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ORIGINAL RESEARCH

The use of meloxicam oral suspension to treat musculoskeletal lameness in cattle

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Abstract: Lameness in beef and dairy cattle is responsible for economic losses and has significant animal welfare implications. It has been proposed that early treatment with analgesics not only reduces acute pain but also leads to reduced long-term sensitization. Fifty-three cattle (309–954 kg body weight [BW], mean: 656 kg) with musculoskeletal lameness were scored for lameness and inflammation, then randomly assigned to a single oral treatment with meloxicam oral suspension (MOS) (28 animals) at 1 mg/kg or saline at 1 mL/15 kg BW. Lameness and inflammation were reevaluated 3 days after treatment, and 26 of 28 (92.8%) MOS-treated animals had a reduced lameness score, while only three of 25 control animals had a reduced lameness score. MOS was effective in treating musculoskeletal disease in cattle. In an accompanying residue depletion study, 22 lactating Holstein cows (BW: 553–927 kg, mean: 713 kg) were used in the study. All 22 animals received MOS at the dose of 1 mg/kg BW once. Milk (500 mL sample from the full milking volume) was collected at approximately 48, 72, 96, and 120 hours after the treatment. Samples were subjected to in vitro analysis for quantification of meloxicam by liquid chromatography and mass spectroscopy. The mean meloxicam concentration at 48 and 72 hours were 30.75 and 2.82 ng/mL, respectively. The meloxicam milk concentration was below the limit of quantification (1 ng/mL) in 15 of 22 animals at 96 hours and in 22 of 22 animals at 120 hours. The milk meloxicam levels in all animals were below the maximum residue limit (Canada: 35 ng/mL; Europe: 15 ng/mL) at the 72-hour sampling.

Keywords: meloxicam, lameness, musculoskeletal, residue, milk, cattle

Introduction

Lameness in beef and dairy cattle is responsible for economic losses and has significant animal welfare implications.[1–3] The causes of musculoskeletal disorders include traumatic injury (eg, handling injuries, pen riding, and slipping), arthritis, hoof abnormalities, infections (infectious pododermatitis and infectious arthritis), and causes of unknown etiology. Lameness constitutes a major cause of involuntary culling of cattle in both the beef and dairy industries, and a prevalence of over 30% has been reported in some herds.[1] It has been proposed that early treatment with an effective analgesic not only reduces acute pain but also leads to reduced long-term sensitization.[1] A multimodal approach to treatment is generally recommended.[1] These include interventions such as corrective foot trimming, local anesthetic antibiotics (if there is an infections component), and nonsteroidal anti-inflammatory drugs.[1,4] Meloxicam is a newer nonsteroidal anti-inflammatory drug in the oxicam group that has preferential (but not specific) binding to cyclo-oxygenase-2 receptors and has been shown to reduce

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pain and inflammation in food and companion animals.[4] Meloxicam oral suspension (MOS) was recently registered for control of pain and inflammation in surgically and band-castrated cattle.[5] MOS has also been shown to effectively treat musculoskeletal disease in horses.[6] The objective of this study was to determine the efficacy of MOS for the treatment of noninfectious musculoskeletal disorders in cattle. As dairy cattle frequently require treatment for musculoskeletal lameness, a milk residue depletion study was conducted to establish a milk withdrawal time.

Methods

Both studies were conducted in compliance with the guidelines of the Canadian Council on Animal Care after the appropriate review and approval by the Institutional Animal Care and Use Committee of Alberta Agriculture, Airdrie, Alberta. A prestudy proportion power calculation was performed to determine the number of animals required to generate meaningful results. With improvement proportions of 0.6 for MOS and 0.2 for saline, it was determined that a minimum of 18 animals in each group were required. Procedures were designed to avoid or minimize discomfort, distress, and pain to the animals.

