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Retrospective analysis of the use of tiludronate in equine practice: safety on 1804 horses, efficacy on 343 horses

A. Tischmacher[1], S. Wilford[2], K. Allen[3], R. D. Mitchell[4], T. Parkin[5], J-M. Denoix[1]*

[1]CIRALE, INRAE, Ecole Nationale Vétérinaire d'Alfort, BPLC, F-94700, Maisons-Alfort, France

[2]Audevard, 42-46 rue Médéric, 92100 Clichy la Garenne, France

[3]Virginia Equine Imaging, 2716 Landmark School Rd, The Plains, VA 20198, USA

[4]Fairfield Equine, 32 Barnabas Rd, Newtown, CT 06470, USA

[5]School of Veterinary Medicine, University of Glasgow, 464 Bearsden Road, Glasgow G61 1QH, United Kingdom

[*]*Corresponding author at*: CIRALE, INRAE, Ecole Nationale Vétérinaire d'Alfort, BPLC, F-94700, Maisons-Alfort, France. *E-mail address*: adeline.tischmacher@vet-alfort.fr

HIGHLIGHTS

> Tiludronate is a bisphosphonate used in numerous bone conditions in horses.

> A large-scale retrospective clinical study was conducted to assess safety and efficacy of tiludronate.

> Tolerance of horses to tiludronate is excellent with < 1% of side effects.

> Data suggest good efficacy of tiludronate with both clinical improvement and return to performance.

Abstract

The objective of this retrospective study was to assess the safety and efficacy of a slow IV administration of 1mg/kg tiludronate in a large number of horses. Each horse that received at least one tiludronate-based treatment between 2006 and August 2019 at Virginia Equine Imaging or

Fairfield Equine was included in the study. Concomitant medical treatments, preliminary NSAID injection and potential side effects were recorded after each administration. Horses for which follow-up was available over one year were subject to clinical evolution assessment via lameness grade evolution and performance data when available. Collected data suggest excellent tolerance to tiludronate with only 0,9% of the 2497 injections (1804 horses) inducing potential side effects, mild colics being the most frequent. Clinical follow-up was available over more than one year for 343 horses. Most horses (>80%) presented an initial lameness score over 1.5/5, approximately half of the population was sound by 30 days and remained so after a year. Mean lameness score improved by more than 1 grade during the follow-up period compared to initial examination. Performance data were available for 129 horses. One year after treatment, 89 (69%) horses were still competing, 73 (82%) of them at a better or similar level. These data suggest good efficacy of tiludronate over a year after treatment. Despite limitations inherent to any field study, this is the first retrospective study of the use of bisphosphonates in horses combining a large group with long-term follow-ups.

Key words

Tiludronate ; Bisphosphonate ; Horse ; Musculoskeletal system

1. Introduction

Because of their ability to reduce bone resorption by inhibiting osteoclastic activity, bisphosphonates have been widely used in human medicine for the treatment of numerous bone diseases[1] as osteoporosis [2], multiple myeloma [3], hypercalcemia of malignancy [4], Paget's disease [5,6] or metastatic bone disease [7]. Tiludronate was the first available bisphosphonate in veterinary medicine and especially in equine medicine. Initially approved and marketed in the equine species for the treatment of bone spavin and navicular disease [8], tiludronate's scope of application has extended over the years and is currently used to treat numerous bone conditions in horses. Multiple controlled studies prove its efficacy in the management of specific affections such as navicular syndrome [9], bone spavin [10,11] and articular process joint (APJ) osteoarthritis in the

thoracolumbar spine [12]. Tiludronate was also proven to significantly reduce bone resorption thus preventing osteopenia during long-term immobilization of a limb [13]. These studies were blinded and placebo-controlled but with a limited number of horses. To the knowledge of the authors, there is no large population study on the efficacy of tiludronate, neither for the previously mentioned indications nor for other purposes. Despite limited data available on its secondary effects, current literature suggests good tolerance of tiludronate [8,13–16]. However, some cases of secondary renal impairment were anecdotally reported by clinicians in the field, highlighting the need for a large-scale retrospective study on side effects.

The objectives of this study were to provide a retrospective study on tiludronate with a large population in order to establish the reality of the side effects on a field practice and to assess the efficacy of tiludronate with lameness evaluations and via performances evolution. Considering previous publications, we hypothesized that horses would present a good tolerance to 1 mg/kg intravenous perfusion of tiludronate and would have a good clinical outcome over more than six months after tiludronate treatment.

2. Materials and methods

A retrospective study was conducted using the veterinary clinical records from two clinics located in the eastern United States: Virginia Equine Imaging (VEI) and Fairfield Equine Associates (FE).

A search into the billing records of both clinics was conducted to establish the list of all Tildren ND billing entries the last 13 years. Due to a change of software in both clinics, clinical records were available from June 2006 at VEI and December 2006 at FE up to August 2019.

2.1. Horses

The study population consisted of all horses treated with tiludronate between June 2006 and August 2019 at VEI and between December 2006 and August 2019 at FE. Only horses who underwent systemic tiludronate intravenous administration by the clinics' staff were included. Billing entries

corresponding to Tildren ND vials or bottles sold to another veterinarian or client were excluded from the study. Intravenous locoregional perfusions represented a very few number of cases so were not included. The age (years), breed, sex (stallion, gelding or mare) and discipline of each horse were recorded.

