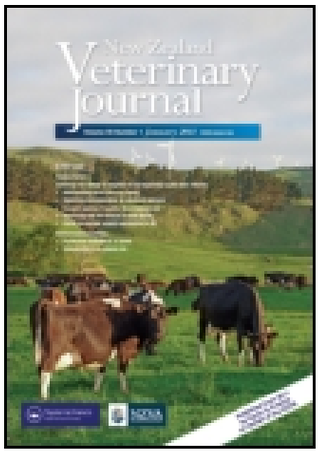

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Use of analgesic drugs for pain management in sheep

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Review

Use of analgesic drugs for pain management in sheep

I Lizarraga*§ and JP Chambers†

Abstract

Awareness of pain and its effects is increasing within the veterinary profession, but pain management in food animals has been neglected. Sheep seldom receive analgesics despite various conditions, husbandry practice and experimental procedures being known to be painful, e.g. footrot, mastitis, vaginal prolapse, castration, vasectomy, penis deviation, and laparoscopy. The evidence supporting use of analgesic drugs in this species is reviewed here. Opioid agonists are of dubious efficacy and are short acting. α_2-agonists such as xylazine are good, short-lived analgesics, but induce hypoxaemia. Non-steroidal anti-inflammatory drugs (NSAID) such as ketoprofen provide long-lasting analgesia, but not as marked as that from α_2-agonists; they should be more widely used for inflammatory pain. Local anaesthetics reliably block pain signals, but may also induce motor blockade. Balanced analgesia using more than one class of drug, such as an α_2 agonist (e.g. medetomidine) and *N*-methyl-D-aspartate antagonist (e.g. ketamine), with the combination selected for the circumstances, probably provides the best analgesia for severe pain. It should be noted that there are no approved analgesic drugs for use in sheep and therefore the use of such drugs in this species has to be off-label. This information may be useful to veterinary practitioners, biomedical researchers, and regulators in animal welfare to develop rational analgesic regimens which ultimately may improve the health and welfare of sheep in both farming and experimental conditions.

KEY WORDS: *Pain evaluation, nociception, analgesics, sheep*

Introduction

Inadequate pain management has deleterious effects in humans and other animal species. Sheep are subjected to husbandry procedures, e.g. castration, tail docking and are prone to develop conditions, e.g. lameness, mastitis associated with pain, as well as being used frequently for educational purposes and in biomedical research, which may involve major surgical procedures. However, veterinary care is rarely sought by farmers, as highlighted in a survey from Scotland, in which 98% of 14,417 sheep suffering from lameness received no veterinary attention despite the awareness by farmers of related welfare issues (Clements *et al.* 2002).

The reasons for not administering analgesics to sheep may include difficulties in assessing pain, lack of knowledge of appropriate use of analgesics, and fear of residues. The need for identifying, assessing, preventing, and managing pain in sheep is evident. This review provides a brief summary of methods used to assess pain, as background information to the way pain can be managed in sheep, with special emphasis on drugs. Pain and distress caused by farming practices in lambs, e.g. tail docking, castration, have been reviewed by Mellor and Stafford (1999).

Methods used to assess pain and analgesia

Recognising pain and assessing its intensity are both essential for its effective management. In sheep, different approaches, including identification of behavioural changes, degree of lameness, plasma constituents and nociceptive threshold testing, have been investigated with the aim to accomplish this.

Behavioural changes

Qualitative observation of behavioural changes by an experienced clinician is probably one of the best methods for capturing the complexity of pain. Some behaviours attributed to pain, e.g. teeth grinding, lip curling, head pressing, and cessation of cuddling, have been recognised for sheep and used to score pain intensity (Sanford *et al.* 1986; Dowd *et al.* 1998; Dobromylskyj *et al.* 2000). However, such assessments are subjective and at the mercy of inter- and intra-observer variability.

One way of confirming that an abnormal behaviour is related to pain is by administering analgesics (Mellor and Stafford 2004). Any non-analgesic actions of the drug(s), which can also cause behaviour modification, must be considered. It is particularly important that drugs that prevent sheep from expressing pain, rather than actually relieving pain, are not used.

Lameness

In sheep suffering from footrot, the degree of lameness (e.g. gait score) and the severity of foot lesions have been used as indicators of the degree of pain (Ley *et al.* 1989a; Welsh and Nolan 1995a).

COX	Cyclo-oxygenase
$GABA_A$	Gamma-aminobutyric acid $_A$
I/T	Intrathecal
NSAID	Non-steroidal anti-inflammatory drug(s)
NMDA	*N*-methyl-D-aspartate
PaO_2	Partial pressure of oxygen in arterial blood
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood.

