Efficacy of tiludronate in the treatment of horses with signs of pain associated with osteoarthritic lesions of the thoracolumbar vertebral column

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Objective—To evaluate the efficacy of tiludronate for the treatment of horses with signs of pain associated with lesions of the thoracolumbar vertebral column.

Animals—29 horses with clinical manifestations of pain associated with lesions of the thoracolumbar vertebral column and abnormal radiographic findings indicative of osteoarthritis of the articular processes–synovial intervertebral joints.

Procedures—Horses were initially examined in accordance with a standardized protocol, which included radiographic, ultrasonographic, and scintigraphic examinations. Fifteen horses were randomly assigned to receive tiludronate (1 mg/kg, IV, as a slow-rate infusion), and 14 horses received a control substance (day 0). Horses were monitored for the subsequent 120 days. Clinical evaluations were performed on days 60 and 120. Horses that had no evidence of clinical improvement on day 60 were administered tiludronate. Statistical analyses were performed to compare efficacy at day 60, improvement of dorsal flexibility at day 120, and dorsal flexibility before and 60 days after administration of tiludronate.

Results—Horses treated with tiludronate had significant improvement in dorsal flexibility between days 0 and 60, compared with control horses. Clinical improvement in dorsal flexibility was still evident at day 120. The percentage of positive responses was higher in the tiludronate group at 60 days.

Conclusions and Clinical Relevance—Tiludronate had efficacy in the treatment of horses with signs of pain induced by osteoarticular lesions of the thoracolumbar vertebral column, causing a significant improvement in dorsal flexibility. Tiludronate may offer a treatment option for the management of horses with intervertebral lesions and the associated pain. (*Am J Vet Res* 2007;68:329–337)

Problems attributable to clinical manifestations of pain associated with lesions of the thoracolumbar vertebral column are often reported as a major cause of poor performance and gait abnormalities in sport and race horses.[1-3] These can result in a wide array of pathologic manifestations during exercise,[2-4] which include reduced performance, changes in behavior, reluctance to jump, difficulties in jumping fence combinations, bucking, rearing, resistance to saddling, stiffness in the thoracolumbar or cervical regions, and ill-defined or intermittent lameness of the hind limbs. Imaging techniques have improved such that they can provide essential information on lesions that potentially are causing the pain. Currently, the combination of radiography, ultrasonography, and scintigraphy allows identification of lesions of the spinous processes, AP–SIVJs, and vertebral bodies.[5-7]

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Abbreviations

AP–SIVJ	Articular processes–synovial intervertebral joint
NSAID	Nonsteroidal anti-inflammatory drug
SRDF	Score for reduction of dorsal flexibility
mSRDF	Mean SRDF
ROI	Region of interest

Management of horses with manifestations of pain associated with lesions of the thoracolumbar vertebral column primarily is aimed at removing or alleviating the pain so that they can comfortably resume regular training programs.[2] This usually is achieved by local injections of corticosteroids at the site of lesions. To our knowledge, no systemically administered treatment has been scientifically assessed for use in the treatment and management of affected horses. Tiludronate is a bisphosphonate that reportedly[8] is efficacious for use in the treatment of horses with bone spavin or navicular disease with osteolytic lesions. Because bone lesions are considered to be a primary cause of pain associated with the thoracolumbar vertebral column, we hypothesized that tiludronate could regulate bone remodelling and result in clinical improvement in horses with pain associated with lesions of the thoracolumbar vertebral column. Therefore, the study reported here was designed to assess the efficacy of tiludronate administered IV as a single slow-rate infusion for the treatment of horses

with pain associated with lesions of the thoracolumbar vertebral column.

Materials and Methods

Sample population—Sport or racing horses examined because of evidence of pain associated with the thoracolumbar vertebral column, such as poor performance or stiffness during exercise, were eligible for inclusion in the study. Written consent was obtained from owners and referring veterinarians indicating their willingness to assist with the study.

Inclusion criteria—Horses were eligible for inclusion in the study when they had clinical manifestations of pain associated with the thoracolumbar vertebral column (ie, restricted thoracolumbar movement during passive mobility and reduction of dorsal flexibility when horses were trotting and cantering, as determined by an experienced clinician [JMD]); no evidence of lameness or lameness of grade 1/5 or lower when evaluated during routine examination; and obvious radiographic evidence of osteoarthritis of the AP–SIVJs (eg, osteolysis, sclerosis, periarticular proliferation, or ankylosis), possibly associated with lesions of the spinous processes (impingement, contact, or overriding of spinous processes and enthesopathy of the interspinous ligament) or spondylosis of the vertebral bodies.

Horses were excluded from the study when they were < 2 years old, had been treated by systematic administration of an NSAID during the 15 days preceding the initial examination or by administration of a corticosteroid during the 30 days preceding the initial examination, had been treated by local administration (perispinous injection, deep paravertebral injection, or mesotherapy) of an NSAID or corticosteroid, or had evidence of lameness (grade 2/5 or higher). Horses were excluded retrospectively by the investigators or at the request of the owner or when they had any event during the follow-up period that could potentially influence the clinical outcome.

