Veterinary Anaesthesia
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Preface

Welcome to 'Veterinary Anaesthesia: Principles to Practice'.

The book was developed from The Liverpool University Veterinary School student notes after much encouragement from both undergraduate and postgraduate students and is now envisaged as a basic study aid for veterinary nurses, veterinary students and particularly post-graduate students studying for professional veterinary anaesthesia qualifications. The book is also designed to be a quick-reference source for veterinary surgeons in practice.

During my first ever dog anaesthetic in practice, on a busy morning when all my colleagues were out on calls, the responsibility of the situation suddenly dawned on me when I realised just how many questions I still had about the subject. Fortunately, a quick call via a temperamental mobile telephone helped to assure me that my calculations of premedication and induction doses were reasonable and thankfully my patient survived. That afternoon, however, I telephoned the RCVS to enrol for the CertVA as I had clearly realised just how much more I needed to learn. And I have been learning ever since, sometimes by my mistakes, but hopefully more often through the guidance and instruction of others, notably Dr. Jackie Brearley and Prof. Ron Jones, and from the written word. My colleagues will attest to my passion for books — I only wish I had time to read them all! So why, might you ask, would I wish to write one? Well, I really enjoy teaching as well as learning. There is a wonderful sense of satisfaction, not without a little pride, that wells up inside when past students go on to achieve great things and especially when they keep in touch by email with all manner of taxing questions which really keep me on my toes! Learning and teaching will always be a two-way process and I can only hope to impart some of my experiences flavoured with a little of my enthusiasm through the pages of this book, but am always open to discussion so please do contact me if you feel the urge!

I hope that you too can develop a passion and enthusiasm for anaesthesia and a deep enjoyment of being able to witness physiology and pharmacology interact at your fingertips.

Happy reading!

Acknowledgements

My grateful thanks are extended to my contributors: Nicki Grint for the Rabbit Anaesthesia chapter and photographs and Mark Senior for sowing the seeds of the chapters on Pain, Monitoring, Fluid Therapy and Equine Anaesthesia.

I would also like to extend my gratitude to all past and present students and colleagues from Liverpool’s Veterinary School and our many visiting residents for their encouragement. In particular, however, I owe much to Claire Dixon for her unfaltering support and technical wizardry with word-processing.

Finally, without the amazing support of Amy, Justinia and Katy at Wiley-Blackwell, this book would not have been published. My debt to them is more than words could ever say.
About the authors

Principal Author: Alexandra Helena Anne Dugdale MA, VetMB, DVA, Dip.ECVAA, PGCert(LT HE), FHEA, MRCVS, RCVS Recognised Specialist in Veterinary Anaesthesia, European Specialist in Veterinary Anaesthesia.

Alex qualified from Cambridge University Veterinary School in 1990 after which she spent 6 years in mixed practice in Lancashire. She gained the RCVS Certificate in Veterinary Anaesthesia and a private pilot’s licence in 1993 (who said anaesthesia was like flying!) and then undertook a Residency in Anaesthesia and Critical Care at the Animal Health Trust in Newmarket between 1996 and 1999 under the supervision of Dr. Jackie Brearley. She was appointed Temporary Lecturer in Veterinary Anaesthesia at Liverpool University in 1999 and gained the Diplomas of both the RCVS and ECVAA in 2001 before becoming Lecturer and later Senior Lecturer in Veterinary Anaesthesia. She became Head of a newly created Division of Veterinary Anaesthesia in 2004 and completed a postgraduate qualification in teaching in 2006. She is currently on sabbatical to undertake a PhD in equine obesity.

Contributor: Nicola Jane Grint BVSc, Dip.ECVAA, DVA, CPS, MRCVS.

Nicki graduated from Bristol Veterinary School in 2000 and completed an Internship and then a Residency in Veterinary Anaesthesia at Bristol before joining the veterinary anaesthesia team at Liverpool Veterinary School in 2005 as Lecturer in Veterinary Anaesthesia. Nicki gained the CertVA in 2002, the Dip. ECVAA in 2005 and the DVA in 2006, shortly followed by a professional teaching qualification (Certificate in Professional Studies) in 2007. She is currently undertaking a PhD at the University of Bristol in the field of donkey analgesia.

Contributor: Jonathan Mark Senior BVSc, CertVA, Dip.ECVAA, PhD, MRCVS.

Mark qualified from Liverpool University Veterinary School in 1997, spending two years in mixed practice in Yorkshire before returning to Liverpool University as a Resident in Veterinary Anaesthesia under the supervision of Prof. Ron Jones. He gained his CertVA in 2000 and the Dip. ECVAA in 2004, becoming Lecturer in Veterinary Anaesthesia in 2002. He gained his Doctorate in 2008 for his thesis on ‘Complement and Endotoxin in Equine Colic.’
1 Concepts of general anaesthesia

Learning objectives

- To be able to define general anaesthesia.
- To be able to discuss general anaesthesia in terms of its component parts, i.e. the triad of general anaesthesia.
- To be able to define balanced anaesthesia.

Definitions

Anaesthesia literally means ‘lack of sensation/feeling’ (from an meaning ‘without’ and aesthésia pertaining to ‘feeling’). Therefore, general anaesthesia means global/total lack of sensations, whereas local anaesthesia relates to lack of sensation in a localised part of the body.

General anaesthesia can be defined as a state of unconsciousness produced by a process of controlled, reversible, intoxication of the central nervous system (CNS), whereby the patient neither perceives nor recalls noxious (or other) stimuli.

General anaesthesia is, however, often referred to as the state of the patient when the three criteria in the triad of general anaesthesia have been met.

The triad of general anaesthesia

1. Unconsciousness: no perception (or memory) of any sensory, or indeed motor, event.
2. Suppressed reflexes: autonomic (e.g. haemodynamic, respiratory and thermoregulatory) and somatic (e.g. proprioceptive reflexes such as the righting reflex). Suppression of autonomic reflexes can be a nuisance (see Chapter 18 on Monitoring), whereas suppression of somatic reflexes can be useful, for example it can provide a degree of muscular weakness/relaxation.
3. Analgesia (or, more correctly in an unconscious patient, antinociception): can also be thought of as suppressed responses/reflexes to nociceptive sensory inputs.

We could potentially produce all three components in a patient following administration of a single ‘anaesthetic’ drug. If, however, that drug did not have very good analgesic properties, then we might need to administer it in large doses to produce sufficiently ‘deep’ unconsciousness to reduce the responses to noxious stimuli. The problem is that such deep anaesthesia is often associated with extreme depression of the central nervous system and homeostatic reflexes. Alternatively, therefore, we can produce the above three components separately by administering drugs that more specifically provide each component. This latter approach is theoretically advantageous because, by ‘titrating to specific effect’, we can often use relatively small doses of each individual drug thereby minimising both each individual drug’s, and the overall, side effects. This ‘polypharmacy’ approach, meaning using several different drugs, is often referred to as balanced anaesthesia.

Balanced anaesthesia

The use of a number of different drugs to produce a state of general anaesthesia, which fulfils our criteria of unconsciousness, muscle relaxation and analgesia.

In this context, we must also consider the whole of the perioperative period, this includes:

- Drugs administered before the induction of anaesthesia (premedication).
- Drugs administered for the induction of anaesthesia.
- Drugs administered for the maintenance of anaesthesia.
- Drugs administered in the recovery phase.

The depth of general anaesthesia

Some texts refer to the stages and planes of anaesthesia that try to mark the progression of the continuum between consciousness and death. When ether was used as the sole anaesthetic agent, these stages and planes could be fairly well defined. Table 1.1 describes their features for the dog. However, the features of these
2 Veterinary Anaesthesia

Table 1.1 Stages of ether anaesthesia in the dog.