Lameness efficacy study

Animals having noninfectious musculoskeletal lameness were identified by collecting the history of the animal and by performing a physical examination. Cattle with musculoskeletal disease were selected from 15 different herds and varied in sex, age, location of disease, and severity of lameness (Table 1). Animals were on a winter pasture in the area of Calgary, Alberta, Canada, and were provided hay and mineral supplement and had free access to water. They were randomly allocated to treatment and control groups. Treatment animals received MOS (Solvet/Alberta Veterinary Laboratories [AVL], Calgary, AB, Canada) at an oral dose of 1 mg/kg body weight (BW) (n=28), and control animals (n=25) received saline 1 mL/15 kg BW. Individuals in charge of the preparation of dosing syringes, treating the animals, and randomization were not blinded. The person evaluating lameness in each animal was blinded.

The degree of lameness was scored using a 0–4 scale (Table 2) adapted from Sprecher et al.[1,7] Lameness scores were determined on day 0 (Treatment day) and day 3 (3 days after first treatment). To eliminate interobserver variation, all lameness scores were assigned by a single-blinded veterinarian (Dr. Denis Nagel) with training and expertise in bovine lameness assessment. All lameness examinations were performed on even, nonsloped floors free of obstructions and debris. Each lameness score was determined by watching the animal walk a minimum of 20 m in a straight line, turn, and walk 20 m back to the starting point.

On day 0 and day 3 (at the times of the lameness evaluation), swelling (inflammation) in the most affected limb was evaluated according to the details listed in Table 2. The same veterinarian performed all the inflammation scores.

Data analysis

The proportion of animals in each group responding to treatment was compared using Fisher's exact test. Nonparametric analysis (Mann–Whitney *U* test) was used to compare lameness scores between treatment groups. Significance was established at a 95% confidence interval, and data are expressed as median, mean, and standard error with *P* values.

Residue depletion study

The study was conducted according to the Veterinary International Cooperation on Harmonization Guidelines for residue depletion (VICH GL48®).[8] Twenty-two lactating Holstein cows (BW: 553–927 kg, mean: 713 kg) from a single farm were enrolled into the study. Animals varied in age from 1.9 to 8.5 years (mean: 3.9 years.) with the number of lactations varying from 1 to 6 (mean: 2.4). The days lactating varied from 55 to 539 days (mean: 215.9 days). All 22 animals were healthy and remained healthy during the adaptation period (prior to day 0), the treatment period (day 0), and the elimination period (0–144 hours). Cattle were treated with MOS at a dosage of 1 mg/kg BW on day 0, and the time of treatment was recorded. Milk samples were collected at approximately 48, 72, 96, 120, and 144 hours after treatment. The milk sampling times were recorded for each animal. The entire milking was collected, and a 500 mL subsample was taken and frozen at –20°C until analysis.

Analysis of milk meloxicam was performed under VICH GL49® guidelines in the Canadian Food Inspection Agency Certified Laboratory (Silliker, JR Laboratories, Burnaby, BC, Canada).[8] Meloxicam was analyzed in the milk samples using a validated procedure (Canadian Food Inspection Agency, CVDR-M-3025.03) using liquid chromatography and mass spectroscopy. The limit of quantification was 1 ng/mL (1 ppb).

Results

Lameness efficacy study

All animals (2 males, 2 male castrates, and 49 females, all mature) were enrolled, allocated, and treated without incident. A total of 28 animals received MOS, while 25 animals received