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Interestingly, a significant relationship was reported between both lameness and pathology scores and mechanical nociceptive thresholds (Dolan *et al.* 2003a). Thus, the degree of lameness and the severity of the lesion may be good indicators of the magnitude of pain a sheep with footrot may be experiencing, and these could be used clinically to determine the analgesic therapy to use and its efficacy.

Active (i.e. gait score) and static (i.e. time limb held off the ground) indices of the use of limbs have been assessed in an induced inflammatory pain model (Colditz *et al.* 2011). This multimodal approach may provide a wider picture of the lameness, and probably pain, that sheep may experience. Further research would establish the utility of this model to assess the efficacy of analgesics.

Plasma constituents

Concentrations of cortisol, adrenaline, noradrenaline, vasopressin, prolactin, and free fatty acids in plasma have been investigated in relation to changes associated with pain due to footrot in sheep (Ley *et al.* 1991a, 1992, 1993, 1994). However the great individual variability, the involvement of the stress response, and the effect of drugs call for caution when interpreting results for these plasma constituents as indicators of pain. Further research to identify reliable biomarkers of pain in sheep is necessary.

Electroencephalography

Characteristics of electroencephalograms have been used to assess pain in conscious sheep (Morris *et al.* 1997; Ong *et al.* 1997). An increase in power spectral components of the electroencephalogram and late amplitudes (>100 ms) of cerebral evoked potentials were recorded after noxious electrical stimulation of a foreleg. Although this highlights the potential usefulness of electroencephalographic changes to measure acute pain in sheep, changes were very brief due to the short duration (milliseconds) of stimuli. Longer duration (hours to days) of noxious stimulation, such as that experienced during some husbandry or pathological conditions, would allow the assessment of both short- and long-term effects on brain activity and ultimately correlate them with changes in behaviour.

Nociceptive threshold testing

Measurements of nociceptive thresholds after mechanical stimulation of a limb or thermal stimulation of the pinna of the ear are well-established techniques for studying pain and analgesics in sheep (Nolan *et al.* 1987a; Chambers *et al.* 1994). These techniques detect hypersensitivity to pain in a number of conditions including experimental models of inflammatory pain (Dolan *et al.* 2003a; Colditz *et al.* 2011), ventral midline laparotomy (Welsh and Nolan 1995b), footrot (Ley *et al.* 1989a; Chambers *et al.* 1994) and chronic mastitis (Dolan *et al.* 2000).

Other ways of inducing nociceptive mechanical stimulation include pinching or pin-pricking of a predetermined anatomical area (O'Hair *et al.* 1988; Aminkov and Hubenov 1995), but these techniques cannot measure nociceptive thresholds and therefore quantify changes on them after drug administration. Electrical stimulation of a limb has also been used to evoke an aversive, nociceptive response (Ludbrook *et al.* 1995). This technique is useful to determine changes in nociceptive thresholds (Grant *et al.* 1996; Haerdi-Landerer *et al.* 2005), but is not specific to any particular type of pain receptor.

In summary, there are no accepted objective criteria to assess the degree of pain a sheep may be experiencing. An integrated approach that combines some of the discussed techniques according to the situation may be more valuable in assessing pain and the effects of analgesics. Such an approach, in addition to being developed, will have to be validated for a variety of situations, and only then our ability to assess and treat pain in sheep will improve.

Analgesic drugs

Conventional analgesic drug classes include opioids, α_2-agonists, non-steroidal anti-inflammatory drugs (NSAID) and local anaesthetics. Other adjunctive drugs, such as ketamine, are also used. The goal of analgesic drug therapy is to prevent and/or reduce pain without adversely affecting the animal by the side effects that the analgesics may induce. In the following sections, information based on evidence about analgesics and their side effects in sheep is presented.

Opioids

These are a wide and diverse group of drugs that interact with opioid receptors: μ, δ, and κ. They can be classified as full μ agonists (e.g. morphine, fentanyl), mixed agonist/antagonists (e.g. buprenorphine, butorphanol, nalbuphine), and antagonists (e.g. naloxone). Most opioids are schedule-controlled drugs and their keeping and administration are subject to stringent legal requirements.

