Journal of Equine Veterinary Science 44 (2016) 26–31

Contents lists available at ScienceDirect

Journal of Equine Veterinary Science

journal homepage: www.j-evs.com

Original Research

The Palatability and Comparative Efficacy of Meloxicam Oral Suspension for the Treatment of Chronic Musculoskeletal Disease in Horses

Merle E. Olson [a,*], Denis Nagel [b], Sherry Custead [b], Waylon Wise [b], Kirby Penttila [c], Les Burwash [d], Brenda Ralston [d], Crystal Schatz [e], Heather Matheson-Bird [f]

[a] Alberta Veterinary Laboratories, Calgary, Alberta, Canada
[b] Nagel Veterinary Services, Crossfield, Alberta, Canada
[c] Burwash Equine Services, Calgary, Alberta, Canada
[d] Alberta Agriculture and Forestry, Airdrie, Alberta, Canada
[e] Bow Valley Research, Calgary, Alberta, Canada
[f] Horse Industry Association of Alberta, Airdrie, Alberta, Canada

ARTICLE INFO

Article history:
Received 18 November 2015
Received in revised form 3 March 2016
Accepted 3 March 2016
Available online 10 March 2016

Keywords:
Meloxicam
Phenylbutazone
Musculoskeletal
Lameness
Palatability
Oral

ABSTRACT

The objective of the study was to evaluate the efficacy and ease of treatment of an oral meloxicam suspension for the treatment of chronic musculoskeletal lameness in horses. A crossover palatability study consisting of 30 healthy horses and ponies was conducted to compare the time to consume a 400-gram meal of oats alone to a 400-gram meal of oats top dressed with meloxicam oral suspension (MOS) (0.6 mg/kg body weight [BW]). The mean time to consume a 400-gram meal of oats only was 301.0 ± 145 seconds and was 286.3 ± 125.6 seconds for MOS. There was no difference between the consumption duration times of oats with or without MOS. Horses (77) were enrolled into a blinded, active-controlled, randomized clinical study. Treatment 1 consisted of animals receiving MOS (0.6 mg/kg BW q24 hours for 5 days), and treatment 2 consisted of animals receiving phenylbutazone paste (1 g/454 kg BW, q12 hours for 5 days). Animals were treated on day 0 and evaluated for lameness associated with of musculoskeletal disease on day 5. For both treatments 1 and 2, the day 5 lameness scores were significantly less than the day 0 lameness scores. At a walk and trot, there were no differences in efficacy between phenylbutazone and MOS (based on absolute score values, differences in scores between day 0 and day 5, and proportion of horses responding to treatment). It was concluded that MOS was palatable and effective for the treatment of musculoskeletal disease.

1. Introduction

Musculoskeletal disease, which manifests itself as lameness, remains as the most common ailment of horses. The most common treatment for musculoskeletal disease is nonsteroidal anti-inflammatory drugs (NSAIDs) which include phenylbutazone, meloxicam, flunixin, and ketoprofen [1–4]. Oral delivery of NSAIDs is preferred over injection as it is considered safer and more practical [5]. Top dressing of feed is also desired as this provides the most convenient method of delivery of a drug that may require administration over extended periods of time. Few studies have evaluated the palatability of top-dressed pharmaceutical products in horses [5]; however, this is important when selecting oral therapeutic products.

Nonsteroidal anti-inflammatory drugs act by reduction in prostaglandin production due to inhibition of the enzyme cyclooxygenase (COX). The isoenzyme COX-1 is

* Corresponding author at: Merle E. Olson, Alberta Veterinary Laboratories, 411 19th Street SE, Calgary, Alberta T2E 6J7, Canada.
E-mail address: merle@avetlabs.com (M.E. Olson).

http://dx.doi.org/10.1016/j.jevs.2016.03.003

present in nearly all cells and has beneficial effects in gastrointestinal and renal homeostasis [1,2]. The COX-2 isoenzyme is expressed in nervous tissue, kidney, bone, and joints and inhibition reduces pain, inflammation, and fever. Selective COX-2 inhibitors are believed to be beneficial in that they provide therapeutic benefits while maintaining important homeostatic functions. Many NSAIDs routinely used in the treatment of musculoskeletal disease are nonselective COX inhibitors (e.g., phenylbutazone, flunixin) and have well-established negative side effects such as colitis, gastrointestinal ulceration, and nephrotoxicity [6–8]. Meloxicam preferentially inhibits the COX-2 isoenzyme and has been shown to be safer in foals and adults horses [9–14].

