EXHIBIT C

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Tiludronate as a new therapeutic agent in the treatment of navicular disease: a double-blind placebo-controlled clinical trial

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Keywords: horse; navicular disease; clinical trial; bone; remodelling; osteolysis; bisphosphonates; tiludronate

Summary

***Reasons for performing study*: Bisphosphonates, such as tiludronate, are used to normalise bone metabolism via inhibition of bone resorption. Areas of increased bone resorption and formation are typical lesions in a diseased navicular bone.**

***Objectives:* To determine if bone remodelling changes occurring in navicular disease may be corrected with therapies regulating bone metabolism.**

***Methods:* We designed a double-blind, placebo-controlled clinical trial to compare 2 doses of tiludronate, 0.5 mg/kg and 1 mg/kg bwt administered via daily i.v. injections over 10 days for the treatment of navicular disease. Seventy-three horses, split into 2 subpopulations of recent and chronic cases, were enrolled to be followed-up over 6 months. Of these, 33 recent and 17 chronic cases meeting the selection criteria were maintained in the final efficacy analyses. Clinical examinations were videorecorded and reviewed blindly by an independent expert.**

***Results:* Horses treated with the higher dose showed optimal improvement of lameness and return to normal level of activity 2–6 months post treatment. The more recent the onset of clinical signs at the time of treatment, the greater the efficacy. The treatment did not modify the response to extension and flexion tests. The lower dose failed to significantly improve the condition.**

***Conclusions:* Tiludronate efficacy is demonstrated in the treatment of navicular disease at the dose of 1 mg/kg bwt.**

***Potential relevance:* Our results support the clinical relevance of bone remodelling changes in the outcome of navicular disease.**

Introduction

The treatment of navicular disease is still today a challenge for practitioners and most recommended treatments are palliative and aimed at the alleviation of pain. Anti-inflammatory drugs (administered locally or parenterally), corrective trimming and shoeing are the most common treatments but palmar digital neurectomy or navicular suspensory desmotomy have also been proposed (Rose 1996). Very few drugs are prescribed to act on the underlying causes of navicular disease, due mainly to the lack of a clear understanding of its aetiopathogenesis. Vasoactive drugs, such as isoxsuprine, are still recommended to modify the vascularisation of the distal sesamoid bone. However, despite positive results obtained with isoxsuprine in controlled clinical trials (Turner and Tucker 1989), its efficacy is not fully recognised.

Bone remodelling changes associated with navicular disease are well-described (Poulos 1983; Pool *et al.* 1989). They include excessive bone resorption identified on radiographic images as radiolucent areas and sclerosis involving the flexor compact bone as well as the spongiosa. Convincing reports of the efficacy of drugs acting on the regulation of bone metabolism to correct the remodelling changes occurring in the distal sesamoid bone have yet to appear. Nevertheless, positive results were published by Fricker *et al.* (1986) with calcitonin, the natural hormone which inhibits bone resorption and regulates calcaemia in combination with parathormone. Drugs such as bisphosphonates, regulators of bone metabolism through inhibition of bone resorption, could potentially help in restoring a normal balance between bone resorption and formation (Fleisch 1998) and consequently may contribute to the improvement of the condition. In a preliminary clinical trial, pamidronate, a bisphosphonate, was not found effective when administered after a 3 month period with corrective shoeing (McGuigan *et al.* 2000).

We report here a trial performed with tiludronate, another bisphosphonate originally developed and marketed for the treatment of Paget's disease in man. Tiludronate was shown to be safe for mature healthy bones as well as for growing bones when administered at therapeutic doses (Bonjour *et al.* 1995). The purpose of this study was to assess the efficacy of tiludronate administered i.v. in the treatment of navicular disease with a controlled, randomised double-blind experimental design comparing 2 doses vs. placebo. Thirty investigators were involved in France, Italy and Germany.

