different mechanism if control is poor. Combining two drugs that act in the same way adds side effects more than benefit.

Status epilepticus and cluster seizures

Status epilepticus means a seizure lasting more than a few minutes, or seizures repeating without recovery between them. It is an emergency because prolonged seizures cause hyperthermia, hypoxia, brain swelling and death. **Cluster seizures** are several seizures within a short period.

The approach is by steps.

1. **Stabilise.** Secure the airway, give oxygen, and place an intravenous catheter. Check blood glucose, calcium and body temperature. Hypoglycaemia and hypocalcaemia are quickly corrected and treat the cause.
2. **Stop the seizure with a benzodiazepine.** Diazepam or midazolam acts within a minute or two on $GABA_A$ receptors. If there is no vein, rectal diazepam or intranasal or intramuscular midazolam can be used. The effect is short, so the next drug must follow.
3. **Give a long-acting drug.** Intravenous phenobarbital or levetiracetam is used to hold the control. Levetiracetam is useful when liver disease or sedation is a concern.

4. **If seizures continue,** a constant rate infusion of midazolam or propofol, or general anaesthesia, is used under monitoring with ventilatory support.

Cool the animal if the temperature is high, and look for the underlying cause once stable. Owners of epileptic dogs may be taught to give rectal diazepam at home for clusters.

Common confusions and species cautions

Seizure is not the same as epilepsy, and a first seizure does not always need a drug. **Phenobarbital is both an anticonvulsant and a sedative,** so early sedation does not mean the dose is too high. **Blood levels are a guide, not a target.** The animal is treated, not the number.

Species points matter. **Dogs** metabolise many anticonvulsants quickly, so drugs such as phenytoin are poor choices. **Cats** are sensitive to many drugs; bromide is avoided, and oral diazepam has been linked to rare, severe liver failure, so liver tests are advised if it is used. Cats also clear drugs slowly because of limited glucuronidation, which is a reason to take care with dosing. **Horses and foals** have seizures from trauma, hypoxic injury or infection, and diazepam, phenobarbital or other drugs are used under veterinary advice. **Cattle, sheep and goats** rarely have true epilepsy. Seizures in these species usually signal a cause such as polioencephalomalacia, hypomagnesaemia, lead poisoning or listeriosis, and treating the cause is the key step. **Food animals** need attention to drug residues and withdrawal periods; check the current rules for any extra-label drug use.

Finally, never stop an anticonvulsant suddenly, and warn owners about the sedation that appears in the first weeks.

Concept cleared

Concept cleared: Raising the seizure threshold

Think of a brake on a car going downhill. Seizure drugs do not remove the hill (the cause of the over-excitable brain); they add brakes. GABA drugs press the brake pedal, sodium channel blockers slow the engine, and SV2A drugs cut the fuel supply. More than one brake can be used together.

Concept cleared: Enzyme induction by phenobarbital
Phenobarbital is like a worker who trains the factory to make more machines. The liver builds more drug-metabolising enzymes, so phenobarbital itself and other drugs are cleared faster. When the worker leaves, the extra machines remain for a while and then fade, so other drugs can suddenly become stronger.

Concept cleared: Bromide and chloride
Bromide enters the body like a guest using chloride's ticket. The kidney cannot easily tell them apart, so a salty diet pushes bromide out, and a low-salt diet keeps it. Because the guest stays for weeks, a steady level takes months and the diet must stay constant.

Concept cleared: Why benzodiazepines are used first in an emergency
A benzodiazepine opens the GABA door wider within a minute, so it stops the seizure quickly. But it leaves quickly too, like a fire extinguisher. A long-acting drug is then needed to keep the fire from restarting.

Memory aid: Phenobarbital side effects: 'SAPPP'
Sedation, Ataxia, Polyphagia, Polydipsia, Polyuria. Also remember Liver and Interactions (induction). For the status epilepticus order, remember 'Safe, Stop, Sustain': Stabilise the animal, Stop with a benzodiazepine, Sustain with a long-acting drug.

Compare and contrast

Main anticonvulsants compared

Drug	Main action	Key strength	Key caution
Phenobarbital	Enhances GABA-A chloride channel	Effective, cheap, widely used	Slow onset, enzyme induction, liver effects, sedation
Bromide	Chloride-channel entry, hyperpolarisation	Not liver metabolised; useful add-on	Weeks to steady state; diet chloride; avoid in cats
Levetiracetam	Binds SV2A, reduces release	Few interactions, well tolerated	Short half-life in dogs; add-on use
Zonisamide	Blocks Na and Ca channels	Add-on in dogs	Check species and availability
Diazepam or midazolam	Enhances GABA-A	Fast emergency control	Short effect; oral diazepam in cats risks liver injury

Emergency step versus maintenance

Feature	Emergency drugs	Maintenance drugs
Examples	Diazepam, midazolam, propofol	Phenobarbital, bromide, levetiracetam
Onset	Seconds to minutes	Days to months
Duration	Short	Long
Purpose	Stop an ongoing seizure	Reduce future seizures
Route	Intravenous, rectal, intranasal	Mostly oral

Species notes

Dog

Idiopathic epilepsy is common. Phenobarbital and bromide are classic drugs, and levetiracetam and others are add-ons. Phenytoin is a poor choice because it is cleared quickly.

Cat

Phenobarbital is commonly used, and levetiracetam is a good add-on. Bromide is generally avoided because of airway disease, and oral diazepam has been linked to rare severe liver failure.

Horse and foal
Seizures in foals often follow hypoxic injury or infection. Diazepam and phenobarbital are used under veterinary advice, and the cause is investigated.

Cattle, sheep and goat
True epilepsy is rare. Seizures usually point to polioencephalomalacia, hypomagnesaemia, lead poisoning or listeriosis, so treating the cause is the key step.

Food-producing animals
Anticonvulsant use is extra-label. Withdrawal periods and residue rules must be checked in the current Indian guidance before any use.

Clinical pearls

Self-test: 10 questions

1. Which is the main action of phenobarbital?

Phenobarbital prolongs chloride channel opening at the GABA-A receptor and makes the neuron harder to fire.

2. Why can phenobarbital blood levels fall on a constant dose over several weeks?

Phenobarbital induces liver enzymes that speed up its own metabolism.

3. Why is bromide avoided in cats?

A good proportion of cats develop cough or asthma-like disease on bromide.

4. A dog on bromide is moved to a high-salt diet. What is expected?

More chloride intake increases bromide excretion by the kidney.

5. Which drug binds SV2A?

Levetiracetam acts at synaptic vesicle protein SV2A to reduce abnormal transmitter release.

6. First drug class for stopping an ongoing seizure in status epilepticus?

Benzodiazepines act within minutes on GABA-A receptors.

7. Which should be checked early in a seizing animal?

Hypoglycaemia and hypocalcaemia are fast, correctable causes.

8. Why is bromide useful in a dog with liver disease?

Bromide is excreted unchanged by the kidney.

9. Seizures in a goat kid are most likely to need which approach?

True epilepsy is rare in ruminants, and causes such as polioencephalomalacia are treatable.

10. What is the risk of sudden withdrawal of an anticonvulsant?

The brain has adapted to the drug, and abrupt removal can provoke severe seizures.

Key points to revise

1. Anticonvulsants raise the seizure threshold; they do not cure epilepsy.
2. Main mechanisms are enhancing GABA inhibition, blocking Na or Ca channels and altering neurotransmitter release.
3. Phenobarbital enhances GABA-A chloride channel opening and is slow to reach steady state.
4. Phenobarbital causes enzyme induction, sedation, polyphagia, polyuria and possible liver injury.
5. Bromide has a half-life of weeks, is cleared by the kidney and is avoided in cats.
6. Levetiracetam binds SV2A and has few interactions and little liver metabolism.
7. Status epilepticus is treated by stabilising, giving a benzodiazepine, then a long-acting drug.
8. Ruminant seizures usually signal a cause that must be treated.

Go deeper on this site

- Ch 7. Behaviour-modifying drugs (in this book)
- Ch 8. CNS stimulants, analeptics and respiratory stimulants (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

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- Wikipedia: Phenobarbital
- Wikipedia: Status epilepticus

CHAPTER 7 OF 33

Behaviour-modifying drugs

How anxiolytics and antidepressants change fear, anxiety and compulsive behaviour in dogs and cats, when drugs actually help, and the safety points and interactions, especially serotonin syndrome, that students must know.

> **After this chapter you can**

- Explain why behaviour drugs are an aid to behaviour modification and not a replacement
- Describe the actions of benzodiazepines, buspirone, trazodone and gabapentin as anxiolytics
- Describe the actions of SSRIs, tricyclic antidepressants and MAO-B inhibitors
- Explain serotonin syndrome and the drug combinations that cause it
- State the main cautions in cats and dogs

When drugs help and when they do not

Fear, anxiety and aggression are common reasons why dogs and cats are surrendered or abandoned. Drugs can help, but they do not teach an animal what to do instead. A **behaviour modification plan** (training, management of the environment, and a calmer routine) is the base, and the drug is a helper that lowers the anxiety enough for the animal to learn.

The first step is always to look for a **medical cause**. Pain, thyroid disease, urinary problems, itching or cognitive decline can all present as a behaviour problem. A cat that urinates outside the box may have cystitis, not a behaviour disorder.

Drugs are most useful in three situations: a **situational** fear, such as thunder, fireworks, travel or a vet visit; a **chronic anxiety** disorder, such as separation anxiety or generalised anxiety; and **compulsive disorders**, such as tail chasing or over-grooming. Drugs are less useful for a normal behaviour that the owner finds unwelcome. Pheromone products (for example, dog or cat appeasing pheromones) are not drugs in the usual sense and can be used alongside.

Anxiolytics: benzodiazepines, buspirone, trazodone and gabapentin

Anxiolytics work fast or work slowly. This difference decides how they are used.

- **Benzodiazepines** (diazepam, alprazolam, lorazepam) enhance $GABA_A$ receptor action and act in an hour or less. They suit predictable events such as thunderstorms. Cautions: sedation, ataxia, and **disinhibition**, in which an anxious animal becomes more bold and may bite. They may also impair learning and can be habit forming. In cats, oral diazepam has been reported to cause rare, serious liver injury.

- **Buspirone** is a partial agonist at serotonin 5-HT_{1A} receptors. It takes weeks to work, has little sedation and does not cause dependence. It has been used in cats with fear or social anxiety and spraying.
- **Trazodone** blocks 5-HT_{2A} receptors and weakly blocks serotonin reuptake. It is used for situational anxiety, for example before a vet visit or during confinement after surgery. It can cause sedation and, with other serotonergic drugs, serotonin syndrome.
- **Gabapentin** acts on calcium channels and is calming in cats before a vet visit. Sedation is its main side effect.
- **Alpha-2 agonists** such as dexmedetomidine given through the cheek are used for noise aversion in some countries. Check what is marketed locally.

Antidepressants: SSRIs, tricyclics and MAO-B inhibitors

Antidepressants are used for long-term anxiety and compulsive behaviour. They do not work at once. Benefit takes **several weeks**, so owners must be told to give them daily and to avoid giving up early.

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and sertraline, block the serotonin transporter, so more serotonin stays in the synapse. Over time the receptors adapt, and this slow adaptation is why the effect is delayed. Common effects are reduced appetite, mild lethargy, gastrointestinal upset and, in some animals, an early increase in restlessness.

Tricyclic antidepressants (TCAs), such as clomipramine and amitriptyline, block reuptake of serotonin and noradrenaline. They also block muscarinic, histamine and alpha-1 receptors, which causes dry mouth, constipation, urine retention, sedation and low blood pressure. They can affect heart rhythm, so a heart check is wise in older animals or those with heart disease. Clomipramine is licensed for separation anxiety in dogs in some countries; check the current Indian status.

Selegiline inhibits monoamine oxidase B and is used in some countries for canine cognitive dysfunction and sometimes for anxiety. It must never be combined carelessly with other serotonergic drugs.

Safety, interactions and serotonin syndrome

Serotonin syndrome is a toxic excess of serotonin, most often caused by combining two or more drugs that raise serotonin. Signs include agitation, tremor, hyperthermia, sweating or panting, diarrhoea, fast heart rate and, in severe cases, seizures. It is treated by stopping the drugs, supportive care and cooling, with a benzodiazepine for tremor and seizures, under veterinary advice.

Drug combinations to be careful about include:

- SSRI or TCA with **selegiline** or other MAO inhibitors.
- SSRI or TCA with **tramadol**, which also affects serotonin, and with **trazodone** or buspirone.
- **Amitraz** (a tick treatment) has MAO-inhibiting effects, so caution is advised in dogs on these drugs.
- Cough preparations or other products containing serotonergic ingredients.

Other points: an SSRI or TCA is stopped by gradual withdrawal, not suddenly. These drugs can lower the seizure threshold, so use caution in epileptic animals. Liver and kidney function influence how they are cleared. Blood tests before and during long-term therapy are usual practice. Never give human preparations without veterinary advice, because the formulations may contain xylitol or other unsafe additives, and the effective amount differs by species. Check the current notifications on controlled drugs, because some of these drugs, such as benzodiazepines, may be regulated.

Dogs and cats in practice

In **dogs**, SSRIs and clomipramine are used for separation anxiety, generalised anxiety and compulsive disorders. Benzodiazepines, trazodone, gabapentin or a cheek-applied alpha-2 agonist are chosen for noise phobias and travel, often started before the event, because they work better when given early than after the fear has set in. Some dogs need a combination, such as a daily SSRI plus a situational drug.

In **cats**, fluoxetine or clomipramine can be used for urine spraying, over-grooming and some anxiety disorders after medical causes are excluded. Buspirone is also used. Cats are sensitive to many drugs, and tablets can be hard to give, so it is important to choose a form the owner can manage. Cats clear many drugs slowly,

so dosing is individual and the veterinarian's advice must be followed. Over-grooming may be itch, not anxiety, so check the skin first.

Follow up is part of the treatment. Review the animal after a few weeks, record appetite, sleep, activity and the target behaviour, and plan a slow reduction after a long period of good control. Do not assume the drug has failed before several weeks have passed.

Common confusions

Sedation is not the same as calming. A drug that makes the animal sleepy may leave the fear unchanged, and it can make learning harder. **Fast drugs and slow drugs are not interchangeable.** A daily SSRI will not help a dog on the day of a thunderstorm unless it has already been given for weeks, and a benzodiazepine does not treat chronic anxiety well.

Antidepressants are used in animals for anxiety and compulsion, not depression. The word describes the drug class, not the problem being treated.

A paradoxical reaction is a known effect. If an animal becomes more excited or aggressive after a benzodiazepine, the drug should be stopped. **Pheromones and nutraceuticals** have a limited evidence base compared with drugs but are safe companions to behaviour work.

Finally, remember the limits of a veterinarian's role in India: many of these drugs are human products used extra-label, so the owner should be told this, and the responsibility for monitoring remains with the veterinarian.

Concept cleared

Concept cleared: Drug as a helper to training
A drug is like training wheels on a bicycle. It keeps the animal steady enough to practise a new skill, but it does not ride the bicycle for it. When training stops, the benefit may fade.

Concept cleared: Why SSRIs take weeks

Raising serotonin in the synapse happens within hours, but the brain's receptors and nerve connections adapt slowly. Think of turning up the volume on a radio at once, but the room taking weeks to get used to the sound.

Concept cleared: Serotonin syndrome

Each serotonergic drug adds water to the same bucket. One drug may keep it below the brim, but two or three can overflow. That overflow is hyperthermia, tremor, agitation and seizures.

Concept cleared: Disinhibition

An anxious animal is held back by fear, like a car with the handbrake on. Some benzodiazepines release the handbrake before the animal has learned to behave calmly, so a fearful animal can become bold or aggressive.

Memory aid: Behaviour drug plan: 'MBD'

Medical cause first, Behaviour modification second, Drug third. For antidepressants remember 'Weeks, not days', and for serotonin syndrome remember 'too much serotonin: hot, shaky, agitated'.

Compare and contrast

Fast and slow behaviour drugs

Group	Examples	Onset	Best use
Benzodiazepines	Diazepam, alprazolam	Minutes to an hour	Predictable events such as storms
Trazodone, gabapentin	Trazodone, gabapentin	About an hour	Vet visits, travel, confinement
Buspirone	Buspirone	Weeks	Mild anxiety, cats
SSRIs	Fluoxetine, sertraline	Weeks	Chronic anxiety, compulsive disorders
TCAs	Clomipramine, amitriptyline	Weeks	Separation anxiety, compulsive behaviour

SSRIs and TCAs compared

Feature	SSRI	TCA
Main action	Blocks serotonin reuptake	Blocks serotonin and noradrenaline reuptake
Other receptor effects	Few	Muscarinic, histamine, alpha-1 blockade
Typical side effects	Reduced appetite, GI upset, restlessness	Dry mouth, constipation, sedation, heart effects
Special caution	Serotonin syndrome with MAO-B inhibitors	Heart disease, urine retention, seizures

Species notes

Dog

SSRIs and clomipramine are used for chronic anxiety and compulsive behaviour. Benzodiazepines, trazodone and gabapentin are used for situational fear. Give situational drugs before the trigger.

Cat

Fluoxetine, clomipramine, buspirone and gabapentin are used. Oral diazepam has been linked to rare severe liver injury. Exclude cystitis and skin disease before treating behaviour.

Horse

Farm animals

Behaviour drugs are rarely used. If used, check the rules for competition animals, because many of these drugs are prohibited substances.

Behaviour-modifying drugs are rarely used, and residue rules apply to food animals. Check the current guidance before any use.

Birds and exotics
Feather plucking has many medical causes, so look for disease and husbandry faults before drugs.

Clinical pearls

Self-test: 10 questions

1. What should be done first in an animal with a new behaviour problem?

Pain, endocrine and urinary disease can all appear as behaviour change.

2. Which drug is a 5-HT1A partial agonist?

Buspirone acts at serotonin 5-HT1A receptors and takes weeks to work.

3. Why do SSRIs take weeks to work?

The delayed effect is due to slow adaptive changes after serotonin rises.

4. Which problem may occur with benzodiazepines in an anxious dog?

Release of inhibition can make a fearful animal bold or aggressive.

5. A drug combination at risk of serotonin syndrome is:

An SSRI plus an MAO inhibitor increases serotonin excessively.

6. A drug that blocks muscarinic and histamine receptors as well as reuptake pumps is:

TCAs have anticholinergic and antihistamine effects.

7. For a dog with storm phobia, the best timing of a situational drug is:

Early dosing prevents the fear response from building up.

8. Selegiline is an inhibitor of which enzyme?

It inhibits MAO-B and is used for canine cognitive dysfunction in some countries.

9. Which cat problem was linked to oral diazepam?

Idiosyncratic hepatic failure has been reported.

10. Which statement about antidepressants in animals is correct?

The name is a class label; the usual targets are anxiety and compulsion.

Key points to revise

1. Behaviour drugs support behaviour modification and do not replace it.
2. Benzodiazepines are fast but may cause disinhibition and sedation.
3. Buspirone is a 5-HT1A partial agonist with a slow onset.
4. Trazodone and gabapentin are used for situational anxiety.
5. SSRIs block the serotonin transporter and take weeks to work.
6. TCAs have extra anticholinergic, antihistamine and heart effects.
7. Serotonin syndrome follows combinations of serotonergic drugs.

8. Check current Indian regulation for controlled drugs and extra-label use.

Go deeper on this site

- Ch 8. CNS stimulants, analeptics and respiratory stimulants (in this book)
- Ch 6. Anticonvulsants and drugs for epilepsy (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Wikipedia: Fluoxetine
- Wikipedia: Serotonin syndrome
- Wikipedia: Buspirone

CHAPTER 8 OF 33

CNS stimulants, analeptics and respiratory stimulants

How doxapram and the xanthines stimulate breathing and the brain, why analeptics are used less today, strychnine as a toxicant, and the practical approach to neonatal resuscitation and drug reversal.

After this chapter you can

- Define analeptics and respiratory stimulants and explain why their use has declined
- Describe the mechanism, uses and cautions of doxapram
- Describe the actions, toxicity and species points of xanthines such as theophylline, caffeine and theobromine
- Explain strychnine toxicity and its treatment
- Outline neonatal resuscitation and the role of specific reversal drugs

What are CNS stimulants and analeptics

CNS stimulants raise the activity of the brain and spinal cord. They work in three broad ways: they **block inhibition** (for example strychnine at glycine receptors and

picrotoxin at GABA channels), they **increase excitatory transmission or release of amines** (amphetamines), or they **block adenosine** (xanthines such as caffeine). **Analeptics** are stimulants used to reverse CNS and respiratory depression, for example after anaesthesia or overdose.

Older analeptics such as nikethamide, pentylenetetrazol and picrotoxin have a very narrow gap between stimulation and convulsion and are no longer used in modern practice. Today the useful drugs are few: doxapram, the xanthines, and, more importantly, **specific antagonists** for the depressant that was given.

The main idea: a stimulant does not replace oxygen or ventilation. A breathing animal that is hypoxic is helped first by airway care, oxygen and ventilation. A stimulant increases oxygen demand of the brain and heart, so it can make a bad situation worse.

Doxapram

Doxapram is the main respiratory stimulant in veterinary use. It acts mainly on the **peripheral chemoreceptors** in the carotid and aortic bodies, which tell the brain that oxygen is low. At larger amounts it also stimulates the respiratory centre in the medulla. Breathing becomes deeper and faster. It is given intravenously and acts within a minute or so, but the effect is short, so it may wear off before the depressant drug does.

Uses include stimulating breathing and wakefulness after anaesthesia, and speeding recovery of respiratory drive in animals depressed by some drugs. It is also used in practice to stimulate newborn animals (see below), although this is debated.

Cautions are important.

- Margin of safety is narrow. Higher exposure causes excitement, tremor, hyperventilation and seizures.
- It raises blood pressure and heart rate and can cause arrhythmias. It is risky in animals with heart disease, hypertension, head injury or a seizure history.
- It increases oxygen use by the brain and heart. If the animal is hypoxic, giving doxapram without oxygen can worsen cell injury.

- It does not reverse the depressant drug. It only masks it, so the animal can slip back into depression.
- It is not a substitute for a patent airway and mechanical ventilation.

Doxapram can also change the interpretation of anaesthetic depth tests, because it temporarily raises respiratory rate. Do not use it as a cover for over-dosed anaesthesia.

Xanthines: caffeine, theophylline and theobromine

Xanthines are plant-derived compounds found in coffee, tea, cocoa and kola. They have two main actions: they **block adenosine receptors** and they **inhibit phosphodiesterase**, which keeps cAMP high. Adenosine normally has a calming effect, so blocking it leads to stimulation.

The effects can be remembered by organ. **CNS:** alertness, restlessness, tremor and, at high levels, seizures. **Heart:** faster rate and stronger contraction, with arrhythmias at high levels. **Smooth muscle:** bronchial relaxation, which is why theophylline and aminophylline are used as bronchodilators in dogs, cats and horses. **Kidney:** mild diuresis. **Respiratory centre:** stimulation of breathing, which is why caffeine is used for apnoea of prematurity in human infants.

Theophylline has a narrow therapeutic range. Its clearance differs between species, individuals and with other drugs, so doses are not copied between species. Some drugs, such as certain fluoroquinolones and cimetidine, can slow its metabolism and raise levels, and this must be considered. Signs of excess are vomiting, restlessness, tachycardia and tremor.

Aminophylline is a water-soluble salt of theophylline. Bronchodilator use has declined because safer drugs exist, but the concept is a common exam question.

Methylxanthine toxicosis and strychnine

Chocolate toxicosis is a common emergency in dogs. The toxic agent is mainly **theobromine**, with some caffeine. Dark chocolate and cocoa powder contain much more than milk chocolate. Dogs clear theobromine slowly, and it is recirculated in the bile, so signs can persist. Signs are vomiting, restlessness, tremor, fast heart rate and seizures. Treatment is decontamination if early, supportive care, control of tremors and seizures, and monitoring of the heart.

Strychnine comes from the seeds of *Strychnos nux-vomica* and has been used in rodent and pest baits. Check the current Indian regulations on its use, because many such products are restricted. It acts by **blocking glycine receptors** in the spinal cord. Glycine normally inhibits motor neurons, so without it the animal has exaggerated reflexes and sudden, violent extensor spasms triggered by light, sound or touch. The animal remains conscious, which makes the signs very distressing. Death results from respiratory muscle spasm and exhaustion.

There is no specific antidote. Treatment is by **control of spasms** with sedation or anaesthesia, a quiet dark environment, a muscle relaxant such as methocarbamol, and support of breathing and temperature, plus decontamination if early. Stimulants are never given. Because strychnine is a spinal stimulant and not a seizure of cortical origin, the pattern is different from epilepsy.

Neonatal resuscitation and specific reversal drugs

A newborn that fails to breathe needs a stepwise approach: **clear the airway**, dry and rub the body to stimulate, keep warm, and give **oxygen and ventilation** as needed. These physical steps are the most important. Many current guidelines favour them over drugs. In calves, foals, puppies and kittens, the most common causes of poor breathing are hypoxia during birth, fluid in the airway, cold and drug depression from the dam's caesarean anaesthesia.

Drugs have a limited role. Doxapram is sometimes used as a stimulant, but its value in newborns is debated and it should not replace ventilation. If the dam was given an opioid, the newborn can be treated with a specific antagonist. **Naloxone** reverses opioid depression. Epinephrine is used for cardiac arrest during resuscitation. Blood sugar and body temperature must also be supported.

Specific antagonists are better than analeptics because they act at the receptor that was blocked: **naloxone** for opioids, **atipamezole** or yohimbine for alpha-2 agonists such as xylazine and medetomidine, and **flumazenil** for benzodiazepines. Remember that the antagonist may wear off before the depressant, so the animal must be watched for re-sedation. In ruminants, xylazine is also reversed by specific agents but sensitivity is high, so reversal is used with care.

Common confusions

Analeptic is not the same as respiratory stimulant. All analeptics stimulate the CNS, and some stimulate breathing, but the term is broader than doxapram. **A stimulant is not an antidote.** Doxapram does not remove the depressant drug, it only temporarily opposes its effect. **Strychnine is a toxicant, not a therapeutic drug,** and it is a spinal glycine antagonist, not a respiratory stimulant used in practice.

Caffeine and theophylline have the same mechanism, but differ in potency on organs. Caffeine is stronger on the CNS, and theophylline is stronger on smooth muscle and the heart. **Strychnine convulsions are reflex driven,** so touching or loudly approaching the animal can trigger a spasm.

In food animals, any extra-label use of these drugs needs attention to residues and the current rules.

Concept cleared

Concept cleared: Stimulant is not oxygen
Whipping a tired horse makes it run for a moment but does not feed it. A stimulant makes a depressed animal breathe harder for a short time, but it does not supply oxygen. Airway and ventilation come first.

Concept cleared: Doxapram acts on the oxygen sensors
The carotid and aortic bodies are like smoke detectors for low oxygen. Doxapram tricks the detectors into ringing louder, so the brain makes the animal breathe more. It does not fix the fire.

Concept cleared: Caffeine blocks the brake of adenosine
Adenosine is a natural calming signal. Xanthines sit on its receptor and stop it from working, so the brain, heart and breathing speed up.

Concept cleared: Strychnine removes a brake

Glycine is the brake on spinal motor neurons. Strychnine cuts the brake cable, so any small stimulus sets off a full muscle spasm while the animal stays awake.

Memory aid: Newborn resuscitation: 'ABC then drug'

Airway clear, Breathing supported with oxygen, Circulation checked, and only then drugs. For reversal agents remember 'N-A-F': Naloxone for opioids, Atipamezole for alpha-2 agonists, Flumazenil for benzodiazepines.

Compare and contrast

Stimulant drugs compared

Drug	Mechanism	Main use or concern	Key caution
Doxapram	Stimulates peripheral chemoreceptors and medulla	Respiratory stimulation after anaesthesia	Narrow margin, raises oxygen demand, short effect
Caffeine	Adenosine block, PDE inhibition	CNS and respiratory stimulation	Tremor, tachycardia, seizures
Theophylline	Adenosine block, PDE inhibition	Bronchodilator	Narrow therapeutic range, varies by species
Theobromine	Same mechanism as xanthines	Cause of chocolate toxicosis in dogs	Slow clearance in dogs
Strychnine	Blocks glycine receptors in the spinal cord	Toxicant, not a therapeutic drug	Convulsions triggered by stimuli; no antidote

Specific antagonists versus analeptics

Feature	Specific antagonist	Analeptic
Examples	Naloxone, atipamezole, flumazenil	Doxapram
Target	The receptor of the depressant drug	General CNS or chemoreceptor stimulation
Risk of seizures	Low	Present at high exposure
Preferred when	The depressant is known	Cause is unknown or antagonist unavailable

Species notes

Dog

Chocolate toxicosis from theobromine is common. Strychnine and other baits are a danger, and signs are triggered by stimuli.

Cat

Sensitive to many stimulants and slow to clear drugs. Use reversal agents with care, and avoid giving human products.

Horse

Theophylline and aminophylline have been used as bronchodilators. Caffeine and theobromine are prohibited substances in competition, so check the current rules.

Cattle and small ruminants

Neonatal calves and lambs depend on clearing fluid, drying and warming. Strychnine and baits can poison livestock, and residue rules apply to any drug used.

Newborn puppy, kitten and foal

Physical resuscitation comes first. Naloxone is useful when the dam received an opioid, and doxapram has a debated role.

Clinical pearls

Self-test: 10 questions

1. Doxapram mainly stimulates breathing through:

It acts on the carotid and aortic bodies and, at higher doses, on the medulla.

2. A main risk of giving doxapram to a hypoxic animal without oxygen is:

It raises oxygen use by the brain and heart.

3. Xanthines act by:

These two actions explain CNS, cardiac and bronchial effects.

4. The main toxin in chocolate poisoning in dogs is:

Theobromine is cleared slowly in dogs and is present in cocoa.

5. Strychnine acts by blocking:

Loss of glycine inhibition leads to reflex spasms.

6. A characteristic of strychnine poisoning is:

The animal stays aware and spasms are reflex driven.

7. Best reversal drug for opioid depression in a newborn after caesarean is:

Naloxone is an opioid antagonist.

8. Atipamezole reverses:

It is an alpha-2 antagonist.

9. The first step in neonatal resuscitation is:

Physical steps are the most important.

10. Why has the clinical use of older analeptics such as nikethamide declined?

They provoke seizures with little margin of safety.

Key points to revise

1. Analeptics reverse CNS depression, but most older ones are obsolete.
2. Doxapram stimulates peripheral chemoreceptors and the medullary respiratory centre.
3. Doxapram has a narrow margin and raises oxygen demand.
4. Xanthines block adenosine receptors and inhibit phosphodiesterase.
5. Theophylline has a narrow therapeutic range and species variation.
6. Strychnine blocks glycine receptors in the spinal cord and causes reflex convulsions.
7. Strychnine has no specific antidote; control spasms and support breathing.
8. Neonatal resuscitation relies mainly on airway, drying, warmth and ventilation.

Go deeper on this site

- Ch 9. Euthanasia agents and humane methods (in this book)
- Ch 7. Behaviour-modifying drugs (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Wikipedia: Doxapram

- Wikipedia: Aminophylline
- Wikipedia: Strychnine poisoning

CHAPTER 9 OF 33

Euthanasia agents and humane methods

Euthanasia means a death with minimal pain and distress. This chapter covers the guiding principles, why barbiturate overdose is the standard agent, species-appropriate methods, how death is confirmed and the legal and ethical points relevant to Indian practice.

After this chapter you can

- State the principles that make a method of euthanasia humane
- Explain how a barbiturate overdose causes unconsciousness, respiratory arrest and cardiac arrest
- Choose an appropriate approach for companion animals, horses, ruminants and other species in concept
- List the signs used to confirm death
- Describe the legal and ethical duties of the veterinarian in India, and the need to check current rules

What makes euthanasia humane

The word means a good death. A method is judged humane when it causes **rapid loss of consciousness** followed by death, with as little pain, fear and distress as possible. Two things matter most: how quickly the animal becomes unconscious, and whether the animal is aware of anything unpleasant before that moment.

Other points that guide the choice are reliability and irreversibility, safety of the people present, emotional effect on the owner and staff, suitability for the species and age, and the ability to confirm death. Euthanasia is a clinical procedure and needs the same planning as anaesthesia.

A common confusion is to mix up *euthanasia* with *slaughter* or *humane killing* in a herd emergency. The aim is similar, but the setting, the restraint and the permitted methods differ.

Planning also includes the place and the people. A quiet area, a non-slip surface, a calm handler and all drugs and equipment ready beforehand reduce stress for the animal and the owner. Owners should be told what to expect, including that the eyes may stay open, and should be offered the choice to be present. Good communication is part of humane practice, not an extra.

Another common confusion is between sedation and euthanasia. A sedated animal is still alive and can recover, so the euthanasia agent must still be given and death confirmed. Likewise, loss of consciousness alone is not death.

Barbiturate overdose: mechanism

An overdose of an injectable barbiturate, usually pentobarbital or a related agent, is the standard method for most species. Barbiturates enhance the action of GABA at the $GABA_A$ receptor, prolonging chloride channel opening. At anaesthetic levels they depress the cerebral cortex. Given in overdose, they go on to depress the brainstem respiratory and cardiovascular centres, and finally the heart.

The sequence is predictable. The animal loses consciousness first, then breathing stops, then the heart stops. Because **unconsciousness comes before the vital centres fail**, the animal does not feel the dying process if the drug is delivered properly.

The best route is **intravenous**, because onset is fastest. A calm animal and a clean vein help. Sedation beforehand makes the process gentler in fractious, fearful or aggressive animals and makes venous access easier.

Practical problems with barbiturates

Barbiturate euthanasia has some well known issues that students should be able to explain.

- **Perivascular injection** is painful because the solution is strongly alkaline. This is the main reason to confirm the needle is in the vein, and to sedate or use an alternative route when veins cannot be found.
- **Excitement stage.** If the drug is given slowly or into a poorly perfused vein, the animal may pass through a phase of excitement before unconsciousness. Fast, complete delivery avoids this.

- **Agonal breaths and muscle twitching** can occur after the heart has stopped or as consciousness is lost. They are reflexes and do not mean the animal is suffering, but owners should be warned beforehand.
- **Carcass hazard.** The drug persists in the body. Scavengers, dogs fed meat, or wildlife can be poisoned. Carcasses must be buried deeply or incinerated and never fed to other animals.

Combination products containing a barbiturate with a local anaesthetic or another agent exist in some countries. Availability and legal status in India vary, so check the current notification and local drug-control rules.

Species-appropriate methods and other agents

Dogs and cats. Sedate, place an intravenous catheter if possible, then give the overdose intravenously. In very small or collapsed patients, other routes such as intraperitoneal or intracardiac may be used only when the animal is already deeply unconscious or anaesthetised.

Horses and large ruminants. Sedation is important for safety and calm. A large volume of barbiturate is needed, which is costly, and the horse may collapse suddenly, so the setting and footing must be planned.

Rabbits, rodents, birds and reptiles. Injectable overdose after sedation or anaesthesia is preferred where veins or other routes are reachable. Inhaled anaesthetic overdose is also used for small mammals and birds, with attention to the induction phase being free of irritation.

Other chemical agents. Potassium chloride is acceptable *only* in an animal already under deep general anaesthesia, since it stops the heart but does nothing for consciousness. Used in a conscious animal it would be extremely cruel. Neuromuscular blockers alone are never acceptable, because they paralyse the animal while leaving it aware.

Physical methods. Properly performed captive bolt or gunshot can be conditionally acceptable in large animals and in field emergencies when the operator is trained and the animal is correctly restrained. They are not a casual substitute for drugs.

Confirming death

Never assume death on one sign. Confirm with several, and allow enough time for the effect of the agent.

- No heartbeat on auscultation, for a sufficient period.
- No respiration.
- No corneal or palpebral reflex, with fixed dilated pupils.
- No response to a firm toe pinch.
- Loss of mucous membrane colour and, later, rigor mortis, which is the final proof.

Muscle twitches or a few gasps after the heart has stopped do not mean the animal is alive. A veterinarian should still re-check after a short interval before releasing the body to the owner.

Time of observation matters. After an intravenous overdose the heart usually stops within a short period, but in cold, shocked or very large animals it may take longer. If any sign of life returns, give more agent. Wait until all signs are absent before declaring death, and before the owner or staff handle the body for disposal.

Legal and ethical notes for India

Veterinarians in India work under the Prevention of Cruelty to Animals Act, 1960 and its rules, and under state veterinary council codes. Rules on euthanasia of stray dogs, incurably ill or suffering animals, and on animal birth control programmes are set by notification and have been amended. **Check the current notification** before acting, and follow the written protocol of the institution, municipal body or animal welfare organisation involved.

Controlled drugs also matter. Barbiturates are regulated, and the supply, storage and record keeping must follow current drug-control law. Locally approved agents and their availability may differ from textbook descriptions from other countries.

Ethical practice includes a clear clinical reason, informed owner consent, a quiet place, a trained person to restrain, and respect for the owner's grief. Staff compassion fatigue is real, and a team should be able to talk about it. The decision should be documented, including the agent used and how death was confirmed.

Concept cleared

Concept cleared: Why unconsciousness comes first

Think of a house where the lights are switched off room by room. The brain's higher centres (the lights that give awareness) go dark before the basic engine rooms for breathing and heartbeat. A barbiturate overdose follows this order, so the animal is unaware by the time breathing and the heart stop.

Concept cleared: Why potassium chloride needs anaesthesia

Potassium chloride is like cutting the power to the pump without telling the person at the desk. It stops the heart but does not remove awareness. So it is acceptable only after the animal has been made fully unconscious by a general anaesthetic.

Concept cleared: Perivascular injection

The barbiturate solution is strongly alkaline, like a mild chemical irritant. If it leaks outside the vein, the tissue stings. Checking the catheter and giving sedation first protect the animal from this pain.

Concept cleared: Secondary poisoning

A barbiturate remains active in the body after death. A carcass left in the open is like a poisoned bait for dogs, vultures and wildlife that feed on it, so disposal must be by deep burial or incineration.

Memory aid: Humane euthanasia checklist

S-I-C-D: Sedate, Intravenous overdose, Confirm death with several signs, Dispose of the carcass safely. Remember that unconsciousness must come before anything that stops the heart.

Compare and contrast

Agents and their acceptability

Agent or method	Acts on	Acceptable when	Key caution
Intravenous barbiturate	Brain then heart	First choice for most species	Perivascular injection is painful; carcass hazard
Inhaled anaesthetic overdose	Brain	Small mammals, birds, reptiles	Choose agent without irritation; time to effect
Potassium chloride	Heart only	Only after deep general anaesthesia	No effect on consciousness
Neuromuscular blocker alone	Muscle	Never acceptable alone	Paralyses an aware animal
Captive bolt or gunshot	Brain physically	Trained operator, large animals, field emergencies	Correct placement and restraint essential

Signs for confirming death

Sign	What to check	Common confusion
Heartbeat	Auscultate for adequate time	Weak heart sounds in a collapsed animal
Respiration	Watch chest, no breaths	Agonal gasps after cardiac arrest are reflex
Corneal and palpebral reflex	Touch gently, no blink	Reflexes can persist briefly at deep anaesthesia
Pupils	Fixed and dilated	Some agents change pupil size early
Rigor mortis	Stiffening of muscle	Appears late, not immediate

Species notes

Dog

Sedation then intravenous barbiturate is the usual approach. Warn owners that twitching, a last breath or loss of bladder control can occur after death.

Cat

Small veins and fear make sedation especially useful. Handle gently and in a quiet place, and confirm the injection is truly intravenous.

Horse
Sedate first and plan the collapse and the body removal. Large volumes of drug are needed, and the carcass must be disposed of safely.

Cattle and small ruminants
Sedation and restraint are needed. In herd emergencies or where drugs are not available, trained operators may use accepted physical methods. Follow current rules.

Birds and small mammals
Anaesthetic overdose by inhalation or injection after sedation is preferred. Avoid methods that cause fear or irritation during induction.

