



Murdoch
UNIVERSITY

MURDOCH RESEARCH REPOSITORY

<http://researchrepository.murdoch.edu.au/7771/>

Musk, G. and Rasis, A. (2012) *Analgesia for patients with neurological disease*. In: Platt, S. and Garosi, L., (eds.) *Small Animal Neurological Emergencies*. Manson Publishing Ltd, London, pp. 557-569.

Copyright: © Manson Publishing

<http://www.mansonpublishing.com/index.php>

<http://www.medicalsciences.com.au/book/9781840761528/Small-Animal-Neurological-Emergencies-H-C>

It is posted here for your personal use, with terms and conditions restricting use to individual non-commercial purposes. No further distribution is permitted.

ANALGESIA FOR PATIENTS WITH NEUROLOGICAL DISEASE

557

*Gabrielle Musk
& Anthea Raisia*

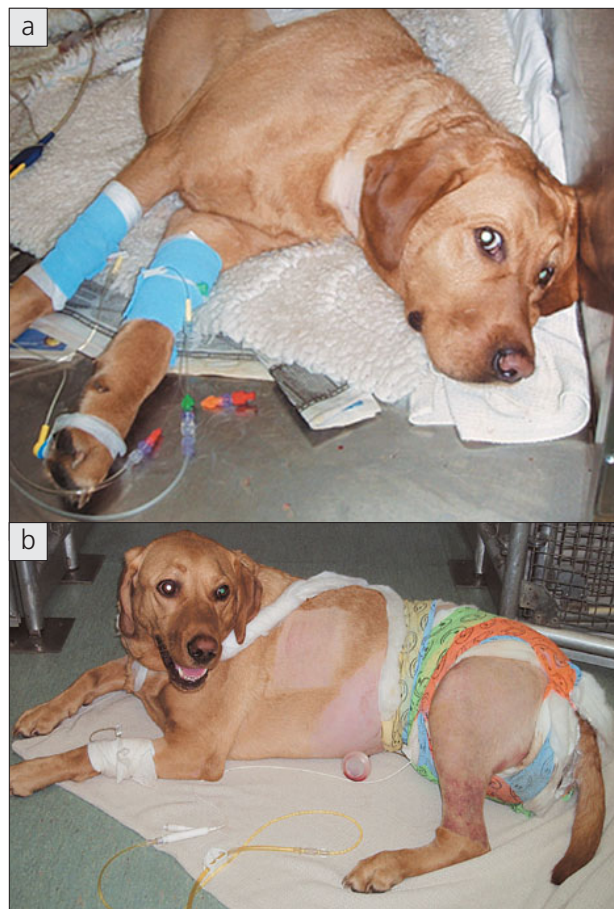
INTRODUCTION

Pain is defined by the International Association for the Study of Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or expressed in terms of such damage. Recognition of the presence of pain and assessment of the severity of pain are essential for optimal management and are integral steps towards appropriate treatment of pain in animals with (and without) neurological disease. Poorly managed pain is a significant contributor to morbidity and mortality, has adverse welfare implications and delays the return to normal function. Good pain management relies on regular pain assessment and includes the administration of analgesic drugs (419).

The aims of pain treatment are to:

- Inhibit the neuroendocrine stress response, which may compromise recovery.
- Maintain tissue perfusion.
- Allow restful sleep.
- Encourage mobility.
- Improve appetite.
- Attenuate peripheral and central sensitization.

A plethora of drugs exist that can be used alone or in combination to manage pain in animals with neurological disease. Analgesic therapy must be tailored to each individual animal based on the cause, duration and severity of pain, the level of consciousness, the presence of coexisting diseases and the impact of expected side-effects (420, p. 559). This chapter describes specific considerations for selecting analgesic agents for pain management of animals with acute neurological disease and provides examples of analgesic regimens that may be suitable for these patients. The physiology of pain and the pharmacology of analgesic drugs are beyond the



▲ 419 (a) A dog following hindlimb amputation with inadequate analgesia. (b) The obvious difference in this animal's behaviour is demonstrated after adequate analgesia was provided.

scope of this book, but a good understanding of both is vital to ensure optimal pain management (see Further reading). Furthermore, familiarity with available drugs will guide the clinician's decision making.

Painful stimuli may cause an acute pain response and poorly managed pain can lead to neurophysiological changes that are permanent. Furthermore, certain types of pain are particularly difficult to manage and require a multimodal approach. The clinician should be prepared to trial therapy and assess the response before committing to a long-term plan. Neuropathic pain is particularly difficult to manage and is often not responsive to opioids. It is produced by peripheral and central sensitization and may be present as allodynia or hypersensitivity (*Table 107*). It may be continuous or sporadic and is described as burning, shooting, tingling or electric in nature.

Pain assessment

Accurate assessment of pain in animals is difficult. In animals with acute neurological disease it is even more challenging, especially if a patient is moribund or depressed. Conversely, physical examination may reveal tachycardia, tachypnoea and hypertension, which complicates objective assessment of autonomic nervous system activity. These cases are easy to misinterpret and concern about the adverse effects of analgesic drugs may influence clinical decision making. Given the scope and variability of responses to painful stimuli in human patients, every effort must be made to perform a thorough pain assessment in each animal patient and treat accordingly. Furthermore, assessment of the response to therapy is essential to ensure that pain is adequately and continuously controlled.