Materials and methods

Selection of horses

Inclusion criteria: Horses presented with a moderate to severe,

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TABLE 1: Clinical and radiographic parameters, scoring system and deriving criteria used for the assessment of tiludronate efficacy in the treatment of navicular disease

Parameter	Scoring		Efficacy criteria
Response to treatment	**[0] Excellent:**	Same level of performance or activity as before Occurrence of clinical signs	**Failure rate** % of horses withdrawn for insufficient response to treatment on Days 38 or 66
	[1] Good:	Clear improvement of lameness	
	[2] Fair:	Slight improvement of lameness	
	[3] Poor:	No improvement or worsening of lameness	**Positive response** % of good or excellent responses on Days 10, 38, 66, 192
Level of exercise	Measured according to a 7-grade scale from [1] (rest with walking hand-held) to [7] maximal level of exercise or competition, according to the type of use of the horse (flat-racing, trotting, show or pleasure horses)		Normal level of activity % of horses with *grade 6* or *7* on Days 0, 10, 38, 66, 192
Lameness score	Examination on hard ground. Lameness scored in each of the 4 examinations: walking an 8, trot in straight line and in right-hand and left-hand circles of 8–10 m diameter (lunging) with the following scale:		
	[0] Absent:	Walk: no stride alteration Trot: symmetrical gaits	**Evolution of the mean lameness score over time**, expressed as the differences of the mean lameness score calculated on Days 10, 38, 66, 192 with the mean lameness score calculated on Day 0
	[1] Mild:	Walk: intermittent or hardly evidenced stride alteration Trot: slight or intermittent dissymmetry of the head (or rump) trajectory	
	[2] Moderate:	Walk: moderate and permanent stride alteration in at least one condition; Trot: moderate and easily evidenced head-bobbing (or rump movement)	
	[3] Severe:	Walk: marked stride alteration and head-bobbing; Trot: marked head-swinging (or rump) with modified trajectory or shortened stride. Interference between forelimbs and hindlimbs	**Horses showing little or no sign of lameness** % of horses with a lameness score ≤0.5 on Days 0, 10, 38, 66, 192
	[4] Extreme:	No weight bearing	
	Calculation of the lameness score as the mean of the 4 scores		
Response to interphalangeal extension test (static test)	**[0] Absent:**	No reaction to a 40° extension	**Negative response to extension test** % of horses with *grade 0* on Days 0, 10, 38, 66, 192
	[1] Mild:	Slight reaction to an intense constraint (muscle tremors or slight avoidance movement)	
	[2] Moderate:	Clear reaction (limb withdrawal) to an intense constraint or slight reaction to a 25° extension	
	[3] Severe:	Clear reaction to a 25° extension	
Response to digital flexion test (dynamic test)	**[0] Negative:**	Unmodified locomotion	**Negative response to flexion test** % of horses with *grade 0* on Days 0, 10, 38, 66, 192
	[1] Slight:	Slight worsening of lameness	
	[2] Moderate:	Worsening of lameness (one grade more)	
	[3] Severe:	Marked worsening of lameness (superior to one grade)	
Radiographic signs on Day 192 in comparison with signs on Day 0	**[0] Clear improvement**		**Improvement of radiographic signs** % of horses with *grade 0* or *1*
	[1] Partial improvement		
	[2] No evolution		
	[3] Worsening		

uni- or bilateral forelimb lameness were eligible if they met the following criteria: 1) a lameness score ≥ [2] in at least one out of 4 lameness assessment conditions (Table 1). 2) a positive interphalangeal extension test. In case of bilateral lameness, only the lamest forelimb was considered to subsequently assess the response to treatment. 3) a substantial improvement of lameness after distal palmar digital nerve block, 4) obvious radiographic findings on 3 projections (lateromedial, dorsoproximal-palmarodistal oblique and palmaroproximal-palmarodistal oblique) with osteolytic lesions of the distal sesamoid bone (radiolucent findings in the compact bone or in the spongiosa, increased number or size of lucent synovial fossae along the distal border of the bone), possibly associated with new bone formation (proximal or distal entheseophytes, periarticular osteophytes), sclerosis of the flexor compact bone or of the spongiosa.

The clinical examination of lameness was videotaped. At the end of the trial, the videotapes and radiographs were reviewed blindly by one of the authors (JMD) as independent expert to validate each enrolment retrospectively.

Noninclusion criteria: Horses less than age 2 years, horses presented with fracture, treated surgically or with NSAIDs in the previous 15 days or with corticosteroids in the previous 30 days were not included.

Exclusion criteria: Exclusions were decided retrospectively in the following cases: 1) early withdrawal (i.e. during the treatment period or within a month after treatment cessation) by the investigators or at the owner's request, 2) any event having occurred during follow-up with potential influence on clinical outcome, 3) change of shoeing pattern, 4) nonconformity between the investigators' and expert's assessments regarding severity of lameness or the radiographic findings.