Table 1 Descriptions of animals selected for musculoskeletal study

Number	Owner	Description	Age (years)	Sex	Body weight (kg)
1	1	Hereford	11	F	805
2	2	Hereford	7	F	750
3	2	Hereford	11	F	727
4	3	Angus	6	F	616
5	3	Angus	13	F	680
6	4	Hereford X	5	F	682
7	4	Charolais X	8	F	786
8	4	Angus	7	F	704
9	4	Angus	1	MC	309
10	5	Angus	6	F	590
11	5	Angus	6	F	613
12	5	Angus	7	F	795
13	5	Angus	5	F	682
14	5	Angus	4	M	954
15	5	Angus	12	F	568
16	5	Angus	6	F	680
17	6	Angus X	8	F	727
18	6	Simmental X	5	F	750
19	6	Angus X	6	F	804
20	6	Angus X	5	F	681
21	7	Angus	5	F	680
22	7	Angus	6	F	750
23	8	Hereford	2	M	863
24	8	Hereford	6	F	738
25	8	Hereford	7	F	660
26	8	Hereford	7	F	590
27	9	Charolais X	10	F	659
28	9	Charolais X	10	F	640
29	9	Charolais X	12	F	705
30	9	Charolais X	10	F	682
31	9	Charolais X	13	F	614
32	9	Charolais X	11	F	705
33	9	Charolais X	12	F	546
34	9	Charolais X	11	F	614
35	10	Hereford	3	F	522
36	10	Hereford	11	F	636
37	11	Angus	3	F	545
38	11	Angus	11	F	682
39	12	Hereford	10	F	704
40	13	Simmental X	14	F	613
41	13	Simmental X	6	F	568
42	13	Angus	1	MC	360
43	14	Hereford X	12	F	590
44	14	Hereford X	10	F	636
45	15	Simmental X	12	F	590
46	15	Angus	9	F	681
47	15	Charolais X	12	F	600
48	15	Simmental X	7	F	636
49	15	Angus	5	F	590
50	15	Charolais X	10	F	636
51	15	Angus	10	F	682
52	15	Simmental X	10	F	590
53	15	Angus	6	F	602

Abbreviations: F, female; M, male; MC, male castrate.

Table 2 Lameness and inflammation scoring

Score	Severity	Description
Lameness scoring		
0	Normal	Stands and walks normally, with all feet placed with purpose
1	Mildly lame	Stands with flat back but arches when walks and gait is slightly abnormal
2	Moderately lame	Stands and walks with an arched back and short strides with one or more legs
3	Lame	Arched back standing and walking, with one or more limbs favored but at least partially weight-bearing
4	Severely lame	Arched back, refuses to bear weight on one limb, or may refuse or have great difficulty moving from lying position
Inflammation scoring		
0	No inflammation	No swelling observed
1	Mild	Slight swelling observed on limb or foot
2	Moderate	Moderate swelling on the limb and/or foot
3	Severe	Severe swelling of limb and/or foot

saline. There were no adverse events following either treatment. The treatment results are summarized in Table 3. The lameness involves the foot (22), fetlock (4), stifle (16), and hip (11). There was no difference in lameness scores between the MOS and saline groups in the pretreatment period (P=0.635). The scores on day 3 (approximately 3 days after treatment) were significantly less in the MOS treatment group than in the saline-treated animals (P<0.0001). The scores on day 0 and day 3 were also significantly different between the MOS- and saline-treated animals (P<0.0001). Animals receiving MOS responded positively to treatment in 26 of 28 cases (92.8%), while saline controls responded in three of 25 cases (12%).

There were 42 animals with hind-limb lameness and eleven with front-limb lameness. There were only eight animals (four in each treatment group) with limb swelling associated with lameness. In the MOS-treated group, four of four had reduced inflammation scores, while there was no improvement in any saline-treated animals. When inflammation occurred, there was a significant reduction in swelling in the MOS-treated compared to saline-treated animals (P=0.0286).

Residue depletion study

The duration from treatment to sample collection and milk meloxicam concentrations is provided in Table 4. The duration of time between treatment and milk sampling was less than or equal to the target times in 15, 16, and 17 of the 22 animals at 48, 72, and 96 hours, respectively. The maximum collection times were no more than 30 minutes over the target times. The mean meloxicam concentration at 48 and 72 hours were 30.75 and 2.82 ng/mL, respectively. The meloxicam milk concentration was below the limit of quantification (1 ng/mL) in 15 of 22 animals at 96 hours and 22 of 22 animals at 120 hours. In all animals, the milk meloxicam levels were well below the maximum residue limit (Canada: 35 ng/mL; Europe: 15 ng/mL) at the 72-hour sampling.[9,10]

