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Review

Using non-steroidal anti-inflammatory drugs around calving: Maximizing comfort, productivity and fertility

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic, anti-inflammatory, anti-endotoxic and anti-pyretic effects in cattle. As such, they could be expected to have significant effects in cows and calves in the post-calving period. This review evaluates the published data on the use of NSAIDs in the dam and its calf after dystocia, the impact of NSAIDs on uterine involution, the restoration of ovarian function and prevention and treatment of the metritis complex, and the benefits of using NSAIDs in the recumbent cow.

Overall, the published data are very limited, despite frequent use of NSAIDs by veterinarians in the post-calving cow, and the small number of published studies focus on blanket treatment of calving cows rather than targeted treatment after dystocia. Blanket treatment had no economic benefit; indeed, some studies reported adverse effects, such as pyrexia and increased risk of metritis. There is even less information on the value of treating calves with NSAIDs after dystocia, despite significant tissue damage which may benefit from NSAID use.

Appreciably more studies have evaluated the influence of NSAIDs on uterine and ovarian function, but clinical relevance is limited. In cows with a normal puerperium, prolonged treatment with NSAIDs may slow the restoration of normal function, but most reported studies are small and use NSAIDs more frequently and for longer periods than is common in general practice. The evidence of a clinical benefit in cows with puerperal disease is limited and equivocal, and the evidence base for the use of NSAIDs in the treatment of recumbent cows is also small, even though an expert panel concluded that NSAIDs were a key aspect of veterinary treatment of downer cows. The lack of evidence identified by this review supports the contention that NSAIDs are likely to be under-used and sub-optimally prescribed in the post calving period. Further research on the use of NSAIDs in the post-calving cow and calf is required.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are weak organic acids with a wide range of structures that act by inhibiting the enzyme cyclooxygenase (COX) so decreasing the release of prostaglandins (Vane, 1971; Espinasse et al., 1994). Two main forms of COX have been reported: COX1, mainly constitutive, and COX2, primarily an inducible enzyme (Xie et al., 1991). The prostaglandins that mediate inflammation, fever and pain are mainly produced by COX2, while those produced by COX1 are used to maintain gut and kidney function. Thus, inhibition of COX2 accounts for most of the therapeutic effects of NSAIDs, such as peripheral and central analgesia, anti-inflammatory effect, anti-pyretic effect and anti-endotoxic effect, while inhibition of COX1 causes side-effects such as nephropathy and ulceration of the gastro-intestinal mucosa (Fitzpatrick et al., 2004). However, this distinction is not as clear as was once thought (for reviews, see Clark, 2006). Most commercially available NSAIDs available for animals inhibit both enzymes with varying selectivity, depending on the test systems used and whether the assays are carried out in vitro, ex vivo or in vivo (Mitchell et al., 1993; Fitzpatrick et al., 2004).

Although NSAIDs are generally well absorbed (whichever route of administration is chosen), in cattle NSAIDs are nearly always given parenterally (Fitzpatrick et al., 2004). Basic, cattle-specific pharmacokinetic data are available for all NSAIDs approved for cattle treatment in Australasia and Europe. However, the relationship between pharmacokinetics and activity is complex. Firstly, the effective concentrations required for different therapeutic effects such as analgesia and anti-endotoxic activity can be very different. For example, a single dose of 0.5 mg/kg meloxicam was shown to have anti-endotoxic activity 57 h later (Königsson et al., 2002a), but the same dose was required to be given daily to provide analgesia after resection of the distal interphalangeal joint (Rehage et al., 2011). Additionally, NSAIDs are all highly protein bound in

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plasma, more than 99% in some cases (Galbraith and McKellar, 1996). This can limit the passage of drug from plasma into the interstitial fluid, but it also means that NSAIDs are trapped in inflamed tissues and can have a longer action than their plasma pharmacokinetics would suggest (Landoni et al., 1996).

Treatment after dystocia

Calving is a critical time for the health and welfare of the cow. A normal calving is a prerequisite for good fertility in the subsequent breeding period and for achieving the genetic potential for milk yield. Dystocia, i.e. calving difficulty resulting from prolonged spontaneous calving or prolonged or severe assisted extraction (Mee, 2008), decreases calf viability, milk production, and fertility and increases the risk of culling (Tenhagen et al., 2007). Much of the impact of dystocia on fertility and production occurs because of the increased risk of inflammatory disease such as metritis and endometritis, often as a consequence of retention of the fetal membranes (Laven and Peters, 1996; Borsberry, 1999; Benzaquen et al., 2007).

Dystocia is also painful. In a survey of 166 dairy cattle veterinarians from New Zealand, where respondents were asked to estimate on a 0–10 scale with 0 as no pain and 10 as the worst pain imaginable, the pain of dystocia due to feto-maternal disproportion requiring traction alone had a median score of 8, while that for a caesarean section was 10 (Laven et al., 2009), a similar survey from the UK reported median scores of 7 and 10, respectively (Huxley and Whay, 2006).