Clinical pearls

Self-test: 10 questions

1. Which sequence best describes death after an intravenous barbiturate overdose?

The cortex is depressed first, so awareness is lost before the brainstem centres and heart fail.

2. The main reason barbiturate solutions are painful if injected outside the vein is that they are

The strongly alkaline solution irritates perivascular tissue.

3. Potassium chloride may be used for euthanasia only when the animal is

It stops the heart but does not cause unconsciousness, so awareness must already be abolished.

4. Why is a neuromuscular blocking agent alone unacceptable for euthanasia?

It does not cause unconsciousness or analgesia, so the animal may feel distress while unable to move.

5. A dog's chest moves in a gasp a few seconds after the heart has stopped. This is best explained as

Agonal breaths are reflex activity of a dying brainstem and do not indicate awareness.

6. Which statement about disposal of a carcass after barbiturate euthanasia is correct?

The drug persists and can poison animals that eat the carcass.

7. Which is the best sign sequence to confirm death?

Several signs are needed, because single signs can mislead.

8. Why is sedation before euthanasia useful in a fractious cat?

Sedation lowers distress and makes a clean intravenous injection more likely.

9. Before euthanising stray animals or for legal questions in India, the veterinarian should

Rules and notifications are amended, so current ones must be consulted.

10. For a small bird or rodent, which approach is commonly accepted?

Anaesthetic overdose gives unconsciousness before death, if induction is free of irritation.

Key points to revise

1. Euthanasia means rapid unconsciousness and death with minimal pain and distress.
2. Barbiturate overdose depresses cortex, then brainstem, then heart.
3. Intravenous route gives the fastest and gentlest result.
4. Sedation helps fearful, aggressive and difficult patients.
5. Agonal breaths and twitching are reflexes and not evidence of suffering, but owners should be told.
6. Potassium chloride is acceptable only in an animal under deep general anaesthesia.
7. Death is confirmed by absent heartbeat, breathing and reflexes, with rigor as final proof.
8. Indian rules and drug availability change, so always check the current notification.

Go deeper on this site

- Ch 10. Histamine and antihistamines (in this book)
- Ch 8. CNS stimulants, analeptics and respiratory stimulants (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- AVMA: Guidelines for the Euthanasia of Animals
- University of Minnesota Libraries: Principles of Pharmacology study guide
- Merck Veterinary Manual: Overview of Anti-inflammatory Agents (general pharmacology reference)

CHAPTER 10 OF 33

Histamine and antihistamines

Histamine is a tissue autacoid released from mast cells and basophils that acts on H1 to H4 receptors. This chapter explains H1 and H2 effects, how anaphylaxis

develops, the antihistamine classes, and why sedation and species differences matter in practice.

After this chapter you can

- Describe where histamine is stored and what triggers its release
- Contrast the actions of H1 and H2 receptors and name the main antagonists for each
- Explain the mechanism of anaphylaxis and why adrenaline, not an antihistamine, is the first-line drug
- Distinguish first-generation from second-generation H1 antihistamines
- State the sedation, anticholinergic and species cautions that apply to antihistamines

Histamine: source, release and receptors

Histamine is a small amine made from the amino acid histidine by the enzyme histidine decarboxylase. It is stored in granules of **mast cells** and **basophils**, and in enterocytochromaffin-like cells of the stomach and in some neurons. In most species mast cells are the main reservoir, found close to skin, gut, airway and blood vessels.

Release happens in two broad ways. The *immunological* route follows cross-linking of IgE on the mast cell surface by antigen, as in allergy and anaphylaxis. The *non-immunological* route follows direct drug or physical action; some drugs such as certain opioids, muscle relaxants and contrast agents can degranulate mast cells without any antibody.

Histamine acts on four G-protein-coupled receptors. **H1** works through Gq and the IP3/DAG pathway. **H2** works through Gs and raises cAMP. **H3** is mainly a presynaptic receptor in the nervous system, and **H4** is found on immune cells. For day-to-day veterinary pharmacology, H1 and H2 matter most.

H1 and H2 actions

The effects of histamine depend on which receptor is stimulated and where.

- **H1:** contraction of bronchial and intestinal smooth muscle, increased capillary permeability (oedema, wheal), vasodilation of small vessels, and itch through sensory nerve endings. In the brain, H1 stimulation promotes wakefulness, which is why blocking it causes drowsiness.
- **H2:** stimulation of gastric acid secretion from parietal cells, plus some cardiac stimulation and vasodilation.

The classic skin response, the "triple response", shows local redness, spread of flare through an axon reflex, and a wheal from leaky capillaries. This is the picture of urticaria seen in a dog after a vaccine reaction or insect sting.

A common confusion is to think histamine alone drives all allergic signs. It does not. Mast cells also release leukotrienes, prostaglandins, platelet-activating factor and proteases, which is why an antihistamine may relieve itch but not fully reverse bronchospasm or shock.

Anaphylaxis

Anaphylaxis is an acute, severe, systemic type I hypersensitivity reaction. A sensitised animal meets the antigen again, IgE on mast cells and basophils is cross-linked, and a sudden mass release of mediators follows. Common triggers in practice include injectable antibiotics (especially penicillins), vaccines, antisera, iron dextran, and insect stings.

The target organ differs between species, and this is a favourite exam point. In the **dog** the liver and gut are the main shock organs, with vomiting, diarrhoea, collapse and hepatic venous pooling. In the **cat** and **horse** the lung is prominent, with bronchospasm and respiratory distress. In **cattle** the lungs and also the udder and skin are involved, and in sheep and pigs respiratory and circulatory signs predominate.

Treatment rests on **adrenaline (epinephrine)** given promptly, together with fluids, oxygen and airway support. Adrenaline acts as a physiological antagonist: through beta and alpha receptors it reverses bronchospasm and vasodilation and stabilises mast cells. An H1 antihistamine is only an *adjunct*. It blocks further histamine action on receptors but does not displace histamine already bound, nor does it counter the other mediators. Corticosteroids are slow and also adjunctive.

Prevention matters too: keep the animal under observation after vaccination or injection, and record previous reactions.

H1 antihistamine classes

H1 antagonists are better described as **inverse agonists**: they stabilise the inactive receptor, and they compete with histamine at the receptor. They are grouped into generations.

First-generation drugs include diphenhydramine, chlorpheniramine, promethazine, pheniramine, hydroxyzine and cyproheptadine. They are lipid soluble and cross the blood-brain barrier easily. They cause sedation, and because they also block muscarinic receptors they cause dry mouth, urinary retention, tachycardia and reduced gut motility. Some, such as promethazine and dimenhydrinate, are used for motion sickness and vomiting through central and vestibular effects. Cyproheptadine also blocks 5-HT receptors, which is why it is used as an appetite stimulant in cats.

Second-generation drugs include cetirizine, loratadine, fexofenadine and levocetirizine. They are less lipophilic or are pumped out of the brain by P-glycoprotein, so sedation and anticholinergic effects are weaker. Their duration of action is generally longer.

Pharmacokinetics differ widely between species, so a human product cannot simply be assumed to work in an animal. Evidence for antihistamine benefit in canine atopic dermatitis is modest, and they are more useful as preventive or mild-case agents than for acute severe itch.

H2 blockers and other antihistaminic drugs

H2 antagonists such as ranitidine, famotidine and cimetidine block the histamine receptor on the parietal cell and reduce gastric acid output. They are used in gastric ulcer, gastritis and oesophagitis, though proton pump inhibitors suppress acid more strongly. Famotidine is generally preferred over cimetidine because cimetidine inhibits hepatic cytochrome P450 enzymes and causes more drug interactions. Check the current availability of ranitidine in India, as regulatory changes have affected it in several countries.

Mast cell stabilisers such as sodium cromoglycate prevent degranulation rather than block receptors. **Functional antagonists** such as adrenaline oppose histamine effects through other receptors. This three-way grouping (receptor blockers, release inhibitors, physiological antagonists) is a useful way to remember how histamine action can be countered.

Do not confuse H1 antihistamines, which give relief from allergy, with H2 blockers, which are used for acid disorders. They are not interchangeable.

Sedation and species cautions

Sedation is the commonest adverse effect of first-generation H1 drugs and is sometimes used on purpose, for example in anxious or itchy animals at night. It adds to the effect of other sedatives, opioids and anaesthetics, so combined use needs care.

Anticholinergic effects make these drugs unsuitable in animals with glaucoma, urinary outflow obstruction, severe cardiac arrhythmia or paralytic ileus. In pregnant or lactating animals, use only when the benefit is clear.

Cats are sensitive to some antihistamine preparations, and chlorpheniramine is one of the few commonly used for pruritus. Avoid human combination products containing decongestants or paracetamol, which are dangerous in cats. **Horses** may show excitement rather than sedation with first-generation drugs. In **food animals**, antihistamines used in anaphylaxis are given under veterinary advice and withdrawal periods and MRLs should be checked in the current notification. Competition horses may also face prohibited-substance rules.

Always weigh the benefit of an antihistamine against what else the animal is receiving. Most serious problems come from drug combinations or from ignoring the anticholinergic burden.

Concept cleared

Histamine is stored, not made on demand
Preformed histamine sits in mast cell granules and is released within seconds. This explains the speed of anaphylaxis.

Two main receptors, two main jobs

H1 mediates allergy, itch, bronchoconstriction and wakefulness. H2 mediates gastric acid secretion. Blockers are receptor specific.

Antihistamines prevent, they do not reverse

H1 blockers compete with free histamine, so they work best given early. In established anaphylaxis, adrenaline is the lifesaving drug.

Generation predicts side effects

First-generation drugs cross the brain and block muscarinic receptors. Second-generation drugs are far less sedating.

Memory aid: H1 and H2 in one line

H1 = 'Hives, Hissing airways, Hypnotic when blocked'. H2 = 'Hydrochloric acid, Two parietal cells'. Adrenaline is the answer to anaphylaxis, not an antihistamine.

Compare and contrast

H1 versus H2 receptors

Feature	H1	H2
G protein / messenger	Gq, IP3 and DAG	Gs, cAMP
Main effects	Bronchoconstriction, vascular leak, itch, wakefulness	Gastric acid secretion
Antagonists	Chlorpheniramine, cetirizine	Famotidine, ranitidine
Main use	Allergy, pruritus, motion sickness	Ulcer, gastritis, reflux

First versus second-generation H1 blockers

Feature	First generation	Second generation
Examples	Diphenhydramine, chlorpheniramine, promethazine	Cetirizine, loratadine, fexofenadine
Brain entry	High	Low
Sedation	Common	Mild or absent
Anticholinergic effects	Marked	Minimal
Duration	Shorter	Generally longer

Species notes

Dog

Liver and gut are the shock organs in anaphylaxis. Urticaria and facial swelling are common after stings and vaccines.

Cat

Respiratory distress is prominent in anaphylaxis. Avoid human combination cold products, which may contain paracetamol.

Horse

Lung involvement is typical in anaphylaxis. First-generation antihistamines may cause excitement in some animals.

Cattle and small ruminants

Anaphylaxis after injectables or feed allergens can show as respiratory and circulatory collapse. Check withdrawal periods and MRLs in the current notification.

Pig and poultry

Reactions to injectables and vaccines occur; treatment relies on adrenaline and supportive care under veterinary advice.

Clinical pearls

Self-test: 10 questions

1. Histamine is mainly stored in:

Preformed histamine sits in granules of mast cells and basophils and is released on degranulation.

2. Which receptor mediates gastric acid secretion?

H2 on parietal cells raises cAMP and promotes acid secretion.

3. First-line drug in anaphylaxis is:

Adrenaline reverses bronchospasm and vasodilation; antihistamines and steroids are adjuncts.

4. The H1 receptor signals through:

H1 is Gq coupled, activating phospholipase C.

5. Which is a second-generation antihistamine?

Cetirizine is poorly sedating because of limited brain penetration.

6. The main shock organ in canine anaphylaxis is typically the:

Dogs show hepatic and gastrointestinal involvement, unlike cats and horses where the lung predominates.

7. Why is cimetidine less preferred than famotidine?

Enzyme inhibition causes more drug interactions.

8. Cyproheptadine is used as an appetite stimulant because it:

Its serotonin antagonism is responsible for the appetite effect.

9. Sodium cromoglycate acts by:

It prevents degranulation instead of blocking receptors.

10. An important anticholinergic caution with first-generation antihistamines is:

Muscarinic blockade raises intraocular pressure and impairs bladder emptying.

Key points to revise

1. Histamine is stored in mast cells and basophils and released on IgE cross-linking or direct drug action.
2. H1 and H2 are G-protein-coupled receptors with different messengers and effects.
3. H1 stimulation causes bronchospasm, vascular leak and itch.
4. H2 stimulation drives gastric acid secretion.
5. Anaphylaxis is a type I hypersensitivity; the shock organ varies by species.
6. Adrenaline is the first-line drug in anaphylaxis.
7. First-generation H1 blockers are sedating and anticholinergic; second-generation drugs are less so.
8. Cats and horses need specific cautions with antihistamines.

Go deeper on this site

- Ch 11. Eicosanoids, serotonin and kinins (in this book)
- Ch 12. NSAIDs and antipyretics (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Antihistamines in animals
- Merck Veterinary Manual: NSAIDs in animals (for COX and adverse-effect context)
- Wikipedia: 5-HT receptor

CHAPTER 11 OF 33

Eicosanoids, serotonin and kinins

These local chemical messengers (autacoids) shape pain, inflammation, vascular tone, smooth muscle activity and vomiting. The chapter follows the arachidonic acid pathways, the 5-HT receptor subtypes and the kinin system, and links each to NSAIDs and anti-nausea drugs.

After this chapter you can

- Trace arachidonic acid through the cyclooxygenase and lipoxygenase pathways
- Name the main prostaglandins, thromboxane and leukotrienes and their effects
- Explain how corticosteroids and NSAIDs act at different points of the pathway
- Describe the main 5-HT receptor subtypes and drugs that act on them
- Explain how kinins are formed and how they link to pain and to ACE inhibitors

Autacoids: local messengers

Autacoids are substances made in tissues and acting close to where they are made. They are not stored like hormones in a gland, and they act briefly. Histamine, serotonin, kinins and eicosanoids belong to this group. Many drugs in this book work by blocking their synthesis or their receptors, which is why this chapter sits before the NSAID chapter.

A useful way to organise the group is by origin. Histamine and serotonin are amines stored in cells and released on stimulation. Kinins are peptides made from plasma proteins. Eicosanoids are lipids made on demand from membrane fat. Different origins explain why they are blocked by different drugs: antihistamines, 5-HT antagonists, ACE-related drugs and NSAIDs or steroids respectively.

Students often confuse autacoids with hormones. Hormones travel in blood to distant targets, while autacoids act locally and are destroyed within seconds to minutes. That brief life is why their effects are intense at the site of injury but do not spread through the whole body in health.

The arachidonic acid cascade

Eicosanoids come from **arachidonic acid**, a fatty acid held in cell membrane phospholipids. When a cell is injured or stimulated, the enzyme **phospholipase A_2** releases arachidonic acid. From there the road splits in two.

- The **cyclooxygenase (COX)** path makes prostaglandins, prostacyclin and thromboxane.
- The **5-lipoxygenase (5-LOX)** path makes leukotrienes.

Corticosteroids act high in the pathway. They induce proteins that inhibit phospholipase A_2 and also reduce COX-2 expression, so both branches fall.

NSAIDs act lower down and block COX only. This is why steroids have broader anti-inflammatory effects, and also why blocking COX may push more substrate towards the lipoxygenase path.

Prostaglandins and thromboxane

The COX enzymes convert arachidonic acid to an unstable intermediate, and tissue-specific enzymes then make the final product. The effect of each product depends on the cell.

- **PGE_2**: vasodilation, sensitises pain nerve endings, raises the hypothalamic temperature set point in fever, and protects the stomach by increasing mucus and bicarbonate and reducing acid.
- **PGI_2 (prostacyclin)**: vasodilation and inhibition of platelet aggregation. It protects the vessel wall.
- **TXA_2 (thromboxane)**: made in platelets, causes platelet aggregation and vasoconstriction. It opposes prostacyclin.
- **$PGF_{2\alpha}$**: contracts uterine and other smooth muscle, and causes regression of the corpus luteum in many species.

Prostaglandins in the kidney keep blood flow to the glomerulus when circulation is poor. This single idea explains why NSAIDs cause stomach and kidney effects while they treat pain.

Synthetic analogues are used clinically. A $PGF_{2\alpha}$ analogue is used to bring on luteolysis and to manage reproductive problems in cattle and other species, and a PGE analogue such as misoprostol is used to protect the stomach from NSAID injury. Exact products and uses should be taken from current labels.

Clinical meaning: because PGE_2 both causes pain and protects the stomach, no single drug can remove the first and keep the second. The best an NSAID can do is shift the balance. Prostaglandins also keep the ductus and uterine tone in the right state in pregnancy, so NSAIDs near parturition need caution and a check of the label.

COX-1, COX-2 and leukotrienes

COX-1 is present in most tissues all the time and supports normal functions: gastric protection, kidney perfusion and platelet function. COX-2 is mainly induced at sites of inflammation, but it is also present constitutively in some tissues such as kidney. So the split of *COX-1 is bad, COX-2 is good* is too simple. The chapter on NSAIDs takes this forward.

Leukotrienes are made by 5-lipoxygenase in white blood cells. **LTB_4** is a strong chemotactic agent attracting neutrophils. The cysteinyl leukotrienes (**LTC_4, LTD_4, LTE_4)** cause bronchoconstriction, mucus secretion and increased vascular permeability. They are important in allergic airway disease. Leukotriene pathways are not blocked by standard NSAIDs.

Clinical meaning: a drug that blocks COX may reduce pain without stopping leukotriene-driven airway constriction. In a coughing or allergic animal, an NSAID therefore does not replace an anti-inflammatory steroid or bronchodilator. In some sensitive individuals, shifting substrate to the lipoxygenase route may worsen airway signs, so caution is advised in animals with airway disease.

Serotonin (5-HT) and its receptors

Serotonin is made from tryptophan. Much of the body's store is in enterochromaffin cells of the gut, with the rest in platelets and in the brain. It acts through many receptor subtypes, and each has a different drug link.

- **5-HT_3** is a ligand-gated ion channel, unlike the other subtypes, which are G-protein-coupled. It is present in the gut and in the vomiting centre pathways. Antagonists such as ondansetron are anti-nausea drugs, and the appetite stimulant mirtazapine also blocks this receptor.
- **5-HT_4** stimulation increases gut motility. Prokinetics such as cisapride act this way where available.
- **5-HT_{2A}** on platelets and vascular smooth muscle promotes aggregation and vasoconstriction.
- **5-HT_{1A}** in the brain is linked to anxiety and mood, and is a target of some behaviour drugs.

Link to anti-nausea drugs: vomiting is triggered through several pathways, including serotonin, substance P (blocked by maropitant at NK_1 receptors), dopamine and histamine. Different drugs block different inputs, which is why one drug may work in one patient and not another.

Excess serotonergic stimulation, for example by combining certain drugs that raise serotonin, can lead to **serotonin syndrome**, with tremor, agitation and hyperthermia.

Common confusion: serotonin in the gut is not mainly the same pool as in the brain. Gut serotonin does not cross into the brain, so drugs that act on gut receptors can change motility or vomiting without changing mood.

Kinins

Kinins are small peptides. **Bradykinin** is formed when the enzyme kallikrein acts on kininogen in plasma and tissues, for example after tissue injury or contact activation. It acts on B_2 receptors to cause vasodilation, increased vascular permeability, smooth muscle contraction in the gut and airway, and pain by direct stimulation of nociceptors. It also stimulates release of prostaglandins, which then amplify pain, so kinins and eicosanoids work together in inflammation.

Bradykinin is broken down by **angiotensin-converting enzyme (ACE)**, the same enzyme that makes angiotensin II. Therefore ACE inhibitors, widely used in heart failure, raise kinin levels as well as lowering angiotensin II. In some species this is linked to cough or other effects, and this is a reason to know the shared enzyme. No kinin-blocking drug is routine in veterinary practice, so the main teaching value is understanding inflammation and the ACE link.

Concept cleared

Concept cleared: Where steroids and NSAIDs act
Imagine a river that starts at a lake (membrane phospholipid) and splits into two channels (COX and lipoxygenase). Steroids close the gate at the lake, so both channels run dry. NSAIDs block only one channel, the COX one.

Concept cleared: Why NSAIDs affect stomach and kidney
Prostaglandins act like quiet maintenance staff in the stomach and kidney, keeping mucus up and blood flowing. NSAIDs send these staff home along with the pain staff. The same drug that relieves pain also removes protection.

Concept cleared: Thromboxane versus prostacyclin
These two are a tug of war. Thromboxane from platelets pulls towards clotting and narrowing, while prostacyclin from the vessel wall pulls towards opening and preventing clots. Drugs that tilt the balance change bleeding and clotting tendencies.

Concept cleared: Why 5-HT3 is different
Most serotonin receptors act through slower G proteins like a thermostat. The 5-HT3 receptor is a channel, like a door that opens at once. That is why blocking it gives a fast anti-nausea effect.

Memory aid: Arachidonic acid fork
COX makes the Calm-and-Clot group (prostaglandins, prostacyclin, thromboxane); LOX makes the Leukotrienes. Steroids block the start, NSAIDs

block COX. For serotonin: 5-HT3 is the Three-letter 'channel' that is the Throw-up (vomiting) target.

Compare and contrast

Main eicosanoids

Mediator	Pathway	Main effects	Clinical link
PGE2	COX	Pain sensitisation, fever, vasodilation, gastric protection	NSAIDs reduce pain and fever but lessen protection
PGI2	COX	Vasodilation, anti-platelet	Vessel wall protection
TXA2	COX	Platelet aggregation, vasoconstriction	Platelet effect of aspirin-type drugs
PGF2 alpha	COX	Uterine contraction, luteolysis	Analogues used in reproduction
LTB4	5-LOX	Neutrophil chemotaxis	Not blocked by standard NSAIDs
LTC4, LTD4, LTE4	5-LOX	Bronchoconstriction, permeability	Allergic airway disease

5-HT receptor subtypes of clinical interest

Receptor	Type	Site	Drug link
5-HT1A	G-protein-coupled	Brain	Behaviour-modifying drugs
5-HT2A	G-protein-coupled	Platelets, vessels, brain	Aggregation and vasoconstriction
5-HT3	Ligand-gated ion channel	Gut, vomiting pathways	Ondansetron, mirtazapine as antagonists
5-HT4	G-protein-coupled	Gut	Prokinetics such as cisapride where available

Species notes

Dog

Cat

Dogs commonly receive 5-HT3 antagonists or maropitant for vomiting. NSAIDs can cause gastric injury because of reduced protective prostaglandins.

Cats have slow glucuronidation of many drugs, which affects NSAID choice. Platelet serotonin and thromboxane are thought to contribute to vasoconstriction in feline thromboembolic disease.

Cattle

PGF2 alpha analogues cause luteolysis and can end pregnancy, so pregnant animals must not be exposed unintentionally, and handlers should follow label safety advice.

Horse

Horses release eicosanoids in endotoxaemia and colic. NSAIDs such as flunixin are used for this reason, and the gut and kidney are watched for adverse effects.

Pigs and small ruminants

PGF2 alpha analogues are used to manage reproduction in some herds. Follow current label instructions and local regulation.

Clinical pearls

Self-test: 10 questions

1. Which enzyme releases arachidonic acid from membrane phospholipids?

Phospholipase A2 liberates arachidonic acid, the substrate for both COX and lipoxygenase.

2. Which pathway is NOT blocked by standard NSAIDs?

NSAIDs block cyclooxygenase. Leukotrienes come from the lipoxygenase route.

3. Corticosteroids reduce eicosanoids mainly by

They act high in the pathway, reducing both branches.

4. Which mediator promotes platelet aggregation?

Thromboxane from platelets causes aggregation and vasoconstriction.

5. Which leukotriene is strongly chemotactic for neutrophils?

LTB4 attracts neutrophils, while the cysteinyl leukotrienes act on airways and vessels.

6. Which serotonin receptor is a ligand-gated ion channel?

5-HT3 is a channel. The others are G-protein-coupled.

7. Ondansetron relieves nausea by blocking

It is a 5-HT3 antagonist. Maropitant blocks NK1.

8. Bradykinin is mainly broken down by

ACE degrades bradykinin, so ACE inhibitors raise kinin levels.

9. Why do NSAIDs cause stomach and kidney effects?

Prostaglandins support gastric mucus and renal blood flow, so reducing them removes protection.

10. A PGF2 alpha analogue given to a pregnant animal may

PGF2 alpha causes regression of the corpus luteum and can end pregnancy.

Key points to revise

1. Eicosanoids are made from arachidonic acid released by phospholipase A2.
2. COX makes prostaglandins and thromboxane, 5-LOX makes leukotrienes.
3. PGE2 causes pain sensitisation, fever and gastric protection.
4. TXA2 promotes platelet aggregation, PGI2 inhibits it.
5. LTB4 attracts neutrophils and cysteinyl leukotrienes constrict airways.
6. 5-HT3 antagonists are anti-nausea drugs, 5-HT4 agonists are prokinetics.
7. Bradykinin causes pain, vasodilation and permeability via B2 receptors.
8. Different anti-nausea drugs block different pathways: serotonin, substance P, dopamine and histamine.

Go deeper on this site

- Ch 12. NSAIDs and antipyretics (in this book)
- Ch 10. Histamine and antihistamines (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Nonsteroidal Anti-inflammatory Drugs in Animals
- Merck Veterinary Manual: Corticosteroids in Animals
- University of Minnesota Libraries: Principles of Pharmacology study guide

CHAPTER 12 OF 33

NSAIDs and antipyretics

NSAIDs relieve pain, inflammation and fever by blocking cyclooxygenase. This chapter explains COX-1 and COX-2, why stomach and kidney effects occur, why paracetamol is dangerous in cats, how food-animal use and withdrawal apply, and the vulture-related restrictions in India.

After this chapter you can

- Explain how NSAIDs produce analgesic, anti-inflammatory and antipyretic effects
- Compare COX-1 and COX-2 and the idea of COX-selective drugs
- Explain gastric and renal adverse effects and who is at risk
- Explain why paracetamol is toxic to cats
- Describe the food-animal and vulture-related issues for NSAIDs in India, and the need to check current rules

Mechanism of action

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the **cyclooxygenase (COX)** enzymes, so less arachidonic acid is turned into prostaglandins and thromboxane. The previous chapter described these mediators.

- **Analgesia:** less PGE_2 means nerve endings are less sensitised to bradykinin and other pain signals. The effect is strongest in inflammatory pain.
- **Anti-inflammatory:** less vasodilation, swelling and prostaglandin-driven signalling at the site of injury.
- **Antipyretic:** during fever, cytokines raise PGE_2 in the hypothalamus and reset the temperature set point upwards. NSAIDs lower PGE_2 and the set point returns. They do not lower normal body temperature, and they do not help heat stroke, where the set point is unchanged.

Most NSAIDs block COX by competing with arachidonic acid. **Aspirin** is different, because it irreversibly acetylates COX. This is why its effect on platelets lasts for the life of the platelet.

Common confusion: students think NSAIDs work on the pain nerve itself like an opioid. They do not. They act at the site of injury by reducing the chemical that sensitises the nerve, which is why they work best in inflammatory pain and have no sedative or addictive effect. Their effect also has a ceiling, so giving more drug does not give more pain relief but does add more risk.

COX-1, COX-2 and selectivity

COX-1 is present all the time and supports stomach lining, kidney blood flow and platelet function. COX-2 rises at sites of inflammation and is the main target for pain relief. Drugs with more activity against COX-2 than COX-1 were developed to give pain relief with fewer stomach problems. Several veterinary drugs, such as meloxicam, carprofen and others, are described as preferentially COX-2 inhibitors in some species.

Do not oversimplify. COX-2 is also present in normal kidney, and in healing tissue, and selectivity differs between species and between laboratory tests. A COX-2 preferring drug is *safer for the stomach in many patients*, but it is not free of kidney, liver or other adverse effects. Some drugs are also described as dual inhibitors, because they affect both COX and lipoxygenase pathways. Learn the principle and check product labels for current claims.

Stomach and kidney effects

Stomach. Prostaglandins increase mucus, bicarbonate and mucosal blood flow, and reduce acid. Without them the mucosa is exposed, and in addition acidic NSAIDs can irritate directly. The result may be vomiting, erosion, ulcer, bleeding or perforation. Signs to teach owners: vomiting, black tarry stool, poor appetite and lethargy. Misoprostol, a prostaglandin analogue, and acid suppressants may be used in selected cases, but the best protection is correct drug choice, avoiding combinations and not giving long courses without need.

Kidney. When blood pressure or blood volume is low, prostaglandins widen the afferent arterioles and protect glomerular filtration. NSAIDs remove this support. The risk is highest in dehydration, shock, anaesthesia with low blood pressure, heart failure, existing kidney disease and in old animals. Hydration and avoiding NSAIDs in these states is the key.

Other points. Avoid NSAIDs together with corticosteroids, which greatly raises the risk of gastric ulcer. Do not switch directly between NSAIDs, and allow the washout time on the label. NSAIDs can also affect platelet function, and may be undesirable before surgery in some animals. Liver injury is an uncommon, individual reaction with some drugs.

Protein binding is another point. NSAIDs are highly bound to plasma protein, so animals with low albumin, for example from liver or protein-losing disease, may

have more free drug and a higher chance of adverse effects. Using two NSAIDs together is not safer, since both add to the same mechanism-based harm.

Animals should be monitored with a clinical check and, in long-term use, with periodic blood and urine tests of kidney and liver function. Owners should be taught to stop the drug and call the clinic if vomiting, poor appetite or dark stool appear.

Paracetamol and cats

Paracetamol (acetaminophen) is a good antipyretic and mild analgesic with little anti-inflammatory effect. In most species it is cleared mainly by conjugation with glucuronic acid, with a small part oxidised to a toxic intermediate that glutathione normally neutralises.

Cats are deficient in glucuronidation, because they have low activity of the relevant enzyme. Metabolism is pushed towards the toxic oxidation route and sulphation saturates quickly. Glutathione runs out, and the toxic metabolite damages red cells. Haemoglobin is oxidised to **methaemoglobin**, which cannot carry oxygen, and Heinz bodies form. Typical signs are brown or muddy mucous membranes, difficulty breathing, facial and paw oedema, and later liver injury. Even a small amount can be dangerous in a cat, so it should not be given.

Dogs tolerate paracetamol better but can develop liver damage and methaemoglobinaemia at higher exposure. Acetylcysteine, which restores glutathione, is a key antidote in poisoning. The same glucuronidation weakness helps explain why cats are sensitive to some other drugs, and why aspirin is cleared slowly in cats.

Food-animal use

NSAIDs are used in cattle, buffalo, pigs, sheep and goats for fever, mastitis, lameness, calving injuries, respiratory disease and endotoxaemia. Because products are consumed as milk and meat, every drug needs a **withdrawal period** and a **maximum residue limit**. Use only a product and a species that the label allows, and follow the time before milk or slaughter. In India, permitted drugs, residue limits and withdrawal rules are set by notifications and may change, so **check the current notification** and product label.

Some NSAIDs are not suitable for food-producing animals or are restricted. Never use extra-label NSAIDs casually in a dairy herd. Young calves, dehydrated animals and those with mastitis-related toxaemia are at higher kidney and gastric risk, so fluids and supportive care are as important as the NSAID itself.

Vulture-related restrictions in India

In the 1990s and 2000s, populations of Gyps vultures in South Asia fell very sharply. The cause was identified as **diclofenac**, used in cattle and buffalo. When a treated animal died shortly after treatment and the carcass was eaten, vultures developed visceral gout and kidney failure. Residues in a carcass can be enough to poison birds feeding on it.

India took regulatory action against veterinary diclofenac in the mid 2000s, and later steps addressed human diclofenac formulations used in animals and some other NSAIDs. The exact list of banned, restricted or advisory products changes with notifications, so students must **check the current notification** of the drug regulator and state authorities. Meloxicam is widely described as a safer alternative for vultures, but any new drug should be considered against current evidence.

The message for a practitioner is wider than one drug. Know the status of every NSAID you use in livestock, avoid human formulations in animals, and dispose of carcasses responsibly. The vulture story is a classic example of a drug harming a non-target species through the food chain.

Concept cleared

Concept cleared: Why fever drops but normal temperature does not
Think of a thermostat set too high by a chemical (PGE2). The NSAID removes that chemical, and the thermostat returns to normal, so the body cools. If the thermostat is already normal, as in heat stroke, there is nothing to reset, and an NSAID does not help.

Concept cleared: Why cats are unique with paracetamol

Most animals have a wide safe road (glucuronidation) for clearing paracetamol. Cats have only a narrow lane, so traffic piles up and diverts into a dangerous side road that makes a toxic product and uses up glutathione. The result is methaemoglobin.

Concept cleared: Aspirin is irreversible

Most NSAIDs are like a person standing in a doorway who can walk away. Aspirin is like a lock that is welded shut. A platelet has no nucleus to make new COX, so the block lasts until the platelet is replaced.

Concept cleared: The vulture chain

A drug given to a cow does not stay with the cow. If she dies soon after, the carcass carries residue to vultures, whose kidneys cannot cope. One treatment decision in a village affected a whole species across a region.

Memory aid: NSAID cautions

G-R-P-F: Gut, Renal, Platelet, Food chain. Check each before choosing an NSAID. And remember: cats and paracetamol never mix.

Compare and contrast

COX-1 and COX-2

Feature	COX-1	COX-2
Expression	Constant in most tissues	Induced in inflammation, also present normally in some organs such as kidney
Main role	Stomach protection, kidney perfusion, platelets	Pain, inflammation, fever
Result of blocking	Gastric injury, renal effects, bleeding tendency	Pain relief, but some renal and healing effects
Drug idea	Non-selective NSAIDs block both	COX-2 preferring drugs aim for fewer stomach effects

Adverse effect risk and what to do

Problem	Mechanism	Risk group	Practical step
Gastric ulcer	Loss of protective prostaglandins	Combined with corticosteroids, long courses	Avoid combinations, watch for black stools
Renal injury	Loss of afferent dilation	Dehydrated, hypotensive, old, kidney disease	Hydrate, avoid NSAIDs in these states
Paracetamol toxicity	Poor glucuronidation, methaemoglobin	Cats	Never give; acetylcysteine in poisoning
Residue in food	Drug in milk and meat	Food animals	Follow withdrawal period and notification
Vulture poisoning	Diclofenac in carcass	Scavenging birds	Avoid banned products, dispose of carcasses safely

Species notes

Dog

Dogs are commonly given veterinary-licensed NSAIDs for osteoarthritis and post-operative pain. Human NSAIDs and combining with steroids carry a high risk of gastric ulcer.

Cat

Cats clear many NSAIDs slowly and paracetamol is dangerous. Use only products and regimes labelled for cats and be careful with kidney status.

Cattle and buffalo

Used for fever, mastitis and lameness, but milk and meat withdrawal and current Indian notifications must be followed. Avoid banned diclofenac products.

Horse

Flunixin and phenylbutazone-type drugs are used for colic and musculoskeletal pain. Watch the stomach and kidney, and note that the drug may mask pain or signs of progressive disease.

Pigs, sheep and goats
NSAIDs are used for fever and lameness. Check that the product and species are approved and observe the withdrawal period.

Clinical pearls

Self-test: 10 questions

1. NSAIDs mainly act by inhibiting

They block COX and so reduce prostaglandin and thromboxane synthesis.

2. NSAIDs reduce fever by lowering

Lower PGE2 allows the hypothalamic set point to return to normal.

3. Aspirin differs from most NSAIDs because it

Irreversible COX block in platelets lasts for the platelet life span.

4. Which tissue function depends mainly on COX-1 products?

COX-1 generated prostaglandins maintain mucus, bicarbonate and mucosal blood flow.

5. NSAID renal injury is most likely in an animal that is

In low perfusion states, prostaglandins maintain glomerular flow, and NSAIDs remove that support.

6. Which combination is especially risky for gastric ulcer?

Both reduce mucosal defence and the combined risk is high.

7. Why is paracetamol toxic in cats?

Poor glucuronidation shifts metabolism to oxidation, leading to methaemoglobin and Heinz bodies.

8. A key antidote to paracetamol poisoning acts by

Acetylcysteine replenishes glutathione to neutralise the toxic metabolite.

9. Vulture population decline in South Asia was linked to

Vultures feeding on carcasses of treated livestock developed visceral gout and kidney failure.

10. Before using an NSAID in a dairy cow in India, the veterinarian should

Residue limits, approved drugs and restrictions are set by notifications that change.

Key points to revise

1. NSAIDs inhibit COX and reduce prostaglandins and thromboxane.
2. Analgesia, anti-inflammatory and antipyretic effects all derive from lower prostaglandins.
3. COX-1 supports stomach, kidney and platelets, COX-2 is mainly induced in inflammation.
4. COX-2 preference does not remove all risk.
5. Stomach ulcer and renal injury are mechanism-based adverse effects.
6. Aspirin irreversibly acetylates COX.
7. Cats lack glucuronidation, so paracetamol causes methaemoglobinaemia.

8. Diclofenac residues in carcasses poisoned Gyps vultures in South Asia, and Indian rules are set by notification.

Go deeper on this site

- Ch 13. Corticosteroids (in this book)
- Ch 11. Eicosanoids, serotonin and kinins (in this book)
- Meloxicam in cats: safety cautions
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Nonsteroidal Anti-inflammatory Drugs in Animals
- Merck Veterinary Manual: Overview of Anti-inflammatory Agents
- University of Minnesota Libraries: Principles of Pharmacology study guide

CHAPTER 13 OF 33

Corticosteroids

Glucocorticoids act on nuclear receptors to switch off many inflammatory and immune pathways at once. This chapter covers the mechanism, the two main uses, the adverse effects, why long courses suppress the adrenal gland, and why steroids and NSAIDs should not be combined.

After this chapter you can

- Explain how glucocorticoids change gene transcription to reduce inflammation
- Distinguish anti-inflammatory from immunosuppressive use and the reason the latter needs higher exposure
- List the main adverse effects of prolonged glucocorticoid therapy
- Explain how the hypothalamic-pituitary-adrenal axis is suppressed and why withdrawal must be gradual
- Explain why glucocorticoids and NSAIDs together raise the risk of gastrointestinal ulceration

What corticosteroids are

The adrenal cortex makes two groups of steroid hormones. **Glucocorticoids** such as cortisol control metabolism and inflammation. **Mineralocorticoids** such as aldosterone control sodium and potassium balance. Drugs such as prednisolone, dexamethasone, betamethasone and triamcinolone are synthetic glucocorticoids.

These drugs differ in potency, duration and in how much salt-retaining activity they keep. Dexamethasone is far more potent and longer acting than prednisolone, and has almost no mineralocorticoid effect. The practical point is that the choice of drug, and not only the dose, decides how long the effect lasts and how severe the side effects are.

A common confusion is to treat all steroids as one thing. Anabolic steroids and sex steroids are different drugs with different receptors. In this chapter, corticosteroid means glucocorticoid.

Mechanism of action

Glucocorticoids are lipid-soluble, so they cross the cell membrane and bind a receptor in the cytoplasm. The drug-receptor complex moves into the nucleus and changes gene expression. This is the nuclear receptor family described in the chapter on receptors, and it explains why the onset is slow (hours) and the effect outlasts the plasma half-life.

Two main things follow. The complex **increases** the production of some anti-inflammatory proteins. One of these, often called lipocortin, inhibits phospholipase A_2. With less phospholipase A_2, less arachidonic acid is released, so fewer prostaglandins, leukotrienes and platelet-activating factor are made. The complex also **decreases** the production of cytokines and of cyclo-oxygenase-2, and reduces the activity and movement of white cells into tissue.

Compare this with NSAIDs, which block cyclo-oxygenase only. Steroids act higher up the pathway, and on more mediators, which is why they are the stronger anti-inflammatory drugs.

