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Investigation of the clinical efficacy, safety and palatability of meloxicam (Metacam®) treatment in horses with musculosceletal disorders

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Summary

This GCP(v) multi centre blinded positive controlled study investigated under field conditions the clinical efficacy, safety and palatability of meloxicam in horses suffering from musculoskeletal disorders. The efficacy of meloxicam (Metacam®) at the recommended dose of 0.6 mg/kg body weight administered once daily was investigated (n=100) in comparison to vedaprofen (Quadrisol®, n=97). Lameness at a trot, walk and rest was recorded before initiation of therapy on Day 1, after a 5, 10 or 14 day treatment period and during the follow-up examination, performed 2 to 4 days after the respective last treatment. The duration of treatment (5, 10 or 14 days) was decided by the veterinarian depending on the clinical condition. Furthermore palatability and relapse rates were recorded. Significantly better results ($p \leq 0.01$) for "lameness at a trot" (primary clinical variable) after 14 days of treatment, and at the follow-up examination ($p \leq 0.001$), were found in the meloxicam group compared to the reference group. Significant differences ($p \leq 0.05$) in "lameness at walk" occurred in favour of meloxicam at the follow-up examination on Day 14. A significant superiority in lameness at a trot ($p \leq 0.001$) and walk ($p \leq 0.01$) was revealed in favour of meloxicam for the evaluation at the time point when therapy was judged no longer necessary. Fewer meloxicam cases showed relapse to lameness ($p \leq 0.05$). Furthermore, meloxicam was superior ($p \leq 0.001$) with regard to overall efficacy and palatability. No adverse events occurred in the meloxicam group compared to two cases in the reference group. The results indicate that 0.6 mg meloxicam/kg bodyweight administered orally once daily is an efficacious, safe, easy to use, and highly palatable NSAID treatment for reduction of inflammation and relief of pain associated with lameness in both acute and chronic musculoskeletal disorders and soft tissue lesions.

Keywords: musculoskeletal disorders, lameness, horses, non-steroidal anti-inflammatory drug, meloxicam

Untersuchungen zur klinischen Wirksamkeit, Sicherheit und Akzeptanz von Meloxicam (Metacam®) bei der Behandlung von Erkrankungen des Bewegungsapparates beim Pferd

In dieser multi-zentrischen, verblindeten, positiv-kontrollierten GCP-Studie wurde unter Feldbedingungen die klinische Wirksamkeit, Sicherheit und Akzeptanz von Meloxicam (Metacam®) bei Pferden mit muskuloskelettalen Erkrankungen untersucht. Die Wirksamkeit von Meloxicam (Metacam®) wurde in der empfohlenen Dosis von 0,6 mg Meloxicam pro kg Körpergewicht einmal täglich oral verabreicht (n=100) und mit Vedaprofen (Quadrisol®) verglichen (n=97). Beurteilt wurde die Belastung im Stand, sowie die Lahmheit in Schritt und Trab vor Beginn der Behandlung, an Tag 1 und nach einer 5-, 10- oder 14-tägigen Behandlungsdauer sowie 2-4 Tage nach Beendigung der Behandlung. Die Behandlungsdauer (5, 10 oder 14 Tage) wurde vom Tierarzt in Abhängigkeit des klinischen Zustandes festgelegt. Weiterhin wurde die Akzeptanz der Applikation und das Auftreten von Lahmheitsrezidiven beurteilt. Signifikant bessere Ergebnisse wurden bei der Beurteilung der Lahmheit im Trab (primärer Parameter) nach einer 14-tägigen Behandlung mit Meloxicam erzielt ($p \leq 0.01$) sowie bei der Nachuntersuchung 2-4 Tage nach Ende der Therapie ($p \leq 0.001$). Meloxicam behandelte Tiere zeigten signifikant bessere Ergebnisse bei der Beurteilung der Lahmheit im Trab ($p \leq 0.001$) und Schritt ($p \leq 0.01$), sofern der jeweils letzte Behandlungstag in die Auswertung einbezogen wurde. In der Meloxicamgruppe war die Anzahl der Rückfälle signifikant niedriger ($p \leq 0.05$). Weiterhin wurden die Wirksamkeit und die Akzeptanz von Meloxicam besser beurteilt ($p \leq 0.001$). Es wurden keine Nebenwirkungen in den mit Meloxicam behandelten Pferden beobachtet, wohingegen zwei Pferde in der Gruppe des Referenz-NSAID Nebenwirkungen zeigten. Die Ergebnisse belegen, dass Meloxicam in einer Dosierung von 0,6 mg pro kg Körpergewicht einmal täglich per os verabreicht bei akuten und chronischen Erkrankungen des Bewegungsapparates, die mit Lahmheit einhergehen, eine wirksame, sichere und einfach anzuwendende Behandlungsmöglichkeit darstellt.