2.2. First part of the study: Safety of tiludronate

For each horse included in the study, the following data were collected: date of tiludronate administration, whether a nonsteroidal anti-inflammatory drug (NSAID) was injected prior to tiludronate administration, whether the horse received concomitant medical treatment, and all potential side effects noticed after administration. Were recorded as such: signs of colic occurring within a week after tiludronate administration, signs of renal failure or any potentially related clinical abnormality recorded within a month after treatment and fractures occurring at any time during follow-up.

2.3. Second part of the study: Efficacy of tiludronate

This part of the study was performed on horses who were reexamined up to more than one year after the first tiludronate administration.

For each horse, lamest limb and corresponding 0-5 AAEP lameness grade [17], diagnostic methods (including diagnostic analgesia) and definitive diagnosis were collected for the initial examination before tiludronate administration. Then, 0-5 AAEP lameness grade of the initial lamest limb was recorded for each follow-up examination.

When available, performance data were recorded on the United States Equestrian Federation (USEF) website from 6 months before tiludronate treatment up to a year after. Each horse's performances at 6 and 12 months after tiludronate treatment were determined as "Same level", "Better level" or "Lower level" when compared to 6 months before treatment. To that end, horses were evaluated by

the competition category they competed in (Novice to 4* for eventers, Training to Grand Prix for dressage horses, height of fences for show jumpers and hunters).

2.4. Statistical analysis

Post-treatment potential side effects, evolution of lameness grade and performance data were evaluated separately. Potential side effects were recorded for all horses included in the study. Influence of NSAID administration prior to tiludronate on post-treatment side effects was evaluated using the Fisher exact test with statistical significance defined as $p < 0.05$. Lameness grades evolution and return to performance were evaluated only in horses for which follow-up was available for longer than a year. A Chi-squared test was used to determine association between the return to performance at 6 months and 1 year with whether or not horses received additional medical treatment with tiludronate, statistical significance being defined as $p < 0.05$.

3. Results

A total of 2497 tiludronate treatments were administered to 1804 horses over the study period. Horses received from 1 (1374 horses) to 9 (3 horses) treatments (Table 1).

Modality of administration was not available for every horse but the vast majority received a single dose of 1 mg/kg of tiludronate diluted in isotonic electrolyte solution, administered through a catheter in a jugular vein and infused over approximately 30 to 45 minutes.

Seventy-three percent of treated horses were geldings, 3% were stallions and 24% were females. The median age was 10 years (range 2-26, data available on 85% of horses). Data on the horses' activity were available on records for only 973 (54%) of them. Out of these 973 horses, 898 (92%) were performing: 862 in equestrian disciplines (dressage, show-jumping, eventing, hunter), 23 in western disciplines, 3 were racing and 39 performing in other disciplines (driving, vaulting, endurance racing ,fox hunting). Seventy-five horses (7,7%) were either leisure or trail horses or retired.

3.1. First part of the study: Safety of tiludronate

A total of 23 horses (1,3%) were noted to display possibly related side effects. Of these 23 horses, 18 presented side effects after first tiludronate treatment and 5 after subsequent treatments.

Eighteen horses presented signs of colic, 13 of which after first tiludronate administration. Colic signs remained mild to moderate in all cases, medical treatment (flunixin, butylscopolamine and/or fluids) was necessary in 12 cases and all of them were resolved within 24 hours. Out of these 13 horses, 6 received 1 to 7 subsequent tiludronate treatments and none displayed any further side effects.

Polyuria/polydipsia was recorded in one horse after tiludronate administration and was resolved within a week. One horse presented laminitis 4 days after treatment and another horse was diagnosed with a proximal interphalangeal joint septic arthritis within a week after tiludronate treatment. Two horses presented traumatic fractures, one of the left front medial splint bone and the other of the third trochanter of the right femur, both several months after tiludronate administration.

Out of the 2497 tiludronate administrations, 2390 were preceded by an injection of NSAID (flunixin in most cases). 4,7% (5/107) of tiludronate administrations that were not preceded with NSAID injection were associated with a recorded side effect while only 0,8% (18/2390) of tiludronate administrations lead to a recorded side effect when preceded by a NSAID injection (Table 2). Side effects are statistically significantly more likely to be seen if the tiludronate administration was not preceded by a NSAID injection (Fisher exact test, p-value = 0.002).

3.2. Second part of the study: Efficacy of tiludronate

Locomotion follow-up was available over a year or more for 343 horses, 305 of which were reported lame at initial examination. Two hundred and seventy-eight horses were diagnosed with appendicular conditions and 114 with axial conditions (Table 3). Diagnosis was confirmed by

diagnostic analgesia on 184 horses. Out of the 305 initially lame horses, 112 received only tiludronate treatment and 193 received additional medications (mostly intra- or periarticular injections).

3.2.1. Lameness grade evolution

The distribution of lameness grades of horses during follow-up is presented in Figure 1 and Table 4 for all 305 horses lame at initial examination and in Figure 2 and Table 5 for horses that received tiludronate as a sole treatment. Over 80% of horses presented an initial lameness score over 1.5/5. Forty-seven % were sound by 30 days and 52% were still sound after a year (Fig. 1, Table 4). A similar evolution is observed for horses treated with tiludronate only (Fig. 2, Table 5). Figure 3 and Table 6 represent the distribution of lameness grades of the 59 horses that were lame at initial examination, whose diagnosis was confirmed by a diagnostic analgesia and who were treated with tiludronate only. The distribution and evolution of lameness grades is similar to the ones on Figures 1 and 2.