Anti-inflammatory and immunosuppressive use

The same mechanism gives two clinical uses, and students should keep them separate.

- **Anti-inflammatory use**: relief of itching and inflammation in allergic skin disease, inflammatory airway disease, arthritis flares, and spinal or brain swelling. The aim is the lowest effective exposure for the shortest time.
- **Immunosuppressive use**: control of immune-mediated disease such as immune-mediated haemolytic anaemia, immune-mediated thrombocytopenia, pemphigus and some lymphoid conditions. Here the exposure needed is higher and the course is longer, so adverse effects are more likely.

Glucocorticoids reduce lymphocyte numbers and function, lower antibody production and impair the phagocytes. This is useful in autoimmune disease but is also the reason infections become worse or silent during treatment.

Other uses include replacement therapy in hypoadrenocorticism, treatment of shock and some emergencies in specific protocols, and certain drug-induced actions such as induction of parturition in cattle. Because a steroid can mask signs, take a diagnosis first. Giving a steroid before a lymph node biopsy, for example, can change the histology and make lymphoma harder to confirm.

Adverse effects

Most serious problems follow long-term or high exposure. A short course for an allergic flare is usually well tolerated. Adverse effects are best learned as an extension of normal physiology: too much cortisol produces the picture of Cushing syndrome, called **iatrogenic hyperadrenocorticism** when the cause is a drug.

- Increased thirst, urination and appetite, with weight gain and a pot-bellied look.
- Muscle wasting and weakness, thin skin, poor wound healing and hair loss.
- Worsening or new diabetes mellitus, because glucocorticoids oppose insulin.
- Greater risk of infection, including urinary tract and skin infection, and masking of fever.
- Gastrointestinal irritation and ulceration.
- Sodium and water retention with potassium loss, more with drugs that retain some mineralocorticoid action.
- In horses, a risk of laminitis, especially with high exposure.

- Delayed bone and wound healing, and in pregnancy, risk of abortion or premature birth, especially in late gestation in ruminants.

Drugs such as triamcinolone and long-acting depot forms carry the same risks and are harder to stop once injected, because the effect cannot be recalled.

Adrenal suppression and withdrawal

The body controls cortisol by negative feedback. The hypothalamus releases CRH, the pituitary releases ACTH, and ACTH tells the adrenal cortex to make cortisol. When a glucocorticoid drug is given, the brain senses plenty of steroid and switches off CRH and ACTH. The adrenal cortex, no longer stimulated, shrinks. This is **suppression of the hypothalamic-pituitary-adrenal axis**.

If the drug is stopped suddenly after prolonged use, the animal has no steroid from the drug and little from its own adrenal glands. The result can be weakness, vomiting, low blood pressure and collapse, a picture of secondary hypoadrenocorticism. The same risk appears in an animal under stress, such as surgery, while recovering from a long course.

Therefore long courses are **tapered** slowly, not stopped. In some cases alternate-day dosing is used because it allows the axis a partial recovery on the off-day, and an intermediate-acting drug such as prednisolone suits this better than long-acting dexamethasone. Recovery of the axis can take weeks after stopping, so the clinician should keep this risk in mind during that period.

Note that suppression follows a feedback mechanism, so even topical, ophthalmic and injectable depot preparations can contribute when used for long periods.

Why not with NSAIDs

Gastric and intestinal mucosa depends on protective prostaglandins to maintain mucus, bicarbonate and blood flow. NSAIDs reduce these prostaglandins by blocking cyclo-oxygenase. Glucocorticoids also lower prostaglandin production and in addition slow mucosal repair and thin protective tissue. Used together, the two drugs add their harmful effects on the gut, and reports describe a clearly higher risk of gastrointestinal ulceration, bleeding and perforation than either drug alone.

This is a pharmacodynamic interaction, not a kinetic one, so a longer gap between doses does not fully remove the risk. When changing from one class to the other, a

washout interval is needed, and the length should be taken from the product information and current references.

Common confusion: some students think adding a gastroprotectant makes the combination safe. It lowers risk but does not remove it, and it does not prevent the kidney and bleeding effects of NSAIDs. The safe rule is to choose one class at a time. If the patient is also on other ulcerogenic drugs or has liver or kidney disease, the case for avoiding combination is even stronger.

In short, treat the steroid as a strong tool with a price. Use the lowest effective exposure, choose one anti-inflammatory class at a time, and review the animal regularly for the signs listed above.

Concept cleared

Concept cleared: Nuclear receptor delay
Think of a steroid as an instruction sent to the factory office, not a switch on the machine. The office must rewrite its orders and the factory must make new products, so the effect arrives hours later and also takes time to fade after the drug has left the blood.

Concept cleared: Steroids act higher than NSAIDs
Picture a river of inflammation. An NSAID closes one gate in the river (cyclo-oxygenase). A steroid reduces the water at the source by lowering phospholipase A2 activity and many cytokines. Hence a stronger effect but also more side effects.

Concept cleared: Adrenal suppression
A farmer hires a contract worker to do the job of the family worker. After months the family worker retires. If the contract worker leaves suddenly, no one is left to do the work. Slowly tapering gives the family worker time to return.

Concept cleared: Same mechanism, two uses

The dose and time decide whether the steroid is a mild anti-inflammatory or a strong immunosuppressant. The longer and stronger the course, the more the animal looks like a Cushing patient.

Memory aid: Steroid adverse effects

Remember 'CUSHING': Calories and appetite up, Urination and thirst up, Skin thin, Healing slow, Infection risk, Nutrient (muscle) loss, Glucose up.

Compare and contrast

Anti-inflammatory versus immunosuppressive use

Feature	Anti-inflammatory use	Immunosuppressive use
Typical aim	Reduce itch, swelling, pain	Control immune-mediated disease
Exposure	Lowest effective	Higher
Duration	Short or intermittent	Weeks to months, with taper
Adverse effects	Usually mild	More frequent and serious
Example	Allergic dermatitis flare	Immune-mediated haemolytic anaemia

Glucocorticoids versus NSAIDs

Feature	Glucocorticoids	NSAIDs
Receptor or target	Nuclear receptor, gene changes	Cyclo-oxygenase enzyme
Onset	Hours	Often faster
Mediators reduced	Prostaglandins, leukotrienes, cytokines	Mainly prostaglandins
Immune effect	Immunosuppressive	Minimal
Key organ risks	Endocrine, infection, GI	GI, kidney, platelets

Species notes

Dog

Dogs are fairly sensitive to glucocorticoids. Polyuria, polydipsia and polyphagia appear early, and iatrogenic Cushing syndrome is common after long courses.

Cat

Cats tolerate steroids better than dogs in terms of visible adverse effects, and prednisolone rather than prednisone is generally preferred. Diabetes mellitus and heart failure risk deserve attention.

Horse

High exposure is linked to laminitis, so the lowest effective course is used, particularly in animals with endocrine disease.

Cattle

Late in pregnancy, glucocorticoids can induce parturition, which is both a use and a risk. Steroids may also reduce milk yield and hide infection.

Food animals in India

Check the current notification on permitted use, withdrawal periods and residue limits before giving any steroid to a food-producing animal.

Clinical pearls

Self-test: 10 questions

1. Glucocorticoids produce most of their anti-inflammatory effect by:

They act on nuclear-type receptors and alter transcription, including induction of phospholipase A2 inhibitors.

2. Which enzyme is indirectly inhibited by lipocortin?

Less phospholipase A2 activity means less arachidonic acid release and fewer eicosanoids.

3. Why does the effect of prednisolone last longer than its plasma half-life?

Altered protein synthesis persists after the drug has left the plasma.

4. Which is an immunosuppressive indication?

Immune-mediated haemolytic anaemia needs suppression of antibody production and phagocyte activity.

5. Polyuria, polydipsia and muscle wasting after a long course suggest:

Excess exogenous glucocorticoid mimics Cushing syndrome.

6. Prolonged steroid therapy suppresses the adrenal cortex because of:

High steroid levels suppress CRH and ACTH so the cortex atrophies.

7. The safest way to end a long course of glucocorticoids is to:

Tapering gives the adrenal axis time to recover.

8. Why should a steroid not be combined with an NSAID?

Both lower protective prostaglandins and steroids impair mucosal repair; the harmful effects add up.

9. Which statement about steroids and infection is correct?

Reduced lymphocyte and phagocyte function lets infection progress with fewer signs.

10. Why should a biopsy ideally be taken before starting a steroid?

Steroids may shrink lymphoid tissue and alter histology, hiding the disease.

Key points to revise

1. Glucocorticoids bind cytoplasmic receptors and alter gene transcription.
2. Lipocortin-mediated phospholipase A2 inhibition lowers prostaglandins and leukotrienes.
3. Effect begins after hours and outlasts the plasma half-life.
4. Anti-inflammatory use needs less exposure than immunosuppressive use.
5. Prolonged use causes iatrogenic Cushing syndrome, diabetes, infection and GI ulceration.
6. Negative feedback suppresses the HPA axis and the adrenal cortex atrophies.
7. Abrupt withdrawal after long use can cause an adrenal crisis, so taper.
8. Glucocorticoids plus NSAIDs sharply increase the risk of GI ulceration.

Go deeper on this site

- Ch 14. Joint-protective and disease-modifying drugs (in this book)
- Ch 12. NSAIDs and antipyretics (in this book)
- Meloxicam in cats: safety cautions
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Corticosteroids in Animals
- MSD Veterinary Manual: Corticosteroids in Animals
- Merck Veterinary Manual: Nonsteroidal Anti-inflammatory Drugs in Animals

CHAPTER 14 OF 33

Joint-protective and disease-modifying drugs

Chondroprotective agents are used in osteoarthritis in the hope of protecting cartilage and not only relieving pain. This chapter explains cartilage and joint fluid, polysulfated glycosaminoglycan, pentosan, hyaluronate and oral supplements, and why the evidence for many of them is weaker than the marketing.

After this chapter you can

- Describe how osteoarthritis damages cartilage and why pain relief alone does not stop it
- Define chondroprotective and disease-modifying and explain the difference from analgesics
- Explain the proposed actions, routes and cautions of polysulfated glycosaminoglycan and pentosan polysulfate
- Explain the role of hyaluronate in joint lubrication and its main species of use
- Judge the strength of evidence for chondroprotectives and nutraceuticals

Osteoarthritis in brief

Osteoarthritis is a slow, progressive joint disease. Articular cartilage loses proteoglycan and collagen, the joint capsule and synovium become inflamed, and the bone below the cartilage changes. Pain, stiffness and reduced movement follow. It is common in older dogs and in working or sport horses, and also occurs in cats and in farm animals.

Cartilage has no blood supply and few cells, so it repairs poorly. Inflammatory mediators and enzymes such as matrix metalloproteinases break down the matrix faster than the chondrocytes can replace it. A vicious circle follows: breakdown products inflame the joint, and inflammation drives more breakdown.

Most treatment is **symptomatic**: NSAIDs for pain, weight control, exercise management and physiotherapy. The drugs in this chapter aim at something extra, protecting the joint structure.

Chondroprotective and disease-modifying: the terms

A **chondroprotective** agent is one that is claimed to protect cartilage, for example by reducing enzymatic breakdown or stimulating matrix production. A **disease-**

modifying drug is one that has been shown to change the course of the disease, not only the symptoms. These two ideas are often confused.

Many agents have shown effects in test tubes and cell cultures. That is not the same as proven benefit in a living animal with naturally occurring disease. Good evidence needs controlled trials with clear outcome measures such as lameness scores, force-plate data or cartilage structure.

For this reason, students should always ask three questions about a joint product: what is the proposed mechanism, what is the best evidence in the target species, and what are the risks and costs. Another point: products sold as nutritional supplements are not always held to the same standard of proof or quality control as licensed drugs.

Polysulfated glycosaminoglycan and pentosan

Polysulfated glycosaminoglycan (PSGAG) is a semisynthetic compound made from bovine tracheal cartilage, with chondroitin sulfate as the main component. It is used in dogs and horses. In dogs it is given by intramuscular injection. In horses it is given intramuscularly or into the joint. After injection it reaches the blood and is incorporated into cartilage.

The exact mechanism is not known. Laboratory studies show that it inhibits prostaglandin E_2 and some cartilage-degrading enzymes, and that it can raise the production of hyaluronic acid, proteoglycan and collagen. These findings fit the idea of protecting and rebuilding cartilage, but their clinical size is debated.

Pentosan polysulfate sodium is a related heparin-like compound used in dogs and horses, and reports in dogs describe less cartilage damage.

Cautions follow from the heparin-like structure. Both agents can interfere with clotting, especially at high exposure, and aspirin may prolong bleeding further. PSGAG should not be put into a septic joint, because it can worsen infection. Intra-articular injection also requires strict asepsis. Check the label for the exact precautions for each product and species.

Hyaluronate

Hyaluronan (hyaluronic acid, hyaluronate) is a natural component of synovial fluid and cartilage. It gives joint fluid its viscosity and lubricates the surfaces, and it helps to cushion load. In osteoarthritis the molecules in joint fluid are smaller and less concentrated, so lubrication falls.

Injected hyaluronate is used mainly in horses, where purified preparations are put directly into the joint. It may improve lubrication, reduce prostaglandin E_2 production and ease pain. Adverse effects in horses are usually few, and the main risks are those of any joint injection, namely infection and joint flare.

A common confusion is to think the injected molecules stay in the joint for long and rebuild cartilage. They are cleared fairly quickly, so benefit is thought to come from both direct lubrication and from effects on the joint lining that outlast the presence of the drug. Hyaluronate is often combined with a corticosteroid in equine joint therapy, which should be done only by clinicians who understand the risks of repeated intra-articular steroid.

Other agents mentioned in references include orgotein, given into joints in some species, which has a slow onset over weeks.

Oral supplements and evidence

Glucosamine and chondroitin sulfate are the best known oral joint supplements. They are building blocks of cartilage matrix, and the theory is that supplying them helps the cartilage to repair. Omega-3 fatty acids, green-lipped mussel extract and avocado-soybean extracts are also sold. These are widely used by owners, and are often chosen because they seem safe.

The scientific problem is that oral absorption, delivery to cartilage and the real clinical benefit are uncertain. Studies are often small, products vary in content, and the placebo response in pain scoring is strong, because owners and clinicians tend to see improvement in an animal given any treatment. The honest position for a student is that evidence is limited and mixed for most nutraceuticals, and that those with the most support in dogs are generally the dietary omega-3 fatty acids, not glucosamine alone. Check current reviews before claiming a benefit.

In practice these products rarely replace analgesics. They are best seen as supporting measures to an overall plan.

Using these drugs sensibly

The foundation of osteoarthritis care is weight reduction, controlled exercise, physiotherapy and appropriate analgesia. NSAIDs relieve pain and inflammation in dogs and horses. Some NSAIDs, such as aspirin, naproxen and ibuprofen, are considered chondrotoxic in laboratory work because they lower cartilage proteoglycan synthesis. Carprofen and meloxicam are regarded as neutral or possibly beneficial, though the clinical meaning is still being clarified. This is one reason NSAID choice in a long-term joint patient is a considered decision.

Chondroprotectives are then added to this base when the clinician and owner accept that the proof is partial. Judge success by the animal: mobility, comfort and activity, recorded before and after, not by the product claims. If there is no clear benefit after a fair trial, stop the product and save the cost.

Other points for exam answers: do not inject any joint without aseptic technique, avoid PSGAG in infected joints, watch for bleeding tendency with heparin-like compounds, and remember that regulation of veterinary supplements and of compounded products varies, so check the current notification and product licensing in India before recommending a product.

In short, these drugs support the joint but do not replace basic care. Record mobility before and after treatment, review the plan regularly, and be honest with owners about what the evidence can and cannot promise.

Concept cleared

Concept cleared: Cartilage repair is slow

Cartilage is like a road with no workers living nearby. Damage is easy but repair crews must come from far away, so a break-down faster than repair gives a pothole that keeps growing.

Concept cleared: Symptom versus structure

An NSAID lowers the pain alarm. A true disease-modifying drug would fix the damage that sets off the alarm. Most joint products are somewhere between, and the proof is partial.

Concept cleared: Lab effect is not clinical benefit

A drug that lowers an enzyme in a dish has passed only the first test. It still has to show better walking in real animals in a controlled trial.

Concept cleared: Hyaluronate as joint oil

Joint fluid works like engine oil. In osteoarthritis the oil becomes thin. Adding hyaluronate thickens it and lubricates for a time, but it is not a new engine.

Memory aid: Three questions for any joint product

Ask M-E-R: Mechanism, Evidence in the target species, Risk and cost.

Compare and contrast

Main joint-protective agents

Agent	Route	Proposed action	Main caution
Polysulfated glycosaminoglycan	Intramuscular (dog); intramuscular or intra-articular (horse)	Lowers PGE2 and degrading enzymes; supports matrix synthesis	Heparin-like, clotting effects; avoid in septic joint
Pentosan polysulfate sodium	Injection, dogs and horses	Heparin-like; reported less cartilage damage in dogs	Clotting interference
Hyaluronate	Intra-articular, mainly horses	Lubrication, less PGE2, pain relief	Infection risk of joint injection
Oral glucosamine and chondroitin	Oral	Matrix building blocks (proposed)	Uncertain evidence and product quality

Analgesic versus chondroprotective aim

Feature	NSAID	Chondroprotective agent
Main aim	Relieve pain and inflammation	Protect or support cartilage
Evidence of effect	Strong for pain relief	Variable, often limited
Speed	Days	Weeks or longer
Role	Core treatment	Add-on

Species notes

Dog

PSGAG is given by intramuscular injection, and pentosan has been studied in dogs. NSAIDs and weight loss remain the basis of treatment; omega-3 fatty acids have the better supported nutritional role.

Horse

Intra-articular hyaluronate and PSGAG are used in joint disease of performance horses, with strict aseptic technique. Check competition rules on drugs before use.

Cat

Osteoarthritis is common but under-recognised in older cats. Analgesic choice is limited by the cat's drug metabolism, so supportive measures matter. Check product labels and current references.

Cattle and buffalo

Joint products are rarely used for economic reasons. Lameness is managed by treating the cause, and any drug use needs attention to withdrawal times under current Indian rules.

Working animals in India

Draught bullocks, buffaloes and horses show arthritis with heavy work. Rest and load management are cheap and effective, and often more important than injections.

Clinical pearls

Self-test: 10 questions

1. Which statement about cartilage is correct?

Poor blood supply and few chondrocytes limit repair.

2. A disease-modifying osteoarthritis drug is one that:

Disease-modifying implies a proven effect on progression, not only symptoms.

3. PSGAG is derived from:

It is a semisynthetic compound from bovine tracheal cartilage with chondroitin sulfate as the main component.

4. PSGAG should not be injected into:

It is contraindicated in septic joints.

5. Why can PSGAG and pentosan affect bleeding?

Their heparin-like structure can interfere with clotting.

6. Hyaluronate is mainly used by which route and species?

Purified hyaluronan is injected into joints in horses.

7. Which statement on oral glucosamine and chondroitin is most accurate?

Absorption, delivery and clinical benefit are uncertain.

8. Why is a strong placebo effect a problem in supplement trials?

Subjective pain scoring is easily biased without blinding and controls.

9. Which NSAID group is considered chondrotoxic in laboratory work?

These lower cartilage proteoglycan synthesis, while carprofen and meloxicam appear neutral.

10. The core of osteoarthritis management is:

Supplements and injections are add-ons to the basic plan.

Key points to revise

1. Osteoarthritis involves cartilage breakdown, synovial inflammation and bone change.
2. Chondroprotective means claimed to protect cartilage; disease-modifying means proven to change the course.
3. PSGAG is derived from bovine tracheal cartilage and used in dogs and horses.
4. PSGAG proposed actions: reduces PGE2 and degrading enzymes, supports hyaluronan, proteoglycan and collagen.
5. PSGAG and pentosan are heparin-like and may affect clotting.
6. Hyaluronate lubricates the joint and is mainly used intra-articularly in horses.
7. Evidence for oral glucosamine and chondroitin is limited and mixed.
8. NSAIDs, weight loss and exercise management are the base of treatment.

Go deeper on this site

- Ch 15. Drugs for heart failure and inotropes (in this book)
- Ch 13. Corticosteroids (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index

- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Chondroprotective Agents in Animals
- MSD Veterinary Manual: Chondroprotective Agents in Animals
- Merck Veterinary Manual: Nonsteroidal Anti-inflammatory Drugs in Animals

CHAPTER 15 OF 33

Drugs for heart failure and inotropes

Heart failure drugs improve contraction, reduce workload on the heart, or block harmful neurohormonal activation. This chapter covers cardiac glycosides, pimobendan, dobutamine and ACE inhibitors, with the species points that matter in practice.

After this chapter you can

- Explain the main problems of the failing heart and how each drug class addresses them
- Describe the mechanism and narrow safety margin of digoxin
- Explain pimobendan as an inodilator and its contraindication
- Describe dobutamine as a short-term intravenous inotrope
- Explain how ACE inhibitors work and the realistic size of their benefit

The failing heart

In heart failure the heart cannot pump enough blood at normal filling pressure to meet the body's needs. The body responds by activating the sympathetic system and the renin-angiotensin-aldosterone system. These responses help in the short term, because they raise heart rate, constrict vessels and retain salt and water. In the long term they overload the heart and cause congestion, with oedema, ascites or pleural effusion.

Drugs therefore have three jobs. First, improve the strength of contraction (**positive inotropes**). Second, reduce preload and afterload, the volume and the resistance the heart works against. Third, block the harmful neurohormonal activation.

Diuretics such as furosemide relieve congestion and are the most commonly used drugs in heart failure, but this chapter concentrates on the other groups.

A common confusion is to think that a stronger beat is always better. Increasing contraction raises oxygen demand and can provoke arrhythmias, so inotropes are used with care and for the right type of failure.

Cardiac glycosides: digoxin

Digoxin comes from the foxglove plant (*Digitalis*). It inhibits the membrane **sodium-potassium ATPase** pump in heart muscle cells. Sodium builds up inside the cell, and the sodium-calcium exchanger then removes less calcium, so intracellular calcium rises and each contraction is stronger. Digoxin also increases vagal tone, slows conduction through the atrioventricular node, and so slows the ventricular rate in atrial fibrillation.

Its inotropic effect is modest, and its **safety margin is narrow**, so the toxic level is close to the useful one. Toxicity is made more likely by low potassium, kidney disease and interacting drugs. Loop diuretics such as furosemide lower potassium, and amiodarone and some other drugs raise digoxin levels. Early signs are gastrointestinal, including anorexia and vomiting, followed by arrhythmias. Cats are more sensitive than dogs.

Because of this, serum monitoring is advised, and digoxin has largely been replaced by pimobendan for most cases of canine failure. Its remaining value is rate control in supraventricular tachyarrhythmias such as atrial fibrillation, often with other drugs. Remember too that the same plant glycosides cause poisoning from oleander and foxglove in animals.

Pimobendan: an inodilator

Pimobendan has two linked actions, which is why it is called an **inodilator**. It **sensitises** the contractile proteins to calcium, which strengthens contraction without a large rise in intracellular calcium or oxygen use. It also inhibits **phosphodiesterase 3**, raising cAMP in vascular smooth muscle, which gives balanced dilation of arteries and veins. The heart thus contracts better and works against less resistance.

In dogs it is approved for congestive failure caused by atrioventricular valve disease or dilated cardiomyopathy, and it improves quality of life and survival. It is contraindicated where the problem is outflow obstruction, as in subaortic stenosis, because a stronger beat against a fixed obstruction can worsen it. The main adverse effects are gastrointestinal.

In cats it is not approved, and evidence is mixed. It is used in selected cases that no longer respond to standard therapy. Do not apply the dog rule to cats without checking current references. Hypertrophic cardiomyopathy in cats is an example where a stronger beat is not the aim.

Dobutamine

Dobutamine is a synthetic catecholamine acting mainly on **beta-1 receptors**. Binding of beta-1 receptors raises cAMP in cardiac cells and strengthens contraction. It does not release noradrenaline, and compared with dopamine it has a stronger inotropic and weaker heart-rate effect.

It is given only as a **continuous intravenous infusion**, because the half-life is a few minutes and it is destroyed in the gut. It is used for short-term support in acute, severe failure, cardiogenic shock and low cardiac output under anaesthesia. It cannot be used for long-term control.

Monitoring of heart rate, rhythm and blood pressure is needed, because tachycardia and ventricular arrhythmias can occur. In cats, lower infusion rates are advised because of longer half-life and central nervous stimulation, with seizures reported. Tolerance can develop with prolonged use since receptors down-regulate, an example of the receptor regulation described earlier.

ACE inhibitors

Angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II. Angiotensin II constricts vessels, triggers aldosterone release and promotes remodelling of heart muscle. ACE inhibitors such as enalapril and benazepril block this step, so they lower afterload, reduce salt and water retention and may limit remodelling.

They are used as part of combination therapy in dogs with heart failure and in some cats. Realistic expectations are important. In dogs with congestive failure, the

benefit is generally mild and, in some reports, short lived, and aldosterone levels can rise again despite treatment, called **aldosterone breakthrough**. They are not a replacement for a diuretic or pimobendan.

Adverse effects include low blood pressure and azotemia, because angiotensin II helps to maintain filtration pressure in the kidney. Kidney values and electrolytes should be checked, especially when used with diuretics or in dehydrated animals. ACE inhibitors should not be used in pregnancy. Their value in other conditions, such as protein-losing kidney disease, is covered in the renal chapters.

Putting the drugs together and species notes

Treatment is chosen by the stage and cause of failure. In a dog with congestive failure from mitral valve disease, a typical plan combines a loop diuretic to clear congestion, pimobendan to improve output, and an ACE inhibitor, with other drugs added by the clinician. Dobutamine is reserved for critical care. Digoxin is kept for rate control in specific arrhythmias.

A few rules help in the exam. A stronger drug is not always better. Match the drug to the problem: congestion needs a diuretic, low output needs an inotrope, high afterload needs a vasodilator. Each has a trade-off, for example the arrhythmia risk of inotropes and the kidney risk of ACE inhibitors and diuretics.

Cattle and horses show heart failure less often, and drug use is limited by cost and, in food animals, by residue concerns, so check the current notification on permitted drugs. Whatever the species, owners need clear teaching about monitoring: breathing rate at rest, appetite and weight, and the need for repeat kidney and electrolyte tests.

In short, match each drug to its job, start with the diagnosis, and review the response. Resting breathing rate, appetite, body weight and repeat laboratory tests guide any change in the plan.

Concept cleared

Concept cleared: Digoxin and calcium

Digoxin jams the sodium pump. Sodium stays inside, so the cell stops pushing calcium out as well. More calcium is left to trigger contraction, like a pump that is switched off so water level in the tank rises.

Concept cleared: Inodilator

A cart-horse with a lighter cart. Pimobendan strengthens the horse (inotrope) and removes some of the load (vasodilation), so the same effort moves more.

Concept cleared: Neurohormonal brake

ACE inhibitors cut off angiotensin II, which is like removing the tightening screw on the vessels and the salt-retaining signal. The gain is steady but small.

Concept cleared: Dobutamine is a rescue

Its half-life is minutes, like a drip that must keep running. It is for a crisis in the ICU, not for home care.

Memory aid: Four heart failure tools

'DPDA': Digoxin (rate), Pimobendan (inodilator), Dobutamine (ICU rescue), ACE inhibitor (afterload and salt). Diuretics clear the congestion alongside.

Compare and contrast

Heart failure drugs at a glance

Drug	Target	Main effect	Main caution
Digoxin	Na+/K+ ATPase	Mild inotropy, slows AV conduction	Narrow margin; low potassium, kidney disease
Pimobendan	Calcium sensitisation and PDE3	Inotropy plus vasodilation	Outflow obstruction; GI signs; cats not approved
Dobutamine	Beta-1 receptor	Short-term inotropy	Arrhythmia; infusion only; cats seizures
ACE inhibitor	Angiotensin-converting enzyme	Less afterload and salt retention	Hypotension, azotemia

Inotropes: dobutamine versus digoxin

Feature	Dobutamine	Digoxin
Route	Intravenous infusion	Oral (or slow intravenous in special cases)
Duration	Minutes after stopping	Days
Use	Acute severe failure	Rate control in atrial fibrillation
Safety margin	Titrated to effect	Narrow

Species notes

Dog
Pimobendan is approved for failure from valve disease or dilated cardiomyopathy and has largely replaced digoxin. ACE inhibitors and a loop diuretic are used alongside it.

Cat
Cats are more sensitive to digoxin and to dobutamine's nervous system effects. Pimobendan is not approved in cats and evidence is mixed, so it is reserved for selected cases.

Horse
Heart failure is uncommon and treatment is mainly a diuretic, with digoxin used for some atrial

Cattle
Failure usually appears as brisket oedema and jugular distension. Treatment is rarely practical, and

fibrillation cases. Check current references and competition rules.

residue rules apply if any drug is used.

Zoo and exotic animals
Species differences in sensitivity to cardiac glycosides are large. Use only with specialist guidance.

Clinical pearls

Self-test: 10 questions

1. Digoxin increases contractility by inhibiting:

Raised intracellular sodium reduces calcium removal, so calcium rises.

2. Digoxin toxicity is more likely with:

Low potassium increases sensitivity to glycoside effect.

3. The earliest signs of digoxin toxicity are often:

Anorexia and vomiting commonly appear before arrhythmias.

4. Pimobendan is called an inodilator because it:

It combines calcium sensitisation with PDE3 inhibition.

5. Pimobendan is contraindicated in:

A stronger beat against a fixed outflow obstruction can worsen it.

6. Dobutamine acts mainly on:

It is a synthetic catecholamine with mainly beta-1 activity.

7. Why is dobutamine given by continuous infusion?

It acts for only minutes, so effect needs constant delivery.

8. An ACE inhibitor lowers afterload by:

Less angiotensin II means less vasoconstriction and sodium retention.

9. A common adverse effect of ACE inhibitors that needs monitoring is:

Reduced angiotensin II lowers glomerular filtration pressure, so kidney values should be checked.

10. In cats, which statement is correct?

Cats are more sensitive to digoxin, and pimobendan is not approved for them.

Key points to revise

1. Heart failure drugs improve contraction, lower workload or block neurohormonal activation.
2. Digoxin inhibits Na+/K+ ATPase, raising intracellular calcium.
3. Digoxin has a narrow safety margin and cats are more sensitive than dogs.
4. Pimobendan sensitises contractile proteins to calcium and inhibits PDE3.
5. Pimobendan is approved for dogs with valve disease or dilated cardiomyopathy failure.
6. Dobutamine is a beta-1 agonist given by short-term intravenous infusion.

7. ACE inhibitors block angiotensin II formation and reduce afterload and salt retention.
8. ACE inhibitor benefit in canine failure is modest and aldosterone breakthrough can occur.

Go deeper on this site

- Ch 16. Antiarrhythmic drugs (in this book)
- Ch 17. Vasodilators and antihypertensive drugs (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Positive Inotropes for Use in Animals
- Merck Veterinary Manual: Heart Failure in Dogs and Cats
- Merck Veterinary Manual: Diuretics for Use in Animals

CHAPTER 16 OF 33

Antiarrhythmic drugs

Antiarrhythmic drugs correct or control abnormal heart rhythm by changing ion movement across heart-cell membranes. This chapter explains the Vaughan-Williams classes, why these drugs can themselves cause arrhythmias, and the common rhythm disturbances of dogs and horses.

After this chapter you can

- Explain how arrhythmias arise from abnormal automaticity, triggered activity and re-entry
- State the Vaughan-Williams classes with a mechanism and an example for each
- Describe why antiarrhythmics can be proarrhythmic and why electrolytes matter
- Recognise the common arrhythmias of dogs and horses and the drug classes used conceptually

- Apply species cautions to antiarrhythmic use

Why hearts go out of rhythm

A normal heartbeat starts in the sinoatrial node, crosses the atrioventricular (AV) node, and spreads through the ventricles in an orderly way. Each cardiac cell fires an **action potential** built from the movement of sodium, calcium and potassium ions. An **arrhythmia** is any disturbance of this sequence in rate, regularity or site of origin.

Three basic mechanisms explain almost every arrhythmia. **Abnormal automaticity** means a cell outside the sinus node starts firing on its own. **Triggered activity** means after-depolarisations during or just after an action potential set off extra beats. **Re-entry** means an impulse travels round a circuit of tissue with slow conduction in one limb, so it keeps re-exciting the heart. Re-entry is the commonest cause of sustained tachycardia and of atrial fibrillation.

Each antiarrhythmic class targets one of these mechanisms by changing a channel or receptor. Knowing the mechanism helps you predict both the benefit and the harm.

The Vaughan-Williams classification

The classification groups drugs by their main effect on the cardiac action potential. It is a teaching framework. Many drugs act on more than one channel, so the classes overlap.

- **Class I: sodium-channel blockers.** They slow the upstroke of the action potential in fast tissue such as ventricle and atrium. Ia (quinidine, procainamide) also prolongs repolarisation. Ib (lidocaine, mexiletine) shortens it and acts mainly on diseased or rapidly firing tissue. Ic (flecainide, propafenone) slows conduction strongly and is little used in animals.
- **Class II: beta-blockers** (propranolol, atenolol, metoprolol, esmolol). They block sympathetic drive, slow the sinus rate and slow AV conduction.
- **Class III: potassium-channel blockers** (amiodarone, sotalol). They prolong repolarisation and the refractory period, which makes re-entry harder. Sotalol also has beta-blocking action.

- **Class IV: calcium-channel blockers** (diltiazem, verapamil). They slow the AV node and are useful for supraventricular tachycardia.
- **Others:** digoxin and adenosine do not fit the four classes. Digoxin slows AV conduction mainly by raising vagal tone.

A simple way to use the scheme is to ask where the rhythm originates. Ventricular rhythms respond to Class I and III drugs. Supraventricular rhythms with fast ventricular rates respond to drugs that slow the AV node, namely classes II, IV and digoxin.

Drugs by site of action

Sodium-channel blockers. Lidocaine is given intravenously for ventricular tachycardia in dogs because it acts quickly and wears off quickly. It has a narrow safety margin, and signs of excess include tremor, seizures and vomiting. Cats are generally more sensitive, so it is used with great caution. Mexiletine is an oral relative. Quinidine is used in horses for atrial fibrillation and is discussed below.

Beta-blockers. They reduce arrhythmias driven by adrenaline and slow the ventricular rate in supraventricular tachycardia. Their negative inotropic effect can precipitate or worsen heart failure in a weak heart, so they are used carefully in animals with decompensated disease. Non-selective drugs may also cause bronchospasm, which matters in cats and in animals with airway disease.

Potassium-channel blockers. Sotalol is widely used for ventricular arrhythmias in dogs. Amiodarone has many effects and a long list of adverse effects, so it is reserved for selected cases.

Calcium-channel blockers and digoxin. Diltiazem and digoxin are commonly combined to control the ventricular rate in atrial fibrillation. Digoxin has a narrow therapeutic index, and hypokalaemia and renal dysfunction increase its toxicity. Verapamil is a stronger negative inotrope and carries more risk in failing hearts.

Arrhythmias in dogs

Dogs most often present with **ventricular premature complexes** and **ventricular tachycardia**, with **atrial fibrillation** and **supraventricular tachycardia** next. Underlying causes include cardiomyopathy, mitral valve disease, myocarditis, gastric dilatation-volvulus, splenic disease, trauma, anaemia and drug effects.

Two breed examples are worth knowing. Boxers and some other breeds develop an arrhythmogenic cardiomyopathy with ventricular arrhythmias and risk of syncope. Giant breeds with dilated cardiomyopathy commonly develop atrial fibrillation, which is treated mainly by slowing the AV node rather than by restoring sinus rhythm.

Treatment is not decided by the ECG alone. Isolated, slow ventricular beats in a stable dog often need no drug. Treatment is considered when the rate is fast, the rhythm is multiform or runs of tachycardia occur, or there are signs such as weakness or collapse. Always look for and treat the cause first.

Arrhythmias in horses

Many equine athletes have physiological bradyarrhythmias, such as sinus arrhythmia and second-degree AV block, which reflect high vagal tone. These disappear with exercise and need no treatment. Do not mistake them for disease.

Atrial fibrillation is the commonest clinically important arrhythmia. It often causes poor performance and exercise intolerance in an otherwise healthy horse. In a horse with no significant heart disease, conversion to sinus rhythm can be achieved by drug therapy, for example quinidine, or by electrical cardioversion. Quinidine has real hazards: hypotension, ventricular tachycardia, gastrointestinal upset and swelling of the nasal mucosa. It also raises plasma digoxin levels, so combined use needs care. Horses are monitored closely during treatment.

Ventricular tachycardia in horses is usually secondary to myocardial disease, electrolyte disturbance or drug effect, and is treated with drugs such as lidocaine under ECG monitoring. Check the current references for protocols.

Proarrhythmia, electrolytes and safe use

Antiarrhythmic drugs can **cause** arrhythmias. This is called proarrhythmia. Drugs that prolong repolarisation can allow dangerous triggered activity, and sodium-channel blockers can slow conduction until re-entry becomes easier. This is why a drug is chosen for a documented, clinically significant rhythm, not for every abnormal beat.

Potassium and magnesium disturbances make arrhythmias worse and reduce the response to drugs. Correct hypokalaemia and hypomagnesaemia first, especially in

animals on loop diuretics. Remember that hyperkalaemia, for example in urethral obstruction or hypoadrenocorticism, can itself produce bradyarrhythmias.

Always record an ECG before, during and after therapy, and treat the underlying disease. Drug interactions matter: diuretic-induced hypokalaemia with digoxin is a classic example.

Concept cleared

Three mechanisms of arrhythmia
Abnormal automaticity, triggered activity and re-entry. Re-entry underlies most sustained tachycardias.

Vaughan-Williams classes
I sodium-channel, II beta-blocker, III potassium-channel, IV calcium-channel. Digoxin and adenosine sit outside.

Proarrhythmia
Antiarrhythmic drugs can create new arrhythmias, particularly with electrolyte disturbance or heart disease.

Treat the rhythm, and its cause
Treat when the rhythm is fast, sustained or causing signs, and always look for the underlying disease and electrolyte problem.

Memory aid: Remembering the classes
Sodium, Beta, Potassium, Calcium gives 1, 2, 3, 4 in the order S-B-P-C. Create your own phrase from these letters. Remember that sodium is first because it opens the action potential.

Compare and contrast

Vaughan-Williams classes

Class	Target	Examples	Main use
I	Sodium channel	Lidocaine, quinidine, mexiletine	Ventricular arrhythmias; quinidine for equine atrial fibrillation
II	Beta receptor	Atenolol, propranolol, esmolol	Catecholamine-driven or supraventricular tachycardia
III	Potassium channel	Sotalol, amiodarone	Ventricular arrhythmias
IV	L-type calcium channel	Diltiazem, verapamil	Slowing AV node in supraventricular rhythms

Dog versus horse arrhythmia picture

Feature	Dog	Horse
Commonest concern	Ventricular premature complexes and tachycardia	Atrial fibrillation
Benign findings	Respiratory sinus arrhythmia	Second-degree AV block, sinus arrhythmia at rest
Typical approach	Treat the cause; drug if fast or signs present	Convert in healthy horses; rate control rarely needed
Key drug caution	Lidocaine toxicity; digoxin narrow margin	Quinidine toxicity and digoxin interaction

Species notes

Dog
Ventricular arrhythmias are common and may follow splenic disease or gastric dilatation-volvulus. Atrial fibrillation in giant breeds is managed with AV node slowing.

Cat
Cats are sensitive to lidocaine, and propranolol may cause bronchospasm. Ventricular arrhythmias are less common than in dogs.

Horse
Atrial fibrillation with poor performance is the key arrhythmia.

Ruminants
Arrhythmias are mostly secondary to electrolyte, toxic or metabolic

Quinidine has marked toxicity and horses must be monitored. High vagal tone causes harmless blocks.

disease, for example hypocalcaemia, and are corrected by treating the cause.

