Brief Communication Communication brève

Evaluation of the effects of treating dairy cows with meloxicam at calving on retained fetal membranes risk

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Abstract — Some non-steroidal anti-inflammatory drugs increase the risk of retained fetal membranes. This is the first study to investigate the effects of meloxicam on the risk of retained fetal membranes. Administration of meloxicam to dairy cattle immediately following calving revealed no differences in the incidence of retained fetal membranes between meloxicam-treated and untreated animals. There was no difference between the 2 groups in the incidence of periparturient diseases following calving. Meloxicam can be used on the day of calving in lactating cows without increasing the risk of retained fetal membranes.

Résumé — L'évaluation des effets d'une injection de méloxicam immédiatement après le vêlage chez la vache laitière sur le risque de rétention des membranes foetales. Certains médicaments inflammatoires non-stéroïdiens augmentent le risque de rétention de membranes fœtales. Cette étude est la première à examiner les effets du méloxicam quant au risque de rétention de membranes fœtales. Aucune différence n'a été notée dans le cas de rétention de membranes fœtales lors du vêlage chez la vache laitière entre les vaches qui ont reçu une injection de méloxicam immédiatement après le vêlage et celles qui n'ont rien reçu. De plus, il n'y avait aucune différence d'incidence de maladies périnatales observées suite au vêlage entre les deux groupes. On peut donc administrer du méloxicam aux vaches laitières le jour du vêlage sans augmenter le risque de rétention de membranes fœtales.

(Traduit par les auteurs)

Can Vet J 2014;55:1196–1199

Considering that mammalian neural elements and biological consequences of pain are essentially the same, it follows that cows feel parturition pain in a similar manner to humans; calving leads to inflammation which causes pain. There is limited work on the effects of analgesia in dairy cows at calving and only a few studies have measured the safety of administering the commonly used analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), at calving. A recent review suggested that further research on the use of NSAIDs in the post-calving cow is required, given that NSAIDs are likely to be under-used and sub-optimally prescribed during this period (1). Available NSAIDs that may be used for that purpose are aspirin, ketoprofen, flunixin meglumine, and meloxicam. Ketoprofen is predominantly a COX-1 inhibitor in dogs and humans (2,3), with a plasma half-life of 2 h after an intramuscular dose of 3 mg/kg body weight (BW) in cattle (1). Flunixin meglumine inhibits both cyclooxygenase isoforms COX-1 and COX-2, but is more selective for COX-1 in horses (4), and has a terminal half-life from 3.14 to 8.12 h after intravenous administration in cattle (5). Meloxicam has a preferential anti-COX-2 activity in horses, rats, humans, dogs, and cats (4,6), but its affinity has not been determined in cattle, in which it has a mean plasma half-life of approximately 26 h (7). COX-2 inhibition is thought to account for most of the therapeutic effects of NSAIDs, while the inhibition of COX-1 likely accounts for most of the undesirable side-effects of NSAIDs such as gastrointestinal irritation, renal toxicity, and inhibition of blood clotting (8). COX-2 has been shown to be involved in contractility during parturition and COX-2 inhibitors would have a negative impact on the contractility (9).

There have been a number of contradicting studies of the impact of NSAIDs in fresh dairy cows. The main findings from studies that evaluated the effects of flunixin meglumine immediately following calving were that there was a significant increase in the odds of having retained fetal membranes (10,11) and increased odds of being diagnosed with metritis after 14 d postpartum (10). Prostaglandin administration should be considered as a routine prophylactic for fetal membrane expulsion following caesarian surgery in animals with a placenta firmly attached to the uterus pre-surgery (11). Ketoprofen administered immediately after calving and 24 h later resulted in a tendency for fewer cases of retained fetal membranes and had no impact on other

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This study was financially supported by Boehringer Ingelheim (Canada) Ltd.