This study evaluated the efficacy of an oral formulation of meloxicam [meloxicam oral suspension (MOS)] and phenylbutazone (Paste) in horses with chronic lameness associated with musculoskeletal disease. In addition, the palatability of MOS was evaluated when top dressed to whole oats. Meloxicam oral suspension (15 mg/mL meloxicam) has been developed for postsurgical pain and inflammation in cattle and horses (Alberta Veterinary Laboratories, Calgary Alberta, Canada) [15,16]. Currently, MOS is registered in Canada for the control of pain and inflammation in cattle undergoing surgical or band castration.

2. Materials and Methods

2.1. Palatability Study

2.1.1. Study Design

The palatability study was a blinded crossover study. All horses received (1) 400 grams of oats and (2) 400 grams of oats top dressed with MOS at a dose of 0.6 mg per kg body weight (BW). Animals were randomly allocated to group 1 (oats only for the first meal and oats with meloxicam for the second meal) or group 2 (oats with meloxicam for the first meal and oats only for the second meal). Oats was offered in a rubber feeding tub to each animal, and the tub was cleaned between the crossover periods. The time between the crossover periods was 2 hours. The duration of time to consume the entire meal was measured with a stop watch by blinded observers. The study was reviewed and approved by an Ethical Care and Use Committee (Alberta Agriculture, Airdrie). For each horse, the duration times to consume the entire meal (treatment 1) with and without (treatment 2) MOS were compared using a paired *t* test.

2.1.2. Animals

Thirty mixed breed, broke horses (26 males and 4 females) from one riding stable were used in the study. These included both ponies and full size horses (Quarter horses). All animals were accustomed to receiving oats as a daily feed supplement. The horses had not received NSAIDs or corticosteroids for at least 8 weeks, and all horses were sound at the time of treatment. Written owner consent was obtained for use of horses enrolled into the study.

2.2. Comparative Efficacy Study

2.2.1. Study Design

This was a blind, active-controlled, randomized clinical study. Seventy-seven horses were enrolled in the study and sequentially randomly assigned to either treatment 1, consisting of animals receiving Meloxicam Oral Suspension (AVL, Calgary, Alberta, Canada), or treatment 2, animals receiving phenylbutazone paste (Butequine 1 g/3 mL, Vetoquinol, Laval Trie, Quebec, Canada). The number of animals in each treatment group was based on power calculations required to demonstrate noninferiority to phenylbutazone (active control) for clinical improvement of musculoskeletal disease. The study was conducted according to good clinical practice [VICH GL GL9 (GCP) – GOOD CLINICAL PRACTISE (June 2000)]. The study was reviewed and approved by an Institutional Ethical Care and Use Committee.

2.2.2. Animals

Seventy-seven horses (49 geldings and 28 mares) of mixed breeds ranged in age from 3 to 28 years (15.5 ± 6.0; mean ± standard deviation) and had a history of chronic lameness for 1 week to 10 years (2.0 ± 2.4 years; mean ± standard deviation) were used in the study. These included both ponies and full size horses (Quarter Horses). Horses were selected from private owners in Southern Alberta, Canada. Horses weighed 136 to 680 kg (506 ± 124 kg; mean ± standard deviation). Written owner consent was obtained for each horse enrolled into the study.

Horses could not have been treated with an NSAID for at least 14 days or a long lasting corticosteroid for 8 weeks to be enrolled in the study.

2.2.3. Feed, Water, and Housing

All horses were fed watered and housed based on the private owners' specific facility management practices.

2.2.4. Treatments and Dose Preparation

Treatment 1 consisted of 38 animals receiving MOS at the dose of 0.6 mg per kg BW q24 hours (1 mL per 25 kg BW every 24 hours) to be delivered as a calculated dose corresponding to within ±1 kg of actual BW. Animals were treated once daily for 5 consecutive days (days 0, 1, 2, 3, and 4). Treatment 2 consisted of 39 animals receiving phenylbutazone oral paste (1 g/3 mL) at the dose of 1 g/454 kg BW q12 hours, (3 mL per 454 kg BW every 12 hours) to be delivered as a calculated dose corresponding to within ±1 kg of actual BW. Animals were treated twice daily for 5 consecutive days (days 0, 1, 2, 3, and 4).