Clinical pearls

Self-test: 10 questions

1. Which Vaughan-Williams class do beta-blockers belong to?

Class II consists of beta-blockers such as atenolol and propranolol.

2. Lidocaine is mainly used for which rhythm in dogs?

Lidocaine is a sodium-channel blocker given intravenously for ventricular arrhythmias.

3. Class III drugs act mainly by

Class III drugs, such as sotalol and amiodarone, prolong the action potential and refractory period.

4. The commonest mechanism of sustained tachyarrhythmias is

A circuit of tissue with slow conduction lets the impulse re-excite the heart repeatedly.

5. Which arrhythmia commonly causes poor performance in an otherwise healthy horse?

Atrial fibrillation is the commonest clinically important equine arrhythmia and often limits athletic work.

6. A known hazard of quinidine in horses is

Quinidine can cause hypotension, ventricular tachycardia, gastrointestinal signs and nasal mucosal swelling.

7. Proarrhythmia means

Antiarrhythmics can induce new rhythm disturbances, especially with electrolyte imbalance or heart disease.

8. Which electrolyte disturbance should be corrected before antiarrhythmic therapy?

Low potassium and magnesium promote arrhythmias and blunt drug response.

9. Digoxin slows the AV node mainly by

Digoxin has a vagomimetic action on the AV node and so slows ventricular rate in atrial fibrillation.

10. Which is true of an isolated, slow, uniform ventricular premature beat in a stable dog?

Treatment depends on rate, complexity and clinical signs, not on the presence of an ectopic beat alone.

Key points to revise

1. Arrhythmias arise from abnormal automaticity, triggered activity or re-entry.
2. Class I blocks sodium channels.
3. Class II drugs are beta-blockers.
4. Class III drugs prolong repolarisation by blocking potassium channels.
5. Class IV drugs are calcium-channel blockers that slow the AV node.
6. Antiarrhythmics can be proarrhythmic.
7. Atrial fibrillation is the key equine arrhythmia.

8. Correct electrolytes and treat the underlying disease.

Go deeper on this site

- Ch 17. Vasodilators and antihypertensive drugs (in this book)
- Ch 15. Drugs for heart failure and inotropes (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Manual: Antiarrhythmic Drugs (Vaughan Williams Classification)
- Merck Veterinary Manual: Heart Failure in Dogs and Cats
- Merck Veterinary Manual: Diuretics for Use in Animals

CHAPTER 17 OF 33

Vasodilators and antihypertensive drugs

How drugs widen blood vessels or slow the heart to lower pressure and workload: arterial, venous and mixed vasodilators, calcium-channel blockers and beta-blockers. The chapter stresses why hypotension is the central risk and how to avoid it.

After this chapter you can

- Distinguish arterial, venous and balanced vasodilators and relate each to preload and afterload
- Explain the mechanism and veterinary use of amlodipine, hydralazine, nitrates, nitroprusside and sildenafil
- Describe how beta-blockers act and why they must not be stopped suddenly or started in decompensated failure
- Contrast dihydropyridine and non-dihydropyridine calcium-channel blockers
- Identify the causes of drug-induced hypotension and how to reduce the risk

Blood pressure, preload and afterload

Blood pressure depends on cardiac output and on resistance in the arterioles. The heart works against **afterload**, which is mainly arteriolar resistance, and is filled by **preload**, which is the volume returning through the veins. Vasodilators lower pressure or cardiac workload by relaxing vascular smooth muscle.

The site of action decides the effect. **Arterial dilators** lower afterload and arterial pressure. **Venous dilators** pool blood in the veins and lower preload, which relieves pulmonary congestion. **Balanced dilators** do both. Knowing which side a drug acts on tells you when to use it and what will go wrong if the dose is too high.

In animals, systemic hypertension is most often secondary to another disease, such as chronic kidney disease or hyperthyroidism in cats, so the underlying cause must also be addressed. Vasodilators are also used in heart failure to reduce the work the failing ventricle must do.

Arterial vasodilators

Hydralazine relaxes arteriolar smooth muscle and has no useful effect on veins. Its exact molecular mechanism is not fully settled. It is potent, so the main danger is systemic hypotension, and the reflex that follows is a rise in heart rate and fluid retention by the kidney. It is therefore used with caution and often with other drugs.

Amlodipine is a calcium-channel blocker that acts mainly on small arteries. It is the calcium-channel blocker most used for hypertension in cats and dogs, especially in cats with kidney disease. It dilates arterioles strongly but has little effect on the force of cardiac contraction or on conduction, which is why it behaves very differently from diltiazem. A recognised adverse effect is gingival overgrowth.

Prazosin is an alpha-1 blocker that gives mixed dilation. Tolerance develops quickly, and it is now rarely used for primary heart disease in small animals.

A common confusion is to think all calcium-channel blockers are alike. They are not, as the next sections show.

Venous, balanced and pulmonary vasodilators

Nitroglycerin and other organic nitrates release nitric oxide, which raises cGMP in smooth muscle and relaxes it. At clinical doses the effect is mostly venous, so preload falls. Use is mainly in acute congestive failure, and evidence is largely

anecdotal. Tolerance develops with sustained use, and accidental skin exposure of handlers is a practical concern with topical forms.

Sodium nitroprusside is a very potent nitric oxide donor that dilates both arteries and veins. It is given only by infusion under close blood pressure monitoring, for hypertensive crisis or severe life-threatening failure. Because it is metabolised to cyanide, it is used only for a short period.

ACE inhibitors block formation of angiotensin II and slow breakdown of bradykinin. They are balanced dilators with a mild effect on afterload. In hypertension they are usually combined with another arterial dilator rather than used alone for severe disease. They can reduce kidney perfusion pressure and cause azotemia, especially with dehydration, diuretics or NSAIDs.

Sildenafil inhibits phosphodiesterase 5, so cGMP is not broken down. It dilates the pulmonary vessels more than the systemic ones and is used as an adjunct in canine pulmonary hypertension.

Beta-blockers

Beta-blockers compete with adrenaline and noradrenaline at beta receptors. Blocking cardiac beta-1 receptors lowers heart rate, slows atrioventricular conduction and reduces the force of contraction. Oxygen demand of the heart falls and diastolic filling time improves. They are used for fast supraventricular and some ventricular rhythms, for hypertrophic cardiomyopathy in cats, and to control the heart rate effects of hyperthyroidism.

- **Propranolol** is non-selective, blocking beta-1 and beta-2.
- **Atenolol** is beta-1 selective and is the beta-blocker used most in veterinary practice.
- **Carvedilol** blocks beta-1, beta-2 and alpha-1 receptors.

Beta-2 blockade narrows airways, so non-selective drugs should be avoided in animals with asthma or other primary airway disease. Selectivity is relative and fades at high doses, so even atenolol needs care.

Two rules matter in practice. First, a beta-blocker should never be started in an animal with active pulmonary oedema, because the heart depends on sympathetic drive at that time. Second, long use up-regulates receptors, so **abrupt withdrawal**

can cause rebound tachycardia and hypertension. Stop by tapering. Adverse effects are bradycardia, hypotension and myocardial depression, especially when systolic function is poor.

Calcium-channel blockers in the heart

Calcium entering through L-type channels triggers contraction of muscle and drives the sinus and AV nodes. Blocking these channels relaxes smooth muscle and slows nodal tissue. The class has two practical groups.

- **Dihydropyridines** such as amlodipine act mainly on vascular smooth muscle. They lower arterial pressure with little direct cardiac depression.
- **Non-dihydropyridines**, mainly **diltiazem** and verapamil, act on the heart. They have negative inotropic effect, slow the rate and slow AV conduction. Diltiazem is used for rate control in atrial fibrillation and other supraventricular tachycardias, and is of no use for ventricular arrhythmias.

Diltiazem can cause hypotension, bradycardia and worsening heart failure, and gastrointestinal upset is common with sustained-release products in cats. It should generally not be combined with a beta-blocker because both depress the node and the muscle, and the effect adds up.

Verapamil is not discussed in the sources used for this chapter, so confirm its use in a veterinary formulary.

Hypotension: why it happens and how to avoid it

Hypotension is the common thread of this chapter. It appears when an animal receives a potent dilator, when two or three drugs that lower pressure are given together, or when the animal is already dehydrated, anaesthetised or in heart failure.

- Combine drugs that lower pressure by different mechanisms, such as an ACE inhibitor with amlodipine, only after starting each low and increasing slowly.
- Diuretics add to the effect of vasodilators by lowering circulating volume.
- General anaesthetics and acepromazine are also vasodilators, so an animal on antihypertensives needs careful monitoring during anaesthesia.

- Measure blood pressure before and after changes, and check kidney values when ACE inhibitors are used.

Signs of overdose include weakness, collapse, pale mucous membranes and fainting. Very high pressure, with a systolic reading above about 160 to 180 mm Hg, can damage the eye, brain, kidney and heart, and is treated more urgently, but the treatment goal is gradual reduction, not a sudden normal value.

In practice, start with one drug at a low starting dose, recheck pressure after a suitable interval, and add a second drug only if needed. Owners should be told to report weakness, fainting or loss of appetite promptly.

Concept cleared

Concept cleared: Preload and afterload
Think of a pump filling a bucket through a narrow pipe. Preload is how full the pump gets before it pushes. Afterload is how hard the pipe resists. Venous dilators reduce the filling, arterial dilators widen the pipe, and balanced dilators do both.

Concept cleared: Two kinds of calcium-channel blocker
Amlodipine is a tap-opener for vessels: it relaxes arterioles and leaves the heart alone. Diltiazem is a brake on the heart: it slows the nodes and weakens each beat. They share a name but do different jobs.

Concept cleared: Beta-blocker withdrawal
If a driver keeps pressing the brake for weeks, the brake system becomes over-sensitive. Releasing it suddenly lets the car lurch forward. Receptors up-regulate under blockade, so sudden stopping lets adrenaline act on too many receptors.

Concept cleared: Additive hypotension

Each blood-pressure-lowering drug takes a little pressure away. Several together can take away more than the animal can spare, especially when volume is low from dehydration or diuretics.

Memory aid: Venous for volume, arterial for afterload

V for Venous and Volume (preload, relieve congestion); A for Arterial and Afterload (lower pressure). Beta-blocker rule: Brake slowly, never Brake-release suddenly. Calcium: Amlodipine Acts on Arteries; Diltiazem Decelerates the heart.

Compare and contrast

Vasodilators by site and use

Drug	Main site	Mechanism	Main concern
Hydralazine	Arterioles	Relaxes arteriolar smooth muscle	Hypotension, reflex tachycardia
Amlodipine	Arterioles	L-type calcium channel block	Gingival overgrowth, hypotension
Nitroglycerin	Veins	Nitric oxide donor, cGMP rise	Tolerance, handler exposure
Nitroprusside	Arteries and veins	Nitric oxide donor	Profound hypotension, cyanide
ACE inhibitor	Balanced	Less angiotensin II, bradykinin kept	Azotemia, hypotension
Sildenafil	Pulmonary vessels	PDE5 inhibition, cGMP kept	Systemic hypotension possible

Beta-blockers and calcium-channel blockers

Feature	Beta-blocker	Dihydropyridine CCB	Diltiazem
Example	Atenolol, propranolol	Amlodipine	Diltiazem
Main target	Cardiac beta receptors	Vascular calcium channels	Cardiac and nodal calcium channels
Heart rate	Falls	Little change	Falls
Force of contraction	Falls	Little change	Falls
Main use	Tachyarrhythmia, feline HCM	Hypertension	Supraventricular tachycardia
Key caution	Do not stop abruptly	Gingival overgrowth	Do not pair with beta-blocker

Species notes

Cat

Amlodipine is the usual first choice for hypertension, which is often secondary to kidney disease or hyperthyroidism. Atenolol is the common beta-blocker, for example in hypertrophic cardiomyopathy. Diltiazem sustained-release often causes gastrointestinal signs.

Dog

Hypertension is usually secondary to kidney disease, endocrine disease or protein-losing disease. Amlodipine and ACE inhibitors are used, and sildenafil is an adjunct for pulmonary hypertension.

Horse

Antihypertensive therapy is uncommon in routine equine practice. Acepromazine, a phenothiazine with alpha-1 blocking vasodilator effect, can cause hypotension, so it should be used

Cattle

Cardiovascular vasodilator therapy is rarely used in cattle, and no drug of this chapter is a routine food-animal treatment. Check the current notification before using any such drug in a food-producing animal.

with care in dehydrated or shocked animals.

Dog (anaesthesia)
Dogs on vasodilators or beta-blockers need blood pressure monitoring under anaesthesia, because anaesthetic drugs add to the pressure-lowering effect.

Clinical pearls

Self-test: 10 questions

1. Which drug acts mainly on veins and lowers preload at clinical doses?

Nitroglycerin releases nitric oxide and relaxes mainly venous smooth muscle.

2. Which calcium-channel blocker is mainly a vascular arteriolar dilator with little cardiac depression?

Amlodipine, a dihydropyridine, acts mainly on arterioles.

3. A recognised adverse effect of amlodipine in dogs and cats is:

Gingival overgrowth is reported with amlodipine.

4. Why should a beta-blocker not be stopped suddenly?

Long blockade up-regulates receptors, so withdrawal can cause rebound tachycardia and hypertension.

5. Which beta-blocker is beta-1 selective and most used in veterinary practice?

Atenolol is beta-1 selective and the most used.

6. Sildenafil is useful in canine pulmonary hypertension because it:

PDE5 inhibition keeps cGMP high and dilates pulmonary vessels.

7. Which combination carries the highest additive risk for conduction block and failure?

Both depress nodal conduction and contractility, so effects add up.

8. Why is nitroprusside used only for short periods?

Nitroprusside is metabolised to cyanide, so use is limited and monitored.

9. Propranolol should be avoided in animals with asthma because of:

Non-selective beta blockade narrows the airways.

10. Which situation most raises the risk of drug-induced hypotension?

Low circulating volume and additive pressure-lowering drugs together produce hypotension.

Key points to revise

1. Arterial dilators reduce afterload; venous dilators reduce preload; balanced dilators do both.
2. Hydralazine is a potent arteriolar dilator and can cause hypotension.

3. Amlodipine is a dihydropyridine calcium-channel blocker used for hypertension, with gingival overgrowth as an adverse effect.
4. Nitrates act mostly on veins through nitric oxide and cGMP, and tolerance develops.
5. Sildenafil inhibits PDE5 and is used for canine pulmonary hypertension.
6. Atenolol is beta-1 selective; propranolol is non-selective.
7. Beta-blockers must be tapered, not stopped suddenly.
8. Diltiazem slows the heart and should not be combined with a beta-blocker.

Go deeper on this site

- Ch 18. Diuretics and drugs acting on the kidney (in this book)
- Ch 16. Antiarrhythmic drugs (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Vasoactive Drugs for Use in Animals
- Merck Veterinary Manual: Antiarrhythmics for Use in Animals
- Merck Veterinary Manual: Angiotensin-Converting Enzyme Inhibitors for Use in Animals

CHAPTER 18 OF 33

Diuretics and drugs acting on the kidney

How loop, thiazide, potassium-sparing and osmotic diuretics act on different parts of the nephron, what each does to electrolytes, how the kidney handles drugs, and which drugs damage the kidney.

After this chapter you can

- Trace the nephron and state where each diuretic class acts
- Explain the electrolyte and acid-base effects of loop, thiazide and potassium-sparing diuretics

- Describe the actions, uses and cautions of mannitol and carbonic anhydrase inhibitors
- Explain filtration, secretion, reabsorption and the effect of urine pH on drug excretion
- List common nephrotoxic drugs and the factors that increase the risk

The nephron and the logic of diuretics

Each kidney nephron filters plasma at the glomerulus, and the tubule then takes back most of the filtered sodium and water. A **diuretic** blocks sodium reabsorption at some site, so more sodium stays in the tubule and water follows it. The site decides how strong the drug is, because the proximal tubule and the loop take back far more sodium than the distal parts.

- **Proximal tubule**: carbonic anhydrase inhibitors and osmotic diuretics.
- **Thick ascending loop of Henle**: loop diuretics, the strongest class.
- **Early distal tubule**: thiazides.
- **Late distal tubule and collecting duct**: potassium-sparing diuretics.

A drug acting upstream is partly compensated by downstream segments, which take back some of the sodium. This is why diuretics from different classes are sometimes combined, and why the combination raises the risk of electrolyte loss and dehydration.

Loop diuretics

Furosemide and **torsemide** block the Na-K-2Cl co-transporter in the thick ascending limb. This segment normally builds the concentration gradient in the medulla, so blocking it gives a large volume of dilute urine. The ceiling of effect is high, so the dose can be scaled from mild to life-threatening congestion.

Furosemide is the most widely used diuretic in veterinary medicine. It acts quickly and briefly, and a constant-rate infusion produces more diuresis than the same total given as boluses. Torsemide is more potent, lasts longer, and is better absorbed by mouth in dogs. It does not lose effect with repeated use as readily as furosemide.

Main uses are pulmonary oedema and ascites from congestive heart failure, and oedema or fluid overload in other conditions. Common adverse effects follow from

the mechanism:

- Loss of potassium, sodium and magnesium, and a metabolic alkalosis.
- Dehydration and a fall in blood volume, which can lower cardiac output, reduce kidney perfusion and cause azotemia.
- Hypokalaemia can increase digoxin toxicity.
- Ototoxicity at high intravenous exposure, and increased aminoglycoside toxicity.

NSAIDs blunt the diuretic effect because prostaglandins help maintain kidney blood flow. In kidney disease, higher doses of furosemide may be needed because less drug reaches the tubular site, but cautious monitoring is essential.

Thiazides and potassium-sparing diuretics

Thiazides such as hydrochlorothiazide block the Na-Cl co-transporter in the early distal tubule. They have mild to moderate potency and need adequate renal blood flow, so they work poorly when kidney perfusion is low and are not used in azotemic patients. In dogs and cats they are rarely first choice and are mostly added to a loop diuretic in refractory heart failure. Unlike loop diuretics, they reduce urinary calcium loss, and may cause hypercalcaemia. They also waste potassium. Paradoxically, thiazides reduce urine volume in diabetes insipidus, a use that is explained in the endocrine chapters.

Potassium-sparing diuretics act in the late distal tubule and collecting duct. **Spironolactone** blocks the aldosterone receptor, so fewer sodium channels and potassium pumps are made and sodium is excreted while potassium is kept. **Triamterene and amiloride** block the sodium channel directly, but are less used in animals.

These drugs are weak diuretics by themselves. Spironolactone is added in chronic heart failure for its protective effect against aldosterone-driven fibrosis, and it is never used alone for congestion. The main risk is **hyperkalaemia**, particularly together with an ACE inhibitor, in kidney disease, or without a loop diuretic. The peak effect of spironolactone takes some days.

Osmotic diuretics and carbonic anhydrase inhibitors

Mannitol is filtered at the glomerulus but is not reabsorbed. It holds water in the tubule by osmotic force, which keeps urine flowing and may protect tubular cells in

acute kidney injury. It also draws water out of tissues into the vascular space, which is why it is used to lower raised intracranial pressure. The expansion of blood volume can overload an animal that already has heart failure or pulmonary oedema, and mannitol should not be repeated if no response appears. In large adult animals, a solvent such as DMSO is sometimes substituted because mannitol is costly.

Carbonic anhydrase inhibitors such as acetazolamide act in the proximal tubule. Without carbonic anhydrase, bicarbonate is not reclaimed, so sodium bicarbonate and water are lost and the plasma becomes acidotic. The diuretic effect is weak and fades because acidosis limits it. Their modern uses are mainly outside the kidney, such as reducing aqueous humour production in glaucoma.

Common confusion: mannitol is an *osmotic* drug that needs a functioning, perfused kidney to give urine, and it should not be given to an anuric animal expecting a response.

How the kidney handles drugs

Drug elimination by the kidney is the sum of three processes. **Glomerular filtration** removes free, unbound drug, so highly protein-bound drugs are filtered poorly. **Tubular secretion** actively moves many drugs, especially organic acids such as penicillins and furosemide, into the tubule through transporters. Competition at these transporters is the basis of drug interactions, and it explains why furosemide reaches its site of action by secretion. **Tubular reabsorption** returns lipid-soluble drug to blood by passive diffusion.

Urine pH changes reabsorption because only the unionised form crosses membranes. Alkalinising the urine ionises weak acids, which are then trapped in the urine and excreted faster. Acidifying the urine does the same for weak bases. This principle is used in some poisonings.

When kidney function falls, drugs that depend on renal excretion accumulate, and the dose or interval may need adjustment. Examples are aminoglycosides and some ACE inhibitors. Always check the product information for the species and consult the current formulary.

Nephrotoxicity

The kidney is exposed to a high blood flow and concentrates drugs in the tubules, so it is a frequent target of toxicity. Important causes in animals:

- **NSAIDs** block prostaglandins that keep afferent arterioles dilated. In dehydration or low blood volume, this can cause ischaemic injury. The risk rises with ACE inhibitors and diuretics.
- **Aminoglycosides** accumulate in proximal tubular cells and cause tubular necrosis. Risk is increased by dehydration, kidney disease and prolonged use.
- **Amphotericin B** is nephrotoxic, and some tetracyclines at high exposure may harm an already damaged kidney.
- **Ethylene glycol** and lilies in cats are non-drug examples examined in toxicology.
- **Contrast agents and some chemotherapy drugs** can also injure the tubule.

Risk factors are dehydration, existing renal disease, old age, hypotension, and combinations of nephrotoxic drugs. Prevention is to correct fluid deficits first, use the lowest effective dose for the shortest time, avoid drug combinations that lower renal perfusion, and monitor urea, creatinine and urine output.

Concept cleared

Concept cleared: Why loop diuretics are strongest
Picture a motorway with three toll gates. The first gates collect most of the traffic, the last only a little. Loop diuretics shut a gate where a large share of sodium would otherwise be collected, so far more sodium and water leave. Distal drugs shut a gate where little traffic passes, so their effect is mild.

Concept cleared: Potassium loss and sparing
Sodium reabsorption in the late tubule is traded for potassium. When more sodium arrives there, as after loop or thiazide drugs, the exchange takes more potassium into the urine. Potassium-sparing drugs shut that exchange, so potassium stays in the body.

Concept cleared: Osmotic diuresis

Mannitol is like a sponge that cannot be squeezed out in the tubule. It stays inside and holds water with it, so urine flows even though sodium handling is unchanged.

Concept cleared: Ion trapping

A weak acid in alkaline urine loses its charge-free form and becomes ionised. The ionised form cannot cross back, so it is trapped in the urine and leaves the body.

Memory aid: Down the nephron

Order of sites, top to bottom: Carbonic anhydrase and Mannitol (proximal), Loop, Thiazide, Spironolactone. Think: 'Can My Little Tiny Sprout grow'. Loop wastes potassium and calcium; thiazide wastes potassium but saves calcium; spironolactone saves potassium.

Compare and contrast

Diuretic classes

Class	Site	Mechanism	Key adverse effect
Loop (furosemide, torsemide)	Thick ascending limb	Blocks Na-K-2Cl co-transporter	Low K, Na, Mg; dehydration; ototoxicity
Thiazide	Early distal tubule	Blocks Na-Cl co-transporter	Low K, high Ca, azotemia risk
Potassium-sparing (spironolactone)	Late distal and collecting duct	Aldosterone receptor block	Hyperkalaemia
Osmotic (mannitol)	Proximal tubule and loop	Non-reabsorbed osmotic load	Volume overload, dehydration if repeated
Carbonic anhydrase inhibitor	Proximal tubule	Bicarbonate not reclaimed	Metabolic acidosis

Common nephrotoxic drugs

Drug	How it harms	Main risk factor
NSAIDs	Reduced prostaglandin-dependent renal blood flow	Dehydration, hypotension
Aminoglycosides	Tubular cell uptake and necrosis	Prolonged use, kidney disease
Amphotericin B	Direct tubular injury and vasoconstriction	High cumulative exposure
Loop diuretic with aminoglycoside	Volume loss plus added toxicity	Concurrent use

Species notes

Dog
Furosemide is the standard diuretic for pulmonary oedema in heart failure, and torsemide and spironolactone are added in chronic cases. Monitor kidney values and electrolytes.

Cat
Cats are more sensitive to loop diuretics than dogs and can become dehydrated or azotaemic quickly. Facial skin lesions have been reported with spironolactone.

Horse
Furosemide is used in some conditions such as pulmonary haemorrhage and oedema. Its use in racing is regulated, so check the current rules of the governing body.

Cattle
Furosemide has been used for udder oedema. Check the current regulatory notification for permitted use and withdrawal in food-producing animals before treating.

All species
Treat dehydration before using NSAIDs or aminoglycosides, and avoid combining them with other agents that lower renal blood flow.

Clinical pearls

Self-test: 10 questions

1. Which diuretic acts on the thick ascending limb of the loop of Henle?

Furosemide blocks the Na-K-2Cl co-transporter in this segment.

2. The main risk of spironolactone is:

It spares potassium, so potassium can rise, especially with ACE inhibitors.

3. Which statement about thiazides is correct?

Thiazides reduce calcium loss and may cause hypercalcaemia.

4. Mannitol produces diuresis because it:

It acts as a non-reabsorbed osmotic load.

5. Carbonic anhydrase inhibitors cause:

Bicarbonate is lost in urine, so plasma becomes acidotic.

6. Which drug combination raises the risk of ototoxicity and nephrotoxicity?

Furosemide can potentiate aminoglycoside toxicity.

7. Why do NSAIDs risk kidney injury in a dehydrated animal?

Prostaglandin-dependent dilation of afferent arterioles is lost, causing ischaemia.

8. Alkalinising urine speeds excretion of:

Weak acids become ionised and are trapped in alkaline urine.

9. Which statement about loop diuretics is correct?

Loop diuretics waste potassium and chloride, producing alkalosis.

10. Which is a key way to reduce aminoglycoside nephrotoxicity?

Dehydration and prolonged exposure increase tubular accumulation and injury.

Key points to revise

1. Diuretics block sodium reabsorption at specific nephron sites, and water follows sodium.
2. Loop diuretics block the Na-K-2Cl co-transporter in the thick ascending limb.
3. Loop diuretics cause hypokalaemia, hyponatraemia, hypomagnesaemia and metabolic alkalosis.
4. Thiazides act in the early distal tubule and reduce calcium excretion.
5. Spironolactone blocks aldosterone receptors and can cause hyperkalaemia.
6. Mannitol is an osmotic diuretic that is filtered and not reabsorbed.
7. Acetazolamide inhibits carbonic anhydrase and produces metabolic acidosis.
8. NSAIDs and aminoglycosides are leading nephrotoxic drugs, and dehydration raises the risk.

Go deeper on this site

- Ch 19. Drugs of the urinary tract (in this book)
- Ch 17. Vasodilators and antihypertensive drugs (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Diuretics for Use in Animals
- Merck Veterinary Manual: Diuretics Used to Treat Urinary Disease in Animals
- Merck Veterinary Manual: Angiotensin-Converting Enzyme Inhibitors for Use in Animals

CHAPTER 19 OF 33

Drugs of the urinary tract

How drugs change urine chemistry and lower urinary tract function: acidifiers and alkalinisers, drugs used for stones, drugs for urinary incontinence and urethral spasm, and urinary antiseptics. The emphasis is on mechanism and on matching the drug to the stone or the sphincter problem.

After this chapter you can

- Explain how urine pH is altered and why the target pH differs with stone type
- Name the main urinary acidifiers and alkalinisers and state their cautions
- Describe medical dissolution and prevention of struvite, urate, cystine and calcium oxalate uroliths
- Match drugs for urinary incontinence and urethral spasm to the receptor or muscle they act on
- Explain how methenamine and nitrofurantoin work as urinary antiseptics and where they fail

Why urine chemistry is a drug target

The urinary tract can be treated from two directions. One is the **chemistry of the urine**: its pH, volume and the concentration of dissolved minerals. The other is the **nerve and muscle control** of the bladder and urethra. Drugs in this chapter act on one or the other.

Urine pH matters because crystals form only when a mineral is present above its solubility, and solubility depends strongly on pH. Struvite dissolves in acid urine and precipitates in alkaline urine. Urate and calcium oxalate behave differently, so one pH target cannot suit every stone. Before giving any drug that changes urine pH, the stone type or the problem being treated must be known.

A common confusion is to treat a urine pH number as a disease. It is only a tool. Diet, urine volume, infection and the frequency of urination often matter as much as the drug.

Urinary acidifiers

Acidifiers lower urine pH by giving the body an acid load that the kidney then excretes. The usual agents are **ammonium chloride** and **dl-methionine**. They are preferred when struvite (magnesium ammonium phosphate) stones or crystals are the concern. Dietary acidification is often used alongside or instead of drugs.

Acidification also helps when a urinary antiseptic such as methenamine needs acid urine to work, and it can increase the renal excretion of weak bases through ion trapping. This links back to the earlier chapter on drug excretion.

The main caution is that **chronic acidification produces systemic metabolic acidosis**. In animals with kidney disease, or in young growing animals, this can be harmful. Acidifiers should not be started without a full clinical evaluation and should be monitored. Ammonium compounds are also unsuitable where hepatic function is poor, because the ammonium load must be handled by the liver.

In cats, struvite plugs causing urethral obstruction have also been flushed through a catheter with an acidic solution (Walpole's solution). This is a local, not systemic, use of acid.

Urinary alkalinisers

Alkalinisers raise urine pH. **Potassium citrate** is the most useful. Citrate is metabolised to bicarbonate, which makes the urine more alkaline. It is given with food.

Potassium citrate has a second action that is easy to miss: citrate binds calcium to form more soluble salts, so it also **inhibits calcium oxalate crystal formation**. This is why it is used both for urate stones and as part of calcium oxalate prevention. Sodium bicarbonate is another alkaliniser, but the sodium load is a problem in animals with heart or kidney disease or hypertension.

Alkalinisation is used for urate stones, for example in Dalmatians and in dogs with portosystemic shunts, where excess ammonium urate is excreted. It also improves

the activity of some drugs (aminoglycosides work better in alkaline urine) and speeds excretion of weak acids.

Allopurinol is often mentioned alongside these drugs but is not an alkaliniser. It inhibits xanthine oxidase and reduces uric acid production. Its use needs a low-purine diet, otherwise xanthine stones can form.

Drugs and diet for uroliths

Stones are named by their main mineral: struvite, calcium oxalate, urate, cystine, silica and others. Identifying the mineral guides treatment. Struvite, urate and cystine stones can be **dissolved medically** by changing urine composition, which works best for bladder stones with a compliant owner. Calcium oxalate stones cannot be dissolved and must be removed, then prevention is attempted.

Struvite. In dogs these stones are usually linked to urease-producing bacteria such as *Staphylococcus*. The bacteria split urea into ammonia, raising pH and favouring struvite. Treatment is therefore an effective antibiotic chosen by culture plus a dissolution diet. In cats, sterile struvite stones are common and diet alone is often enough.

Urate. Allopurinol and urine alkalinisation, with diet.

Cystine. These form in animals with an inherited tubular defect and are managed with diet, alkalinisation and thiol-containing binding drugs.

Calcium oxalate. Prevention rests on increasing water intake and dilute urine, avoiding acidifying diets, and potassium citrate where indicated.

Dissolution fails when infection is uncontrolled, when the owner feeds other food, or when the stone is not constantly bathed in urine, as in urethral or kidney stones. Radiography and ultrasound, urinalysis and culture are repeated during treatment. Specific protocols follow consensus guidelines.

Incontinence and urethral spasm

Storage and voiding depend on the detrusor muscle (bladder wall) and the urethral sphincters. Parasympathetic muscarinic receptors contract the detrusor. Sympathetic alpha-1 receptors tighten the internal urethral sphincter and beta

receptors relax the detrusor. The external sphincter is skeletal muscle under somatic control.

Urethral sphincter mechanism incompetence is the commonest cause of urinary leakage in spayed bitches. The aim is to raise urethral tone. **Phenylpropanolamine**, an indirect alpha-agonist, does this. Its side effects include restlessness, hypertension and tachycardia. **Oestrogens** (for example estriol) are thought to increase alpha-receptor sensitivity of the urethral smooth muscle. High oestrogen exposure risks bone marrow toxicity in dogs, so the choice of agent matters.

Detrusor instability (urge incontinence) is treated with antimuscarinic drugs such as oxybutynin or propantheline, which relax the detrusor. **Detrusor atony**, with a weak, overfilled bladder, needs a parasympathomimetic such as bethanechol, but only after any obstruction is excluded, because bethanechol against a blocked urethra is dangerous.

Urethral spasm or functional obstruction, particularly in male cats and dogs, is treated by relaxing the sphincter. Alpha-1 blockers (prazosin, phenoxybenzamine) relax the internal sphincter. Skeletal muscle relaxants such as diazepam or dantrolene act on the external sphincter. Hypotension is the main side effect of alpha blockers.

Urinary antiseptics

Urinary antiseptics are drugs that act mainly within the urine and lower tract and achieve little effect elsewhere in the body. They are used for lower urinary tract infection, not for kidney or systemic infection.

Methenamine (as hippurate or mandelate) is inactive until it breaks down in acid urine into **formaldehyde**, which kills bacteria non-specifically. So it needs a urine pH low enough, and it should not be combined with sulfonamides, which can precipitate with formaldehyde. Resistance is unlikely because the action is non-specific. Its role is chiefly long-term prevention of recurrent infection, not treatment of an active infection.

Nitrofurantoin is excreted in the urine in active form and reaches high concentrations there while blood levels stay low. It is less effective in alkaline urine and in renal failure, where it fails to concentrate and may accumulate.

Gastrointestinal upset is the common side effect, and long-term use can damage the lung and nerves in humans.

Indian availability and legal status of these products vary, so check the current notification and product listings before prescribing. In all cases urine culture and sensitivity should guide therapy, and antimicrobial stewardship applies equally to urinary infections.

Concept cleared

pH follows the stone
Struvite dissolves in acid urine; urate and cystine dissolve better in alkaline urine. Always name the stone before choosing the pH direction.

Citrate does two jobs
Potassium citrate raises urine pH and also binds calcium into soluble salts, so it helps against urate and calcium oxalate stones.

Sphincter versus detrusor
Leakage from a weak sphincter needs more urethral tone (alpha-agonist). Retention from a spastic sphincter needs relaxation (alpha-blocker). Detrusor drugs go the other way.

Antiseptic means local
Methenamine and nitrofurantoin work in urine, not in tissues. They suit cystitis prevention, not pyelonephritis or septicaemia.

Memory aid: STRUVITE loves ACID
Struvite dissolves in acid, forms in alkaline, infected urine. Urate and cystine are the opposite: alkalinise.

Compare and contrast

Acidifiers versus alkalinisers

Feature	Acidifiers	Alkalinisers
Examples	Ammonium chloride, dl-methionine	Potassium citrate, sodium bicarbonate
Main stone target	Struvite	Urate, cystine, calcium oxalate prevention
Main risk	Metabolic acidosis	Sodium or potassium load, struvite if infection present
Drug effect on antimicrobials	Helps methenamine, nitrofurantoin	Helps aminoglycosides

Drugs for bladder and urethral dysfunction

Problem	Drug type	Example
Weak urethral sphincter	Alpha-agonist, oestrogen	Phenylpropanolamine, estriol
Unstable detrusor	Antimuscarinic	Oxybutynin, propantheline
Atonic bladder	Parasympathomimetic	Bethanechol
Urethral spasm	Alpha-1 blocker, skeletal relaxant	Prazosin, diazepam

Species notes

Dogs

Struvite stones are usually infection-related; treat the infection as well as the diet. Dalmatians form urate stones. Spayed bitches commonly respond to sphincter-tightening drugs.

Cats

Sterile struvite stones and plugs are common and often dissolve on diet. Calcium oxalate is increasingly common, and over-acidifying diets may favour it.

Ruminants

Horses

Urolithiasis in male goats, sheep and steers causes obstruction at the urethral process or sigmoid flexure. Ammonium chloride is used in feed in some herds for prevention; check the current guidance.

Urolithiasis is less common; stones are usually calcium carbonate in alkaline urine. Herbivore urine is naturally alkaline, so acidifying is hard.

Birds

Birds excrete uric acid, not urea, so urate handling is normal; use of small animal urinary drugs is not routine.

Clinical pearls

Self-test: 10 questions

1. Which stone type is best dissolved in acid urine?

Struvite is more soluble at lower pH, and acid diets dissolve it. Calcium oxalate cannot be dissolved medically.

2. A main risk of chronic urinary acidification is:

Acid load leads to systemic acidosis, especially in animals with kidney disease.

3. Potassium citrate helps prevent calcium oxalate stones because it:

Citrate complexes calcium, and it also raises urine pH.

4. Allopurinol acts by:

Blocking xanthine oxidase reduces uric acid production.

5. Phenylpropanolamine is used for:

It is an alpha-agonist that increases urethral smooth muscle tone.

6. Which drug is an antimuscarinic for detrusor instability?

Oxybutynin relaxes the detrusor; bethanechol does the opposite.

7. Bethanechol must not be used when:

It contracts the detrusor and can rupture the bladder against an obstruction.

8. Methenamine is active because it:

In acid urine methenamine breaks down to formaldehyde, a non-specific antibacterial.

9. Which is an alpha-1 blocker used for functional urethral obstruction?

Prazosin relaxes the internal urethral sphincter.

10. Nitrofurantoin is a poor choice in:

Reduced renal function means the drug does not concentrate in urine and may accumulate.

Key points to revise

1. Struvite dissolves in acid urine.
2. Ammonium chloride and dl-methionine acidify urine.
3. Chronic acidification can cause metabolic acidosis.
4. Potassium citrate alkalinises and binds calcium.
5. Allopurinol inhibits xanthine oxidase and is used for urate stones.

6. Phenylpropanolamine increases urethral tone.
7. Oxybutynin relaxes the detrusor.
8. Methenamine releases formaldehyde in acid urine.

Go deeper on this site

- Ch 20. Haematinics, anticoagulants, coagulants and blood substitutes (in this book)
- Ch 18. Diuretics and drugs acting on the kidney (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Controlling Urine pH in Animals
- Merck Veterinary Manual: Overview of Urolithiasis in Small Animals
- Merck Veterinary Manual: Urolithiasis in Dogs

CHAPTER 20 OF 33

Haematinics, anticoagulants, coagulants and blood substitutes

Drugs that build red cells (iron, vitamin B12), prevent clotting (heparin, warfarin), promote clotting (vitamin K, tranexamic acid) and restore blood volume or clotting factors (plasma and plasma expanders), with the mechanism and clinical logic behind each.

After this chapter you can

- Explain why iron deficiency and vitamin B12 deficiency give different types of anaemia
- Describe how heparin and warfarin prevent clotting and why their monitoring differs
- Explain the role of vitamin K in clotting factor synthesis and its use in rodenticide poisoning
- Describe how tranexamic acid works as an antifibrinolytic

- Distinguish crystalloids, colloids and plasma products and the situations for each

Haematinics and the idea of building blood

A **haematinic** supplies a nutrient needed to make red blood cells. The nutrient must be the one that is actually missing, so the first step is to find the cause of the anaemia. Giving iron to an animal whose anaemia comes from another cause is useless, and iron overload is harmful.

The red cell appearance shows the problem. **Iron deficiency** gives small, pale cells (microcytic, hypochromic) because haemoglobin cannot be made. **Vitamin B12 or folate deficiency** gives large immature cells (macrocytic, megaloblastic) because DNA synthesis and cell division fail. Erythropoietin, made by the kidney, drives red cell production, and a failing kidney is a cause of non-regenerative anaemia.

Always ask why the deficiency exists. In animals, iron deficiency usually means chronic blood loss, for example from heavy parasite burdens such as hookworms, ticks or haemonchosis, or from a bleeding gastrointestinal lesion. Treating the loss is as important as supplying the iron.

Iron

Iron is the central atom of haem, and it is also needed for myoglobin and many enzymes. Oral iron, usually ferrous salts, is absorbed in the duodenum. Absorption is better in the fasting state, but giving iron with food reduces gastric upset. The body has no efficient way to excrete iron, so absorption is regulated and storage is as ferritin.