Schlüsselwörter: muskulo-skelettale Erkrankungen, Lahmheit, Pferde, nicht steroidale Antiphlogistika, Meloxicam

Introduction

Potential therapies for treatment or alleviation of pain associated with lameness, a condition that can interfere with performance (*Rossdale* et al. 1985, *Goodmann* and *Baker* 1990, *Short* 1994) and has considerable economic impact on the racing industry (*Jeffcott* et al. 1982), continue to be explored. The associated pain has been described as a response to actual or perceived tissue damage and alters the well being of the horse and its ability to function in an expected manner or level of performance (*Short* 1994).

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used by equine practitioners as stand alone therapy or in combination with other treatments depending on the diagnosis. Treatment of acute or chronic inflammatory conditions related to musculoskeletal disorders, such as degenerative joint disease, arthritis, arthrosis, or soft tissue disorders (*McIlwraith* and *Vachon* 1988, *Gregoricka* et al. 1991, *Owens* et al. 1995, *Berthommé* et al. 2001) are commonly treated with NSAIDs, with or without concomitant therapies. NSAIDs effectively diminish signs of pain and inflammation, thus allowing early return to athletic function (*Owens* et al. 1996). The traditional rational for NSAID use is their ability to inhibit cyclo-oxygenase (COX) and hence suppress inflammatory processes and pain. However, many of the currently recognised therapies for lameness are associated with undesirable adverse effects (*MacAllister* et al. 1991, *Kamerling* 2003). Recent studies investigated the effect of NSAIDs on articular cartilage and it is now recognized that many NSAIDs can directly modify synthesis and degeneration of proteoglycans by chondrocytes in vitro (*Armstrong* and *Lees* 1999). Extended use for treatment may increase cartilage damage as it has been shown in case of phenylbutazone (*Beluche* et al. 2001). Furthermore, it has to be considered if NSAID stand alone therapy is sufficient or concomitant therapies are required. The most appropriate study design to investigate the clinical efficacy of NSAIDs is to evaluate efficacy when used as stand alone therapy in selected animals.

Additionally, the ease of administration of any therapy (especially for chronic conditions) is a relevant practical consideration as well as any potential adverse reaction (especially over a long duration of treatment). Based on anecdotal reports from horse owners it is thought that the palatability of certain equine lameness treatments is relatively poor and this may often present difficulties in administration. This may be problematic for owners, particularly over the extended periods of treatment usually required to alleviate the condition, and could detrimentally affect the administration of repeated accurate doses.

Meloxicam, a member of the oxicam class of NSAIDs, inhibits the synthesis of prostaglandins and has potent anti-inflammatory, anti-exudative, analgesic and antipyretic properties. It is already widely used in several species i.e. dogs, cats, cattle and swine. Meloxicam was recently approved for use in horses for reduction of inflammation and relief of pain associated with both acute and chronic musculoskeletal disorders and soft tissue lesions associated with lameness. The objective of this blinded study was to investigate the clinical efficacy, safety and palatability of meloxicam (Metacam® 15 mg/ml oral suspension) at the recommended dose of 0.6 mg/kg bodyweight under field conditions in comparison to the reference NSAID vedaprofen.

Materials and Methods

Study Design

This blind, positive controlled, randomised multi-centre clinical study was performed in Germany under GCP(v) requirements. Horses of any breed and sex with musculoskeletal disorders associated with lameness at least at a trot were included in the study. Animals with a concomitant disease or clinical history that included treatment with short acting corticosteroids or NSAIDs fourteen days before receiving the first treatment or long acting corticosteroids within eight weeks before treatment were not enrolled. Horses requiring additional systemic or local treatment for the actual musculoskeletal disorder or specific conditions or treatment (e.g. rest, shoeing), with severe renal, hepatic or gastro-intestinal diseases and animals with lameness due to fracture, fissure or rupture of tendon, ligament or muscle were not evaluated. Horses requiring additional therapy during the study period were excluded from the evaluation. Overall ten veterinary practices were included in this study.

