Use of non-steroidal anti-inflammatory drugs at calving

Abstract

In recent years farmers, veterinary surgeons, and consumers have all shown increasing awareness of pain in cattle (and its associated negative welfare impacts), and accordingly there is increased focus on the use of analgesia following painful procedures such as disbudding and castration. Calving is a necessary event for cows and their calves, and is painful; however, pain-relief is not routinely provided, particularly to calves. This article reviews the literature regarding non-steroidal anti-inflammatory drug usage around calving to aid practitioners in making evidence-based decisions regarding management of calving-related pain in cows and calves.

Key words

Calving; cow; calf; analgesia; NSAID; welfare

Key points

- Analgesia is under-used around calving, particularly for treatment of calves.
- There is increasing evidence that calving is painful for both cow and calf. Available data strongly suggest that NSAID pain-relief leads to improved welfare of both cows and calves in the postpartum period.
- Postpartum treatment of cows with NSAIDs has the potential to result in productivity gains, which may incentivise use.
- Evidence for adverse effects is limited and appears to be NSAID specific.
- Administration of NSAIDs at calving is recommended for veterinary practitioners and farmers seeking to optimise the care of parturient cattle and newborn calves.

Introduction

Calving is a necessary event for productive cows; assisted parturition is common and is most frequently performed by farmers (Egan *et al.*, 2001). Whilst difficult calving is believed to be painful and stressful for cows and their calves, data to support this view are limited. Previous studies have found that veterinary surgeons and farmers often administer analgesia to cows, and less commonly calves, following assisted parturition (Laven *et al.*, 2009; Moggy *et al.*, 2017; Remnant *et al.*, 2017). However, results of existing studies investigating analgesia administration after calving are conflicting and very few studies report analgesia effects in newborn calves. As such, whilst it is well described that cattle experiencing painful conditions, or following surgery, benefit from provision of analgesia (Coetzee, 2013; Herskin *et al.*, 2018), the benefits of analgesic usage at calving are less clear. This article aims to review the literature regarding analgesia usage around calving to aid practitioners in making evidence-based decisions regarding management of calving-related pain in cows and calves. For a more general overview of bovine analgesia, readers are referred to relevant reviews in this journal and elsewhere (e.g. Orr *et al.*, 2014; Laven, 2020; Reader *et al.,* 2020; Steagall *et al.*, 2021).

Calving and pain

Calving is a complex process with three recognised stages [Figures 1 and 2], each associated with different sources of pain. Pain is a subjective experience defined by the International Association for the Study of Pain as "*an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*" (Loeser *et al.*, 2008). In human medicine childbirth is recognised to be very painful, and it is known that women experience postpartum pain related to normal uterine involution (Deussen *et al.*, 2020). By contrast, calving pain is poorly

Stage 1: Myometrial contraction, together with relaxation and dilation of the cervix, results in positioning of the foetus ready for expulsion, visceral pain predominates (Mainau *et al.*, 2011). This stage often presents as restlessness or isolation-seeking in cattle and may last for several hours (Mee, 2004; Proudfoot *et al.*, 2014).

Stage 2: Abdominal contractions are observed and the amniotic sac ruptures, followed by expulsion of the foetus. Somatic pain predominates during this stage and completion is typically achieved within two hours, although this may be longer (Mainau *et al.*, 2011; Kovács *et al.*, 2016). Animals are typically in stage 2 when veterinary assistance is sought.

Stage 3: Following expulsion of the foetus myometrial contractions reduce in intensity and frequency and placental membranes are expelled (Mainau *et al.*, 2011). Stage 3 is usually completed within 6 hours but retention of foetal membranes is not typically considered abnormal until 24 h have elapsed (Sheldon *et al.*, 2008).

Figure 1: The three stages of parturition

Figure 2: Cow and calf following successful completion of stage 2 parturition. Image: K. Ellis, reproduced with permission.

researched in cattle and it is unclear if cattle also experience postpartum pain in normal circumstances, or only following calving injury; although recent research suggests that discomfort following calving is experienced by all cattle, regardless of calving experience (Gladden *et al.*, 2021). Moreover, pain experienced by calves during (or immediately after) birth is rarely studied (Laven *et al.*, 2012). Interestingly, veterinary surgeons typically consider neonatal calves to experience less pain than adult cattle, even following dystocia (Huxley *et al.*, 2007; Laven *et al.*, 2009; Remnant *et al.*, 2017), and accordingly analgesic use following painful procedures is more common in adult cattle than calves (Andrighetto Canozzi *et al.*, 2020); however, data to support this belief are absent. Moreover, newborn babies have been found to experience pain similarly to adults (Goksan *et al.*, 2015), and substantial forces are applied to calves during assisted birth (Pearson *et al.*, 2020); therefore, it is likely that newborn calves experience pain at birth (in particular if assisted), and this needs to be considered by practitioners.