Initial examination—A standardized clinical examination was performed on the day of enrollment in the study. Examination included qualitative and quantitative assessment of atrophy of the dorsal musculature and passive mobility (range of motion and sensitivity). A value for SRDF was determined for each of 5 conditions during examination of ambulatory horses (slow trot [3 to 4 m/s] in a straight line, fast trot [6 to 7 m/s] in a straight line, trot in a circle [in both directions] on a hard surface, trot in a circle [in both directions] on a soft surface, and canter in a circle [in both directions] on a soft surface). All examinations were videotaped to allow final review by investigators (JMD, VC, and BR) after completion of the study.

The SRDF was determined for each of the 5 conditions by use of a scale from 0 (not detected) to 3 (severe; **Appendix 1**). The SRDF values for each of the 5 conditions were used to calculate an mSRDF value for each horse.

Five radiographic views of the thoracolumbar vertebral column were obtained for each horse to allow investigators to completely assess the thoracic, thoracolumbar, and lumbar regions (**Figure 1**). For each region, a severity score (range, 0 [normal] to 3 [severe]) was determined for abnormal findings of the spinous processes, AP–SIVJs, and vertebral bodies (**Appendix 2**). Transrectal ultrasonographic examination of the pelvis was performed to assess the lumbosacral joint, fifth lumbar intervertebral disk, and sacroiliac joints.

Nuclear scintigraphy of the thoracolumbar vertebral area and pelvis was performed on 20 horses (the first 10 and the last 10 horses enrolled in the study). Scintigraphy was performed on days 0 and 120. Each horse received technetium ^{99m}Tc-dicarboxypropan-diphosphonic acid[a] (1 GBq/100 kg, IV) and was evaluated 3 hours later by use of a gamma camera.[b] Dorsal thoracic and lumbar views and left and right oblique thoracic and lumbar views were acquired. In addition, left and right oblique, dorsal, and dorsocaudal views of the pelvis were obtained. Horses remained in quarantined stalls for at least 48 hours after scintigraphic examination.

Motion correction software[c] was used for each image. Increased radiopharmaceutical uptake was subjectively graded as mild, moderate, or severe. For the quantitative evaluation, left and right oblique views of the abnormal area were acquired over a period of 3 minutes. An ROI was manually drawn over an area of increased radiopharmaceutical uptake on the oblique views (**Figure 2**). The mean count per pixel in the ROI

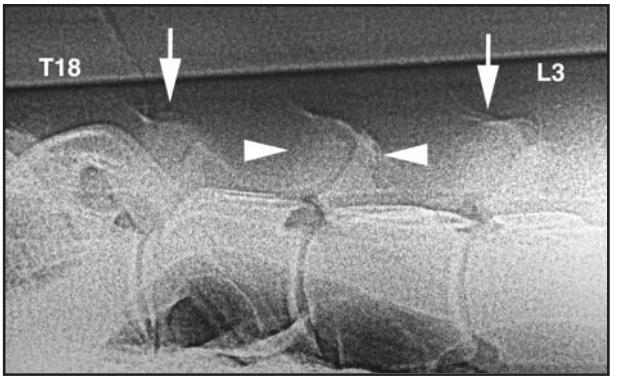

Figure 1—Representative radiographic image of the AP–SIVJ between T18 and L3 in a horse. Notice the dorsal periarticular proliferations (arrows) on the T18-L1 and L2-L3 AP–SIVJs and bone sclerosis (arrowheads) of the L1-L2 AP–SIVJ. There is also a lesion attributable to contact of the spinous processes evident between T18 and L1.

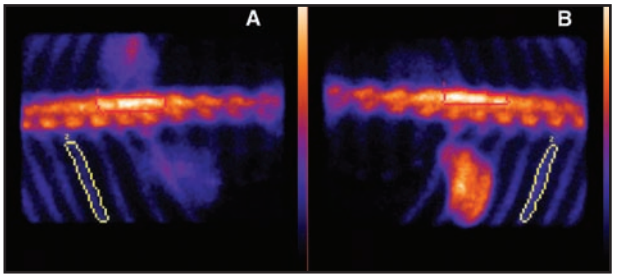

Figure 2—Left (A) and right (B) oblique nuclear scintigraphic scans of the thoracolumbar region of the horse in Figure 1 on day 0. Notice the increased radiopharmaceutical uptake over the articular processes between T17 and L2. The ROI (red line) was manually drawn over the area of increased radiopharmaceutical uptake, and the ratio between the mean count per pixel of the ROI and the mean count per pixel of the reference region (15th rib [yellow line]) was determined for each view. The ratios were compared between days 0 and 120.

was measured and compared with the mean count per pixel of the 15th rib, which was used as a reference. The ratio between the values for the ROI and the values for the 15th rib were calculated on both oblique views (ratio for the left and right views).