<table>
<thead>
<tr>
<th>Stage of anaesthesia</th>
<th>Depression of CNS</th>
<th>MM colour</th>
<th>Pupil size</th>
<th>Eyeball activity</th>
<th>Breathing</th>
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<tbody>
<tr>
<td>Stage I: stage of voluntary movement/excitement</td>
<td>Sensory cortex</td>
<td>N / flushed</td>
<td>Small</td>
<td>Voluntary</td>
<td>Rapid/irregular</td>
</tr>
<tr>
<td>Stage II: stage of involuntary movement/excitement 'delirium'</td>
<td>Motor cortex</td>
<td>Flushed</td>
<td>Dilated</td>
<td>Increased</td>
<td>Irregular</td>
</tr>
<tr>
<td>Stage III (light surgical): plane 1</td>
<td>Midbrain</td>
<td>Flushed / N</td>
<td>Smaller</td>
<td>Increased</td>
<td>Slow/regular</td>
</tr>
<tr>
<td>Stage III (moderate surgical): plane 2</td>
<td>Spinal cord</td>
<td>N</td>
<td>Miotic</td>
<td>Fixed, ventral rotation</td>
<td>Slow/regular</td>
</tr>
<tr>
<td>Stage III (deep surgical): plane 3</td>
<td>Spinal cord</td>
<td>N / pale</td>
<td>Miotic</td>
<td>Ventral rotation</td>
<td>Large abdominal component</td>
</tr>
<tr>
<td>Stage III (excessive surgical): plane 4</td>
<td>Spinal cord</td>
<td>Pale</td>
<td>Bigger</td>
<td></td>
<td>Abdominal/shallow</td>
</tr>
<tr>
<td>Stage IV: paralysis (death follows respiratory and subsequent cardiac arrest)</td>
<td>Medulla</td>
<td>Pale/cyanotic</td>
<td>Mydriatic</td>
<td>Central</td>
<td>None/agonal gasps</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pulse rate &amp; BP</th>
<th>Palpebral reflex</th>
<th>Corneal reflex</th>
<th>Swallowing</th>
<th>Cough</th>
<th>Pedal withdrawal</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Rapid/high</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Analgesia?</td>
</tr>
<tr>
<td>II</td>
<td>Rapid/high</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Unconscious</td>
</tr>
<tr>
<td>III (plane 1)</td>
<td>N/N</td>
<td>Poss slight</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>III (plane 2)</td>
<td>N/N</td>
<td>–</td>
<td>Slight</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>III (plane 3)</td>
<td>Rapid/low</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>III (plane 4)</td>
<td>Rapid/low</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Anal reflex poor</td>
</tr>
<tr>
<td>IV</td>
<td>‘Shocky’</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Anal/bladder sphincters relax</td>
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N = normal
Changes tabled above refer specifically to those observed during ether anaesthesia in the dog.
Surgical stimulation may alter haemodynamic and respiratory variables via autonomic reflexes which persist into stage III, planes 2–3.

Table 1.2 Summary of effects of general anaesthesia.

CNS depression
- Loss of consciousness
- Damping of reflexes
  - Cardiovascular $\rightarrow$ Hypotension
  - Respiratory $\rightarrow$ Hypoventilation
  - Thermoregulatory $\rightarrow$ Hypothermia
  - Postural $\rightarrow$ Reduced muscle tone
- Central modulation of nociception (hopefully providing analgesia/antinociception)

CVS depression
- Reflex (e.g. baroreflex) suppression (centrally and peripherally)
- Changes in autonomic balance
- Changes in vasomotor tone (drug effects, centrally and peripherally)
- Myocardial depression
  - Direct (drugs)
  - Indirect (e.g. hypoxaemia, hypercapnia [acidosis])

Respiratory depression
- Reflex suppression (ventilatory response to ↑PCO$_2$, ↓pH and ↓PO$_2$)
- Reduced respiratory muscle activity (↓ sighing and yawning)
- Alveolar collapse/small airway closure (atelectasis)
- Reduced functional residual capacity
- Ventilation/perfusion mismatch

$\rightarrow$ Hypotension
$\rightarrow$ Hypoventilation (hypercapnia/hypoxaemia)
stages/planes of canine ether anaesthesia do not necessarily apply when we do not want to use ether, when we need to consider species other than dogs, when we prefer to practice ‘polypharmacy’ to achieve the desired state/depth of general anaesthesia and when we add surgical stimulation to the anaesthetised patient, because depth of anaesthesia is not only related to the ‘dose’ of drug/s administered, but is also dependent upon the degree of stimulation (usually surgery) at the time. Nevertheless, consideration of anaesthetic depth does make us think about patient monitoring.

Table 1.1 is included purely for interest, but it is important to note that during the induction of anaesthesia, stage II (involuntary excitement/movement) may be witnessed; and during recovery from anaesthesia, all the stages are traversed in the reverse order, such that emergence excitement (stage II) may be observed.

**Important stages of anaesthesia**

- **Pre-operative assessment**: patient stabilisation; provision of analgesia.
- **Premedication**: anxiolysis/sedation and initiation of analgesia provision if not already provided.
- **Induction** of anaesthesia.
- **Maintenance** of anaesthesia: continuation of analgesia/anti-nociception provision.
- **Recovery** from anaesthesia (sometimes referred to as ‘re-animation’): aftercare; continuation of analgesia provision.

**Conclusions**

The effects of general anaesthesia are summarised in Table 1.2. Our main objective is to maintain tissue perfusion, with delivery of oxygen and removal of waste products. If this fails, we can expect increased patient morbidity and mortality. There are no safe anaesthetics; there are only safe anaesthetists.

**Further reading**


Schupp M & Hanning C (2003) Physiology of Sleep. British Journal of Anaesthesia: CEPD Reviews 3 (3), 69–74. (Distinguishes sleep from general anaesthesia; useful information on effects of sleep deprivation for the anaesthetist.)

Learning objectives

- To be familiar with the American Society of Anesthesiologists’ physical status classification scheme.
- To be able to recognise features of the patient’s signalment (e.g. species, breed, age) that have implications for choice of anaesthetic drugs and technique/s.

Pre-operative assessment

History and clinical examination

A good history and thorough clinical examination are vital. They can give you clues as to the health status of the animal, which may influence your choice of anaesthetic drugs and techniques and can affect the outcome of general anaesthesia.

In addition to a normal thorough clinical examination, try to establish the following:

- **Degree of jaw opening**: important if tracheal intubation is required.
- **Loose teeth or tartar**: important during laryngoscopy and tracheal intubation as loose things tend to get displaced down the airway.
- **Venous access**: for horses, assess the patency of the jugular veins bilaterally. For small animals, assess superficial limb veins, and ear veins for breeds like Basset hounds, as these may be more accessible than limb veins. If a patient has undergone, or is to undergo, limb amputation, the options are reduced. Patients with cardiac pacemakers may have one ligated external jugular vein.

American Society of Anesthesiologists (ASA) physical status classification

Having completed the history and clinical examination, assign the animal to one of the ASA physical status classes below, as this can help to decide whether anaesthesia can proceed, or whether further investigations or patient stabilisation are warranted first.

I **Minimal risk**. Normal healthy animal. No detectable underlying disease.

II **Slight risk**. Slight to mild systemic disease, but causing no obvious clinical signs or incapacity (i.e. animal compensating well).

III **Moderate risk**. Mild to moderate systemic disease, causing clinical signs (animal not compensating fully).

IV **High risk**. Extreme systemic disease constituting a threat to life.

V **Grave risk**. Moribund and not expected to survive >24h.

Add ‘E’ to any class if the animal presents as an emergency.

Factors affecting anaesthetic risk

The factors affecting anaesthetic risk are listed below, not all are patient-related. The duration of anaesthesia and surgery are particularly related to risk.

- Patient’s health.
- Urgency: elective or emergency procedure.
- Surgery: surgeon’s experience, duration of surgery, type of surgery, gravity of surgery, surgery that involves the airway/lungs and interferes with the anaesthetist’s ‘space’.
- Facilities available (surgical and anaesthetic): equipment, drugs, referral hospital, general practice or field.
- Help available and experience of available personnel.
- Anaesthetist: experience, duration of surgery (tiredness/vigilance/boredom), type of surgery.
- Duration of anaesthesia and surgery.

Anaesthetist

Tiredness can be a problem; 17 h without sleep results in a reduction of psychomotor performance equivalent to a blood alcohol concentration of 50 mg/dl; and 24 h of sleep deprivation reduces
Physiological function

Anaesthesia ('enforced unconsciousness') is accompanied by depression of normal physiological functions and often incurs a degree of hypoventilation, hypotension and hypothermia, due to depression of respiratory, cardiovascular and brain functions. Whilst the majority of animals cope with this suppression well, when the stressors of surgery with possible hypovolaemia, hypothermia and pain are added, animals may become more physiologically compromised, which increases their risk of perioperative morbidity and mortality. Therefore, when animals are under anaesthesia, we must monitor their physiological condition with the overarching aim of maintaining adequate tissue oxygen delivery (see Chapter 18 on monitoring).

Poor oxygen delivery to the tissues means trouble. Tissues susceptible to hypoperfusion/hypoxia are:

- CNS (visual cortex)
- myocardium
- kidneys
- liver.

The gastrointestinal tract mucosa and pancreas are also relatively susceptible to periods of hypoperfusion/hypoxia; and in horses, hypoperfusion/hypoxia of large muscle masses can lead to post-anaesthetic myopathy.

Hypoperfusion can result from hypovolaemia and/or hypotension. Tissue hypoxia may be secondary to hypoperfusion (ischaemia), but may also occur secondary to hypoxaemia (i.e. reduced oxygen carriage in the blood), due to lack of haemoglobin (anaemia), or to respiratory gaseous exchange failure. The latter may follow reduced inspired oxygen percentage, reduced air/oxygen entry into the respiratory tree (hypoventilation/obstruction), reduced gaseous exchange at the alveoli, or abnormal ventilation/perfusion ratios.

Reducing peri-operative morbidity and mortality

To reduce peri-operative morbidity and mortality, we must consider the effects of anaesthesia on any disease processes already present and the problems that those disease processes pose for anaesthesia.

We can improve the overall safety of anaesthesia with adequate pre-operative assessment, medical treatment and stabilisation of the patient where possible, and anticipation of the possible complications.

