CONSTANT-rate infusions (CRIs) of analgesic drugs are a useful treatment modality when dealing with moderately to severely painful conditions.

This article outlines the pathophysiology of pain and the rationale for CRI use. The second part of the article will deal with the pharmacology of the drugs commonly used in CRIs and the practicalities of administration.

Acute pain may be associated with trauma, surgery or disease and, as veterinary surgeons, we have an ethical responsibility to ensure our patients receive adequate analgesia, thus minimising any discomfort and distress.

Uncontrolled pain may have broader consequences than just discomfort – excess activation of the neuroendocrine stress response may encourage catabolism, weight loss and increased demands on the cardiovascular system. Pain may cause anorexia and energy store depletion.

Thoracic and cranial abdominal pain may prevent animals from ventilating effectively, and animals that are restless and in pain may not sleep properly.

Immobility caused by pain may predispose to oedema, thromboembolism, urinary retention and constipation.
In humans, poorly treated acute pain may also contribute to chronic pain syndromes, although this is difficult to document in animals. It has been shown in human medicine that good postoperative analgesia reduces mortality, complications and hospital stay. This is probably also true for the ill or injured veterinary patient. Good evidence to prove the effects of pain on morbidity and mortality in veterinary medicine does not exist, although it is safer to assume that the situation is similar and make aggressive pain management a priority in all our patients.

**Pain assessment**

Pain is both individual and dynamic, and responses to analgesics may vary in different patients. Therefore, analgesics should be administered to effect, depending on the patient’s response, rather than administering a fixed dose and ticking the “analgesia box”. Assessment of animals’ pain levels may also be difficult, as species, breed, age, individual temperament and the presence of stressors could influence behavioural signs.

It is clearly advantageous to be familiar with the individual patient’s character before the onset of the pain, so behavioural changes can be evaluated realistically. Disease may reduce the number of behavioural indicators the animal is capable of showing, and some animals may respond to pain through withdrawal – this is especially true of cats.

Where there is any doubt as to the presence of pain, an analgesic should be administered and the response observed. Given the difficulties in pain assessment, a positive response to an analgesic may be the goldstandard diagnostic technique. The level of perceived pain may alter rapidly, and animals should be re-assessed regularly. Vital signs such as heart rate and serum hormone concentrations are also notoriously unreliable, and may be affected by anxiety, fear and disease.

No single behavioural sign is pathognomonic for pain. Behavioural assessments of pain should concentrate on key areas, including posture, mobility, activity, response to touch, attention to the painful area, facial expressions and vocalisation. Animals may adopt hunched or abnormal postures to guard or splint painful areas. Examples include the characteristic praying position seen with cranial abdominal pain, and the extended head and neck in patients with neck pain. A reluctance to move or lie down, restlessness and frequent changes of position may be features of pain behaviour. A stilted gait, limping or a lack of weight bearing on a limb are most often due to painful conditions. Activity levels may be reduced and a decrease in social interaction is often evident. Animals in pain are often inappetent and some may even become aggressive. They often respond to gentle palpation of any tender area with purposeful movement or aggression, and may look, bite or chew at the area in question. Vocalisation is often non-specific for pain, but should be evaluated carefully. Some non-painful animals vocalise continuously, where some severely painful animals don’t vocalise until pain becomes excruciating.

Vocalisation may also be a feature of emergence delirium after anaesthesia, or dysphoria due to analgesic drugs (see later). The above is far from a complete summary of pain behaviours, and full
reviews may be found elsewhere (see further reading).

It may be useful to use behavioural scoring systems to allow for a more objective measurement of analgesic efficacy. A number of veterinary pain scores exist, and this author favours the Glasgow composite pain score (it can be downloaded at www.gla.ac.uk/faculties/vet/smallanimalhospital/ourservices/painmanagementandacupuncture). This scale is validated for use in dogs and can be incorporated into acute pain management programmes for use postoperatively and in traumatised or diseased patients.

**Pain physiology**

Pain pathways are complex and not fully understood, but a good understanding of the physiology and pathophysiology of pain should underlie any treatment plan. The pain pathway may be broken down into five steps – these are:

• transduction;

• transmission;

• modulation;

• projection; and

• perception (see Figure 1).

Noxious stimuli are initially converted into electrical signals (action potentials) at peripheral nociceptors and this is termed transduction. These signals are then transmitted along nerve fibres to the central nervous system. Two nerve fibre types are responsible for pain transmission – Aδ and C fibres.

Aδ fibres are small, myelinated fibres that relay fast pain, such as cuts or pin pricks. C fibres are smaller, unmyelinated fibres responsible for the slow burning sensation we associate with pain. These afferent fibres transmit the signal from the periphery to the dorsal horn of the spinal cord. Once the signal reaches the dorsal horn, three things may happen:

• the signal may invoke a spinal reflex, such as a withdrawal response;

• the signal is projected along spinal tracts to higher centres, where pain may be perceived; and

• the signal may be modulated.