Treatments

Treatment groups and products: Two tiludronate treatments and a placebo were allocated randomly to horses after enrolment. Tiludronate and its placebo were supplied as physically identica

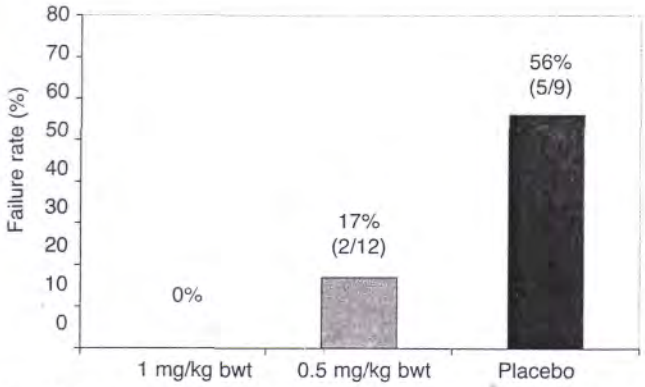


Fig 1: Failure rates (percentage of horses withdrawn from study for insufficient response 2 months post treatment). Differences between groups were highly significant (P = 0.008).

pharmaceutical preparations[1] (freeze-dried powders) to allow their administration under blind conditions. The injected volume into a jugular vein was 1 ml reconstituted solution per 50 kg bwt, s.i.d. for 10 days. In the tiludronate-treated groups, the daily dose was 0.1 mg/kg bwt (expressed as tiludronic acid). One group received 10 daily doses (i.e. a total dose of 1 mg/kg bwt); the second group received 5 daily doses (i.e. a total dose of 0.5 mg/kg bwt) followed by 5 daily placebo doses.

The investigators could treat a horse a second time when they judged that the case was not sufficiently improved 2 months after enrolment. The second treatment was given at the dose of 1 mg/kg bwt split into 10 daily doses under nonblinded conditions. Horses receiving a second treatment were considered as failures and withdrawn from the main analysis but a further lameness examination had to be performed 2 or 3 months later in order to assess the overall response to both treatments.

Authorised associated treatments: Change of shoe pattern was only authorised once, at least 2 weeks before enrolment and treatment. The same type of trimming and shoeing had to be used during the course of the study. Other relevant treatments were authorised in case of concomitant disease.

Nonauthorised associated treatments: Anti-inflammatory drugs were forbidden over the entire monitoring period except when needed to treat a concomitant disease. If used, the next monitoring visit had to be performed at least 2 weeks after their last administration. Chondroprotective drugs and surgical treatments of lameness were not allowed.

Monitoring

Treatments were administered from Days 0 to 9. Horses were monitored over 6 months, with a complete clinical examination for lameness assessment on the day after the last injection (Day10), after one month (Day 38), 2 months (Day 66) and 6 months (Day 192) post treatment. Clinical examinations were video taped for review by the expert. A second series of radiographs was taken at the end of the monitoring period. The criteria used to assess treatment efficacy are listed in Table 1. Housing and feeding were not changed during the monitoring period. No rest was required during treatment and the level of exercise was progressively increased after treatment according to individual horse requirements.

TABLE 2: Distribution of enrolled, excluded and retained cases according to treatment groups and age of signs of navicular disease at the time of treatment

	Total	Tiludronate 1 mg/kg bwt	Tiludronate 0.5 mg/kg bwt	Placebo
Enrolled cases	73	29	23	21
Excluded cases	23	9	4	10
Cases maintained in the efficacy analyses	50	20	19	11
Of which recent cases	33	12	12[a]	9[a]
Of which chronic cases	17	8	7[b]	2

[a,b]Groups with partial exclusions due to concomitant disease during the course of the trial; [a]1 case in each group excluded after Day 38; [b]1 case excluded after Day 66.

Statistical analysis

The statistical tests applied to the data sets were:

Chi² test or Fisher exact test: Percentage of failures at Day 66, response to treatment assessed by the investigator, percentage of horses with a normal level of activity, responses to extension and flexion tests, radiographic signs.

ANOVA with repeated measures (covariate): Lameness score on Day 0) for the evolution of the mean lameness score. The last recorded lameness score of the withdrawn horses was prolonged up to Day 192,

Log linear model: Percentage of horses showing little or no sign of lameness. Prerequisites to run each test were checked. A significance threshold of 5% was used for each test. In case of multiple comparisons, the alpha risk was adjusted with the Bonferonni procedure. Statistical analyses were run on SAS Institute Inc Software (version 6.12)[2] and Epi-Info (version 6)[3].