Treatment

Horses proving suitable for the study (n = 197) were randomly allocated into two blinded treatment groups. Horses were treated for up to 14 consecutive days either with meloxicam once daily at a 24 hour interval at a dose of 0.6 mg/kg body weight administered on top of the feed (corresponding to 4.0 ml Metacam® 15 mg/ml oral suspension per 100 kg body weight). The reference NSAID was administered twice daily directly into mouth (12 hour interval) at an initial dose of 2.0 mg vedaprofen/kg body weight followed by the maintenance dose of 1.0 mg/kg body weight, (corresponding to 2.0 ml and 1.0 ml Quadrisol® per 100 kg body weight respectively). In order to ensure blinding, the investigator gave a sealed medication package for a 14 day treatment to the horse owner. All packages looked identical except the case report form number; therefore the investigator was not aware of the treatment the animal received. The person who administered the drug was not allowed to inform the investigator about the study treatment.

Clinical Examinations and Evaluation

Lameness in horses at a trot, walk and rest was assessed visually prior to and following treatment 2 and 5 days after first treatment and depending on treatment duration on 10 and 14 days after first treatment. Clinical judgement on Day 5 determined whether treatment was terminated or continued until Day 10. If treatment was continued until Day 10, a further clinical judgement on Day 10 was conducted to decide if treatment may be extended until Day 14, based on the clinical improvement under practical conditions. Owners reported on feed intake (scored on a 4 point scale) and appraisals of palatability (3 point scale). The clinician gave for each case a summarising conclusion on the overall efficacy (scored on a 4 point scale) on Day 5 and if treatment was continued on Day 10 and Day 14. A single follow-up clinical examination (of lameness and feed intake assessments) was performed 2 to 4 days following the last treatment. Additionally the incidence of relapse, i.e. horse having a higher lameness score at the follow-up clinical examination than at the end of treatment examination for any type of lameness, was evaluated. In case any adverse events were observed, horse owners had to inform the veterinarian immediately for recording. The primary variable for efficacy was the visual assessment of lameness at a trot, with reference to a 7 point scoring scale (see Table 1). Secondary variables were the visual assessment of lameness at walk, at rest, the assessment of overall efficacy (see Table 1), the evaluation of adverse events and the palatability assessment (see Table 3).

Table 1 Clinical Observations Scoring System
Score-System für die Beurteilung der klinischen Untersuchungen

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
– at a walk and trot	1	No lameness
	2	Uneven gait, but not apparently in any particular limb
	3	Head movements or asymmetry of the gluteal rise barely perceptible: repeated walking/trotting of horse necessary to identify lameness
	4	Weight bearing on affected limb, but with obvious head and neck lifting (front limb lameness) or asymmetry of the gluteal rise (hind limb lameness)
	5	Weight bearing on affected limb only at tip of hoof
	6	No weight bearing on affected limb
	7	Not possible to induce the horse to walk or trot
Overall efficacy	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*

Statistical Analyses

For the primary variable, a difference of the scores of up to ± 0.6 was considered equivalent from the clinical point of view. The meloxicam treatment was said to be at least equivalent to the reference NSAID treatment, if the lower bound of the 95% confidence interval for the Mann-Whitney statistic of the one-sided test was higher than a threshold value corresponding to the lower limit of the equivalence range. The equivalence range was set to score mean ± 0.6. Corresponding threshold values were calculated using normal distribution. In case of significance an additional one-sided Wilcoxon-test on superiority of meloxicam was performed with $\alpha = 0.05$ without exceeding the type I error rate of 5 % for both comparisons. The same statistical methods were employed for the comparisons between the groups using the data at the end of treatment of the secondary parameters lameness at a walk and rest. Additionally, data of the three lameness scores (trot, walk, rest) on each day of examination were evaluated for comparisons between groups with a Wilcoxon-test. The parameters feed intake, overall efficacy and palatability were tested for differences between the treatment groups using Cochran-Mantel-Haenszel tests. Incidences of relapse for both groups were compared using the Fisher´s exact test. All tests on differences between groups were designed as two-tailed tests. For all tests, differences were considered to be statistically significant only if $p \leq 0.05$. All statistical analyses were performed using SAS, software; release 6.12 (1996, SAS Institute Inc., Cary, North Carolina, USA) and TESTIMATE 5.2 (1994, IDV, 82131 Gauting, Germany).