Treatments—On the day of enrollment, horses were randomly allocated to treatment groups. Randomization was performed on each block of 10 horses to provide an equal number of treated and control horses examined by use of scintigraphy. Each randomization box consisted of 10 vials, each of which contained control or tiludronate[d] powder. Tiludronate and control substances were supplied as physically identical preparations (freeze-dried powders) to allow their administration without the investigators, owner, or referring veterinarian being aware of which product was administered to each horse.

Powders were reconstituted in 1 L of isotonic (0.9% NaCl) solution. Horses in the treatment group were administered tiludronate (1 mg/kg, IV) as a single slow-rate infusion. Horses in the control group were administered a similar volume of a solution containing an inert substance. All infusions were administered IV during a period of 30 to 60 minutes. Day of infusion was designated as day 0.

Horses were evaluated on days 60 and 120. When investigators judged that a horse had not improved sufficiently by 60 days after enrollment, they could administer a treatment of tiludronate (1 mg/kg, IV) as a slow-rate infusion at that time. Horses receiving a second treatment were considered treatment failures for the initial infusion.

Monitoring—Horses were monitored for 120 days after enrollment in the study. Treatments were administered by the referring veterinarian 1 to 7 days after enrollment. A complete clinical examination (same examinations as on day 0) was repeated on days 60 and 120. On day 120, a complete diagnostic imaging evaluation, including radiography and ultrasonography of the pelvis, was performed. In addition, 20 horses (the first and last 10 horses enrolled in the study) were examined by use of scintigraphy on day 120.

Criteria were established for assessing treatment efficacy (Appendix 1). Horses were not required to be rested during the monitoring period, and the duration and intensity of exercise were progressively increased on the basis of each horse's perceived comfort. Failure rate for the treatment administered on day 0 was determined as the percentage of horses that required treatment with tiludronate because evaluation on day 60 revealed a response to treatment that was not sufficient.

In addition, the number of horses with a positive response to treatment was determined 60 days after treatment with tiludronate for 22 horses (15 horses administered tiludronate on day 0 and evaluated on day 60 and 7 control horses administered tiludronate on day 60 and evaluated on day 120). Response to treatment was assessed on a scale of 0 to 3 (0, excellent; 1, good; 2, fair; and 3, poor; Appendix 1). A positive response was considered an assessment of excellent, good, or fair.

None of the horses were allowed local administration (perispinous injections, deep paravertebral injections, or mesotherapy) of anti-inflammatory drugs during the entire monitoring period. It was permissible to administer antimicrobials or NSAIDs during the monitoring period when needed for concomitant disease. When NSAIDs were administered systematically to treat horses with a concomitant disease, the subsequent evaluation was performed at least 15 days after that administration. We did not allow chondroprotective drugs to be administered to the horses, and changes in the type of shoes or shoeing characteristics were not allowed during the 120-day monitoring period.

Statistical analysis—Groups were compared with regard to descriptive variables (breed, type of use, age, sex, and amount of exercise before onset of evidence of pain) and results of clinical examinations. To assess drug efficacy, 3 comparisons were statistically analyzed for clinical variables. Results for efficacy variables were compared between the control and tiludronate groups at day 60 by use of the Student *t* test (SRDF), Fisher exact test (failure rate), and χ^2 test or Fisher exact test (response to treatment as assessed by the investigators and owners). The percentage change in values at day 120 (relative to values on day 0) was compared between the control and tiludronate groups by use of the Wilcoxon test (mSRDF), and the percentage of horses with substantial improvement in the mSRDF (improvement of $\geq 33\%$) was evaluated by use of the Fisher exact test. For horses treated on day 60 with tiludronate (ie, failure of initial treatment), the mSRDF for each horse on day 60 was used to calculate the mean group SRDF at day 120, assuming that for these horses judged as treatment failures, there would be no change in mSRDF between days 60 and 120. Finally, results for the main clinical variables determined before and 60 days after a single administration of tiludronate were compared. This analysis was conducted on 15 horses treated with tiludronate on day 0 and assessed at day 60 and on 7 control horses treated with tiludronate on day 60 and assessed at day 120. Analysis was performed by use of a *t* test on paired series for SRDF and the χ^2 test or Fisher exact test for response to treatment as assessed by the investigators and owners.

Statistical analyses were conducted by use of commercially available statistical software.[e] For each test, values of $P < 0.05$ were considered significant.

Results

Sample population—Thirty horses were initially enrolled in the study, but 1 horse in the control group was excluded at the end of the monitoring period because of lack of compliance by the owner with management instructions. Thus, 29 horses completed the study. The horses (mean age, 7.6 years) comprised 14 mares, 3 stallions, and 12 geldings. Treatment groups were comparable with respect to all clinical variables assessed on day 0.

