PERIOPERATIVE PAIN MANAGEMENT

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Introduction

- **Pain** is defined as an unpleasant sensory and emotional experiences associated with actual or potential tissue damage or described in terms of such damage (Merskey 1979).
- Pain is a universal experience for every living being, and we all know what it feels like, but it is still very difficult to clearly define or quantify.
- Pain management in animals at perioperative and postoperative periods presents a significant challenge not only to veterinarians but also to the owners of the animals.
- Humans can express and describe the sensations they experience, and these descriptors are well accepted. However, in animals the difficulty of obtaining feedback through communication complicates the management of pain, as one can only attempt to help alleviate the pain when it is expressed.
- It is, therefore very important that one is familiar with the signs associated with pain and interpretation of these behavioral changes for the benefit of clinical pain management in animals.
- The ability to feel pain has clear survival advantages;
  - limits movement of the damaged part so that it promotes healing
  - the individuals learn to avert similar noxious stimuli in the future
- However, ongoing pain has no benefit and offers disadvantages;
  - Animals feeling pain postoperatively get distressed and the stress response interferes with normal resumption of activity
  - Delay in wound healing has been demonstrated in animals in more painful condition
  - Decreased food intake impairs nutrition and speed of recovery from the operation
  - Impaired respiration, especially in animals undergoing thoracic surgery, contributes to development of hypoxia, pulmonary atelectasis, pneumothorax, and retention of mucus and sputum etc.
  - May self-mutilate
  - Causes central sensitization which is more resistant to conventional analgesic therapy
- The reasons for relative reluctance in treating pain have been;
  - The clinician is not absolutely sure whether the animals are in pain
  - Belief of over-rated concerns regarding the pain and subsequent over-prescription of analgesics is dangerous due to its adverse side effects
  - Many effective analgesics are controlled substances and require a tight inventory log
  - Belief of analgesics should be withheld so that protective function of pain is maintained.
  - Insufficient knowledge about the analgesics, especially regarding opioids.
- There is no doubt that a skilled interpretation of the animal behavior will play a significant role in the management of suffering in animals.
- In addition, sound knowledge in physiology of pain and pharmacology of pain control substances (analgesics) will be valuable to maximize the therapeutic outcome in animals.

- A variety of drugs are available to treat pain in animals
- It is not uncommon to combine a specific analgesic drug with an anxiolytic. This combination works synergistic in controlling pain, maximizing the analgesic effect of a drug.
- A clinician may experience signs of pain clearly dissipate with administration of tranquillizer such as acepromazine alone at postoperative period, suggesting pain is a complex phenomenon which can be controlled by even through behavior modification.
- A good pain management in suffering animals is not only obligation but professional privilege

Physiology of pain

- The receptors that mediate the noxious signal which ultimately converts to the pain sensation are called **nociceptors**.
- The nervous system plays a key role in **transducing**, **transmitting**, **modulating** and **projecting** a signal that is generated when the nociceptors are sensitized.
- Noxious stimuli activate nociceptors that are at the termination of free nerve endings of A-delta and C afferent fibers.
- The pain sensory fibers (nociceptor) have cell bodies in dorsal root ganglia and project to the dorsal horn of the spinal cord where they synapse in Rexed laminae I, II, V, VII and X.
- Following synapses at this level, the information is transmitted further via several spinal tracts (most notably spinothalamic tract) to the supraspinal level
- The synapses at the level of the thalamus then transmit the information diffusely to the cortex (thalamocortical projection)
- Pain perception takes place when the cortex processes the information as noxious
- Different neurotransmitters are involved in these pathways, including GABA, glutamate, endogenous opioids, substance P, norepinephrine, and many other neuropeptides, and the interaction can be modulated at each step in the pathway (providing basis for the **multimodal (or balanced)** analgesic approach)
- Pain can be typed into ‘acute’ or ‘chronic’ based on the duration, or ‘somatic’, visceral’ or ‘neuropathic’ based on the origin/involvement of the damaged tissues
- For full details of the mechanisms and definitions, review physiology/pharmacology texts.