Familiarity with an anaesthetic technique is often a more important safety factor than the theoretical pharmacological advantage of an unfamiliar drug/technique.

Factors that may influence anaesthesia

Breed susceptibilities

There are specific problems in some animals that may affect anaesthesia.

- Brachycephalics: brachycephalic airway obstruction syndrome (BAOS), also called brachycephalic upper airway syndrome (BUAS) or brachycephalic obstructive airway syndrome (BOAS). Use acepromazine with caution (see Chapter 4 on premedication).
- Sight hounds (particularly Greyhounds, in which the original work was done): have very little body fat, relatively little muscle mass compared with bone mass and different/slower metabolism so recovery from drugs such as thiopental is prolonged.
- Doberman Pinschers: dilated cardiomyopathy; von Willebrand’s disease; cervical spinal instability.
- Boxers: brachycephalic; sub-aortic stenosis.
- St Bernards: atrial fibrillation; laryngeal paralysis.
- Terriers: idiopathic pulmonary fibrosis.
- Bedlington terriers: copper storage hepatopathy.
- Persian cats: polycystic kidneys; brachycephalic.
- Draught horses: polysaccharide storage myopathy; atrial fibrillation; laryngeal paralysis.
- Quarter horses: hyperkalaemic periodic paralysis.
- Welsh Mountain Ponies: ventricular septal defects.
- Pietrain and Landrace pigs: malignant hyperthermia.

Body mass

Is the animal overweight or too skinny, even debilitated? Is there a recent history of weight gain or loss? For obese animals, try to assess what their lean mass ought to be.

Age

Very young (neonatal) and very old (geriatric) animals may require dose adjustments (see Chapter 37 on neonates and Chapter 38 on geriatrics). Some chronologically old animals act as if they are still very young and some very young animals act as if they are very old, so be aware that the animal’s chronological (true) age may not match its physiological/behavioural age. An animal’s response to anaesthesia often matches its physiological age more than its chronological age.

Hypovolaemia, cardiac disease and respiratory disease

Hypovolaemia, cardiac disease or respiratory disease may compromise the patient’s ability to maintain adequate tissue perfusion/oxygen delivery, even before the physiological insult of anaesthesia.

Exercise tolerance is the best indication of how compromised an animal is by its cardiac and/or respiratory disease. Resting heart and breathing rates are also useful, especially in dogs.

Renal disease

Renal disease may influence pharmacokinetic behaviour (e.g. reduced renal clearance or excretion of anaesthetic agents and their metabolites), so may affect the course of anaesthesia (see Chapter 5 on induction agents and Chapter 17 on muscle relaxants). Anaesthesia may exacerbate reduced renal function, especially if periods of hypotension result in further renal injury. Protein-losing nephropathies, in which albumin and small plasma proteins are preferentially lost, may result in reduced plasma protein binding of acidic drugs (e.g. thiopental), peripheral
To determine the exact effects of anaesthesia, it is important to consider the pre-operative period. Where possible, a careful history and thorough clinical examination will reveal any problem areas. If there is time, further work-up may be warranted, such as laboratory tests, imaging or electrodiagnostics. The whole peri-anaesthetic period (including the pre-operative and post-operative periods) can then be tailored to suit each individual animal (see Chapter 18 on monitoring).

Pre-operative support/stabilisation should be considered, which could involve:
- anxiolysis/sedation
- analgesia
- pre-oxygenation/oxygen supplementation
- fluid therapy/diuresis
- medical support (e.g. for diabetes or cardiac arrhythmias)
- surgical procedures (e.g. tracheostomy, chest or pericardial drainage).

Appropriate monitoring should be considered and may be instigated in the pre-operative phase.

**Choice of anaesthetic drugs and techniques**

The choice of anaesthetic drugs and technique/s may be influenced by the following conditions. The reader is also referred to the chapters concerning specific body system problems.

**Pre-existing respiratory compromise**

Try to minimise any further respiratory compromise. Pre-existing respiratory compromise includes BAOS and laryngeal paresis. These are potential problems for airway management, requiring increased vigilance following premedication and after tracheal extubation. Patients with these conditions require rapid, smooth anaesthetic induction techniques allowing quick intubation and control of the airway, followed by rapid recoveries without ‘hang-over’. Have plenty of endotracheal tubes of different sizes available and even a choice of tracheostomy tubes at hand. Consider pre-oxygenation if this can be performed in a stress-free manner. Light premedication (perhaps opioid alone with or without benzodiazepine) is often suitable because the animal maintains its ability to ventilate. Obese dogs may require assistance with ventilation once they are anaesthetised. Consider using 100% inspired oxygen. Pulse oximetry and capnography may be useful, as may blood gas analysis. During recovery, turn the animal into sternal recumbency and stretch out its head/neck and tongue after tracheal extubation to help breathing with minimal obstruction. Monitor breathing for some time after tracheal extubation.

**Pre-existing cardiovascular disease**

Try to minimise further cardiovascular compromise. Animals with pre-existing cardiovascular disease include hypovolaemic animals and those with primary cardiac disease. Where possible, pre-operative stabilisation should be carried out. Fluid therapy is an important part of the overall peri-operative management. Circulatory support may also require drug intervention. Patients with cardiac problems may require ventilatory support, but beware compromising venous return and therefore cardiac output by overzealous intermittent positive pressure ventilation. Choose drugs with minimal cardiovascular effects. Benzodiazepine/opioid combinations are finding favour for premedication, and can be ‘topped up’ or followed with minimal doses of injectable or volatile agents. Reduce doses, and give intravenous agents slowly.
Pulse oximetry, capnography, electrocardiography, central venous pressure and arterial blood pressure monitoring should be considered (and possibly blood gas analysis).

**Pre-existing renal disease**

Try to minimise further renal insult. Careful fluid therapy is warranted and, if possible, measure the intraoperative arterial blood pressure to give an indication of tissue/organ perfusion. (Peri-operative urine output measurements are not always helpful as the stress response results in antidiuretic hormone (ADH) secretion, which reduces urine production.) Support arterial blood pressure with fluids and positive inotropes, but be careful with concomitant cardiovascular disease. Renal disease may delay drug elimination. Carefully consider the timing of NSAID administration; if you are unsure, wait until the animal has recovered and its arterial blood pressure is 'normal'.

**Pre-existing hepatic disease**

Try to minimise further hepatic insult. Use drugs that require minimal hepatic metabolism for their elimination (i.e. propofol, isoflurane, sevoflurane). Remember that the half-lives of other drugs may be prolonged and, with some ‘reversal’ agents, the half-life of the initial drug may be longer than its antagonist so be aware of the potential for re-narcosis. Altered pharmacokinetic behaviour can accompany liver disease, for example the plasma protein concentration may be low, and many drugs are protein bound, so in the presence of hypoproteinaemia there is the potential for a higher concentration of free (and usually ‘active’) drug in the plasma, so be prepared to reduce doses. Coagulation may be affected, so you may prefer not to attempt epidural injections. Monitor the blood glucose if liver function is very poor. Monitor the body temperature.

**Thermoregulatory requirements**

Take extra care with very young, old or thin animals, and those with endocrinopathies or liver disease. Hypothermia will delay recovery. Remember that hypoglycaemia may also be a compounding factor in very young animals, those with insulinsomas, or poorly controlled diabetes mellitus.

**Further reading**


**Self-test section**

1. Which of the following dog breeds would make you suspicious for the presence of some, perhaps as yet subclinical, problem?
   A. Border Collie
   B. Labrador
   C. Doberman Pinscher
   D. Greyhound

2. Which of the following is the best indicator of cardio-respiratory compromise?
   ● Tachycardia
   ● Arrhythmia
   ● Heart murmur
   ● Poor exercise tolerance
   ● Weak peripheral pulses
   ● Pale mucous membranes
   ● Congested mucous membranes
   ● Prolonged capillary refill time
3

Pain

Learning objectives

- To be able to define pain (IASP definition).
- To be able to outline the neurophysiological pain pathways and different sites for intervention.
- To be able to recognise the importance of pre-emptive analgesia.
- To be able to discuss the concept of balanced (multimodal) analgesia.
- To be familiar with the different classes of ‘analgesic’ drugs available, their proposed sites and mechanisms of action and their side effects.

Introduction

Two of the main challenges facing vets are to recognise when an animal is in pain and how to treat that pain adequately.

The current definition of pain by the International Association for the Study of Pain (IASP) is that Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Since 2001, there has been an accompanying note to this definition, which states: The inability to communicate in no way negates the possibility that an individual is experiencing pain and is in need of appropriate pain relieving treatment.

Although acute pain can be beneficial because it can help protect against injury and enable healing; chronic unrelenting pain is detrimental to health, physiologically (homeostatically), immunologically and psychologically and it can result in suffering and distress.

Evolution of pain

Even in the ‘primordial soup’ it seems reasonable to assume that organisms that had some way of detecting and reacting to noxious stimuli had an evolutionary advantage, indeed it has been shown that protozoa can respond to certain noxious stimuli. We find similarity between higher order organisms in the anatomy and physiology of their nervous systems, such that it may be reasonable to assume that the way in which they respond to pain is similar.