All horses had osteoarthritic changes of the AP–SIVJs, most of which were in the lumbar region. Abnormal findings of the AP–SIVJs were primarily grades 1 and 2 in each region (thoracic, thoracolumbar, and lumbar), with an almost equal representation of sclerosis, periarticular proliferation, and osteolytic lesions

(**Table 1**). Only 1 horse had ankylosis of AP–SIVJs in the lumbar area. Twenty horses had concomitant abnormal radiographic findings of the spinous processes (19 with contact of the spinous processes and 1 with enthesopathy of the interspinous ligament). Most of the lesions of the spinous processes were detected in the thoracic region (16 thoracic, 11 thoracolumbar, and 8 lumbar), with 8 spinous processes impinging only in the thoracic area. Five horses had lesions that extended from the thoracic to the lumbar regions. Abnormal findings of the spinous processes were primarily grades 2 and 3. Two horses had spondylosis of the vertebral bodies in the midthoracic region concomitant with lesions of osteoarthritis in the thoracolumbar or lumbar region.

Comparison between tiludronate and control groups at day 60—An analysis was conducted to compare values between days 0 and 60 for 15 horses in the tiludronate group and 14 horses in the control group (**Table 2**). The failure rate was only 20% (3/15) for the tiludronate group, compared with 50% (7/14) for the control group; these values did not differ significantly ($P = 0.095$). Change of the SRDF for horses evaluated while cantering differed significantly ($P = 0.019$) between the control and tiludronate groups. No signifi-

Table 1—Distribution of the radiographic findings of the AP–SIVJs, spinous processes, and vertebral bodies on the basis of region of the vertebral column and severity score* on the day of initial examination and infusion with tiludronate or a control substance (day 0).

	Thoracic				Thoracolumbar				Lumbar			
Variable	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**
AP–SIVJs												
Dorsal proliferation	15	7	6	1	9	9	10	1	3	10	14	2
Sclerosis	16	7	6	0	10	7	10	2	3	10	14	2
Osteolysis	21	6	2	0	12	8	9	0	5	19	5	0
Ankylosis	29	0	0	0	29	0	0	0	28	0	0	1
Spinous processes	13	3	7	6	18	2	3	6	21	1	5	2
Vertebral bodies	27	0	1	1	29	0	0	0	29	0	0	0

*Severity score for abnormal radiographic findings was graded on a scale of 0 (normal) to 3 (severe).

Table 2—Mean ± SD values for efficacy criteria evaluated on days 0 and 60 in 14 control horses and 15 horses treated with tiludronate.

Efficacy criteria	**Treatment**	**Day 0**	**Day 60**
SRDF*			
Slow trot in straight line	Control	1.29 ± 0.47	1.57 ± 0.51
	Tiludronate	1.53 ± 0.74	1.40 ± 0.83
Fast trot in straight line	Control	1.50 ± 0.52	1.36 ± 0.63
	Tiludronate	1.67 ± 0.72	1.33 ± 0.82
Trot in circle in both directions on a hard surface	Control	1.77 ± 0.60	1.54 ± 0.52
	Tiludronate	1.54 ± 0.66	1.29 ± 0.83
Trot in a circle in both directions on a soft surface	Control	1.62 ± 0.51	1.31 ± 0.48
	Tiludronate	1.33 ± 0.62	1.13 ± 0.64
Canter in a circle in both directions on a soft surface	Control	1.58 ± 0.67	1.58 ± 0.67[a]
	Tiludronate	1.62 ± 0.51	0.92 ± 0.64[b]
mSRDF†	Control	1.53 ± 0.40	1.44 ± 0.41
	Tiludronate	1.57 ± 0.53	1.24 ± 0.64
Positive response to treatment‡			
As evaluated by the investigators§	Control	NA	4/14 (28.6)
	Tiludronate	NA	9/15 (60.0)
As evaluated by the owners§	Control	NA	8/14 (57.1)
	Tiludronate	NA	13/15 (86.7)
Failure rate at day 60‖	Control	NA	7/14 (50.0)
	Tiludronate	NA	3/15 (20.0)

*A value for SRDF was determined for each of 5 conditions in ambulatory horses by use of a scale of 0 (normal) to 3 (severe). †The SRDF values for each of the 5 conditions were used to calculate an mSRDF value for each horse. ‡Response to treatment was assessed on a scale of 0 to 3 (0, excellent; 1, good; 2, fair; and 3, poor); a positive response was considered an assessment of excellent, good, or fair. §Value reported is number of horses that had a positive response/number of horses treated (percentage). ‖Value reported is number of horses treated with tiludronate on day 60 because of an insufficient response to the initial treatment/number of horses treated on day 0 (percentage).

[a,b]Within a variable, values with different superscript letters differ significantly ($P = 0.019$).

NA = Not applicable.

Table 3—Mean ± SD values for efficacy criteria evaluated before and 60 days after a single treatment with tiludronate in 22 horses (15 horses treated with tiludronate on day 0 and evaluated on day 60 and 7 control horses administered tiludronate on day 60 and evaluated on day 120).