Modulation describes the amplification or suppression of signals, and modulator mechanisms are
important targets for analgesic drugs. This modulation may be due to local endogenous mediators, such as the opiates (enkephalins, endorphins etc), noradrenaline and many others (serotonin, $\gamma$-aminobutyric acid, substance P etc).

Pain signals may also be modulated by other afferent inputs, such as touch via A$\delta$ fibres, and this is termed the gate theory of pain. Although an oversimplification, it underlines the point that painful stimuli must pass a series of “gates” controlled by other inputs before being projected to higher centres. It also explains why rubbing a painful area may make it hurt less.

Descending serotoninergic and noradrenergic neurones from the brain may also modulate pain, and these pathways are responsible for suppressing painful stimuli during periods of stress. They are thought to be responsible for the apparent absence of pain sensation in racehorses that sustain a fracture during a race, but only show pain and stop using the limb once the race is over. As well as its action at opioid receptors, tramadol may potentiate these pathways, thus resulting in analgesia.

Projected stimuli may activate widespread areas of the brain, causing arousal, fear, and autonomic and motor responses. Pain is perceived in the cerebral cortex, and the magnitude of these responses may be conditioned by anxiety, fear, mood, attention and, in humans, the administration of placebo analgesics. Using a combination of drugs that act at different steps in this pathway may produce better analgesia and reduce individual drug doses and associated side effects. The use of multiple drugs is termed multimodal analgesia, and this should be practised wherever possible.

A simple example would be the use of an NSAID to manage pain due to peripheral inflammation, combined with an opioid to modulate pain at the spinal and cortical levels.

Sensitisation

Painful stimuli may cause changes in the pain pathway, resulting in an animal’s pain worsening clinically. These changes are called sensitisation and may occur peripherally or centrally, inducing a phenomena termed hyperalgesia and alldynia.

Hyperalgesia is an increased response to a normally painful stimulus, whereas alldynia is the production of a painful response to a normally innocuous stimulus (Figure 2).

Peripheral sensitisation occurs due to an inflammatory response at the site of injury. Inflammatory mediators, such as prostaglandins, histamine and bradykinins, stimulate nociceptors directly and decrease the threshold of nociceptors, leading to hyperalgesia and alldynia.

These phenomena also occur due to changes in the spinal cord, called central sensitisation or “wind-up”. The spinal pain pathway is inherently plastic, and can change in response to intensely painful stimuli.
As a result of intense nociceptive stimuli, the threshold of the central neurones fall and their receptive field enlarges, leading to the painful stimuli becoming more painful and more widespread. Although this phenomenon is thought to be an adaptive response to encourage protective behaviour, it is clearly maladaptive in most situations. Many neurotransmitters are involved in central sensitisation, but N-methyl D-aspartate glutamate receptors would appear to be the most important, and this is the rationale for the use of ketamine as an analgesic (Figure 3).

To prevent these phenomena, pain should be treated before it occurs, and this is termed preemptive analgesia. Although not always possible in the trauma patient, surgical patients should receive analgesics before surgery starts. It has been shown that any subsequent pain is easier to treat when pre-emptive analgesia is employed.

Non-pharmacological factors are also very important in the treatment of pain. Distressed animals should be comforted, and sympathetic nursing staff have a major role to play in pain alleviation. Animals should be kept clean and dry, and assisted with urination and defaecation. Visits from owners and familiar toys and blankets from home will help to reduce fear and anxiety, which may contribute to pain.

**Administration routes**

Analgesics can be administered in many different ways, and these differ markedly.

The oral route is probably the most popular, and is particularly suited to chronically painful conditions where owners can medicate their animals at home with NSAIDs and some opioids (tramadol). However, absorption is erratic, and there may be some time lag between administration and effect, which makes oral administration unsuitable for animals in acute severe pain.

Subcutaneous and intramuscular administration both require frequent and potentially painful injections. Again, absorption may be unreliable, especially in shocked animals with poor peripheral perfusion.

Intravenous (IV) analgesic administration results in a rapid rise in plasma concentration and quick effects. Analgesic administration may be titrated to effect. Providing repeated IV boluses of a drug results in peaks and troughs in plasma concentration that may be associated with excessive side effects and inadequate analgesic efficacy, respectively. The use of a CRI following an administration of a loading dose will maintain stable plasma concentrations, resulting in good analgesic efficacy and potentially fewer side effects. Loading doses are required to achieve target plasma concentrations quickly.

CRIs are a very versatile technique for acute pain management and should be considered in any severely painful patient. It is important to recognise other novel analgesic delivery routes, and use them to contribute to good multimodal analgesia. Other routes and techniques include epidural...
administration, transdermal drug delivery, transmucosal administration and the use of local anaesthetics for specific nerve blocks.

**Further reading**

Figure 1. The pain pathway.

Figure 2. Hyperalgesia and allodynia.
Figure 3. Dogs in acute pain require adequate analgesia. This postoperative total ear canal ablation and lateral bulla osteotomy case responded well to a CRI of morphine, lidocaine and ketamine.