Assessing pain

- The obvious lack of communication with animals dictates the therapists to depend on animal’s behavior to assess the degree of pain. e.g., does the cat walk round, is it purring or is it hunched up in the back of its cage; is the dog reluctant to move etc.? The ability to relate such signs with pain management will ultimately affects the success of pain control one aims to achieve. The experienced veterinary technician is probably better able to judge levels of post-operative pain than is the veterinarian!
- Animals are generally less expressive of the pain than humans as it offers survival advantages to potential predators.
- Altered behavior to human contact may indicate as first line signal that the animal is in discomfort.

- Acute postoperative pain accompanies signs of guarding and aversion of the site, particularly when it is manipulated.
- Although vocalization may indicate discomfort, lack of vocalization should not be interpreted as lack of pain
- Moderate discomfort often leads to attempts to bite or scratch the site
- Animals in visceral pain tend to exhibit restless and agitation, while those that are in somatic pain would be reluctant to move
- Cats and dogs may exert common signs when in pain, but they also differ markedly in their behavioral response to sufferings.
- Cats in general tend to demonstrate less signs of pain compared to dogs, to a same degree of surgical procedures that may inflict similar tissue damages (e.g., ovariohysterectomy).
- However, this does not necessarily indicate the cat feels less pain than the dog, but rather indicates a fundamental difference in how each species responds to the pain, which presents a need to study animal behavior in a species specific way.
- The following table 1 describes some examples of differences in behavior in dogs, cats and horses in response to pain.
- Assessment of pain and of the efficacy of analgesia is difficult. Studies of analgesics are based on experimental “analgesiometry”. The results of which bear little relation to the apparent efficacy in the practice situation.
- Pain assessment methods used by veterinary researchers include the followings
    - Verbal rating scales (VRS)
    - Simple descriptive scales (SDS)
    - Numeric rating scales (NRS)
    - Visual analogue scales (VAS)
    - VRS and SDS rare pain as ‘none’, ‘mild’ ‘moderate’. or ‘severe’, and although simple to use it lacks sensitivity
    - Using two or more of different pain assessment scales may provide better sensitivity of the pain measurement, although it may require more time and effort

Table 1 The behavioral characteristics in dogs and cats which are related to pain response (Modified from: Carrol GL. Small animal pain management. Lakewood: American animal hospital association press 1998).

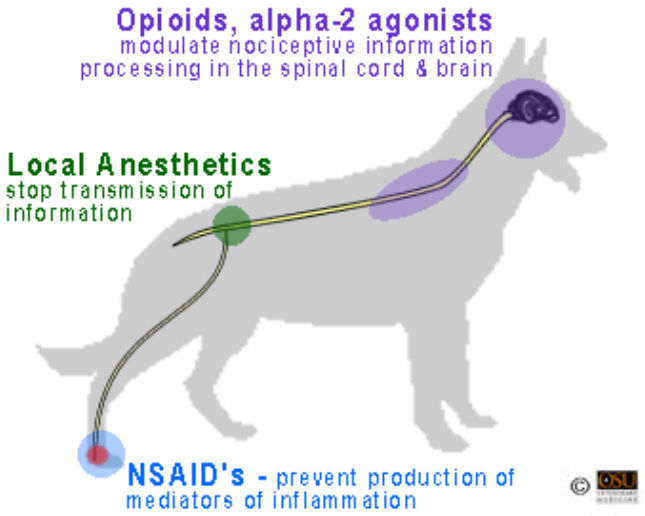
Behavioral response	Dogs	Cats	Horses
vocalization	Groan, whine, whimper, growl, scream, cry	Groan, growl, hiss, scream, cry	Grunt, moan, quiet
Facial expression	Fixed stare, glazed appearance, ears pulled back	Furrowed brow, squinted eyes, ears pulled back	Dull eyes, teeth grinding, ears pulled back
Body posture	Hunched, laterally recumbent, prayer position	Generally sternal, laterally recumbent	Standing with head down, standing on 3 legs, recumbent
Self awareness (guarding and self mutilating)	Protective of wounds, licking, chewing, and rubbing wounds and surgical sites, limping, loss of weigh bearing	Protective of wounds, licking, chewing, and rubbing wounds and surgical sites, limping, loss of weight bearing	Protective of wounds, licking, chewing, and rubbing wounds and surgical sites, limping, loss of weight bearing
Activity	Restless or restricted movement, trembling (shivering)	Restricted movement, stereotypies (meaningless encircling movement)	Restless or restricted movement, trembling (shivering)
Attitude: Socialization and comfort/attention-seeking	Increased aggressiveness or timidity (fearfulness)	Comfort seeking or hiding; aggressiveness	Uncooperative, aggressive, hiding
Appetite	decreased	decreased	decreased
Urinary and bowel habits	Increased urination, failure of house training, urinary retention	Failure to use litter box	Increased urination, urinary retention, fecal retention
Grooming	Loss of sheen in hair coat, particularly in chronically painful dogs	Failure to groom, particularly in chronically painful cats.	Disinterested
Response to palpation	Protecting, biting, vocalizing, withdrawing, orienting, escape	Protecting, biting, scratching, vocalizing, withdrawing, orienting, escape	Aggressive, kicking, biting, fighting, escape