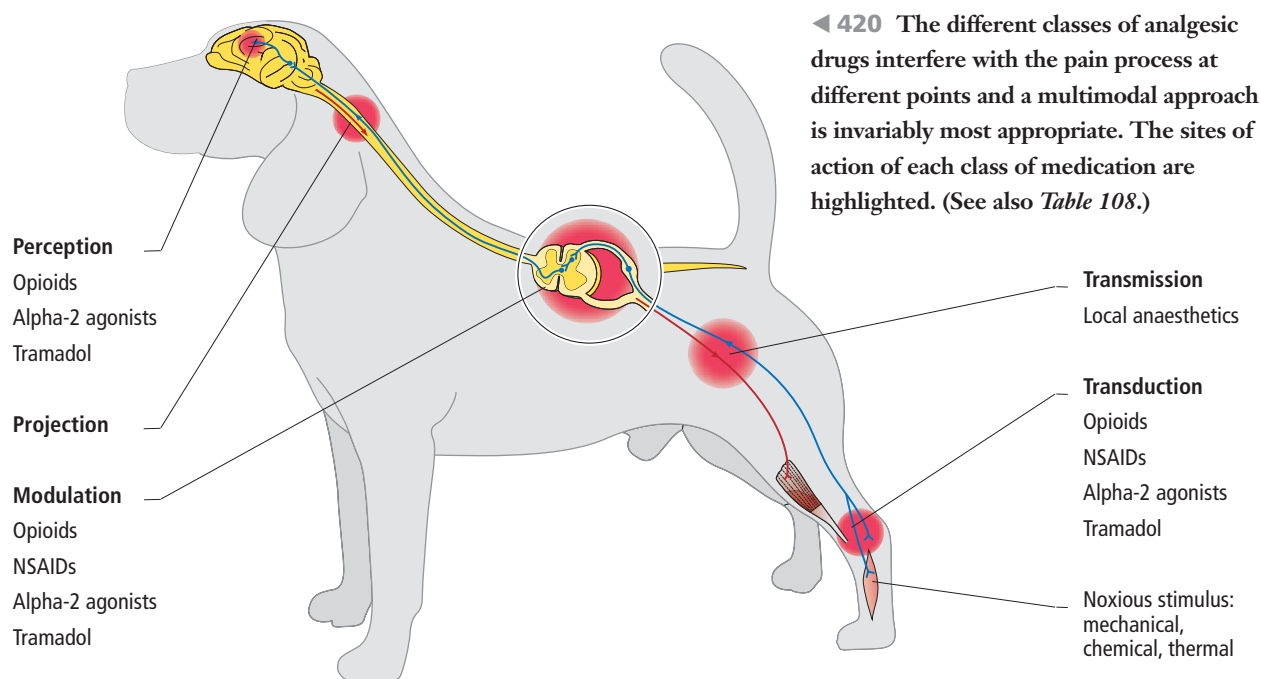
In human medicine, self-reporting of pain is the gold standard method of pain assessment. In veterinary medicine, pain assessment has been performed somewhat subjectively or by applying pain scales used in humans. These include simple descriptive scales, numerical rating scales and visual analogue scales. There are inherent limitations with each of these scales; they are one-dimensional and they have been shown to be unreliable in the setting of acute postoperative pain in dogs. They have, however, had their place in the evolution of pain assessment in animals and have contributed to the understanding of the complexity of the pain experience.

Table 107 **Neuropathic pain**

TERMINOLOGY	DEFINITION
Allodynia	A pain response to a non-painful stimulus. This is usually localized to the area of the initial injury
Hypersensitivity	An exaggerated pain response to a painful stimulus. This phenomenon occurs as a result of 'sensitization'
Peripheral sensitization	'Wind up' of peripheral nociceptors leading to an exaggerated pain response to stimulation
Central sensitization	'Wind up' of central nociceptors leading to generalized exaggerated pain response to stimulation

Table 108 **The multiple steps of the nociceptive pathway**

TERMINOLOGY	DEFINITION
Noxious stimulus	A mechanical, chemical or thermal stimulus that causes pain. Pain is the sensory and emotional experience associated with actual or potential tissue damage resulting from a noxious stimulus
Transduction	Processing the noxious stimulus from the peripheral site to the sensory nerve endings
Transmission	Signalling along sensory nerves to the central nervous system. Sensory nerves may be small myelinated A fibres associated with sharp mechanical-type stimuli or unmyelinated C fibres associated with dull, burning or longer lasting pain
Modulation	Alteration of the incoming signal by synapsing in the dorsal horn of the spinal cord. Neurotransmitters are involved in the propagation of ongoing impulses in the central nervous system. Synapses within the grey matter of the spinal cord also connect with the ventral horn to complete the reflex arc. This manifests as a withdrawal response to a noxious stimulus



The only validated pain scoring system for acute pain in dogs is the Glasgow Composite Measure Pain Scale (GCMPS), which is a multidimensional scale taking into account not just the intensity of pain, but its consequences. The GCMPS is based on psychometric principles that are well established in human medicine for the measurement of complex constructs such as intelligence, pain and quality of life. It categorizes and weights spontaneous and evoked behaviour and interactive and clinical observations (comfort, vocalization, mobility, demeanour, posture, attention to surgical wound and response to touch), resulting in a composite score. It is practical in a clinical setting and easy to become familiar with and use. As it forces the assessor to evaluate behaviour that may be associated with pain and draw conclusions about whether or not the animal requires additional analgesia, it contributes to improved pain management.