Table 1. Summary of parturient and postparturient events in 462 Holstein cattle that were either untreated (cow $n = 53$, 1st lactation heifer $n = 174$, total $n = 227$) or received 0.5 mg/kg BW meloxicam (cow $n = 46$, 1st lactation heifer $n = 189$, total $n = 235$) within the hour following calving up to 24 h recorded by the farm worker or veterinarian

Event	Meloxicam number of events for male calves	Meloxicam number of events for female calves	Meloxicam incidence of events total	Control number of events for male calves	Control number of events for female calves	Control incidence of events total	Chi-square *P*-value*
Calf gender	113	118	48.1%	102	113	44.9%	0.79
Missing gender information	4			12			
Calving difficulty:							
Missing calving score	6	2		1	2		
Missing calving score and gender information	4			11			
Unassisted	19	36	23.4%	15	25	17.6%	0.23
Easy	71	71	60.4%	71	78	65.6%	
Hard	16	8	10.2%	16	8	10.6%	
Surgery	1	1	0.85%	0	0	0	
Stillborn calves	8	15	11.5%	13	5	11.9%	0.86
Stillborn calves — missing gender information	4			9			
Twins	1	1	0.85%	1	0	0.44%	1.00
Retained fetal membranes	13	8	8.9%	14	8	10.6%	0.55
Retained fetal membranes — missing gender information	0			2			
Metritis	2	6	3.4%	5	3	4.4%	0.58
Metritis — missing gender information	0			2			
Mastitis	8	17	10.6%	14	15	13.2%	0.39
Mastitis — missing gender information	0			1			
Displaced abomasums	1	2	1.3%	3	2	2.2%	0.49

*Note: Fisher's exact test used where < 5 per any cell existed.

measures of uterine or reproductive health (12). However, this result may have been inadvertently confounded by more first parity animals being treated with ketoprofen (35% treated *versus* 26% non-treated) (12), with a possible lower risk of retained fetal membranes in first parity animals (13). Meloxicam administered within 12 h following calving in both heifers and cows resulted in no difference in milk yield, but in greater activity in heifers treated with meloxicam compared to heifers treated with the placebo; however, postparturient health events such as retained placenta were not reported (14).

While it is likely that there may be positive benefits of treating dairy cows post-calving with NSAIDs (especially cows that experience a dystocia), 2 important questions are the timing of administration post-calving and which NSAID is more appropriate. There have been reported health issues with administering flunixin meglumine on the day of calving (10,11), and no increased health risk to administering ketoprofen on the day of calving (12). This implies that there are no common effects for all NSAIDs on retained placenta following calving. The goal of this study was to evaluate the effects of meloxicam, a COX-2-selective NSAID, on the health of early lactation dairy cows when it was administered as soon as possible following calving. The hypothesis was that meloxicam treatment soon after calving would have no detrimental effect on the incidence of retained fetal membranes.

The present trial was conducted on a large commercial Ontario dairy farm that has a freestall barn with sand bedding, milking on average 900 animals (78% first lactation animals, 18% second lactation animals, and 4% 3rd lactation or greater) and calving over 3000 animals/y. The major part of the business is selling milking cows. Enrollment of Holstein cattle occurred from June to Oct 2011, and was approved by the Animal Care Committee, University of Guelph (AUP# 11R044). Animals were randomly assigned to receive either a single 0.5 mg/kg BW dose of meloxicam (Metacam 20 mg/mL solution for injection; Boehringer Ingelheim, Burlington, Ontario) subcutaneously (cow $n = 46$, 1st lactation heifer $n = 189$, total $n = 235$) or no treatment (cow $n = 53$, 1st lactation heifer $n = 174$, total $n = 227$) within 1 h following calving. Random number tables using repeating and balanced blocks of 30 animals were constructed using computer generated numbers. As cows calved they were assigned the next treatment indicated in the random number table. Treatment administration was conducted by maternity barn staff and recorded in the calving binder. The calf gender, the occurrence of twins, as well as calving difficulty (unassisted = cow calved on her own with no assistance; easy = 1 person pull with no mechanical assistance; hard = 2 or more people or with mechanical help; surgery = caesarean section) were recorded by hired maternity staff or the herd veterinarian immediately following calving. A calf was determined to be stillborn if it died within the first 24 h. The occurrence (or absence) of retained fetal membranes (defined in this study as placental separation that failed to occur within 24 h post-calving) or metritis within the first 14 d following calving [diagnosis included systemic signs of illness such as inappetence, depression, and fever > 39.5°C accompanied with fetid discharge from the vulva; (15)] was recorded for every cow by the herd manager. The herd manager was blinded to the treatment assignments at calving.