Analgesia

Agonists at μ and κ, but not δ, receptors are clinically used in animals for provision of analgesia. They achieve this by hyperpolarising neurons due to both the opening and closing of K^+ and Ca^{2+} channels, respectively. Opioid receptors are located throughout the brain and spinal cord as well as throughout peripheral tissues, but at least in healthy sheep the centrally located ones, especially within the spinal cord, are responsible for the analgesic effects of these drugs (Waterman *et al.* 1991a; Main *et al.* 1997).

Use of intrathecal (I/T) bolus administration of opioid agonists did not increase mechanical thresholds in healthy sheep (Ley *et al.* 1989b) or improve lameness scores in sheep submitted to stifle surgery (Wagner *et al.* 1996). Furthermore, locomotor activity and pruritus or pain-like behaviours, including vocalisation, biting and pulling of wood, and hypersensitivity to touch, were common after I/T or epidural bolus administration of opioid agonists (Rawal *et al.* 1991; Coombs *et al.* 1994; Wagner *et al.* 1996). Similarly, chronic continuous I/T and epidural infusions of larger than clinically recommended amounts of morphine and hydromorphone in healthy sheep produced locomotor effects and pain-like behaviours within the first few days. All treatments except hydromorphone, induced inflammation around the catheter tip (Coombs *et al.* 1994; Gradert *et al.* 2003; Johansen *et al.* 2004a). Bolus I/T administration of butorphanol and high doses of sulfentanil, but not nalbuphine, also produced inflammatory reactions (Rawal *et al.* 1991). Epidural or I/T administration of opioid agonists cannot be recommended in sheep as analgesia is not reliable and increasing the dose and/or the concentration in an attempt to achieve analgesia increases the risk of neurotoxicity.

In healthy sheep under experimental situations, systemic administration of most opioid agonists did not affect leg withdrawal responses to mechanical or electrical noxious stimuli

(Nolan *et al.* 1987b; Waterman *et al.* 1991c; Grant *et al.* 1996), However, fentanyl dose-dependently increased mechanical thresholds for up to 40 minutes (Waterman *et al.* 1990; Main *et al.* 1997). Analgesia, assessed by behavioural responses to pinching with forceps, was also detected up to 120 minutes after butorphanol or nalbuphine administration (O'Hair *et al.* 1988), and opioid agonists consistently induced hypoalgesia for up to 120 minutes after thermal stimulation of the ear or the nose (Nolan *et al.* 1987b; Waterman *et al.* 1991b; Cook 1997). Opioid agonists seem to be effective at inducing analgesia in response to thermal, but have variable efficacy against mechanical noxious stimuli.

Sheep hypersensitive to pain showed short-term analgesia after I/V administration of opioid agonists. For instance, buprenorphine prevented for no more than 60 minutes the development of thermal hyperalgesia after laparotomy for embryo retrieval (Welsh and Nolan 1995b) and fentanyl prevented for 27 minutes the development of mechanical hyperalgesia after inflation of a tourniquet on one foreleg (Welsh and Nolan 1994). To maximise their analgesic potential, opioid agonists should be administered before the afferent pain barrage has been established. Buprenorphine (5–10 μg/kg I/V or I/M every 4 h), butorphanol (0.5 mg/kg I/M or S/C every 2–3 h), morphine (0.2–0.5 mg/kg I/M every 2 h), and pethidine (2.0 mg/kg I/M or I/V every 2 h) have been recommended for the control of postoperative acute pain in sheep (Dobromylskyj *et al.* 2000), although these dose regimes have been extrapolated from other species.

Transdermal fentanyl has been used experimentally in clinical settings to control postoperative orthopaedic pain (Shafford *et al.* 2004; Guedes *et al.* 2006; Ahern *et al.* 2009). However, the use of fentanyl patches is not recommended outside the clinic as they could easily be abused.

Side effects

A number of potential side effects have been attributed to the use of opioids. In sheep, however, changes in behaviour seem to be the most important ones. Sedation or excitement can occur with opioids. For instance, butorphanol and nalbuphine induced sedation that lasted <90 minutes (O'Hair *et al.* 1988), and ataxia was reported with butorphanol (Waterman *et al.* 1991b).

Excitement was induced by I/V injection of a number of opioids including buprenorphine, butorphanol and fentanyl (Nolan *et al.* 1987b; Acevedo *et al.* 1991; Waterman *et al.* 1991b). Agitation, loud and continuous bleating, compulsive chewing, increased locomotor activity, ataxia, head jerking, and nystagmus were described after drug injection. The intensity of these effects decreased with time and animals were calm and quiet 30 minutes (fentanyl) to 180 minutes (buprenorphine) post-administration.