Bovine analgesia

Bovine pain has been subject to increased interest in recent decades, and it is now well-recognised by farmers and veterinary surgeons that cattle experience pain (Whay *et al.*, 2005; Huxley *et al.*, 2007; Laven *et al.*, 2009; Thomsen *et al.*, 2012; Remnant *et al.*, 2017). The most commonly used analgesic drugs used in cattle practice are non-steroidal anti-inflammatory drugs (NSAIDs); only this category of analgesic drugs have been investigated in the peri-partum period, therefore this article focuses on this type of analgesia. As well as providing analgesia, NSAIDs have anti-inflammatory and antipyretic properties, and share a common mechanism of action: cyclo-oxygenase (COX) enzyme inhibition, resulting in prostaglandin and thromboxane inhibition (Smith *et al.*, 1971; Vane, 1971). Detailed discussion of NSAIDs is outwith the scope of this article but can be found elsewhere (e.g. Laven, 2020), and a selection of products licensed for use in cattle in the UK are summarised in Table 1.

Table 1: NSAIDs available for use in UK cattle practice[1]

NSAID	Commercial products	Licensed route	Dose rate	Withdrawal period	
				Milk	Meat
Carprofen	Carprieve (Norbrook) Rimadyl (Zoetis)	IV, SC	1.4 mg/kg (1 ml/35 kg)	0 h	21 d
Flunixin[2]	Allevinix (Ceva)	IV, IM	2mg/kg (2ml/50kg)	24 h (IV)/ 36 h (IM)	10 d (IV)/ 31 d (IM)
	Cronyxin (Bimeda)	IV	2.2mg/kg (2ml/45kg)	12 h	8 d
	Finadyne transdermal (MSD)	Transdermal (pour-on)	3.33mg/kg (1ml/15kg)	36 h	7 d
	Finadyne (MSD)	IV	2.2mg/kg (2ml/45kg)	24 h	5 d
	Pyroflam (Norbrook)	IV	2.2mg/kg (2ml/45kg)	24 h	10 d
Ketoprofen[2]	Dinalgen (Elanco)	IV, IM	3mg/kg (1ml/50kg)	0 h	2 d
	Ketofen (Ceva) Ketodolor (Virbac)	IV, IM	3mg/kg (3ml/100kg)	0 h	1 d (IV)/ 4 d (IM)
	Nefotek (Bimeda) Rifen (Chanelle Pharma)	IV, IM	3mg/kg (3ml/100kg)	0 h	4 d
Meloxicam[2]	Inflacam (Virbac) Loxicom (Norbrook) Meloxidyl (Ceva)	IV, SC	0.5mg/kg (2.5ml/100kg)	5 d	15 d
	Metacam 20mg/ml (Boehringer Ingelheim) Rheumocam (Chanelle Pharma)			120 h	15 d
	Metacam 40mg/ml (Boehringer Ingelheim)	IV, SC	0.5mg/kg (1.25ml/100kg)	120 h	15 d
	Meloxidolor (Dechra)	IV, SC	0.5mg/kg (2.5ml/100kg)	Not available	15 d
Sodium salicylate	Solacyl (Dechra)	PO (in milk or water)	40mg/kg	Not licensed for use in lactating cows	0 d

IV = intravenous. IM = intramuscular. SC = subcutaneous. PO = *per os*.

Information correct at the time of writing – the authors accept no responsibility regarding the use of these products. Readers are recommended to refer to relevant product datasheets.

1. List is restricted to products appearing in the NOAH compendium (National Office of Animal Health, 2022) and is not exhaustive.
2. Available antibiotic/NSAID combination products are not included

Health and productivity effects of NSAID administration at calving

Although an inflammatory response is a normal finding in postpartum cattle, this response is greater in cattle that subsequently go on to develop postpartum disease (Humblet *et al.*, 2006; Qu *et al.*, 2014). Accordingly, there has been interest in the potential for NSAIDs to reduce the risk of postpartum disease. Findings at a biochemical level have been promising with postpartum NSAID administration being associated with reduced serum haptoglobin and β-hydroxybutyrate concentration (Barragan *et al.*, 2020b; Pascottini *et al.*, 2020), but a consistent improvement in clinical disease outcomes has not been shown. Use of different NSAIDs in various studies may be one factor contributing to the inconsistent findings reported. For example, Barragan *et al.* (2021) administered two doses of acetylsalicylic acid (Aspirin) to cows 12 and 24 hours after calving and found that NSAID treated cows had a lower risk of developing metritis, but this finding was not supported by the results of Richards *et al.* (2009), who found no effect of ketoprofen on postpartum disease status.