The expression of pain has probably evolved differently in different species. Social animals (e.g. dogs, monkeys) may cry out in pain to get help from others. Prey species tend to hide pain. Predators preferentially attack weak animals, thus it is not in the interests of prey species (e.g. sheep, cattle, horses) to express pain or distress signals. In both groups, however, there are similar increases in glucocorticoid and β-endorphin levels when ‘painful’ or stressful conditions exist.

The different types and qualities of pain

You may hear pain referred to as:

- Somatic versus visceral
- Superficial versus deep
- Fast (transmitted by Aδ fibres) versus slow (transmitted by C fibres)

Pain components

- Sensory/discriminative allows determination of the site of origin of the pain and the stimulus intensity, duration and quality.
- Motivational/affective/behavioural results in cortical arousal, neuroendocrine responses, limbic system responses (fear/ anxiety) and activation of reflexes, such as the withdrawal reflex. Limbic system responses can feed back to the cortex to enhance the individual’s perception of the input. It is important to realise that fear and anxiety can enhance the perception of pain.
- Cognitive/evaluative the higher level information processing that exists in man and possibly animals.
Pain when carried to completion, results in the conscious perception of pain. For pain to be perceived, consciousness is required, some degree of brain analysis occurs, emotions may be displayed, and memory and learning occur. Animals under an adequate depth of general anaesthesia are incapable of perceiving painful stimuli, but the first three steps of nociception can still occur.

Clinical pain, or pathological pain, occurs when excessively intense or prolonged stimuli induce tissue damage that results in extended discomfort and abnormal sensitivity. It can take several forms: inflammatory, neuropathic and sympathopathic (i.e. where the autonomic nervous system becomes involved); which are not mutually exclusive.

Features of physiological pain

- Much is due to Aδ fibre activity.
- The ‘pain’ is acute, transient and localised.
- The ‘pain’ is stimulus-specific and rapidly adapting (see below).
- One could argue that it has protective functions, in that it may prevent further tissue damage; and it may add to ‘learned avoidance’ responses.

Features of pathological pain

- Much is due to C fibre activity.
- The ‘pain’ is persistent/chronic (outlasts the stimulus duration) and diffuse.
The pain is not stimulus-specific, but is slowly adaptive.

Chronic pain is not generally protective (it offers no useful biological function or survival advantage), but is debilitating and increases patient morbidity.

Adaptation to painful stimuli
Unlike the situation for most other sensory neurones, the adaptation that occurs in pain fibres (especially C fibres) tends to be a sensitisation rather than a fatigue, especially in the situation of pathological pain. It is important to remember that pain is a dynamic and multidimensional experience and that neuronal plasticity is important in the ‘progression’ of pain.

The pain pathway

Afferent fibres
- Aδ (myelinated) fibres relay ‘fast pain’ (e.g. mechanical pain, cuts, pin-pricks); sometimes called ipicritic pain. The conduction velocity is 5–20 m/s.
- C (unmyelinated) fibres relay ‘slow pain’ (e.g. dull pain, burning pain, aches); sometimes called protopathic pain. The conduction velocity is 0.5–1 m/s.

Aδ and C fibres have peripheral sensory receptors (nociceptors), which respond to various noxious stimuli. These fibres transmit signals from the periphery to the dorsal horn of the spinal cord via the dorsal roots. Three basic things happen here:
- The signal may invoke a spinal/segmental reflex (e.g. withdrawal type response) because interneurones may synapse with motor fibres in the ventral roots to form reflex arcs.
- The signal may be passed on up to the brain (thalamus/reticular formation/cortex).
- The signal may undergo some processing (modulation).

If the original stimulus was intense enough, or caused enough tissue damage, then an inflammatory reaction will have been initiated. This involves the release of cytokines and inflammatory mediators (prostaglandins, histamine, bradykinin) that result in warmth, swelling, erythema and pain. The pain occurs because these mediators are algogens. Some of them stimulate nociceptors directly to elicit pain (e.g. histamine); and others decrease the threshold of nociceptors at the site of inflammation (e.g. prostaglandins), and as time progresses, of nociceptors around the site too. We have all experienced this when immediately after a cut, only the cut itself is painful, but after a few minutes the skin around the cut becomes painful too.

Hyperalgesia
Hyperalgesia is an increased sensitivity to a normally painful stimulus. It occurs at the site of injury (primary hyperalgesia) due to inflammatory mediators either activating or sensitising the nociceptors (peripheral sensitisation), lowering their thresholds for firing; and it spreads to the surrounding non-injured tissues (secondary hyperalgesia) due to events in the spinal cord (central sensitisation).

Allodynia
Allodynia is a painful response to a normally innocuous stimulus. Allodynia refers to previously ‘silent’ high threshold mechanoreceptors that become recruited to relay pain information, for example tissue inflammation reduces their thresholds (part of the peripheral sensitisation). Besides this peripheral change, there is also a ‘central’ component to this altered interpretation of information/allodynia (part of the central sensitisation).

Spinal cord
The sensory nerve synapses in the dorsal horn of the grey matter are the first site where neurotransmitters and neuromodulators influence the further propagation of the signal. This is also where some modulation may occur. The so called gate control theory (Melzack and Wall) (Figure 3.2) was put forward in an attempt to try to explain this. The signal may then travel up the spinal cord (possibly on the contralateral side). Most of these ascending pathways are in the spinoreticular and spinothalamic tracts of the spinal cord, and there are probably several levels of ‘gating’ in these ascending pathways.

<table>
<thead>
<tr>
<th>Aβ fibre (fast)</th>
<th>Activity in this ‘touch’ nerve fibre prevents ‘pain’ information in C fibre from being transmitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ fibre (fast)</td>
<td>Inactivity in this ‘touch’ nerve fibre allows ‘pain’ information in C fibre to be transmitted</td>
</tr>
</tbody>
</table>

Figure 3.2 Gate control theory.
Descending pathways in the spinal cord, both inhibitory and facilitatory, also exist, and can influence the gating processes. If the mechanoreceptor fibre (Aβ) is inactive, the gate is open for onward and upward C fibre transmission. However, activity in the Aβ fibre can close the gate, so that C fibre transmission is interrupted. In simple terms, the gate theory highlights that a painful nerve signal has to ‘cross over or through’ many ‘gates’ (other synapses) before that signal will be further transmitted. This is why, for example, when you bang your elbow, it hurts; but if you rub it, it hurts less.

**Pain pathways in the brain**

The thalamus is the part of the brain which most of the ascending paths reach first. From the thalamus billions of nerve fibres run to all parts of the brain including the cerebral cortex (i.e. this is where the signal is probably first perceived as pain), the reticular activating system (sleep centre), and the limbic system (emotion). All these neuronal connections and communications result in what we experience as pain, but they also influence further transmission and interpretation of the signal.

**Neuroplasticity/neuromodulation**

This is how the perception of a painful stimulus changes over time. This is an important feature of the CNS response to pain. There are two main types of adaptation: desensitisation and central sensitisation.

**Desensitisation**

If there is a persistent painful stimulus, and if the animal continuously feels the same degree of pain, then that animal may not be able to behave and function normally. It is physiologically beneficial for the CNS to modify its response to these signals so that the level of pain is decreased, that is for desensitisation to occur. This is a more medium to long-term response to a painful stimulus and does not always occur. The mechanisms by which it is mediated are poorly understood but the descending pathways (see below) are thought to be involved.

**Central sensitisation**

Plasticity works in the other direction too and can result in central sensitisation. It is thought to be an adaptive response to pain that encourages the animal to develop protective behaviour. However, it may become maladaptive in the long term. The mechanisms involved are complex but we know that N-methyl D-aspartate (NMDA) receptors are involved. The result is that any subsequent painful stimulus is likely to be perceived as being more painful. It is this central sensitisation that led to the practice of pre-emptive analgesia in which analgesics are given before the pain starts, so that they are working when the noxious stimulus occurs, and hopefully prevent central sensitisation. The result is that any subsequent pain is easier to control than if analgesic treatment had been delayed until after the noxious stimulus had occurred. Central sensitisation can result in changes to the CNS that may last much longer than minutes or hours. Some studies have shown that babies that had repeated blood samples taken when they were new-born have a lower pain threshold in later life than those babies that did not.

**NMDA receptors** control non-specific cation channels (allowing Na⁺ and Ca²⁺ influx and K⁺ efflux) in nerve fibres, and are involved in memory and learning and synaptic plasticity in general. NMDA receptors are unusual because they are both voltage-gated and ligand-gated and both conditions must be satisfied for them to open. In order to open, the receptor requires initial membrane depolarisation (e.g. following opening of other ion channels) which displaces Mg²⁺ from the channel so that glutamate binding can then open it. Glutamate is an excitatory neurotransmitter. Glycine (usually thought of as an inhibitory neurotransmitter) is a co-agonist for the NMDA receptor. Its binding can potentiate glutamate’s binding and action. NMDA receptor/channels activate slowly and remain activated (open) for a relatively lengthy time (several hundred milliseconds) so they are well placed for their role in neuroplasticity. Prolonged ion fluxes, especially the influx of calcium (the channel’s main permeability) can affect intracellular processes and signalling, including the activation of enzymes, altered gene expression and synthesis and activation of receptors.