Pain relief within the perioperative period

- Pain management within the perioperative period is needed and there are three stages to be covered;
  - Preoperatively if in pain (or preemptively)
  - Intraoperative for surgery
  - Postoperatively; short and long term
- In man, there is evidence that adequate analgesia throughout the operation results in less surgical **stress**, a more rapid recovery and a shorter period of time in hospital.
- Analgesia is most effective if given before pain commences (**preemptive analgesia**); it is, therefore, recommended to be given at premedication or while the animal is still anaesthetized and repeat doses be given at adequate intervals
- There is also some evidence that, despite general anesthesia **intraoperative pain** may prevent good post-operative analgesia; thus the rationale for using opioids in premedication. (NB: This comes from human work where neuromuscular blockers were used, so general anesthesia was questionable)
- The need for analgesia in the immediate post-operative period is well recognized. However, pain of a lesser degree may persist for some time, and analgesia in this later period must not be neglected
- Discomfort may also cause distress
- In the post-operative period, TLC (Tender Loving Care) with a quiet warm comfortable environment can reduce analgesic requirements considerably
- A full bladder (very likely after fluid therapy and/or the use of alpha 2 adrenoceptor agonists) can be a source of serious discomfort.

METHODS OF PROVIDING ANALGESIA

Figure 1. Site of action for various analgesics in a dog



- Local analgesics
- General anesthetic. (NB, unconsciousness does not mean that all response to pain is removed; some general anesthetics are poor analgesics).
- Opioids
- NSAIDs
- Alpha 2 adrenoceptor agonists
- NMDA antagonists
- Adjunctive methods (unconventional analgesics)
- Choice of suitable one depends on type of pain, ease of use (how given) speed of effect, duration of effect, and are the side effects acceptable.
- For example, anesthetic agents are mainly used during surgery (although residual effects, e.g., with methoxyflurane, may provide useful post-op analgesia).
- The respiratory depression of the potent opioid agonists may be acceptable during surgery (with oxygen and IPPV) but not post-operatively.

Local analgesic techniques

- These can provide useful (even complete) analgesia at all three stages of the perioperative period.
- Where practicable, local nerve blocks provide superb analgesia. The long-acting local anesthetic, bupivicaine, gives 6-8 hours analgesia.
- Intercostal nerve blocks are particularly useful after thoracotomy
- Epidural analgesia may be used after abdominal, pelvic or pelvic limb surgery, although this will also cause muscle paralysis of the hind region.
- The only contraindication to the use of local analgesia post-operatively is where it is important that the operated site must not be used e.g. a fracture. Local analgesia is the only form of analgesia which is so complete as to allow this to happen.
- NB. Epidural analgesia may also be achieved with opioids and/or alpha 2 agonists. The advantage of this route of administration is that analgesia can be achieved with limited respiratory depression or sedation. Another advantage is that loss of motor function is much less seen with these drugs. However, the drugs are slowly absorbed from the epidural site, so delayed respiratory depression can occur, and the animal should be kept under observation.