Results

Study population

In total, 197 horses were recruited to the study, 100 to the meloxicam group and 97 to the vedaprofen group. The most common tentative diagnoses were arthritis in 15% or arthrosis in 12 % of all cases, followed by tendinitis (9%), pododermatitis (9%), laminitis (8%) and distortion (6%), various inflammatory processes (6%), tendovaginitis (5%), navicular disease (4%), overstrain (4%), muscle disorders (2%), above mentioned tentative diagnosis in combination with either arthrosis (10%) or arthritis (4%) or various combinations of above mentioned tentative diagnosis (6%). The majority (72%) of horses included in the study were warmblood breeds, with an age of 12.0 ± 7.2 years and 11.3 ± 6.6 years in the meloxicam and vedaprofen group respectively. The mean body weight was 535.0 ± 121.8 kg in the meloxicam group and 514 ± 128.5 kg in the vedaprofen group. The mean number of days since onset of lameness was 37.2 ± 109.1 days in the meloxicam group and 32.9 ± 133.2 days in the vedaprofen group. Related to sex distribution 58% geldings, 8% stallion and 34 % mares were included in the meloxicam group and 56% geldings, 6 % stallion and 38% mares in the vedaprofen group. There were no significant differences between the groups for the distribution of tentative diagnosis, age, body weight, number of days since onset of lameness and sex distribution. The duration of treatment was not statistically significant different between groups. An evaluation of all cases in the study based on whether the condition was acute (duration of symptoms > 30 days) or chronic (duration of symptoms > 30 days) revealed no statistically significant difference between the groups.

Lameness at a trot

For the initial examination the majority of horses 64% (64 of 100) in the meloxicam group and 54% (52 of 97) in the vedaprofen group were categorised as score 4 (bearing weight on the affected limb but with obvious neck/head lifting or asymmetric step) for visual assessment of lameness at a trot. The mean lameness score improved in both treatment groups over the course of the study (see Figure 1). Significant differences between treatment groups were observed after 14 days of therapy ($p \leq 0.01$) and after cessation of thera-

py on Day 14 ($p \leq 0.001$) in favour of meloxicam treatment. The evaluation of "improvement from baseline" (see Table 2) revealed significant differences in favour of meloxicam at Day 5, Day 14 and for the time when treatment was completed.

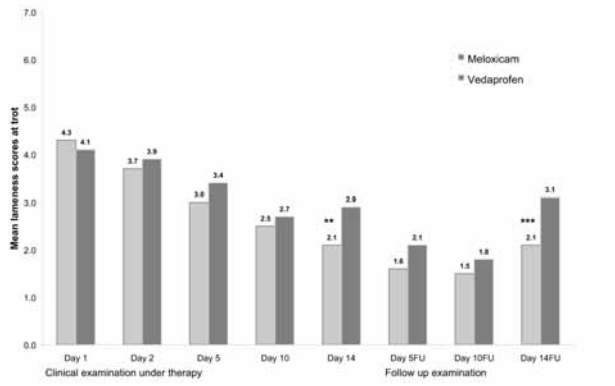

Fig 1 Lameness at trot: Mean scores at each examination day. Mean scores of visual assessment of lameness at trot for each treatment group at each assessment day during the treatment period, and at follow-up examinations. Significance: $**p \leq 0.01$ and $***p \leq 0.001$. FU = follow-up examination (2 to 4 days after the respective last treatment).
Lahmheit im Trab: Score Mittelwerte der einzelnen Untersuchungstage. Mittelwerte der Scores für die visuelle Beurteilung der Lahmheit im Trab für die einzelnen Behandlungsgruppen zu jedem Untersuchungszeitpunkt während der Behandlungsdauer und der Nachuntersuchung. Signifikanz: $**p \leq 0.01$ und $***p \leq 0.001$. FU = Nachuntersuchung (jeweils 2 bis 4 Tage nach der letzten Behandlung).

Table 2 Lameness At Trot: Changes In Mean Scores From Baseline Values. Means and standard deviations of changes in lameness at trot scores from baseline values at Day 1 to all other study time points including the respective end of treatment (ET). Values of changes are shown as positive to illustrate a measure of improvement, although the lameness at trot scores themselves decrease from the Day 1 values.
Lahmheit im Trab: Veränderungen der Score-Mittelwerte gegenüber den Ausgangswerten. Mittelwerte und Standardabweichungen der Veränderungen gegenüber dem Ausgangswert an Tag 1 für die Scores der Beurteilung der Lahmheit im Trab an allen anderen Untersuchungstagen sowie am Ende der Behandlung. Die Werte der Veränderungen sind positiv angegeben um die Verbesserung anzugeben, obwohl die Punktezahl für die Lahmheit im Trab von Tag 1 an abgenommen hat.