There has been concern over the possible negative effects of NSAID administration around calving, with particular focus on the increased risk of retained foetal membranes (RFM). As prostaglandins are important in the postpartum period for placental expulsion, these concerns are not unfounded. Different NSAIDs appear to have variable effects on placental retention. More than twenty years ago a study associated flunixin administration with increased RFM risk following caesarean-section (Waelchli *et al.*, 1999), but did not include animals that calved *per vaginum*. More recently, this finding has been supported by a study of unassisted calvings that found flunixin administration was associated with not just an increased risk of RFM, but also an increased risk of stillbirth (Newby *et al.*, 2017). However an absence of negative effects of other NSAIDs has been reported, with studies investigating effects of ketoprofen, meloxicam and acetylsalicylic acid all finding no difference between NSAID-treated and untreated or placebo-treated animals (Richards *et al.*, 2009; Swartz *et al.*, 2018; Barragan *et al.*, 2021).

Results of studies investigating the effects of NSAID administration (at calving) on subsequent productivity are mixed; however, the different NSAIDs used, and different measures of milk production analysed, makes comparisons between studies difficult. Most studies analysing the effects of meloxicam, carprofen, flunixin and ketoprofen have found that milk production is not affected by NSAID administration (Richards *et al.*, 2009; Shwartz *et al.*, 2009; Newby *et al.*, 2013; Mainau *et al.*, 2014; Meier *et al.*, 2014); however, these studies are restricted to short-term measures. Studies analysing longer-term measures of milk production (such as 305-d yield) are fewer, but provide more promising results — suggesting NSAID treatment may be associated with improvements in milk production (Farney *et al.*, 2013; Stilwell *et al.*, 2014) — a finding supported by our recent work (Gladden, 2021). Milk production is affected by many factors and some studies have found that NSAID administration interacts with other factors affecting milk yield. For example, Farney *et al.* (2013) found that sodium salicylate treatment at calving was associated with increased 305-d yield of cows in the 3rd lactation and over, but not younger cows. By contrast, Stilwell *et al.* (2014) found that milk yield at 305 days in milk (DIM) was increased in heifers treated with carprofen (compared to untreated heifers), but milk yield of carprofen-treated multiparous cows at 305 DIM was no different to untreated cows.

Persistent postpartum inflammation is associated with delayed ovarian resumption (Cheong *et al.*, 2017), therefore it is possible that NSAID treatment at calving may be associated with improved reproductive performance in the subsequent lactation. Few studies have analysed the effects of NSAID treatment at calving on subsequent lactation performance; however, the limited available data are promising. Acetylsalicylic acid treatment has been associated with improved reproductive performance, with treated cows conceiving sooner and needing fewer insemination attempts to conceive than placebo-treated cows (Barragan *et al.*, 2020a, 2021). Acetylsalicylic acid is not licensed for use in adult cattle in the UK, but the results of our study suggest that ketoprofen treatment has a similar beneficial effect (Gladden, 2021).

Welfare effects of NSAID administration at calving

The limited number of studies on NSAID treatment at calving suggest welfare is improved if NSAIDs are administered. For example, we recently observed that ketoprofen-treated cattle engaged in lying postures consistent with improved comfort more than placebo-treated cattle (Gladden *et al.*, 2021). Additionally, previous studies have found NSAID-treated cows are more active, and engage in feeding directed behaviours more frequently, than untreated or placebo-treated cows (Newby *et al.*, 2013; Mainau *et al.*, 2014; Stilwell *et al.*, 2014; Barragan *et al.*, 2020a). Furthermore, a recent study has found that, although NSAID treatment was provided 24 h after calving, behavioural signs of postpartum pain (such as back-arching and tail lifting) of NSAID-treated cows were reduced compared to placebo-treated cows (Schmitt *et al.*, 2022). Collectively, these results strongly suggest NSAID administration at, or soon after, calving has a positive impact on postpartum welfare of cattle, and routine use should be considered by farmers and veterinary surgeons seeking to optimise postpartum welfare.