A short form of the GCMPS for dogs suffering acute postoperative pain has been developed for use in a clinical setting where the emphasis is on speed, ease of use and guidance for provision of analgesia as opposed to precise measurement of pain in a research environment. The short form comprises six behavioural categories (vocalization, mobility, demeanour, posture, attention to surgical wound and response to touch). The maximum

pain score is 24 (or 20, if mobility is impossible to assess) and it is reported that a clinical decision point for analgesia gave an intervention level of 6/24 (or 5/20 if mobility could not be assessed).

Analgesic drugs

Analgesic drugs fall into the following categories:

- Opioids.
- NSAIDs.
- Local anaesthetics.
- Alpha-2 adrenoceptor agonists (e.g. medetomidine).
- N-methyl-D-aspartate antagonists (e.g. ketamine).
- Miscellaneous drugs (e.g. gabapentin, tramadol, nitrous oxide).

Most analgesic drugs will diminish pain; they are hypoalgesic in effect, rather than entirely abolishing it. The effects are usually dose dependent and an understanding of nociceptive pathways, pain transmission, modulation and perception, the chemical mediators of pain and inflammation and their impact on pain processing will help the decision-making process (420 and *Table 108*). The different classes of analgesics interfere with the pain process at different points and a multimodal approach is invariably most appropriate.

INTRACRANIAL DISEASE

Overview

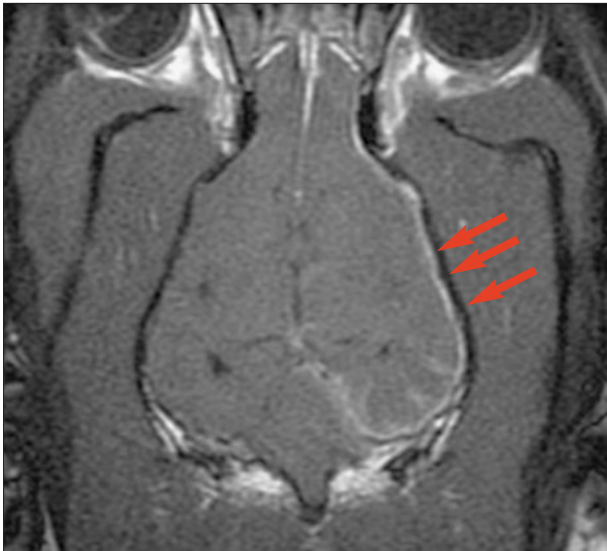
Management of pain in animals with intracranial disease is important from a welfare perspective and because pain itself may increase ICP. This occurs because of sympathetic nervous system-modulated increases in BP.

Considerations

- **Cerebral perfusion.** Selected analgesic drugs and management techniques should have little impact on regulation of CBF. Minimal depression of the cardiovascular and respiratory systems is important for maintaining adequate cerebral perfusion and oxygenation while minimizing secondary neuronal injury. Hypoventilation and consequent hypercapnia may increase CBF and therefore increase ICP, while hyperventilation and hypocapnia may cause cerebral vasoconstriction and compromise CBF. Higher doses of opioids may contribute to hypoventilation through respiratory depression,

while pain may cause either hypoventilation if chest excursions are uncomfortable or hyperventilation if the pain is poorly managed. Close monitoring of pulmonary function and careful adjustment of doses are required to provide appropriate analgesia without respiratory depression.

- **Neurological assessment.** Analgesic drugs often cause tranquilization or sedation. Caution should be exercised if these side-effects are likely to impede assessment and mask neurological deterioration. Low doses of short-acting drugs are preferable and a neurological examination should be performed prior to the administration of any medication.
- **Severity of pain.** As nociceptors are present in the meninges and skull, the severity of pain will depend on involvement of these structures in the disease process. Animals with meningitis (421) or skull fractures (422) are expected to suffer from severe pain and should be treated accordingly. Animals with concurrent trauma to other body systems are also expected to suffer severe pain.



▲ 421 Meningitis is suspected based on the meningeal enhancement present in this dorsal T1-weighted post-contrast MR image (arrows). This condition can be extremely painful. (Photo courtesy Victoria Johnson)



▲ 422 Radiograph of a frontal bone fracture (arrow) in a dog. This lesion would be expected to contribute to the pain present in the animal following its head trauma. (Photo courtesy Victoria Johnson)

Drug selection**Opioids**

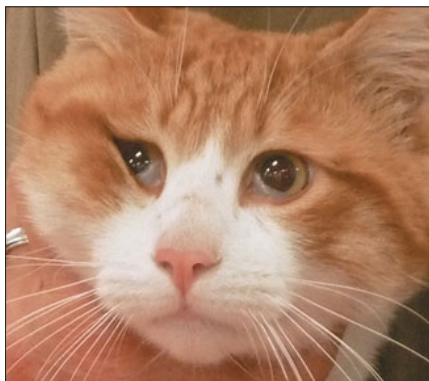
Opioids are often administered to patients with intracranial disease. A summary of the characteristics and dose regimes of commonly used opioids is presented in *Table 109*.