Excitement seems to be mediated, at least partially, by opioid receptors as naloxone reduced pethidine-induced behavioural effects, though some excitement was still present for ~5 minutes post-agonist injection (Nolan *et al.* 1988). Activation of opioid receptors on dopaminergic neurons may play an important role in opioid agonist-induced dysphoria. The dopaminergic D_2 receptor antagonist droperidol prevented the dysphoric effects of fentanyl (Acevedo *et al.* 1991; Livingston *et al.* 1991; Kyles *et al.* 1993a). The administration of tranquillisers, therefore, may offset opioid-induced excitement. Also, the effects are probably dose-dependent as I/V injection of small dose butorphanol (Waterman *et al.* 1991b) and I/M injection (and therefore slower absorption) of buprenorphine and methadone (Grant *et al.* 1996) produced no behavioural changes.

Cardiovascular and respiratory depression should not preclude the use of opioid agonists in sheep as no significant effects have been observed after administration of buprenorphine, butorphanol or nalbuphine (O'Hair *et al.* 1988; Waterman *et al.* 1991b, 1991c). Even the potent opioid agonist fentanyl only decreased the partial pressure of oxygen in arterial blood (PaO_2) for 10 minutes and increased the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) for 5 minutes post-injection (Waterman *et al.* 1990).

In summary, opioids only produce brief analgesia against some types of pain, and some may need to be given at higher doses than in other species (e.g. fentanyl as compared with dogs). Behavioural side effects are common and may interfere with pain assessment. Residues are likely to be a problem unless long withholding times are applied. Furthers studies are necessary to determine the true clinical analgesic value of these drugs in sheep.

α_2-agonists

α_2-agonists have been used in ruminants since the 1960s to provide sedation and analgesia. Xylazine was the first drug from this class and is still widely used. Newer clinically useful drugs include detomidine, romifidine, medetomidine, and dexmedetomidine. All these drugs have different α_2/α_1 receptor selectivity, and xylazine interacts also with imadazoline receptors (Kästner 2006).

Analgesia

Agonists at α_2-adrenergic receptors induce dose-dependent analgesia by hyperpolarising neurons due to the opening of K^+ channels. α_2-adrenoceptors are widely distributed throughout the body, and the sheep spinal cord densely expresses them in laminae I–II (Brandt and Livingston 1990). Analgesia is mediated mainly in the spinal cord (Kyles *et al.* 1993b) and other mechanisms, including cholinergic and nitric oxidergic, may also contribute to the spinal analgesic actions of α_2-agonists (Detweiler *et al.* 1993; Xu *et al.* 1996; Klimscha *et al.* 1997).

The analgesic effectiveness of I/T α_2-agonists is high compared with I/V administration. Clonidine, for instance, was 10 times more potent than xylazine when given I/V, but only twice as potent when injected I/T in sheep submitted to noxious mechanical stimulation of a forelimb (Waterman *et al.* 1988; Ley *et al.* 1989b). This may be partly caused by a local anaesthetic effect (Chambers 1993), which may occur clinically after I/T injection of large doses of α_2-agonists.

The analgesia α_2-agonists provide when given systemically is intense but of short duration (Nolan *et al.* 1987a; Chambers *et al.* 1994; Muge *et al.* 1994). In this regard, I/M xylazine provided longer-lasting analgesia compared with I/V administration, but the peak analgesic effect was smaller; it was proposed that I/M xylazine be used to provide analgesia in sheep (Grant and Upton 2004). A maximum I/M dose of 100 μg/kg for xylazine has been recommended (Hodgkinson and Dawson 2007). Further studies examining repetitive dosing of xylazine and other α_2-agonists may produce therapeutic regimens that could provide long-term pain control.

Some variations in analgesia following administration of xylazine have been reported in different breeds of sheep (Ley *et al.* 1990; Kyles *et al.* 1993b; Lizarraga *et al.* 2008). It may be possible that differences in bodyweight for the different breeds, rather than a

real genetic effect, may have contributed to the different analgesic sensitivity. However, despite significant differences in bodyweight and age, a similar analgesic response to xylazine was observed in Merino lambs and adult sheep (Grant and Upton 2001a). Further studies, with age-matched individuals from the same breed but different bodyweights, and/or bodyweight-matched individuals from different breeds, are necessary to more fully characterise the analgesic effects of xylazine.

The analgesia produced by α_2-agonists was reduced in sheep suffering chronic pain from footrot compared with sound sheep, and these differences persisted for 3 weeks after apparent resolution of the lameness-causing lesion (Ley *et al.* 1991b; Chambers *et al.* 1994). Thus, α_2-agonists may be less effective in the treatment of chronic pain than when used for acute pain or under control conditions.