The treatment syringes were prepared by the veterinary technician, labeled with study number and animal identification, and provided to the owner with treatment instructions. The treatment was provided to the owner of the horse after a clinical examination, and pretreatment lameness score was recorded and the examining veterinarian had left the study site. After the treatment phase, the syringes were recovered from the owner and weighed to determine the actual weight and volume of each treatment.

2.2.5. Lameness Evaluation Procedure

On day 0, lameness in each limb was scored at standing, walking, and trotting based on the six-point lameness scale of the American Association of Equine Practitioners. The limb with the most severe lameness was used for scoring in the study. Lameness at a trot, walk, and rest was assessed visually before (day 0) and one day after the last treatment (day 5) by a veterinarian experienced in equine lameness evaluation. The veterinarian was blinded to the treatments for the lameness evaluation on days 0 and 5. The scores were recorded according to the scale described in Table 1.

2.2.6. Overall Efficacy Score

After the lameness examination on day 5, the veterinary clinician was unblinded and gave each case a summarizing conclusion on the overall efficacy (scored on a four-point scale) according to Table 2. A reduction in score of one or greater was considered a successful outcome to treatment.

2.2.7. Palatability Score

A palatability score was awarded by horse owners at the time of each treatment according to the following definition: good (score 1) = horse took treatment willingly, satisfactory (score 2) = horse took treatment reluctantly, and poor (score 3) = horse refused to take treatment willingly. This was entered each day of treatment. A score of 1 was considered a positive palatability score.

2.2.8. BW and Physical Examination

Body weight was determined as part of the general physical examination conducted on day 0. Body weights were measured using a portable electronic scale. The day 0 BWs were used to calculate the dosage of the treatments.

2.2.9. Statistical Analysis

The pretreatment and posttreatment lameness scores were compared using a Wilcoxon signed rank test with a 95% confidence interval. The proportion of animals with lameness at a stand, walk, and trot were compared using a Fisher's exact test with a 95% confidence interval.

Noninferiority and superiority between the test group (MOS) and the active control group (phenylbutazone) were performed based on the FDA Guidance Document: Active Controls in Studies to Demonstrate Effectiveness of a New Animal Drug for Use in Companion Animals (October 2013). The study was analyzed by calculating from the study data a two-sided 95% confidence interval where p_{ID} is the proportion of cures with the investigational drug and p_{AC} is the proportion of cures with the active control. The number of animals in the active control and investigational drug is represented by n_{AC} and n_{ID}, respectively. The upper bound confidence level (UCL) is determined by the following calculation:

$$UCL = (p_{AC} - p_{ID}) + Z_{(1-0.025)} \times \sqrt{\frac{p_{AC}(1-p_{AC})}{n_{AC}} + \frac{p_{ID}(1-p_{ID})}{n_{ID}}}$$

If the UCL is less than 0.15 (or 15%), then one can conclude statistically that the investigational new animal drug is noninferior. If the upper confidence interval is less than 0 (negative), then the investigational drug is superior to the active control.

The overall efficacy and lameness scores assigned by the clinical veterinarian providing clinical evaluations were compared using a two-sided Mann–Whitney test with a 95% confidence interval. Palatability scores provided by the horse owner were compared using a two-sided Mann–Whitney test with a 95% confidence interval.

Table 1
Lameness scoring system.

Clinical Observation	Score	Description
Lameness at rest	1	Equal weight bearing on all limbs
	2	Weight bearing on affected limb, with shift of weight to unaffected limb
	3	Weight bearing on affected limb only at tip of hoof
	4	No weight bearing on affected limb
Lameness at a walk and trot	1	Sound or undetectable lameness
	2	Barely detectable lameness, lame rarely or intermittently when turning
	3	Mild lameness, mild head bob when walking or turning
	4	Moderate lameness, obvious head bob at walk, toe pointing frequently
	5	Nonweight bearing on affected limb only at tip of hoof
	6	Nonweight bearing 100% of the time

Table 2
Efficacy score.