Mean evolution of lameness grades during follow-up period is shown in Table 7. For the general population, lameness score improved by 1.1 grade 30 days after treatment and by 1.2 grade a year after. Lameness grade of horses with a diagnosis confirmed by diagnostic analgesia and treated with tiludronate only improved by 1.2 after a month and by 1.3 after a year.

3.2.2. Return to performance

Performance data were available for 129 horses during the selected period (Figure 4). Ninety-three (72%) of them were back to competition 6 months after tiludronate, 78 (84%) of them at a better or similar level than 6 months before treatment. A year after treatment, 89 (69%) horses were still competing, 73 (82%) of them at a better or similar level. Thirty-six horses (28%) were not found in the online database 6 months after tiludronate treatment and 40 horses (31%) a year after. Out of the 129 horses, 41 received no other treatment than tiludronate. Twenty-nine of them (71%) were still in competition 6 months and a year after tiludronate, 23 (79%) of them at a better or similar

level 6 months after treatment and 21 (72%) of them a year after compared to 6 months before treatment (Figure 5).

Performance data of horses who received additional medical treatment with tiludronate did not significantly differ at any point from those of horses who were treated with solely tiludronate (Chi-squared p-value remained ≥ 0.05).

4. Discussion

Collected data suggest excellent tolerance of horses to tiludronate in both practices with only 0,9% of injections inducing potential side effects. The incidence of recorded potential side effects is lower in this study than in the summary of product characteristics (≤ 5%) [14] and available literature (10-40%) [8,14,16]. As described in published data [14–16], the most frequent side effect was mild to moderate signs of discomfort/colic (18 horses/23). Two thousand three hundred ninety tiludronate administrations out of 2497 were preceded by a NSAID injection, flunixin in most cases, in order to prevent those colic signs. Indeed, they were less likely to be observed when tiludronate perfusion was preceded by NSAID administration. This may explain why the proportion of reported side effects in this study is lower than in published data. The concurrent use of a NSAID is not recommended due to the known nephrotoxicity of both bisphosphonates [18] and NSAIDs [19,20]. It has been yet widely used in practice including in this study in order to prevent the colic signs frequently seen after tiludronate administration. It must be noted that tiludronate was only administered to horses that were deemed healthy by the treating veterinarian and a preliminary systematic screening blood work was conducted for most horses over 15 years old at the time of treatment (approximatively 150 horses). Despite the prominent use of NSAID concurrently to tiludronate, no case of severe acute renal failure was reported. Only one 12-year-old thoroughbred gelding eventer presented polyuria/polydipsia during a week after tiludronate treatment, without any other systemic sign of renal failure. Although it is highly unlikely that acute renal failure would go unnoticed and thus unrecorded, subclinical or mild renal impairment may have been missed. Clinical signs of renal

impairment are indeed mild and non-specific (loss of appetite, poor general condition, polyuria/polydipsia, etc.). Despite our reassuring results, precautions should still be taken and we would like to remind that use of any potential nephrotoxic drug is not recommended concurrently with tiludronate. The two fracture cases (splint bone, third trochanter of the femur) were considered non-related to tiludronate administration since they both occurred several months after treatment as a consequence of a trauma. Laminitis had not yet been described as a potential side effect of tiludronate administration and the case observed in this study 4 days after tiludronate administration could either be an actual secondary effect or a coincidental event. Likewise, the proximal interphalangeal joint septic arthritis diagnosed within the week following tiludronate administration is unlikely to be related to it. Considering the low occurrence of side effects and their transient and moderate nature, this study demonstrated excellent tolerance of horses to tiludronate. Regarding this first part on the safety of tiludronate, our main limitation is the use of medical records that might be incomplete and the lack of consistent follow-up on many horses. Indeed, part of the activity of the two clinics involved in this study consists in referral cases so many horses were sent back to their treating veterinarians for follow-up. Nevertheless, immediate aftercare surveillance was conducted by the veterinarian administrating the tiludronate treatment so we assumed that they would have detected immediate secondary effects. Besides, any major side effect - such as severe acute renal failure or fracture - would not have gone unnoticed by the usual treating veterinarian and would probably have been communicated to the referral centre.

Both evolution of lameness score and return to performance after treatment suggest good efficacy of tiludronate over a year after treatment. Approximately half of the horses were sound by 30 days after treatment and remained so after 6 months and a year (Fig. 1, Table 4). In order to compensate the lack of control group and to bring the most objective data possible, the authors decided to compare the clinical evolution of the general population to the one of two sub-population: the horses treated only with tiludronate and the horses whose diagnosis was confirmed by a diagnostic analgesia and who were treated with only tiludronate. The repartition of these 3 populations per

lameness grade was similar and followed the same evolution over the follow-up (Fig. 1,2 and 3, Tables 4,5 and 6) and the mean evolution of lameness grade was also almost identical in the 3 groups (Table 4). This similarity is in favour of tiludronate playing a critical role in the evolution of the cases. The results concerning the evolution of lameness grade in this study are consistent with those of available literature assessing tiludronate efficacy [9–12,16]. For instance, in previous studies, the mean lameness improved by 0,6 grade two months after tiludronate treatment in horses with navicular syndrome [9] and by 1,9 grade in horses with bone spavin [10] where in the current study horses improved by a mean of 1,1 grade at this time. Six months after a tiludronate treatment, Denoix et al reported that 50% of horses with navicular syndrome [9,11] and about 60% of horses with bone spavin [11] were no or little lame (lameness grade ≤ 0,5) where in the current study, approximately 53% of treated horses presented a lameness grade ≤ 0,5.