Efficacy criteria	Before treatment with tiludronate	60 days after treatment
SRDF*		
Slow trot in a straight line	1.59 ± 0.67	1.32 ± 0.84
Fast trot in a straight line	1.64 ± 0.66[a]	1.23 ± 0.75[b]
Trot in a circle in both directions on a hard surface	1.68 ± 0.68[c]	1.25 ± 0.72[d]
Trot in a circle in both directions on a soft surface	1.43 ± 0.60[e]	1.14 ± 0.57[f]
Canter in a circle in both directions on a soft surface	1.72 ± 0.57[c]	1.00 ± 0.59[d]
mSRDF†	1.61 ± 0.48[c]	1.18 ± 0.57[d]
Positive response to treatment‡		
As evaluated by the investigators§	NA	14/22 (63.6)
As evaluated by the owners§	NA	17/22 (77.3)‖

‖Percentage of positive responses was significantly ($P = 0.011$) higher, compared with the percentage of negative responses.

[a-f]Within a row, values with different superscript letters differ significantly ([a,b]$P = 0.001$; [c,d]$P < 0.001$; and [e,f]$P = 0.01$).

See Table 2 for remainder of key.

cant differences were noticed between groups with regard to change of the mSRDF or change of the SRDF when horses were evaluated for the other conditions (ie, fast or slow trot in a straight line or trot in circles on a soft or hard surface). Positive response to treatment, as judged by the investigators and owners, was approximately 30% higher for the tiludronate group, compared with that for the control group; however, these values did not differ significantly for the investigators ($P = 0.092$) or for the owners ($P = 0.086$).

Comparisons between tiludronate and control groups at day 120—An analysis was conducted to compare values between days 0 and 120 for 15 horses in the tiludronate group and 14 horses in the control group. At the end of the 120-day monitoring period, horses treated with a single IV injection of tiludronate on day 0 had a mean ± SD improvement in mSRDF (–30.0 ± 24.1%) that was better than the improvement for the control group (–10.6 ± 41.1%); however, these values did not differ significantly ($P = 0.07$). The percentage of horses with substantial improvement (≥ 33%) of the mSRDF was also clearly higher in the treated group (46.7% [7/15]) than in the control group (21.4% [3/14]); however, these values also did not differ significantly ($P = 0.15$).

Change in efficacy variables 60 days after single administration of tiludronate—An analysis was conducted to compare results for 15 horses treated with tiludronate on days 0 and 7 with those of control horses that were judged to be treatment failures on day 60 and administered tiludronate at that time (**Table 3**). Values for mSRDF and SRDF measured for each condition except slow trotting in a straight line differed significantly ($P < 0.001$) between before and 60 days after treatment with tiludronate. At 60 days after administration of a single infusion of tiludronate, the percentage of positive responses to treatment as assessed by the owners (77.3% [17/22]) was significantly ($P = 0.011$) higher, compared with the percentage of negative responses (22.7% [5/22]). Investigators assessed that there was a positive response for 14 of 22 (63.6%) tiludronate-treated horses; however, this percentage did not differ significantly ($P = 0.086$) from the percentage of negative responses (36.4% [8/22]) assessed by the investigators.

Scintigraphy—The ratio between the value for the ROI and the reference value for the 15th rib did not change significantly between days 0 and 120 for the treatment or control groups.

Discussion

The study reported here was designed to assess the efficacy of a single dose of tiludronate (1 mg/kg) administered as a slow IV infusion for the treatment of horses with pain induced by osteoarticular lesions of the thoracolumbar vertebral column. This study included a limited number of horses. In addition, the clinical criteria were assessed for the first time. The experimental design (comparison with a control substance, randomized allocation of horses to treatment groups, and investigators unaware of the treatment administered to each horse) permitted adequate assessment of drug efficacy.

Clinical assessment of problems involving the thoracolumbar vertebral column or associated muscles is a challenge for equine practitioners,[2,9,10] and pain in that region is primarily associated with a wide array of manifestations that include poor performance, behavior abnormalities, and gait abnormalities, rather than with overt signs of pain. Therefore, reliable and quantitative clinical criteria for assessment of such conditions have not yet been developed.[9] Atrophy of muscles associated with the thoracolumbar vertebral column may reflect reduction of mobility in the area as a result of a painful condition.[2] However, this variable is difficult to ascertain because it is related to body weight, body condition, and the training program. Assessment of the dorsum during passive mobility is also important for identifying signs of pain or restriction in the amount of movement tolerated, but it also can be misinterpreted when a horse is naturally sensitive to any kind of stimulation of the dorsal region.[2,9]

Therefore, examination of horses during walking, trotting, and cantering is essential when evaluating horses with clinical manifestations of pain associated with lesions of the vertebral column because it allows evaluation of natural movements of the trunk and identification of functional disorders, such as reduction of dorsal flexibility.[2,7] Flexibility of the vertebral column in trotting horses is characterized by passive movement of flexion and extension in the thoracic, thoracolumbar, and lumbosacral areas.[11-14] When a horse senses pain in its dorsal regions, it will have a reduction of dorsal flexibility and appear to maintain a stiff posture,[13] or it may have a short choppy stride in the hind limbs. Lumbosacral mobility is also adequately evaluated during cantering by assessing lumbosacral flexion and the engagement and propulsion of the hind limbs.[2,13]

