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Analgesics: what use are they in farm animals?

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ABSTRACT

The use of analgesic drugs in veterinary practice is increasing, particularly in companion animals. However, farm animals often suffer from conditions (such as foot rot), or are subjected to operations (such as dehorning), which are likely to be painful. Assessment of pain in farm animals can present difficulties and analgesic drugs have not been investigated in any systematic way. Most assessment of analgesic drugs in ruminants has been carried out using experimental models of pain rather than clinical cases. Some indications for analgesics are obvious, such as castration and dehorning. Others are not so obvious, such as mastitis, which is very painful in women, and presumably in cows. Animals in pain are likely to be less productive and there is good evidence that chronic pain will change an animal's metabolism adversely. Valid reasons for not using analgesics include cost and concerns about residues, which ultimately also means cost. There are several different classes of analgesics, with different attributes. Local anaesthetics are cheap, but short acting. Residues in food have not been an issue in the past, but concerns have been raised in Europe about some metabolites being carcinogenic. Morphine-type drugs are cheap, but less effective in ruminants than other species, are likely to cause residues in food and are strictly controlled by law. Adrenergic alpha-2 agonists are effective, but also cause sedation. Residues can be managed by relatively short withholding times. Probably the most effective analgesics for ruminants are the non-steroidal anti-inflammatory drugs, such as ketoprofen. These have long withholding times for meat, but zero for milk.

Keywords: analgesics; ruminants

INTRODUCTION

The use of systemic analgesics in companion animal practice is increasing. Nevertheless, only about 50% of cats and dogs receive analgesia after ovariohysterectomy (Capner *et al.*, 1999; Lascelles *et al.*, 1999) and whilst analgesics are used to treat arthritis they are less frequently used in the treatment of other painful medical conditions. This reluctance to use analgesics even in companion animals is difficult to understand given that almost all veterinarians believe that animals feel pain in some way or other.

In farm animals, systemic analgesics are used very infrequently. The use of analgesics in research laboratories where invasive surgery is practiced is now mandatory almost everywhere, regardless of species, and most of the relevant research into the usefulness of analgesics in farm animals has been carried out in research laboratories.

The use of analgesics in farm practice is low for reasons that include cost, fear of residues, the Misuse of Drugs Act and, most importantly, tradition. In addition, there is also a lack of knowledge about the use of analgesics in farm animals.

A point often overlooked is that pain is likely to reduce productivity: foot lameness in dairy cattle has been shown to produce very long lasting changes in pain perception, even when treated (Whay *et al.*, 1998). This is likely to cause stress which will reduce milk yield and fertility.

Clinical analgesia in farm animals

There are many clinical indications for analgesics drugs in farm animals, but the range of drugs available is small, and they all have their drawbacks. In New Zealand nine NSAIDS are licensed for use in cattle, four of which are also licensed for pigs. There are no NSAIDs licensed for use in sheep or deer. Of the opioids, pethidine is licensed for use in cattle and a fentanyl/azaperone/xylazine mixture in deer. Lignocaine is the only local anaesthetic licensed for use in farm animals.

In cattle systemic analgesia is indicated in the treatment of obviously painful disease (lameness), injury (for example after extensive foetotomy) and during and after surgery whether it is routine (dehorning), occasional (caesarian section, claw removal) or experimental. In dairy cows mastitis is almost certainly painful but the use of analgesics may be considered too expensive.

Ketoprofen has been shown to be a useful analgesic in calves after dehorning (McMeekan *et al.*, 1998; McMeekan *et al.*, 1999) and castration (Stafford *et al.*, 2002) and might be effective in relieving the pain caused by mastitis or lameness. However, in New Zealand a course of ketoprofen (Ketofen 10%, Rhone Merieux, France) for a dairy cow for 3 days would cost about $100 and if that is added to the cost of antibiotics it makes the use of analgesics in the treatment of mastitis prohibitive. An NSAID may be used for toxic mastitis but usually for its anti-inflammatory effect rather than its analgesic effect.

There is concern that drugs may leave residues in milk. Methods not involving drugs can be used to reduce pain. In cows with sore feet, placing a block under the sound claw thus taking pressure off the lame claw will avoid making the pain worse. Interestingly, in a review of bovine lameness Ward (2001) did not mention the possibility of using analgesia in the treatment of lameness in cattle but he may have been influenced by European concerns about residues in milk or meat.

In sheep the indications for systemic analgesics are similar to those of cattle but the costs become even more important because the value of individual sheep is so much lower than that of cattle. In older pigs, arthritis and foot problems are common, and would benefit from NSAIDs.