General anesthesia

- Main use is intraoperatively.
- Not all general anesthetics are good analgesics; with some (e.g., isoflurane) very deep levels are needed for adequate analgesia. In these cases, other analgesics (e.g. opioids, alpha 2 agonists) are useful intraoperatively as well as providing good post operative analgesia (as long as antagonists have not been used).
- NB: The use of opioid antagonists to reverse opioids used intra-operatively will prevent often the use of further opioids for post-operative analgesia

Opioids

- Opium (the plant) has been used for its analgesic and euphoric effects over thousands of years for men.
- All opioids (referring all endogenous and exogenous substances that possess morphine-like properties) are chemically related and subject to regulatory controls, governed by the Controlled Substance Act 1970
- In man and dog these are the mainstay of perioperative analgesia, and can be used in all three phases; pre/intra/post-operative periods.
- The potential excitement in cat and horse limit the use of the very potent drugs.
- The choice of opioid suitable for each phases is based on the following points.
- Premedication
  - This needs a long acting opioid to have effect before, during and after surgery.
  - Hypnosis and sedation is an acceptable side effect.
  - Respiratory depression must be *minimal*.
  - Ideally there would be no vomiting.
- Intraoperative
  - This requires a very short acting and very potent drug.
  - Onset of action must be rapid.
  - Respiratory depression is acceptable as long as oxygen and the ability to give artificial ventilation are available for use if necessary.
  - In the dog the use of the fentanyl group of compounds is suitable, but oxygen and IPPV is essential.
  - In the horse, all studies have shown that intraoperative opioids do *not* decrease the dose of general anesthetic, and in some instances may increase it, presumably through an excitement effect.
- Post-operative
  - Drugs used must cause minimal respiratory depression.
  - Although in general a long action is required, (e.g. buprenorphine) care must be taken not to overdose whilst any anesthetic effects, which may be synergistic, remain.
  - For this reason a short acting analgesic such as fentanyl may be used initially, followed later by a longer acting drug.
  - Also, note that when sedatives and opioids are combined, the effects are synergistic, so post-operative sedation may be profound.

Clinical pharmacology of opioid analgesics

- See pharmacology notes for details of modes of action, receptor theories, and of main properties.
- Briefly, the properties of the opioids of clinical importance are a balance between depression and stimulation. The result of the balance depends on dose, receptor type and species.
- **Depression** gives analgesia (wanted), hypnosis (possibly useful) respiratory depression and bradycardia (unwanted) and depression of the cough reflex (care needed during recovery)

- **Stimulation** causes the generalized excitement seen in horses and cats (often together with tachycardia); euphoria (tends to abuse); dysphoria (unwanted), and vomiting and defecation (unwanted).
- All opioids exert similar mode of action, but their activity varies depending on degree of affinity of the specific subtypes
- Mechanism of action
  - Mainly through its agonist activity at opioid receptors that results in modulation of inbibitory/excitatory effects in the CNS.
  - This causes analgesia, (and sedation to a lesser extent)
- Clinically important subtypes of the opioid receptors are: mu_1, mu_2, kappa, delta subtypes
  - μ_1: supraspinal analgesia, euphoria, sedation
  - μ_2: respiratory depression, bradycardia, increased gastroinstestinal transmit time, hypothermia, physical dependence
  - κ: spinal analgesia, sedation, meiosis
  - δ: spinal analgesia, respiratory depression
- ***Ideal opioid***
  - The purpose of looking for a new opioid is to improve on morphine by reducing respiratory depression (so far without success; if respiratory depression is limited, so is analgesia).
  - Reducing the potential for abuse - The partial agonists cause dysphoria, therefore are less pleasant, so are less likely to abuse.
  - To alter the length of action (longer or shorter) and/or the speed of onset of action. There is now a good choice available
  - To increase potency. The more specific a drug, the less the side effects other than those related to stimulation of that receptor
  - To reduce other side effects (vomiting, excitement, euphoria, dysphoria, vagal stimulation)
- Cardiovascular effects of opioids
  - In general they do not cause myocardial depression, and for this reason the potent agonists are routinely used as part of the induction technique for anesthesia of people with heart disease.
  - However, they can cause very severe bradycardia (counteracted with anti-cholinergics); in the dog some may cause hypotension, and in the horse, excitement is accompanied by tachycardia and hypertension.