Side effects

Sedation, hypoxaemia, bradycardia and hypotension are common side effect of α_2-agonists in sheep. A variety of other side effects are occasionally seen; these have been reviewed by Kästner (2006).

Analgesia with α_2-agonists is accompanied by deep sedation. The degree of sedation is dose-dependent and correlates well with concentrations of drug in plasma. Thus, I/V α_2-agonists produce faster and longer sedation than when administered I/M and recumbency is also observed at high doses (Mohammad *et al.* 1993; Muge *et al.* 1994; Kästner *et al.* 2003). There is some evidence that the α_{2D} receptor subtype in the sheep brainstem may be responsible for the sedative effects (Schwartz and Clark 1998).

Hypoxaemia is the limiting factor for the use of these drugs and is well documented (Waterman *et al.* 1987; Celly *et al.* 1997; Ranheim *et al.* 2000). The fall in PaO_2 is observed within 2 minutes following administration and lasts up to an hour.

Apnoea followed by tachypnea was induced after rapid I/V injection or high I/M doses of α_2-agonists (Singh *et al.* 1994; Celly *et al.* 1997). This could be a compensatory response to the fall in PaO_2 although there was no increase in $PaCO_2$ (Celly *et al.* 1997). Mild increases in $PaCO_2$ for 5 minutes after I/V detomidine and 30 minutes after I/V xylazine have been reported (Waterman *et al.* 1987).

α_2-agonists increased the airway pressure of anaesthetised sheep (Nolan *et al.* 1986), and increased the alveolar-to-arterial oxygen tension gradient as a result of an increase in intrapulmonary shunt fraction (Celly *et al.* 1999a). These changes appear to be caused by release of inflammatory mediators from pulmonary intravascular macrophages following α_2 agonist activation (Celly *et al.* 1999b). Although hypoxaemia could prove life threatening in sheep with pre-existing respiratory or cardiovascular disease, it could be counteracted by supplementing oxygen via a facial mask or a nasal tube (Ranheim *et al.* 2000; Read *et al.* 2001; Risling *et al.* 2011).

α_2-agonists can cause a peripherally mediated constriction, followed by a central relaxation of smooth muscles. Dose-dependent bradycardia without a compensatory increase in mean arterial pressure has been observed following administration of detomidine and medetomidine (Mohammad *et al.* 1993; Singh *et al.* 1994; Haerdi-Landerer *et al.* 2005), and clonidine decreased heart rate and both mean and diastolic arterial pressures from 15–90 minutes post-treatment (Hood *et al.* 1995; DeRosi *et al.* 2006). Similar effects have been demonstrated in pregnant sheep and rams following epidural administration of clonidine and xylazine (Eisenach *et al.* 1989b; Aminkov and Hubenov 1995). In contrast to all these studies, no significant changes in heart rate, mean arterial pressure and cardiac output were observed after using a relatively low analgesic I/M dose of xylazine (Grant and Upton 2001b).

α_2-agonists can induce hyperglycaemia by reducing insulin concentration due to a direct effect on α_2-adrenoceptors in pancreatic cells (Muggaberg and Brockman 1982) and this can last up to 24 h if large enough doses are given (e.g. 60–90 μg/kg I/V detomidine) (Singh *et al.* 1994). In pregnant sheep, maternal and fetal hyperglycaemia was observed following I/V or epidural clonidine treatment (Eisenach *et al.* 1989a, 1989b). The hyperglycaemic effects should be considered if diagnostic laboratory testing is to be carried out in animals receiving α_2-agonists.

In summary, α_2-agonists can produce profound analgesia with sedation and potential hypotension and hypoxaemia, for which supplementary oxygen is advisable. Low doses given I/V (e.g. 2 μg/kg medetomidine) during surgery can provide intense analgesia of short duration (20 minutes).

Non-steroidal anti-inflammatory drugs

This large and chemically diverse group of drugs have a common mechanism of action inhibiting cyclo-oxygenase (COX) enzymes, thus reducing the production of prostaglandins. They have analgesic and anti-inflammatory effects, but they also reduce fever and platelet aggregation. The potency for each effect seems to vary with the drug. Acetylsalicylic acid, dipyrone, flunixin, ketoprofen, phenylbutazone, and tolfenamic acid are examples of NSAID used in farm animals.