Full mu agonist opioids can be reversed in the event of undesirable side-effects. The potential complications of opioid administration, particularly important to animals with intracranial disease, include bradycardia (with potential hypotension) and respiratory depression (with associated hypercapnia). Hypotension associated

Table 109 Opioid analgesic agents used for perioperative pain control in dogs and cats with neurological disease

AGENT	ADVANTAGES	DISADVANTAGES	DOSE
Morphine	Excellent analgesia (full mu agonist). Can be infused intravenously	Nausea and vomiting may occur, but are more likely if given to a pain-free animal. Histamine release is reported following rapid IV injection	0.1–0.4 mg/kg IV/IM* q2–6h** CRI: 0.05–0.1 mg/kg/hour
Methadone	Excellent analgesia (full mu agonist). Moderate duration of action. Antagonizes NMDA receptors	Pharmacokinetics in small animals unclear. May accumulate with repeated dosing	0.1–0.4 mg/kg IV/IM* q2–6h**
Oxymorphone (US)	Excellent analgesia (full mu agonist)	Bradycardia, respiratory depression, sedation occur at conservative doses	0.05–0.2 mg/kg IV/IM
Hydromorphone (US)	Excellent analgesia (full mu agonist)	Hyperthermia associated with >0.1 mg/kg. Vomiting (especially with SC injection)	0.05–0.2 mg/kg IV/IM
Pethidine (meperidine US)	Good analgesia (full mu agonist)	Potent releaser of histamine when given IV. Pain on IM injection. Large volume. Short duration of action (1–2 hours)	2–5 mg/kg IM/SC q1–2h**
Fentanyl	Excellent analgesia (full mu agonist). Short duration of action (15–20 minutes). Suitable for infusion	High doses cause respiratory depression and bradycardia	CRI: 3–24 µg/kg/hour; transdermal patches: 2–5 µg/kg/hour
Remifentanyl	Excellent analgesia (full mu agonist). Short duration of action (3 minutes). Suitable for infusion	Short duration of action (3 minutes). Higher doses cause respiratory depression and bradycardia	CRI: 3–24 µg/kg/hour
Tramadol	Analgesia for moderate pain. Capsules and syrup available for oral administration	May cause nausea, vomiting, dizziness. Increases risk of seizures in susceptible patients. Use cautiously with head injuries	1–2 mg/kg PO/IM/IV q6–12h
Buprenorphine	Long duration of action (6–8 hours). May provide more analgesia than morphine in cats	Analgesia for moderate pain (partial mu agonist). Prolonged onset of action (30–60 minutes)	dog: 0.006–0.01 mg/kg IV/IM/SC* q6–8h; cat: 0.005–0.01 mg/kg IV/IM q4–8h.
Butorphanol	Good sedative	Analgesia for mild pain (kappa agonist). Short duration of action (1–2 hours). mu receptor antagonist	0.05–0.4 mg/kg IV/IM*

* Where a dose range is given, the lower doses are recommended for IV administration (where specified) or IM injection in depressed animals and the higher doses for IM administration in alert animals/animals in pain.
** Cats may have slower metabolism and may require less frequent administration.
CRI = continuous rate infusion.



▲ 423 Pupillary dilation in a cat after premedication with an opioid.

with opioid-induced bradycardia is not common in normovolaemic patients with normal myocardial function. Often, the arterial BP remains stable or improves as the increased time during diastole associated with the slight reduction in heart rate allows for improved ventricular filling and an increased stroke volume. Conservative doses of opioids are unlikely to cause significant respiratory depression in normal dogs and cats, but in those with increased ICP the effects may be more marked. Care should be taken and therefore the adequacy of ventilation should be closely monitored. Opioids are also reported to cause pupillary constriction in dogs and pupillary dilation in cats (423), which has the potential to interfere with neurological assessment. In conscious animals these side-effects do not appear to be a problem at the low doses used clinically. However, in animals with CNS depression, these side-effects can be exacerbated.

Animals in severe pain, without pre-emptive analgesia (e.g. trauma)

The use of short-acting reversible opioids, such as fentanyl or remifentanyl, is preferred in patients in severe pain. These drugs have a relatively fast onset and short duration of action, giving them a pharmacokinetic profile suitable for infusion. The infusion rate can therefore be titrated to achieve the desired clinical effect. A balance

between adequate analgesia and minimal CNS, cardiovascular and respiratory depression (and increase in PaCO_2) must be achieved. Patients with high ICP may be extremely sensitive to the sedative, cardiovascular and respiratory depressant effects of opioids, so great care should be taken and conservative doses should be administered in the first instance. The authors have observed markedly reduced mentation using low infusion rates of fentanyl. It is recommended that infusions of fentanyl are started as low as $1 \mu\text{g}/\text{kg}/\text{hour}$ in animals with head trauma and increased gradually to achieve the desired level of pain management without causing further deterioration in mentation. When analgesia cannot be achieved without respiratory depression, the application of IPPV (manual or mechanical) will be required to maintain normocapnia.

Animals with moderate to severe pain (e.g. postoperative period), having received pre- and intraoperative analgesia

Intermittent dosing of full mu receptor agonists (e.g. methadone, $0.1\text{--}0.4 \text{ mg}/\text{kg}$ IM) may be adequate for animals with severe to moderate pain. However, pain management can only be achieved by maintaining a stable therapeutic plasma concentration of drug. This in turn ensures a stable, effective (e.g. brain or peripheral nociceptor) concentration of drug. To achieve a stable plasma concentration of opioid, an infusion that can be adjusted according to clinical effect is best. Intermittent 'bolus' dosing will cause periods of relative overdose and periods of relative underdose. Morphine and other opioids that may induce emesis should not be used if there is any contraindication to vomiting (e.g. raised ICP). The use of tramadol for perioperative analgesia is currently popular, but there are only a few reports in the literature documenting its use and efficacy in dogs. While it may be appropriate for animals in moderate to severe pain, it is the authors' opinion that it should be reserved for use as an adjunct to an analgesic protocol. A reported side-effect of tramadol in humans is seizures, and while this seems to be a risk for veterinary patients as well, it is unknown how significant a problem this may be. If the patient is receiving other medication that affects the reuptake of serotonin, drug interactions should be taken into account. In such cases a low dose of tramadol or an alternative analgesic drug should be used.

