TILUDRONATE AND BONE RESORPTION

IT'S TIME FOR AN UPDATE

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TILUDRONATE AND BONE RESORPTION IT'S TIME FOR AN UPDATE

Tiludronate ; 15 years of scientific perspective.

Via this document, we aimed to summarize the scientific literature available on tiludronate for the benefit of European veterinary surgeons. The sources for this document are the 12 equine tiludronate studies available on PubMed (search terms: 'tiludronate', 'horse'). Link: http://www.ncbi.nlm.nih.gov/pubmed/ (1-12) and recent studies published on various themes relating to bisphosphonates (13-20).

Bisphosphonates are not all equivalent.

As explained in this document, all **bisphophonates are different.** Some mechanisms and properties are common to the entire class but each molecule has its own specific effects.

The approach to osseous disorders should continue to showcase equine veterinary expertise and procedures across Europe.

The treatment of bone remodelling in the horse is an important axis of valorisation of the veterinary surgeon's diagnostic ability and therapeutic approach. Also, this area is in constant development in the European veterinary sector.

Treatment with bisphosphonates is only likely to work if they are used when abnormal osteolytic processes are occurring. This can only be identified **via specific diagnostics.** Client satisfaction relies therefore entirely on the identification of a lameness with an osseous component as well as the establishment of adequate preventative measures of **the potential side-effects associated with bisphosphonate usage.**

As these elements **require veterinary expertise**, bisphosphonate usage should not be trivialized nor be reduced to a simple prescription.

As a supporter of veterinary expertise Audevard has chosen to accompany equine vets over the long term.

Did you know ?

The principles of scintigraphy are based on bisphosphonate properties.

Scintigraphy is an imaging technique used mainly to quantify osseous metabolism and localise areas of pathological remodelling.

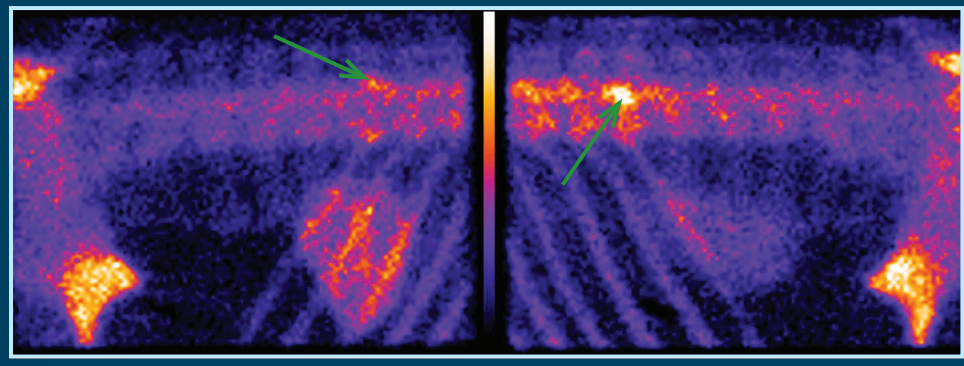
A **bisphosphonate** is coupled with an isotope then injected intravenously. After transiting through the circulation, the bisphosphonate **will be rapidly taken up by exposed hydroxyapatite crystals.**

All bones undergo continuous remodelling. The bisphosphonate-isotope molecule bonds to the entire skeleton, though fixation will be more intense in the areas of increased remodelling, where hydroxyapatite exposure is more pronounced. In this manner these areas will be more visible on the scintigraphic images.

However, it is essential that this coupling should only be transient, in order for example to be able to repeat an examination without risk or artefact. In view of this, the bisphosphonate that serves as a vector should only have a short duration of action and be rapidly eliminated.

This is the case, for example, of methylene-diphosphonate (or medronate) and dicarbonate-diphosphonate (DPD), that are bisphosphonates frequently used in bone scintigraphy. Most of their fixation on bone occurs within 20-30 minutes. A 2 hour waiting time is necessary to allow renal elimination of the circulating non-fixed product.

The principle of this imaging technique is a good illustration that each bisphosphonate has its own distinctive characteristics that dictate therapeutic effects and utilisation.

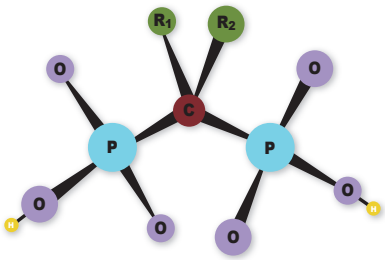


Scintigraphy of the back (thoracolumbar region). Increased radiopharmaceutical uptake of the T18-L1 left articular processes
Courtesy of CIRALE-ENVA

How to distinguish between bisphosphonates.