Ketamine, and possibly pethidine and one of methadone’s isomers (d-methadone), can antagonise NMDA receptor activation by glutamate. This can prevent central sensitisation and can even reverse it once it has occurred. Ketamine, at sub-anaesthetic doses, is commonly used in the treatment of chronic pain states. Nitrous oxide and xenon also have some NMDA antagonistic actions, and even benzodiazepines may modulate NMDA receptor activity.

You may hear the term wind up, which many people use interchangeably with ‘central sensitisation’. However, in the strictest terms, wind-up is a laboratory phenomenon, whereby repetitive (low frequency) and prolonged C fibre input to the dorsal horn can result in reduced firing thresholds of dorsal horn neurones. Temporal and spatial summation of depolarisation increases the likelihood of NMDA receptor activation, which then results in enhanced and prolonged depolarisation of dorsal horn neurones, which finally increases the overall response. This ‘wind up’ is only seen during the period of actual repetitive stimulation.

**Hyperalgesia** strictly refers to a patient’s overall exaggerated response to a given painful stimulus; whereas sensitisation/hypersensitivity refers to an exaggerated response of an individual neurone to a noxious stimulus.

**Descending pathways**

There are a number of descending pathways (Figure 3.3) through which the brain can exert a modulatory effect on nerve fibres involved in the transmission of pain. We usually talk of descending inhibitory pathways, but descending facilitatory pathways also exist. The four tiers of descending inhibition are considered to be:

- Cortex and thalamus
- Peri-aqueductal grey matter in the midbrain
- Nucleus raphe magnus in the pons and rostral medulla
- Medulla oblongata and spinal cord (dorsal horns).
probably means that we should be careful of using very high doses of opioids, and for long periods (especially if patients are not in that much pain), and perhaps be careful not to use very high doses of opioids in premedications before noxious stimulation occurs, unless we combine their use with an NMDA antagonist (e.g. low dose ketamine). We must practise balanced analgesia.

Visceral and referred pain

There are very few true nociceptors in the viscera, but many mechanoreceptors with different thresholds. Nociceptors show a graded response to increasing stimulus intensity (e.g. distension, ischaemia, inflammation). Visceral noxious stimuli are ‘intensity-coded’. The viscera have a low density of innervation, and the nerves have huge and overlapping receptive fields and so stimuli cannot be localised very well, which is why visceral pain is often vague. The innervation density of skin compared with viscera is around 100:1, with the ratio of Aδ:C fibres for skin being 1:2, compared with viscera, where the ratio is 1:8–10. C fibres are truly polymodal, they can transduce mechanical, chemical and thermal information. Temporal and spatial summation of visceral ‘nociceptor’ activity is important.

Sensory afferents from the viscera enter the dorsal horns of the spinal cord. Here they synapse with cells that receive afferent inputs from other sensory nerves (e.g. somatic nerves) so there is a somato-visceral convergence of information at the dorsal horn cells. Visceral afferents may be accompanied by sympathetic fibres so autonomic effects may accompany visceral nociception.

Referred pain is also common. This is pain that can be localised to a distant structure. The pain is usually referred to superficial somatic structures innervated by the same segmental spinal nerve that supplies the affected viscus (or up to one or two segments on either side). For example angina is associated with upper arm pain alongside the visceral (heart) pain.
Antihyperalgesia is defined as the prevention, and/or reversal of, sensitisation to pain. By definition then, analgesia is the absence of all pain, but most of the methods we use to try to achieve analgesia are only partially successful, so we only really effect hypoalgesia. The term analgesia is often used loosely to mean both true analgesia and also hypoalgesia. We probably should be using the term hypoalgesics (e.g. for opioids, which raise the threshold to pain AND alter its perception), antihyperalgesics (for drugs that help to reset increased central sensitisation such as NSAIDs and NMDA antagonists), and true analgesics (e.g. for local anaesthetics). For patients under general anaesthesia, and therefore unable to consciously perceive pain, the term antinociception is preferred to analgesia or hypoalgesia. We can achieve analgesia/hypoalgesia by:

- Pharmacological agents
- Surgical intervention (e.g. neurectomy)
- Nerve stimulation e.g. (TENS, acupuncture).

Analgesia

- Analgesia is defined as a lack of pain sensation.
- Hypoalgesia is defined as a reduction of pain sensation to a more tolerable level.

Other aspects of pain

The placebo effect occurs when a patient obtains pain relief after taking a pharmacologically inactive or inert compound. About 20% of patients respond to a placebo analgesic; demonstrating a strong psychological component to pain.

Psychological pain is the pain experienced by a patient when there is no apparent pathology, although it usually follows a previous painful incident (now look back at the definition of pain).

Phantom pain occurs when an individual perceives pain from a part of the body that has been removed (e.g. limb, kidney, tooth). There have been a few case reports of this phenomenon in animals (see Chapters 12 and 14 on local anaesthetics and Chapter 41 on orthopaedic concerns).

Analgesia is defined as a lack of pain sensation.

Hypoalgesia is defined as a reduction of pain sensation to a more tolerable level.

Antihyperalgesia is defined as the prevention, and/or reversal of, sensitisation to pain.

By definition then, analgesia is the absence of all pain, but most of the methods we use to try to achieve analgesia are only partially successful, so we only really effect hypoalgesia. The term analgesia is often used loosely to mean both true analgesia and also hypoalgesia. We probably should be using the term hypoalgesics (e.g. for opioids, which raise the threshold to pain AND alter its perception), antihyperalgesics (for drugs that help to reset increased central sensitisation such as NSAIDs and NMDA antagonists), and true analgesics (e.g. for local anaesthetics). For patients under general anaesthesia, and therefore unable to consciously perceive pain, the term antinociception is preferred to analgesia or hypoalgesia. We can achieve analgesia/hypoalgesia by:

- Pharmacological agents
- Surgical intervention (e.g. neurectomy)
- Nerve stimulation e.g. (TENS, acupuncture).
Pharmacological agents

We can attempt to provide analgesia/hypoalgesia in the following ways.

Interrupt the pain pathway at the site of noxious signal transduction

Local anaesthetics will prevent nociceptor activation. Anti-inflammatories (e.g. NSAIDs) will also reduce nociceptor stimulation by reducing the amount of inflammatory mediators at the site of tissue injury. We also know that α2 receptors and opioid receptors are expressed in inflamed tissues, so opioids and α2 agonists may have peripheral actions too. We are also learning that drugs like corticosteroids and NSAIDs have central actions in addition to their peripheral actions.

Interrupt the pain pathway at the site/s of signal transmission

These sites are the peripheral and central neurones. Local anaesthetics prevent nerve conduction and can be used for, e.g. nerve blocks, ring blocks and neuraxial anaesthesia.

Affect modulation of the signal

This reduces 'onward' transmission to higher centres by affecting activity at receptors in the dorsal horns and higher centres, including opioid receptors, α2 adrenoceptors, NMDA receptors and other ion channels. Opioids, α2 agonists and NMDA receptor antagonists can be administered systemically or neuraxially. Tramadol, tricyclic antidepressants and anticonvulsants (e.g. gabapentin) can also be used.

Reduce perception of incoming signals in the higher centres

This can be achieved by anxiolysis, sedation or general anaesthesia, using anxiolytics/sedatives (phenothiazines, α2 agonists, benzodiazepines), opioids (provide some sedation), and injectable and inhalational general anaesthetic agents.

This chapter focuses on the main groups of analgesic drugs that you are likely to come across.

Pre-emptive and preventive analgesia

It is recognised that if analgesia (true analgesia being better than hypoalgesia) can be provided before a noxious stimulus is applied, then any subsequent pain experienced is of lesser intensity and duration, and is more easily controllable with analgesic drugs, because the initiation and establishment of peripheral and central sensitisation is prevented (or at least reduced). This is called pre-emptive analgesia.

A one-off dose of analgesic/hypoalgesic given before surgery, however, may have only a limited duration of action and may not outlast the pain and inflammation that follows surgical intervention, and therefore will not continue to pre-empt all post-operative pain. It is for this reason that pain relief should be provided before surgery and should be continued into the post-operative period for as long as the pain is likely to be present and not bearable. The concept of this provision and continuation of pre-emptive analgesia is what is called preventive analgesia. In this case, both the establishment and the maintenance of peripheral and central sensitisation are prevented or reduced.

Multimodal (balanced) analgesia

The pain pathway can be interrupted at more than one site; and the more sites we can target, the better will be the overall analgesia provision. Another aim of this balanced analgesic approach is to maximise the analgesia provision by using drugs from different classes with complementary analgesic activities, whilst simultaneously minimising the overall side effects for the patient.