Analgesia

It was originally thought that NSAID induced analgesia by reducing inflammation through inhibition of COX enzymes and prostanoid production in the periphery, thus preventing sensitisation of the peripheral nerve terminals, but other mechanisms or sites have been proposed that may also contribute to their analgesic actions. The peripherally mediated anti-inflammatory or analgesic effects have been demonstrated in sheep following administration of phenylbutazone (Dowd *et al.* 1998), flunixin (Welsh and Nolan 1995a) and meloxicam (Colditz *et al.* 2011). Some NSAID (flunixin, dipyrone, ketoprofen and tolfenamic acid), but not others (I/V salicylic acid and phenylbutazone), induced long-lasting analgesia in the absence of inflammation in sheep (Chambers *et al.* 1995; Lizarraga and Chambers 2006). This suggests that the analgesic potency of NSAID may be drug dependent and not entirely due to COX enzyme-inhibition. In this regard, the opioid antagonist naloxone and the α_2-adrenoceptor antagonist atipamezole prevented I/V NSAID-induced analgesia in sheep (Chambers *et al.* 1995; Lizarraga and Chambers 2006). In addition, carprofen prevented increased serotonin concentration in the cerebrospinal fluid of sheep during stifle arthroscopy (Otto and Adams 2005). Hence, NSAID seem to activate opioidergic and α_2-adrenergic descending inhibitory systems and inhibit serotoninergic descending excitatory systems, all of which converge on the spinal cord. These findings do not exclude the possibility that supraspinal COX inhibition also plays a part.

A direct spinal analgesic action for NSAID has been investigated in healthy sheep without achieving analgesia (Lizarraga and

Chambers 2006; Lizarraga *et al.* 2008). However, I/T administration of ketoprofen attenuated mechanical hypersensitivity induced by I/T *N*-methyl-D-aspartate (NMDA) (Lizarraga *et al.* 2008). This suggests that NSAID have no direct analgesic effect on the spinal cord, but they are effective at reducing central sensitisation. In fact, flunixin prevented the development of central sensitisation in sheep subjected to midline laparotomy (Welsh and Nolan 1995b), which has been associated with lumbar spinal increase of COX-2 mRNA and protein (Dolan *et al.* 2003b).

Despite being able to prevent the development of central sensitisation, the degree of analgesia induced by flunixin and dipyrone was reduced in sheep suffering from chronic pain due to footrot compared with sound sheep (Chambers *et al.* 1995), as observed with opioids and α_2-agonists. This highlights the importance of timing of analgesia, with most drugs being more effective before the afferent barrage has been established. The preventive and/or therapeutic use of NSAID for conditions in which central sensitisation may develop, especially due to inflammation, should be more widespread in sheep.

Side effects

Gastric ulceration is a common but rarely serious side effect in monogastric animals; renal failure is rare but serious. Abomasal ulceration and renal toxicity in susceptible sheep should be considered when giving NSAID. Decreased gastrointestinal motility was observed in sheep after treatment with lysine-acetylsalicylic acid that was attributed to an α_2-adrenergic effect (Hondre and Buéno 1984).

Non-steroidal anti-inflammatory drugs are not approved for use in sheep, but several are licensed for cattle. Most NSAID bind to protein and long withholding times for meat are appropriate. The long withholding times and the high cost of treatment are reasons for NSAID being one of the most underused group of analgesics in farmed sheep.

Local anaesthetics

These drugs reversibly block voltage-gated Na^+ channels, which reduces Na influx and depolarisation of axons. Lignocaine, bupivacaine, mepivacaine, and ropivacaine are local anaesthetics commonly used in clinical practice, but the latter two have not been evaluated systematically in sheep.

Analgesia

Perineural infiltration blocks most sensation in particular anatomical regions, and epidural, paravertebral, cornual, retrobulbar, and testicular block techniques as well as an I/V regional anaesthesia technique have been described for sheep (Hodgkinson and Dawson 2007). Clinically, indications for sacrococcygeal epidurals include replacement of a cervicovaginal or uterine prolapse, correction of dystocia, replacement of a rectal prolapse, and perineal urethrostomy. Indications for lumbar epidurals include vasectomy, caesarean section, and treatment of hindlimb fractures (Shafford *et al.* 2004).