	Score	Description
Overall efficacy score	1	Very good—excellent improvement of clinical condition
	2	Good—marked improvement of clinical condition
	3	Moderate—only slight improvement of clinical condition
	4	Poor—unchanged or deteriorated clinical condition

3. Results

3.1. Palatability Study

The palatability data are summarized in Table 3. All horses consumed their entire oat only meal or oats with MOS meal. There was no significant difference between the

Table 3
Summary of statistical parameters for palatability study (numbers represent the combined values of periods 1 and 2 of the crossover).

Variable	Oats Only	Oats and Meloxicam Oral Suspension
Number of horses	30	30
Percent of horses consuming meal	100	100
Minimum consumption duration (s)	138.0	165.0
Maximum consumption duration (s)	738.0	642.0
Median consumption duration (s)	245.0	235.5
Mean consumption duration (s)	301.0	286.3
Std. deviation (s)	145.0	125.6

consumption times of oats only and oats with MOS ($P = .6762$).

3.2. Musculoskeletal Efficacy Study

The results of the lameness, efficacy, and palatability scores are summarized in Table 4.

3.2.1. Lameness Evaluation

The number of horses with lameness (score of 2 or greater) was greatest at a walk and trot, and therefore, the lameness scores at these activities provided the most power. For both treatment 1 (MOS) and treatment 2 (phenylbutazone), the day 5 lameness scores were significantly less ($P < .05$) than the day 0 lameness scores which indicated that both products were effective in treatment of musculoskeletal disease in horses. At a trot and walk, there were no differences in efficacy between phenylbutazone and MOS (based on absolute score values, differences in scores between day 0 and day 5, and proportion of horses responding to treatment). Using a noninferiority test, MOS was both noninferior and superior to the phenylbutazone active control at a walk and noninferior to the active control (phenylbutazone) at a trot (Table 4).

3.2.2. Overall Efficacy Score

The assessment of overall efficacy by the veterinarian performing the examination showed that MOS was significantly ($P < .05$) superior to oral phenylbutazone (Table 4).

3.2.3. Owner Palatability Assessment

The assessment of owners demonstrated that MOS was significantly more palatable ($P < .05$) than phenylbutazone paste (Table 4).

Table 4
Pharmacokinetic parameters following administration of meloxicam oral suspension to horses (*P* value represents the comparison between phenylbutazone and meloxicam treatment groups).

Variable	Phenylbutazone	Meloxicam	*P* Value
Standing score			
Median pretreatment score (day 0)	1	1	.5268
Mean pretreatment score (day 0)	1.15	1.21	.5268
Median posttreatment score (day 5)	1	1	1.0000
Mean posttreatment score (day 5)	1.03	1.03	1.0000
Median difference	0	0	.5061
Mean difference	0.13	0.18	.5061
Number lame	6	8	
Number positive response	5	6	1.000
Percent responding	83.3	75.0	1.000
Noninferiority/superiority test	UCL = 33.4%, insufficient animals for conclusion		
Walking score			
Median pretreatment score (day 0)	2	2	.9570
Mean pretreatment score (day 0)	1.97	1.95	.9570
Median posttreatment score (day 5)	1[a]	1[a]	.2583
Mean posttreatment score (day 5)	1.44[a]	1.18[a]	.2583
Median difference	1.97	1.95	.2116
Mean difference	0.54	0.76	.2116
Number lame	22	23	
Number positive response	15	21	.0706
Percent responding	68.2	91.3	.0706
Noninferiority/superiority test	UCL = −0.5%, noninferior, superior		
Trotting score			
Median pretreatment score (day 0)	3	3	.9474
Mean pretreatment score (day 0)	3.33	3.34	.9474
Median posttreatment score (day 5)	2[a]	2[a]	.1042
Mean posttreatment score (day 5)	2.13[a]	1.92[a]	.1042
Median difference	1	1	.1522
Mean difference	1.21	1.42	.1522
Number lame	39	38	
Number positive response	32	34	.5170
Percent responding	82.1	89.5	.5170
Noninferiority/superiority test	UCL = 8.1%, noninferior		
Efficacy score			
Total scored	39	38	
% with positive score (1 or 2)	53.8	76.3	.0559
Median score	2	2	.0216
Mean score	2.38	2.06	.0216
Palatability score			
Total scored	38	38	
% with positive score (1)	42.1	94.7	<.0001
Median score	2	1	<.0001
Mean score	1.68	1.05	<.0001

Abbreviation: UCL, upper bound confidence level.
[a] Significantly different from pretreatment score (Mann–Whitney test, $P < .05$).

