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Peri-operative Analgesia for Veterinary Surgery

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Introduction

That all mammals (and indeed most animals) perceive, feel, and suffer from pain is accepted by those who are concerned with animal welfare. That pain is detrimental for practical reasons is also accepted – pain can delay healing following surgery, induce a catabolic response, and in the farm animals can reduce productivity and slow growth. The best analgesic is to remove the cause, (for example, stabilise a fracture) but where not practicable, drugs are used commonly to treat and prevent pain. The choice and efficacy will be governed by the type of pain, the species concerned and drug availability. With the exception of non-steroidal anti-inflammatory agents (NSAIDs) the drugs used have changed little over the past 50 years, although newer versions may have specific advantages. What has developed, however, is the concepts of pre-emptive analgesia, combinations of different analgesics, differing methods of administration, and the concept of multi-modal analgesia. This presentation will highlight the recent practical developments in pharmaceuticals and in concepts. However, there is much current research into the understanding of the pathways of pain perception at receptor level [1], and exciting new discoveries may well change our methods of administration of pain relief in the future.

Pre-emptive and Peri-operative Analgesia

Peri-operative analgesia must provide pain relief for the pre-operative, intra-operative and post-operative periods. The need for post-operative analgesia is generally accepted but there has been less appreciation that additional analgesia should be incorporated into premedication and into the intra-operative regimen. For some time, on the basis of evidence in animals demonstrating that pain itself results in a decrease in pain threshold, it has been accepted that analgesia is most effective if provided before pain commences. This concept has recently been questioned [1] but nevertheless analgesic drugs in

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premedication will contribute effective pain relief both during and after surgery. Many general anaesthetic agents (for example, propofol) do not provide sufficient analgesia to prevent this 'wind up', or only do so at unacceptably high dose levels.

Detection and Assessment of Pain

If we cannot assess pain, we cannot assess the efficacy of treatment. Such assessment is difficult even in humans, - the philosophers say' only I feel pain'. In experimental circumstances, detection of pain (and recognition that a drug provides analgesia) is based usually on the animals response to a specific (and often single) nociceptive stimulus. Not surprisingly results obtained from such studies are most relevant when treating intra-operative pain, and do not translate always to the treatment of clinical pain in the conscious animal.

Attempts have been made to use behavioural responses as indicative of pain in conscious animals. This work has been well reviewed[1]**.** The responses differ markedly between species; predator species such as the dog and cat may become quiet and hide at the back of their kennel, whilst it is in the interests of species which are 'prey' to hide their pain and vulnerability. Also the side effects of analgesic treatments (in particular the hallucinatory effects of opioids and of ketamine) may influence behaviour in ways that may be misinterpreted as pain, for example by making dogs howl, or horses 'box walk'. In dogs, the current 'gold standard' for assessment is the Glasgow Composite Pain Score [2] . Although the horse's violent response to colic is easy to interpret, as a prey animal it will also 'suffer' pain quietly (for example, as may occur post-operatively after colic). Price [3] scored detection of such pain on the basis of the horse spending less time eating, less time at the front of the box, less time moving, holding its head level or lower than the withers, and abnormal ear position. Cattle and small ruminants also are prey animals and although there have been behavioural studies, in particularly in lambs [2], the changes are subtle. Objective parameters used to assess pain resulting from 'husbandry' surgical interventions, such as castration include measurement of blood levels of epinephrine (adrenaline) and/or norepinephrine, and corticosteroids. These do demonstrate that the animal has suffered 'stress' but as they require laboratory analysis they are of limited clinical use. In all species, if the animal's behaviour changes for the better following analgesic drugs, it is reasonable proof that the animal had been in pain.

Criteria for assessment of intra-operative analgesia in dogs and cats depends on physiological reflexes, - elevations in respiratory and heart rates and blood pressure, and dilation of the pupil of the eye. These reflexes are relatively reliable, unless blocked by other drugs used within the anaesthetic process. An example would be if an anti-cholinergic drug had been used, pupils would be dilated, and the heart rate already elevated. In horses anaesthetised with an inhalation agent, however, heart rate and blood pressure rarely change until, if anaesthesia becomes too light, the horse moves (usually violently). In particular the horse retains marked and rapid spinal reflexes until anaesthesia is very deep (or even dead): these reflexes are best blocked by the use of local anaesthesia.

Pharmaceutical agents used for analgesia

The pharmaceutical analgesic agents most commonly used in animals are local analgesics, opioids, non-steroidal anti-inflammatory drugs (NSAIDS), alpha2 adrenoceptor agonists, ketamine, and very occasionally gabapentin.

Local analgesic agents - *Examples:* lidocaine, mepivicaine, bupivicaine (long acting) ropivicaine (long acting). All vasodilate so may be combined with epinephrine to induce vasoconstriction, delay uptake and lengthen duration of effect. Epinephrine-containing solutions must not be used where vasoconstriction would be harmful – e.g. in the epidural space.