Classification

- Opioids are generally classified as pure agonists, antagonists, partial agonists, and mixed agonists-antagonists
- Pure agonists
  - Drugs that produce a **maximal** biologic response through binding opioid receptors
  - In general the pure mu agonist gives the best analgesia, which with the most potent drugs is dose related in effect.
  - Unfortunately it has been impossible to separate this analgesia from respiratory depression (all claims to date have proved false in clinical practice); or from the liability for addiction and abuse.

    - e.g., morphine, fentanyl, meperidine
- Antagonists
    - Drugs that competitively reverse (antagonize) the effects of agonists by preventing their access to a receptor.
    - They have low (or no) intrinsic activity at the receptors themselves
    - e.g., naloxone, nalmefene, naltrexone
- Partial agonists
    - Drugs that produce a submaximal response at a particular receptor type, even at high doses
    - The slope of dose-response curve is **less steep** that that of pure (full) agonist
    - Dose-response curve also exhibit **ceiling** effect; i.e., **submaximal**
    - Concomitant administration of partial + pure agonist can reduce (antagonize) the pure agonist's clinical effect
    - Partial agonists give much more less analgesia (the only really effective one is buprenorphine), but also have less respiratory depression, and are often less subject to the schedule regulations.
    - Partial agonists often have a bell shaped dose-response curve; once maximal analgesia is achieved further doses only reverse the effect. Thus if these partial agonists are ineffective, do not give a further dose.
    - Partial agonists also have a tendency to cause dysphoria, with unpleasant hallucinatory effects, so less potential for abuse.
- Mixed agonists-antagonists
    - These have divergent activities on different receptors, acting simultaneously as an agonist at one receptor (e.g., kappa + delta) while acting as an antagonist at another (e.g., mu);
    - e.g., pentazocine, butorphanol
- It is important to know into what category an opioid analgesia falls as it influences the ease of antagonism.
    - For example, naloxone will antagonize morphine very well, but will be less efficient in its antagonism of the partial agonist, pentazocine.
    - If pentazocine is given to a dog which has had morphine, then it partially antagonizes it, reducing the total analgesia even though both drugs and their own exert analgesic properties.
    - Ideally, one should not mix the use of agonist and partial antagonist drugs when trying to obtain analgesia in an animal. However, if a partial agonist fails to be effective, a pure agonist (at higher than normal doses) may be effective.
    - The term **sequential analgesia** has been used to describe the use of the partial agonists--- buprenorphine or nalbuphine to reverse a pure agonist, whilst allowing some analgesia to remain.

Opioid agonists

Morphine

- This is the gold standard against which the others are compared; the prototype opioid agonist
- Primarily mu agonist, with less of kappa and delta agonism
- Provides excellent analgesia with some sedation (most species)

- Use with care in the horse (maximum 0. 1mg/ kg, preferably *with sedation).* Vomiting and defecation is a common side effect.
- It can be used at all perioperative stages.
- Inexpensive
- Time of onset after IV injection is 10 minutes; IM takes longer.
- Rapid IV injection causes more predictable histamine release (give it slow in this route)
- Doses of 0.1-0.3 mg/kg provide 4 h ours analgesia in the dog.
- Vomiting and defecation is not uncommon
- Urinary retention and constipation with prolonged usage