Performance data were collected at 6 and 12 months after tiludronate treatment and compared to those 6 months prior to treatment. It was indeed hypothesized that horses necessitating lameness evaluation and tiludronate treatment would have had progressively impaired performance over the months prior to treatment. Performance data close to the date of initial evaluation and tiludronate treatment would then not be an appropriate baseline to compare to in our study. The level of performance 6 months prior to the initial lameness evaluation and tiludronate treatment was elected as the baseline/regular performance level of each horse. Respectively 72% and 69% of horses were back to competition 6 months and 1 year after tiludronate treatment, with more than 80% of them at a similar or higher level than 6 months before treatment at both times (Fig. 4). These data are not statistically different from the ones of horses treated with only tiludronate (Chi-squared tests, p-value ≥ 0.05). This information on performance complements previous studies with data only available up to 6 months after treatment and is consistent with their findings [9,11,16]: six months after tiludronate treatment, 75% of horses with navicular syndrome [9,11] and 44% of horses with bone spavin [11] returned at a normal level of activity. If a normal level of activity is defined in our

current study by a return to the same or a better level of performance, 60% of horses were back at a normal activity 6 months after treatment and 57% one year after.

Concerning the assessment of tiludronate's efficacy, our main limitation was the lack of a control group to compare the outcome to. Also, further medical treatments, shoeing and/or activity adaptation were not recorded and thus not taken into account in this study. The use of past medical records that were not designed specifically to be used in such retrospective study limits indeed the amount of information that can be used reliably. The evolution of lameness grade is assessed non-blindly by the clinician in charge of the case and is therefore subjective. However, performance data are completely independent from the owner or the veterinarian's subjective evaluation and thus provide an objective way of assessing the evolution of the horse after treatment. In this study, both clinical evaluation and return to activity attest to positive outcome and thus suggest a good efficacy of tiludronate treatment.

Although the efficacy of tiludronate has only been proven in the treatment of navicular disease, bone spavin, pain associated with APJ osteoarthritis of the thoracolumbar spine and prevention of osteolysis secondary to limb immobilization, it is widely used in numerous other bone conditions. In this study, only 39% (132/343) of the horses received tiludronate treatment after diagnosis of one of the three indications listed before. Forty-one percent (142/343) of the horses were treated for other arthropathies, involving both appendicular and axial (cervical or pelvic) regions. Arthropathies (appendicular and/or axial joints) represent then by far the main indication of tiludronate treatment in this study with 61% of the horses involved. These data are consistent with previously published studies on the efficacy of tiludronate to treat navicular disease, bone spavin and thoracolumbar osteoarthrosis and suggest that tiludronate could also be indicated to treat other osteoarticular affections.

The imaging follow-up of the horses was not analysed here despite a majority of cases well documented at the time. Very few studies reported evolution of imaging signs during follow-up after

tiludronate treatment. No significant radiographic changes were observed in neither navicular disease [9] nor APJ thoracolumbar osteoarthritis [12]cases. Only a recent study conducted by Bertuglia *et al* reported inhibition of radiographic progression of osteoarthritis in fetlocks of racehorses 6 months after tiludronate treatment [21]. In contrast, magnetic resonance imaging (MRI), although very sparsely included in tiludronate's studies, is more sensitive to bone remodelling and demonstrated significant evolution after tiludronate treatment [16,22,23]. Yet the studies in question are with limited cases and without control groups. Future prospective study with clinical and advanced imaging (MRI in particular) follow-up would probably be beneficial for the exact understanding of the role of tiludronate in various osteo-articular diseases.

5. Conclusion

This work represents the first retrospective study on tiludronate with such a large population and long-term follow-up. Despite limitations inherent to any retrospective study, collected data suggest both excellent tolerance and good efficacy of tiludronate over a year after treatment. Performance data allows for objective assessment of the outcome and is consistent with clinical follow-up results and previously published data. Further prospective study including a control group might provide stronger proof of both safety and efficacy of tiludronate.

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Ethical statement

At the time of data collection, author S. Wilford was employed by the company Audevard, France, that manufactures and markets the product. The travelling of the first author A. Tischmacher to the USA for data collection and the epidemiological analysis for this study were financed by Audevard France.
Adeline Tischmacher

Conflict of interest statement

At the time of data collection, author S. Wilford was employed by the company Audevard, France, that manufactures and markets the product. The travelling of the first author A. Tischmacher to the USA for data collection and the epidemiological analysis for this study were financed by Audevard France.

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Table 1: Number of horses receiving from 1 to 9 treatments

Number of Tildren treatments	Number of horses
1	1374
2	254
3	102
4	30
5	19
6	10
7	10
8	2
9	3

Table 2: Distribution of tiludronate administrations on whether they were preceded by a non-steroidal anti-inflammatory drug (NSAID) injection and whether side effects were noticed afterwards

NSAID injection prior to tiludronate perfusion ?	**Any side effect recorded ?**	
	Yes	**No**
No	5 (4,7%)	102 (95,3%)
Yes	18 (0,8%)	2372 (99,2%)

Table 3: Conditions (documented with imaging) presented by the 343 horses with locomotion follow-up

Appendicular affections	**Number of horses**
Navicular disease (= podotrochlear syndrome)	64
Distal articular affections *(distal interphalangeal joint, proximal interphalangeal joint, metacarpo/metatarso-phalangeal joint)*	52
Distal tarsus arthropathy	43
Proximal Suspensory Lesions	41
Bone contusion	23
Soft tissue lesions *(mainly suspensory apparatus, flexor tendons, collateral ligaments)*	18
Fracture	13
Cyst-like lesions	10
Proximal articular affections (stifle, shoulder, elbow)	6

Enostosis	5
Splint bone	2
Total	**278**
Axial affections	**Number of horses**
Pelvic arthropathy	56
Kissing spines	49
Cervical articular process joints arthropathy	28
Thoracolumbar articular process joints arthropathy	25
Total	**114**

Table 4: Number and percentage of horses with different grades of lameness at each follow-up examination (among *the 305 horses lame at initial examination)*. Written in brackets for each grade are the percentage of horses concerned out of the total of horses assessed at the time point.