Animals with mild pain

Mild pain can be managed with drugs such as buprenorphine (0.01–0.02 mg/kg IM q4–6h) or pethidine (2–5 mg/kg IM q1–2h). The appropriate interval between drug administrations will depend on the anticipated duration of action of an individual drug. It is always better to aim for a continuum of pain control, so regular dosing is important. To achieve a continuum, subsequent doses of drug should be administered before the plasma concentration of the drug has decreased. Pethidine is a full mu agonist, but it does not produce analgesia comparable to morphine, methadone or other full mu agonists. It is often associated with an increase in heart rate as it has an atropine-like structure. Pethidine should only be given intramuscularly as the potential for histamine release following intravenous injection is high. Furthermore, pain associated with intramuscular injection and the frequent dosing required for continuous analgesia make pethidine a less desirable option for pain management compared with other opioids.

Other agents

A summary of other agents available for use in animals with neurological disease is presented in *Table 110*. NSAIDs are also useful, but if any contraindication is identified (e.g. circulatory shock, coagulopathies, gastric mucosal bleeding, corticosteroid administration, renal disease), they should be avoided. Ketamine should be avoided in patients with intracranial disease and associated increased ICP, as they may be exacerbated by ketamine. Alpha-2 adrenoceptor agonists should be used with extreme caution, as their vasoconstrictive effects may further compromise CBF. Corticosteroid administration may contribute to pain management in certain disease processes (e.g. meningitis or neoplasia associated with marked peritumoural oedema) through their anti-inflammatory action. However, corticosteroids may potentiate neuronal ischaemia in a hypoxic environment (see Chapter 20).

Table 110 Non-opioids used as part of pain management in animals with spinal disease

AGENT	ADVANTAGES	DISADVANTAGES	DOSE REGIMEN
Benzodiazepines: diazepam, midazolam	Muscle relaxation	Disinhibition in healthy animals. Respiratory depression in animals with underlying respiratory disease/insufficiency	Diazepam: 0.1–0.2 mg/kg IV/PO. Midazolam: 0.1–0.4 mg/kg IV/IM
Phenothiazine tranquilizers: acepromazine	Anxiolysis, sedation	Hypotension; avoid in hypovolaemia. Contraindicated in carbamate and organophosphate poisoning	0.01–0.05 mg/kg IV/IM
Alpha-2 agonists: medetomidine, dexmedetomidine	Sedation, muscle relaxation, analgesia. Dexmedetomidine is associated with fewer cardiovascular side-effects than medetomidine	Adverse cardiovascular effects: avoid in animals with heart disease, hypovolaemia. Hyperglycaemia: avoid in diabetics and head trauma. High incidence of vomiting in cats	Medetomidine: bolus, 1–2 µg/kg IV up to 3–5 µg/kg IM; CRI, 0.5–3 µg/kg/hour. Dexmedetomidine: Bolus, 1 µg/kg IV; CRI, 0.5–1 µg/kg/hour
NMDA antagonists: ketamine, amantadine	Analgesia. May be useful to treat neuropathic pain. Interferes with central sensitization. Reverse tolerance associated with prolonged opioid administration	Dysphoria associated with accumulation of norketamine with prolonged infusion, therefore requires dose reduction with time. Arrhythmogenic: avoid in chest trauma. Increased skeletal muscle tone may potentiate pain due to muscle spasm. Pain on IM/SC injection. Cerebellar dysfunction reported anecdotally in some breeds of cat	Ketamine: CRI, 5–10 µg/kg/minute (can be used with morphine or lidocaine CRI). Amantadine: 3–5 mg/kg PO q24h

(Continued)

Table 110 **Non-opioids used as part of pain management in animals with spinal disease** (continued)

AGENT	ADVANTAGES	DISADVANTAGES	DOSE REGIMEN
Tricyclic antidepressants: amitriptyline	May be useful in the treatment of neuropathic pain. Blocks nor-adrenaline and serotonin reuptake in the brain, increasing the effect of these neurotransmitters	Vomiting and diarrhoea, excitability, arrhythmias. Consider drug interactions if using anaesthetics or antiepileptics. Enhanced sedation if used with other sedating drugs	1–2 mg/kg PO q12h
Lidocaine	Analgesia. May be useful in neuropathic pain	Sedation may interfere with mobility. Myocardial depression can cause hypotension in unstable patients. Vomiting reported. DO NOT USE IN CATS	Initial bolus of 2 mg/kg followed by 20–50 µg/kg/minute
Gabapentin	Supplementary analgesia for neuropathic pain	Sedation and ataxia	Titrate dose from 2 mg/kg up to 10–20 mg/kg PO q8–12h

SPINAL DISEASE

Considerations

- **Neuronal function.** Aiming to preserve neuronal function by maintaining perfusion and oxygenation is vital. Agents that cause excessive depression of cardiovascular and pulmonary functions should be avoided. Arterial BP and adequacy of ventilation (using a capnograph) should be monitored closely.
- **Pain.** Pain associated with spinal disease (424) is likely to be severe, necessitating the use of potent analgesic drug combinations by continuous infusion.