Bisphosphonate molecules are characterised by a P-C-P centre linked to 2 lateral chains R1 and R2.

Bisphosphonates are characterised by the composition and structure of their lateral R1 and R2 chains. Each molecule will therefore have their own characteristics.



R_1 : short chain that determines the chemical and pharmacokinetic properties of the molecule.

R_2 : chain that determines chemical properties, mode of action and effects of the molecule.

Molecule	R_1	R_2
Elidronate	— OH	— CH_3
Clodronate	— Cl	— Cl
Tiludronate	— H	— S–⬡–Cl

Bisphosphonates are recognised for their ability to 'fix' on to bone: they bind to minerals used for the elaboration of crystals that are part of the bone framework.

Bone matrix mineralisation occurs partly via hydroxyapatite crystals formation. This organised structure traps minerals, specifically calcium ions and maintains them within the osseous matrix.

After their administration, bisphosphonates rapidly fix onto the minerals that contribute to hydroxyapatite crystal formation. They will be retained there until released. Their level of retention will depend partly on the number of bonding sites available.

In view of this bisphosphonates will be integrated preferentially in the areas where hydroxyapatite crystals will be more readily available. This will occur in the areas of increased remodelling. Here their release will occur following crystal disintegration by osteoclasts.

The literature highlights the differences between bisphosphonates that are relative to their composition and structure.

Bone binding affinity (R_1)	Elimination process and intensity of action (R_2)
The degree of bone affinity dictates skeletal fixation; it varies between molecules and thereby conditions therapeutic efficacy. Literature demonstrates that different bisphosphonates have a varying ability to bind to bone receptors and that the quantity of fixed molecules may influence their duration of action. As a result balanced distribution of the molecule towards resorption sites could explain a longer duration of action (13).	Pyrophosphates, precursors to bisphosphonates have a strong bone affinity. However this affinity is transient due to enzymatic hydrolysis and rapid elimination; In view of this they were the first to be used as a diagnostic tool in scintigraphy. Following on from this bisphosphonates, more complex molecules were developed to better resist hydrolysis and present a stronger biological activity. Furthermore, their ability to interact with their target (osteoclasts) may vary. These molecules are used therapeutically in osteolytic processes. Finally other bisphosphonates that are eliminated at a faster rate are now also used diagnostically in scintigraphic examination.

Secondary effects of bisphosphonates in the horse.

In view of their similar mode of action and elimination, all bisphosphonates carry the same risks.

Colics

Occasionnally low grade spasmodic colics can occur following the administration of bisphosphonates. The proposed mechanism of action behind these is the transient hypocalcemia that induces an equally transient dysmotility (16). To avoid this as much as possible it is paramount to respect slow administration of the product.

Renal failure

As with the colic cases, the risk of renal failure is dependent on dose and speed of administration. This highlights the importance of taking in to account product recommendations.

Bisphosphonate elimination is mainly renal via glomerular filtration even if the mechanism is incompletely understood. There is therefore a risk of causing acute renal failure in a horse that may already have low grade kidney disease or compromised glomerular filtration.

In view of this, it is advisable not to administer tiludronate when glomerular filtration is compromised (renal failure or hypovolemia) or in conjunction with other potentially nephrotoxic drugs (aminoglycosides, non-steroidal anti-inflammatories and iodinated contrast products for example).

The potential risks of side-effects on kidney function are low but should nevertheless not be overlooked. As a precaution, it is recommended to evaluate kidney function prior to bisphosphonate administration.

Side-effects : avoiding liability.

Even if serious problems following bisphosphonate administration are rare, it is preferable to anticipate and take necessary precautions to avoid liability. When in doubt, further investigation measures should be performed. The extent of further tests is conditioned in part by the terms utilised in the SPC of the chosen drug.

Renal failure, for example, describes the group of symptoms associated with a reduction in glomerular filtration rate. This can be diagnosed via a complete clinical examination together with **a complete history** (urine output, water intake, condition change…) and **as a minimum via serum creatinine dosage**.

Alteration of renal function is a broader notion and implies a reduction in glomerular filtration rate not necessarily associated with clinical signs. **This implies carrying out more extensive tests such as urinary specific gravity, fractional electrolyte excretion as well as the dosage of serum creatinine.**

Focus on Tiludronate

An exclusive equine injectable bisphophonate.