Local anaesthetics are often used clinically in combination with α_2-agonists in epidural or I/T administration to obtain long-lasting analgesia; this use of α_2-agonists may also induce local anaesthetic-like effects (Chambers 1993). Sacrococcygeal epidural administration of lignocaine induced caudal analgesia for up to 4 h, but when it was combined with xylazine analgesia lasted for up to 36 h and was accompanied by mild ataxia and weakness of the pelvic limbs (Scott 1996). Combining clonidine with lignocaine for lumbosacral I/T injection produced longer-lasting analgesia (187 minutes) than lignocaine alone (55 minutes), with similar intervals to onset of analgesia. Clonidine and lignocaine induced moderate sedation and decreased PaO_2 15–90 minutes after treatment (De Rossi *et al.* 2006). The longer-lasting analgesia obtained with such combinations may outweigh their potential side effects, i.e. limb weakness and ataxia, sedation, hypoxaemia. An alternative, which is not voided of side effects either, is to use the longer-acting local anaesthetic bupivacaine. This induced at least 3 h of sensory block after low-thoracic I/T injection (Rose *et al.* 1996).

Desensitisation of a more limited body area can be achieved by using local anaesthetic techniques other than epidural or I/T administration, such as an I/V regional anaesthesia technique with lignocaine (Main *et al.* 1997).The addition of adrenaline to local anaesthetics induces vasoconstriction in the infiltrated zone, which delays the removal of the local anaesthetic and therefore prolongs its local anaesthetic effects. Local anaesthetics for epidural or I/T administration should be free from adrenaline and if possible, preservatives.

Side effects

The major signs of toxicity involve the central nervous and the cardiovascular systems. Large I/V doses of local anaesthetics induce convulsions and cardiovascular depression that can be fatal in conscious, but not in anaesthetised sheep (Copeland *et al.* 2008). Caution should be exercised to avoid inadvertent I/V administration and volumes for local infiltration should not exceed the toxic doses.

Hypotension and motor blockade are potential side effects of spinal anaesthesia. After low-thoracic I/T injection of bupivacaine, hypotension was observed, which was reduced by neostigmine (Rose *et al.* 1996). Ataxia followed by sternal recumbency was reported after lumbosacral I/T injection of lignocaine, clonidine or their combination (De Rossi *et al.* 2006).

In the European Union, lignocaine and most other local anaesthetics are prohibited in food animals as their metabolite 2,6-xylidine is potentially carcinogenic. This has been demonstrated to be excreted in the milk of cows following lignocaine injection (Puente and Josephy 2001). The only licensed local anaesthetic in the European Union for food animals is 5% procaine.

Miscellaneous drugs

A number of other drugs have been shown to produce analgesia in experimental situations. These include NMDA antagonists (Welsh and Nolan 1995b; Dolan and Nolan 1999; Lizarraga *et al.* 2008), gamma-aminobutyric acid $_A$ ($GABA_A$) agonists (Kyles *et al.* 1995), 5-hydroxy tryptamine agonists (Roberts *et al.* 2000), dopamine D_2 antagonists (Kyles *et al.* 1993a; Main *et al.* 1995; 1997), nitric oxide synthase inhibitors (Dolan and Nolan 1999) and cholinesterase inhibitors (Bouaziz *et al.* 1995; Xu *et al.* 1996). The tricyclic antidepressant amitriptyline may induce analgesia in sheep (Cerda *et al.* 1997), but probably by blocking NMDA receptors. The drugs most likely to be useful clinically are the NMDA antagonists.

Activation of spinal NMDA receptors increases the responsiveness of dorsal horn neurons which can make innocuous stimulation feel painful (allodynia) and noxious stimulation even more painful (hyperalgesia). This happens, at least in part, by increasing the inflow of Ca^{2+} and activating the COX and nitric

oxide signalling pathways. I/T administration of the NMDA receptor blockers dizocilpine and ketamine, and the nitric oxide synthase inhibitor N^{ω}-nitro-L-arginine methyl ester reduced the pronociception induced by I/T NMDA (Dolan and Nolan 1999; Lizarraga *et al.* 2008). Ketamine also prevented thermal hyperalgesia in sheep subjected to laparotomy (Welsh and Nolan 1995b) and improved locomotor activity after unilateral hind limb orthopaedic surgery (Guedes *et al.* 2006). There is also some evidence that low-dose ketamine can potentiate the analgesia produced by xylazine (Chambers 1992). Ketamine is probably one of the most underused analgesic drugs in sheep.

Benzodiazepines increase the activity of $GABA_A$ receptors, which are coupled with a Cl^- channel and therefore hyperpolarise the neuronal membrane reducing the release of excitatory amino acids and neuropeptides. Only midazolam has been assessed in sheep, and dose-dependent analgesia was accompanied by motor dysfunction (Kyles *et al.* 1995). Further research is necessary before $GABA_A$ agonists can be recommended as analgesics.