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The mastitis component of metritis - mastitis - agalactia syndrome is likely to be painful. Most broiler chickens suffer from leg weakness, which is probably painful. They are never treated.

Drugs

The only way of making absolutely certain that an animal can feel no pain is to kill it. Euthanasia is often cheaper than analgesic drugs and is the treatment of choice where the prognosis is poor. The next most reliable method of producing analgesia is general anaesthesia but this is impracticable in most circumstances and is only indicated for surgery. The choice is then reduced to systemic or local analgesia.

There are three major groups of systemic analgesics; NSAIDs, opioids, and alpha-2 adrenoceptor agonists. However, some systemic analgesics can also be used epidurally. This route of administration means that good analgesia can be produced with a smaller amount of drug, and so with less risk of residues.

NSAIDs

The analgesic effect of these drugs was initially considered to be due to their peripheral anti-inflammatory actions but some of them have been shown to have central nervous system effects also (Chambers *et al.*, 1995). The list of neuromodulators with which NSAIDS interact directly or by altering transcription is growing daily.

The effectiveness of any particular drug as an analgesic will depend partly on its pharmacokinetics, partly on the cause of pain and partly on poorly understood characteristics of the drug itself. Some NSAIDS, notably phenylbutazone, are more anti-inflammatory than analgesic; others such as carprofen are more analgesic than anti-inflammatory.

Some of the NSAIDs are very effective analgesics in ruminants. Ketoprofen used with local anaesthesia eliminated the cortisol response and by inference prevented pain following dehorning (McMeekan *et al.*, 1998; McMeekan *et al.*, 1999) and surgical castration in calves (Stafford *et al.*, 2001-2) for at least 8 hours. When ketoprofen was given by itself, it reduced the plasma cortisol response significantly and by inference the pain in the hours following dehorning (McMeekan *et al.*, 1998).

Diclofenac reduced the peak cortisol response and the time spent trembling or abnormal postures following castration in lambs (Molony *et al.*, 1997) but had contradictory effect when given to lambs before docking and may not have provided effective analgesia to lambs afterwards (Graham *et al.*, 1997).

Phenylbutazone did not prevent the delayed cortisol response seen following dehorning when the effect of local anaesthetic wore off (Sutherland *et al.*, in press). This probably indicates that, as in other species, it is mainly anti-inflammatory rather than analgesic.

Aspirin did not act as an effective analgesic when given by mouth to lambs immediately after docking (Pollard *et al.*, 2001). This may be because it was given after surgery or because it was rapidly metabolised. It was also ineffective when given by mouth to piglets being castrated (McGlone *et al.*, 1993).

Repeated injections of flunixin alleviated chronic inflammatory pain in lame sheep, (Welsh & Nolan, 1995), and both it and carprofen attenuated artificially induced hyperalgesia in sheep (Welsh & Nolan, 1994). A single IV injection of flunixin had some analgesic effect in cows with mastitis (Fitzpatrick *et al.*, 1999). Carprofen had no effect in lambs being castrated or tail docked (Price & Nolan, 2001).

The longer period of activity of the some NSAIDs may make them more useful in clinical practice than opioids but price remains prohibitive. Pharmacokinetics vary widely between species and extrapolation between species is problematical. Some NSAIDS, notably phenylbutazone, have a very long half- life in sheep and cattle. (Cheng *et al.*, 1998; Volner e*t al.*, 1990). Aspirin has a very short half-life in cattle, and possibly sheep. NSAIDS can interfere with prostaglandin production during reproduction and parturition.

NSAIDs, because of their acidic nature, do not penetrate into milk to any great extent and usually have a zero milk withholding period. Ketoprofen was shown to have a very short half-life and to leave no significant residue in meat and milk from cows given ketoprofen intravenously (De Graves *et al.*, 1996). However, most NSAIDs are highly protein bound and tend to have long meat withholding times.

Opioids

Opioids are generally considered to be ineffective in ruminants. Pethidine has a short period of action in sheep as in most other animals; it is effective for less than 30 minutes (Nolan *et al.*, 1988) which limits its use in clinical practice. It is a class B Controlled Drug.

