Analgesia in ruminants

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Ruminants are the largest group of domestic animals, but the study of pain in food animals has been neglected. Ruminants seldom receive analgesics despite various conditions (e.g., foot rot, mastitis, vaginal prolapse), husbandry practices (e.g., castration, dehorning or velvetting, mulesing), and experimental procedures (e.g., orthopaedic surgery, laparoscopy) known to be painful. There are several reasons for this, but apart from cost and residue concerns (in the commercial situation), there is only limited evidence of efficacy for commonly used drugs.

There are a number of general strategies for reducing pain. The most obvious (and best) is to prevent the condition causing pain in the first place. This can be done in some situations, such as using polled breeds to avoid dehorning. In an experimental setting, trying to obtain the same information using a less invasive technique is sometimes possible. The next strategy is to treat the condition causing the pain. This is always desirable but rarely enough on its own. Good husbandry – keeping the animal warm, dry and calm – will also help. Using analgesic drugs is usually necessary, but which drug at what dose and by which route? For surgical pain, anaesthesia, either local or general, is necessary. Unfortunately, euthanasia is often the only solution for some forms of pain.

Part of the problem of treating pain in ruminants is assessing the pain. There are a number of ways of doing this, none of which is ideal. Assessing behaviour is most commonly used, but ruminants have evolved as herd animals which are subject to predation; in these circumstances to behave differently from the herd is likely to lead to being eaten. This means that assessing pain (and thus response to analgesic drugs) in ruminants using behaviour can be difficult. Changes in behaviour are usually subtle and there is much individual variation. Some behaviours commonly seen are teeth grinding, lip curling, head pressing, cessation of rumination and loss of function, such as lameness. None of these is pathognomonic or specific for pain. One approach is to give analgesic drugs and see if the animal's behaviour returns to normal. However, many drugs can cause behaviour changes which are not related to analgesia. For instance, opioids can cause increased activity and eating behaviour, depending on the dose used. There are probably also sex differences in pain behaviour (and response to drugs).

Another way of assessing efficacy of analgesic drugs is to use nociceptive testing. This involves giving the animal a stimulus known to be painful and assessing its response, with and without analgesic drugs. If the drug suppresses the response to the stimulus, it is assumed to be analgesic. There are a number of reasons why this assumption may not be correct, however. For instance, many drugs alter blood flow to the skin, either directly or by altering core temperature, which will alter the sensitivity of nerve endings in the skin. There are four different types of painful stimuli commonly used, which probably stimulate different populations of nociceptors. Mechanical stimulation usually involves applying pressure to the skin, and is the sort of stimulus most likely to be encountered in real life. Thermal stimuli (usually hot) are sometimes used, probably because these produce results for opioids in people which correlate with their clinical efficacy in that species. Heat stimuli are almost never

encountered in nature by ruminants in New Zealand! Both of these types of stimuli have the advantage that as soon as the animal responds, the stimulus can be stopped. Chemical stimuli involve injecting an irritant substance, usually intradermally in ruminants, and are supposed to replicate inflammatory pain. Most commonly used irritants produce a biphasic response, with the first phase caused by direct stimulation of nociceptors and the second by release of inflammatory mediators. Once injected, the stimulus cannot be stopped. Finally electrical stimuli will cause firing in all types of neurones, both sensory and motor, causing pain among other things.

Endocrine effects have been used to assess pain and analgesia. Plasma cortisol concentrations are most commonly used, but adrenaline, or surrogates such as blood pressure or heart rate, are also used. The problem with these is that they measure stress, rather than pain. The stress can be caused by pain, but it can also be caused by other factors such as handling. This means that suitable control groups are critical in any assessment of analgesic drugs which relies on endocrine responses. There is also the possibility that some drugs may alter cortisol production directly.

Changes in the electroencephalogram in response to pain have also been used to measure the analgesic effects of drugs. Apart from being subject to artefacts, the major problem with an electroencephalogram (EEG) analysis is that changes probably represent differences in the central nervous system arousal rather than pain as such, although an anaesthetised animal would be expected to show arousal if subjected to a sufficiently noxious stimulus. Another problem is that different analgesic drugs produce different patterns of change or arousal, making the effects difficult to interpret.

The relative importance of various pain pathways and their receptors in ruminants appears to be different from the more intensively studied species such as rats and people. Sheep have large numbers of adrenergic alpha-2 receptors in the dorsal horn of the spinal cord, and the numbers increase dramatically in painful conditions. Sheep are very sensitive to the analgesic effects of drugs which bind to alpha-2 receptors as agonists.