Oral iron suits dietary deficiency and mild chronic loss. Treatment is slow, and takes weeks to months to rebuild red cell mass and stores. **Parenteral iron**, such as iron dextran, is used for initial treatment when oral drug is not tolerated or not practical, and in young animals.

Newborn piglets are the classic example. Sow's milk has little iron and piglets grow rapidly, so without supplementation they develop anaemia in the first weeks.

Adverse effects are dose-related. Oral iron causes gastrointestinal upset, and large overdoses cause serious injury to the gut, heart and liver. Injection can be painful

and can stain tissue. Iron should not be given to an animal with a normal iron status. Erythropoietic drugs used in chronic kidney disease work only if iron is available, so iron is usually given with them.

Vitamin B12 and erythropoietic drugs

Vitamin B12 (cobalamin) is needed for DNA synthesis and for red cell maturation. Animals depend on gut microbes or diet for it. In ruminants, rumen bacteria make B12 from **cobalt**, so cobalt-deficient pasture produces B12 deficiency, poor appetite and ill-thrift, and the treatment is cobalt or B12 supply. Cobalt deficiency is a regional problem, so local advice should be sought.

In dogs and cats, deficiency is mostly due to poor absorption, for example in inflammatory bowel disease or exocrine pancreatic insufficiency, since B12 uptake in the ileum needs intrinsic factor and healthy mucosa. The answer is injection, because oral supplementation will not overcome a malabsorption defect fully. Toxicity of B12 is very low.

Erythropoiesis-stimulating agents such as epoetin and darbepoetin are used for anaemia of chronic kidney disease. A serious problem is that animals may make antibodies against the product that also neutralise their own erythropoietin, causing pure red cell aplasia. This is why the drug is used selectively and with monitoring.

Anticoagulants: heparin and warfarin

Clotting is a cascade in which each factor activates the next, ending in thrombin converting fibrinogen to fibrin. Anticoagulants prevent new clots or extension of existing ones. They do not dissolve a clot that is already formed.

Heparin works at once and only by injection. It binds **antithrombin** and speeds up its inhibition of thrombin (factor IIa) and factor Xa. Unfractionated heparin acts on both, while **low-molecular-weight heparins** such as enoxaparin and dalteparin act mainly on Xa and have a more predictable effect. Heparin is used for thromboembolic disease and in disseminated intravascular coagulation, and to keep catheters and circuits patent. The therapeutic window is narrow, and monitoring uses clotting time (ACT, aPTT) or anti-Xa activity. The main complication is bleeding. **Protamine** neutralises heparin.

Warfarin blocks vitamin K epoxide reductase, so the liver cannot recycle vitamin K and makes inactive factors II, VII, IX and X. Effect is delayed by days because existing factors must first be used up. Warfarin has great variation between individuals and a narrow therapeutic index, and it is no longer recommended for routine veterinary use because safer alternatives exist. The same mechanism, however, explains **anticoagulant rodenticide poisoning**, which is common in dogs.

Coagulants: vitamin K and tranexamic acid

Vitamin K (phytonadione) is the cofactor for the liver enzyme that adds carboxyl groups to factors II, VII, IX and X, which they need in order to bind calcium and work. It is the specific antidote to warfarin-type rodenticides, to dicoumarol poisoning from spoiled sweet clover in cattle, and it is used in liver failure or deficiency. It does not act at once, because new factors take hours to be made, so plasma products may be needed in a bleeding animal. After second-generation rodenticide poisoning, treatment is continued for weeks, since these compounds persist. Intravenous injection has been linked to anaphylactoid reactions with some products, and intramuscular injection can bleed into muscle.

Tranexamic acid is an antifibrinolytic. It blocks the lysine-binding sites of plasminogen, so plasmin cannot form and bind to fibrin, and clots persist. It is used where excess clot breakdown contributes to bleeding, including surgery and some haemorrhage. Adverse effects include vomiting and a risk of thrombosis, and the dose must be reduced in kidney failure.

A frequent confusion: vitamin K helps the clotting factors to be made, while tranexamic acid protects the clot from breakdown. They act at different stages and are not interchangeable.

Blood substitutes and plasma expanders

In haemorrhage or shock, the first need is to restore circulating volume and then oxygen-carrying capacity or clotting factors if they are lacking.

- **Crystalloids** such as balanced electrolyte solutions and normal saline spread rapidly into the whole extracellular space, so only a fraction stays in the vessels. They are first-line for most dehydration and shock.

- **Colloids** such as hydroxyethyl starch and gelatin contain large molecules that hold water in the vessels by oncotic pressure, and so expand plasma volume longer. Starch products can impair clotting and have been linked to kidney injury in some patients, so use is selective and the current product guidance should be checked.
- **Plasma products** such as fresh frozen plasma supply clotting factors, albumin and antithrombin. They are used for coagulopathies, including rodenticide poisoning with active bleeding.
- **Whole blood or red cell concentrate** replaces oxygen-carrying capacity, and needs blood typing or cross-matching, especially in cats and in dogs that have been transfused before.

All transfusions risk allergic, febrile and lung injury reactions, and infusion must be slowed in animals that cannot tolerate fluid overload, such as those with heart disease.

Concept cleared

Concept cleared: Microcytic versus macrocytic anaemia
Haemoglobin is like paint, and cell division is like cutting fabric. Without iron the cells are made on time but are small and pale because there is little paint. Without B12 the cutting stalls, so cells grow big and immature before dividing.

Concept cleared: Heparin versus warfarin
Heparin is a hand on the brake of already-circulating factors, so it works at once. Warfarin stops the factory from making new factors, so it works only after the old stock runs out, which takes days.

Concept cleared: Vitamin K as a charger
Factors II, VII, IX and X are made as flat batteries and need vitamin K to charge them. Warfarin and rodenticides block recharging, and vitamin K restores it, though new batteries still take hours to make.

Concept cleared: Crystalloid versus colloid

Crystalloids are like water poured onto a garden, which soaks into everything. Colloids are like water in a sponge, which stays in the vessel for longer because large molecules hold it there.

Memory aid: Vitamin K factors

Factors 1972 depend on vitamin K: II, VII, IX, X (ten, nine, seven, two). For anaemia size: Iron gives Itty-bitty cells, B12 gives Big cells. Heparin is Hurried (fast, injection); Warfarin is Waiting (slow, days).

Compare and contrast

Haematinics and clotting drugs

Drug	Action	Main use	Key caution
Iron	Supplies haem iron	Iron-deficiency anaemia, piglets	GI upset, overload toxicity
Vitamin B12	DNA synthesis, red cell maturation	Malabsorption, cobalt deficiency	Very low toxicity
Heparin	Enhances antithrombin; inhibits IIa and Xa	Thromboembolism, DIC	Bleeding; monitor clotting
Warfarin	Blocks vitamin K recycling	Historic anticoagulant; rodenticide mechanism	Narrow index; no longer recommended
Vitamin K	Allows synthesis of II, VII, IX, X	Rodenticide, dicoumarol, liver failure	Delay of hours; IV reactions
Tranexamic acid	Blocks plasminogen binding to fibrin	Hyperfibrinolytic bleeding	Thrombosis risk, vomiting

Fluids for volume replacement

Product	Stays in vessels	Provides	Main concern
Crystalloid	Short time	Water and electrolytes	Oedema if excessive
Colloid (starch, gelatin)	Longer	Oncotic volume support	Clotting effects, kidney injury risk
Plasma product	Longer	Clotting factors, albumin	Allergic and transfusion reactions
Whole blood or red cells	Yes	Oxygen-carrying capacity	Blood typing, reactions

Species notes

Pig

Piglets raised without access to soil are given iron early, as sow milk is low in iron, and untreated piglets develop anaemia.

Cattle and sheep

Rumen bacteria need cobalt to produce vitamin B12, so cobalt-poor pasture causes deficiency. Spoiled sweet clover contains dicoumarol and causes bleeding, treated with vitamin K.

Dog

Anticoagulant rodenticide poisoning is a common emergency, treated with vitamin K and plasma if bleeding. Cobalamin deficiency is seen with malabsorptive bowel disease.

Cat

Cats have distinct blood types and may carry naturally occurring antibodies, so type or cross-match before transfusion. Heparin is given by subcutaneous route in sources reviewed.

Horse

Anaemia is investigated for blood loss or chronic disease before iron is given, since iron therapy is rarely needed and excess can be harmful.

Clinical pearls

Self-test: 10 questions

1. Iron deficiency anaemia produces:

Without iron, haemoglobin cannot be made, so cells are small and pale.

2. Which clotting factors depend on vitamin K?

Factors II, VII, IX and X need vitamin K for carboxylation.

3. Heparin works by:

Heparin binds antithrombin, increasing inhibition of thrombin and factor Xa.

4. Why does warfarin take days to act?

It stops new factor synthesis, and the circulating factors decay over days.

5. The antidote for heparin overdose is:

Protamine binds and neutralises heparin.

6. Tranexamic acid acts by:

This prevents plasmin formation and fibrin breakdown.

7. Why do piglets need iron supplementation?

Low milk iron and fast growth lead to anaemia without supplementation.

8. Cobalt deficiency in cattle causes disease because:

Cobalt is a component of vitamin B12 made by rumen bacteria.

9. In active bleeding from rodenticide poisoning, vitamin K alone may be insufficient because:

Plasma products give factors immediately while vitamin K takes effect.

10. Which fluid stays in the vessels longest?

Large molecules hold water in the vessels by oncotic pressure.

Key points to revise

1. Iron deficiency causes microcytic hypochromic anaemia; B12 deficiency causes macrocytic anaemia.
2. Piglets need supplementary iron because sow milk contains little.
3. Ruminants need cobalt to make vitamin B12.
4. Heparin enhances antithrombin and inhibits thrombin and factor Xa; protamine reverses it.
5. Warfarin inhibits vitamin K recycling and is no longer recommended for routine use.
6. Vitamin K is needed for factors II, VII, IX and X and is the antidote for anticoagulant rodenticides.
7. Tranexamic acid is an antifibrinolytic that blocks plasminogen binding.
8. Crystalloids leave the vessels quickly; colloids and plasma products stay longer.

Go deeper on this site

- Ch 21. Respiratory drugs (in this book)
- Ch 19. Drugs of the urinary tract (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index

- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Drugs Acting on the Blood or Blood-Forming Organs in Animals
- Merck Veterinary Manual: Systemic Pharmacotherapeutics of the Cardiovascular System
- Merck Veterinary Manual: Pharmacology

CHAPTER 21 OF 33

Respiratory drugs

How drugs act on the airways: bronchodilators, mucolytics, expectorants, antitussives, decongestants and respiratory stimulants. The chapter stresses why a cough or wheeze should be treated at its cause, and where each class helps or harms.

After this chapter you can

- Explain how beta-2 agonists, anticholinergics and methylxanthines relax airway smooth muscle
- Distinguish mucolytics from expectorants and state the evidence behind each
- Describe when a cough should and should not be suppressed
- Explain why decongestants are rarely used in animals and why some are dangerous
- Describe the action and limits of doxapram as a respiratory stimulant

Principles of respiratory drug therapy

Respiratory signs such as cough, wheeze, nasal discharge and laboured breathing are **symptoms**, not diagnoses. Drugs that act on the airway are mostly supportive. The main treatment is usually the removal of the cause: an antimicrobial for bacterial pneumonia, a glucocorticoid and environmental change for equine asthma, a diuretic for cardiogenic pulmonary oedema.

The drug classes in this chapter are grouped by the goal: open the airway (bronchodilators), thin or move secretions (mucolytics and expectorants), quieten the cough reflex (antitussives), clear the nose (decongestants) and drive breathing (respiratory stimulants). Anti-inflammatory and antimicrobial drugs are covered in other chapters.

A useful habit is to ask before prescribing: is the airway narrowed by muscle spasm, by mucus, by oedema, or by inflammation? A bronchodilator helps only the first. This single question prevents most prescribing errors.

Bronchodilators

Airway smooth muscle is controlled by two opposing signals. Parasympathetic fibres release acetylcholine, which acts on muscarinic M_3 receptors and causes contraction. Beta-2 adrenergic receptors, linked to Gs and a rise in cAMP, cause relaxation. Bronchodilators either stimulate the relaxing pathway or block the constricting one.

- **Beta-2 agonists** such as salbutamol (albuterol), terbutaline and clenbuterol raise cAMP in smooth muscle and relax it. Inhaled salbutamol is a rescue drug for acute bronchoconstriction. Long-acting agents such as salmeterol are slow in onset and are not for acute rescue.
- **Anticholinergics** block muscarinic receptors. Atropine does this but also causes tachycardia, dry mucus and gut stasis. Ipratropium is a quaternary derivative that is poorly absorbed after inhalation, so systemic effects are less likely.
- **Methylxanthines** such as theophylline and aminophylline inhibit phosphodiesterase, so cAMP is not broken down, and they block adenosine receptors. They have a narrow safety margin.

Common confusion: a bronchodilator does *not* treat inflammation. Beta-2 agonists used alone in chronic asthma can leave the inflammation uncontrolled, so they are combined with a glucocorticoid. Also, airflow may stay poor despite a bronchodilator when the real problem is mucus plugging or wall oedema.

Mucolytics and expectorants

These two terms are often mixed up. **Mucolytics** change the mucus itself, making it less viscous. **Expectorants** are meant to increase the volume or the clearance of

secretions so that the cough becomes more productive.

Acetylcysteine is the classic mucolytic. It breaks disulphide bonds in mucoprotein, so mucus thins. Given as a nebulised solution, it can cause reflex bronchoconstriction, so a bronchodilator is given first. Bromhexine and its metabolite ambroxol, and dembrexine in some countries for horses, alter mucus structure and improve mucociliary clearance. Check the products licensed locally.

Traditional expectorants include ammonium salts, iodides such as potassium iodide, and volatile oils such as eucalyptus. They are believed to stimulate secretion through a reflex from the stomach, but well-designed studies in animals are lacking. Iodide products should not be given to pregnant, hyperthyroid or lactating animals because iodine crosses the placenta and enters milk.

Guaifenesin is a centrally acting muscle relaxant. It may be listed as an expectorant, but its benefit on secretion is uncertain.

Note that the most reliable aid to mucus clearance is simple: good hydration, humidified air, and, where possible, controlling dust and ammonia in the housing. Systemic dehydration makes mucus thicker.

Antitussives

Cough is a protective reflex. It clears secretions and foreign material, so a **productive** cough should not be suppressed. Suppressing it can let mucus pool in the lung and allow infection to persist.

Antitussives are suitable for a dry, unproductive, exhausting cough, such as one caused by tracheal collapse or chronic bronchitis where it disturbs rest, or when the cough itself keeps irritating the airway. Most act on the cough centre in the medulla.

- **Opioids** such as codeine, hydrocodone and butorphanol are the commonest. Butorphanol is a potent antitussive in dogs but causes sedation. Codeine slows gut motility and should be avoided after intestinal surgery.
- **Maropitant**, an NK1 antagonist, has reduced coughing in dogs with chronic bronchitis in a study, which fits the role of substance P in the cough pathway.
- **Dextromethorphan** is widely used in people but is poorly effective in dogs because of its short half-life and poor oral bioavailability.

Remember that opioid antitussives are controlled substances in India. Check the current regulations on storage and prescription before use.

Cough in animals usually points to disease such as kennel cough, bronchitis, feline or equine asthma, or heart disease. In a cardiac patient, a cough caused by left atrial enlargement pressing on the bronchus is treated by managing the heart, not by suppressing the cough alone.

Decongestants

Nasal decongestants are alpha-adrenergic agonists such as phenylephrine, oxymetazoline and pseudoephedrine. They constrict the blood vessels of the nasal mucosa, reduce swelling and open the nasal passage. They are used rarely in animals.

There are three reasons for caution. First, most nasal obstruction in animals is caused by infection or a foreign body, and these need their own treatment. Second, topical decongestants can cause **rebound congestion** if used for more than a few days, because the vessels dilate again when the drug wears off. Third, oral pseudoephedrine and similar sympathomimetics are toxic to dogs and cats. Accidental ingestion of human cold tablets causes agitation, tachycardia and hypertension, and is a recognised poisoning in small animals. Many human cold products also contain paracetamol, which is dangerous in cats.

Antihistamines are sometimes used for allergic rhinitis, but their benefit in animals is modest.

The practical message for students: never hand an owner a human cold remedy for a pet, and treat the cause of nasal discharge rather than the discharge.

Respiratory stimulants and oxygen

Doxapram is the main respiratory stimulant in veterinary practice. At low doses it stimulates the peripheral chemoreceptors in the carotid and aortic bodies, and at higher doses it stimulates the respiratory centre in the medulla. It is used to hasten recovery of breathing after anaesthesia and, in some practices, to stimulate newborn animals that are slow to breathe.

Its limits matter more than its uses. The effect is short, so respiratory depression can return when it wears off, particularly when the depressant drug is long-acting. Stimulating breathing increases oxygen demand, and it can cause excitement, hypertension and arrhythmia. It does not replace ventilation, airway clearance or oxygen. In a hypoxic animal, the first steps are a clear airway, oxygen and, where needed, assisted ventilation.

When the cause is an opioid, a specific antagonist such as naloxone is more logical. When the cause is an alpha-2 agonist, atipamezole is the specific reversal. A non-specific stimulant is the second choice.

Methylxanthines such as caffeine are used in human neonates for apnoea. Do not extend this to animals without a veterinary source.

Concept cleared

Concept cleared: Bronchodilator is not an anti-inflammatory
A bronchodilator loosens the tight muscle ring round a pipe. It does not clean the rust or the sludge inside it. If the airway is narrowed by swelling and mucus, relaxing the muscle gives only partial relief, so an anti-inflammatory is also needed.

Concept cleared: Mucolytic versus expectorant
A mucolytic is like adding water to thick paste so it flows. An expectorant is meant to make the body produce more fluid mucus or move it out. The first changes the mucus, the second targets the secretion process.

Concept cleared: Why not to suppress a productive cough
A cough is the airway's broom. Taking away the broom from a dirty floor does not clean the floor. Suppress only a dry, useless cough that harms the animal.

Concept cleared: Rebound congestion

A topical decongestant squeezes nasal vessels shut. When its effect ends, the vessels spring open wider than before, like a spring held down. Long use makes the nose worse.

Memory aid: Open, thin, quiet, clear, drive

Five goals in order: Open the airway (bronchodilators), Thin the mucus (mucolytics and expectorants), Quiet the cough (antitussives), Clear the nose (decongestants), Drive the breathing (stimulants). Remember: B, M, A, D, R.

Compare and contrast

Bronchodilator classes

Class	Examples	Mechanism	Main caution
Beta-2 agonist	Salbutamol, terbutaline, clenbuterol	Gs, raises cAMP, relaxes smooth muscle	Tachycardia, tremor, tolerance; does not control inflammation
Anticholinergic	Ipratropium, atropine	Blocks M3 muscarinic receptors	Atropine dries mucus and slows gut; ipratropium has fewer systemic effects
Methylxanthine	Theophylline, aminophylline	Inhibits phosphodiesterase, blocks adenosine receptors	Narrow safety margin

Mucolytic versus expectorant versus antitussive

Class	Goal	Example	Use when
Mucolytic	Thin mucus	Acetylcysteine, bromhexine	Thick, hard-to-clear secretions
Expectorant	Aid clearance of secretions	Ammonium salts, iodides, volatile oils	Evidence in animals is weak
Antitussive	Suppress cough reflex	Butorphanol, codeine, hydrocodone	Dry, unproductive, distressing cough only

Species notes

Dog

Dry coughs of tracheal collapse and chronic bronchitis may be given an opioid antitussive. Accidental ingestion of human decongestants or a chewed salbutamol inhaler can cause severe tachycardia and low potassium.

Cat

Feline asthma is treated with inhaled glucocorticoid and a bronchodilator by spacer and mask. Codeine is poorly suited to cats, and human cold medicines containing paracetamol are dangerous.

Horse

Equine asthma is managed first by reducing dust in hay and stable. Inhaled bronchodilators and glucocorticoids are used, and clenbuterol is a bronchodilator whose use in competition horses is subject to medication rules.

Cattle

Respiratory disease in calves is mostly infectious, so antimicrobials and supportive care matter more than bronchodilators or antitussives. Check withdrawal periods before using any drug in food animals.

Neonates

A newborn that does not breathe needs airway clearing, stimulation, warmth and oxygen first. Doxapram is only an adjunct.

Clinical pearls

Self-test: 10 questions

1. Which receptor mediates airway smooth muscle relaxation when stimulated by salbutamol?

Beta-2 receptors act through Gs and raise cAMP, relaxing smooth muscle.

2. Why is ipratropium preferred to atropine for inhalation?

Ipratropium is a quaternary derivative with poor absorption after inhalation.

3. A mucolytic acts by:

Mucolytics such as acetylcysteine break bonds in mucus and thin it.

4. Acetylcysteine nebulisation may cause which problem?

Aerosolised acetylcysteine can trigger bronchospasm, so a bronchodilator is given first.

5. Which cough is most suited to an antitussive?

Productive coughs clear secretions and should not be suppressed.

6. A problem with long use of topical nasal decongestants is:

Vessels dilate again beyond baseline when the vasoconstrictor wears off.

7. Which statement about human decongestants is correct?

Oral sympathomimetics such as pseudoephedrine cause serious toxicity in small animals.

8. Doxapram stimulates breathing mainly by acting on:

Low doses act on carotid and aortic body chemoreceptors, higher doses on the medulla.

9. In an animal with opioid-induced respiratory depression, the most logical drug is:

A specific antagonist reverses the cause; a non-specific stimulant is second choice.

10. Why can a bronchodilator fail to relieve airflow obstruction?

Obstruction from wall oedema and mucus is not relieved by muscle relaxation alone.

Key points to revise

1. Respiratory drugs are mostly symptomatic and supportive.
2. Beta-2 agonists relax airway smooth muscle by raising cAMP.
3. Anticholinergics block muscarinic constriction; ipratropium is poorly absorbed.
4. Methylxanthines inhibit phosphodiesterase and have a narrow safety margin.
5. Mucolytics change the mucus; expectorant evidence in animals is weak.
6. Antitussives are for dry, unproductive coughs only.
7. Topical decongestants cause rebound congestion; oral ones are toxic to small animals.
8. Doxapram stimulates chemoreceptors and the medulla but is short-acting.

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- Ch 23. Laxatives, purgatives, antidiarrhoeals and probiotics (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Inhalation Treatment of Airway Disease in Animals
- Merck Veterinary Manual: Expectorants and Mucolytic Drugs in Animals
- Merck Veterinary Manual: Antitussive Drugs in Animals

CHAPTER 22 OF 33

Gastric acid suppressants, antiemetics and prokinetics

How drugs reduce gastric acid, protect ulcerated mucosa, stop vomiting and speed up gut emptying. The chapter links each drug to its receptor or pump target so that the choice in a vomiting or ulcer case makes sense.

After this chapter you can

- Explain how H2 blockers and proton pump inhibitors reduce acid secretion and why PPIs are stronger
- Describe how sucralfate protects ulcers and why its timing and interactions matter
- Compare the receptor targets of maropitant, ondansetron and metoclopramide
- Explain what a prokinetic does and when it must not be used
- Outline the logic of appetite stimulants and their limits

Why control acid and vomiting

Gastric acid is made by the parietal cells of the stomach. It helps digestion and kills many ingested microbes, but it also damages the mucosa when protective mechanisms fail. Ulcers are seen with NSAID or corticosteroid use, stress, mast cell tumours, liver or kidney disease and severe systemic illness. Vomiting is a separate problem: it is a reflex with several inputs, and one drug rarely blocks all of them.

This chapter groups the drugs by purpose: reduce acid, coat the ulcer, stop the vomit, and move the gut contents forward. Always treat the cause as well. A drug that hides a foreign body or an obstruction can be harmful.

Reducing acid: H2 blockers and proton pump inhibitors

The parietal cell is driven by three signals: histamine (H2 receptor), gastrin and acetylcholine. All three end at the same final step, the **H+/K+-ATPase**, or proton pump, which pushes acid into the lumen.

H2 receptor antagonists (famotidine, ranitidine, cimetidine) compete with histamine at the H2 receptor. They block only one of the three signals, so suppression is

partial. Famotidine is the most potent of the group, while cimetidine inhibits liver enzymes and can interfere with the metabolism of other drugs. With repeated use, tolerance develops, and stopping suddenly may cause rebound acid secretion, so withdrawal is usually gradual. Ranitidine has been withdrawn from many markets; check the current availability.

Proton pump inhibitors (omeprazole, pantoprazole, esomeprazole) act at the final common step. They are prodrugs that are activated in the acid space of the parietal cell and bind the pump irreversibly. Acid returns only when new pumps are made, so one dose can act for days, and suppression is deeper than with H2 blockers. Because they need active pumps and an acid environment, oral PPIs are given in protected (enteric) forms and usually before feeding. Pantoprazole and esomeprazole are options when injection is needed.

Common confusion: higher gastric pH is not always better. Long-term suppression may alter the gut microbiota and reduce absorption of some drugs, so prolonged use needs a clear reason.

Protecting the ulcer: sucralfate and related agents

Sucralfate is a complex of aluminium and sulphated sucrose. In an acid stomach it turns into a sticky paste that binds preferentially to the ulcer crater and forms a physical barrier against acid and pepsin. It is hardly absorbed, so it is safe systemically, and its action is local.

Three practical points follow from this mechanism. First, it needs acid to activate, so it is best given on an empty stomach and is somewhat contradictory with heavy acid suppression. Second, it can bind other drugs in the gut (for example some fluoroquinolones, tetracyclines and levothyroxine), so give it apart from other oral drugs. Third, it can be constipating. The Merck Veterinary Manual notes that evidence for its effect in animals is limited and that it is considered inferior to PPIs for gastroduodenal ulcers, so it is an adjunct rather than a stand-alone treatment in severe cases.

Misoprostol, a prostaglandin E analogue, is a different approach: it replaces the protective prostaglandins lost with NSAID use. It must not be given to pregnant animals, as it may cause abortion.

Antiemetics: matching the drug to the pathway

Vomiting is coordinated by the vomiting centre in the brainstem. It receives input from the **chemoreceptor trigger zone** (CRTZ), which sits outside the blood-brain barrier and detects toxins and drugs; from the vestibular apparatus (motion sickness); from higher centres; and from the gut via the vagus. The main transmitters are dopamine (D2), serotonin (5-HT3), histamine (H1), acetylcholine (muscarinic) and **substance P** (NK1 receptor).

- **Maropitant** blocks NK1 receptors. Because substance P is the final common transmitter in the vomiting centre, it works against many triggers, central and peripheral, and also reduces visceral pain input. It is licensed in dogs and cats, and it is also useful for motion sickness. Check product labels for species and age limits.
- **Ondansetron** blocks 5-HT3 receptors on vagal afferents in the gut and in the CRTZ. It is especially useful when serotonin release is high, as with chemotherapy and severe enteritis.
- **Metoclopramide** blocks D2 receptors in the CRTZ and has prokinetic action (below). It is a weaker antiemetic in cats and dogs than maropitant for many causes.
- **Phenothiazines** (chlorpromazine, prochlorperazine) block dopamine and histamine and also sedate and lower blood pressure.

Remember that antiemetics are not a substitute for fluids and diagnosis. Animals that are vomiting because of a gastrointestinal obstruction need the obstruction removed.

Prokinetics

Prokinetics increase coordinated propulsive motility. They help in delayed gastric emptying, reflux oesophagitis, ileus and some cases of constipation.

Metoclopramide blocks D2 receptors, which removes a dopamine brake on the gut, and it also stimulates 5-HT4 receptors to promote acetylcholine release. It acts mainly on the stomach and proximal small bowel. It is not effective in the colon. It crosses the blood-brain barrier and can cause restlessness or behaviour changes.

Cisapride acts through 5-HT4 receptors and is effective across the stomach and colon, which is why it is used in feline megacolon. Availability is limited in many

places, so check what is available. **Ranitidine** and related cholinesterase inhibiting effects have also been described in some references, but the evidence is variable.

The key safety rule: **never give a prokinetic when there is a mechanical obstruction**. Increasing contractions against a blockage risks pain and perforation.

Appetite stimulants

Anorexia delays recovery, and in cats prolonged anorexia can lead to hepatic lipidosis. Appetite stimulants work only after the underlying disease, pain and nausea are addressed.

- **Mirtazapine** blocks alpha-2 and 5-HT2/5-HT3 receptors. It raises appetite and has an antiemetic effect. Kidney or liver disease prolongs its action, so interval matters. A transdermal cat product exists in some countries.
- **Capromorelin** mimics ghrelin, the hunger hormone, and is licensed for dogs in some countries.
- **Cyproheptadine**, a serotonin and histamine antagonist, has been used in cats.
- **Benzodiazepines** can stimulate eating briefly but are unreliable.

Stimulants are an aid, not a replacement for nutrition. If an animal does not eat, a feeding tube is often the better option.

Concept cleared

Final common pathway
PPIs block the last step of acid secretion, the proton pump, so they outperform drugs that block one of several input signals.

Prodrug activation by acid
PPIs need an acidic space to become active, which is why oral forms are protected from stomach acid and the timing before feeding matters.

Substance P as the common vomiting transmitter

NK1 blockade by maropitant covers many vomiting triggers, while ondansetron and metoclopramide cover narrower pathways.

Prokinetic against obstruction

Stimulating motility against a physical blockage can cause pain and rupture, so rule out obstruction first.

Memory aid: Acid drugs by step

H2 = one lane closed (histamine), PPI = the gate shut (pump), sucralfate = a bandage on the wound. Three drugs, three levels.

Compare and contrast

Acid-reducing and protecting drugs

Drug	Target	Strength / onset	Key caution
Famotidine	H2 receptor (competitive)	Moderate; partial block	Tolerance, rebound on abrupt stop
Cimetidine	H2 receptor	Weaker	Inhibits liver enzymes, drug interactions
Omeprazole	H+/K+-ATPase (irreversible)	Strong; lasts days	Long-term use needs justification
Sucralfate	Local ulcer coating	Local, not systemic	Binds other oral drugs; give separately
Misoprostol	Prostaglandin E analogue	Mucosal protection	Contraindicated in pregnancy

Antiemetics and prokinetics

Drug	Receptor action	Best used for	Note
Maropitant	NK1 antagonist	Broad: central and peripheral vomiting, motion sickness	Check species and age on label
Ondansetron	5-HT3 antagonist	Chemotherapy and enteritis vomiting	Narrower pathway
Metoclopramide	D2 antagonist, 5-HT4 agonist	Nausea plus gastric emptying	Not for obstruction; CNS effects
Cisapride	5-HT4 agonist	Gastric and colonic motility	Limited availability
Mirtazapine	Alpha-2 and 5-HT antagonist	Appetite and nausea	Slower clearance in organ disease

Species notes

Dog

Vomiting is common; maropitant is widely used. Check for foreign body before any prokinetic. PPIs have longer action in dogs than many expect.

Cat

Cats are sensitive to some drugs (for example salicylates and some opioid or dopamine effects). Prolonged anorexia risks hepatic lipidosis, so early feeding support matters.

Horse

Equine gastric ulcer syndrome is treated mainly with PPIs such as omeprazole; the product label and current regulations decide use, particularly for competition horses.

Ruminants

Forestomach fermentation differs, so monogastric acid drugs are not routinely applied; abomasal ulcers are treated on the basis of cause and local guidance.

Pig

Gastric ulceration near the oesophageal region is linked to fine-ground feed and stress;

management is generally more important than acid drugs.

Clinical pearls

Self-test: 10 questions

1. Which drug irreversibly blocks the gastric H+/K+-ATPase?

Omeprazole is a proton pump inhibitor that binds the pump irreversibly, so acid suppression lasts until new pumps are made.

2. Maropitant works by blocking which receptor?

Maropitant blocks NK1 receptors for substance P, the final common transmitter in the vomiting centre.

3. Why should sucralfate be given apart from other oral drugs?

Sucralfate forms a sticky paste that can bind co-administered drugs and reduce their absorption.

4. A prokinetic is contraindicated in:

Stimulating contractions against an obstruction risks pain and perforation.

5. Which statement about H2 blockers is correct?

H2 blockers block only the histamine signal, so suppression is partial compared with PPIs.

6. Which drug is mainly a 5-HT3 antagonist?

Ondansetron blocks 5-HT3 receptors on vagal afferents and in the chemoreceptor trigger zone.

7. Metoclopramide is NOT effective as a prokinetic in the:

Metoclopramide acts mainly on the upper gut and has little colonic effect, unlike cisapride.

8. Which agent replaces protective prostaglandins lost with NSAID use?

Misoprostol is a prostaglandin E analogue; it is contraindicated in pregnancy.

9. Capromorelin stimulates appetite by acting as a mimic of:

Capromorelin is a ghrelin receptor agonist and so signals hunger.

10. Abrupt withdrawal of long-term H2 blocker may cause:

Chronic suppression can up-regulate acid secretion, so stopping suddenly may produce a rebound.

Key points to revise

1. Parietal cells are stimulated by histamine, gastrin and acetylcholine, all converging on the proton pump.
2. H2 blockers block one input; PPIs block the pump irreversibly and are stronger.
3. Sucralfate is a local, acid-activated ulcer barrier with limited systemic effect.
4. Sucralfate can bind other drugs, so separate dosing.
5. Maropitant acts on NK1 receptors; ondansetron on 5-HT3; metoclopramide on D2.
6. Prokinetics must not be used in mechanical obstruction.
7. Cisapride acts on the colon through 5-HT4, unlike metoclopramide.
8. Appetite stimulants help only after nausea, pain and the underlying disease are addressed.

Go deeper on this site

- Ch 23. Laxatives, purgatives, antidiarrhoeals and probiotics (in this book)
- Ch 21. Respiratory drugs (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Drugs Used to Treat Gastrointestinal Ulcers in Monogastric Animals
- Merck Veterinary Manual: Drugs Used to Treat Diarrhea in Monogastric Animals
- Merck Veterinary Manual: Vomiting in Dogs

CHAPTER 23 OF 33

Laxatives, purgatives, antidiarrhoeals and probiotics

How the main laxative groups work, what adsorbents and opioid antidiarrhoeals really do, why oral rehydration is the life-saving step in diarrhoea, and what the evidence says about probiotics and prebiotics.

After this chapter you can

- Classify laxatives by mechanism and give an example and a caution for each
- Explain why adsorbents have limited proven benefit in diarrhoea
- Explain how oral rehydration solutions work through sodium-glucose co-transport
- Define probiotic, prebiotic and synbiotic
- Judge the quality of evidence and product quality problems in probiotics

Constipation, diarrhoea and the purpose of treatment

The gut moves about as much fluid across its wall each day as the animal drinks. A small shift in absorption or secretion therefore changes the stool quickly. **Diarrhoea** is increased stool water, usually with increased frequency, caused by excess

secretion, reduced absorption, increased osmotic load or faster transit. **Constipation** is the opposite: hard, dry, infrequent stool.

Drugs in this chapter change stool consistency, but the first questions are always about the cause. Diarrhoea may be infectious, dietary, parasitic or toxic. Constipation may be due to low fibre, dehydration, pain, pelvic narrowing, or obstruction. A laxative given to an animal with an obstruction can be dangerous, and an antidiarrhoeal given to an animal with an invasive infection can hold bacteria and toxins in the gut.

The most important treatment in acute diarrhoea is replacing fluid and electrolytes. Most other drugs are secondary.

Types of laxative and purgative

A laxative softens stool and eases passage. A **purgative** or cathartic acts strongly and produces fluid stool. The difference is mainly one of degree and dose.

- **Bulk-forming laxatives** (psyllium, methylcellulose, bran, fibre sources) absorb water and add indigestible mass. The stretched bowel wall stimulates peristalsis. They need adequate water, otherwise they can worsen the problem.
- **Hyperosmotic laxatives** (magnesium sulphate or hydroxide, sodium sulphate, lactulose, polyethylene glycol, sugar alcohols) are poorly absorbed and hold water in the lumen. This distends the bowel and promotes movement. Excess dose causes dehydration.
- **Lubricants** (liquid paraffin, mineral oil, white petroleum) coat the faeces and the mucosa so that passage is easier. Prolonged use can reduce absorption of fat-soluble vitamins, and aspiration of the oil is a risk if dosed carelessly.
- **Emollients or surfactants** (docusate salts) lower the surface tension of the stool so that water enters it. Docusate should not be combined with mineral oil, since it may increase oil absorption.
- **Stimulant laxatives** (senna, castor oil, bisacodyl) irritate the mucosa or stimulate the enteric nerves, increasing motility and secretion. They can cause heavy fluid and electrolyte loss and colic.

Lactulose is also used in liver failure. Gut bacteria break it down to acids, which acidify the colon, and ammonia is trapped as ammonium ion that cannot be absorbed. This lowers the ammonia load on the failing liver.

Magnesium salts are partly absorbed and cleared by the kidney. In renal disease, magnesium can accumulate to toxic levels.

Species notes on laxatives

The choice of laxative follows anatomy. In the horse, the large colon has narrow points and large volumes of fluid, so impaction colic is common. Mineral oil by stomach tube and osmotic salts are used for impaction, along with fluids. The belief that bran mash is laxative is not supported by the standard reference. Repeated doses of a stimulant such as senna should be avoided in horses because of the risk of severe purging. Boiled linseed oil is dangerous because of metallic driers.

In the cat, megacolon is managed with diet, osmotic agents such as lactulose and sometimes prokinetics. Sodium phosphate enemas must not be given to cats because they can cause fatal electrolyte disorders.

In ruminants, the large rumen volume dilutes purgatives. Mineral oil and magnesium sulphate are used in some conditions, but these are covered in the ruminant chapter.

In all species, dehydration is both a cause and a consequence. A laxative works best when the animal is well hydrated.

Antidiarrhoeals and adsorbents

Antidiarrhoeal drugs fall into a few groups.

- **Adsorbents and protectants** such as kaolin-pectin, bismuth subsalicylate and activated charcoal. Kaolin-pectin is claimed to bind toxins and coat the mucosa, but clinical studies have not shown that it shortens illness or reduces fluid loss. It can also bind other oral drugs and reduce their absorption. Activated charcoal binds many toxins and drugs and is not absorbed, but it does not treat the diarrhoea itself.
- **Opioid antimotility drugs** such as loperamide and diphenoxylate increase segmental contractions, slow transit and increase absorption. They can be harmful in infectious diarrhoea because they slow the clearance of the pathogen. Loperamide can cause severe central nervous system effects in dogs with the MDR1 mutation.

- **Antisecretory drugs** such as bismuth subsalicylate reduce fluid secretion. Salicylate is absorbed, so it should be avoided in cats and used cautiously in others.
- **Antimicrobials** are indicated only when there is evidence of invasive bacterial infection or systemic illness. Most acute diarrhoeas do not need them.

A common confusion: stopping the diarrhoea is not the same as treating the patient. A calf with watery diarrhoea can die from dehydration and acidosis even while stool looks firmer on an opioid.

Oral rehydration

In the small intestine, glucose is absorbed together with sodium by a co-transporter on the villus cell. Water follows by osmosis. This coupled uptake continues to work even when toxins such as those of *E. coli* have switched on secretion in the crypts. Oral rehydration solution (ORS) uses this principle to replace fluid and sodium by mouth.

A good ORS contains sodium, glucose or another substrate, and often a base such as acetate or bicarbonate to correct acidosis. Calf electrolyte products also provide glycine and other aids. Because the solution should be iso-osmotic or slightly hypo-osmotic, mixing it with too much powder or adding extra sugar can worsen diarrhoea.

Oral rehydration is used for mild to moderate dehydration in animals that can still swallow. Severe dehydration, shock, inability to stand or suck, or ileus needs intravenous fluids. ORS also should not replace the calf's milk feeding for long, as the animal still needs energy.

This is the point where students often misjudge: the drug that saves most lives in diarrhoea is not an antidiarrhoeal, it is salt, sugar and water.