Buprenorphine was found to provide effective analgesia to sheep subjected to tibial osteotomy (Otto *et al.*, 2000). It was ineffective (Grant *et al.*, 1996) against an electrical or mechanical stimulus but produced definite antinociceptive effects in sheep subjected to a thermal stimulus (Nolan *et al.*, 1987). It has a duration of about three hours in sheep (Nolan, 2000), in comparison to about eight hours in people. Buprenorphine may depress milk production. Although the amount excreted in milk may be small, it can still be enough to cause problems in people (Marquet *et al.*, 1997)

The evidence for butorphanol's efficacy is conflicting in most species, including people. Waterman *et al.* (1991) found it to be an effective analgesic in sheep using a thermal stimulus but not when a mechanical stimulus was used. Cows clear it rapidly from the plasma, but it is detectable in milk for up to 36 hours (Court *et al.*, 1992). It produced no measurable analgesia in castrated piglets (McGlone *et al.*, 1993).

Morphine has been used clinically in sheep and pigs subject to experimental surgery. High doses are required, and analgesia is not always obvious, especially in sheep.

Fentanyl has been given intravenously to sheep (Waterman *et al.*, 1990) and it was much more effective against a noxious heat stimulus than a mechanical stimulus. Even at high doses, its effect did not last more than two hours. Fentanyl patches have been used for

postoperative pain in pigs (Wilkinson *et al.*, 2001; Harvey-Clark *et al.*, 2000). Concentrations in plasma reached analgesic levels in six hours, peaked at about 48 hours, and persisted for about 72 hours. High dose fentanyl patches produced good clinical analgesia comparable to a high dose of buprenorphine.

Opioids tend to produce hyperactivity, particularly chewing behaviour, in ruminants. Opioids are generally lipid soluble, which allows them to get into the CNS, but also means that they are likely to get into the milk and cause residue concerns.

Alpha-2 adrenoceptor agonists

Ruminants have many alpha-2 adrenoceptors in their spinal cord and alpha-2 agonists are effective analgesics. Xylazine intramuscularly has been shown to produce a significant analgesic effect in adult sheep (Grant *et al.*, 1996) and an antinociceptive effect in response to an electrical stimulus was demonstrated in lambs (Grant & Upton, 2001). However, alpha-2 agonists act as sedatives so there are problems in assessing their analgesic effect under clinical conditions.

A combination of xylazine and ketamine did not appear to have any analgesic effects as measured by plasma cortisol and prolactin plus behaviour in sheep after laparotomy and hysterotomy (Hughan *et al.*, 2001). Ketamine alone has to be given in anaesthetic doses to produce analgesia in sheep, but may potentiate other analgesic drugs.

Alpha-2 agonists are effective when given epidurally or intrathecally a longer period of analgesia can be produced with a lower dose and fewer side effects. Xylazine has been used clinically in sheep and cattle, and medetomidine in cows.

Alpha-2 agonists are not very effective in pigs. In ruminants, they tend to produce dyspnoea and hypoxaemia in sheep, particularly xylazine. They penetrate tissues well and are likely to cause residues in milk, although they are rapidly metabolised.

Local analgesia

Lignocaine is the only drug in common use. It is always applied to either nerves or the spinal cord as it is metabolised very quickly once absorbed systemically. Its effect can be prolonged from about 45 mins to 60 - 70 mins by including a vasoconstrictor to slow absorption. Bupivacaine is much longer acting (6 - 8 hours) but is rarely used in farm animals. Local analgesics have the disadvantage that they block motor as well as sensory nerves, which can cause paralysis. Both lignocaine and bupivacaine are likely to be converted to the carcinogenic metabolite 2, 6 xylidine. This has caused concerns in Europe.

LONG-TERM PAIN CONTROL

Many farm animals are likely to suffer chronic pain (osteoarthritis, foot problems) but there is no clinical experience or scientific data on the treatment of chronic pain in stock. Intermittent dosing with NSAIDs has been used in people and small animals for many years; its effectiveness is only limited by side effects. There is no experience, even in small animals, of the psychotropic drugs used in people for chronic pain.

THE FUTURE?

We are at the beginning clinically and scientifically. Our use of analgesics in farm livestock will be forced to increase by social pressure, especially in the treatment of animals subjected to routine husbandry procedures. In addition, there will be pressure from important trading partners attempting to use animal welfare as a trade barrier. At the same time, there will also be pressure from those trading partners and consumers not to use drugs which leave residues in food. From a professional standpoint we should be advocating the use of analgesics, wherever possible, as we are legally and ethically obliged to prevent unnecessary and unreasonable pain.

In the short term, the use of techniques such as epidural analgesia which use small quantities of drug, and the formulation of depot compounds will make the use of analgesics more feasible. In the longer term, the development of drugs which either break down very quickly or are completely innocuous will be necessary.

The development of useful models (dehorning, castration) to test the efficacy of analgesics in farm animals makes the routine testing of available and new analgesics practicable. These models could be used to screen the efficacy of analgesics on different types of injuries.

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