	Treatment group				
Time point	Meloxicam (SD)	n	Vedaprofen (SD)	n	P
Day 5	2.7 (±1.6)	26	1.5 (±1.1)	20	**
Day 10	2.6 (±1.2)	24	2.3 (±1.4)	26	ns
Day 14	2.2 (±1.3)	50	1.2 (±0.9)	51	***
ET[a]	2.4 (±1.4)	100	1.6 (±1.2)	97	***

ns: not significant, $p > 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$,
[a] respective end of treatment
ns: nicht significant, $p > 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$,
[a] jeweiliges Behandlungsende

Lameness at a walk and rest

Secondary parameters in the study were the visual assessments of lameness both at a walk and at rest. At the initial examination, 58% (58 of 100) of cases in the meloxicam group and 59% (57 of 97) in the vedaprofen group exhibited symptoms of lameness whilst walking with a corresponding mean score of 2.3 in both groups. By Day 14 of the study this proportion had improved to 10% (5 of 50) in the meloxicam group and 24% (12 of 51) in the vedaprofen group. At the follow-up examination of horses completing treatment at 14 days mean scores at a walk had improved to 1.3 in meloxicam and 1.5 in vedaprofen treated horses ($p \leq 0.05$). Only few cases had symptoms of lameness at rest initially, the corresponding mean scores were 1.5 in both groups. Over the course of the study, the mean lameness scores improved to 1.2 on Day 5 and 1.1 on Days 10 and 14 in both groups. There were no significant differences found between both treatment groups.

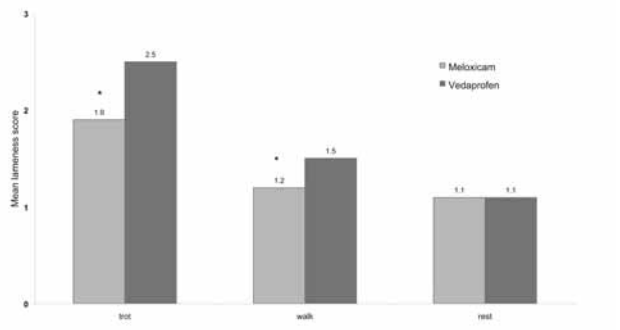

Fig 2 Lameness At A Trot, Walk And Rest: Mean Scores At End of Treatment. Mean scores of visual assessment of lameness at trot, walk and rest for each treatment group at the end of the treatment period, and the statistical significance of any differences between groups. Significance for superiority: $*p \leq 0.001$ (trot) and $*p \leq 0.01$ (walk).
Lahmheit im Trab, Schritt und die Belastung der Gliedmaßen im Stand: Score Mittelwerte am Behandlungsende. Mittelwerte der visuellen Beurteilung der Lahmheit im Trab, Schritt und die Belastung der Gliedmaßen im Stand für die einzelnen Behandlungsgruppen am Ende der Behandlung und die statistische Signifikanz zwischen den Behandlungsgruppen. Signifikanz für den Test auf Überlegenheit: $*p \leq 0.001$ (Trab) and $*p \leq 0.01$ (Schritt).

Lameness at the end of treatment

The lameness data was further evaluated to compare the groups for all three categories of lameness, at a trot, walk and rest at the point when each case was judged to require no further treatment (end of treatment; see Figure 2). No symptoms of lameness at a trot were found in 53% (53 of 100) of meloxicam treated horses when treatment was discontinued compared to 32% (31 of 97) of horses in the reference NSAID group and corresponding mean scores were 1.9 and 2.5 respectively. No symptoms of lameness whilst walking were seen in 91% (91 of 100) of horses treated with meloxicam and 77% (75 of 97) of the vedaprofen group with corresponding mean scores of 1.2 and 1.5 respectively. No significant differences were seen for lameness at rest. Significant differences at the end of treatment were revealed in analyses for non-inferiority of meloxicam, further analysis showed a superiority of meloxicam for the parameters of lameness at a trot and walk.

Overall efficacy

Significant differences were observed between treatment groups in the distribution of scores for the assessment of the overall efficacy at all time points in favour of meloxicam treatment (Fig 3).