▲ 424 Animals with spinal disease, such as the one in this picture, will be in pain and require administration of analgesic agents.

- **Anxiolysis.** Anxiety in weak or paralysed animals may decrease the pain threshold. The judicious administration of anxiolytics is a useful part of pain management in haemodynamically stable animals.
- **Muscle relaxation.** The administration of muscle relaxants is useful in reducing pain associated with muscle spasm. (*Note:* Do not use in animals with unstable fractures.)
- **Neuropathic pain.** When present, neuropathic pain is often resistant to opioid analgesia and requires a multimodal analgesic regime.
- **Multimodal analgesia.** A combination of analgesic agents can be administered concurrently to optimize pain management and minimize the frequency and severity of side-effects associated with individual agents.

Drug selection

Opioids

Due to the severity of pain in most animals with spinal disease, opioid analgesics are often the best choice. The advantages and disadvantages of commonly used opioids and appropriate dose rates are described in *Table 109*.

Animals in severe pain (e.g. spinal trauma)

As previously described for animals with intracranial disease (see above), the use of short-acting reversible opioids, such as fentanyl or remifentanyl, is preferred in animals with severe pain (e.g. trauma victims with multiple organ damage and orthopaedic injury).



▲ **425** Steps for placement of a fentanyl patch. (a) Clip the skin prior to placement of the patch. (b) Wipe the skin with a dry swab only. (c) Wear gloves when positioning the patch. In this case two patches are being used (25 µg/hour and 50 µg/hour). (d) Ensure even adherence to the skin with gentle digital pressure. (e) Cover the patches with a light adhesive dressing and label with the name of the drug and the time and date of application.

Stable animals requiring intensive pain control

During the immediate post-trauma or post-surgical period, the continuous infusion of opioids (e.g. fentanyl or morphine) is more likely to prevent breakthrough pain. Opioid infusions can be combined with other agents to achieve multimodal pain management (e.g. an opioid in combination with ketamine and/or lidocaine). Infusion rates for each of the individual drugs are provided in *Tables 109* and *110*.

The transdermal delivery of drug from a patch applied to the skin (e.g. fentanyl patches, **425**) may provide a useful adjunct to perioperative analgesia. It may take up to 24 hours for therapeutic plasma concentrations to be achieved, so analgesia will be required until this time. The delay is shorter in cats than in dogs. Because there is also marked individual variation in absorption and, therefore, plasma concentrations achieved, fentanyl patches should not be relied on as the

sole method of providing analgesia. Buprenorphine patches are also available and should be used with the same caveats as fentanyl patches. Patches should not be cut in half. If a lower dose is required, then creating a barrier between the patch and the skin is most appropriate. It is best to place the patch on a clipped area of skin out of reach of the patient. The lateral thorax, dorsum or neck may be appropriate.

Stable animals requiring less intensive pain control

When less intensive management of the animal is required, intermittent administration of full mu opioids such as methadone or morphine can be used. Although vomiting is less likely in animals in pain, the use of morphine is generally avoided in animals with cervical injury where violent movements associated with vomiting can cause further injury to an unstable spinal lesion. In addition, recumbent animals that vomit may not be able to clear vomitus from the pharynx and mouth, predisposing to airway obstruction and aspiration.

Other agents

A variety of other agents can be used in conjunction with opioids to improve pain management. A summary of these agents can be found in *Tables 110* and *111*.

Non-steroidal anti-inflammatory drugs

NSAIDs may be used to decrease inflammatory pain and they are potent analgesics in their own right. The cyclo-oxygenase inhibitors carprofen, meloxicam and meclufenamic acid are registered for perioperative use (*Table 111*). The lipoxygenase and cyclo-oxygenase inhibitor tepoxalin was available to the veterinary market, but it has been associated with an increased incidence of adverse side-effects.

Concurrent administration of NSAIDs and corticosteroids is contraindicated due to increased risk of gastrointestinal ulceration and haemorrhage, therefore the use of NSAIDs is best delayed until it has been decided whether the patient will benefit from corticosteroid therapy. For animals receiving either steroids or NSAIDs, concurrent administration of gastrointestinal protectants may help reduce the incidence of gastrointestinal ulceration.

Muscle relaxants

Benzodiazepines (diazepam or midazolam, 0.25–0.5 mg/kg PO q6–8h) may provide a useful adjunct to pain management in patients with stable spinal injury by alleviating muscle spasm, which is commonly observed in animals with spinal disease. In animals with unstable spinal lesions (e.g. fractures), skeletal muscle relaxation may be detrimental as it reduces the splinting effects of the epaxial muscle.

Alpha-2 agonists, such as medetomidine, can also be used to provide muscle relaxation. In addition, these agents are analgesic. Because of sedative and cardiovascular side-effects, these agents are generally limited to animals that do not have cardiovascular pathology. The authors have found that infusing medetomidine at 1–3.5 µg/kg/hour is useful in healthy dogs that have pain or anxiety that is unresponsive to other drugs. As with benzodiazepines, these agents should be avoided in animals with unstable spinal fractures.