In the study reported here, an SRDF was determined for 5 relevant conditions (slow and fast trotting in a straight line, trotting in a circle in both directions on a hard surface, and trotting and cantering in a circle in both directions on a soft surface). All examinations were videotaped to enable an accurate assessment of changes in the SRDF over time. The study revealed significant improvement of SRDF in horses treated with tiludronate, compared with values for horses receiving the control solution, and from before to 60 days after treatment with tiludronate. This confirms, retrospectively, the choice of SRDF as the main criterion for use in evaluating the efficacy of a treatment of horses with clinical manifestations of pain associated with lesions of the thoracolumbar vertebral column. Indeed, the examination of walking, trotting, and cantering horses conducted here was a more natural situation with little influence of humans or the behavior of each horse. Therefore, assessment of restriction of the mobility of the vertebral column and associated muscles during various gaits is more reliable than physical criteria assessed during a static examination. Evaluation of the horses while being ridden was not used in this study because of the lack of repeatability of this type of examination among horses and riders and over time for the same horse (subjectivity of the rider's assessment).

The study reported here revealed efficacy of tiludronate (1 mg/kg) administered as a slow IV infusion for use in the treatment of horses with clinical signs of pain associated with lesions of the thoracolumbar vertebral column. Twelve (80%) horses in the tiludronate group had clinical improvement between days 0 and 60, whereas only half of the control group had clinical improvement (50% failure rate). Improvement in the mSRDF was observed 60 and 120 days after administration of a single dose of tiludronate. Dorsal flexibility appeared to be improved in examinations conducted on days 60 and 120 but was more pronounced for horses cantering in a circle on a soft surface. Interestingly, cantering is the condition that provides the most accurate evaluation of active thoracolumbar and lumbosacral mobility as well as propulsion and coordination of the hind limbs.[13] The positive response to treatment was approximately 30% higher for the tiludronate group, with almost 90% of the owners being satisfied. Similarly, investigators judged that the tiludronate treatment resulted in improvement for approximately 60% of the assessments.

The positive responses for the control horses (58.1% for the owners and 28.6% for the investigators) can partly explain the reason that we did not detect significant differences between tiludronate-treated and control horses at day 60. In addition, there was a limited number of horses in each group. Sixty days after a single treatment, horses had a significant improvement during clinical evaluation, with a decrease of approximately 0.5 points for mSRDF and SRDF, except when horses were trotting slowly in a straight line. The owners judged that 17 of 22 (77.3%) horses had sufficient improvement, which is consistent with the judgement of the investigators (14/22 [63.6%]).

In the study reported here, 7 of 14 control horses had an improvement in mSRDF. This can be partly explained by the fact that signs of pain associated with lesions of the thoracolumbar vertebral column in horses can be alleviated by use of a good management program[2] or may resolve without treatment.[9] Analysis of the overall results indicated that tiludronate may accelerate the improvement of horses with signs of pain associated with the vertebral column and associated muscles, with noticeable improvement 60 days after a single treatment and then a stabilization of the clinical condition between 60 and 120 days after treatment.

It should be mentioned that the 3 horses treated with tiludronate that had treatment failure had a higher mSRDF on day 0, which indicated a more severe lack of flexibility. As reported in another study,[8] a second treatment may be necessary to achieve clear improvement of horses with a chronic severe condition. Interestingly, 2 of these 3 treatment failures had improvements in dorsal flexibility after the second treatment with tiludronate.

Interest in the combined use of radiography and scintigraphy to identify and characterize lesions of the thoracolumbar vertebral column has been reported.[2,3,6] However, abnormal radiographic and scintigraphic findings have also been described in clinically normal horses.[4,15] Thus, the clinical relevance of abnormal findings is based on concomitant physical abnormalities or manifestations during ambulatory movements. This is consistent with our criteria for inclusion, which were clinical manifestations of pain in the dorsal region in combination with abnormal radiographic findings indicative of osteoarthritis of the AP–SIVJs. Lack of radiographic changes over time was expected because of the results of another study.[8]

Scintigraphic changes were not detected during the course of the study, although we hypothesize that tiludronate could decrease bone metabolic activity and, therefore, radiopharmaceutical uptake. The lack of changes in radiopharmaceutical uptake may be related to binding of the agent, which is found primarily in newly formed bone along mineralization fronts,[16] whereas osteoclasts are the major cell targets of tiludronate.[8,f] Another explanation could be that radiopharmaceutical uptake is correlated with biomechanical repartition of stresses, which cannot be decreased by tiludronate. This would be consistent with reports[6,15] in which investigators conducted scintigraphic examinations of dorsal regions of clinically normal horses. In 1 of those studies,[6] investigators reported that horses that returned to full work had more

radiographic and scintigraphic changes than horses that did not return to full work. The study reported here confirmed that radiographic and scintigraphic examinations are essential for the diagnosis of lesions of the thoracolumbar vertebral column, but these imaging modalities are not suitable or are insufficiently sensitive to provide indirect evidence of tiludronate efficacy.

