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Critical review of the clinical use of tiludronate in horses

Olivier M. Lepage
Equine Department, VetAgro Sup - Veterinary Campus of Lyon
University of Lyon, Marcy l’Etoile, F-69280 France

Tiludronate is a non-nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption and that is used in equine since a decade (Lepage, 2002; Delguste et al., 2007a). The action on resorption is consecutive to cellular effects on osteoclasts, rather than by purely physico-chemical mechanism (Rogers et al., 1999). Used in the nineties to prevent bone resorption in humans, tiludronate is nowadays replaced by more powerful bisphosphonate such as residronate (Leu et al., 2006).

As tiludronate shown some clinical efficacy in horses? This question is probably the most relevant one for an equine practitioner and the best way to answer is to follow principles of evidence-based medicine which aims to apply the best available evidence gained from the scientific method to medical decision making. A search of all papers on PubMed and ScienceDirect for the period between 2000 and 2010 shows a production of 7095 and 1717 publications respectively for the keywords combination bisphosphonate-human and bisphosphonate-animals. If we apply the same combination of keywords but with tiludronate instead of bisphosphonate we find 35 publications for humans and 13 for animals including 5 involving strictly the equine species (Table 1). The origin of these five papers are from France and are supported by CÉVA Santé Animale sponsor of the only intravenous form of tiludronate licensed for horses in Europe at this time. Because we are searching for treatment information we can consider these publications having a very high score in the pyramid of evidence.

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Tiludronate is licensed in Europe at a dosage of 0.1 mg/kg bodyweight (b.w.) for intravenous bolus once daily for 10 consecutive days. But if we compare in adult healthy horses 2 dosage regimens (1 mg/kg b.w. once, versus 0.1 mg/kg b.w. 10 days), the bioavailability and the pharmacological effects of tiludronate are the same (Delguste et al., 2008a). This study suggests that a more practical dosage regimen is to replace the administration of 10 daily boluses by a single constant rate infusion at a total dose of 1 mg/kg b.w. It was previously shown that at this dosage regimen for tiludronate induce a rapid and marked decrease in horse serum CTX-I, indicating an antiresorptive effect (Varela et al., 2002). The drug is also well tolerated without any clinically relevant adverse effects. The adverse problems reported being a slight non-significant increase in heart rate without dysrhythmia, very light intermittent colic symptoms and a transient slight hypocalcaemia (Varela et al., 2002). Pre-treatment with flunixin meglumine, sedation products or such drugs is not needed.

Efficacy of tiludronate has been confirmed by three studies in horses suffering either from navicular disease (Denoix et al., 2003), disuse osteoporosis (Delguste et al., 2007b) or pain associated with lesions of the thoracolumbar vertebral column (Coudry et al., 2007).
O.M. Lepage

In a multicentre study horses affected with navicular disease (n=39) received tiludronate at 0.1 mg/kg b.w. for 5 or 10 days (Denoix et al., 2003). To see a significant statistical effect cases were broken down into a group of horses with clinical signs less than 6 months and another group including individuals with signs of more than 6 months. The efficacy of tiludronate is demonstrated only at the cumulative dosage of 1 mg/kg b.w. (10 days) in horses with a more recent onset of clinical signs (less than 6 months). An incomplete characterisation of the source of lameness (no differentiation between bone and soft tissue) may have lead to error of interpretation. An antiresorptive activity was maybe inappropriate in some cases. Tiludronate administered at 1 mg/kg b.w., two times, 28 days apart, was found to significantly reduce bone resorption during a long-term immobilization model (Delguste et al., 2007b). Application for 2 months of a lower-limb fibreglass cast in this experimental study induced a disuse osteopenia in the metacarpus III of controlled horses. Simultaneously the loss in bone mineral density, measured by DEXA, was significantly less in the immobilized canon bone of the tiludronate treated individuals. If this study suggests tiludronate in the prevention of disuse osteopenia in case of long term immobilisation we have no ideas on the effect of this drug on equine bone repair. Practitioners should therefore select the long term immobilised patient (flexor tendon rupture, fetlock luxation...) that will receive tiludronate for his preventive effect.

To evaluate the efficacy on the pain associated with lesions of the thoracolumbar vertebral column, tiludronate was administered at 1 mg/kg b.w., once or two times at 2 months interval. All 29 horses were monitored 120 days with clinical, radiographic, ultrasonographic and scintigraphic examination (Coudry et al., 2007). Results of this study show a significant improvement (P = .019) in dorsal flexibility at the canter mainly at 60 days for the treated group.

To get more evidence or opinions on the use of tiludronate in horses we looked in refereed and non refereed proceedings and publications collected in University libraries or on the web. We found another 13 papers including 3 theses (Poircuitte 2004; Riccio 2006; Delguste 2008b). From the work of Riccio we learn that intra-articular injection of tiludronate in the distal interphalangeal and metacarpophalangeal joint of horses rapidly diffuse from the joint to the blood circulation and can induce synovitis confirmed by histological examination of the synovial membrane. We also learn that an unpublished study on the effects of tiludronate on distal hock pain (n=8 horses) localised with perineural analgesia or intra-articular anaesthetic injection was not very conclusive (Dyson, 2004). Results that are in contrast with the ones reported in another non refereed paper that shows a beneficial effect of tiludronate one month after an iv administration at a dosage of 0.1 mg/kg b.w. for 10 days in horses (n=9) affected with bone spavin (Sachot, 2002).

At the exception of a case-report of a single horse with coffin joint DJD that did not answer to conventional treatment but resolved with tiludronate 4 months after the last injection with absence of lameness and resolution of a PII oedema (Schulze, 2005), the other publications are usually of a low scientific interest. They often resume or comment the 5 main papers with the idea to make a transfer of information to practitioners about the arrival of a new class of therapeutic agent (bisphosphonate) in veterinary medicine (Kamm et al., 2008; Perrin, 2009).

In conclusion, ten years after we have started using tiludronate on a large scale in equine medicine we still have a major lack of evidence and we are still waiting to get more clinical relevant information. For example tiludronate is often used in young exercising Thoroughbreds with the idea to prevent stress fracture. If the high price of repetitive tiludronate administration is not a barrier for these cases, we have no evidence of the effectiveness of such a preventive treatment. Furthermore we do not know the effect of such a drug on a growing equine skeleton. On the other hand if we have not enough reliable information specific for tiludronate in the equine species to answer the question, we can refer to scientific data about other bisphosphonate used in horse (Lepage et al., 1999; McGuigan et al., 2000; Gray et al., 2002) or data obtained with tiludronate in other species.

A consequence from these data, having in mind that we can not make any direct conclusion from one species to another one, is the fact that tiludronate administration in a growing horse has to be made in a thoughtful way. Indeed we found scientific evidence that on a long term or in a repetitive manner high doses of tiludronate in growing rats and baboons induce the accumulation of unresorbed calcified cartilage, adjacent to the skeletal growth plate (Neer, 1995). This predictable side effect of the drug primary action indicates that tiludronate should be used with caution in growing equids. In a profession often confronted to osteochondrosis and to pressure from owners and trainers to use new drugs these studies are especially relevant in young exercising horses. We also learn from these data that tiludronate-treated rats cannot maintain normal serum calcium levels when fed a low-calcium diet probably indicating that horses should also have a normal calcium intake during tiludronate treatment.

All these examples warn us of the importance of a constant search in scientific evidences for a better use of bisphosphonate in orthopaedic equine patients. Many more studies being needed to gain confidence in the efficacy of such drugs.
REFERENCES