Anxiolytics

Acepromazine is an extremely useful agent for anxious animals with spinal disease. Due to its hypotensive effects, the use of this agent should be limited to normovolaemic and normotensive animals. The side-effects are dose dependent; the authors use 0.01–0.05 mg/kg to a maximum of 1 mg/kg. Acepromazine is also more effective if combined with an opioid (e.g. 0.03 mg/kg acepromazine with 0.3 mg/kg morphine for sedation). Trazodone can also be used for this function (see p. 545).

N-methyl-D-aspartate antagonists

Ketamine is becoming increasingly popular as part of a multimodal analgesic protocol in small animals. Ketamine interferes with the process of CNS sensitization (wind-up), which may manifest as hyperalgesia (exaggerated pain response to a painful stimulus) or allodynia (pain response to a non-painful stimulus) from peripheral and central sensitization. It plays an extremely important role in the management of animals with chronic pain, animals with direct nerve trauma, amputees and trauma patients. Care is required when using this agent in trauma patients where the arrhythmogenic effects of ketamine may exacerbate myocardial contusions or

Table 111 Non-steroidal anti-inflammatory drugs

DRUG	SIDE-EFFECTS	DOSE RATE: DOGS	DOSE RATE: CATS
Carprofen	Minimal. Vomiting	2 mg/kg PO, SC or IV q12h or 4 mg/kg q24h	2 mg/kg SC once only
Meloxicam	Minimal. Diarrhoea	0.2 mg/kg PO, SC or IV q24h then 0.1 mg/kg q24h thereafter	0.1–0.2 mg/kg PO or SC once only. 0.1 mg/kg q24h for 3 days
Meclofenamic acid	Vomiting and diarrhoea	1–2 mg/kg PO q24h	Not used

ischaemia and associated arrhythmias. At higher doses the cardiovascular effects of ketamine can become problematic (increased heart rate and BP). The authors use 2–10 µg/kg/minute by infusion for analgesia (higher end of dose rate if intraoperatively and lower end if conscious). A 'bolus' dose of ketamine may be incorporated into a premedication for cats (5–10 mg/kg) and very difficult dogs (1–2 mg/kg). Dogs are more prone to the dissociative effects of ketamine, so lower doses should be used in this species. As part of an induction combination, ketamine can be given at 5 mg/kg with a benzodiazepine (e.g. diazepam or midazolam, 0.25–0.5 mg/kg).

Methodone may also act as an antagonist at the NMDA receptor and this is thought to be especially beneficial in the treatment of neuropathic pain that may otherwise be resistant to typical opioids.

Lidocaine

The effectiveness of this agent in spinal pain has not been determined. It should, however, be considered if pain is unresponsive to other agents. It can be administered either alone or in combination with morphine and/or ketamine. Infusion of each drug is adjusted to optimize analgesia but minimize sedation. Lidocaine can depress cardiovascular function and contribute to hypotension, therefore it is essential that animals are normovolaemic and that cardiovascular function is monitored during administration. It should also be used cautiously in cats

and at lower doses than in dogs, as the former species is more sensitive to the neuroexcitatory effects of lidocaine.

Lidocaine patches are also available and may be useful for topical analgesia prior to attempting vascular access or for the management of incisional pain. The onset of action is relatively rapid. (The area should be clipped and the patch secured in position to avoid inadvertent ingestion by the patient. Care should also be taken to avoid heating the area, as this may accelerate absorption and increase the potential for side-effects.)

Tramadol

Tramadol is an agent with weak mu opioid agonist and non-opioid analgesic properties. The non-opioid effects are associated with increased noradrenaline (norepinephrine) and 5-hydroxytryptamine (serotonin) at central neuronal synapses, which reduces the excitability of spinal nociceptive activity, partly via alpha-2 adrenergic activity. The activities of the opioid and non-opioid mechanisms are synergistic, resulting in greater analgesia than that expected for each component acting separately. The efficacy of tramadol postoperatively in humans appears to be similar to that of µ opioid agonists. It can be administered parenterally and enterally. Comprehensive clinical studies in animals are currently lacking. Tramadol has a wide therapeutic margin and while most dosing is based on anecdotal reports it is common to use 1 mg/kg q12h or q8h.

NEUROPATHIC PAIN

Neuropathic pain (426) is classically less responsive to opioids and difficult to manage. It may occur in patients with lumbosacral disease, neuropathy, nerve root trauma and a number of other conditions. Other agents that may be useful in animals suffering neuropathic pain include ketamine, amantadine, medetomidine, lidocaine, tramadol, gabapentin and tricyclic antidepressants. A summary of these agents and doses rates are found in *Table 110*.

Gabapentin's mode of action in the treatment of neuropathic pain is thought to be by prevention of the release of glutamate in the dorsal horn via interaction with the alpha-2/delta subunit of the voltage-gated calcium channels. While gabapentin has been used safely in dogs, only anecdotal reports of its efficacy have been published.

NEUROMUSCULAR DISEASE

Considerations

- **Severity of pain.** The type of NM disease will influence the severity of pain and the choice of analgesic agents. Some conditions may not be painful, so careful pain assessment is essential.
- **Ventilation.** Animals with NM disease frequently have impaired ventilation. This may be exacerbated by drugs that depress spontaneous ventilation (e.g. opioids).
- **Vomiting.** Animals with NM disease may not be able to protect their airway. In addition, vomiting may trigger laryngeal spasm in animals with tetanus. Agents that predispose to vomiting (e.g. morphine) should be avoided.
- **Sedation.** The use of analgesic agents with sedative properties may exacerbate recumbency and immobility in animals with NM weakness. In contrast, sedation can be useful in animals that are hyperaesthetic (e.g. polyradiculoneuritis). (*Note:* Acepromazine is contraindicated in methiocarb and organophosphate poisoning.)