Sequential analgesia

Sequential analgesia was once commonly used, especially in small rodents. It refers to the administration of a potent μ agonist (e.g. morphine) pre-operatively, which was then (especially after ‘mild’ surgery), partially reversed post-operatively (e.g. by buprenorphine or butorphanol), in the hope of minimising the side effects of the full μ agonist (drowsiness), while maintaining decent analgesia (by the partial agonist or agonist/antagonist).

Opioids

Throughout most of recorded history, the opium poppy (Papaver somniferum) has been used to provide pain relief. Despite all we have learned about pain, morphine is still the mainstay of analgesic therapy for severe pain in human medicine.

- Opiates are drugs derived from the opium poppy (e.g. morphine, papaveretum, codeine).
- Opioids are drugs that work in a similar manner to morphine.
- Narcotic analgesics are basically any of the opioids, as they provide analgesia but can also induce a state similar to sedation or euphoria (a sense of well-being) called narcosis.

Opioids exert their effects by binding to opioid receptors. Originally it was thought that opioid receptors could only be found in the CNS. It is now known that they also occur in the periphery, such as in the gastrointestinal tract and in the joints (especially after inflammation). The receptor distribution in the CNS (and probably elsewhere) differs between species (and probably some extent between individuals of the same species), so that different species may respond differently to different opioids and/or may require different doses. For instance, μ agonists in humans tend to cause narcosis, whereas in horses (and cats) they can cause increased locomotor activity and excitement (in large doses). This is thought to be because horses and cats have fewer μ receptors in their CNS compared with humans and so require lower doses. Another example is that some birds and reptiles have more κ-receptors in their CNS and so respond much better to κ-agonist than μ agonist analgesics.
The known receptor types are listed below. They are now classified according to the chronological order by which they were cloned. However, most people still use the traditional classification (Greek letters) for everyday use.

- OP-1 (δ delta) (δ₁, δ₂).
- OP-2 (κ kappa) (κ₁, κ₂, κ₃).
- OP-3 (μ mu) (μ₁, μ₂).
- σ sigma is no longer classified as an opioid receptor. It is now thought to be closely associated with NMDA receptors, perhaps the phencyclidine binding site.
- ε epsilon is the theoretical receptor that the endogenous β-endorphins bind to, but has only been found in rat vas deferens; its existence elsewhere has yet to be proven.
- Nociceptin/Orphanin FQ peptide (NOP) receptor: the role of this receptor is uncertain, but it may help set the thresholds to pain, and may be involved in neuronal plasticity and tolerance to opioids.

The receptors shown in italics are some of the subtypes of each receptor that are thought to exist. The existence of some of the different subtypes is controversial as although there is pharmacological evidence that they exist, they have not all been isolated in cloning studies. There may, however, be some post-translational processing of receptors that results in expression of the different subtypes. There are also likely to be species differences.

The different receptors mediate their effects mainly via G-protein interactions, resulting in, e.g. membrane ion permeability changes or intracellular enzyme activation or inhibition.

**Endogenous ligands**

- Pro-opiomelanocortin → β endorphin → acts on μ and δ receptors.
- Pro-enkephalin → (Met)enkphalin, (Leu)enkphalin and metorphamide → act on δ (κ and μ) receptors.
- Pro-dynorphin → dynorphin A, dynorphin B, α-neoendorphin, β-neoendorphin → act on κ (δ and μ) receptors.
- Unknown precursor → endomorphin 1 and endomorphin 2 → act on μ receptor.
- Pre-pro N/O FQ → N/O FQ → acts on NOP receptor.

The location of the receptors in the CNS determines their effects. In the spinal cord (dorsal horn) opioid receptors inhibit the release of primary pain neurotransmitters (e.g. glutamate, substance P). There are a large number of opioid receptors in the peri-aqueductal grey matter where they stimulate descending pain control systems, so opioids are very effective against pain, and especially C fibre second pain or dull pain. There are not many opioid receptors in the reticular formation ('state of arousal' centre) and opioids are less effective against sharp pain (the reticular formation is an important reception site for sharp pain information). Opioid receptors are, however, found in the limbic system and are probably involved in the emotional aspect of pain. It seems that NOP receptors and N/O FQ are also involved in pain information processing.

### Table 3.1 Comparison of opioid receptor effects.

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>μ</th>
<th>κ</th>
<th>δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td>+++</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Spinal</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Peripheral</td>
<td>++</td>
<td>++</td>
<td>−</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>+++</td>
<td>−</td>
<td>Antitussive</td>
</tr>
<tr>
<td>Pupil</td>
<td>Miosis (dog); mydriasis (cat, horse)</td>
<td>Miosis</td>
<td>Mydriasis</td>
</tr>
<tr>
<td>Gastrointestinal motility</td>
<td>↓</td>
<td>?</td>
<td>↓</td>
</tr>
<tr>
<td>Euphoria</td>
<td>+++</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>−</td>
<td>+++</td>
<td>−</td>
</tr>
<tr>
<td>Sedation</td>
<td>++</td>
<td>++</td>
<td>−</td>
</tr>
<tr>
<td>Dependence</td>
<td>+++</td>
<td>+</td>
<td>−</td>
</tr>
</tbody>
</table>

**Opioid effects**

Apart from the analgesic effects described, opioids have a number of other effects, which differ between agents and species. Some of the more common effects are outlined in Table 3.1. It is an interesting fact that when an animal is in pain, any side effects of opioid administration are very much reduced. All tend to produce analgesia at lower doses than those required for sedation.

**Respiratory depression**

Opioids reduce the sensitivity of the respiratory centre to changes in blood carbon dioxide tension and can cause respiratory depression. This effect does not seem to be as great a problem in the common veterinary species as it is for humans, unless the potent μ agonists, such as fentanyl, are used in high doses.

**Gastrointestinal effects**

In animals that can vomit, many opioids act on the chemoreceptor trigger zone (CTZ; not protected by the blood–brain barrier) in the medulla (CNS), to initiate vomiting. However, most opioids also act on the vomiting centre itself (inside the blood–brain barrier) to produce anti-emetic effects. The more fat-soluble the opioid (e.g. methadone compared with morphine) the more likely it is to cross the blood–brain barrier faster, so its emetic activity (action in the CTZ) is offset by its anti-emetic activity (action in the vomiting centre) so no vomiting occurs.

In general, with the exception of pethidine (see below), opioids increase the motility (they increase the smooth muscle tone) of the gastrointestinal tract, but this motility is uncoordinated and so the propulsive peristaltic activity is reduced overall. Sphincter tone is increased. Sometimes evacuation (defecation) occurs.
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Table 3.2 Relative receptor affinities of some opioids.

<table>
<thead>
<tr>
<th></th>
<th>µ receptor</th>
<th>κ receptor</th>
<th>δ receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pethidine</td>
<td>++</td>
<td>+/-</td>
<td>–</td>
</tr>
<tr>
<td>Morphine</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Methadone</td>
<td>+++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>+++</td>
<td>–</td>
<td>–(-+)</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>+++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Etorphine</td>
<td>+++</td>
<td>+</td>
<td>+ (+)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>++(partial agonist)</td>
<td>+ (antagonist)</td>
<td>+/−</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>+ (agonist/antagonist)</td>
<td>+ (agonist)</td>
<td>−</td>
</tr>
<tr>
<td>Naloxone</td>
<td>+++ (antagonist)</td>
<td>+ (antagonist)</td>
<td>+ (antagonist)</td>
</tr>
</tbody>
</table>

Potency can be described in terms of affinity for a receptor or in terms of clinical efficacy (dose required for effect), as in Table 3.3. Potency can be confusing when applied to the opioids. Affinity for receptor types is shown in Table 3.2, but an opioid’s affinity for a receptor does not give any information about its efficacy. For example, naloxone (an antagonist) has the same (and probably slightly greater) affinity for the µ receptor as morphine (an agonist); but they have opposite effects.

Table 3.3 Relative analgesic efficacies (partly explained in terms of access to central opioid receptors).

<table>
<thead>
<tr>
<th>Analgesic efficacy</th>
<th>% protein binding</th>
<th>Drug</th>
<th>pKa</th>
<th>Lipid solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>Morphine</td>
<td>7.9</td>
<td>Low</td>
</tr>
<tr>
<td>1/10</td>
<td>70</td>
<td>Pethidine</td>
<td>8.5</td>
<td>Medium</td>
</tr>
<tr>
<td>100</td>
<td>80</td>
<td>Fentanyl</td>
<td>8.4</td>
<td>Very high</td>
</tr>
<tr>
<td>10–25</td>
<td>90</td>
<td>Alfentanil</td>
<td>6.5</td>
<td>High</td>
</tr>
<tr>
<td>1000</td>
<td>90</td>
<td>Sufentanil</td>
<td>8</td>
<td>Very high</td>
</tr>
<tr>
<td>50</td>
<td>70–90</td>
<td>Remifentanil</td>
<td>7.1</td>
<td>Medium</td>
</tr>
</tbody>
</table>

‘Pure’ µ agonists

Morphine; 0.1–1.0 mg/kg (tend towards lower doses for cats and horses) IM, IV, SC

Morphine is the ‘gold standard’ analgesic to which others are compared. Can cause histamine release if administered IV. Dose interval 2–4 h (dogs, horses); 4–6 h (cats) after IM or IV administration. Poor bioavailability if administered orally. Can cause vomiting. Can also be administered extradurally and intrathecally. Cats have poor glucuronid transferase activity, so there is slow glucuronidation of morphine; and they tend to produce less morphine-6-glucuronide than morphine-3-glucuronide. Morphine-6-glucuronide is an even more potent analgesic than the parent morphine. Morphine-3-glucuronide is inactive (or may have some antagonistic properties).