Results

Seventy-three horses (mean age: 10.4 ± 3.8 years, 31% females, 65% geldings and 4% males) were enrolled (Table 2), the majority of which were either jump (63%) or pleasure horses (22%). Exclusions resulted from early withdrawals (6 cases), discrepancy on severity of clinical signs between the investigators' and expert's assessments (11 cases) or absence of radiolucent lesions on X-ray images (6 cases). Initial comparability of treatment groups was checked with respect to breed, type of use, age, sex, shoeing, level of exercise before onset of lameness and previous treatments. Treatment groups were also comparable for all clinical parameters assessed on Day 0. The population maintained in the efficacy analyses was split into 2 subgroups to take into account the evolution of bone remodelling changes in a diseased navicular bone: recent cases (cases for which clinical signs appeared 6 months or less before enrolment), and chronic cases (cases with clinical signs older than 6 months of age).

Results on recent cases

Significant differences over placebo were found in the group treated at the dose of 1 mg/kg bwt on the following criteria: failures at Day 66 (P = 0.008; Fig 1), percentages of horses with a normal level

TABLE 3: Evolution over time of the investigators' assessments on the positive response to treatment, percentages of horses showing little or no sign of lameness and negative responses to flexion and extension tests in placebo horses and horses treated with 2 doses of tiludronate

Efficacy criteria	Time	1 mg/kg bwt (n = 12)	0.5 mg/kg bwt (n = 12)*	Placebo (n = 9)*	Global comparison between groups (treatment comparisons)
Positive response to treatment	Day 10	50% (6/12)	25% (3/12)	44.4% (4/9)	NS
	Day 38	41.7% (5/12)	33.3% (4/12)	33.3% (3/9)	NS
	Day 66	41.7% (5/12)	54.5% (6/11)	37.5% (3/8)	NS
	Day 192	66.7% (8/12)	36.4% (4/11)	12.5% (1/8)	P = 0.03 (1 mg vs. placebo P = 0.015)
Horses showing little or no sign of lameness	Day 0	0%	0%	0%	
	Day 10	16.7% (2/12)	16.7% (2/12)	22.2% (2/9)	Evolution over time between groups: P<0.0001 (1 mg vs. placebo P = 0.015)
	Day 38	25% (3/12)	33.3% (4/12)	44.4% (4/9)	
	Day 66	41.7% (5/12)	27.3% (3/11)	37.5% (3/8)	
	Day 192	50% (6/12)	27.3% (3/11)	12.5% (1/8)	
Negative response to extension test	Day 0	33.3% (4/12)	41.7% (5/12)	11.1% (1/9)	
	Day 10	50% (6/12)	58.3% (7/12)	33.3% (3/9)	
	Day 38	50% (6/12)	58.3% (7/12)	77.8% (7/9)	NS
	Day 66	50% (6/12)	63.6% (7/11)	75% (6/8)	
	Day 192	50% (6/12)	72.7% (8/11)	25% (2/8)	
Negative response to flexion test	Day 0	0%	8.3% (1/12)	11.1% (1/9)	
	Day 10	41.7% (5/12)	33.3% (4/12)	44.4% (4/9)	
	Day 38	33.3% (4/12)	33.3% (4/12)	44.4% (4/9)	NS
	Day 66	41.7% (5/12)	36.4% (4/11)	25% (2/8)	
	Day 192	33.3% (4/12)	27.3% (3/11)	25% (2/8)	

NS: not significant. *One horse partially withdrawn from the analysis after Day 38 due to concomitant disease.

of activity on Day 192 (P = 0.017; Fig 2), percentages of horses showing little or no sign of lameness (P = 0.015; Table 3) and positive response to treatment on Day 192 (P = 0.015; Table 3). No significant differences were noticed between groups in the response to the flexion and extension tests (Table 3) or in the evolution of radiographic findings. At inclusion, the mean lameness score was similar between groups (1.61 ± 0.13 for the pooled groups). Although animals receiving 1 mg/kg bwt had a greater decrease of lameness, the difference was not statistically significant between groups for either investigator or expert assessments. Both assessments showed a similar trend in lameness improvement in the group treated with 1 mg/kg bwt but this was not apparent in the placebo group (Fig 3).