Involvement of pathologic conditions of bone as a source of pain in the dorsal region has been established.[2,3,5,17] Although impingement of the spinous processes is reportedly[2-4,17] the most common abnormal radiographic finding of the thoracolumbar portion of the vertebral column, it is not consistently associated with overt signs of pain and can be found in clinically normal horses.[2,15] Osteoarthritis of the AP–SIVJs is more often associated with signs of pain in the thoracolumbar vertebral column, compared with the incidence of clinical manifestation associated with contact of the spinous processes.[2,5] Spondylosis has a low prevalence[4] and is usually considered painful during early stages. Each type of lesion is associated with various degrees of bone remodelling, which range from osteolysis to sclerosis. The role of subchondral bone remodelling in the development of osteoarthritis has been established.[18] Tiludronate counteracts this pathologic process by inhibiting osteoclastic metabolism without impairing osteoblastic activity.[8] It helps regulate bone metabolism and restore a physiologic balance between bone resorption and bone formation.[f] In humans, osteolytic processes, such as those involving bone metastases, generate bone pain. By inhibiting bone resorption, bisphosphonates act as valuable tools to alleviate pain associated with such processes.[8] Tiludronate stabilizes bone lesions by restoring the balance between resorption and formation and relieves pain associated with bone alteration (primarily osteolysis).

On the basis of analysis of results for the study reported here, tiludronate offers an efficacious treatment option for the management of horses with clinical manifestations of pain associated with lesions of the vertebral column. This can result in significant improvement of dorsal flexibility and perceived comfort of a horse within 60 days after administration of a single dose of tiludronate.

a. Teceos, CIS Bio International Schering, Gif-sur-Yvette, France.
b. Ecam Siemens Erlangen, Siemens, Saint Denis, France.
c. Hermes, version 3.4, Nuclear Diagnostics Ltd, Northfleet, Kent, UK.
d. Tildren, Ceva Santé Animale, Libourne, France.
e. SAS, version 8.2, SAS Institute Inc, Cary, NC.
f. Varela AM, Lepage OM, Garnero P, et al. Tiludronate in horses: tolerance and effects on bone resorption (abstr). *J Bone Miner Res* 2001;16(suppl 1):S407.

References

1. Jeffcott LB. The diagnosis of disease of the horse's back. *Equine Vet J* 1975;7:69–78.
2. Denoix JM, Dyson SJ. The thoracolumbar spine. In: Ross MR, Dyson SJ, eds. *Diagnosis and management of lameness in horses*. St Louis: WB Saunders Co, 2003;509–521.
3. Hendrickson D. The thoracolumbar spine. In: Stashak TS, ed. *Adams' lameness in horses*. 5th ed. Philadelphia: Lea & Febiger, 2002;1053–1057.
4. Jeffcott LB. Disorders of the thoracolumbar spine of the horse—a survey of 443 cases. *Equine Vet J* 1980;12:197–210.
5. Denoix JM. Lesions of the vertebral column in poor performance horses, in *Proceedings*. World Equine Vet Assoc 1999; 99–109.
6. Weaver MP, Jeffcott LB, Nowak M. Back problems. Radiology and scintigraphy. *Vet Clin North Am Equine Pract* 1999;15:113–129.
7. Townsend HGG, Leach DH, Doige CE, et al. Relationship between spinal biomechanics and pathological changes in the equine thoracolumbar spine. *Equine Vet J* 1986;18:107–112.
8. Denoix JM, Thibaud D, Riccio B. Tiludronate as a new therapeutic agent in the treatment of navicular disease: a double-blind placebo-controlled clinical trial. *Equine Vet J* 2003;35:407–413.
9. Jeffcott LB. Historical perspective and clinical indications. *Vet Clin North Am Equine Pract* 1999;15:1–12.
10. Martin BB, Klide AM. Physical examination of horses with back pain. *Vet Clin North Am Equine Pract* 1999;15:61–70.
11. Audigié F, Pourcelot P, Degeurce C, et al. Kinematics of the equine back: flexion-extension movements in sound trotting horses. *Equine Vet J Suppl* 1999;30:210–213.
12. Wernnerstrand J, Johnston C, Roethlisberger-Holm K, et al. Kinematic evaluation of the back in the sport horse with back pain. *Equine Vet J* 2004;36:707–711.
13. Denoix JM, Audigié F. The neck and back. In: Back W, Clayton H, eds. *Equine locomotion*. London: WB Saunders Co, 2001; 167–191.
14. Schlacher C, Peham C, Licka T, et al. Determination of the stiffness of the equine spine. *Equine Vet J* 2004;36:699–702.
15. Erichsen C, Eksell P, Roethlisberger-Holm K, et al. Relationship between scintigraphic and radiographic evaluations of spinous processes in the thoracolumbar spine in riding horses without clinical signs of back problems. *Equine Vet J* 2004;36:458–465.
16. Subramanian G. Radiopharmaceuticals for bone scanning. In: Collier BD Jr, Fogelman I, Rosenthall L, eds. *Skeletal nuclear medicine*. St Louis: Mosby Year Book Inc, 1996;9–20.
17. Haussler KK. Osseous spinal pathology. *Vet Clin North Am Equine Pract* 1999;15:103–111.
18. Kawcak CE, McIlwraith CW, Norrdin RW, et al. The role of subchondral bone in joint disease: a review. *Vet Clin North Am Equine Pract* 1999;15:120–126.