Days post initial assessment (Number of horses assessed)	Grade of lameness - Number of horses (% out of horses assessed)									
	0	**0,5**	**1**	**1,5**	**2**	**2,5**	**3**	**3,5**	**4**	**4,5**
0 days (305)	0 (0,0)	11 (3,6)	45 (14,8)	65 (21,3)	94 (30,8)	42 (13,8)	32 (10,5)	9 (3,0)	6 (2,0)	1 (0,3)
30 days (146)	69 (47,3)	7 (4,8)	15 (10,3)	21 (14,4)	21 (14,4)	4 (2,7)	7 (4,8)	1 (0,7)	1 (0,7)	0 (0,0)
60 days (141)	64 (45,4)	5 (3,5)	18 (12,8)	17 (12,1)	21 (14,9)	5 (3,5)	8 (5,7)	2 (1,4)	1 (0,7)	0 (0,0)
90 days (133)	66 (49,6)	7 (5,3)	20 (15,0)	18 (13,5)	11 (8,3)	8 (6,0)	2 (1,5)	1 (0,8)	0 (0,0)	0 (0,0)
90 - 180 days (122)	63 (51,6)	3 (2,5)	16 (13,1)	13 (10,7)	17 (13,9)	3 (2,5)	5 (4,1)	1 (0,8)	1 (0,8)	0 (0,0)
180 days (158)	77 (48,7)	6 (3,8)	20 (12,7)	19 (12,0)	22 (13,9)	8 (5,1)	4 (2,5)	1 (0,6)	1 (0,6)	0 (0,0)
180-365 days (177)	89 (50,3)	6 (3,4)	21 (11,9)	19 (10,7)	26 (14,7)	3 (1,7)	9 (5,1)	1 (0,6)	3 (1,7)	0 (0,0)
365 days (198)	103 (52,0)	13 (6,6)	22 (11,1)	20 (10,1)	24 (12,1)	8 (4,0)	6 (3,0)	1 (0,5)	1 (0,5)	0 (0,0)

Figure 1: Distribution of horses per lameness grades at each examination, among 305 initially lame horses. (Size of the circles proportioned to the number of horses.)