Routes of administration: epidural and spinal, specific nerve blocks, local infiltration, intra-articular, intravenous (iv) as a constant rate infusions (CRI).

Local anaesthetic nerve blocks give total intra- and post-operative analgesia, with minimal side effects. They are particularly useful in horses and farm animals, for 'standing surgery', as an adjunct to general anaesthesia, and for post-operative pain relief. They should be used more frequently in small animals – even where individual nerve blocks are impracticable, local can be used around the wound by what, in human anaesthesia, is termed the 'splash technique'. Long-acting local anaesthetic agents can give up to 12 hours of post-operative analgesia. Original fears that such use would delay healing appear unfounded.

Problems associated with local analgesic are swelling (lidocaine is the worst) and block of motor nerves, which may lead to recumbency. Serious side effects are total overdose (twitching, convulsions, eventually coma and death) and accidental intravenous injection (cardiac arrest). Serious side effects in large animals are very rare, but is it relatively easy to overdose small animals, as demonstrated by the dangers to goat kids when local analgesia is used for disbudding. In Europe, the only local analgesic licenced for ruminants as food animals is procaine as some of the metabolites of lidocaine may be potentially carcinogenic, so a 6 month withdrawal period is required for the meat.

Lidocaine infusions. Lidocaine CRIs are used to provide intra-operative and post-operative analgesia in horses [4,5] and dogs. They may also be combined with other analgesic drugs for multi-modal effects. In cats they should be avoided as they cause profound bradycardia [6]. Advantages additional to analgesia of CRI lidocaine include a prokinetic action (of particular use in equine colic) and also an anti-inflammatory action with free radical scavenging properties**.** Doses used both in dogs and horses are

a loading dose of 1.3mg/kg over 15 minutes, followed by
a maintenance infusion of 50 mcg/kg/min (3mg/kg/hour).

Toxic effects of muscle tremors and/or twitching can be seen after prolonged use. When used intra-operatively in horses, the infusion should be stopped 30 minutes before the end of anaesthesia, or the quality of recovery may be compromised [7].

Opioids

Examples:-mu (OP3) agonists - morphine, pethidine, methadone, fentanyl, remifentanil. Partial agonists: butorphanol, buprenorphine

Routes of administration: oral, injection routes, epidural, trans-dermal, intra-articular.

Major side effects (dose dependant) respiratory depression, bradycardia (unless excited) dysphoria (which can result in excitement - cats and horses), sedation (dogs) gut stasis (impacted colic in horses), box-walking in horses. *Antagonists* (naloxone, naltrexone)
Opioids have been used for analgesia for thousands of years, and despite the known (dose dependant) side effects have a good safety record. Agents differ in speed of onset, duration of action and in the degree of histamine release they might cause. Mu agonists provide the best analgesia- usually dose dependant; partial agonists are used primarily because they have less addictive properties.
Respiratory depression is acceptable intra-operatively as the patient can be ventilated. Fentanyl, and remifentanil [8] (very short acting and non-cumulative), CRIs provide excellent intra-operative analgesia in man and dogs. In horses intra-operative opioid use is controversial - it does not reliably reduce the requirement for inhalation anaesthetics (the one report of fentanyl doing so was not repeatable). In horses there is also controversy as to the degree that opioid use increases the incidence of post-operative box-walking (not ideal following orthopaedic surgery) or of impacted colic. Sedation will prevent box-walking.
Opioids are very effective by the epidural route - morphine given this way has a slow onset (up to 8 hours in horses) but prolonged duration (up to 24 hours). Combinations with the alpha 2 agonists speed up onset of analgesia. Epidural morphine can cause pruritis.
Fentanyl and buprenorphine are available as dermal patches which allow continuous slow release of the drug. Onset of analgesia is slow and patches have to be placed at least 24 hours prior to surgery. All studies have demonstrated that the pharmacokinetic results from fentanyl patches in animals are very variable, and effective concentrations of drug cannot be guaranteed [9].

Non-steroidal Anti-inflammatory agents (NSAIDS)
Examples – carprofen, meloxicam, ketoprofen, flunixin, phenylbutazone and many others. Aspirin. Paracetamol (acetaminophen) (not strictly a NSAID).
Routes of administration – oral, as creams/gels. iv, subcutaneous (sc) and intramuscular (im). Practicable routes depend on the agent concerned.
Side effects. Overdose (short or long term) leads to renal damage and to gut ulceration resulting in vomiting, diarrhoea, and abdominal pain.