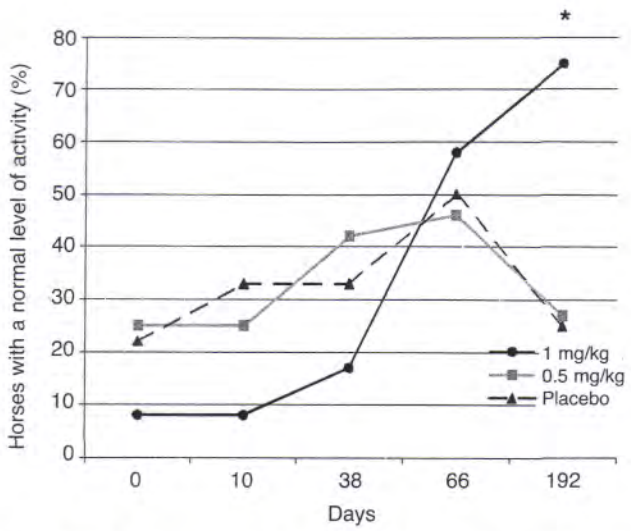
Results on chronic cases

No significant differences were evidenced between treatment groups whatever the efficacy criterion, although the limited number of horses, particularly in the placebo group, did not allow for powerful statistical analyses. A single series of i.v. injections was not sufficient to improve clinical signs significantly. Among the 6 horses treated with the highest dose and considered as failures at Day 66, 2 received a second treatment and one received 2 additional treatments 2 months apart. All 3 horses were judged as having responded positively 2 months after the last additional treatment. Overall, 5 out 8 horses responded positively after 1, 2 or 3 treatments at the total dose of 1 mg/kg bwt. The 3 remaining horses were not treated a second time.

Discussion

This study was designed in order to assess the intrinsic efficacy of tiludronate in the treatment of navicular disease. Comparison with a placebo, randomised allocation of treatments, administration under blind conditions and long follow-up permitted adequate assessment of drug efficacy. Further, the provision of a detailed video of each clinical assessment permitted direct comparison of the investigators' assessments with those of an independent expert. Objective assessment of qualitative or semi-qualitative clinical parameters such as those used here for lameness scoring is difficult, particularly when clinical examinations are performed in different countries and over a prolonged time period. However, videorecording allowed virtual concurrent visualisation of what might otherwise be quite disparate examinations, facilitating consistent and reliable assessment. Results obtained for the placebo group serve to highlight the difficulties of objective clinical assessment of lameness over time. There were clear differences in the measured improvement of the mean lameness scores when one compares the results from the investigators with those of the expert over the whole follow-up period and, especially, during the first month after treatment. The improvement in lameness recorded in placebo-treated horses is typical of a placebo effect: improvement was recorded 1 or 2 months after treatment with a subsequent relapse. However improvement was either maintained over the entire follow-up period or plateaued at 1 or 2 months in the tiludronate-treated groups. Such a placebo effect might explain the absence of a statistically significant difference between the groups in the first 2 months post treatment.

The study demonstrated unambiguously the efficacy of tiludronate in the treatment of navicular disease at a total dose of 1 mg/kg bwt administered in 10 daily injections of 0.1 mg/kg bwt. However, efficacy appears to be influenced by the age of signs at the time of treatment: the earlier the treatment, the greater the efficacy. This confirms, retrospectively, the hypothesis made when we decided to split the initial population into 2 subgroups according to the age of clinical signs at the time of treatment. However, in some older cases of navicular disease, repeated treatments with tiludronate



*Statistical differences were found between groups on Day 192 (P = 0.01): 1 mg v placebo P = 0.017, 1 mg v 0.5 mg P = 0.014.

Fig 2: Evolution of the percentages of horses with a normal level of activity (grade 6 or 7) between groups from enrolment (Day 0) to the end of the monitoring period (Day 192). Placebo and the lowest tiludronate dose gave the same pattern of evolution with no changes of level of activity at the end of the monitoring period compared to enrolment. The dose 1 mg/kg produced a sharp increase of activity.