The alleviation of pain and inflammation is the primary goal of therapy with NSAIDs. The use of NSAIDs in cows with dystocia would therefore seem appropriate and this is reflected in their use by veterinarians. Huxley and Whay (2006) reported that 66% of dairy cattle veterinarians in the UK used NSAIDs in cows with dystocia at least occasionally and 68% in cows given a caesarean; in New Zealand the equivalent figures were 72% and 83%, respectively (R.A. Laven unpublished observations). However, on most farms, the majority of dystocia cases are dealt with by farm staff, so the relatively high use by veterinarians may have little bearing on the actual numbers of animals treated. Huxley and Whay (2007) surveyed 1029 farmers, and reported that only 448 (49.6%) thought that analgesia was necessary for moderate dystocia, while 66% of farmers were not willing to pay more than £10[1] for such analgesia. This suggests that many (probably most) cases of dystocia do not receive NSAIDs.

However, despite their relatively common use by veterinarians, there have been no published studies specifically focusing on the potential short-term benefits of treating dystocia with NSAIDs, such as the impact of treatment on feed intake or cow behaviour. Most studies which have evaluated the benefits of treating cows with NSAIDs post-calving have either concentrated on the impact of treatment on placental retention or future fertility or have analysed the benefits of treating all calving cows rather than evaluating the benefits of treating dystocia. An example of the latter is Shwartz et al. (2009) who evaluated the benefit of treating cows with flunixin after calving based on the hypothesis that the uterine tissue trauma and subsequent inflammation resulting from normal parturition could be alleviated by treatment with NSAIDs. They randomly allocated 26 cows to either 3 days of flunixin (at 2.2 mg/kg bodyweight [BW]) or to saline control. Treatment was given within 5 h of calving and then daily for the next 2 days. They recorded a wide range of parameters including individual daily milk yields and feed intakes for the first 35 days, twice daily rectal temperature for the first 7 days and multiple samples for NEFA, urea and glucose concentrations. None of the cows were recorded as having dystocia. Shwartz et al. (2009) reported that treatment with flunixin significantly increased rectal temperature; on Days 3 and 4 flunixin-treated cows had a mean temperature of 39.2 °C which was >0.5 °C higher than the mean temperature of the untreated cows. Additionally, 9/13 flunixin treated cows became pyrexic (>39.5 °C) in the first 7 days post partum, whereas only four of the control group did ($P = 0.08$). The only other significant effects they found were that flunixin treatment decreased dry matter intake (DMI) and plasma urea concentration. They concluded that, overall, flunixin treatment had no significant benefit. However the cows in this study were apparently normal cows with no clinical indication that they required NSAID treatment, so extrapolation to cows with dystocia is not appropriate.

Another similar study was undertaken by Duffield et al. (2009), where heifers and cows were randomly allocated to treatment with flunixin (1.25 g intramuscularly [IM] for cows and 1.1 g for heifers) or a negative control. Treatment was given approximately 2 h following calving with a repeat injection approximately 24 h later. No significant effect of treatment was found on the risk of subsequent hypocalcaemia, displaced abomasum, clinical ketosis, or mastitis, or on milk yield. However, cows treated with flunixin were more likely to retain their fetal membranes and had a higher risk of developing metritis. Based on these results, Duffield et al. (2009) concluded that NSAID therapy on the day of calving should not be recommended. This was a large scale study with over 1200 cows enrolled, but as no data were presented on dystocia rates, this conclusion should not be extrapolated to cows with dystocia.

A large scale study which did include data on cows with dystocia was undertaken by Richards et al. (2009) who evaluated the benefit of treatment with ketoprofen after calving on milk yield and fertility. Cows were not allocated to treatment on a random basis; instead allocation was based on their official ear tag; even numbers were treated by farm staff with 3 mg/kg BW of ketoprofen 'as soon as possible after calving' and 24 h later. Two-hundred and twenty cows were allocated to ketoprofen treatment with 227 cows acting as controls. Farmer records were kept on ease of calving (cows requiring caesareans were excluded from analysis), sex and number of calves, vaginal tears, retention of the fetal membranes (RFM) for >24 h and hypocalcaemia. Each animal was assessed at a pre-breeding exam (21–31 days post-partum) for endometritis (manual vaginal examination) and ovarian structures (transrectal ultrasound). Individual milk yield records were obtained from the first recording of lactation for each cow (average 22 days post partum), and breeding records were used to calculate fertility parameters. Richards et al. (2009) concluded that ketoprofen treatment tended to reduce the risk of RFM ($P = 0.075$), but had no effect on any of the other peripartal diseases, milk production or any of the fertility parameters they evaluated, such as proportion of cows with a corpus luteum at the pre-breeding check, pregnancy rate to first insemination and calving to conception interval. However, the lack of equality between the two groups means that these results are not as robust as they could be.

Of the 447 cows in the study, 160 (93/220 in the ketoprofen group) required at least some calving assistance, with 98 (60) requiring the use of a calving aid. Although the authors claimed that similar proportions of both groups required assistance, the proportion of cows in the ketoprofen group with dystocia was significantly higher than in the control group (93/220 (42%) vs. 57/227 (25%); $P < 0.01$). This may be related to the higher proportion of first lactation heifers in the ketoprofen treated group than the control group (35 vs. 26%; $P = 0.04$) (Mee et al., 2011).

It is not clear how much the difference in dystocia was taken into account in the analysis by Richards et al. (2009), but as dystocia tends to increase the risk of peripartal disease, the higher rate of dystocia would tend to bias against identifying a benefit of keto-

[1] £1 = approx. US$1.60, €1.14, as at 27 October 2011.