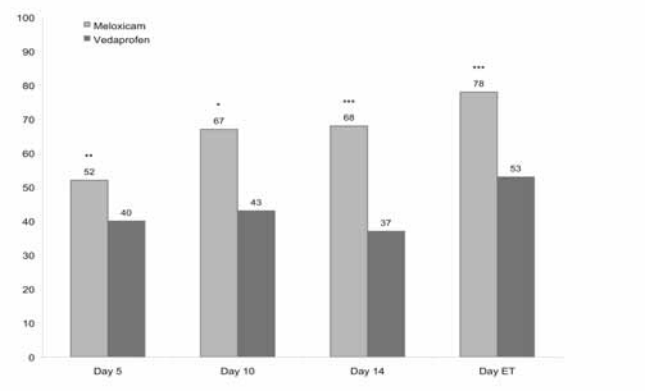

Fig 3 Overall Efficacy. Percentage of animals with very good and good overall efficacy at each of the assessment days during the treatment period and at the end of treatment, and the significant differences between groups. Significance: *p ≤ 0.05 (on Day 10), **p ≤ 0.01 (on Day 5), ***p ≤ 0.001 (on Day 14 and at the end of treatment = ET).
*Beurteilung der Wirksamkeit. Prozentsatz der Tiere, bei denen eine sehr gute und gute Wirksamkeit an den einzelnen Untersuchungstagen während der Behandlung und am Ende der Behandlung festgestellt wurde; signifikante Unterschiede zwischen den Gruppen: *p ≤ 0.05 (an Tag 10), **p ≤ 0.01 (an Tag 5), ***p ≤ 0.001 (an Tag 14 und am Ende der Behandlung = ET).*

At all times during the study the feed intake of all animals in the meloxicam group remained unchanged, whereas there were episodes of reduced feed intake in horses in the vedaprofen group. The difference was significant (p ≤ 0.05) between the groups on Day 5 and at the end of treatment when 5% and 6% (5 and 6 of 97 respectively) of cases showed a reduction in feed intake. Drug palatability scores between the two groups were significantly different (p ≤ 0.001) at all assessments in favour of meloxicam (see Table 3). None of the owners reported poor palatability for meloxicam during the study but this score was given in up to 45% of cases in the vedaprofen group. Good palatability was recorded in 94% of the meloxicam cases compared to 36% of vedaprofen treated horses at the respective end of treatment assessment.

Adverse events occurred in two horses in the vedaprofen group whereas no adverse event was recorded in the meloxicam group. One horse had irritation of the mucosa in the mouth 12 hours after administration, which had resolved by Day 5, the other showed increased salivation after each administration of the drug from Day 2 to Day 14. In both cases treatment was continued and no concomitant therapy was administered; therefore both cases had been considered in the evaluation according to the inclusion and exclusion criteria.

Discussion

Participating veterinary surgeons based at 10 different German centres performed this blinded, randomised, positive controlled clinical field study to compare the clinical efficacy, safety and palatability of meloxicam to vedaprofen in 197 lame horses. The effective treatment of lameness is of major importance in competitive horse racing as lameness is considered to be the most significant factor in loss of racing revenue (*Jeffcott* et al. 1982). Epidemiological studies show that lameness caused the greatest number of days lost to training (*Rossdale* et al. 1985). The alleviation of symptoms of pain

Table 3 Palatability. Scores for palatability awarded by owners and the proportion of cases for each treatment group, according to the following definition: good (score 1) = horse took treatment willingly, satisfactory (score 2) = horse took treatment reluctantly, poor (score 3) = horse refused to take treatment willingly (significance: *** p ≤ 0.001).
*Akzeptanz. Die Akzeptanz der Applikation wurde von den Pferdebesitzern beurteilt; angegeben wurde die absolute Anzahl sowie der prozentuale Anteil für jede Behandlungsgruppe gemäß folgender Beurteilungsskala: gut (Score 1) = das Pferd nimmt die Medikation bereitwillig auf, genügend (Skala 2) = das Pferd nimmt die Medikation zögernd auf, schlecht (Skala 3) = das Pferd verweigert die freiwillige Aufnahme (Signifikanz: *** p ≤ 0.001).*

			Palatability score						
Treatment day	Group	n	good		satisfactory		poor		P
5	Meloxicam	26	25	(96%)	1	(4%)	0	(0%)	***
	Vedaprofen	20	4	(20%)	7	(35%)	9	45%)	
10	Meloxicam	24	23	(96%)	1	(4%)	0	(0%)	***
	Vedaprofen	26	10	(38%)	10	(38%)	6	(23%)	
14	Meloxicam	50	46	(92%)	4	(8%)	0	(0%)	***
	Vedaprofen	51	21	(41%)	18	(35%)	12	(24%)	
ET[a]	Meloxicam	100	94	(94%)	6	(6%)	0	(0%)	***
	Vedaprofen	97	35	(36%)	35	(36%)	27	(28%)	

*** p ≤ 0.001, [a] respective end of treatment
*** p ≤ 0.001, [a] jeweiliges Behandlungsende

Other variables: Relapse, feed intake, palatability and safety

A significant difference (p ≤ 0.05) in the incidence of relapse was revealed between the two groups, 8% of meloxicam cases compared to 21% of vedaprofen cases suffered a relapse of lameness symptoms at the follow-up examination 2 to 4 days after the end of treatment.