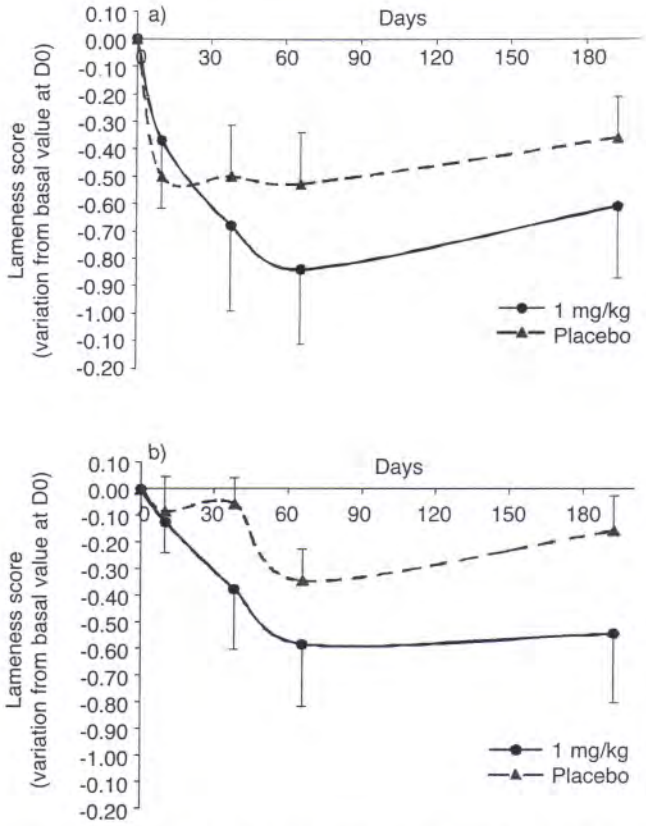


Fig 3: Changes over time of the mean (± s.e.) decrease of lameness score in the placebo group and the group treated with 1 mg/kg bwt tiludronate according to a) the investigators and b) the expert. Both assessments gave a clearly different patterns over the first month post treatment in the placebo group. Afterwards, the patterns were similar with a lesser degree of improvement for the expert. No statistically significant differences between treatments were evidenced at all time points.

apparently produced significant improvement of clinical signs as demonstrated by the positive trend seen in horses treated with 2 or 3 series of 10 daily injections every 2 months. The effect of tiludronate appears to be dose-related as a total dose of 0.5 mg/kg bwt gave inconclusive results. This observation confirms previous findings in man during clinical studies assessing the dose-effect relationship with oral administration of tiludronate in the treatment of Paget's disease (Fraser *et al.* 1997) and during studies assessing bone loss associated with immobilisation in paraplegic patients (Chappard *et al.* 1995).

Despite the complexity of the disease and its poorly understood aetiopathogenesis, there is converging evidence demonstrating the importance of bone remodelling changes within the distal sesamoid bone in horses diagnosed with navicular disease (Østblom *et al.* 1982, 1989; Poulos 1983; Pool *et al.* 1989; Wright *et al.* 1998). The most prominent changes reported from gross examination, histological and histomorphometric studies are: 1) enlargement of the synovial fossae of the distal border, 2) thickening of the flexor compact bone frequently combined with a decreased compact bone volume due to increased bone porosity in relation with an intense osteoclastic activity and increased osteoid volume suggestive of an increased osteoblastic activity, 3) decreased area of the spongiosa combined with an increased volume of its trabeculae and 4) radiolucent area within the spongiosa surrounded by osseous regions of increased resorption and formation. These changes reflect an increased bone turnover resulting from the increased osteoclastic and osteoblastic activities. The concomitant presence of areas of increased resorption and areas of increased formation is typical of a diseased navicular bone. In that perspective, a parallel can be drawn between a diseased navicular bone and a pagetic bone.

Besides the increased bone turnover, Østblom *et al.* (1989) demonstrated the uncoupling between resorption and formation in a diseased navicular bone. In a normal remodelling cycle, resorption and formation are coupled: the newly formed bone replaces to the same degree the bone which was resorbed at the initiation of the remodelling cycle. Each remodelling cycle is a long process, lasting several months (about 7 months in man according to Jee [2001]) but the duration of each phase is very different: the resorption phase is rapid, lasting a few weeks while the formation phase is completed in a few months. Østblom *et al.* (1989) estimated that the formation phase in a normal navicular bone in the horse is 7 times longer than the resorption phase. But they also found a resorption/formation ratio (defined as the ratio of bone surfaces subjected to resorption to newly formed bone surfaces) of 0.51 in the spongiosa when navicular disease was present compared to 0.10 in a normal navicular bone. The difference between both ratios was essentially related to excessive bone resorption in horses with navicular disease. Under such circumstances, bone formation may not be sufficient to replace the resorbed bone. This decoupling between formation and resorption leads to increased bone porosity, bone loss and, possibly, decreased bone mechanical resistance.