Oxymorphone

- It is μ agonist, and very similar to morphine; approximately 10 times more potent
- Vomiting is rare and produces some mild sedation
- Unlike morphine, IV injection is not associated with histamine release
- Duration of action is similar or marginally shorter than morphine
- It cause the dog to pant, but is of little clinical significance
- More expensive than morphine, and current supply is very limited due to contamination of the manufacturing plant

Hydromorphone

- It is μ agonist, and very similar to morphine; approximately 5-7 times more potent (the dose range is 0.05 – 0.2 mg/kg)
- Vomiting is not as common as morphine, but more common than seen with oxymorhpone,
- It provides slightly better sedation than morphine/oxymorphone
- It cause the dog to pant, but is of little clinical significance
- Unlike morphine, IV injection is not associated with histamine release
- Duration of action is slightly shorter than morphine
- More expensive than morphine, but cheaper than oxymorphone, so it is being used as a good substitute for oxymorphone

Meperidine (Pethidine)

- It is μ and kappa agonist
- It is $1/10^{th}$ as potent as morphine, and doses of 1-3 mg/kg are required in the dog. It can be used at doses of 1-2 mg/kg in the cat, and 1 mg/kg in the horse
- It provides less sedation than morphine
- IV administration occasionally causes severe anaphylactic reaction
- It has myocardial depressant effect
- Molecular structure is similar to atropine and it tends to increase heart rate
- Analgesia is short: ~ 2 hours
- Its advantage is that it causes smooth muscle relaxation, therefore can be used in spasmodic colic in the horse, and in biliary and renal colic in all species, and dose not cause vomiting.

Methadone

- This is equipotent to morphine but gives more prolonged analgesia
- It causes less vomiting than morphine
- IV administration does not cause histamine release, so given this route for faster onset of drug action
- In horses, use at 0.1 mg/kg IM (IV can get them excited if not with sedatives); dogs and cats up to 0.5 mg/kg (but beware of respiratory depression)

Fentanyl

- μ agonist
- Very potent short acting quick onset analgesic
- Popular as intra-operative (and post-operative) CRI analgesic
- Transdermal patch offers advantage of prolonged duration of effect
- The patches come in several doses each accordingly recommended for different patient sizes
- They need to be applied at least 12 hours before the expected time of expected start of the operation to be effective in dogs (much faster onset in horses)
- However, once the plasma level is established the analgesia lasts for a few days.
- It does not cause histamine release
- Analgesia is dose related, but is accompanied by respiratory depression, and at high doses (up to 20 mcg/kg) its use may be only with O_2 and IPPV.
- In dogs, an infusion could start with a 3-5 mcg/kg as bolus followed by an infusion of 3 to 6 mcg/kg/hr. In cats, half of these doses can be used.
- Cardiovascular effects are minimal, but bradycardia may be seen
- It tends to cause excitement (manifested by walking) in the horse
- Other congeners (e.g., sufentanyl, remifentanyl, alfentanyl etc.) are too expensive for current veterinary use
- Carfentanyl, another analogue, is very very potent, and has been primarily used for darting wild lifes.
- Pre-mixed formulations (typically with butyrophenones; e.g., droperidol or fluanisone) may be available

Opioid antagonists

Naloxone

- It is pure antagonist
- It attaches to opioid receptors but have no effect
- The most common use is for reversing opioid induced sedation, respiratory depression, excitement.
- It is recommended agent for treating opioid overdose in man.
- Doses are 1 to 25 mcg/kg
- Naltrexone and nalmefene are longer acting pure antagonists, but have been used less than naloxone
- NB1. The duration of an antagonist may not be the same as that of the agonist, so the animal may return to sleep or respiratory depressant. (Close observation must be continued until the negative agonist effect fully wanes)

- NB2. If an opioid antagonist is used, it will reverse analgesia, and post-operative analgesia cannot be easily supplied with further opioids. The term **sequential analgesia** refers to the use of a partial agonist such as buprenorphine or nalbuphine to reverse a pure agonist such as morphine or fentanyl; the idea then being that some analgesia will remain. There are differing views as to whether this works in practice.