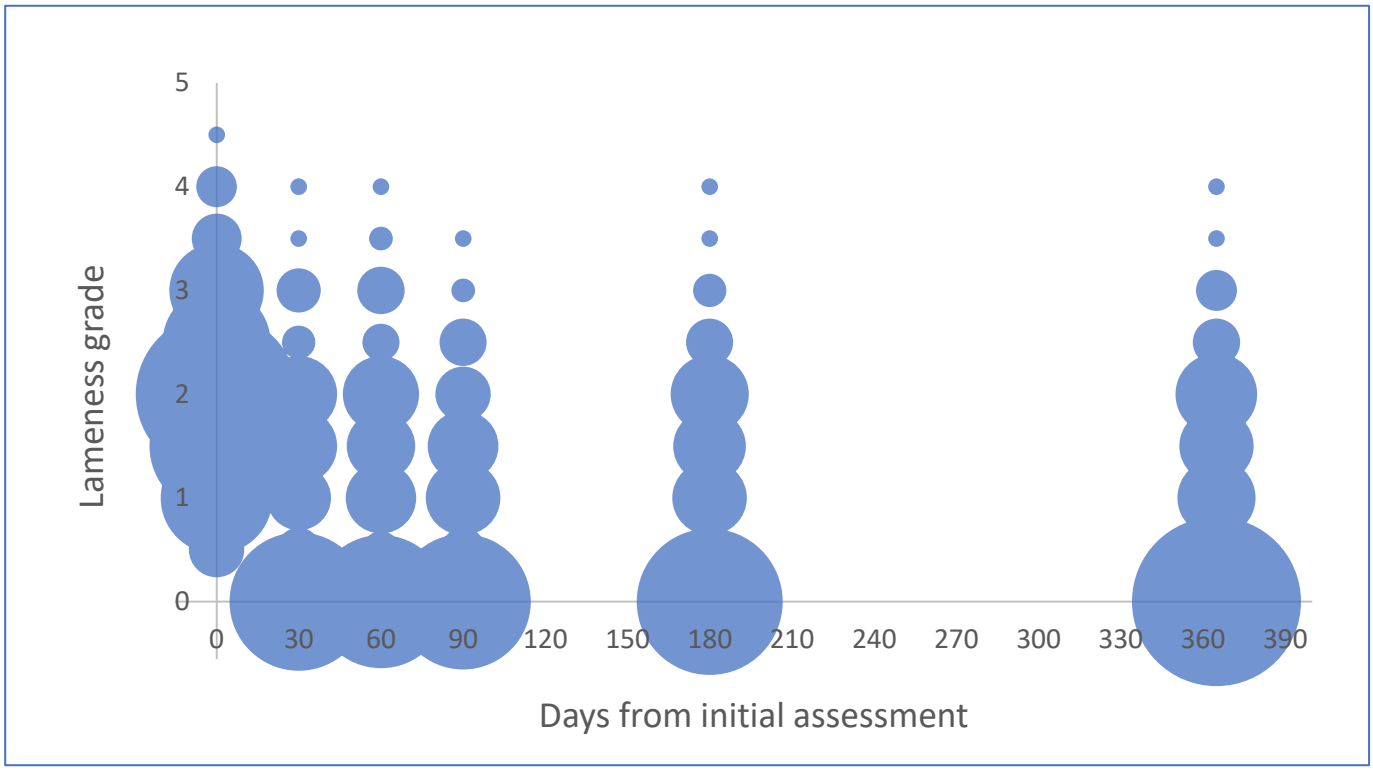

Table 5: Number and percentage of horses with different grades of lameness at each follow-up examination *(among the 98 horses lame at initial examination* ***that received no other medical treatment than tiludronate****).* Written in brackets for each grade are the percentage of horses concerned out of the total of horses assessed at the time point.

Days post initial assessment (Number of horses assessed)	Grade of lameness - Number of horses (% out of horses assessed)									
	0	**0,5**	**1**	**1,5**	**2**	**2,5**	**3**	**3,5**	**4**	**4,5**
0 days (98)	0 (0,0)	2 (2,0)	10 (10,2)	21 (21,4)	33 (33,7)	16 (16,3)	11 (11,2)	2 (2,0)	3 (3,1)	0 (0,0)
30 days (48)	20 (41,7)	5 (10,4)	2 (4,2)	10 (20,8)	8 (16,7)	0 (0)	3 (6,3)	0 (0,0)	0 (0,0)	0 (0,0)
60 days (44)	17 (38,6)	2 (4,6)	6 (13,6)	5 (11,4)	7 (15,9)	2 (4,6)	4 (9,1)	1 (2,3)	0 (0,0)	0 (0,0)
90 days (49)	21 (42,9)	3 (6,1)	9 (18,4)	7 (14,3)	6 (12,2)	2 (4,1)	1 (2,0)	0 (0,0)	0 (0,0)	0 (0,0)
90 - 180 days (43)	24 (55,8)	0 (0,0)	4 (9,3)	5 (11,6)	8 (18,6)	1 (2,3)	1 (2,3)	0 (0,0)	0 (0,0)	0 (0,0)
180 days (58)	28 (48,3)	1 (1,7)	8 (13,8)	8 (13,8)	6 (10,3)	4 (6,9)	2 (3,5)	0 (0)	1 (1,7)	0 (0,0)
180-365 days (54)	28 (51,9)	2 (3,7)	4 (7,4)	6 (11,1)	8 (14,8)	2 (3,7)	2 (3,7)	1 (1,9)	1 (1,9)	0 (0,0)
365 days (67)	29 (43,3)	5 (7,5)	7 (10,5)	7 (10,5)	10 (14,9)	5 (7,5)	3 (4,5)	0 (0,0)	1 (1,5)	0 (0,0)

Figure 2: Distribution per lameness grades at each examination of the 98 horses that received tiludronate as sole treatment. (Size of the circles proportioned to the number of horses.)