Among the factors acting on the remodelling rate, mechanical factors may play a critical role in triggering bone remodelling through the activation of the network of osteocytes, lining cells

and osteoblasts which stimulates osteoclasts to resorb bone (Huiskes *et al*. 2000). Important mechanical forces are applied on the navicular bone in horses with navicular disease, as recently demonstrated by Wilson *et al*. (2001). The continuous mechanical stimulus may largely contribute to the increased bone turnover and to the progressive uncoupling between resorption and formation reported by Østblom *et al*. (1989).

The knowledge of bone remodelling changes described in a diseased navicular bone and their relation with bone loading may help in better understanding the positive results obtained with tiludronate in our study. Bone remodelling changes are one of the pathological processes induced by the excessive mechanical load of the navicular bone. Tiludronate counteracts this pathological process. By partially inhibiting bone resorption through the inhibition of the osteoclasts, without adversely modifying the osteoblastic activity, tiludronate slows down bone turnover. It helps in restoring a normal balance within a bone subjected to an excessive resorption (Bonjour *et al*. 1995). As such, it acts as a regulator of bone metabolism. However, if the mechanical stimulus is maintained, the drug alone could not be sufficient to normalise bone remodelling. Therefore, corrective shoeing should be combined with tiludronate therapy to expect the best results in the treatment of navicular disease.

Tiludronate, like other bisphosphonates, has a strong affinity for bone where it is quickly fixed onto hydroxyapatite crystals; incorporation into bone is higher in bones with a high bone turnover such as trabecular bones (Davi *et al*. 1999). Release from the hydroxyapatite crystals is very slow as it occurs when a new remodelling cycle is starting ; it is directly linked with the bone remodelling rate. This explains why persistence of active concentrations over long periods when the right dosage is used. We found in horses (D. Thibaud, unpublished data) that pharmacologically active concentrations of tiludronate are still present in navicular bone 3 to 6 months after one single series of 10 daily injections at the dose of 0.1 mg/kg bwt. These very specific pharmacological properties may explain the apparent long-lasting effect of tiludronate evidenced in our study. As bone remodelling is a long process, the counterbalancing effects of the treatment on the remodelling changes may not be expected before a few weeks or months. We found that the most significant benefice of the treatment occurred 2 to 6 months after administration. The decrease of lameness during the first month after treatment may be an indirect consequence of the antiresorptive action of tiludronate. In human medicine, it is known that extensive or intense osteolytic processes, such as those seen in bone metastases, generate bone pain. By quickly inhibiting bone resorption, bisphosphonates are now recognised as valuable tools to alleviate the pain associated with these pathological processes (Mannix *et al*. 2000). We hypothesise that, in horses with navicular disease, alleviation of pain may also be the result of the inhibition of the resorptive process accompanying the disease.

The absence of significant changes on radiographic lesions in tiludronate-treated horses might have been anticipated as radiography can not detect small variations in bone mineral density. Longterm treatments of osteoporosis in man with bisphosphonates produce a slight increase in density with an average range from 1 to 7%, only detectable with sensitive methods such as densitometry (Woo and Adachi 2001). Scintigraphy may be useful, not only to detect early bone remodelling changes in navicular disease, but also to detect changes of remodelling rate over time. However, we do yet not know if it is sensitive enough to measure changes in bone remodelling after bisphosphonate therapy.

The positive results obtained with tiludronate are not in agreement with those reported by McGuigan *et al*. (2000) with pamidronate. However comparisons between the studies must be made with caution. In the McGuigan study, a limited number of horses were treated with 3 monthly injections of 1 mg/kg bwt pamidronate at the end of, or 3 months after, a 3 month period of corrective shoeing which may have already significantly improved bone remodelling changes as shown by Østblom *et al*. (1989). We do not have information on how the dose was selected. Tiludronate and pamidronate belong to 2 different subgroups of bisphosphonates (nonamino- and aminobisphosphonates, respectively) with different cellular modes of action (Rogers *et al*. 1999). Extrapolation from one compound to the other within the bisphosphonate family should always be done with caution. This study demonstrates that, when a dose is properly selected, a bisphosphonate therapy is a successful medical treatment of navicular disease. In practice, this therapy is expected to be a useful adjunct to corrective shoeing for the management of the condition.

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Manufacturers' addresses

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[2]SAS Institute, Cary, North Carolina, USA.
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