Discussion

The economic and animal welfare impact of lameness has been documented in numerous studies and reviews.[1–3] Lameness causes involuntary culling of beef and dairy cattle and is usually underreported by producers.[1,2] Early analgesic treatment intervention may affect the outcome of lameness as this can prevent hyperalgesia (increased sensitivity to pain). Hyperalgesia can contribute to chronic lameness and culling.[1] A multimodal approach to lameness treatment with the use of analgesics, corrective trimming, and antibiotics can reduce cases of chronic lameness and culling.[1] Nonsteroidal anti-inflammatory drugs have been demonstrated to be effective in reducing lameness associated using a visual locomotion score.[1,4] Sodium salicylate, flunixin, and ketoprofen have had mixed results in the treatment of musculoskeletal lameness in both field and experimental models.[1,11,12] This may be due to the short half-life and the ability to penetrate the affected tissues.[4] There are recent studies that have shown meloxicam to be effective in the treatment of musculoskeletal disease in horses.[6] Meloxicam has also been shown to be effective in the treatment of experimental lameness model in cattle.[13] Postoperative treatment with meloxicam after cesarean section and resection of the distal interphalangeal joint has been shown to be effective in increasing comfort and effective analgesia.[14,15] This study has shown that meloxicam reduces inflammation and decreases lameness scores for 3 days after a single treatment. The long half-life (27 hours) and high response rate (92.8%) make MOS ideally suited for the treatment of musculoskeletal disease in cattle.[4] Pharmacokinetics and milk secretion of oral meloxicam and gabapentin in a limited number of cattle have been previously reported with similar residue depletion in milk.[16] Although the milk withdrawal time has not been established for MOS at the time this article was published, the milk concentration in all 22 animals in this study are well below the Canadian and European maximum residue limits at 72 hours posttreatment.

Table 3 Pre- and posttreatment lameness and inflammation scores of affected limbs

Meloxicam (1 mg/kg body weight)							Saline (1 mL/15 kg body weight)						
Animal number	Location	Pretreatment		Posttreatment		Lameness score difference	Animal number	Location	Pretreatment		Posttreatment		Lameness score difference
		Lameness score	Inflammation score	Lameness score	Inflammation score				Lameness score	Inflammation score	Lameness score	Inflammation score	
2	LH foot	1	0	0	0	1	1	RH stifle	2	0	2	0	0
3	LRH stifle	3	0	1	0	2	5	LH stifle	2	0	2	0	0
4	RH hip	3	0	1	0	2	7	LH hip	2	0	2	0	0
6	LH hip	2	0	2	0	0	8	LH hip	2	0	2	0	0
9	LH hip	2	0	3	0	−1	11	LH foot	3	1	3	1	0
10	LH foot	3	2	1	1	2	13	LH foot	3	2	3	2	0
12	RF foot	3	2	1	1	2	15	LH foot	4	2	4	2	0
14	RF fetlock	3	1	2	1	1	17	LH hip	2	0	2	0	0
16	LH foot	3	2	1	1	2	19	RF foot	3	0	1	0	2
18	RF fetlock	2	0	1	0	1	22	RF foot	2	2	2	2	0
20	LF foot	3	0	0	0	3	24	RF foot	2	0	2	0	0
21	LRH feet	2	0	0	0	2	25	LRH feet	2	0	2	0	0
23	LRH feet	2	0	1	0	1	28	RF foot	2	0	2	0	0
26	RF foot	2	0	0	0	2	29	LRH feet	2	0	2	0	0
27	RH hip	2	0	1	0	1	30	LH hip	2	0	1	0	1
31	LRH feet	2	0	1	0	1	34	RH stifle	3	0	3	0	0
32	RH fetlock	2	0	0	0	2	37	RH foot	2	0	2	0	0
33	RH stifle	3	0	1	0	2	38	RH stifle	2	0	2	0	0
35	RH stifle	4	0	3	0	1	39	RH hip	2	0	2	0	0
36	LH stifle	3	0	1	0	2	40	RH hip	2	0	3	0	−1
43	RH stifle	3	2	1	2	2	41	RH stifle	3	0	3	0	0
44	LRF feet	2	0	1	0	1	42	RH stifle	4	0	4	0	0
45	LRF feet	2	0	1	0	1	49	LRH stifle	2	0	2	0	0
46	LRH feet	2	0	0	0	2	50	LH hip	2	0	1	0	1
47	RH fetlock	2	2	1	2	1	51	LH stifle	2	0	2	0	0
48	LH stifle	2	0	1	0	1							
52	LH stifle	2	0	1	0	1							
53	RH stifle	2	0	0	0	2							
	N	28	4	28	4	28			25	4	25	4	25
	Mean	2.39	2	0.96	1	1.43			2.36	1.25	2.24	1.75	0.12
	SD	0.63	0	0.79	0	0.79			0.64	0.96	0.78	0.50	0.53
	# Respondents			26	4	26					3	0	3
	% Respondents			92.8	100	92.8					12	0	12