Probiotics, prebiotics and the evidence

A **probiotic** is a live microorganism which, in adequate amounts, gives a benefit to the host. Common examples are *Lactobacillus*, *Bifidobacterium*, *Enterococcus* and the yeast *Saccharomyces*. A **prebiotic** is a non-living food component, such as fructo-oligosaccharide or inulin, that feeds beneficial bacteria. A **synbiotic** combines both. In livestock they are often called direct-fed microbials.

Proposed mechanisms are production of organic acids that lower gut pH, production of antimicrobial substances, competition with pathogens for nutrients and sites, and support of the gut barrier and immune system.

The evidence is mixed. In calves, a review of direct-fed microbials reported benefit in some trials and no effect in others, with the most plausible value in stressed animals. Most products are mixtures of strains, so it is hard to know which organism does what, and strains of the same species can behave differently.

Product quality is a major concern. Organisms die with heat, moisture, oxygen and storage. In calves, adding a product to hot milk replacer can kill it, and antimicrobials in feed can interfere. Labels may not match the actual content. Probiotics should not replace fluids, nutrition and treatment of the cause. Regulation of such products varies. Check the current guidance of the relevant Indian authority.

Probiotics are generally safe in healthy animals, but live organisms in severely ill or immunosuppressed animals need caution.

Concept cleared

Concept cleared: Osmotic laxative
Think of a salt shaker on a cut tomato. Salt that cannot be absorbed sits in the gut and pulls water into the lumen, just as salt draws water from tomato. The extra water softens and moves the stool.

Concept cleared: Bulk laxative needs water
A bulk laxative is like a dry sponge. Wet, it swells and fills the bowel. Dry, in a dehydrated animal, it just becomes a hard lump. Always ensure water intake.

Concept cleared: Why ORS works in diarrhoea
Secretion is a leaking tap, but the sodium-glucose pump is a separate door that still works. ORS opens that door, so water and salt enter the body even while the tap leaks.

Concept cleared: Probiotic versus prebiotic

A probiotic is the seed, a living microbe. A prebiotic is the fertiliser that helps the useful seeds grow. A synbiotic gives both.

Memory aid: Laxatives: B-H-L-E-S

Bulk, Hyperosmotic, Lubricant, Emollient, Stimulant, from the gentlest, slow ones to the harshest. Antidiarrhoeal order of priority: Fluids first, then protect, then slow, and antimicrobials last.

Compare and contrast

Laxative groups

Group	Example	Mechanism	Caution
Bulk	Psyllium, bran	Absorbs water, adds mass, stretches wall	Needs adequate water
Hyperosmotic	Magnesium sulphate, lactulose, PEG	Holds water in lumen	Dehydration; magnesium in renal disease
Lubricant	Mineral oil	Coats stool, eases passage	Vitamin A, D, E, K malabsorption; aspiration
Emollient	Docusate	Lowers stool surface tension	Do not combine with mineral oil
Stimulant	Senna, castor oil, bisacodyl	Irritates mucosa, raises motility and secretion	Fluid and electrolyte loss, colic

Antidiarrhoeal groups

Group	Example	Action	Limitation
Adsorbent	Kaolin-pectin, charcoal	Binds toxins and drugs	No proven shortening of illness; binds other drugs
Opioid	Loperamide	Slows transit, raises absorption	Avoid in infectious diarrhoea; MDR1 dogs at risk
Antisecretory	Bismuth subsalicylate	Reduces secretion	Salicylate absorption; avoid in cats
Rehydration	ORS	Replaces fluid and sodium by co-transport	Not enough in shock or ileus

Species notes

Dog

Loperamide can cause serious neurological signs in dogs carrying the MDR1 mutation, which is seen in some herding breeds. Avoid antimotility drugs in infectious diarrhoea such as parvovirus.

Cat

Do not use sodium phosphate enemas. Salicylate products such as bismuth subsalicylate are best avoided. Lactulose and diet are used for megacolon.

Horse

Mineral oil and osmotic salts are used for impaction, with fluids. Do not repeat stimulant doses. Foal diarrhoea needs fluid and electrolyte care first.

Calf

Calf scours kills mainly by dehydration, acidosis and electrolyte loss. Oral electrolyte solutions are the base of treatment, and milk feeding should continue. Probiotic evidence is mixed.

Cattle and small ruminants

Check withdrawal times and local rules before using any drug in food animals. Ruminant-specific

purgatives are discussed in the next chapter.

Clinical pearls

Self-test: 10 questions

1. Which laxative group works by holding water in the intestinal lumen?

Poorly absorbed salts and sugars retain water by osmosis.

2. What must be ensured when giving a bulk laxative?

Without water the bulk can harden the stool.

3. A risk of prolonged mineral oil use is:

Oil dissolves fat-soluble vitamins and carries them out.

4. Which enema is dangerous in cats?

Sodium phosphate enemas can cause fatal hyperphosphataemia and hypocalcaemia in cats.

5. Lactulose helps in hepatic encephalopathy because it:

Bacterial breakdown to acids lowers colonic pH and ammonium is not absorbed.

6. What is the evidence for kaolin-pectin in diarrhoea?

Studies have not shown benefit, and adsorption of other drugs is possible.

7. Why is loperamide avoided in infectious diarrhoea?

Slowing transit can retain organisms and toxins.

8. Oral rehydration solutions work because:

Coupled sodium-glucose uptake remains functional in secretory diarrhoea.

9. A prebiotic is:

Prebiotics such as inulin are food for beneficial microbes.

10. Which statement about probiotic products in calves is correct?

Trials show mixed outcomes, and heat, oxygen and moisture kill organisms.

Key points to revise

1. Laxative groups are bulk, hyperosmotic, lubricant, emollient and stimulant.
2. Bulk laxatives need adequate water.
3. Magnesium salts can accumulate in renal disease.
4. Lactulose acidifies the colon and traps ammonia in hepatic encephalopathy.
5. Adsorbents have little proven clinical benefit.
6. Opioid antimotility drugs are unsuitable in infectious diarrhoea.
7. ORS works because glucose-coupled sodium uptake persists during secretory diarrhoea.
8. Probiotics are live microbes, prebiotics are their food; evidence is mixed and strain-specific.

Go deeper on this site

- Ch 24. Ruminant digestive drugs (in this book)
- Ch 22. Gastric acid suppressants, antiemetics and prokinetics (in this book)

- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Cathartic and Laxative Drugs Used in Monogastric Animals
- Merck Veterinary Manual: Drugs Used to Treat Diarrhea in Monogastric Animals
- USDA APHIS: Direct-fed microbials (probiotics) in calf diets

CHAPTER 24 OF 33

Ruminant digestive drugs

Drugs and procedures that act on the rumen: rumenotorics, antibloat agents, antizymotics, buffers and acidifiers, bypass nutrients and cud or rumen-fluid inoculation. The chapter explains why restoring the rumen environment matters more than any single drug.

After this chapter you can

- Explain what the rumen microbial population does and why drugs can upset it
- Describe rumenotorics and the cautions on parasympathomimetics
- Distinguish frothy bloat from free-gas bloat and match antibloat agents to each
- Explain when buffers and acidifiers are and are not appropriate
- Describe rumen inoculation (transfaunation) and bypass nutrients

The rumen as a fermentation vat

The rumen, reticulum and omasum are a fermentation chamber. Bacteria, protozoa and fungi break down fibre and starch into volatile fatty acids (VFAs), which supply most of the ruminant's energy, and into microbial protein. Saliva, rich in bicarbonate, buffers the acids. Regular contractions mix the contents, and eructation removes the gas.

This system works only within a narrow range of pH, substrate and motility. When any of these fails, the animal shows **indigestion**: reduced appetite, reduced rumen contractions, abnormal rumen contents, and falling milk yield.

Two points guide all drug use here. First, drugs given by mouth enter a large volume of fluid, so they are diluted and may be altered by microbes. The rumen environment can inactivate some drugs, and some oral antimicrobials upset the microbial balance. Second, the best treatment is usually to correct the cause, such as diet, and to restore the microbial population. Drugs are only one tool.

Rumenotorics

Rumenotorics (ruminotorics) are agents meant to stimulate forestomach motility and fermentation. Traditional preparations contain bitters such as nux vomica, minerals, cofactors and sugars. Their current evidence is limited, and restoring the normal rumen environment is considered more satisfactory.

Parasympathomimetics such as neostigmine and bethanechol increase smooth muscle contraction, but they are seldom suitable. They can cause cholinergic effects such as salivation, abdominal pain and bradycardia, and neostigmine may increase the frequency of contractions without improving their strength. Metoclopramide may cause restlessness in cattle. Several of these drugs are not approved for cattle in some countries, and their value has not been confirmed in controlled trials.

Where hypomotility is due to impaction, mineral oil or a surfactant such as docusate given by tube with massage may help move the contents. Docusate can sharply reduce rumen protozoa, so rumen fluid transfer should follow if motility remains poor.

The practical view: a rumenotoric will not rescue an animal whose problem is hypocalcaemia, a displaced abomasum, pain or a toxic rumen. Look for the primary cause, which is the commonest cause of rumen stasis.

Bloat and antibloat agents

Bloat is excess gas in the rumen. There are two types, and the drug depends on the type.

- **Frothy bloat** (primary) occurs on lush legumes or high-grain diets. Gas is trapped in stable foam, so it cannot be belched. The treatment is to break down foam.
- **Free-gas bloat** (secondary) occurs when eructation is blocked, for example by oesophageal obstruction or vagal damage. Gas is free on top of the contents, and it is relieved by a stomach tube or, in an emergency, a trocar.

Antifoaming agents reduce the stability of the foam so gas can escape. Poloxalene is a surfactant used for treatment and prevention. Silicone products are used in a similar way. Docusate can relieve frothy bloat. Vegetable oils such as groundnut, sunflower and soybean oil are also used. Mineral oil is less suited because it does not mix well with the froth. Monensin, an ionophore, may lower the incidence of frothy bloat in feedlot cattle by changing the rumen flora.

Common confusion: a stomach tube relieves free-gas bloat dramatically but does little for frothy bloat, as froth blocks the tube. An animal that does not respond to the tube should be suspected of frothy bloat. Severe bloat compressing the diaphragm and the vena cava is an emergency, and decompression should not be delayed.

Prevention is by management: avoid sudden access to lush legumes, give dry roughage first, and use anti-foaming agents in the feed or water where this is the practice.

Antizymotics

An **antizymotic** is an agent that inhibits excessive fermentation by microbes. Zymotic means related to fermentation. Such agents were once given for tympany and for conditions of abnormal fermentation.

The idea has limits. The rumen needs fermentation, and a broad inhibitor harms the useful flora as well as the harmful. Many older antizymotic preparations have little supporting evidence. Modern thinking uses specific measures instead: correct the diet, use ionophores such as monensin for managing acidosis and bloat in feedlot systems where permitted, and avoid broad antimicrobials by mouth.

Indian use of ionophores and other feed additives is subject to regulation and may change. Check the current notification before use in dairy or meat animals, and observe withdrawal periods.

When an exam asks for antizymotics, the key points are the definition, the examples listed in your textbook, and the caution that suppressing fermentation also suppresses digestion.

Buffers, alkalinisers and acidifiers

The main condition needing a buffer is **acute ruminal lactic acidosis** after grain engorgement or sudden carbohydrate overload. Lactic acid accumulates, pH falls below about 5.5, the flora change and the animal can become dehydrated and acidotic.

Antacids used in such cases include magnesium hydroxide, magnesium oxide, magnesium carbonate and sodium bicarbonate. They are given as a large volume of warm water. Magnesium oxide and hydroxide strongly alkalinise the rumen and reduce protozoa, so they should be given only when grain overload is confirmed. Sodium bicarbonate raises rumen pH quickly but releases large amounts of carbon dioxide, and in an animal with weak motility this increases the risk of free-gas bloat. Systemic dehydration and acidosis also need correcting, and in severe cases the rumen contents are replaced with fresh fluid.

Acidifiers are used where the rumen pH is too high. In simple indigestion and stasis the pH may be above 7.5. In ammonia (urea) poisoning, high pH favours free ammonia absorption, so a weak acid such as dilute acetic acid or vinegar in cold water helps by lowering pH and slowing urease action.

Do not give alkalinisers or acidifiers routinely in indigestion. Correct the cause first, and match the agent to the measured rumen pH where you can.

Bypass nutrients and rumen inoculation

Microbes degrade most protein and fat that enter the rumen, so a nutrient given by mouth may never reach the intestine in useful form. **Bypass (rumen-protected) nutrients** are treated so that they escape rumen degradation and are digested in the abomasum and small intestine. Examples are protected protein, protected fat and protected amino acids. They are used in high-yielding dairy cows in early lactation to supply what the rumen cannot. Protected drugs and vitamins follow the same logic.

The idea also applies to calves. Before the rumen is developed, the oesophageal groove reflex directs milk straight to the abomasum, so it bypasses the rumen. The reflex weakens with age.

Rumen inoculation or transfaunation gives fresh rumen fluid from a healthy donor. It supplies bacteria, protozoa, VFAs, buffers and nutrients, and is described as the best available rumenotoric. It is used for stasis, after prolonged anorexia and after antimicrobials or docusate have disturbed the flora. The fluid is strained and given by stomach tube. The best dose is not known. If the existing contents are putrefied or very acidic, they may need to be removed first. Donors on a similar ration are preferred. Cud from a healthy animal is a traditional farm version of the same idea.

The success of inoculation depends on the underlying disease responding.

Concept cleared

Concept cleared: The rumen is a living vat
Think of curd-making: the right bacteria in the right conditions give a good result. Add too much acid or kill the starter and the batch is spoiled. Rumen drugs aim to protect the vat, not to override it.

Concept cleared: Frothy versus free-gas bloat
Frothy bloat is a bottle of soda that has foamed over: you cannot pour it out. Free-gas bloat is a bottle with a blocked mouth. The first needs a foam breaker, the second needs a tube or trocar.

Concept cleared: Why bicarbonate can cause bloat
Sodium bicarbonate meeting acid releases carbon dioxide, like a fizzy tablet in water. In a rumen that cannot belch, that gas builds up.

Concept cleared: Bypass nutrient
A courier parcel with a hard wrapper survives the first sorting station (rumen) and is opened only at the final one (abomasum). Protected protein or fat is wrapped so rumen microbes do not consume it.

Memory aid: Ruminant digestive drugs: R-A-A-B-B-I

Rumenotorics, Antibloat, Antizymotics, Buffers, Bypass nutrients, Inoculation.

For bloat remember: Froth needs a Foam breaker; Free gas needs a Flow tube.

Compare and contrast

Frothy and free-gas bloat

Feature	Frothy bloat	Free-gas bloat
Cause	Stable foam from lush legumes or grain	Failure of eructation (obstruction, vagal damage)
Stomach tube	Little relief, froth blocks tube	Rapid relief
Main treatment	Antifoaming agent (poloxalene, silicone, oil, docusate)	Tube or trocar, remove cause
Prevention	Diet management, antifoam, monensin where permitted	Treat primary obstruction

Alkalinisers and acidifiers

Group	Example	Used for	Caution
Alkaliniser	Magnesium hydroxide or oxide	Confirmed grain overload, low rumen pH	Reduces fermentation and protozoa; not routine
Alkaliniser	Sodium bicarbonate	Fast pH rise	Carbon dioxide release, bloat risk
Acidifier	Dilute acetic acid, vinegar	High pH, ammonia poisoning	Treat the cause, not only the pH

Species notes

Cattle

Frothy bloat on lush legume pasture and acidosis after grain overload are the main problems. Check

Buffalo

Buffalo are also prone to bloat and grain overload with wheat or rice-based feeds. The principles are the

withdrawal periods and current Indian rules before using any additive or drug in milk or meat animals.

same as in cattle; do not assume cattle product doses apply, and consult a veterinarian or label.

Sheep and goat

Small ruminants develop acidosis and bloat on sudden grain or lush feed. Volumes of antacids and oils are smaller, so use a species-specific source.

Calf

The oesophageal groove carries milk directly to the abomasum. Oral drugs given to a preruminant calf may bypass the rumen, whereas in an older animal they are diluted in the rumen.

Camel

Camels have a different forestomach, so extrapolating ruminant digestive drug use from cattle should be done with care.

Clinical pearls

Self-test: 10 questions

1. Which type of bloat is relieved dramatically by a stomach tube?

In free-gas bloat the gas is free above the contents and escapes through the tube.

2. An antifoaming agent acts by:

It breaks the stable foam trapping the gas.

3. Which drug may lower frothy bloat incidence in feedlot cattle?

Ionophores alter the rumen flora and may reduce frothy bloat.

4. Why is sodium bicarbonate a risk in acute acidosis with poor motility?

Reaction with acid releases CO2 that the stasis rumen cannot eructate.

5. An acidifier is helpful in which situation?

Lower pH reduces free ammonia absorption and slows urease.

6. Which drug can markedly reduce rumen protozoa?

Docusate lowers protozoa, so transfaunation may be needed afterwards.

7. Why are parasympathomimetics seldom suitable as rumenotorics?

Effects such as salivation, colic and bradycardia limit their use.

8. What is transfaunation?

It restores bacteria, protozoa, VFAs and buffers.

9. A bypass nutrient is designed to:

Protection allows protein or fat to reach the abomasum and intestine intact.

10. The main reason a broad antizymotic is a poor idea is that it:

The rumen depends on fermentation for energy, so broad inhibition harms digestion.

Key points to revise

1. The rumen is a microbial fermentation vat buffered by saliva.
2. Rumenotorics have limited evidence; parasympathomimetics have hazardous cholinergic effects.
3. Frothy bloat needs antifoam; free-gas bloat needs decompression.
4. Poloxalene, silicones, oils and docusate act as antifoams.
5. Antizymotics inhibit fermentation but also harm useful flora.
6. Alkalinisers are for confirmed acidosis, acidifiers for high pH and ammonia poisoning.
7. Bypass nutrients escape rumen degradation to be digested lower down.
8. Transfaunation restores flora with fresh strained rumen fluid.

Go deeper on this site

- Ch 25. Hepatic, pancreatic and biliary drugs (in this book)
- Ch 23. Laxatives, purgatives, antidiarrhoeals and probiotics (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Drugs for Specific Purposes in the Ruminant Digestive System
- Merck Veterinary Manual: Drug Disposition in the Ruminoreticulum
- USDA APHIS: Direct-fed microbials (probiotics) in calf diets

CHAPTER 25 OF 33

Hepatic, pancreatic and biliary drugs

How drugs support the liver, pancreas and bile system: hepatoprotectants, lactulose for hepatic encephalopathy, pancreatic enzyme replacement and choleretics, plus why liver disease changes the way every other drug is handled.

> **After this chapter you can**

- Explain why the liver is central to drug metabolism and what changes in liver disease
- Describe the rationale and the limits of evidence for hepatoprotectants such as silymarin, SAMe and ursodeoxycholic acid
- Explain how lactulose lowers blood ammonia in hepatic encephalopathy
- Describe how pancreatic enzyme replacement works and why it is given with food
- Apply general principles for choosing and adjusting drugs in animals with liver disease

The liver as the body's drug-processing plant

The liver takes up drugs from portal blood, converts them to more water-soluble forms and excretes them in bile or returns them to blood for the kidney. Phase I reactions (mainly cytochrome P450 enzymes) oxidise the drug. Phase II reactions (such as glucuronidation) attach a polar group. Many drugs lose activity in this way, but some are **prodrugs** that must be activated by the liver.

Drugs absorbed from the gut pass through the liver first. This *first-pass effect* can remove a large part of an oral dose before it reaches the general circulation. Liver disease, and especially a portosystemic shunt, lets blood bypass this filter, so oral drugs can reach much higher blood levels than expected.

This chapter covers three linked organs. The liver makes bile and detoxifies; the biliary tract carries bile to the intestine; the exocrine pancreas supplies digestive enzymes. Drugs here either support the organ, replace what it no longer makes, or manage the complications of its failure.

Hepatoprotectants: what they try to do

A **hepatoprotectant** is a drug or supplement given to limit liver injury or help repair. The common ideas behind them are antioxidant action, support of the cell's own protective chemistry and reduction of toxic bile acid damage.

- **Silymarin** (milk thistle extract) is described as an antioxidant and membrane stabiliser. It is widely used, but the clinical evidence in animals is limited.

- **S-adenosylmethionine (SAMe)** supports the production of glutathione, the liver's main antioxidant. It is usually given with the aim of supporting hepatocytes in chronic disease or after toxic injury.
- **N-acetylcysteine** supplies cysteine for glutathione. It is the best-known antidote for paracetamol (acetaminophen) toxicity, which is a real danger in cats.
- **Vitamin E** is a lipid-soluble antioxidant sometimes added in chronic hepatopathies.

A common confusion is to treat these as proven curative drugs. They are supportive. They never replace treating the underlying cause, such as infection, copper accumulation, toxins or obstruction. Also remember that supplements are not tightly regulated, so product quality varies.

Ursodeoxycholic acid and choleretics

A **choleretic** increases bile flow. Bile contains bile acids, which are needed to absorb dietary fat and fat-soluble vitamins (A, D, E, K) and which carry waste out of the body.

Ursodeoxycholic acid (ursodiol) is the most important drug in this group. It is a hydrophilic bile acid. It replaces part of the pool of toxic hydrophobic bile acids, stimulates bile flow and has some anti-inflammatory and immune-modulating effects. It is used in cholestatic and chronic inflammatory liver disease.

The key safety rule is that choleretics are unsuitable when the bile duct is completely blocked. Pushing more bile into an obstructed system can do harm, so obstruction must be excluded (usually by imaging) before use.

Do not confuse a choleretic with a *cholagogue* (stimulates gallbladder emptying) or with drugs that merely relieve dyspepsia. In animals, many traditional herbal 'liver tonics' sold in the field are marketed as choleretics or appetite stimulants. Their evidence is generally weak, so judge them cautiously.

Lactulose and hepatic encephalopathy

Hepatic encephalopathy (HE) is a neurological syndrome in which the failing liver, or a shunt, cannot clear gut-derived toxins. The best-known toxin is **ammonia**, formed when colonic bacteria break down dietary protein and urea. Signs include

depression, circling, head pressing, blindness and seizures, often worse after a protein-rich meal.

Lactulose is a synthetic disaccharide that animals cannot digest or absorb. It reaches the colon intact, where bacteria ferment it to organic acids. This produces three useful effects:

1. The colonic pH falls. Ammonia (NH_3) is converted to ammonium (NH_4^+), which is charged and poorly absorbed, so it is 'trapped' in the lumen.
2. The acid environment discourages ammonia-producing bacteria.
3. The osmotic laxative effect speeds transit and removes toxins in faeces.

The Merck Veterinary Manual describes lactulose as the standard against which other HE treatments are compared. Dose is adjusted to produce a few soft stools per day; too much causes cramping and severe diarrhoea, which dehydrates the animal and can worsen HE. Lactulose can also be given as a retention enema when an animal cannot take oral drugs.

Adjuncts include a protein diet of high quality and appropriate amount (protein is not simply withdrawn), and selected antibiotics given orally to reduce urease-producing gut bacteria. Always treat the trigger as well, such as gastrointestinal bleeding, infection or electrolyte disturbance.

Pancreatic enzyme replacement

In **exocrine pancreatic insufficiency (EPI)** the pancreas does not make enough lipase, amylase and protease. Food passes undigested. The animal eats well but loses weight and passes large, pale, greasy, foul stools. It is seen especially in dogs, often in German Shepherds, and less commonly in cats.

Treatment is **enzyme replacement**, taken by mouth with every meal for life. Key concepts:

- **Acid inactivates lipase.** Much of the enzyme is destroyed in the stomach before it reaches the duodenum, where it must act.
- **Form matters.** The Merck Veterinary Manual states that powdered products are more effective than tablets, capsules and, especially, enteric-coated products. Enteric-coated forms were designed to resist acid, but in dogs they may release their enzyme too late or poorly.

- **Mix with food.** Enzyme must meet the food in the intestine. Giving it away from meals defeats the purpose.
- **Acid suppression.** Antacids are usually unnecessary, but an acid-reducing drug may be tried if response is poor.

Cobalamin (vitamin B_{12}) deficiency is common in EPI, particularly in cats, and is often corrected separately. Do not use enzyme replacement in acute pancreatitis; it is a different disease and does not treat inflammation.

Liver disease and drug dosing

There is no simple blood test that predicts how well a diseased liver will metabolise a drug. Liver enzyme tests (ALT, ALP) show injury, not capacity. Use judgement, and apply a few general principles.

- **Prefer drugs that are not heavily metabolised** or are eliminated mainly by the kidney.
- **Drugs with high first-pass extraction** reach higher levels when blood bypasses the liver, as in a shunt.
- **Low albumin** increases the free fraction of highly protein-bound drugs.
- **Prodrugs** that need hepatic activation may work poorly.
- **Sedatives and anaesthetics**, especially benzodiazepines and other CNS depressants, can push an animal with HE into coma. Choose carefully.
- **Known hepatotoxic drugs**, such as paracetamol in cats, certain azole antifungals and some anticonvulsants, call for caution or monitoring.
- **Cats** are limited in glucuronidation, so some drugs accumulate in them even with a healthy liver.

Reduce the dose or lengthen the interval when in doubt, use the lowest effective amount, monitor clinical response and liver values, and consult the product literature.

Concept cleared

First-pass effect

Oral drugs pass through the liver before reaching the body. Liver disease or a shunt removes this filter and raises systemic exposure.

Ammonia trapping

Lactulose acidifies the colon, converting diffusible NH3 into charged NH4+ that is not absorbed.

Acid-labile lipase

Pancreatic lipase is destroyed by gastric acid, so form of enzyme product and giving with meals matter.

Support, not cure

Hepatoprotectants support liver cells but never replace removing the underlying cause.

Memory aid: Lactulose three actions

ACID: Acidifies colon, Cuts ammonia-producing bacteria, Increases transit, Drains toxins with faeces.

Compare and contrast

Hepatoprotectants compared

Agent	Proposed action	Note
Silymarin	Antioxidant, membrane stabiliser	Limited clinical evidence
SAMe	Raises glutathione	Supportive in chronic disease
N-acetylcysteine	Supplies cysteine for glutathione	Antidote for paracetamol toxicity
Ursodeoxycholic acid	Hydrophilic bile acid, choleretic	Avoid in complete bile duct obstruction

Lactulose versus pancreatic enzymes

Feature	Lactulose	Pancreatic enzymes
Problem treated	Hepatic encephalopathy	Exocrine pancreatic insufficiency
Site of action	Colon	Duodenum, with food
Mechanism	Acidifies and traps ammonia, osmotic laxative	Replaces missing lipase, amylase, protease
Overdose sign	Diarrhoea, dehydration	Rarely serious; oral irritation possible

Species notes

Dogs

Portosystemic shunts and chronic hepatitis are common reasons for lactulose and hepatoprotectants. EPI is usually due to pancreatic acinar atrophy and needs lifelong enzyme replacement.

Cats

Slow glucuronidation makes cats sensitive to paracetamol and some other drugs. Hepatic lipidosis and cholangitis are important liver diseases. EPI often coexists with low cobalamin.

Cattle

Liver disease is often linked to fatty liver in early lactation, liver fluke and plant toxins. Management of the cause is usually more important than hepatoprotectants.

Horses

Hepatic encephalopathy can occur with liver failure. Horses have no gallbladder, so bile flows continuously into the duodenum.

Pigs and poultry

Dietary liver injury is mainly managed by correcting toxins such as mycotoxins in feed rather than by drugs.

Clinical pearls

Self-test: 10 questions

1. Which statement best describes how lactulose reduces ammonia absorption?

Colonic bacteria ferment lactulose to acids, lowering pH and trapping ammonia as ammonium.

2. A common sign of excess lactulose dosing is:

Overdose causes osmotic diarrhoea and dehydration, which can worsen encephalopathy.

3. Ursodeoxycholic acid should be avoided in:

Stimulating bile flow against a blocked duct is hazardous.

4. N-acetylcysteine is best known as an antidote for:

It replenishes cysteine and glutathione, which neutralise the toxic paracetamol metabolite.

5. Why are enteric-coated pancreatic enzymes often less effective in dogs?

Powder is considered more effective than tablets or enteric-coated products.

6. Pancreatic enzyme replacement should be given:

The enzyme must mix with food to digest it.

7. Which change in liver disease most increases the free fraction of highly protein-bound drugs?

Albumin is made by the liver; low levels leave more drug unbound.

8. A portosystemic shunt increases exposure to oral drugs mainly because:

Portal blood skips the liver, so high-extraction drugs reach the circulation unchanged.

9. Which species is notably limited in glucuronidation?

Cats have poor glucuronide conjugation, so some drugs accumulate.

10. Which statement about hepatoprotectants is most accurate?

They support hepatocytes but do not replace cause-directed therapy.

Key points to revise

1. The liver metabolises most drugs; first-pass loss is reduced in shunts and severe disease.
2. Hepatoprotectants are supportive and their clinical evidence is limited.
3. SAMe and N-acetylcysteine support glutathione; N-acetylcysteine is an antidote for paracetamol.
4. Ursodeoxycholic acid is a hydrophilic bile acid and choleretic; avoid it in complete obstruction.
5. Lactulose is fermented in the colon, acidifies it and traps ammonia as ammonium.
6. EPI needs lifelong oral enzyme with every meal, in an acid-stable, effective form.
7. In liver disease prefer renally cleared drugs and avoid unnecessary CNS depressants.
8. Cats are deficient in glucuronidation and are vulnerable to hepatotoxic drugs.

Go deeper on this site

- Ch 26. Hypothalamic and pituitary hormones (in this book)
- Ch 24. Ruminant digestive drugs (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Hepatic encephalopathy in small animals
- Merck Veterinary Manual: Exocrine pancreatic insufficiency in dogs and cats

CHAPTER 26 OF 33

Hypothalamic and pituitary hormones

How the hypothalamus and pituitary control reproduction, water balance, lactation and growth, and how oxytocin, vasopressin, GnRH, gonadotropins, prolactin inhibitors and somatotropin are used in animals. The chapter also notes the regulatory issues around oxytocin and somatotropin in India.

After this chapter you can

- Describe the hypothalamic-pituitary axis and which hormones come from the anterior and posterior pituitary
- Explain the actions, uses and cautions of oxytocin and why its misuse in dairy animals is a concern in India
- Explain the V1 and V2 actions of vasopressin and the use of desmopressin in diabetes insipidus
- Explain why GnRH works as a stimulant when pulsatile but as a suppressant when continuous, and compare FSH, LH, hCG and eCG
- Describe how dopamine agonists lower prolactin and how somatotropin is regulated and used

The hypothalamic-pituitary axis

The hypothalamus is the control room that links the nervous system to the endocrine system. It makes releasing and inhibiting hormones that travel through a small portal blood system to the **anterior pituitary** (adenohypophysis). The anterior pituitary then releases trophic hormones such as FSH, LH, prolactin, growth hormone, TSH and ACTH, which act on target glands.

The **posterior pituitary** (neurohypophysis) is different. It does not make hormones. It stores and releases **oxytocin** and **antidiuretic hormone** (vasopressin), both made in hypothalamic nerve cell bodies and carried down the axons.

Most hormone-based drugs in this chapter work in one of three ways: they replace a missing hormone, they mimic a hormone to push a target organ, or they exploit feedback so that a target gland is switched off. Keep this logic in mind and the long list of drug names becomes easier.

Oxytocin

Oxytocin is a nonapeptide that acts on oxytocin receptors, which are G-protein-coupled and raise intracellular calcium. It has two main targets: the **myometrium** (uterine contraction) and the **myoepithelial cells** of the mammary gland (milk let-down or ejection).

Uterine sensitivity depends on the stage of the cycle. Oestrogen increases oxytocin receptors, so the uterus responds well at term and in the early postpartum period but poorly under progesterone. Low blood calcium also weakens uterine contractions, which is why a cow with hypocalcaemia and retained fetal membranes may need calcium as well as oxytocin.

Uses include assisting uterine contractions in selected cases of uterine inertia once obstruction is excluded, promoting involution and expulsion of fluids after parturition, helping with retained placenta, and supporting milk let-down in true let-down failure.

Cautions. The cervix must be open and the fetus correctly positioned. Giving oxytocin against an obstruction risks uterine rupture and fetal death. Oxytocin has weak antidiuretic-like activity, so very large or prolonged infusions can cause water retention.

Regulation in India. Oxytocin is widely misused to force milk let-down in dairy animals, and misuse has been linked to animal welfare problems and reduced fertility. The Indian government has placed restrictions on its manufacture and sale. Students should check the current notification for exactly who may manufacture, import and sell it, and on what prescription terms.

Vasopressin and desmopressin

Vasopressin (ADH) has two receptor actions. **V2 receptors** in the renal collecting duct raise cAMP and insert aquaporin-2 water channels into the membrane, so water is reabsorbed and urine becomes concentrated. **V1 receptors** on vascular smooth muscle act through calcium and cause vasoconstriction, which is why vasopressin is sometimes used in vasodilatory shock.

Desmopressin (DDAVP) is a synthetic analogue that is mostly V2-selective with a longer duration and little pressor effect. It is the drug of choice for **central diabetes insipidus**, where the pituitary fails to release ADH. It can be given as eye drops or by injection in animals, depending on the product available.

A common confusion is **nephrogenic diabetes insipidus**, where the kidney does not respond to ADH. Desmopressin will not fix this, and the response to a desmopressin trial is in fact one way to tell the two forms apart. Giving too much desmopressin to an animal that is drinking freely can cause water retention and low blood sodium.

GnRH and its analogues

Gonadotropin-releasing hormone (GnRH) is a decapeptide released from the hypothalamus in pulses. Each pulse causes the pituitary to release LH and FSH. The key concept is **pulsatility**. Pulsatile exposure stimulates the gonadotroph cells, while continuous exposure causes receptor desensitisation and down-regulation, so LH and FSH output falls.

This gives two opposite uses of the same drug class:

- **Stimulation**: short-acting analogues such as gonadorelin and buserelin cause an LH surge, used to induce ovulation, to treat follicular cysts, and in timed breeding programmes where GnRH is combined with prostaglandin F2-alpha to synchronise the oestrous cycle in cattle.

- **Suppression**: long-acting agonists such as deslorelin, given as slow-release implants, produce sustained exposure and reversible suppression of the reproductive axis. The labelled species and uses differ between countries, so check the product in your market.

Note that an agonist may cause a short initial flare of gonadal activity before suppression begins.

Gonadotropins: FSH, LH, hCG and eCG

Gonadotropins are glycoprotein hormones that act directly on the ovary or testis.

- **FSH** (from pituitary extracts) stimulates follicle growth and is used for superovulation in embryo transfer programmes.
- **LH** triggers ovulation and luteinisation.
- **hCG** (human chorionic gonadotropin, from the urine of pregnant women) has mainly LH-like action. It is used to induce ovulation or luteinisation of follicles.
- **eCG** (equine chorionic gonadotropin, formerly PMSG, from pregnant mare serum) has both FSH-like and LH-like activity and a long half-life. It is used to stimulate follicle growth in anoestrus animals and for superovulation.

Because hCG and eCG are foreign proteins, repeated use can lead to antibody formation and a falling response. A single long-acting dose of eCG can also keep stimulating follicles after they are no longer wanted, which is one cause of overstimulation.

The common exam confusion is between hCG and eCG. Remember: *hCG is LH-like, eCG is FSH-like with some LH*.

Prolactin inhibitors and somatotropin

Prolactin is controlled mainly by inhibition. Dopamine from the hypothalamus acts on D2 receptors of the lactotroph cells and keeps prolactin low. **Dopamine agonists** such as cabergoline and bromocriptine therefore suppress prolactin. They are used in bitches and queens to stop lactation and to treat pseudopregnancy. Cabergoline is longer acting and usually causes less vomiting than bromocriptine. The reverse also holds: dopamine antagonists such as metoclopramide and domperidone raise prolactin and are sometimes used to stimulate milk production. Cabergoline is also

used with other drugs in some pregnancy termination protocols, subject to local guidance.

Somatotropin (growth hormone) is released under the push of GHRH and the brake of **somatostatin**. It acts partly directly and partly by liver production of IGF-1. Recombinant bovine somatotropin (rbST) increases milk yield in dairy cows by redirecting nutrients to the udder, and carries risks to cow welfare such as mastitis and lameness. Rules on its use differ between countries, and students should check the current Indian notification before treating it as legal or available. Growth hormone is also diabetogenic, so excess causes insulin resistance, as in acromegaly in cats or progestin-induced excess in dogs.

Concept cleared

Concept cleared: Pulsatile versus continuous GnRH
Think of knocking on a door. Short knocks with gaps bring someone out, but a continuous bell press that never stops makes them ignore it. Pulsatile GnRH keeps the pituitary responsive, while continuous GnRH makes its receptors desensitise, so LH and FSH fall.

Concept cleared: Why oxytocin needs oestrogen priming
Oxytocin receptors are like locks that the uterus builds only when oestrogen is high. Near term the locks are many and the oxytocin key works well. Under progesterone dominance there are few locks and the same dose does little.

Concept cleared: Central versus nephrogenic diabetes insipidus
In central DI the message (ADH) is missing, so sending a synthetic message (desmopressin) works. In nephrogenic DI the message arrives but the kidney cannot read it, so more messages do nothing.

Concept cleared: Dopamine as a brake

Prolactin is the only anterior pituitary hormone mainly held down by hypothalamic dopamine. Giving a dopamine agonist presses the brake harder, and giving a dopamine blocker releases the brake.

Memory aid: Posterior pituitary pair

Posterior stores, not makes: OA, as in Oxytocin and ADH. For eCG versus hCG think: e for equine gives FSH plus LH, h for human gives LH-like. For prolactin remember: Dopamine Drops prolactin.

Compare and contrast

Gonadotropin preparations

Preparation	Source	Main activity	Typical use
FSH	Pituitary extract	FSH	Superovulation
hCG	Urine of pregnant women	LH-like	Induce ovulation or luteinisation
eCG (PMSG)	Pregnant mare serum	FSH-like with LH activity, long-lasting	Anoestrus, superovulation
GnRH analogues	Synthetic	Release endogenous LH and FSH	Ovulation induction, follicular cysts, synchronisation

Oxytocin versus vasopressin

Feature	Oxytocin	Vasopressin (ADH)	Desmopressin
Release site	Posterior pituitary	Posterior pituitary	Synthetic
Main receptor	Oxytocin receptor	V1 and V2	Mostly V2
Key action	Uterine contraction, milk let-down	Water reabsorption, vasoconstriction	Water reabsorption
Clinical use	Uterine inertia, retained placenta	Shock (V1), DI	Central diabetes insipidus

Species notes

Cattle

Oxytocin is used in retained placenta and milk let-down problems, and GnRH combined with prostaglandin is the basis of many timed breeding programmes. Oxytocin misuse in dairy animals is a regulatory concern in India.

Dog

Bitches with pseudopregnancy or unwanted lactation respond to dopamine agonists such as cabergoline. Central diabetes insipidus is treated with desmopressin. Dogs with progestin-induced excess growth hormone may show insulin resistance.

Cat

Cats with acromegaly, usually from a pituitary tumour, develop insulin-resistant diabetes. Queens can be treated with dopamine agonists to stop lactation, with attention to vomiting.

Horse

eCG originates in pregnant mares, and oxytocin is used in mares for retained placenta and uterine clearing after foaling, as well as to help milk let-down. Check product labelling for use in lactating mares.

Buffalo

Buffalo are particularly dependent on milk let-down, and the oxytocin misuse problem in Indian dairying

involves both cattle and buffalo. Follow the current Indian notification for legal use.

Clinical pearls

Self-test: 10 questions

1. Which hormones are stored and released by the posterior pituitary?

Oxytocin and ADH are made in hypothalamic neurons and released from the posterior pituitary. The others come from the anterior pituitary.

2. Why is oxytocin dangerous in a case of uterine obstruction?

Strong contractions against an obstructed or unprepared passage can rupture the uterus and kill the fetus.

3. Which receptor mediates the antidiuretic action of vasopressin?

V2 receptors in the collecting duct raise cAMP and insert aquaporin-2 channels.