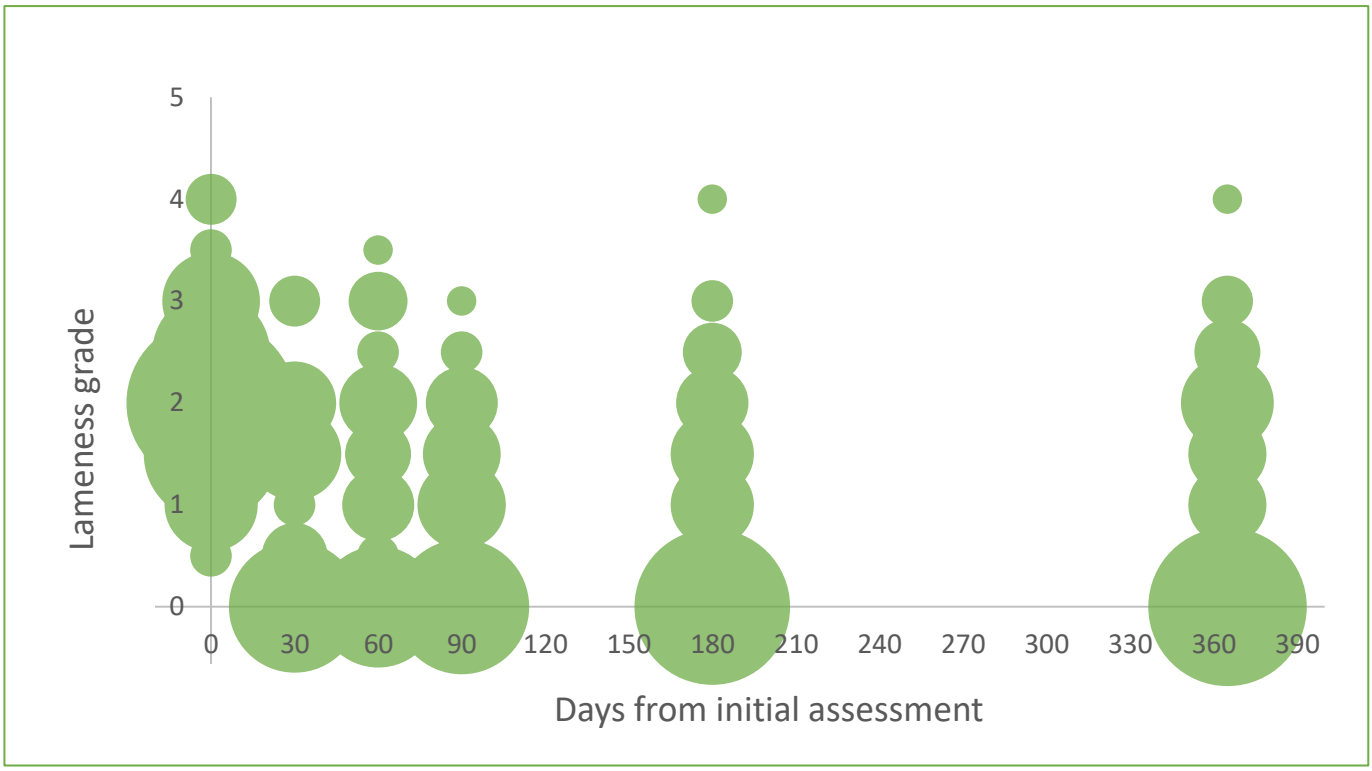

Table 6: Number and percentage of horses with different grades of lameness at each follow-up examination *(among the 58 horses lame at initial examination whose **diagnosis was confirmed by diagnostic analgesia** and **that received no other medical treatment than tiludronate**).* Written in brackets for each case are the percentage of horses concerned out of the total of horses assessed at the time point.

Days post initial assessment (Number of horses assessed)	Grade of lameness - Number of horses (% out of horses assessed)								
	0	**0,5**	**1**	**1,5**	**2**	**2,5**	**3**	**3,5**	**4**
0 days (58)	0 (0,0)	0 (0,0)	2 (3,4)	10 (17,2)	19 (32,8)	13 (22,4)	10 (17,2)	1 (1,7)	3 (5,2)
30 days (29)	11 (37,9)	4 (13,8)	0 (0,0)	5 (17,2)	7 (24,1)	0 (0,0)	2 (6,9)	0 (0,0)	0 (0,0)
60 days (29)	9 (31,0)	0 (0,0)	6 (20,7)	2 (6,9)	5 (17,2)	2 (6,9)	4 (13,8)	1 (3,4)	0 (0,0)
90 days (26)	11 (42,3)	2 (7,7)	5 (19,2)	4 (15,4)	1 (3,8)	2 (7,7)	1 (3,8)	0 (0,0)	0 (0,0)
90 - 180 days (27)	15 (55,6)	0 (0,0)	3 (11,1)	4 (14,8)	4 (14,8)	0 (0,0)	1 (3,7)	0 (0,0)	0 (0,0)

180 days (31)	13 (43,3)	1 (3,3)	3 (10,0)	4 (13,3)	2 (6,7)	4 (13,3)	2 (6,7)	0 (0,0)	1 (3,3)
180-365 days (32)	16 (50,0)	0 (0,0)	1 (3,1)	4 (12,5)	7 (21,9)	1 (3,1)	2 (6,3)	1 (3,1)	0 (0,0)
365 days (37)	15 (40,5)	3 (8,1)	2 (5,4)	5 (13,5)	6 (16,2)	3 (8,1)	2 (5,4)	0 (0,0)	1 (2,7)

Figure 3: Distribution per lameness grades at each examination of the 58 horses whose diagnosis was confirmed by diagnostic analgesia and that received tiludronate as sole treatment. (Size of the circles proportioned to the number of horses.)