Abbreviations: SD, standard deviation; LH, left hind; RH, right hind; LRH, left and right hind; RF, right front; LF, left front; LRF, left and right front

Table 4 Meloxicam in milk after administration of MOS (ng/mL)

Animal	Milk meloxicam concentration (ηg/mL)ng							
	48-hour sample		72-hour sample		96-hour sample		120-hour sample	
	Real duration (hour:minute)	Milk meloxicam (ηg/mL)	Real duration (hour:minute)	Milk meloxicam (ηg/mL)	Real duration (hour:minute)	Milk meloxicam (ηg/mL)	Real duration (hour:minute)	Milk meloxicam (ηg/mL)
1	47:35	14.46	71:45	2.64	95:30	<1.0	119:20	<1.0
2	48:05	19.30	71:45	1.94	95:30	1.11	118:35	<1.0
3	46:55	22.24	71:10	1.99	95:10	<1.0	119:15	<1.0
4	48:05	15.83	71:55	<1	96:05	<1.0	120:10	<1.0
5	46:45	24.31	71:10	3.67	95:05	<1.0	118:45	<1.0
6	48:00	12.50	72:05	1.11	96:05	<1.0	120:05	<1.0
7	47:35	26.99	71:30	3.66	95:35	<1.0	119:30	<1.0
8	47:40	26.16	71:45	2.79	95:25	<1.0	119:35	<1.0
9	47:15	43.46	71:10	3.12	95:15	<1.0	119:05	<1.0
10	47:20	50.54	71:25	5.14	95:15	1.29	119:30	<1.0
11	47:40	15.51	71:45	2.53	95:35	<1.0	119:35	<1.0
12	47:35	46.12	71:33	4.22	95:25	<1.0	119:30	<1.0
13	48:05	19.60	71:40	3.60	96:05	<1.0	120:05	<1.0
14	47:40	27.15	71:45	1.47	95:45	<1.0	119:45	<1.0
15	47:10	39.20	70:48	3.45	94:35	<1.0	118:55	<1.0
16	48:00	44.54	72:06	2.69	95:41	1.15	121:00	<1.0
17	48:15	44.16	72:06	3.70	95:50	<1.0	120:17	<1.0
18	47:55	46.42	72:10	3.78	95:40	1.59	120:05	<1.0
19	48:20	20.86	72:30	1.32	96:08	<1.0	120:30	<1.0
20	48:25	21.44	72:20	3.72	95:54	<1.0	120:20	<1.0
21	48:27	28.79	72:27	1.30	96:07	1.37	120:15	<1.0
22	48:05	67.00	71:57	3.30	95:36	1.25	120:05	<1.0
Mean	47:46	30.75	71:45	2.82	95:36	1.08	119:44	N/A
Median	47:47	26.58	71:45	2.96	95:35	1.00	119:40	N/A
Minimum	46:45	12.5	70:48	<1.00	94:35	<1.00	118:35	N/A
Maximum	48:27	67.00	72:30	5.14	96:08	1.59	121:00	N/A
SD	0:28	14.56	0:26	1.13	0:23	0.16	0:36	N/A
# <MRL		14		22		22		22
% <MRL		63.6		100		100		100

Abbreviations: N/A, not applicable; SD, standard deviation; MRL, maximum residue limit; MOS, meloxicam oral suspension.

Disclosure

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