related to lameness is considered important for the assessment of analgesic efficacy of NSAIDs and other pain relieving drugs. NSAIDs have been used in horses for decades and their clinical value has been previously investigated in the treatment of equine musculoskeletal disorders in clinical field studies (*Gregoricka* et al. 1991, *Owens* et al. 1995, *Berthommé* et al. 2001). Both acute as well as chronic low-grade synovitis are believed to have the potential for initiating progressive cartilage breakdown, and therefore, adequate treatment of these conditions is essential in prevention of equine osteoarthritis (*Todhunter* and *Lust* 1990). Recognition of the mediators and products of inflammation as important factors in the initiation of articular cartilage degeneration has put an emphasis on the inflammatory response in the pathogenesis of equine osteoarthritis (*Palmer* and *Bertone* 1994). Meloxicam has been acknowledged as a potentially useful NSAID for the treatment of equine inflammation and relief of pain. The tendency of this type of NSAID to accumulate in inflammatory exudates may explain a longer duration of action than that anticipated based on elimination half - life (*Lees* et al. 1987). Subsequent investigation of the pharmacodynamics and pharmacokinetics of meloxicam in the horse indicates that once daily dosing at 0.6 mg/kg bodyweight may be an appropriate dosing regimen (*Lees* et al. 1991, *Toutain* and *Cester* 2004). The suggested once daily dose regimen was investigated in this randomised, blinded, positive controlled clinical study, where the tentative diagnosis included a range of clinical conditions either of acute or chronic duration characterised by varying degrees of severity. All cases included had to fulfil defined inclusion and exclusion criteria. Concomitant therapies were not allowed to be conducted as they would have directly influenced the evaluation of clinical efficacy of NSAID drug use.

Significantly better results ($p \leq 0.01$) for "lameness at a trot" (primary clinical variable) after 14 days of treatment and at the follow-up examination were found in the meloxicam group compared to the reference group. Significant differences in "lameness at walk" occurred in favour of meloxicam at the follow-up examination on Day 14. A significant superiority in lameness at a trot and walk was revealed in favour of meloxicam for the evaluation at the time point when therapy was judged no longer necessary. Furthermore, the overall clinical efficacy achieved significant better results compared to vedaprofen treated horses for all time points assessed and fewer meloxicam cases relapsed to lameness. Data from literature confirm efficacy of NSAIDs, however due to different study designs with regard to treatment duration, selection criteria for study animals and inclusion of defined diagnosis and the assessment and evaluation of lameness, data obtained are not directly comparable.

The toxic potential of some NSAIDs to horses is recognised, and has been investigated experimentally (*MacAllister* et al. 1991). It has been suggested that phenylbutazone which is a widely used NSAID in horses should be used judiciously because chronic administration may suppress proteoglycan synthesis and potentiate cartilage damage (*Beluche* et al. 2001). Several authors have suggested that NSAID side effects are associated with inhibition of one isoform of cyclooxygenase (COX-1) whereas the therapeutic effects of NSAIDs are due to COX-2 inhibition (*Brideau* et al. 2001, *Clegg* and *Booth* 2000, *Kamerling* 2003, *McIlwraith* and *Vachon* 1988, *Moses* et al. 2001). The COX-2 selectivity of meloxicam on equine synovial explants has been shown to be greater than that for phenylbutazone, flunixin meglumine, ketoprofen and carprofen (*Moses* et al. 2001). Additionally, it has been suggested that meloxicam use is associated with fewer adverse effects than some other NSAIDs (*Kamerling* 2003). No adverse events have been reported in the present study in 100 clinical cases treated with meloxicam. This supports the safety of meloxicam compared to 2 adverse events amongst 97 horses in the vedaprofen treatment group.

Palatability of a product is considered to be an important factor in the ease of use by horse owners, and for the accuracy and compliance of dosing. Convenience in extended periods of administration in chronic cases of lameness should be taken into account. In literature, no findings are reported on previous studies investigating the palatability of equine oral NSAID therapy. In this multi-centred study owners reported good palatability in 94% of meloxicam treated cases compared to only 36% of cases in the vedaprofen group at the end of therapy.

It is considered to be of major practical importance that an orally administered NSAID given to a horse for several days should be easy to use and palatable. In this study, meloxicam administered once daily showed significantly better results for palatability compared to vedaprofen, which was administered twice daily according to label instructions.

Conclusion

The results of this positive controlled blinded field trial indicate that 0.6 mg meloxicam/kg bodyweight administered once daily is an efficacious, safe, easy to use, and highly palatable NSAID treatment for reduction of inflammation and relief of pain associated with lameness in both acute and chronic musculoskeletal disorders and soft tissue lesions.