Difficult calving

It is often thought that dystocia is more painful than unassisted calving, but data to support this view are limited. A factorial study design including analgesia-treated and placebo-treated animals, as well as animals affected by a painful experience and unaffected control animals, in a 2 x 2 design [Figure 3], is considered optimal for assessment of animal pain (Weary *et al.*, 2006). This type of study design allows determination of whether an observed difference in measured outcomes is a) related to the painful experience and b) ameliorated by analgesia (suggesting that pain is the source of the change in outcome). However, this type of study design is rarely used in studies of postpartum pain in cattle, with only three studies (reported across five publications) employing a factorial design (Gladden *et al.*, 2018, 2021; Swartz *et al.*, 2018; Barragan *et al.*, 2020a, 2020b). We did not identify any effects of the interaction between calving assistance and NSAID treatment on biomarkers of stress and inflammation or postpartum behaviour (Gladden *et al.*, 2018, 2021), although an

interaction effect on some measures of productivity were identified (Gladden *et al.* unpublished data). Swartz *et al.* (2018) found that the daily milk yield of cows experiencing eutocia (unconventionally defined as calving lasting ≤ 70 min) that were treated with a NSAID before calving was nearly 7 kg/d higher than cows in other calving type x NSAID treatment groups. By contrast, Barragan *et al.* (2020a) measured daily milk yield for 30 d postpartum and found that milk yield on some days was higher for NSAID-treated cows in the dystocia group but there was no treatment effect on unassisted cows. Similar to our study (Gladden *et al.*, 2018), Barragan *et al.* (2020b) did not identify any assistance x treatment interaction effects on biomarkers of stress, inflammation, or nociception. As such, it is unclear whether assisted cows (or cows experiencing dystocia) experience different effects of NSAID administration to unassisted cows, and further work is needed.

		Condition group	
		Painful condition present (*P*)	Painful condition absent (*p*)
Treatment group	Analgesia treatment (*A*)	*PA*	*pA*
	Placebo treatment (*a*)	*Pa*	*pa*

Figure 3: Illustration of a 2 x 2 factorial study design (Modified from: Weary et al., 2006)
PA, Pa, pA, pa each represent the pain x analgesia interaction group determined by the presence/absence of a painful condition (e.g. dystocia) and the (randomly) allocated treatment group

Administration of NSAIDs to newborn calves

Few studies have investigated the effects of post-birth analgesic treatment of newborn calves; however, the available data suggest that NSAIDs show promise as an additional tool for improving calf health and welfare. Post-birth meloxicam treatment has been associated with increased vigour (Murray *et al.*, 2016), improved feed consumption (Murray *et al.*, 2016; Clark *et al.*, 2020), and improved early-life growth rate (Pearson *et al.*, 2019). Similarly, ketoprofen administration immediately after birth was associated with increased engagement in behaviours consistent with improved welfare (Gladden *et al.*, 2019).

The use of NSAIDs in newborn calves is off-licence for all products available in the UK and consideration needs to be paid to potential risks of use in such young animals. The effects of NSAIDs on renal development of young calves has not been studied; however, although COX-2 selective inhibitors have been found to affect renal development of mouse pups, COX-1 inhibitors have not been found to have the same effect (Kömhoff *et al.*, 2000). At birth, bovine renal function is thought to be similar to that of adults (Dalton, 1968), which may reduce the nephrotoxic associated risks posed by NSAIDs. This hypothesis is supported by Pearson *et al.* (2019), who did not find any differences in renal and hepatic parameters of meloxicam and placebo-treated calves. Additionally, in our work we did not identify any clinically adverse effects of ketoprofen administration to newborn calves compared to a saline treatment (Gladden, 2021). Nevertheless, cattle practitioners should adopt a risk-based approach when administering NSAIDs to young, potentially compromised calves after a dystocia event as, although no studies report adverse effects, all studies only include clinically healthy calves.

Conclusion

This article provides an overview of the currently available evidence for administration of NSAIDs to parturient cows and newborn calves. Although results of different studies are sometimes conflicting, when assessed collectively the data generally support NSAID treatment of cows at calving — particularly from a welfare perspective, where the evidence supporting use is most consistent. Furthermore, there is evidence that newborn calf welfare is also improved by NSAID administration.

Non-steroidal anti-inflammatory drugs are widely available to bovine practitioners in the UK and are a cost-effective tool with the capacity to aid improvements in the welfare of postpartum cattle. Additionally, there is the potential for productivity gains to be made, which may incentivise use. The wide availability, overall beneficial impact, and limited adverse effects reported, mean that administration of NSAIDs at calving (with the exception of flunixin) can be recommended to

1 veterinary practitioners and farmers seeking to optimise the care of parturient cattle and newborn

2 calves.

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