Balanced (multimodal) analgesia

A more efficient way of managing pain may be to combine smaller doses of analgesics, which may potentiate each other's analgesia while producing a wider range of smaller side effects. For instance, the anticholinesterase neostigmine increased clonidine-induced analgesia (Detweiler *et al.* 1993; Xu *et al.* 1996) and counteracted the bradycardia and hypotension of clonidine (Hood *et al.* 1995). Similarly, we found that the combination of ketamine and ketoprofen I/T prevented the development of I/T NMDA-induced mechanical hypersensitivity, but the combination was not more effective than either drug alone (Lizarraga *et al.* 2008). Additive analgesia has been described for the combination of fentanyl plus medetomidine, and analgesia was increased for a non-analgesic dose of ketamine when combined with an analgesic dose of xylazine (Chambers 1992). However, xylazine plus ketamine given immediately before, and 2 h after, laparotomy and hysterotomy in pregnant sheep produced no analgesia as assessed behaviourally (Hughan *et al.* 2001).

Subanalgesic doses of fentanyl and the dopaminergic D_2 receptor antagonist droperidol or zuclopenthixol induced analgesia for ~35 minutes. Dysphoric effects were observed with the combination fentanyl plus droperidol that were prevented, without affecting analgesia, by giving an I/T subanalgesic dose of droperidol followed by I/V fentanyl (Kyles *et al.* 1993a). Further research to find combinations that could be used clinically to induce better analgesia with lesser side effects is necessary.

Conclusions

Analgesics are underutilised in sheep. They should be administered when performing any surgery and if the animal is identified as or believed to be suffering from any form of pain. Pain is a welfare issue and the moral obligation of those who are responsible for the wellbeing of that animal is to prevent and/or alleviate its pain. Farmer support and the prevention of painful conditions are essential to achieve this on a larger scale. A broad knowledge of pain assessment and management, the farming system, operative technique, and the training of personnel performing those techniques may help practitioners to propose reasonable, practical and profitable measures crucial to long-term improvement in the prevention and treatment of pain in farmed sheep (Clements *et al.* 2002). It is important to remember that, apart from removing the aversive experience of pain, effective analgesia can reduce subsequent morbidity and mortality (Rutherford 2002). In general, analgesics are less effective once a painful condition is established and should be administered before the pain starts. Moreover, most conditions associated with chronic pain, such as footrot, are preventable, either by good husbandry or vaccination. This is preferable to the subsequent use of analgesic drugs and incomplete pain control if the disease develops.

The main groups of drugs are opioids, α_2-agonists, NSAID and local anaesthetics, with some other adjunctive drugs. Opioid agonists, although the standard analgesics in other species, are of dubious efficacy in sheep and are short acting. α_2-agonists are good, short-lived analgesics, but sheep are very sensitive to their hypoxaemic effects. These can be mitigated by providing supplementary oxygen. NSAID provide longer-lasting analgesia than opioids and α_2-agonists, but analgesia is not as marked as that from α_2-agonists. Lignocaine and bupivacaine are the most widely used local anaesthetics and reliably block pain signals, but may also induce motor blockade. It should be noted that there are no approved analgesic drugs for use in sheep and therefore the use of such drugs in this species has to be off-label.

Individual differences mean that a standard dose of drug will be too much for some animals and too little for others. Under-treated animals will still suffer pain, and over-treatment may cause toxicity. We believe is better to use the smallest effective analgesic dose for a particular animal and type of pain. It may be necessary to increase the dose to improve pain management though the potential of inducing side effects with large doses is also increased. A strategy to overcome this is to administer small doses of analgesics by alternative routes e.g. epidural, I/T, or modalities e.g. I/V infusion, and/or combine lower doses of two analgesics to induce better analgesia with fewer side effects. Some options have been studied experimentally in sheep, but further research is necessary to provide practitioners alternatives that could be applied clinically, in particular in the field of multimodal analgesia.

Our recommendations for typical situations are as follows. For strong analgesia under general anaesthesia for major surgery, low-dose (0.5–1 mg/kg I/V) ketamine plus low-dose (2–5 μg/kg I/V) medetomidine given as necessary, followed by NSAID (e.g. ketoprofen 3 mg/kg I/V or I/M) postoperatively. For minor surgery in the perineal area, epidural α_2-agonists, e.g. xylazine. For other surgery, local block using a 50% mixture of lignocaine and bupivacaine. For pain associated with inflammation, NSAID.

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