The management of this herd meant that cows/heifers were being sold to other farms for dairy production in early lactation and thus the majority (79%) of animals that calved were primiparous animals.

Sample size estimates were calculated to detect a 2-fold increase, based on studies that investigated flunixin meglumine (10,11), in retained fetal membrane risk, and a total of 225 animals per treatment group were required with a confidence of 95% and 80% power, based on a 9% expected frequency of retained placenta in the control group for sample size calculations. Statistical software was used (SAS version 9.3; SAS Institute Inc., Cary, North Carolina, USA). The chi-square analysis was used to screen disease outcomes and calving events for association with treatment. *A priori* it was determined that any association with a *P*-value ≤ 0.20 would be subjected to further analysis with logistic regression. The exception was retained placenta since this was the primary outcome and parity was forced into the model since it is a known confounder. Treatment effect for retained placenta was further evaluated using a logistic regression model controlling for potential confounding of other variables. The occurrence of twins, stillbirth, calving difficulty, parity, and calf gender were all included in a model and then removed in a stepwise backward elimination procedure. Each variable with the highest *P*-value was removed until the model contained only those variables that were significant ($P < 0.05$) or if removal caused more than a 25% change in the model coefficient for treatment effect on RP, with the exception of parity which was forced into the model.

Table 1 summarizes the parturient and postparturient events in both groups. Calf gender was split evenly between the 2 groups, and the majority of calvings were easy pulls and all levels of calving difficulty were similar between the 2 groups (Table 1). The incidences of twins and stillborn calves were similar in both groups (Table 1) and within the range of the stillbirth rates (between 0 and 17.3%) found in 2007 on 162 dairy farms in central and western Canada (16). The randomizations of treatment *versus* control between heifers and cows were successful as there were no differences between the proportion of animals in the treated *versus* control group within each parity group (80% treated *versus* 77% control in the heifer group and 20% treated versus 23% control in the cow group; $P = 0.32$). There were no differences in the incidence of periparturient disease between treatment groups (Table 1). The lack of difference between groups in the incidence of metritis in the first 14 d following calving suggests that there were no immediate negative effects of meloxicam on uterine health.

The results of the logistic regression model suggest that there are no detrimental effects of administering meloxicam in the hours following calving on the risk of retained fetal membranes [odds ratio (OR) = 0.83, 95% confidence interval (CI) = 0.44 to 1.54; $P = 0.55$]. Overall incidence of retained fetal membranes in this study was 8.9% in the meloxicam group and 10.6% in the untreated group. In the same statistical model there were no differences in the odds of having retained fetal membranes after controlling for parity (OR = 0.90; 95% CI = 0.48 to 1.69, $P = 0.73$), but there was an increased odds of retained fetal membranes if the calf gender was male (male OR = 1.95; 95% CI = 1.02 to 3.73, $P = 0.04$). There were no interactions with calf gender and treatment on retained fetal membrane risk. The current study had sufficient power to detect a 2-fold increased risk of retained fetal membranes. In fact, 2 of the flunixin meglumine studies reported a 3-fold increased risk of retained fetal membranes associated with treatment (10,11). The lack of significant difference between treatment groups for the incidence of retained fetal membranes in the present study is similar to the one seen in the study that provided ketoprofen following calving (12) and indicates that there are no negative impacts of meloxicam on the expulsion of fetal membranes. This difference in meloxicam effect on retained fetal membranes is puzzling because of its strong affinity to inhibit COX-2 rather than COX-1 (4) but further studies are required to confirm this phenomenon and determine the mechanism of meloxicam activity in cattle at parturition.

In conclusion, the administration of meloxicam to Holstein cows immediately after calving had no detrimental effect on either the risk of retained placenta or on post-partum metritis. The results of the present study indicate that meloxicam can be used immediately following calving with no increased risk of retained fetal membranes in primiparous cows. Future studies are required to investigate the analgesic and anti-inflammatory properties of meloxicam after calving for the cow's health and welfare, as well as potential cost benefits to the farmer.

Acknowledgments

We are grateful for the participation and assistance of the producer and farm staff and the herd veterinarian. CVJ

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