WARNING. The pharmacokinetics and the toxicity of the NSAIDS vary between species in a totally unpredictable manner. Only NSAIDS which have a marketing licence (somewhere) for that particular species should be used, and at the dose and duration advised unless there is published evidence to supplement more chronic use. Particular care is necessary for the cat. *Examples of unexpected toxicity;* Low dose ibuprofen causes renal failure in dogs. Diclofenac (given to dying cattle) causes renal failure in vultures! There is a genetic susceptibility in some North American dogs to the toxic effects of carprofen (very safe when used in Europe). Paracetamol (acetaminophen) is lethal to cats (although this could be predicted). Asprin has a half-life of over 24 hours in the cat.
NSAIDs are very effective anti-inflammatory and analgesics. Part of their analgesic action is mediated through reduction in swelling but there is also a central analgesic

effect. They do not contribute significantly to intra-operative analgesia but when given as a premedicant, they are effective prior to onset of post-operative pain. In dogs the renal sensitivity to NSAID toxicity is increased by hypotension, so only those with a known safety record as a pre-medicant (eg carprofen, meloxicam) should be used. In horses, despite hypotension being common under inhalation anaesthesia, renal damage has never been reported and most NSAIDs are suitable for premedication.

The "cox' story. Traditionally cycloygenase (COX) has been divided into 2 isoenzymes with separate functions – COX-1 being responsible for homeostatic functions such as renal blood flow and maintaining gastric mucosal lining. COX-2 is an inducible enzyme which is increased at sites of inflammation. Theoretically COX-2 inhibition should reduce inflammation and minimise side effects. In recent a years a number of COX-2 specific drugs (the coxibs) such as rofecoxib, celecoxib and valdecoxib, have been produced, mainly for human use. Unfortunately, used for prolonged periods they were associated with thrombotic problems – strokes and myocardial infarction. Most have been withdrawn. Firocoxib, which is highly COX-2 selective has recently been licenced as an oral analgesic for dogs [10,11].

In the UK the market leaders of the NSAIDs for dogs are carprofen and meloxycam both of which have some COX-2 selectivity. Tepoxalin is marketed for long term oral use in dogs. It is a dual inhibitor – both of COX 1 and 2, but also of lipo-oxygenase. In cats, carprofen is licenced for a one-off dose, meloxycam for several days, and ketoprofen for more prolonged use. In horses – flunixine meglumate and phenybutazone remain the market leaders, but concern in relation to the use of phenybutazone in food animals means that it may soon become unavailable. Meloxicam, although expensive, appear effective and safe. There are many NSAIDs with food animal licences (eg flunixine meglumate, meloxycam) as anti-inflammatory agents - these may be used for analgesia as the pharmacokinetics, withdrawal times and safety profiles are known - no other form of analgesics are so readily available for farm species.

Alpha 2 adrenoceptor agonists

Examples. medetomidine dexmedetomidine xylazine detomidine romifidine.

Routes of administration. iv, sc, im, trans-mucous membrane, epidural and spinal.

Main Side effects. Deep sedation (plus ataxia/recumbency), bradycardia so reduced cardiac output, vasoconstriction whilst sedated – delayed vasodilation, reduction in insulin and ADH. Can be antagonised by alpha 2 adrenoceptor ANTAGONISTS (eg atipamezole).

The modern very specific alpha 2 adrenoceptor agonists medetomidine and dexmedetomidine are powerful analgesics [12], but it is difficult to separate analgesia from sedation. They can contribute greatly to intra- anaesthetic analgesia. Medetomidine has a short half-life - is non cumulative, and is therefore commonly used as a CRI to provide intra-operative analgesia with total intravenous anaesthesia (TIVA) with propofol [13] and to give additional analgesia with inhalation agents [14]. It is also uses as part of multi-modal CRI combinations (with ketamine, and/or lidocaine) for intra-operative and post-operative analgesia in situations where sedation is not a problem.

Given epidurally (all species) the alpha 2 adrenoceptor agonists provide analgesia by an action at the dorsal horn of the spinal cord. Epidural use often combines them with

opioids and/or local anaesthetic agents. Epidural xylazine may cause motor paralysis through a direct local anaesthetic action.
In the domestic species, medetomidine and dexmedetomidine have short half-lives of elimination, are non- cumulative and are therefore ideal for CRIs. They are often used as such in combination with opioids and/or other analgesics such as ketamine**.**

Ketamine.
Routes of administration Any injectable route (painful im) - absorbed across mucous membranes. Some experience of the epidural route .
Side effects. Hallucinatory effects (dysphoria) - accumulation of nor-ketamine.
Ketamine acts via the NMDA receptor, and as well as causing dissociative anaesthesia, is a very potent analgesic. In horses, it is used for intra-operative analgesia either as intermittent 'top up' injections or as a CRI - alone or in combination with other agents. Ketamine has been used as a CRI for several days for analgesia in conscious horses at doses of 0.4-0.8mg/kg/hour[15,16]. In dogs, doses of 0.1-0.2mg/kg/hour have been effective[17]. In our clinic we find it useful following spinal surgery. In human medicine ketamine infusions are associated with a high onset of dreaming - not necessarily unpleasant, but it is important to recognise the potential for dysphoria, so it can be treated (sedatives) accordingly.

Gabapentin
This agent is used to treat neuropathic pain[18] and is rarely used in the peri-operative period. Its mode of action is unknown. Recently there has been veterinary interest in its use in chronic post-operative pain, and in the horse, its pharmacokinetics have been elucidated [19].

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