4. Desmopressin will fail to correct polyuria in which condition?

In nephrogenic DI the kidney does not respond to ADH or its analogues.

5. Continuous exposure to a GnRH agonist results in:

Continuous stimulation desensitises and down-regulates pituitary GnRH receptors.

6. Which preparation is mainly LH-like?

hCG binds the LH receptor and acts like LH. eCG has both FSH and LH-like activity.

7. Which drug is a dopamine agonist used to suppress lactation in bitches?

Cabergoline stimulates D2 receptors on lactotrophs and lowers prolactin. Metoclopramide and domperidone raise prolactin.

8. Which statement about eCG is correct?

eCG comes from pregnant mares, has a long half-life and can cause antibody formation on repeated use.

9. What is the effect of excess growth hormone on glucose metabolism?

Growth hormone is diabetogenic and antagonises insulin action.

10. Which statement is the most appropriate about oxytocin regulation in India?

Controls have been placed on oxytocin because of misuse in dairy animals, and rules can change, so the current notification should be consulted.

Key points to revise

1. The posterior pituitary stores and releases oxytocin and ADH, which are made in the hypothalamus.
2. Oxytocin contracts the uterus and the mammary myoepithelium, and the uterus responds best under oestrogen.
3. Oxytocin carries a risk of uterine rupture if given against obstruction.
4. Oxytocin has regulatory controls in India, so check the current notification.
5. ADH acts through V2 (water retention) and V1 (vasoconstriction).
6. GnRH is stimulatory when pulsatile and suppressive when continuous.
7. hCG is LH-like and eCG is FSH-like with LH activity; repeated use can cause antibodies.

8. Somatotropin raises milk yield and is diabetogenic; its legal status in India should be checked.

Go deeper on this site

- Ch 27. Thyroid and antithyroid drugs (in this book)
- Ch 28. Pancreatic hormones and antidiabetic drugs (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Overview of the pituitary gland
- Merck Veterinary Manual: Diabetes insipidus
- University of Minnesota Libraries: Principles of Pharmacology

CHAPTER 27 OF 33

Thyroid and antithyroid drugs

How thyroid hormones are made and controlled, and how levothyroxine and methimazole are used for hypothyroidism in dogs and hyperthyroidism in cats. The chapter also covers monitoring, adverse effects and the common traps in diagnosis.

After this chapter you can

- Outline thyroid hormone synthesis and feedback control
- Explain levothyroxine therapy for canine hypothyroidism and the principles of monitoring
- Explain how methimazole works and list its adverse effects in cats
- Compare the treatment options for feline hyperthyroidism
- Recognise drugs and illnesses that confuse thyroid testing

Thyroid hormone synthesis and control

The thyroid gland makes **thyroxine (T4)** and a smaller amount of **triiodothyronine (T3)**. T4 is the main secreted product, and tissues convert it into the more active T3

by removing one iodine atom. T3 binds nuclear receptors and changes gene expression, which is why thyroid hormone effects on metabolism, heart rate and growth appear slowly and last for days.

Synthesis has clear steps, and each is a possible drug target:

1. **Iodide trapping**: the follicular cell actively takes up iodide from blood.
2. **Oxidation and organification**: the enzyme thyroid peroxidase (TPO) oxidises iodide and attaches it to tyrosine residues on thyroglobulin.
3. **Coupling**: iodinated tyrosines join to form T4 and T3 on thyroglobulin, which is stored as colloid.
4. **Release**: thyroglobulin is taken back into the cell, broken down, and T4 and T3 are secreted.

Control is by negative feedback. The hypothalamus releases TRH, the pituitary releases TSH, and the thyroid responds. High T4 switches off TRH and TSH. Most circulating thyroid hormone is bound to plasma proteins, and only the free fraction is active.

Why the signs follow the hormone

Thyroid hormone sets the pace of metabolism in almost every tissue. It raises oxygen use, heat production, heart rate and the sensitivity of the heart to catecholamines. It also drives normal skin turnover, hair growth and nerve function. That one idea explains most clinical signs.

When hormone is low, everything slows: the dog is dull and gains weight on little food, feels the cold, grows a poor coat and heals skin infections slowly. When hormone is high, everything speeds up: the cat loses weight despite eating well, has a fast heart and is restless and warm.

This also explains therapy. Levothyroxine in a hypothyroid dog should bring the pace back to normal over weeks, so a dog that becomes agitated and thin on treatment is being overdosed. Methimazole in a cat should slow the pace gradually, so a cat that becomes dull and gains weight may now be over-suppressed and needs a dose review. Always match the signs to the direction of the drug effect.

Hypothyroidism in dogs

Hypothyroidism is common in dogs. It is usually caused by immune-mediated lymphocytic thyroiditis or by idiopathic atrophy of the gland, so the gland slowly fails. Typical signs are lethargy, weight gain, cold intolerance, a dull coat with hair loss and recurrent skin infections. Because many other diseases mimic these signs, laboratory confirmation matters.

Levothyroxine (synthetic L-T4) is the treatment of choice. It replaces the missing hormone, and the dog converts it to T3 as needed. Therapy is lifelong, and the aim is to control the clinical signs and bring blood hormone levels into a suitable range, not to produce a rapid change.

Key practical points:

- The drug has a fairly long half-life in dogs, but absorption varies between products and with food, so a consistent routine is important.
- Clinical response is gradual. Activity may improve within a few weeks, while skin and coat changes take longer.
- Monitoring uses a blood T4 measured at a defined time after the tablet, together with clinical assessment. The sampling time and the target range should follow the guidance for the product used.
- Overdosing causes signs of thyrotoxicosis: restlessness, panting, weight loss, tachycardia and polyphagia.

Diagnosis comes before treatment. Giving thyroid hormone to a euthyroid dog does not help and can suppress the normal gland.

Hyperthyroidism in cats

Hyperthyroidism is the commonest endocrine disease of older cats. It is usually caused by benign adenomatous change in one or both thyroid lobes, and the overactive tissue makes too much hormone. Signs include weight loss despite a good appetite, restlessness, vomiting, polyuria, a fast heart rate and sometimes a palpable thyroid nodule. Untreated disease can cause cardiac changes and high blood pressure.

Treatment options include:

- **Antithyroid drugs** (methimazole, carbimazole), which suppress synthesis and are reversible.

- **Radioactive iodine**, which is taken up by overactive tissue and destroys it, and is often curative but requires a licensed facility.
- **Surgical thyroidectomy**, which can cure the disease but requires anaesthesia of a cat that may have heart disease and risks damage to the parathyroid glands.
- **Iodine-restricted diet**, which works only if the cat eats nothing else.

In India, radioiodine services are limited, so drug treatment or surgery is often the realistic choice. Check what facilities are available locally.

Methimazole and other antithyroid drugs

Methimazole (thiamazole) inhibits thyroid peroxidase, so iodine cannot be attached to thyroglobulin and new T4 and T3 are not made. It does not block release of hormone already stored, so improvement takes a few weeks. It does not cure the underlying tumour, and the gland may continue to enlarge.

Carbimazole is a prodrug that is converted to methimazole in the body. **Propylthiouracil** also blocks TPO and peripheral T4 to T3 conversion, but it is toxic in cats, causing haemolytic anaemia, so it is avoided.

Adverse effects in cats are mostly in the first weeks and include:

- Vomiting and loss of appetite.
- Intense facial itching with skin excoriation.
- Blood disorders such as neutropenia, thrombocytopenia and, less commonly, haemolytic anaemia.
- Liver injury with raised enzymes and jaundice.
- Positive antinuclear antibody tests.

Serious reactions usually mean stopping the drug. Many cats are also given a transdermal gel preparation applied to the ear, which can reduce gastrointestinal upset but may cause local skin irritation.

An important trap is **masked kidney disease**. Hyperthyroidism increases renal blood flow and glomerular filtration. When the thyroid is controlled, blood flow falls and a pre-existing chronic kidney disease may become obvious. Renal values should be checked before and after starting treatment.

Adjuncts and thyroid-related traps

Beta-blockers such as propranolol or atenolol can control the fast heart rate and tremor of hyperthyroidism while the main treatment takes effect. They do not lower thyroid hormone levels. Stable iodide solutions block hormone release for a short time and are sometimes used before surgery.

Interpreting thyroid tests needs care. **Non-thyroidal illness** (sick euthyroid) can lower T4 in a dog that has no thyroid disease. Drugs that can lower measured T4 include glucocorticoids, phenobarbital and potentiated sulfonamides. Long-term sulfonamides can also cause true, reversible hypothyroidism in dogs. Testing during illness or while on these drugs can lead to a wrong diagnosis and unnecessary lifelong therapy.

Other thyroid problems in animals include **goitre** in newborn lambs, kids and calves from iodine deficiency in the diet or from goitrogens such as certain brassica feeds. Here the gland enlarges because low iodine reduces feedback inhibition and TSH rises. The fix is correcting the diet, not an antithyroid drug.

Thyroid hormone is also a banned or controlled substance in some performance contexts, and growth promoters containing antithyroid substances are not acceptable in food animals. Check current regulations in India.

Concept cleared

Concept cleared: Why methimazole is slow
Imagine a factory with a full warehouse. Methimazole shuts down the production line, but the warehouse (stored colloid) still ships products for a while. Hormone levels fall only when the stock runs low, so improvement takes weeks.

Concept cleared: Why the kidney problem appears later
Hyperthyroidism is like a pump running too fast, which pushes extra blood through the kidneys and hides kidney weakness. When the pump is slowed to normal, the weakness shows.

Concept cleared: Sick euthyroid

In serious illness the body lowers thyroid hormone to save energy. The low reading is a response, not a diagnosis, so treating it with levothyroxine does not help.

Concept cleared: Goitre from low iodine

Without iodine the gland cannot make hormone, so T4 falls, TSH rises, and TSH pushes the gland to grow. The gland is enlarged because it is working harder, not because hormone is excessive.

Memory aid: Thyroid synthesis steps

Trap, Oxidise, Organify, Couple, Release: think 'Tom Often Orders Cold Rice'. Methimazole blocks the O steps through TPO. For signs remember: hypothyroid dogs are Slow and Heavy, hyperthyroid cats are Fast and Thin.

Compare and contrast

Hypothyroidism in dogs versus hyperthyroidism in cats

Feature	Canine hypothyroidism	Feline hyperthyroidism
Usual cause	Lymphocytic thyroiditis or atrophy	Benign adenomatous hyperplasia
Typical signs	Lethargy, weight gain, skin disease	Weight loss, ravenous appetite, restlessness
Main drug	Levothyroxine, lifelong	Methimazole or carbimazole
Key risk of therapy	Overdose giving thyrotoxicosis	Blood, liver and skin reactions; masked kidney disease

Options for feline hyperthyroidism

Option	Mechanism	Advantage	Limitation
Methimazole or carbimazole	Inhibit TPO	Reversible, widely available	Lifelong dosing and adverse effects
Radioactive iodine	Destroys overactive tissue	Often curative	Needs a licensed facility
Thyroidectomy	Removes tissue	Can cure	Anaesthetic risk, parathyroid damage
Iodine-restricted diet	Limits substrate	No drugs	Only works if the diet is exclusive

Species notes

Dog

Hypothyroidism is the common disorder and levothyroxine is lifelong. Hyperthyroidism is rare and usually due to a thyroid carcinoma, so surgery or other cancer treatment is the focus rather than antithyroid drugs alone.

Cat

Hyperthyroidism is common in old cats. Methimazole is widely used and requires monitoring of blood counts, liver and kidney values. Propylthiouracil should be avoided. Hypothyroidism is rare and mostly follows treatment.

Cattle

Goitre in newborn calves reflects iodine deficiency in the dam's diet. Correct the diet and check local iodine status, which varies between regions.

Sheep and goat

Newborn lambs and kids born to iodine-deficient dams may show goitre, weakness or high mortality, and the same dietary correction applies.

Horse

Foals from mares with iodine imbalance can develop goitre. Both deficiency and excess of iodine are possible, so supplement based on

dietary assessment rather than guesswork.

Clinical pearls

Self-test: 10 questions

1. Which enzyme is inhibited by methimazole?

Methimazole blocks thyroid peroxidase, preventing iodination of thyroglobulin and hormone synthesis.

2. The drug of choice for canine hypothyroidism is:

Levothyroxine replaces the missing hormone and is given lifelong.

3. Why does methimazole take weeks to act?

Stored hormone in colloid keeps being released until it is used up.

4. Which drug is avoided in cats due to haemolytic anaemia?

Propylthiouracil is toxic in cats.

5. What is carbimazole?

Carbimazole is converted to methimazole in the body.

6. Why should renal values be checked when treating a hyperthyroid cat?

Hyperthyroidism raises glomerular filtration, and falling flow after control may reveal pre-existing kidney disease.

7. Which of these can falsely lower T4 in a dog?

Glucocorticoids, phenobarbital, potentiated sulfonamides and non-thyroidal illness can lower measured T4.

8. A newborn lamb with a goitre most likely reflects:

Low iodine reduces hormone synthesis, raising TSH, which enlarges the gland.

9. Which sign suggests levothyroxine overdose in a dog?

Excess hormone causes thyrotoxic signs such as restlessness, tachycardia and weight loss.

10. Beta-blockers in feline hyperthyroidism are used to:

They relieve adrenergic signs while the main therapy takes effect, but do not reduce hormone production.

Key points to revise

1. T4 is the main secreted hormone and T3 is the more active form made by peripheral conversion.
2. Thyroid peroxidase is the enzyme needed for iodination and coupling.
3. Canine hypothyroidism is mostly lymphocytic thyroiditis or atrophy and needs lifelong levothyroxine.
4. Levothyroxine is monitored by timed T4 and clinical response, not by quick dose changes.
5. Feline hyperthyroidism is treated with drugs, radioiodine, surgery or diet.
6. Methimazole inhibits TPO and is slow in effect.
7. Adverse effects of methimazole include gastrointestinal upset, facial itching, blood and liver problems.
8. Non-thyroidal illness and some drugs lower T4 and can mimic hypothyroidism.

Go deeper on this site

- Ch 28. Pancreatic hormones and antidiabetic drugs (in this book)
- Ch 26. Hypothalamic and pituitary hormones (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Hyperthyroidism
- Merck Veterinary Manual: Hypothyroidism
- Merck Veterinary Manual: Overview of the thyroid gland

CHAPTER 28 OF 33

Pancreatic hormones and antidiabetic drugs

How insulin and glucagon control blood glucose, which insulin types are used in dogs and cats, what oral agents and SGLT2 inhibitors can and cannot do, and the logic of treating diabetic ketoacidosis. The emphasis is on mechanism and on why mistakes happen.

After this chapter you can

- Explain how insulin and glucagon regulate glucose and why insulin lowers potassium
- Group insulin preparations by onset and duration and match them to the usual species choice
- Describe the role and limits of oral hypoglycaemic agents in cats and dogs
- Explain how SGLT2 inhibitors work in cats, who they suit, and the euglycaemic ketoacidosis risk
- Outline the stepwise logic of diabetic ketoacidosis treatment: fluids, potassium, then insulin

Insulin and glucagon: the basic physiology

The pancreatic islets release two opposing hormones. **Insulin** from the beta cells is the hormone of the fed state. **Glucagon** from the alpha cells is the hormone of fasting. Together they hold blood glucose in a narrow range.

Insulin binds a receptor with intrinsic tyrosine kinase activity on the cell surface. The signal moves glucose transporters (GLUT4) to the membrane of muscle and fat cells, so glucose enters. In the liver insulin switches off glucose production and promotes glycogen and fat storage. It also drives potassium into cells. This last action matters in practice: giving insulin lowers serum potassium.

Glucagon does the reverse in the liver, raising glucose through glycogen breakdown and new glucose synthesis. Diabetes mellitus is a failure of insulin action, either because beta cells are lost or damaged, or because tissues respond poorly, or both. Without insulin, glucose stays in the blood and the body burns fat instead, producing ketones.

A common confusion: hyperglycaemia causes the clinical signs of polyuria and polydipsia only after glucose passes the renal threshold. Glucose then spills into urine and drags water with it (osmotic diuresis).

Insulin preparations and how they are chosen

Insulins differ in how fast they start and how long they last. This is the single most important idea for choosing one.

- **Short-acting (regular, soluble) insulin**. Rapid onset and short duration. It is the one used in emergencies such as ketoacidosis because it can be given by infusion or intramuscularly and adjusted quickly.
- **Intermediate-acting (NPH, lente)**. NPH has protamine added to slow absorption. Lente (porcine insulin zinc suspension) is a mixture of crystalline and amorphous zinc insulin. These are the usual starting insulins in dogs, given twice daily. Product availability differs between countries, so check what is marketed locally.
- **Long-acting (protamine zinc insulin, glargine, detemir)**. Slower and flatter action. Protamine zinc insulin and glargine are commonly chosen for newly diagnosed cats, since cats often need a longer duration than dogs. Detemir may be considered when control in dogs is poor.

Insulin is a protein, so it is destroyed by gut enzymes and must be injected, normally subcutaneously. Store it as the label directs and avoid vigorous shaking of

suspensions, which makes dose delivery uneven.

The same insulin does not behave identically in every animal. Absorption, peak and duration vary, so the right insulin is judged by a glucose curve and clinical response, not by label duration alone.

Complications of insulin therapy

The main danger is **hypoglycaemia**: weakness, tremor, collapse, seizures. Causes include too high a dose, a missed meal, or a sudden change in insulin need (for example after remission in a cat or after treating an interfering disease). Owners must be taught the signs and an emergency plan.

Two confusing states follow poor control. In the **Somogyi effect**, an overdose causes hypoglycaemia followed by a counter-regulatory surge of glucagon, adrenaline, cortisol and growth hormone, giving high glucose later. In **insulin resistance**, glucose stays high despite adequate doses. Distinguishing them needs serial glucose measurement, because the treatment for one (reduce dose) is opposite to the other (look for the cause).

Common causes of resistance are concurrent disease (infection, pancreatitis, hyperadrenocorticism, acromegaly), drugs such as glucocorticoids and progestins, obesity, and technique or storage errors. Remember this when prescribing other hormones in a diabetic animal.

Oral agents: what they can and cannot do

Oral drugs only help if some functioning beta-cell mass remains. This is why they have a place in a few cats and almost none in dogs, whose diabetes usually involves severe insulin deficiency.

- **Sulfonylureas** (for example glipizide) close ATP-sensitive potassium channels on beta cells, causing depolarisation, calcium entry and insulin release. They are used only in cats that are well, not thin and not ketotic, and the response is limited and often not sustained. Long-term stimulation may exhaust beta cells.
- **Alpha-glucosidase inhibitors** (acarbose) slow carbohydrate digestion in the gut and blunt the post-meal rise. They are an adjunct to diet and insulin, with gut side effects such as flatulence and diarrhoea.

- **Biguanides and thiazolidinediones** are important in human type 2 diabetes but have little established role in small animals.

The take-home point is that oral agents are not a substitute for insulin in an animal that is sick, ketotic or thin.

SGLT2 inhibitors in cats

Sodium-glucose cotransporter 2 (SGLT2) in the proximal renal tubule reabsorbs most filtered glucose. SGLT2 inhibitors block it, so glucose is lost in urine and blood glucose falls without needing insulin. Two agents (velagliflozin and bexagliflozin) have been licensed for cats in some countries. Availability in India is uncertain, so check the current notification and market status before relying on them.

They suit only selected cats: newly diagnosed, otherwise well, eating normally, and not previously on insulin, so that some beta-cell function remains. They are not for cats with significant liver or kidney disease, pancreatitis, or those who are anorexic, dehydrated or lethargic at diagnosis.

The key hazard is **ketoacidosis, including euglycaemic ketoacidosis**. Because the drug removes glucose through urine, the blood glucose may look normal or only mildly raised even while ketones accumulate. A cat that becomes dull, anorexic or dehydrated must be assessed for ketosis whatever the glucose reading. Treatment is to stop the drug, give insulin, and provide carbohydrate and nutritional support, which also helps prevent hepatic lipidosis. Other effects include glucosuria-related urinary and gut signs.

Diabetic ketoacidosis: a stepwise approach

Diabetic ketoacidosis (DKA) arises when insulin lack lets fat breakdown run unchecked. Ketoacids accumulate, causing metabolic acidosis, dehydration and electrolyte loss. It is an emergency, often triggered by pancreatitis, infection or another concurrent illness.

1. **Rehydrate first.** Intravenous isotonic fluids restore perfusion and also lower glucose by dilution and improved renal clearance.
2. **Replace electrolytes.** Total body potassium and phosphate are depleted, though the serum level may look normal because acidosis shifts potassium out of cells.

Insulin then pushes potassium back in and can cause dangerous hypokalaemia, so supplement potassium and monitor.

3. **Give insulin.** Short-acting insulin is used, by infusion or intermittent injection, usually after fluids have started. The aim is a gradual fall in glucose, not rapid normalisation, because a fast drop can contribute to cerebral oedema.
4. **Treat the trigger** and support nutrition. Add dextrose to fluids when glucose falls while ketosis persists, so insulin can continue to suppress ketone production.
5. **Transition** to longer-acting insulin once the animal is hydrated, eating and stable.

A frequent exam error is to start insulin before fluids and potassium. Remember the order: fluids, potassium, then insulin.

Concept cleared

Insulin lowers potassium
Insulin moves potassium into cells. In DKA, serum potassium may be deceptively normal, and falls once insulin starts, so potassium is replaced alongside insulin.

Duration decides the choice
Regular insulin is for emergencies, intermediate insulins for typical dogs, and long-acting insulins for typical cats. Always confirm by glucose curve.

Oral drugs need beta cells
Sulfonylureas and SGLT2 inhibitors depend on some remaining insulin secretion. They fail or are unsafe when insulin lack is severe.

Normal glucose does not exclude ketoacidosis
SGLT2 inhibitors can cause euglycaemic ketoacidosis. Check ketones in any unwell cat on these drugs.

Memory aid: DKA order: F-P-I

Fluids, Potassium, Insulin. Treat the dehydration and electrolytes before pushing insulin, then treat the trigger.

Compare and contrast

Main insulin groups

Group	Examples	Speed and duration	Typical use
Short-acting	Regular (soluble)	Fast, short	DKA and emergencies
Intermediate	NPH, lente	Moderate, medium	Starting insulin in dogs
Long-acting	Protamine zinc, glargine, detemir	Slow, flatter	Newly diagnosed cats; poorly controlled dogs

Oral and non-insulin agents

Drug	Mechanism	Main limit
Sulfonylurea (glipizide)	Stimulates beta-cell insulin release	Needs functioning beta cells; not for thin or ketotic cats
Acarbose	Slows carbohydrate digestion	Gut side effects; adjunct only
SGLT2 inhibitor	Blocks renal glucose reabsorption	Ketoacidosis risk; only selected cats; check availability

Species notes

Dogs
Diabetes is usually insulin-deficient and permanent. Twice-daily intermediate insulin with consistent diet is the base. Oral agents are not effective.

Cats
Often resembles human type 2 diabetes with insulin resistance, and remission is possible with early good control. Long-acting insulin is common. Avoid glucocorticoids and progestins.

Cattle and small ruminants

Classical diabetes is rare. Ketosis in cows is an energy deficit problem, not insulin failure, and is treated with glucose precursors rather than long-term insulin.

Horses

Insulin dysregulation is linked with equine metabolic syndrome and pituitary disease rather than insulin-dependent diabetes. Management is by diet, exercise and treating the cause.

Clinical pearls

Self-test: 10 questions

1. Which action of insulin explains hypokalaemia during DKA treatment?

Insulin drives potassium into cells, lowering serum levels, so supplementation is needed.

2. Which insulin is preferred for acute DKA management?

Regular insulin acts quickly and can be given by infusion or intermittent injection and adjusted.

3. A sulfonylurea lowers glucose by:

Sulfonylureas close K-ATP channels on beta cells, triggering insulin secretion.

4. Which statement about SGLT2 inhibitors in cats is correct?

They act on the proximal tubule so glucose is lost in urine; they can cause ketoacidosis and suit only selected cats.

5. A cat on an SGLT2 inhibitor becomes anorexic and dull with only mildly raised glucose. The best step is to:

Euglycaemic ketoacidosis can occur with near-normal glucose.

6. In DKA, the correct treatment order is:

Rehydration and electrolyte replacement come before or with the start of insulin to avoid hypokalaemia and shock.

7. Why avoid very rapid glucose reduction in DKA?

Rapid osmolar shifts can contribute to cerebral oedema.

8. Which drugs commonly cause insulin resistance in diabetic animals?

Both antagonise insulin action and worsen control.

9. Which describes the Somogyi effect?

Counter-regulatory hormones are released after hypoglycaemia, raising glucose later.

10. Oral hypoglycaemics are generally ineffective in dogs because:

These agents need remaining beta-cell function, which is typically lost in canine diabetes.

Key points to revise

1. Insulin promotes glucose uptake via GLUT4 and drives potassium into cells.
2. Glucagon raises blood glucose by liver glycogen breakdown and glucose production.

3. Insulin types differ in onset and duration; choice is species and case dependent.
4. Hypoglycaemia is the main complication of insulin therapy.
5. Somogyi effect and insulin resistance look alike but need opposite responses.
6. Oral agents depend on remaining beta-cell function and have limited roles.
7. SGLT2 inhibitors block renal glucose reabsorption and can cause euglycaemic ketoacidosis.
8. DKA treatment is fluids, potassium and phosphate, then insulin, with a gradual glucose fall.

Go deeper on this site

- Ch 29. Adrenal hormones and the glucocorticoid axis (in this book)
- Ch 27. Thyroid and antithyroid drugs (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Diabetes mellitus in dogs and cats
- FDA CVM: Dear Veterinarian letter on Bexacat safety
- Merck Veterinary Manual: Hormonal treatment for integumentary disease in animals

CHAPTER 29 OF 33

Adrenal hormones and the glucocorticoid axis

The hypothalamic-pituitary-adrenal axis, the actions of glucocorticoids and mineralocorticoids, and the drugs used for hypercortisolism (Cushing) and hypocortisolism (Addison). Includes why steroid withdrawal is dangerous and what stress dosing means.

After this chapter you can

- Describe the CRH-ACTH-cortisol axis and its negative feedback
- Distinguish glucocorticoid and mineralocorticoid actions and give examples of each drug

- Explain how trilostane and mitotane treat canine hyperadrenocorticism and their key risks
- Outline maintenance and emergency treatment of Addison disease
- Explain iatrogenic adrenal suppression and the concept of stress dosing

The adrenal axis

The adrenal cortex makes three families of steroid. The outer zone makes **mineralocorticoids** (mainly aldosterone), the middle zone makes **glucocorticoids** (cortisol in most species, corticosterone in rodents) and the inner zone makes sex steroids.

Cortisol release is controlled by a chain: the hypothalamus releases corticotropin-releasing hormone (CRH), the pituitary releases ACTH, and ACTH drives the adrenal cortex. Cortisol then feeds back negatively on both hypothalamus and pituitary. Aldosterone is controlled mainly by the renin-angiotensin system and by serum potassium, not by ACTH, although ACTH has a minor effect.

This difference explains much of the clinical pattern. If ACTH is lost (secondary hypoadrenocorticism, or after long steroid therapy), the cortisol zone shrinks but aldosterone remains. If the cortex is destroyed (primary Addison disease), both are lost.

Actions of glucocorticoids and mineralocorticoids

Glucocorticoids act on intracellular receptors that change gene transcription, so their effects begin over hours. They raise blood glucose, break down protein and redistribute fat, suppress inflammation and immunity, and are needed to maintain blood pressure and respond to stress. Their use as drugs is covered in the earlier chapter on corticosteroids, but the same actions explain the signs of excess: polyuria, polydipsia, polyphagia, muscle wasting, a pot belly, thin skin, and infection risk.

Mineralocorticoids act in the distal nephron, retaining sodium and water and excreting potassium and hydrogen ions. Loss produces hyponatraemia, hyperkalaemia, hypovolaemia and bradycardia.

Drugs overlap. Hydrocortisone has both actions. Prednisolone and dexamethasone are almost purely glucocorticoid, dexamethasone being far more potent and longer acting. Fludrocortisone has strong mineralocorticoid action with some glucocorticoid effect. Desoxycorticosterone pivalate (DOCP) is a long-acting injectable that is essentially mineralocorticoid only.

Cushing disease: reducing cortisol

Hyperadrenocorticism in dogs is most often due to a pituitary tumour secreting ACTH (pituitary-dependent), and less often an adrenal tumour. Long-term glucocorticoid therapy produces a similar picture, called iatrogenic Cushing. In horses the equivalent is pituitary pars intermedia dysfunction, managed with a dopamine agonist such as pergolide because the affected cells lose dopamine inhibition.

Two main drugs are used in dogs.

- **Trilostane** is an enzyme inhibitor that blocks steroid synthesis in the adrenal, decreasing cortisol output. The effect is reversible and the drug is usually given with food. The main concerns are over-suppression, a transient hypocortisolism that can be missed on routine testing, reversible mineralocorticoid deficiency, and rarely adrenal necrosis with permanent insufficiency. Therapy is monitored by clinical signs and by cortisol testing.
- **Mitotane (o,p'-DDD)** is an adrenolytic: it selectively damages the cortical zones that make cortisol. It is given as an induction phase followed by maintenance and needs careful monitoring. Side effects include vomiting, lethargy, ataxia and, if overdone, hypoadrenocorticism, which requires stopping the drug and giving glucocorticoids.

Neither drug cures a pituitary tumour. The aim is to control clinical signs, not to normalise every laboratory value. Surgery is the usual choice for an operable adrenal tumour.

Addison disease: replacing what is lost

Hypoadrenocorticism is deficiency of adrenocortical hormones, most commonly immune-mediated destruction in dogs. Signs are vague: lethargy, vomiting,

weakness, weight loss, sometimes collapse. In crisis, hyperkalaemia and hypovolaemia threaten the heart and circulation.

Emergency (Addisonian crisis). Intravenous fluids are the mainstay. Hypoglycaemia and hyperkalaemia are treated directly. A rapid-acting glucocorticoid is given, and dexamethasone is often preferred because it does not interfere with a diagnostic ACTH stimulation test. Mineralocorticoid is added when electrolytes indicate deficiency.

Maintenance. Two parts are needed: a mineralocorticoid (DOCP by periodic injection, or daily fludrocortisone) and a glucocorticoid (low-dose prednisolone or prednisone, tapered to the lowest level that controls signs). Dogs with atypical disease, where only glucocorticoids are lacking at first, still need electrolyte checks because mineralocorticoid deficiency can appear later.

Overtreatment mimics Cushing: increased thirst, urination, appetite and infections.

Iatrogenic suppression and stress dosing

Giving glucocorticoids for more than a short course suppresses CRH and ACTH. The adrenal cortex then atrophies. If the drug is stopped abruptly, the animal cannot make cortisol and may collapse. The remedy is a gradual tapering, and a recognition that recovery can take weeks.

Stress dosing is the idea that a normal animal increases cortisol output during illness, surgery, anaesthesia or trauma. An animal with Addison disease, or one on long-term steroids, cannot do this, so the dose must be increased temporarily during stress. Concerning signs include unexplained collapse, hypotension, hypoglycaemia and vomiting after a stressful event.

Remember also that topical, ocular and injectable depot steroids can suppress the axis. Progestins such as megestrol have glucocorticoid-like activity and cause adrenal suppression as well.

Mineralocorticoids and other uses

Mineralocorticoids have little use outside Addison disease in small animals. Fludrocortisone's sodium retention can cause hypertension and oedema if overdosed, and its effect on potassium is the monitoring target.

In ruminants, glucocorticoids have specific uses. A potent glucocorticoid given late in gestation can induce parturition because it mimics the fetal cortisol surge that triggers labour. This also explains why such drugs are a risk for abortion in pregnant animals. Prolonged use in livestock may raise glucose and suppress immunity. Check withdrawal periods and the current regulatory position before use in food animals.

Concept cleared

Negative feedback
Cortisol suppresses CRH and ACTH. Exogenous steroid does the same, which is why long-term therapy atrophies the adrenal cortex.

ACTH controls cortisol, not aldosterone
Aldosterone is controlled mainly by renin-angiotensin and potassium, so secondary adrenal failure spares electrolytes.

Trilostane inhibits; mitotane destroys
Trilostane reversibly blocks steroid synthesis. Mitotane damages adrenal cortex tissue, so over-treatment can be more lasting.

Stress dosing
Animals that cannot raise cortisol need a temporary dose increase during illness or surgery to avoid adrenal crisis.

Memory aid: Cushing is Cortisol Crowded
Excess cortisol gives thirst, hunger, thin skin, pot belly and infections. Addison is the opposite: low sodium, high potassium, shock.

Compare and contrast

Cushing drugs in dogs

Drug	Mechanism	Key risk
Trilostane	Reversible adrenal enzyme inhibition	Over-suppression, rarely adrenal necrosis
Mitotane	Adrenolytic damage to cortex	GI and CNS effects, iatrogenic Addison

Corticosteroid activity

Drug	Glucocorticoid	Mineralocorticoid	Use
Hydrocortisone	Yes	Some	Crisis, replacement
Prednisolone	Yes	Little	Maintenance and anti-inflammatory
Dexamethasone	Very potent	Almost none	Emergency, testing-friendly
Fludrocortisone	Some	Strong	Addison maintenance
DOCP	Minimal	Yes	Addison maintenance

Species notes

Dogs
Both Cushing and Addison disease are common. Trilostane is the usual drug for Cushing and DOCP with a glucocorticoid for Addison.

Cats
Spontaneous Cushing and Addison disease are uncommon. Cats are relatively resistant to the side effects of glucocorticoids but fragile skin and diabetes can occur.

Horses
Pituitary pars intermedia dysfunction causes hirsutism and laminitis. Dopamine agonist therapy is used, not adrenal enzyme inhibitors.

Cattle and sheep
Corticosteroids can induce parturition, and may cause abortion in pregnancy. Check withdrawal periods and local rules for food animals.

Clinical pearls

Self-test: 10 questions

1. Which hormone mainly stimulates cortisol release from the adrenal cortex?

ACTH from the pituitary drives cortisol secretion.

2. Aldosterone secretion is controlled mainly by:

ACTH has only a minor effect on aldosterone.

3. Trilostane acts by:

It is an adrenal enzyme inhibitor.

4. Mitotane is best described as:

It damages adrenal cortical tissue.

5. A dog on mitotane develops anorexia, vomiting and diarrhoea. The best action is to:

These signs suggest hypoadrenocorticism.

6. A long-acting injectable mineralocorticoid for Addison disease is:

Desoxycorticosterone pivalate replaces aldosterone-type activity.

7. Why is dexamethasone often chosen in an Addisonian crisis before testing?

Dexamethasone does not cross-react with the cortisol assay.

8. Overtreatment of Addison disease with prednisolone causes signs resembling:

Excess glucocorticoid produces iatrogenic hyperadrenocorticism.

9. Stress dosing is needed in an animal with Addison disease because it:

Normal animals boost cortisol under stress; these animals cannot.

10. Equine pituitary pars intermedia dysfunction is usually treated with:

Loss of dopaminergic inhibition drives the disease, so a dopamine agonist is used.

Key points to revise

1. Cortisol release follows CRH to ACTH to adrenal cortex with negative feedback.
2. Aldosterone is controlled mainly by renin-angiotensin and potassium.
3. Glucocorticoid excess produces PU/PD, polyphagia, muscle wasting and infection risk.
4. Trilostane is a reversible adrenal enzyme inhibitor used for canine Cushing.
5. Mitotane is adrenolytic and needs careful monitoring.
6. Addison disease needs mineralocorticoid plus glucocorticoid replacement.
7. Addisonian crisis is treated with fluids, glucocorticoid and correction of metabolic derangements.
8. Prolonged steroid use causes adrenal atrophy and requires tapering and stress cover.

Go deeper on this site

- Ch 30. Sex hormones, anabolics and growth promoters (in this book)
- Ch 28. Pancreatic hormones and antidiabetic drugs (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index

- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Addison disease (hypoadrenocorticism) in animals
- Merck Veterinary Manual: Cushing disease (pituitary-dependent hyperadrenocorticism) in animals
- Merck Veterinary Manual: Cushing syndrome (hyperadrenocorticism) in animals

CHAPTER 30 OF 33

Sex hormones, anabolics and growth promoters

The actions, uses and hazards of oestrogens, progestins, androgens and anabolic steroids in animals, with emphasis on pyometra and bone marrow toxicity, and on why hormonal growth promoters and doping are regulated.

After this chapter you can

- Describe the main actions of oestrogens, progestins and androgens
- Explain why oestrogens and progestins predispose to pyometra
- Recognise oestrogen-induced bone marrow suppression and species sensitivity
- Describe uses and adverse effects of anabolic steroids
- Explain the regulatory and ethical issues in hormonal growth promotion and misuse

Sex steroids: one family, many effects

Oestrogens, progestins and androgens are steroid hormones made from cholesterol in the gonads, adrenal cortex and placenta. They act like other steroids: they enter the cell, bind intracellular receptors and change gene transcription. Effects are slow in onset and often long in duration.

Natural hormones are largely destroyed in the liver when swallowed, so drug forms are usually modified for oral activity, esterified for depot injection, or implanted. These changes alter potency and duration but not the basic receptor action.

A key idea for this chapter is that these drugs are not simple tools for one organ. They act on the uterus, mammary gland, prostate, bone marrow, liver, pituitary and behaviour all at once. Most serious adverse effects come from this wide action.

Oestrogens

Oestrogens such as oestradiol, and the synthetic diethylstilbestrol, promote development of the female tract, mammary tissue and secondary sex characteristics, and sensitise the uterus to progesterone.

Uses in small animals are now narrow. A weak oestrogen is used for urethral sphincter incompetence in spayed bitches, because oestrogen increases the sensitivity of the urethral smooth muscle to adrenergic stimulation. Oestrogen has also been used for mismating, but this is **not advised**: injectable oestrogens can cause pyometra and fatal bone marrow suppression, and oral oestrogen given during diestrus raises pyometra risk and is unreliable. Safer alternatives such as prostaglandins or antiprogestins are preferred where available.

Bone marrow toxicity is the dangerous effect. Oestrogens can cause bone marrow hypoplasia, with an initial rise and then a fall in neutrophils, followed by thrombocytopenia and anaemia. The effect may be delayed and is not always dose-predictable. Cats are especially sensitive. Weekly blood counts are needed if oestrogens are used.

Other effects include induced oestrus, hepatotoxicity, prostatic changes in male dogs and abortion.

Progestins and the pyometra problem

Progesterone maintains pregnancy by quietening the myometrium and promoting uterine gland secretion. Synthetic progestins (megestrol acetate, medroxyprogesterone) have been used to suppress oestrus, treat some behavioural and skin conditions, and in some prostatic or mammary disorders.

The problem is the uterus. Progesterone thickens and secretes from the endometrium, closes the cervix and reduces local immune defence. Repeated or prolonged exposure leads to **cystic endometrial hyperplasia**, which fills with fluid and becomes an ideal site for bacterial growth. This is **pyometra**. Oestrogen primes

the uterus to respond, so oestrogen followed by progestin or diestrus is the worst combination.

Other adverse effects of progestins include mammary hyperplasia and tumours, diabetes mellitus in cats, adrenal suppression, acromegaly-like growth hormone excess in dogs, and behavioural change. Because of these risks, they are generally avoided where alternatives exist.

Pyometra patients are acutely ill and often need surgery. A drug history of oestrogen or progestin should always be asked for.

Androgens

Testosterone and its derivatives drive male sexual development and behaviour, spermatogenesis and sex accessory glands, and also have anabolic effects on muscle and bone. Clinical uses are limited, for example in some libido or hormone-responsive conditions, and drugs must be chosen carefully.

Adverse effects include aggression, greasy coat, prostatic enlargement in dogs, suppression of the animal's own gonadal function (feedback inhibition of LH and FSH), and liver toxicity, especially with oral 17-alpha-alkylated forms. Liver function should be checked during treatment. Androgens given to a female can virilise her, and they can harm a pregnant female's fetuses.