Opioid partial agonists

- Principles of using antagonists are similar to those relating to sedative antagonists
- It is important that the length of action of the agonists and antagonists are matched. Where opioid antagonists are used, analgesia is also reversed

Buprenorphine

- a μ partial agonist, κ antagonist
- It has been widely used in dogs and cats (5-20 mcg/kg)
- It is a potent analgesic, with the advantage of a prolonged duration of action (6-8 hours).
- It has a very slow onset of effect (up to 45 minutes for full action even after IV injection).
- It delays recovery from anesthesia
- Its disadvantages include the prolonged induction time and a "bell-shaped" dose-response curve, in which increasing doses antagonizes the analgesia already present, so, if, following its use, analgesia is inadequate, further doses must not be given (it may be followed by any mu agonist, such as morphine or hydromorphone)
- Its high affinity to mu receptos means that the reversal would be hard as it will have very slow dissociation as well. If naloxone is ineffective to reverse respiratory depression, doxapram can be used as temporary reversal.
- In man, when used in ambulatory patients (as opposed to post-op), it causes severe hallucination
- Class III drug (used to be V)

Nalbuphine

- κ partial agonist, μ antagonist
- Relatively new, and has proved to give effective analgesia, and has been particularly widely used in laboratory animals
- It lasts 1-2 hours
- Not classified

Diprenorphine (Revivon)

- Used to reverse etorphine

Mixed agonists-antagonists

Butorphanol

- κ partial agonist, μ antagonist
- It was initially used as a cough suppressant in animals

- It is 5 to 10 times more potent than morphine, but analgesic efficacy is much less (NB, do not confuse 'potency' with 'efficacy'), and is not very effective in managing severe pain (exception is in bird as this seems provide a good analgesia).
- It provides mild sedation
- Cardiopulmonary effects are minimal
- With increasing dose there is a ceiling effect on respiratory depression (i.e., further increase do not increase respiratory depression)
- In dogs, 0.1 to 0.5 mg/kg, in cats, 0.1-0.4 mg/kg, and in horses, 0.02-0.05 mg/kg can be given IV, IM, or SQ. In the horse 0.1 mg/kg IV causes marked 'walking behavior'. In dogs, IM is painful so beware of being bitten.
- It has a duration of action lasting approximately 2 hours

Pentazocine

- κ partial agonist, μ antagonist, has some σ activity at higher doses
- Frequently causes dysphoria, and is now only occasionally used
- It lasts approximately 1 to 2 hours
- Class IV drug

Use of opioids with sedatives

- When sedative and opioid drugs are used in combination, their effects are synergistic (ie the total effects are greater than the sum of the effects of the two drugs used individually).
- Use of such combinations is not new; there are veterinary reports as far back as 1932. However, the first widespread use involved combining opioids with the "neuroleptic" agents (ie, the phenothiazines and the butyrophenones). Thus the terms "**neuroleptanalgesia**, and **neuroleptanesthesia**" were coined.
- With neuroleptanalgesia, the combinations were used to produce sedation, with mild analgesia; the use of much more potent and higher doses of opioids give increased analgesia so that surgery can be performed. Since this time the concept has been extended further, and any sedative type drug (i.e., benzodiazepines and alpha 2 adrenoceptor agonists) has been used in combination with the opioids- thus the term neuroleptanalgesia has been replaced by that of **sedative/opioid combinations.**
- The initial idea of using the combinations was not only that there would be synergism of sedative effect, but that the sedative would counteract the unwanted side effects of the opioids (in particular, excitement and muscle rigidity) but would not increase the opioid induced respiratory depression. Unfortunately respiratory depression is often increased and in human anesthesia sedative/opioid combinations are only used together with the administration of oxygen, often with IPPV (intermittent positive pressure ventilation). unfortunately this simple safety precaution is not always carried out by vets!

Caution regarding the use of potent opioids

- The potent opioids are absorbed across mucous membrane, so great care must be taken to avoid dangerous spillages.

- Carfentanyl and Etorphine are the most dangerous, but buprenorphine and fentanyl and its analogues are also effective by this route.
- Always must be handled by the veterinary professionals, and have emergency CPR kits and personnel who can perform the CPR available when handling the potent opioids.