Pethidine; 3.5–10 mg/kg IM, SC, (not IV because of potential histamine release)

Pethidine is less potent than morphine (about 1/10th). Duration of effect 45–60+ min in dogs (at about 5 mg/kg), probably nearer 120 min in cats (at about 10 mg/kg) (the dose interval is often quoted as 1–2 h), and duration probably nearer to 30 min in horses and cattle. It has anticholinergic spasmylic effects. Pethidine is said to be vagolytic (whereas other opioids tend to be vagomimetic), and is supposed, therefore, not to lower the heart rate; although this supposed vagolytic effect may be partly due to histamine release and the reflex tachycardic response to a fall in arterial blood pressure. There are, however, conflicting reports of the effects of pethidine on heart rate. A reduction in heart rate, reported with high (10 mg/kg) doses, may be due to pethidine’s agonistic action on α2B receptors, which results in peripheral vasoconstriction with subsequent increase in arterial blood pressure followed by reflex bradycardia. Pethidine also has some direct negative inotropic effect (via calcium channel blockage) at doses >3.5 mg/kg, but this may have little clinical relevance. One of its metabolites, norpethidine, has some analgesic activity, and can cause seizures at high doses, but this is highly unlikely to be a problem with clinical usage. Pethidine also has local anaesthetic-like activity, and is antagonistic at NMDA receptors.

Cardiovascular effects

Cardiovascular effects are wide ranging and depend on the agent and species. Some opioids cause histamine release and can cause hypotension. Morphine can cause a centrally mediated (vagomimetic) hypotension and bradycardia. Etorphine and carfentanil can cause massive hypertension.

Metabolism

Metabolism is hepatic, with biliary and urinary excretion of the metabolites, so with any active metabolites there is the potential for enterohepatic recycling.

Classification of opioids

Opioids are classified depending on the receptors they mainly act upon and their effects on those receptors. However, many opioids have effects on more than one receptor type as shown in Table 3.2. The terms receptor affinity and potency can be confusing when applied to the opioids. Affinity for receptor types is shown in Table 3.2, but an opioid’s affinity for a receptor does not give any information about its efficacy. For example, naloxone (an antagonist) has the same (and probably slightly greater) affinity for the µ receptor as morphine (an agonist); but they have opposite effects.

When discussing potency, the context should be clarified. Potency can be described in terms of affinity for a receptor or in terms of clinical efficacy (dose required for effect), as in Table 3.3. Alfentanil has a more rapid onset and shorter duration than fentanyl. The more rapid onset is because its pKa is lower. The shorter duration is because its volume of distribution is less (it is more protein bound and less lipid soluble), which allows more rapid clearance; and it is not taken up by the lungs. It also has no active metabolites, whereas fentanyl has a partially active metabo-
Methadone; 0.1–0.4 mg/kg IM, IV, SC (0.1–0.5 mg/kg for cats)

Methadone is very similar to morphine, except it does not tend to initiate vomiting (a useful property), probably because of its greater lipid solubility; so it crosses the blood–brain barrier to produce anti-emetic effects in the vomiting centre at the same time that it reaches the CTZ (outside the blood–brain barrier) where it has emetic effects. (Morphine reaches the CTZ much earlier than the vomiting centre, so emesis occurs initially). This also means that the peak activity is quicker after methadone (about 5 min after IV administration) than after morphine (about 10–20 min after IV administration). Methadone may have a longer duration of action than morphine and it is slightly cumulative. Its NMDA antagonistic effects may be useful.

Papaveretum; 0.2–1.0 mg/kg IM (0.1–0.3 mg/kg for cats)

This is a mixture of morphine and other opiate alkaloids. Its effects are very similar to morphine. Papaveretum can cause histamine release if given IV. It appears to provide a very effective neuroleptanalgesic combination along with acepromazine (ACP) for aggressive animals.

Fentanyl; 0.001–0.005 mg/kg IV

Fentanyl is a very potent analgesic and is useful for controlling intra-operative pain. It has a fast onset of action (within 1–2 min), and a short effective half-life of about 10 min making it suitable for repeated boluses or infusions, at least in the short to medium term (see later). It is, however, a potent respiratory depressant, so that mechanical ventilation is often required in anaesthetised patients. Fentanyl actually has a very large volume of distribution and long elimination half-life due to its high degree of fat solubility, so (a bit like thiopental), too many repeated doses or too prolonged an infusion, may result in accumulation of the drug.

Fentanyl is combined with fluanisone (a butyrophenone) in the product ‘Hypnorm’ (marketed as a neuroleptic anaesthetic/analgesic for rabbits, rats, mice and guinea pigs).

Transdermal fentanyl patches are available which slowly release fentanyl at a constant rate, the fentanyl then being readily absorbed across the skin. The ‘dose rate’ required is 2–5 μg/kg/h; and patches are available with release rates of 12.5, 25, 50, 75 and 100 μg/h (corresponding to 1.25, 5, 7.5 and 10 mg). For patch application, the hair should be shaved off to ensure that the patch actually contacts the skin; the dorsum of the neck is a good place; and the edges of the patch can be secured with tissue glue before a light bandage is applied. Heavy bandaging may result in local vasodilation secondary to a thermal insulating effect, which may result in too rapid drug absorption. After patch application in dogs, peak plasma levels take about 20 h to be achieved and last for 72 h; in cats, plasma levels take 12 h to peak, and patches last for 5 days. Beware local skin lesions and the effects of, for example heat pads, which cause local vasodilation and increase absorption. For horses, one 10 mg patch per 150 kg body mass is suggested; onset time is about 1–3 h and duration about 32–48 h.

Alfentanil, sufentanil and remifentanil are synthetic analogues of fentanyl with even shorter half-lives and are used in human medicine as boluses and infusions intra-operatively for analgesia. Their use in general veterinary practice is not yet common. Remifentanil is metabolised by red blood cell cholinestrase, and its elimination is therefore independent of hepatic function, which is very useful in cases with hepatic disease. However, its duration is so short that when an infusion is terminated, other analgesics must be ‘on board’ to ensure continuation of analgesia.

Etorphine

This is an extremely potent μ agonist reputedly having 10,000 times the analgesic potency of morphine. It is a highly dangerous drug in the case of accidental self-administration, and its use should not be contemplated unless antagonists are available. In the UK, etorphine gained notoriety as part of the cocktail that makes up ‘Large Animal Immobilon’. Immobilon is only available in packs that also contain its antagonist, Reviron (diprenorphine).

Partial μ agonists

Buprenorphine: 0.005–0.02 mg/kg IM, IV or SC

Buprenorphine has a very high affinity for μ receptors but only a partial agonist activity at these receptors. Some sources report an antagonist action at κ receptors. Buprenorphine is licensed for use in the dog and cat. It has a slow onset time (about 30 min) but a correspondingly long duration of action of about 6–8 h. It has shorter durations of actions in some pain models and some other species (about 2 h in sheep). The drug has poor oral bioavailability (if swallowed), because of first-pass metabolism, but recent work in cats has shown excellent absorption following oral (buccal) transmucosal (OTM) administration of the solution intended for injection. The dose used in cats for OTM administration is the same as that for analgesia following IV or IM injection, i.e. 0.01–0.02 mg/kg. Unfortunately, similarly good OTM absorption does not occur in dogs because of their different salivary pH. Horses, however, have similar salivary pH to cats (approx. 9).

Agonist-antagonists

Butorphanol: 0.2–0.5 mg/kg IM, IV, SC, dogs and cats; (0.05–0.2 mg/kg horses)

This drug is the source of much confusion in anaesthesia and pharmacology textbooks. It is an agonist-antagonist with affinity for both μ and κ receptors. It has mainly antagonistic effects on μ receptors and mainly agonist effects on κ receptors. In the majority of studies it also has a short duration of action of about 45 min (but may be longer, up to 1–2 h, even up to 5 h, depending on dose, species and circumstance). Butorphanol is also a potent antitusive and it was first licensed for this use.

Butorphanol is now commonly used in the UK in various combinations with α2 agonists (i.e. medetomidine/ketamine/butorphanol combinations in small animals, especially cats; and α2-agonist/butorphanol combinations in horses). Butorphanol has been associated with excitement and dysphoria in horses, dogs and cats. Whereas dysphoria is more likely following butorphanol, euphoria is more likely after buprenorphine. Nevertheless, and especially in combination with acepromazine, α2 agonists or
benzodiazepines, butorphanol appears to have synergistic sedative effects. Although in theory buprenorphine and butorphanol are more potent analgesics than morphine (2–5 times), pharmacological studies have shown that the agonist-antagonists tend to have a ceiling effect of analgesia where higher doses do not seem to provide greater analgesia. Buprenorphine has a bell-shaped curve, where very high (higher than likely to be used clinically) doses produce less analgesic effects than lower doses. A pure μ agonist should therefore be the choice for patients in severe pain.