Drug selection

Any of the drugs used for management of spinal pain can be used for management of animals with painful NM disease. The choice will depend on the stability of the animal and the severity of the pain.

Regional and local anaesthesia in animals with neurological disease

While pain associated with intracranial disease and generalized NM disease is not amenable to regional anaesthesia, this modality may be useful for managing pain associated with trauma to other regions of the body. Regional anaesthesia may also be used in certain spinal diseases. Regional and local anaesthesia provide the ultimate in analgesia if the innervation of an area can be isolated and completely desensitized.

In patients with chest wall trauma, intrapleural or intercostal nerve blocks are effective as an adjunct to an analgesic regime. A maximum dose of 2 mg/kg of bupivacaine should be administered every 6 hours. For intrapleural analgesia this dose may be diluted to increase the volume or combined with NaHCO₃ to minimize the discomfort associated with the low pH of the solution. For intercostal nerve blocks, two intercostal spaces either side of the lesion or surgical wound should be blocked (five spaces in total). The intercostal nerves cross-innervate, so it is essential to block at least five spaces. The nerve runs caudal to the rib. Epidural administration of analgesic drugs will provide additional analgesia in animals with concurrent pelvic and abdominal trauma (see Further reading). Epidurals have also been used to provide analgesia in animals with spinal fractures, although the use of local anaesthetic by this route, and consequent motor (and sensory) blockade, should generally be avoided, as motor function is an essential part of neurological assessment. Local anaesthetic drug preparations may be diluted to minimize motor blockade (e.g. 0.25% bupivacaine can be diluted to 0.125%) or ropivacaine may be used. Epidural administration of local anaesthetics should be avoided in haemodynamically unstable animals as sympathetic nerve blockade will

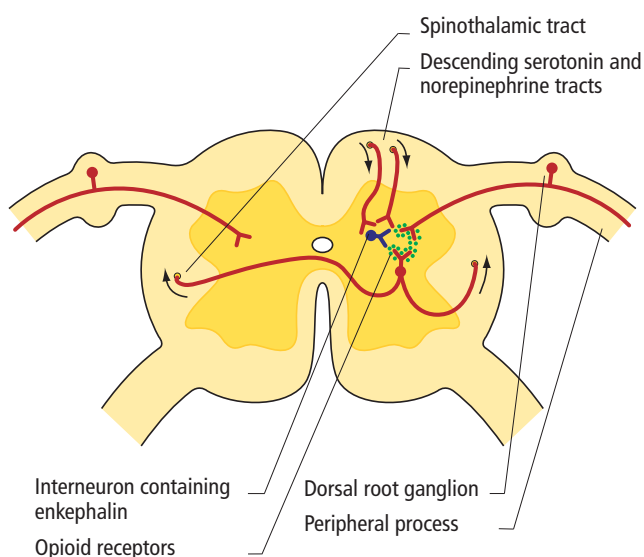
exacerbate hypotension. In these cases, epidural administration of morphine alone (0.1 mg/kg diluted in sterile saline to the desired volume) can still provide useful regional analgesia. The volume of injection is a factor that determines the degree of cranial spread of the drug and, therefore, the clinical effect. Opioids are lipophilic, so will spread cranially, but increasing the volume of injection will facilitate this. As a rule of thumb, 1 ml of diluted drug per 4.5 kg to a maximum of 6 ml is appropriate.

For infiltration of surgical or traumatic wounds, a combination of lidocaine with NaHCO_3 (1 mmol/ml) in a ratio of 9:1 will help reduce irritation on injection. Lidocaine 2% can be combined with 0.5% bupivacaine in a 1:1 ratio to provide a more rapid onset and longer duration of action.

Prior to placement of an intravenous or intra-arterial catheter, a eutectic mixture of local anaesthetic (EMLA) cream can be applied to the site at least 30 minutes beforehand. EMLA will facilitate painless placement of a catheter and is especially useful for arterial catheterization in conscious patients. Lidocaine patches are also useful in this situation. For nasal cannula or urinary catheter placement, topical application of a local anaesthetic, such as xylocaine or lidocaine spray, is helpful if administered a few minutes beforehand.

Non-specific aspects of pain management in animals with neurological disease

- Bedding should be well padded, able to wick moisture away from the patient, easy to clean and easy to replace as often as required.
- A comfortable ambient temperature will help prevent hypothermia or panting.
- A urinary catheter may be necessary to prevent urinary retention, especially if an epidural has been administered. Placement of a urinary catheter also facilitates the measurement of urine output, which is useful to ensure adequate fluid therapy and renal function (see Chapters 31 and 2, respectively). Placement of the urinary catheter must be performed aseptically.
- Any wounds should have regular dressing changes. If dressings are wet or odorous, they should be changed immediately.
- Patients that require exercise should be managed carefully by skilled personnel with a good understanding of the individual patient's history and treatments.
- ICUs can be busy places and animals may find it difficult to sleep quietly and rest. It is important to provide quiet times with the lights out, so sleep deprivation does not contribute to morbidity.



◀ 426 Neuroanatomy and neurotransmitters involved in pain pathways. Descending pathways modulate the incoming pain sensation, which stimulates glutamate release.