Appendices appear on the next pages

Appendix 1

Clinical variables, scoring system, and criteria used for the assessment of tiludronate efficacy when administered to horses with clinical manifestations of pain associated with lesions of the thoracolumbar vertebral column.

Variable	Score	Description	Efficacy criteria
SRDF*	0 (Not detected)	Normal thoracic and lumbosacral flexibility, horse is extremely supple.	Change of the mSRDF over time.
	1 (Mild)	Dorsal mobility mildly decreased, but horse is still supple.	Change of SRDF for each condition over time.
	2 (Moderate)	Dorsal mobility is decreased, reduction of propulsion by hind limbs, shortened strides, horse appears stiff.	
	3 (Severe)	Dorsal mobility is markedly decreased, lack of propulsion by hind linds, extremely shortened strides, horse appears extremely stiff.	
Failure rate	Percentage	Proportion of horses treated with tiludronate on day 60 because of an insufficient response to the initial infusion (control or tiludronate) administered on day 0.	Failure rate on day 60.
Response to treatment As assessed by investigators	0 (Excellent)	Same degree of performance or activity as before onset of clinical signs.	Positive response (percentage of fair, good, or excellent responses on days 60 and 120).
	1 (Good)	Clear improvement in clinical condition.	
	2 (Fair)	Mild improvement in clinical condition.	
	3 (Poor)	No improvement or worsening of clinical condition.	
As assessed by owners	0 (Excellent)	Same degree of performance or activity as before onset of clinical signs.	Positive response (percentage of fair, good, or excellent responses on days 60 and 120).
	1 (Good)	Clear improvement in clinical condition; locomotion is markedly improved but not completely normal.	
	2 (Fair)	Mild improvement in clinical condition; locomotion is improved, but horse is unable to achieve previous degree of performance or activity.	
	3 (Poor)	No improvement or worsening of condition; locomotion is not improved or has become worse.	

*Reduction of dorsal flexibility was scored during examination for each of 5 conditions: slow trot (3 to 4 m/s) in a straight line, fast trot (6 to 7 m/s) in a straight line, trot in a circle (both directions) on a hard surface, trot in a circle (both directions) on a soft surface, and canter in a circle (both directions) on a soft surface. The SRDF values for each of the 5 conditions were used to calculate an mSRDF value for each horse.

Appendix 2

Severity scores for radiographic findings of the AP–SIVJs, spinous processes, and vertebral bodies of horses with clinical manifestations of pain associated with lesions of the thoracolumbar vertebral column.

Anatomic structure	Variable	Score	Description
AP–SIVJ	Periarticular proliferation	0 (Normal)	No abnormal radiographic findings.
		1 (Mild)	Mild and regular periarticular proliferation.
		2 (Moderate)	Moderate and irregular periarticular proliferation
		3 (Severe)	Extensive and irregular periarticular proliferation.
	Sclerosis	0 (Normal)	No abnormal radiographic findings.
		1 (Mild)	Mild increased density of the cranial AP.
		2 (Moderate)	Increased density of the cranial and caudal APs.
		3 (Severe)	Severe and diffuse increased density of the cranial and caudal APs.
	Osteolysis	0 (Normal)	No abnormal radiographic findings.
		1 (Mild)	Small radiolucent areas in the subchondral bone of the cranial AP.
		2 (Moderate)	Diffuse radiolucent areas in the subchondral bone of the cranial AP.
		3 (Severe)	Extensive and diffuse radiolucent areas of the subchondral bone of the cranial and caudal APs.
	Ankylosis	0 (Normal)	No abnormal radiographic findings.
		1 (Mild)	Small periarticular dorsal bridge.
		2 (Moderate)	Periarticular dorsal bridge interrupting the joint space.
		3 (Severe)	Extensive periarticular dorsal bridge or osteolysis of the APs; no joint space.
Spinous processes	NA	0 (Normal)	No abnormal radiographic findings.
		1 (Mild)	Narrowing of the interspinous space with mild sclerosis of the margins of the spinous processes.
		2 (Moderate)	Loss of the interspinous space with moderate sclerosis of the margins of the spinous processes or small radiolucent areas.
		3 (Severe)	Severe sclerosis of the margins of the spinous processes, extensive osteolysis, or change in shape of the spinous processes.
Vertebral bodies	NA	0 (Normal)	No abnormal radiographic findings.
		1 (Mild)	Mild ventral or ventrolateral bony proliferation on 1 joint space.
		2 (Moderate)	Extended ventral or ventrolateral bony proliferation on 2 joint spaces.
		3 (Severe)	Extended ventral or ventrolateral bony proliferation with osteolysis or sclerosis on 3 or more joint spaces.

NA = Not applicable.