Since most analgesic drugs act to block or stimulate the pain pathways, different groups of drugs should probably be used in ruminants from other animals. The analgesic drugs used in most ruminant species are usually chosen from: non-steroidal anti-inflammatory drugs (NSAIDs), alpha-2 agonists, opioids, local anaesthetics and N-methyl-D-aspartic acid (NMDA) blockers.

NSAIDs have been shown to have a small but long-lasting effect on mechanical pain thresholds in lame sheep. They have also been shown to reduce the duration of raised cortisol concentrations in sheep subjected to minor surgery. This agrees with clinical experience in sheep and other species of ruminants. There is some evidence of synergy between ketoprofen and other analgesics at the spinal level. The common side effects seen in monogastric animals – gastric ulceration and kidney failure – have not been described in ruminants, although they may still occur. NSAIDs interfere with prostaglandin production, and since prostaglandinF2a is involved in luteolysis in ruminants, they can be expected to interfere with reproduction. Reduced fertility has been reported, although not consistently, in cattle given NSAIDs in the post partum period.

Alpha 2 agonists, such as xylazine, appear to be the most potent analgesics in ruminants. They produce intense but short-acting analgesia in mechanical threshold testing, and completely abolished cortisol responses to minor surgery. However, they all have the limiting side-effect of producing hypoxaemia, probably by the release of unknown inflammatory mediators from pulmonary intravascular macrophages. There is anecdotal evidence that xylazine is worst. Low doses must be used to avoid this, but these limit the duration of action. Supplementary oxygen can be provided to avoid this if the animals are sufficiently sedated by the drugs or under light general anaesthesia.

Opioids, although the mainstay of analgesia in other species, do not work very well in ruminants. High doses (5-10x dog doses) are necessary and even these have a short duration of action. These high doses cause various excitatory behaviours such as increased movements and manic chewing.

Luckily ruminants are good candidates for local anaesthesia. Restraint can be a problem in some species, such as deer, but if suitable facilities are available, local anaesthesia can work very well. Care should be taken to avoid intravenous administration, which can cause collapse, either by directly affecting the heart and blood vessels or through central vasomotor depression. Lignocaine is most commonly

used and lasts for about 45 minutes to an hour, but the duration of action can be prolonged by using a 50% mixture of 2% lignocaine with 0.5% bupivacaine. The epidural route is useful for providing perineal analgesia: xylazine given epidurally can cause analgesia without interfering with motor function. Intravenous local anaesthetic infusion has not been extensively investigated, but seems to provide a small amount of general anaesthesia.

Glutamate is the main excitatory neurotransmitter in the brain, and one subtype of receptor, the NMDA receptor, is involved in pain sensitisation. NMDA blockers (usually ketamine) are rarely used in ruminants, but sub-anaesthetic doses have been shown to markedly potentiate alpha-2 analgesia without having an effect alone in mechanical threshold testing.

There have been no comparative trials of analgesics in ruminants reported. My preferences, which are mainly based on clinical experience, but backed up by science where possible, are:

- **Mild or Inflammatory pain**: NSAIDs, usually ketoprofen 3 mg/kg iv. There is some evidence that ketoprofen has a small synergistic effect on the spinal cord with other analgesics. It is registered for use in cattle.
- **Severe / Surgical pain**: alpha 2 agonists (medetomidine 2 μg/kg iv or dexmedetomidine 1μg/kg iv as necessary or every 20 mins, plus local block with lignocaine and bupivacaine where possible, plus NSAIDs for postoperative pain. Ketamine 1 mg/kg (iv or im) may also potentiate the other analgesics. Note that the dose of alpha 2 agonist is **much** lower than that used for sedation.

Conclusion

Adrenergic alpha-2 agonists are probably the single most useful group, but balanced analgesia using more than one class of drug (such as an alpha-2 agonist and NMDA antagonist), with the combination selected for the circumstances, probably provides the best analgesia for severe pain. Non-steroidal anti-inflammatory drugs should be more widely used for pain with an inflammatory component, but can be expensive in the larger animals. The study of analgesia in ruminants is in its infancy and recommendations for general analgesia are likely to change, but luckily ruminants are good subjects for local analgesia. Some form of local analgesia can be used in most circumstances for painful procedures, often in conjunction with sedation or light general anaesthesia, and is currently the most reliable way of reducing pain.

Remember that all common ruminants are food animals and either apply withholding times or ensure that they cannot enter the food chain.