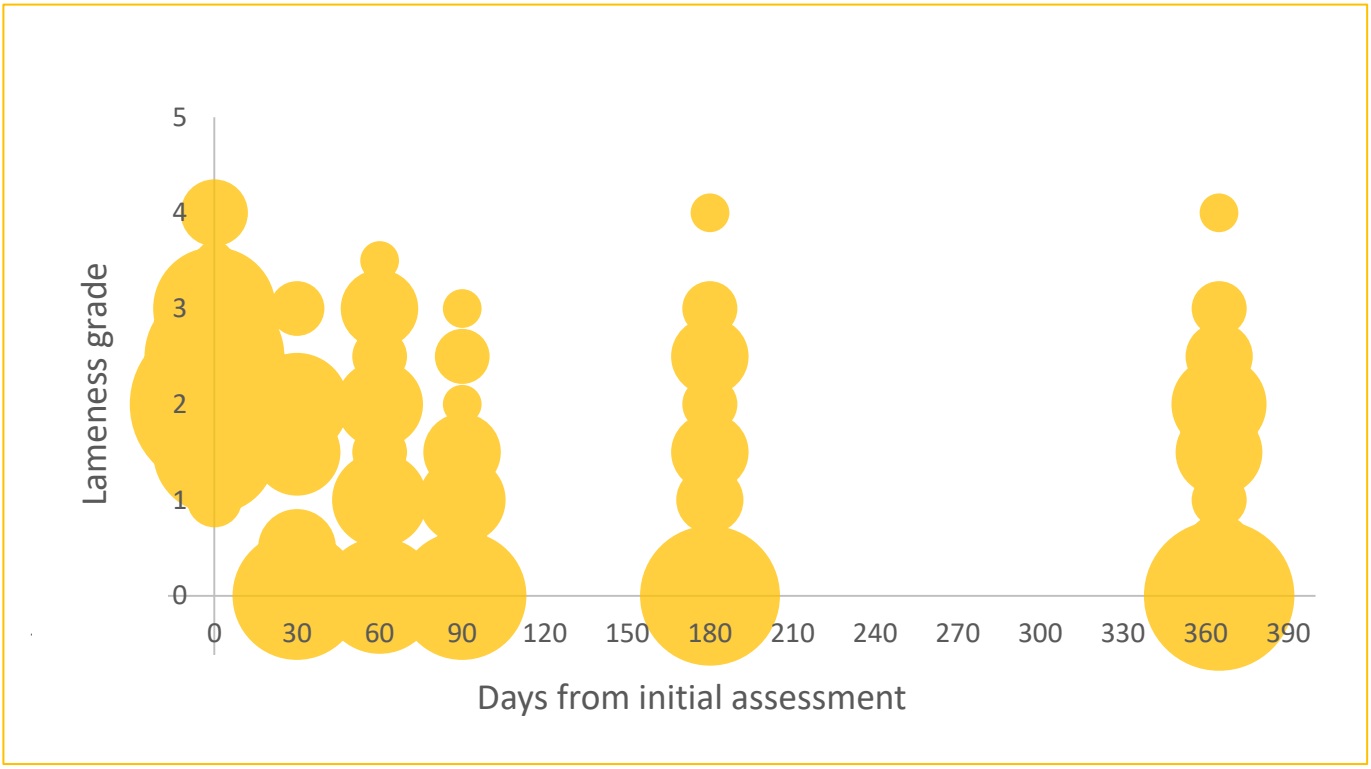

Table 7: Mean evolution of lameness grade in horses between tiludronate administration and the different follow-ups.

	Horses treated with tiludronate +/- another medication (305 horses)		*Horses treated with tiludronate only (98 horses)*		*Horses with a diagnostic analgesia, treated with tiludronate only (58 horses)*	
Date	*Number of horses per exam*	Mean evolution of lameness grade	*Number of horses per exam*	Mean evolution of lameness grade	*Number of horses per exam*	Mean evolution of lameness grade
30 days	*146*	-1,12	*48*	-1,09	*29*	-1,17

60 days	*141*	-1,10	*44*	-1,08	*29*	-1,05
90 days	*133*	-1,26	*49*	-1,18	*26*	-1,44
90 - 180 days	*122*	-1,15	*43*	-1,27	*27*	-1,61
180 days	*158*	-1,15	*58*	-1,21	*31*	-1,39
180-365 days	*177*	-1,04	*54*	-1,11	*32*	-1,23
365 days	*198*	-1,18	*67*	-1,06	*37*	-1,26

Figure 4: Evolution of level of activity compared to 6 months prior to tiludronate treatment (129 horses).

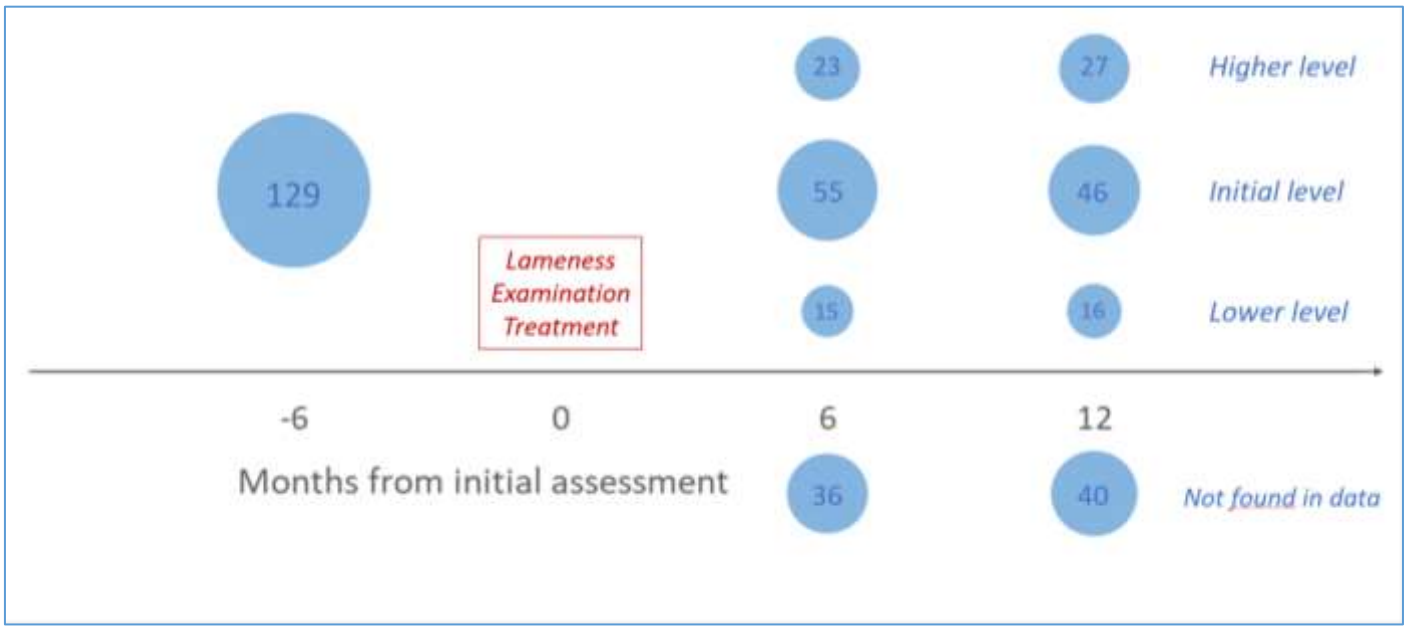

Figure 5: Evolution of level of activity compared to 6 months prior to tiludronate treatment for horses that received no other medication (41 horses).