4. Discussion

Meloxicam oral suspension was developed for cattle, sheep, goats, and horses to control pain and inflammation. The efficacy of MOS for controlling surgical pain and inflammation in horses and cattle has been previously reported [15,16]. It was also developed to treat musculoskeletal disease in horses. The product was designed for easy to delivery by direct oral dosing or top dressed on feed. These studies were conducted to document efficacy and palatability in horses.

This study objectively demonstrated the palatability of MOS. Although few studies have been conducted measuring palatability of drugs, the authors believe that measuring consumption times using a familiar feed is the best way to measure palatability. In the horse, consumption of a meal is driven by pregastric stimulation such as appearance, taste, odor, and texture [17] and not by pretreatment fasting [18]. Horses can completely reject a medicated feed or have delayed consumption time [5,19]. Horses provided a familiar meal will usually consume the product, but when the feed has been spiked with an oral pharmaceutical with an offensive taste, it will be reject [5,18]. Nonsteroidal anti-inflammatory drugs such as phenylbutazone can cause rejection or delayed feed intake [3–5,19]. In this study, there was no difference in consumption times of medicated and nonmedicated oats in the horses. In addition, there was a significantly different palatability score between phenylbutazone paste and MOS when provided by oral gavage. These studies demonstrate that MOS is highly palatable.

A blinded, active-controlled, randomized study was conducted as it can be used to evaluate the efficacy and address ethical issues regarding not treating animals with a painful medical condition. Phenylbutazone was selected as the active control as it is a well-established effective treatment for musculoskeletal disease throughout the world [3,4]. The oral paste formulation of phenylbutazone was used because it is a registered formulation with a twice daily dose which is supported by the pharmacokinetics of oral phenylbutazone [3,5]. The objective of the study and the development of MOS was to provide horse owners with an alternative NSAID that is safer, easier to administer and more effective product than currently available NSAIDs. The active ingredient, meloxicam, is a COX-2 selective NSAID which has been shown to have reduced toxicity to horses and other mammalian species [9–14]. An oral safety study was conducted by the authors on 40 horses with MOS according to VICH guidelines and was shown to be safe at doses up to five times the recommended dose for 15 days (unpublished results). Other comparative studies using phenylbutazone as the active control have been conducted with suxibuzone [20], flunixin [21–23], and firocoxib [24]. In these studies, there was no difference in efficacy between the test NSAID and phenylbutazone although there was certain palatability and/or safety benefits to meloxicam [9–14]. Similarly, this efficacy study has shown that MOS was noninferior at treating musculoskeletal lameness to the nonselective COX inhibitor product, phenylbutazone paste at a trot, and superior at a walk. There was a subjective belief by the examining veterinarian that MOS was more effective than phenylbutazone. The additional benefits of safety and palatability make MOS well suited as an alternative therapy for phenylbutazone and other NSAIDs, for the treatment of horses with musculoskeletal disease.

5. Conclusion

Meloxicam oral suspension is highly palatable when top dressed to feed. It is effective for the treatment of lameness associated with musculoskeletal disease and as a selective COX-2 inhibitor, safer for horses than phenylbutazone.

Acknowledgments

M.E.O. is an employee of Alberta Veterinary Laboratories, the manufacturer of meloxicam oral suspension. The remaining authors do not have any financial or personal relationships that could bias the content of the article. Financial support from Alberta Livestock and Meat Agency (#2013R053R) is gratefully acknowledged.