Anabolic steroids

Anabolic steroids (nandrolone, stanozolol, boldenone) are androgen derivatives chosen for greater protein-building effect relative to male-type effects. Receptor activation increases nitrogen retention and muscle mass and may stimulate red cell production by enhancing erythropoietin response.

Veterinary uses are limited and include convalescence, debilitation and some anaemias. Evidence is variable and these are not substitutes for nutrition, treating the cause, or adequate calories.

The separation of anabolic and androgenic effects is incomplete. Hepatotoxicity, behavioural change, and fluid retention occur. They are subject to doping control in racing and sport animals and are controlled substances in many places.

Growth promoters, regulation and misuse

Some countries allow implants of sex-steroid or anabolic agents (for example trenbolone, zeranol, oestradiol) in beef cattle to increase growth and feed efficiency. Others, including the European Union, prohibit them. The concern is residues in meat and public-health effects, together with trade barriers and welfare issues.

For India, rules on hormonal growth promoters, hormone use in dairy animals, and maximum residue limits (MRLs) are set through national notifications and food-safety regulations. Check the current notification before advising on any use in food animals.

Misuse includes using anabolic steroids to improve appearance of show or racing animals, giving hormones to hasten maturity, and using hormones to increase milk. These are ethically and legally problematic, and some are harmful to the animal. A student should also know that residues carry a withdrawal period issue, and that clinical use must follow label and legal requirements.

Remember: a drug being available is not the same as being permitted for a given species or purpose.

Concept cleared

Oestrogen primes, progesterone promotes
Oestrogen sensitises the uterus and progesterone creates the secretory, immunologically weak environment. Together they predispose to pyometra.

Marrow toxicity is delayed
Oestrogen bone marrow suppression may appear after the drug has been given, so monitoring continues beyond the treatment.

Anabolic is not safe
Anabolic steroids retain androgenic and liver effects. Their benefits are modest and the risks real.

Residues and regulation

Hormonal growth promoters are restricted or banned in many jurisdictions to prevent residues in food and for trade and ethical reasons.

Memory aid: Oestrogen: B-P-L

Bone marrow, Pyometra, Liver. The three serious oestrogen hazards.

Compare and contrast

Sex hormone classes

Class	Examples	Main concern
Oestrogens	Oestradiol, diethylstilbestrol	Bone marrow suppression, pyometra, hepatotoxicity
Progestins	Megestrol, medroxyprogesterone	Pyometra, mammary tumours, diabetes in cats, adrenal suppression
Androgens and anabolics	Testosterone, nandrolone, stanozolol	Liver toxicity, behaviour, prostatic effects, doping

Mismating: choices

Option	Comment
Oestrogens	Not advised: pyometra and marrow risk
Prostaglandin analogues	Effective, with systemic effects to manage
Antiprogestins	Effective, availability limited in some countries

Species notes

Dogs

Pyometra follows diestrus and is made likelier by oestrogens and progestins. Oestrogen for

Cats

Highly sensitive to oestrogen toxicity. Megestrol can cause diabetes, adrenal suppression and mammary disease.

incontinence is used with blood monitoring.

Cattle
Hormonal growth implants are allowed in some countries and banned in others. Check the current Indian notification and withdrawal rules.

Horses
Anabolic steroids and sex hormones are prohibited substances in competition. Always check the rules of the governing body.

Poultry and pigs
Hormone growth promotion is not an accepted practice in most regulatory systems. Ask for current guidance.

Clinical pearls

Self-test: 10 questions

1. Which is the most serious haematological effect of oestrogens?

Oestrogen can cause marrow suppression with thrombocytopenia and anaemia.

2. Pyometra is promoted mainly by:

Oestrogen sensitises, progesterone drives glandular secretion and lowers defences.

3. Which species is especially sensitive to oestrogen toxicity?

Cats are highly sensitive to oestrogen-induced marrow toxicity.

4. A known adverse effect of megestrol in cats is:

Progestins have glucocorticoid-like activity and can cause diabetes in cats.

5. Oral 17-alpha-alkylated androgens are notable for:

This chemical modification increases liver toxicity.

6. Why are oestrogens not advised for mismating?

Injectable oestrogens carry a great risk of serious adverse effects.

7. The anabolic effect of these drugs is mainly:

They increase protein synthesis and nitrogen retention.

8. Why are hormonal growth promoters controversial?

Residue and public health concerns drive regulation, and rules differ between countries.

9. Prolonged progestin use may cause which uterine change?

Progestins stimulate endometrial glands, creating a setting for infection.

10. Before advising hormone use in a dairy cow in India, you should:

Regulations and MRLs change and must be checked.

Key points to revise

1. Sex steroids act through intracellular receptors and change gene expression.
2. Oestrogens can cause bone marrow suppression, pyometra and hepatotoxicity.
3. Cats are very sensitive to oestrogen toxicity.

4. Progestins predispose to cystic endometrial hyperplasia and pyometra.
5. Progestins can cause mammary disease, diabetes in cats and adrenal suppression.
6. Androgens and anabolics can be hepatotoxic and alter behaviour.
7. Hormonal growth promoters are restricted or banned in many countries.
8. Misuse in sport, show or food animals has legal, ethical and welfare consequences.

Go deeper on this site

- Ch 31. Calcium, phosphorus, vitamin D and bone drugs (in this book)
- Ch 29. Adrenal hormones and the glucocorticoid axis (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Prevention or termination of pregnancy in bitches and queens
- Merck Veterinary Manual: Hormonal treatment for integumentary disease in animals
- Merck Veterinary Manual: Hormonal control of the estrous cycle in dogs

CHAPTER 31 OF 33

Calcium, phosphorus, vitamin D and bone drugs

How parathyroid hormone, vitamin D and calcitonin hold blood calcium steady, and how calcium salts, vitamin D analogues and bisphosphonates are used. The chapter explains the treatment concepts for milk fever in cows and eclampsia in bitches.

After this chapter you can

- Explain how PTH, vitamin D and calcitonin regulate calcium and phosphorus
- Describe the activation steps of vitamin D and the therapeutic use of its analogues
- Explain how bisphosphonates work and where they are used in animals
- Describe the treatment principles and safety rules of intravenous calcium in milk fever

- Explain how prepartum diet prevents hypocalcaemia in dairy cows

Calcium balance in outline

Calcium is needed for nerve conduction, muscle contraction, clotting and bone strength. Blood ionised calcium is held in a narrow range, because even small falls cause tremor, weakness and seizures, and rises cause weakness, polyuria and kidney damage. Three organs defend the level: bone (the store), the intestine (absorption) and the kidney (excretion and activation of vitamin D).

Phosphorus moves in the opposite direction of calcium in many controls. Raised blood phosphate drives calcium down, and the body also tries to remove excess phosphate through the kidney. This is why kidney failure upsets calcium and phosphorus together.

Three hormones do the work: **parathyroid hormone** (PTH), **calcitriol** (active vitamin D) and **calcitonin**.

Parathyroid hormone and calcitonin

PTH is released from the parathyroid glands when ionised calcium falls. It raises blood calcium in three ways: it increases bone resorption, it increases calcium reabsorption in the distal kidney tubule while promoting phosphate loss in urine, and it stimulates the kidney enzyme 1-alpha hydroxylase to make calcitriol, which then raises intestinal calcium absorption.

PTH is a hormone for minute-to-minute and day-to-day defence of calcium. Continuous excess, as in primary hyperparathyroidism or renal secondary hyperparathyroidism, causes bone loss. This distinction matters in therapy: in humans, intermittent PTH analogues can build bone, but they are not standard veterinary drugs.

Calcitonin comes from the C cells of the thyroid and lowers calcium by inhibiting osteoclasts. Its physiological role in adult animals is minor, and its clinical use in veterinary medicine is limited. Calcitonin has a possible role in cows during early lactation, though it is not the main defence in milk fever, where PTH and vitamin D response matter more.

Vitamin D and its analogues

Vitamin D is a hormone precursor. Cholecalciferol (D3) comes from the skin by sunlight in many species, or from the diet. The liver adds a hydroxyl group to make 25-hydroxyvitamin D, the storage form. The kidney then adds a second hydroxyl group through 1-alpha hydroxylase to make **calcitriol**, the active hormone. This last step is controlled by PTH, low calcium and low phosphate.

Calcitriol acts on nuclear receptors and increases intestinal absorption of calcium and phosphate, supports bone mineralisation and helps PTH action. Dogs and cats make little vitamin D in the skin and depend on the diet.

Therapeutic uses include:

- **Calcitriol** for hypoparathyroidism (with calcium) and sometimes in chronic kidney disease to reduce secondary hyperparathyroidism.
- Dietary vitamin D to prevent rickets in growing animals and osteomalacia in adults.

Toxicity is important. Excess vitamin D causes hypercalcaemia, mineralisation of soft tissues including the kidney, and kidney failure. In dogs, a frequent cause is ingestion of cholecalciferol-based rodenticides or human vitamin D skin creams such as calcipotriol, so owners should be asked about household products.

Bisphosphonates

Bisphosphonates are stable analogues of pyrophosphate that bind strongly to bone mineral at sites of active remodelling. When an osteoclast resorbs this bone, it takes in the drug. Nitrogen-containing agents such as pamidronate, zoledronate and alendronate inhibit an enzyme (farnesyl pyrophosphate synthase) needed for osteoclast function, which causes the cell to lose activity or die.

The result is reduced bone resorption and a lower blood calcium. Uses in animals include:

- Hypercalcaemia of malignancy and other causes of severe hypercalcaemia, usually given by slow intravenous infusion with fluids.
- Pain from bone tumours in dogs, as part of a wider plan.
- Bone-related disease in horses, such as navicular disease, with tiludronate approved in some countries. Check the product status locally.

Oral absorption is poor and the drugs irritate the oesophagus, so oral forms need care. They are excreted by the kidney, so kidney function should be considered. Rare risks include low blood calcium and jaw bone necrosis with long use. Their effects persist for long periods because they stay in bone.

Milk fever and intravenous calcium

Milk fever (parturient paresis) is a fall in blood calcium in dairy cows around calving. A sudden demand for calcium in colostrum and milk exceeds the supply, and the cow's PTH and vitamin D response has not yet risen. Signs progress from restlessness and tremor to inability to rise, cold extremities, a weak pulse, a cow lying with her head turned to the flank, and eventually coma.

Treatment is calcium given by intravenous injection, using calcium borogluconate or similar salts. Many products also contain magnesium and phosphorus, which helps when those minerals are also low. The key safety rules are:

- Give the solution **slowly** and listen to the heart. Rapid injection can cause arrhythmia, bradycardia and cardiac arrest. If the rhythm changes, stop the infusion.
- Keep the solution warm and avoid leakage around the vein, which causes severe tissue damage. Subcutaneous routes are used for some products, with attention to local reactions.
- Expect relapse in some cows, and do not assume that the cow that stood up is cured.
- A cow that does not respond may have low phosphorus or magnesium, mastitis, or muscle damage from lying, and needs reassessment.

Prevention relies on diet. A low calcium diet before calving prompts the cow to mobilise bone calcium in advance. Alternatively, a diet with a negative dietary cation-anion difference, using anionic salts, makes the blood slightly acidic and increases PTH effectiveness. Both need feed analysis, since high potassium forages raise the risk.

Similar treatment principles apply to **eclampsia** in lactating bitches, where calcium is given slowly with monitoring of heart rhythm, and puppies are weaned or supplemented. In bitches the main cause is high milk calcium loss, not a fall in

dietary calcium before whelping, and calcium supplementation during pregnancy is generally discouraged.

Phosphate binders and avoiding errors

In chronic kidney disease, phosphate builds up, which lowers calcium and stimulates PTH. Dietary phosphate restriction is the first step. If needed, oral phosphate binders such as aluminium hydroxide, calcium carbonate or lanthanum are mixed with food to bind phosphate in the gut. Aluminium products carry a toxicity concern in long-term use, and calcium products can raise blood calcium.

Common errors to avoid:

- Treating a low total calcium without considering albumin or ionised calcium.
- Giving calcium and vitamin D together without monitoring, which risks hypercalcaemia.
- Giving rapid intravenous calcium to a cow because she is critically ill.
- Giving calcium to an animal that is already hypercalcaemic.

Treatment of mild hypercalcaemia centres on the cause, intravenous fluids and stopping contributing drugs. Bisphosphonates and other options come later.

Concept cleared

Concept cleared: Why milk fever happens
Think of a bank account where a huge withdrawal (colostrum) is made suddenly while deposits (PTH and vitamin D response) have not yet been set up. The balance drops before the system adapts.

Concept cleared: Why low-calcium dry cow diets prevent it
A cow fed little calcium before calving is already forced to run her PTH system hard, so when milk demand begins her bone and gut mechanisms are ready.

Concept cleared: Why rapid calcium is dangerous

Calcium raises heart muscle excitability and contractility. A sudden surge can push the heart into abnormal rhythm or stop it in systole, so the injection must be slow.

Concept cleared: Bisphosphonates stick to bone

They are like glue that coats the bone surface where osteoclasts are working. The osteoclast eats the coated bone and is poisoned, so resorption stops.

Memory aid: Remembering the calcium trio

PTH pulls calcium UP from bone, kidney and gut (via D). Calcitonin takes it DOWN, 'tone it down'. For calcium injections remember: Slow and Listen, because fast calcium stops the heart.

Compare and contrast

Calcium-regulating hormones

Hormone	Source	Trigger	Net effect on blood calcium
PTH	Parathyroid gland	Low calcium	Raises it: bone, kidney, activates vitamin D
Calcitriol	Kidney (from vitamin D)	PTH, low phosphate	Raises it: gut absorption
Calcitonin	Thyroid C cells	High calcium	Lowers it: inhibits osteoclasts

Drugs for calcium and bone disorders

Drug	Mechanism	Main use	Key caution
Calcium borogluconate	Replaces calcium	Milk fever, eclampsia	Give slowly with cardiac monitoring
Calcitriol	Active vitamin D	Hypoparathyroidism, renal hyperparathyroidism	Hypercalcaemia
Bisphosphonates	Inhibit osteoclasts	Hypercalcaemia, bone pain	Renal excretion, oesophagitis
Phosphate binders	Bind dietary phosphate	Chronic kidney disease	Aluminium toxicity, hypercalcaemia

Species notes

Cattle

Milk fever occurs in high-yielding dairy cows soon after calving, and treatment is slow intravenous calcium with heart monitoring. Prevention uses prepartum diet management.

Buffalo

Hypocalcaemia is reported in dairy buffalo around calving, and the same treatment principles apply. Practical feeding in India often relies on locally available forages, so mineral content should be checked.

Dog

Eclampsia occurs in lactating bitches, especially small breeds with large litters. Calcium is given slowly with monitoring, and puppies are fed separately. Cholecalciferol rodenticides cause severe hypercalcaemia and kidney injury.

Cat

Cats can develop hypocalcaemia after thyroidectomy through parathyroid injury. Dietary vitamin D is essential. Check ionised calcium after surgery.

Horse

Lactation tetany can occur in mares, usually with stress or transport. Tiludronate is used for some bone

conditions in countries where it is approved.

Clinical pearls

Self-test: 10 questions

1. Which organ activates vitamin D to calcitriol?

The kidney 1-alpha hydroxylase makes calcitriol. The liver makes 25-hydroxyvitamin D.

2. Which of the following is a PTH action?

PTH increases phosphate excretion and calcium reabsorption and stimulates vitamin D activation.

3. The main danger of rapid intravenous calcium is:

Rapid calcium excites the myocardium and can cause bradycardia, arrhythmia or arrest.

4. Bisphosphonates act by:

They bind to bone and impair osteoclast function.

5. A negative DCAD diet before calving helps prevent milk fever by:

Mild metabolic acidosis increases tissue response to PTH.

6. Which cause of hypercalcaemia is typical in dogs?

Cholecalciferol and calcipotriol cause severe vitamin D toxicity.

7. Calcitonin is produced by:

Calcitonin comes from thyroid C (parafollicular) cells.

8. A cow with milk fever stands after treatment and then relapses. What is the best interpretation?

Relapse occurs in some cows, and other minerals or complications may be involved.

9. Which agent is used to lower raised blood phosphate in chronic kidney disease?

Oral phosphate binders reduce intestinal phosphate absorption.

10. In bitches, which is generally discouraged to prevent eclampsia?

Supplementing calcium in pregnancy can suppress parathyroid response and increase risk.

Key points to revise

1. PTH raises blood calcium by acting on bone and kidney and by activating vitamin D.
2. Calcitriol is made by 1-alpha hydroxylation in the kidney and raises intestinal calcium absorption.
3. Calcitonin lowers calcium by inhibiting osteoclasts, but plays a minor role in adults.
4. Bisphosphonates inhibit osteoclasts and treat hypercalcaemia and bone pain.
5. Milk fever is treated with slow intravenous calcium, with the heart monitored.
6. Prepartum low calcium or negative DCAD diets help prevent milk fever.
7. Eclampsia in bitches is treated with slow calcium and puppies are removed from nursing.
8. Phosphate binders are used in chronic kidney disease along with dietary restriction.

Go deeper on this site

- Ch 32. Drugs in reproduction (in this book)
- Ch 30. Sex hormones, anabolics and growth promoters (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Parturient paresis (milk fever) in cows
- Merck Veterinary Manual: Hypocalcemia in small animals
- University of Minnesota Libraries: Principles of Pharmacology

CHAPTER 32 OF 33

Drugs in reproduction

How hormones and related drugs are used to time oestrus, support or end pregnancy, control uterine activity and lactation, and treat infertility. The chapter links each drug class to the physiology it borrows.

After this chapter you can

- Explain the physiological basis of oestrus synchronisation with prostaglandins, progestogens and GnRH
- Distinguish uterotonics, abortifacients and tocolytics by mechanism and clinical purpose
- Describe how lactation is stimulated or suppressed pharmacologically
- Outline drug approaches to common infertility problems
- State the main cautions and species differences in reproductive drug use

Why reproductive drugs work

Reproduction is run by a hormone chain: the hypothalamus releases GnRH, the pituitary releases FSH and LH, the ovary makes oestrogen and progesterone, and the uterus releases prostaglandin F2-alpha (PGF2a) when the cycle must end. Reproductive drugs copy, block or time one link of this chain.

If you can draw the chain, you can predict the drug. A drug that mimics GnRH pushes LH release. A drug that mimics PGF2a destroys a functional corpus luteum. A drug that mimics progesterone holds the animal in the luteal phase. Most exam questions are really questions about this chain.

A second idea is timing. The same drug can be useful or useless depending on the day of the cycle or the stage of gestation, so always ask where the animal is in the cycle before choosing a drug.

Oestrus synchronisation

The aim is to bring many females into oestrus, or ovulation, at a predictable time so that artificial insemination can be planned. There are two basic strategies.

- **Shorten the luteal phase.** PGF2a and its analogues cause regression of the corpus luteum (luteolysis). Progesterone then falls and the animal returns to oestrus after a few days. The key limitation is that it works only when a mature, functional corpus luteum is present. In a cow in the early days after ovulation, or one that is not cycling, it does nothing.
- **Extend the luteal phase artificially.** Progestogens given as intravaginal devices, implants or feed additives hold the animal under progesterone. When the source is withdrawn, the animals come into heat together.
- **Control follicular waves.** GnRH given at the start of a protocol makes a new follicular wave emerge by causing ovulation or luteinisation of the dominant follicle. A later PGF2a injection removes the corpus luteum, and a second GnRH synchronises the ovulation. Protocols of this type are called fixed-time AI programmes, with Ovsynch as the best-known example.

Equine chorionic gonadotropin (eCG) is often added in anoestrous animals because it has FSH-like and LH-like activity and stimulates follicle growth. In small ruminants, progestogen sponges with eCG are widely used to bring out-of-season animals into breeding.

Common confusion: PGF2a does not induce oestrus by acting on the ovary directly as a stimulant; it removes the progesterone brake. Also, PGF2a is of no use for synchronisation in the bitch, because the dog has a different luteal control system.

Uterotonics

Uterotonics increase uterine contraction. The main drugs are **oxytocin**, **ergot alkaloids** such as ergometrine, and **prostaglandins**.

Oxytocin acts on oxytocin receptors in the myometrium, which increase in number near term. This is why the same drug is weak in early gestation but powerful at parturition. It is used to hasten delivery in uterine inertia, to expel retained fetal membranes or uterine contents, to control postpartum haemorrhage and to help milk let-down.

The most important safety rule is to **exclude obstruction first**. If the fetus is malpositioned or the pelvis is too narrow, a uterotonic can rupture the uterus. Oxytocin is also less effective if the animal is hypocalcaemic, because calcium is needed for muscle contraction. In bitches with weak labour, calcium is often considered together with oxytocin.

Ergot alkaloids give sustained contraction, so they are used only after the fetus and placenta are out. Their sustained tone would trap a fetus if given earlier.

Prostaglandins also contract the uterus, which is why they help empty the uterus in pyometra and retained contents. Do not confuse this with the milk let-down action of oxytocin.

Abortifacients and pregnancy termination

Abortifacients end an unwanted pregnancy, for example in mis-mating, or empty the uterus in disease. The mechanisms differ.

- **PGF2a** is luteolytic, and in species where the corpus luteum maintains pregnancy it ends gestation. This applies strongly to cattle in the first half and to mares in early pregnancy. In the later stages of cattle pregnancy the placenta also makes progesterone, so effects vary with stage.
- **Glucocorticoids** such as dexamethasone can trigger abortion or parturition in late-gestation cattle because they mimic the fetal cortisol signal that begins normal birth.
- **Progesterone receptor blockers** such as aglepristone terminate pregnancy in bitches by removing progesterone action.
- **Dopamine agonists** such as cabergoline lower prolactin, which supports the corpus luteum in the bitch, and are used for termination alone or combined with

a prostaglandin.

Prostaglandins can cause vomiting, salivation, diarrhoea and abdominal discomfort, especially in dogs and cats. They must also be handled carefully by pregnant women and by people with asthma, because skin absorption can cause effects.

Tocolytics and holding pregnancy

A **tocolytic** relaxes the uterus or reduces its contraction. Beta-2 agonists such as clenbuterol and terbutaline relax uterine smooth muscle through cAMP-mediated pathways. In practice they are used to relax the uterus before obstetric manipulation or caesarean preparation in cattle and horses. They are not used to hold a normal pregnancy for long.

For maintaining pregnancy in mares with placentitis or a threatened loss, a synthetic progestogen such as altrenogest is used to support progesterone activity. The benefit comes only when the cause of progesterone failure is understood; extra progesterone does not cure infection.

Side effects of beta agonists include tachycardia and tremor. Because clenbuterol is also a misused growth promoter in food animals, it is a drug where legal status must always be checked before use. This is discussed in the next chapter.

Lactation control and infertility concepts

Stimulating milk. Oxytocin causes milk ejection by contracting the myoepithelial cells, not by making more milk. Prolactin, in turn, drives milk synthesis. Dopamine antagonists such as domperidone raise prolactin and are sometimes used to promote milk in dams.

Suppressing milk. Dopamine agonists (cabergoline, bromocriptine) inhibit pituitary prolactin release. They are used in false pregnancy of the bitch and after weaning to dry off a bitch or queen. Bromocriptine has more vomiting than cabergoline.

Infertility. Treat the cause, not the symptom. Common concepts follow.

- Anoestrus due to a persistent corpus luteum or pyometra: PGF2a to remove luteal tissue.
- Follicular cysts: GnRH or hCG to induce luteinisation and ovulation.

- Luteal insufficiency: progesterone support, or GnRH after insemination to improve luteal function.
- Delayed ovulation in mares: hCG or a GnRH agonist to time ovulation.
- Pyometra in the bitch: PGF2a or aglepristone with antibiotics, only where the cervix is open and the animal is stable, because spillage of pus is a serious risk.

Always combine drugs with good management. Nutrition, body condition, heat detection and uterine infection matter more than any injection.

Concept cleared

Luteolysis needs a corpus luteum
PGF2a analogues act only when a mature functional corpus luteum exists. If there is none, there is nothing to lyse.

Receptor density decides response
Myometrial oxytocin receptors rise near term, so the same oxytocin dose has little effect early in pregnancy and a strong effect at parturition.

Remove the brake or press the pedal
Synchronisation either removes progesterone (PGF2a, progestogen withdrawal) or stimulates the cascade (GnRH, eCG, hCG). Knowing which one is used explains the protocol.

Oxytocin ejects milk but does not make it
Milk synthesis depends on prolactin; oxytocin only triggers let-down. Prolactin is controlled by dopamine, which is why dopamine agonists dry off milk.

Memory aid: Reproductive drug triad: G-P-O
GnRH starts the chain, Prostaglandin ends the luteal phase, Oxytocin empties the uterus and milk gland. Check the chain order when you are unsure which drug fits.

Compare and contrast

Uterotonics compared

Drug	Main action	Typical use	Key caution
Oxytocin	Rhythmic myometrial contraction, milk ejection	Uterine inertia, retained membranes, let-down	Exclude obstruction; check calcium
Ergometrine	Sustained contraction	After placenta is delivered, haemorrhage	Never before fetal delivery
PGF2a	Luteolysis and contraction	Pyometra, abortion, synchronisation	Adverse effects in dogs; handler safety

Synchronisation approaches

Approach	Example drugs	How it works	Limitation
Luteolytic	PGF2a, cloprostenol	Destroys corpus luteum	Needs functional corpus luteum
Progestogen	Intravaginal device, altrenogest	Holds luteal phase, then withdrawal	Needs device or feeding for days
GnRH based	GnRH, Ovsynch	Controls follicular wave and ovulation	Needs strict timing

Species notes

Cattle
Prostaglandin and GnRH based fixed-time AI programmes are central to dairy herd reproduction. Dexamethasone can induce late-gestation abortion or parturition.

Horses
PGF2a is used to shorten dioestrus, hCG or GnRH agonists to time ovulation, and altrenogest to suppress oestrus or support pregnancy.

Dogs and cats
The bitch does not respond to PGF2a for simple synchronisation.

Sheep and goats
Progestogen sponges with eCG are used to bring ewes and does into

Cabergoline and aglepristone are the key concept drugs, and prostaglandin side effects are marked.

breeding outside the natural season.

Buffalo

Buffaloes show weak oestrus signs and seasonal anoestrus, so synchronisation with fixed-time AI is of special practical interest; response depends on nutrition and season.

Clinical pearls

Self-test: 10 questions

1. A PGF2a analogue will induce oestrus in a cow only if she has:

PGF2a acts by luteolysis, so a mature functional corpus luteum is required.

2. Which drug is a progesterone receptor blocker used to terminate pregnancy in bitches?

Aglepristone blocks progesterone receptors.

3. Before giving oxytocin to a bitch with delayed labour, the most important step is to:

Uterotonics can rupture the uterus if there is obstruction.

4. Ergot alkaloids should be used:

Sustained contraction would trap the fetus.

5. Oxytocin helps lactation by:

Oxytocin causes let-down, not synthesis.

6. Cabergoline is used to suppress lactation because it:

Dopamine inhibits prolactin release.

7. In Ovsynch type programmes the first GnRH injection mainly:

It induces ovulation or luteinisation of the dominant follicle.

8. eCG is added to progestogen protocols in anoestrous animals because it:

It stimulates follicular growth.

9. Which agent can be used as a tocolytic before obstetric manipulation?

Beta-2 agonists relax uterine smooth muscle.

10. Which statement about prostaglandin handling is correct?

Skin absorption can cause effects in these people.

Key points to revise

1. Reproductive drugs copy, block or time the GnRH-FSH/LH-steroid-prostaglandin chain.
2. PGF2a needs a functional corpus luteum.
3. Progestogen withdrawal brings animals into heat together.

4. GnRH based protocols time follicular waves and ovulation.
5. Oxytocin is a uterotonic and milk ejection drug; obstruction must be excluded.
6. Ergot alkaloids are used only after delivery.
7. Abortifacient choice depends on species and pregnancy stage.
8. Dopamine agonists suppress prolactin and milk.

Go deeper on this site

- Ch 33. Hormone misuse and Indian regulation (in this book)
- Ch 31. Calcium, phosphorus, vitamin D and bone drugs (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual
- Food Safety and Standards Authority of India (FSSAI)
- Codex Alimentarius (FAO/WHO)

CHAPTER 33 OF 33

Hormone misuse and Indian regulation

Why hormones such as oxytocin and anabolic agents are misused in animals, what harm this does to animals and to food safety, and how residues and legal controls are approached. Regulatory details change often, so students must check current notifications.

After this chapter you can

- Explain why oxytocin is misused in dairy animals and the harm to animals
- Describe illegal use of anabolic agents and growth promoters in food animals
- Explain how milk and meat residues arise and what withdrawal periods and MRLs mean
- State the role of regulators and the reporting route in broad terms
- Describe the veterinarian's professional responsibility

The problem in perspective

Hormones are legitimate and valuable drugs. The problem is not the molecule but the use: giving a drug to change production or appearance of a healthy animal, without a diagnosis, outside the legal route, or without respecting withdrawal times.

This chapter explains the concepts. Laws, bans and limits in India are revised by notification, so all regulatory statements here are general. **Always check the current notification** from the competent authority before you advise or act.

Three questions help in every case. Is there a diagnosis? Is the drug being used by a lawful route? Will the animal's milk or meat enter the food chain before residues have fallen?

Oxytocin misuse in dairy animals

Oxytocin triggers milk let-down. Some dairy keepers inject it routinely to draw out more milk quickly, or to make a buffalo or cow release milk without her calf. This is a misuse of a drug whose real indications are obstetric.

The harms are concrete.

- **Animal welfare.** Repeated injections are painful and stressful. Animals can become dependent on the injection for let-down, a learned and hormonal response that makes hand milking without the injection difficult.
- **Reproduction.** Chronic exposure is thought to disturb the reproductive cycle and may contribute to fertility problems. The strength of evidence differs among reports.
- **Udder health.** Forced emptying can raise the risk of teat and udder injury and cause incomplete milk let-down in the long term.
- **Human health.** Oxytocin given to milking animals is not the main concern for the consumer, because it is a peptide broken down in the gut; the larger concern is the pattern of unsupervised drug use and its hygiene. Do not overstate residue risk from oxytocin itself.

India has restricted the manufacture, sale and supply of oxytocin through drug-control notifications and court proceedings in recent years, with controls on who may produce and distribute it. The details, including any veterinary provisions, have changed over time, so check the current notification.

A practical approach for the veterinarian is to treat the underlying reason for poor let-down, such as stress, pain, an unfamiliar milker or a missing calf, and to teach calm milking routines. Teat preparation and a short, consistent routine stimulate the animal's own oxytocin release.

Illegal anabolics and growth promoters

Growth promoters are drugs that increase weight gain or leanness. In some countries certain anabolic hormones are permitted under regulation for beef production; in others they are banned. For students, the key points are these.

- **Anabolic steroids** (androgenic, oestrogenic and similar compounds) and **beta-agonists such as clenbuterol** may be abused to improve carcass leanness or growth.
- **Stilbenes** such as diethylstilbestrol were once used as growth promoters, but they are carcinogenic and are widely banned in food animals.
- In India, use of hormonal growth promoters in food animals is controlled under drug and food laws; check the current notification for what is prohibited.
- Because of safety concerns, use of drugs on **extra-label or growth-promotion grounds** in food animals is professionally unacceptable.

Use in companion animals and in sport animals raises separate issues, such as doping control in racing horses, where banned substances and testing rules apply.

Hormones used in sport or in companion animals are not exempt from rules. A veterinarian should know whether a drug is permitted for the species and purpose, and should never supply a drug when the stated purpose is growth promotion in food animals.

How residues arise

A **residue** is the drug or its metabolites that remain in edible tissue, milk or eggs after treatment. Residues depend on dose, route, formulation, animal age, liver and kidney function, and time since treatment. Milk is a special route because many drugs are secreted into it, and milk is consumed daily by the very young and the sick.

Two terms are essential.

- **Withdrawal period (withholding time)**: the minimum time between the last dose and slaughter, or the use of milk or eggs, so that residues fall to a safe level.
- **Maximum residue limit (MRL)**: the highest concentration of a residue legally accepted in a food, set from toxicology and exposure data. International reference values are developed under Codex, and national authorities set their own limits.

Withdrawal times given on a label apply to the licensed dose and route. Extra-label use, higher dose or longer treatment can make the label time unsafe, which is why the veterinarian must advise a longer period when required.

Some substances have no safe level at all and cannot be used in food animals. For these, regulators set zero tolerance or ban use.

Milk from treated animals must also be kept out of the supply for calves that will later be sold for meat. Mixed bulk milk can dilute a residue, but dilution is never an acceptable plan for handling treated animals.

Detection, enforcement and reporting

In India, food safety limits and testing are the responsibility of the food safety regulator, the Food Safety and Standards Authority of India (FSSAI), with state food authorities. Drug licensing and sale are governed by drug-control authorities. Animal husbandry departments and veterinary councils play their own roles.

Residue monitoring uses laboratory methods such as chromatographic and immunoassay screening. Positive samples can lead to action against the producer or supplier.

If you find or suspect illegal hormone use, the broad route is as follows. Details of the competent office differ by state, so confirm locally.

1. Record what you saw: animal, product, drug, source, dates and persons involved.
2. Do not sell or supply the milk or meat from treated animals during withdrawal.
3. Report to the local authority as required, which may include the state animal husbandry department, the drug controller or the food safety officer.
4. Keep copies of records and follow your professional council's code.

Check the current notification for the correct reporting channel and forms.

Good records make tracing possible: animal identity, drug, batch, dose, route, date and the withdrawal end date. Without records neither the farmer nor the veterinarian can show compliance.

The veterinarian's responsibility

The veterinarian is the gatekeeper. Prescribing only for a diagnosed condition, keeping treatment records, giving clear withdrawal advice in writing and refusing to supply drugs for production enhancement protect animals, farmers and consumers.

Education of farmers is as important as enforcement. Many farmers use oxytocin because they believe it is necessary; showing safe milking practice and calf-at-foot stimulation reduces the demand.

Finally, remember that law follows science and politics, so it changes. Reading the current notification is a professional habit, not a one-time task.

Concept cleared

Use, not molecule, is the issue
The same hormone is a drug in disease and a misuse in a healthy animal. Indication, route and record keeping decide legality and ethics.

Withdrawal period
The label time only protects consumers when the licensed dose and route are followed.

MRL
A maximum residue limit is a science-based legal ceiling, and zero tolerance applies to substances with no safe level.

Verify the notification
Indian orders on hormones change. State the principle and look up the current notification.

Memory aid: D-R-W-R

Diagnose, Record, Withdrawal advice, Report. Four duties of a veterinarian handling hormones in food animals.

Compare and contrast

Legitimate versus misuse

Drug	Legitimate use	Misuse
Oxytocin	Obstetric indications and defined clinical needs	Routine injection to force milk let-down
Anabolic steroid	Defined therapy where lawful	Growth promotion in food animals
Clenbuterol	Bronchodilator or tocolytic where permitted	Leanness enhancer in meat animals

Withdrawal period and MRL

Term	Meaning	Who sets it
Withdrawal period	Time to wait before milk or meat use	Label, regulator and veterinarian advice
MRL	Maximum residue concentration allowed in food	Regulators, with Codex as an international reference

Species notes

Cattle

Oxytocin misuse is a welfare and herd reproduction issue, and milk withdrawal periods apply to any treatment.

Buffalo

Buffalo milk letdown is strongly linked to the calf and handling, and this is a common setting for oxytocin misuse; check local control orders.

Sheep and goats

Poultry

Treated animals entering the meat chain need withdrawal respect; hormonal growth promotion is not acceptable.

Hormone use for growth is not an accepted practice, and residue concern extends to eggs and meat; check current rules.

Horses
Racing and sport horses fall under doping control, a separate regulatory field from food safety.

Clinical pearls

Self-test: 10 questions

1. The main reason oxytocin is misused in dairy animals is to:

It triggers milk ejection.

2. A withdrawal period is:

It allows residues to fall to safe levels.

3. An MRL is:

It is a ceiling concentration.

4. Which class is banned widely as a carcinogenic growth promoter?

Diethylstilbestrol is a stilbene.

5. Clenbuterol misuse in food animals aims at:

It is a beta agonist used as repartitioning agent.

6. Which statement about Indian regulation is most appropriate?

Rules are revised by notification.

7. Which body is the national food safety regulator?

FSSAI sets food safety standards.

8. Extra-label higher dose in a dairy cow means the label withdrawal time is:

The veterinarian must advise a longer period.

9. A harm of repeated oxytocin injection includes:

Animals can come to depend on injection for let-down.

10. On suspecting illegal hormone use, a veterinarian should first:

Documentation and reporting are the duties.

Key points to revise

1. Misuse means use without diagnosis, outside the legal route or ignoring withdrawal.
2. Oxytocin misuse harms welfare, udder and fertility.
3. Clenbuterol and anabolic agents are abused as growth promoters.
4. Residues depend on dose, route, species and time.
5. Withdrawal periods protect consumers.
6. MRLs are legal ceilings; some substances have zero tolerance.
7. FSSAI and drug control authorities have different roles.
8. The veterinarian keeps records, advises, and reports.

Go deeper on this site

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Sources

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- Food Safety and Standards Authority of India (FSSAI)
- Codex Alimentarius (FAO/WHO)

How to use Book 2: a short discussion

Book 1 explained how drugs behave in general. Book 2 applies those ideas to the drugs themselves, organised the way the body is organised: nerves, brain, inflammation, heart and blood vessels, blood and kidney, lungs and gut, and finally hormones and reproduction. Learning drugs by body system is the method most veterinary colleges follow, because a drug is easiest to remember when you know the organ it acts on and the problem it is used to solve.

Why the autonomic chapters come first

The first five chapters cover the autonomic nervous system and the drugs that mimic or block it. They are the key to the whole book. Atropine, neostigmine, adrenaline, the alpha-2 sedatives and the muscle relaxants all work by changing the signals carried by acetylcholine and noradrenaline. If you understand which receptor sits in which organ, you can predict the effect of a drug you have never met, and you can also predict its side effects. Students who skip these chapters usually find the cardiovascular, respiratory and gut chapters harder than they need to be.

Three questions for every drug

Each chapter is built around three questions. What does the drug do at the cell or receptor level? What does that mean for the animal in front of you? And what changes between species? The third question matters more in veterinary medicine than in human medicine. A drug that is routine in a dog can be dangerous in a cat, and a medicine that is safe in a cow may leave residues in milk. The Species section of each chapter collects those differences in one place so that you do not have to hunt for them.

Concepts, not dose tables

You will not find dose tables in this book. Doses change with the product, the formulation and the country, and a number copied from a study book is a poor guide at the bedside. Instead the book explains the reasoning that sits behind a dose: why a drug needs a loading phase, why a narrow safety margin demands monitoring, why a long half-life makes accumulation likely. For actual doses use the product label, a current formulary or a clinical pharmacologist. Statements about Indian regulation are marked with a reminder to check the current notification, because notifications and bans change.

A study plan that works

Read the Learn section once for the story, then move to Concepts and Compare, which turn the story into a few clear ideas and side-by-side tables. Take the quiz before you read the Revise points, not after. Getting a question wrong and reading the explanation teaches more than getting it right by guessing. Return to a chapter after a week and repeat the quiz; the progress bar at the top of the book records which chapters you have already tested on this device.

Many chapters link onward to related chapters and to other guides on this site, such as the veterinary drugs list, the Drug Index and the dose calculation guide. Following those links is the quickest way to connect a mechanism to a real product and a real case. Book 3 continues the series with chemotherapy: antibacterials, antiparasitic drugs, antifungals, anticancer drugs and the stewardship ideas that protect them.

If you are preparing for an examination, use the search box above the chapter list to jump to a term, then read the chapter around it so the term stays attached to its

mechanism. Short revision sessions of one chapter a day, each ending with the quiz, are far more effective than a single long session before the paper.

This material is written for education. It does not replace the judgement of a registered veterinarian, and it must not be used to treat an animal without professional advice.