μ antagonists

Naloxone (0.04–1.0 mg/kg)

Naloxone is a pure antagonist with affinity for all three opioid receptors. It is used mainly to antagonise the effects of full or partial μ agonists. It has a short duration of action of less than an hour so repeated doses may be required.

Clinical use of opioids

There are a number of applications where opioids may be used in veterinary medicine:

- Treatment of pain.
- Neuroleptanalgesia (see Chapter 4 on premedication).
- As part of a balanced analgesia regimen (multimodal pain therapy).
- As part of a balanced anaesthesia regimen.
- As an extradural (epidural) analgesic (see Chapters 12, 14 and 16 on local anaesthetics and techniques).
- As antitusives.
- As spasmyotics (pethidine).
- To decrease gut motility (antidiarrhoeals e.g. Codeine).

There are two main considerations before using opioids. The first (apart from choosing the right drug at the right dose), is to make sure there are no contra-indications for use such as respiratory depression, increased intra-cranial pressure, oesophageal or biliary/pancreatic duct obstruction. The second involves the legal implications, as many opioids are controlled drugs.

Corticosteroids

Corticosteroids are extremely effective anti-inflammatory drugs. Because they are such potent anti-inflammatory agents, steroids can be thought of as having analgesic properties. It is generally accepted that these ‘analgesic’ properties come from the reduction in the production of inflammatory mediators and the resulting effects these can have on inflammation and nociceptors. It is controversial as to whether it can be stated that steroids have any direct analgesic action. They are included in this chapter because clinically they can be a potent tool in some circumstances.

The effects of corticosteroids include:

- Altered carbohydrate, lipid and protein metabolism.
- Altered fluid and electrolyte balance.
- Immunosuppression.

- Anti-inflammatory action (inhibit phospholipase A2).
- Inhibit catechol-o-methyl transferase, and up-regulate β adrenergic receptors to facilitate the effects of catecholamines.

Anti-inflammatory actions

Glucocorticoids enter the cell and bind to cytoplasmic receptors. The steroid–receptor complex then enters the cell nucleus where it affects expression of various genes. Depending on the cell, steroids can have a multitude of anti-inflammatory effects:

- Corticosteroids enhance the synthesis of lipocortin 1, which inhibits phospholipase A2 (PLA2), therefore there will be a reduction of PLA2 products, i.e. a decrease in arachidonic acid and platelet activating factor (PAF) production. (PAF is a vasodilator, it increases vascular permeability, and is a potent chemotaxin too). Arachidonic acid is a 20 carbon fatty acid which contains 4 double bonds. Its chemical name is eicosa-(twenty) tetra-enoic (4 double bonds) acid (or ETE for short) (Figure 3.5).
- Reduction of COX-2 products, i.e. decrease in arachidonic acid metabolites, so decreased prostaglandin/leukotriene production.
- Reduction of iNOS products, i.e. decreased NO. (NO is a potent vasodilator).
- Increased amount/activity of IkBα, which normally inhibits nuclear transcription factor kappa B (NFκB is a transcription factor which promotes cytokine production).
- Membrane stabilising effects, so reduction of mast cell degranulation (histamine release); and decreased lysosomal enzyme release.

Potency and routes of administration

The glucocorticoids have variable mineralocorticoid effects (Table 3.4).

Glucocorticoids can be administered via a wide variety of routes depending on the product formulation:

- Intravenous
- Intramuscular
- Oral
- Inhalation (e.g. beclometasone)
- Intra-articular
- Topical.

Table 3.4 Relative effects of common corticosteroids.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Anti-inflammatory action</th>
<th>Mineralocorticoid action</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>1</td>
<td>1</td>
<td>8–12</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>0.5</td>
<td>12–36</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25</td>
<td>0</td>
<td>36–72</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25</td>
<td>0</td>
<td>36–72</td>
</tr>
</tbody>
</table>
The carboxylic acids include:
- Salicylic acids (e.g. aspirin).
- Acetic acids (e.g. phenylacetic acids such as diclofenac and eltenac).
- Propionic acids (e.g. ketoprofen, carprofen, ibuprofen, vedaprofen).
- Fenamic acids (e.g. meclofenamic acid, tolfenamic acid).
- Nicotinic acids (e.g. flunixin).

**Figure 3.5** Site of corticosteroid action.
The principal eicosanoids (arachidonic acid metabolites) are the prostaglandins, thromboxanes and leukotrienes. Others include the lipoxins. The term prostaglandins is often reserved for just the prostaglandins and thromboxanes.

Side effects are numerous and include:
- Immunosuppression.
- Laminitis in susceptible animals.
- Hypothalamo-pituitary axis suppression.
- Abortion, so care is required in pregnant animals.
- Usually contraindicated in corneal ulceration.
- May result in gastrointestinal and renal compromise secondary to reduction in prostaglandin production; beware combination with NSAIDs.

**Non-steroidal anti-inflammatory drugs (NSAIDs)**
NSAIDs include any drug with anti-inflammatory properties that is not a steroid. NSAIDs specifically are drugs that inhibit formation of prostaglandins (PG) and thromboxanes (TX) from arachidonic acid. NSAIDs classically have **anti-inflammatory, analgesic** and **antipyretic** effects.

The two main groups are enolic acids and carboxylic acids. The enolic acids include:
- Pyrazolones (e.g. dipyrone, tepoxalin).
- Pyrazolidines (e.g. phenylbutazone).
- Oxicams (e.g. piroxicam, meloxicam).

The carboxylic acids include:
- Salicylic acids (e.g. aspirin).
- Acetic acids (e.g. phenylacetic acids such as diclofenac and eltenac).
- Propionic acids (e.g. ketoprofen, carprofen, ibuprofen, vedaprofen).
- Fenamic acids (e.g. meclofenamic acid, tolfenamic acid).
- Nicotinic acids (e.g. flunixin).

**Paracetamol** is a non-acidic compound, and a para-aminophenol derivative. It is a good antipyretic, but usually referred to as a weak analgesic and weak anti-inflammatory. It appears to have mainly central actions (see below). **Cats** cannot glucuronidate phenols very well, so tend to get methaemoglobinemia and hepatic toxicity much more readily after paracetamol than other species.

The specific COX-2 inhibitors (the coxibs such as rofecoxib, celecoxib) are pyrazoles (see later). Despite their theoretically better safety profile, their use has been associated with procoagulant and adverse cardiovascular effects (stroke and myocardial infarction; due to vasoconstriction, and hypercoagulation, possibly due to more inhibition of PGI₂ production than of TXA₂ production) in man, and rofecoxib was withdrawn from the market.
**Effects of NSAIDs**

NSAIDs have the following effects:
- **Anti-inflammatory** via COX inhibition; see below.
- **Antipyretic** via COX inhibition, see below.
- **Analgesic** by several possible mechanisms, see below.
- **Antihyperalgesic** by preventing sensitisation to pain via COX inhibition effects (i.e. they decrease PG synthesis), and NMDA receptor effects (see below under analgesia and anti-hyperalgesia).
- **Anti-endotoxic effects** via COX inhibition and reduction of NFkB activity, which is normally important in amplifying the various inflammatory, complement and coagulation cascades.
- **Antithrombotic effects** via platelet COX inhibition, reduction of TXA₂ production, and thus reduction of platelet aggregation.
- **Weak antispasmodic effects** via inhibitory action on gastrointestinal tract smooth muscle.
- Some may be **chondroprotective** (meloxicam, and carprofen at recommended doses).

Although the different drugs may be structurally and pharmacokinetically dissimilar, their main mechanisms of action (and side effects) tend to be shared. These mechanisms include:

- **Peripheral actions**: anti-inflammatory, analgesic, anti-endotoxic, antithrombotic, antispasmodic.
- **Central actions**: primarily analgesic and antipyretic effects. The analgesic effects may include antihyperalgesic effects (neuromodulation).

**Cyclo-oxygenase (COX) inhibition**

NSAIDs inhibit COX enzymes (Figure 3.6). COX enzymes act on arachidonic acid (a product of cell membrane phospholipid breakdown, especially in damaged cells); inhibition of COX enzymes therefore reduces PG and TX synthesis. (Cyclo-oxygenase used to be called prostaglandin G/H synthase).

Tepoxalin (Zubrin™) (and ketoprofen) also inhibit 5-LOX and thus reduce leukotriene (LT) production, which results in anti-inflammatory and antibronchospasm effects. Classic NSAIDs are contra-indicated in asthmatic patients because inhibition of COX results in the shunting of more arachidonic acid down the 5-LOX pathway, with more LT production, which can worsen asthma attacks.

- There are two main isoforms of COX: COX-1 and COX-2.
- COX-3 may be a splice variant of COX-1, and seems to be expressed in the CNS (see later).

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**Figure 3.6** Site of NSAID action.