Literature

Armstron S. and *P. Lees* (1999): Effects of R and S enantiomers and a racemic mixture of carprofen on the production and release of proteoglycan and prostaglandine E2 from equine chondrocytes and cartilage explants. Am J Vet Res 60, 98-104

Beluche L. A., A. L. Bertone, D. E. Anderson and *C. Rohde* (2001): Effects of oral administration of phenylbutazone to horses on in vitro articular cartilage metabolism. Am J Vet Res 62, 1916-1921

Berthommé I., N. Franz and *L. Goossens* (2001): Vergleichende Untersuchung zur Wirksamkeit von Flunixin bei der Behandlung von akuten Erkrankungen des Bewegungsapparates beim Pferd. Prakt. Tierarzt 82, 688-693

Brideau C., C. Van Staden and *C. C. Chan* (2001): In vitro effects of cyclooxygenase inhibitors in whole blood of horses, dogs, and cats. Am J Vet Res 62, 1755-1760

Clegg P. and *T. Booth* (2000): Drugs used to treat osteoarthritis in the horse. In Practice 22, 594-603

Goodmann N. L. and *B. K. Baker* (1990): Lameness diagnosis and treatment in the Quarter Horse racehorse. Vet. Clin. North. Am. 6, 85-108

Gregoricka M. J., K.-R. Busch and *R. A. Pollet* (1991): Clinical evaluation of ketoprofen: a new nonsteroidal anti-inflammatory drug for use in horses. Proc. Am. Assoc. Equine Pract. 37, 19-26

Jeffcott L. B., P. D. Rossdale, J. Freestone, C. J. Frank and *P. F. Towers-Clark* (1982): An assessment of wastage in thoroughbred racing from conception to 4 years of age. Equine Vet J 14, 185-198

Kamerling S. G. (2003): Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Affect Pain and Inflammation. Louisiana State University Equine Veterinary Research Program Newsletter

Lees P., A. J. Higgins, A. D. Sedgwick and *S. A. May* (1987): Applications of equine models of acute inflammation. The Ciba-Geigy Prize for Research in Animal Health. Vet Rec 120, 522-529

Lees P., A. D. Sedgwick, A. J. Higgins, K. E. Pugh and *U. Busch* (1991): Pharmacodynamics and pharmacokinetics of miloxicam in the horse. Br Vet J 147, 97-108

MacAllister C. C., S. J. Morgan, A. T. Borne and *R. A. Pollet* (1991): A Comparison of the Adverse Effects of Phenylbutazone, Flunixin Meglumine and Ketoprofen in horses. Abstracts of the American College of Veterinary Internal Medicine New Orleans

McIlwraith C. W. and *A. Vachon* (1988): Review of pathogenesis and treatment of degenerative joint disease. Equine Vet J, Suppl 1, 3-11

Moses V. S., J. Hardy, A. L. Bertone and *S. E. Weisbrode* (2001): Effects of anti-inflammatory drugs on lipopolysaccharide-challenged and -unchallenged equine synovial explants. Am J Vet Res 62, 54-60

Owens J. G., S. G. Kamerling, S. R. Stanton and *M. L. Keowen* (1995): Effects of ketoprofen and phenylbutazone on chronic hoof pain and lameness in the horse. Equine Vet. J. 27, 296-300

Owens J. G., S. G. Kamerling ,S. R. Stanton, M. L. Keowen and *J. S. Prescott-Mathews* (1996): Effects of pretreatment with ketoprofen and phenylbutazone on experimentally induced synovitis in horses. Am J Vet Res, 57, 866-874

Palmer J. L. and *A. L. Bertone* (1994): Joint structure, biochemistry and biochemical disequilibrium in synovitis and equine joint disease. Equine Vet J 26, 263-277

Rossdale P. D., R. Hopes and *N. J. Digby* (1985): Epidemiological study of wastage among racehorses 1982 and 1983. Vet Rec 116, 66-69

Short C. (1994): Equine pain: use of non-steroidal anti-inflammatory drugs and analgesics for it's prevention and control. Proceedings of the 10th International Conference of Racing analysts and Veterinarians

Todhunter R. and *G. Lust* (1990): Synovial joint anatomy, biology and pathobiology. Equine Surgery, 844-865

Toutain P.-L. and *C. Cester* (2004): Pharmacokinetic-pharmacodynamic relationships and dose response to meloxicam in horses with induced arthritis in the right carpal joint. Am J Vet Res 65, 1533-1541

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