References

[1] Moses VS, Bertone AL. Nonsteroidal anti-inflammatory drugs. Vet Clin North Am Equine Pract 2002;18:21–37.
[2] Kallings P. Nonsteroidal anti-inflammatory drugs. Vet Clin North Am Equine Pract 1993;9:523–41.
[3] Tobin T, Chay S, Kamerling S, Woods WE, Weckman TJ, Blake JW, Lees P. Phenylbutazone in the horse: a review. J Vet Pharmacol Ther 1986;9:1–25.
[4] Soma LR, Uboh CE, Maylin GM. The use of phenylbutazone in the horse. J Vet Pharmacol Ther 2011;35:1–12.
[5] Longhofer SL, Reinhemeyer CR, Radecki SV. Evaluation of the palatability of three nonsteroidal anti-inflammatory top-dress formulations in horses. Vet Ther 2008;9:122–7.
[6] Hough ME, Steel CM, Bolton JR, et al. Ulceration and stricture of the right dorsal colon after phenylbutazone administration in four horses. Aust Vet J 1999;77:785–8.
[7] McConnico RS, Morgan TW, Williams CC, et al. Pathophysiologic effects of phenylbutazone on the right dorsal colon in horses. Am J Vet Res 2008;69:1496–505.
[8] MacAllister CG, Morgan SJ, Borne AT, et al. Comparison of adverse effects of phenylbutazone, flunixin meglumine and ketoprofen in horses. J Am Vet Med Assoc 1993;202:71–7.
[9] Little D, Brown SA, Campbell NB, et al. Effects of the cyclooxygenase inhibitor meloxicam on recovery of ischemia injured equine jejunum. Am J Vet Res 2007;68:614–24.
[10] de Grauw JC, van de Lest CH, Brama PA, et al. In vivo effects of meloxicam on inflammatory mediators, MMP activity and cartilage biomarkers in equine joints with acute synovitis. Equine Vet J 2009;41:693–9.
[11] Beretta C, Garavaglia G, Cavalli M. COX-1 and COX-2 inhibition in horse blood by phenylbutazone, flunixin, carprofen and meloxicam: an in vitro analysis. Pharm Res 2005;52:302–6.
[12] Arcy-Moskawa ED, Noble GK, Weston LA, Boston R, Raidal SL. Effects of meloxicam and phenylbutazone on equine gastric mucosal permeability. J Vet Intern Med 2012;26:1494–9.
[13] Menozzi A, Pozzoli C, Poli E, et al. Effects of nonselective and selective cyclooxygenase inhibitors on small intestinal motility in the horse. Res Vet Sci 2009;86:129–35.
[14] Noble G, Edwards J, Lievaart J, Pippia J, Boston R, Raidal SL. Pharmacokinetics and safety of single and multiple doses of meloxicam in adult horses. J Vet Intern Med 2012;26:1192–201.
[15] Olson ME, Fierheller E, Burwash L, Ralston B, Schatz C, Matheson-Bird H. The efficacy of meloxicam oral suspension for controlling pain and inflammation after castration in horses. J Equine Vet Sci 2015;35:724–30.
[16] Olson ME, Ralston B, Burwash L, Matheson-Bird H, Allan N. Efficacy of oral meloxicam suspension for prevention of pain and inflammation following band and surgical castration in calves BMC Veterinary. London, UK: BioMed Central; 2016.
[17] Ralston SL. Controls of feeding in horses. J Anim Sci 1984;59:1354–61.

[18] Forbes JM. Dietary awareness. Appl Anim Behav Sci 1998;57:287–97.
[19] Anderson FL, Wright PD, Walters GT. Palatability and efficacy of a powder formulation of thiabendazole and trichlorfon for horses. J Am Vet Med Assoc 1973;162:206–7.
[20] Sabate D, Homedes J, Sust M, Monreal L. Multicentre, controlled, randomised and blinded field study comparing efficacy of suxibuzone and phenylbutazone in lame horses. Equine Vet J 2009;41:700–5.
[21] Keegan KG, Messer NT, Reed SK, Wilson DA, Kramer J. Effectiveness of administration of phenylbutazone alone or concurrent administration of phenylbutazone and flunixin meglumine to alleviate lameness in horses. Am J Vet Res 2008;69:167–73.
[22] Toutain PL, Autefage A, Legrand C, Alvinerie A. Plasma concentrations and therapeutic efficacy of phenylbutazone and flunixin meglumine in the horse: pharmacokinetic/pharmacodynamics modelling. J Vet Pharmacol Ther 1994;17:459–69.
[23] Foreman JH, Ruemmler R. Phenylbutazone and flunixin meglumine used singly or in combination in experimental lameness in horses. Equine Vet J 2011;43(Suppl 40):12–7.
[24] Foreman J, Foreman C, Bergstrom B. Efficacy of phenylbutazone versus firocoxib in experimental lameness in horses. Equine Vet J 2014;S46:3.