Non steroidal anti-inflammatory drugs (NSAIDs).

- Until relatively recently it has been stated that NSAIDs were not effective in acute pain, and therefore (although useful later) were inadequate for immediate post-operative analgesia
- However, the modem potent NSAIDs such as carprofen and ketoprofen give useful post-operative analgesia.
- It is probable that they do not provide any surgical analgesia (carprofen does not reduce the MAC of halothane in dogs by an appreciable amount and they do not reduce the sensitivity to acute pain in analgesiometric tests in sheep).
- When compared with opioids for post-operative analgesia, the NSAIDs have the advantage of not decreasing consciousness or causing respiratory depression.
- Their anti-inflammatory action speeds healing and decreases pain.
- They are toxic, and tend to be cumulative.
- There are major species differences in elimination times and toxicity, and data and doses cannot be transposed between species.
- In general it is not advisable to administer these drugs intravenously during anesthesia, as the delay in elimination (through anesthetic induced cardiovascular depression) again increases toxicity.
- *For all NSAIDs, never exceed the data sheet dose in quantity or in frequency of administration.*
- Flunixine meglumate (Banamin)
  - It has been used in the horse for some years.
  - There appear to be no problems with single dose IV use during anesthesia.
  - However, cumulation through multiple dosing can cause colitis, particularly in sick horses.
  - Overdose causes death. It has been shown to produce worth while analgesia during and after surgery when given as premedication.
  - Possible renal toxicity has been reported when it has been given to halothane anaesthetised dogs.
- Carprofen (Rimadyl)
  - It is very widely used analgesic in the dogs
  - Appears very effective at doses of 4mg/kg IV or SQ given at premedication or induction.
  - It is very long acting and has a much greater safety margin than has flunixine
  - The range available is enormous. For details of doses, half-lives, and toxicity (in dog and cat) see the physiology reference)
- Many NSAIDs may be given by the oral route, making them useful for the later stages of postoperative analgesia.
- Other useful perioperative NSAID analgesics include meloxicam, firocoxib, etodolac, and tepoxalin, and much of the toxicity is claimed to have been lessened due to their selective COX (particularly COX2) or LOX inhibitory action. For full details of the dosing and duration etc see the suggested references below

Alpha 2 adrenoceptor agonists

- It provides some effective analgesia, particularly effective in visceral pain in comparison to somatic pain
- When used during anesthesia it reduce the dose of other anesthetics required
- However, as analgesia is accompanied by sedation, in addition to all the other side effects their use for post-operative analgesia is not common.
- Alpha 2 agonists and opioid combination shows marked synergism, and it is possible to obtain all degrees of sedation and, in some cases, anesthesia with such combinations. No pre-prepared combinations exist.
- They can provide effective analgesia with minimal side effects when used by the epidural route.
- If antagonists have been used, analgesia is reversed alongside sedation.

NMDA antagonists

- Ketamine falls into this classification
- Tends to provide better somatic analgesia than visceral analgesia
- CRI infusion now commonly used in some severely painful animals, particularly in the ICU setting, but usually is combined with other analgesics and sedatives to enhance the analgesic efficacy and reduce dissociative side effects
- Amantadine has been used in man with varying success, and seems to have a place in controlling a neuropathic pain

Other adjunctive analgesic therapy

- Acupuncture
- Transcutaneous electrical stimulation (TENS)
- Physical therapy
- Antidepressant
- Anticonvulsants etc.
- For further information on these modalities see the references cited below

Conclusion

- What determines which agents and methods for pain control should be used would depend on the type of procedures, severity of pain and economic consideration for each individual circumstance.
- Our understanding of pain in its manifestation, mechanisms, assessment, and alleviation in animals is still, although improving, limited
- It is imperative to ensure continuous effort in establishing information on safe and appropriate use of analgesics in animals
- However, it must be remembered that no pharmacological intervention can supersede tender loving care which animals deserve most during their suffering

Further suggested references

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