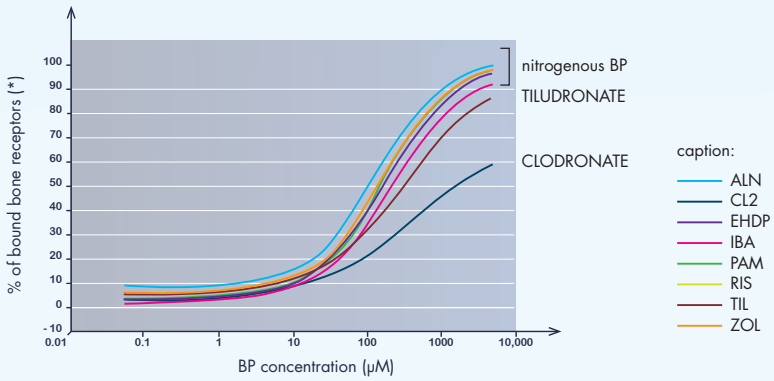
Tiludronate is a non-nitrogen containing bisphosphonate with a therapeutic goal. It is currently exclusively available in an injectable form in equine veterinary medicine, where its application is supported by more than 15 years of use.

As in scintigraphy, bisphosphonates are injected intravenously and are rapidly taken up by hydroxyapatite crystals that are part of the osseous matrix; this occurs in the areas where bone remodelling is most active. Molecules that are not fixed are eliminated in urine.

Bone affinity of tiludronate is superior to other non-nitrogen containing bisphophonates.

The bone affinity of Tiludronate has been evaluated and compared to other bisphosphonates: the results of the study demonstrated that the binding ability of tiludronate was superior to other non nitrogen containing bisphosphonates (13).

N.B Nitrogen containing bisphosphonates are not currently marketed in the horse. The reasons for this may be their rather long half-life, which would render their usage during racing and FEI competitions complicated, as well as their non-negligible side-effects.

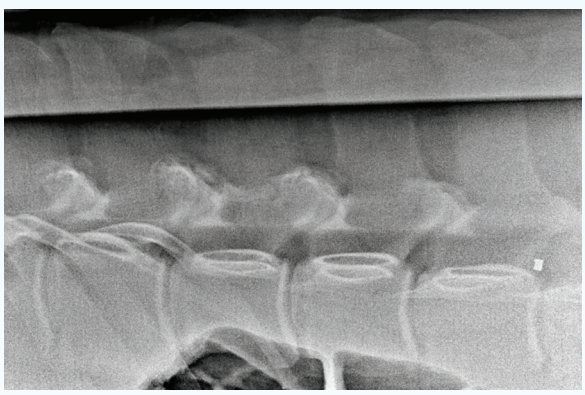


(9)Leu CT, Luegmayr E, Freedman LP, Rodan GA, Reszka AA., 2006. Relative binding affinities of bisphosphonates for human bone and relationship to antiresorptive efficacy. Bone. May;38(5):628-36.

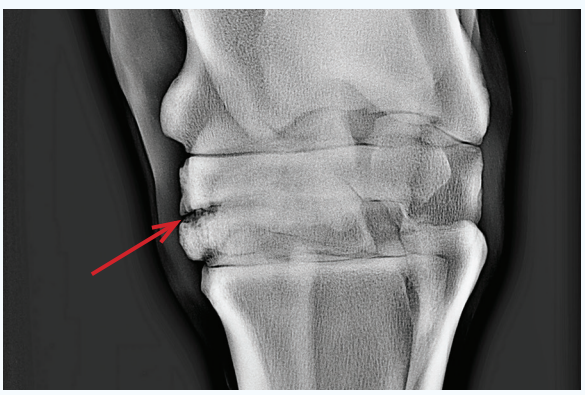
(% of inhibition of the fixation of a competing bisphophonate)*

Therapeutic properties: Tiludronate aims to re-establish the balance between bone resorption and formation, by slowing the actors of resorption.

The therapeutic effects of tiludronate have been thoroughly investigated (1-4, 10). During remodelling, osteoclasts, the cells in charge of bone resorption, are exposed to tiludronate bound to hydroxyapatite crystals. The molecule adheres to the brush border of the osteoclasts, is internalised and metabolised within the cell and disturbs cellular metabolism as well as the structure of the cytoskeleton. Following this the cell dies via apoptosis. The process of bone destruction is thereby slowed down. However, the osteoblasts, cells responsible for bone formation, continue to synthesise organic bone matrix upon which hydroxyapatite crystals will fix.



Intervertebral articular facet arthropathy (thoracolumbar region)
Courtesy of CIRALE-ENVA.



Osteoarthritis of the hock (bone spavin)
Courtesy of CIRALE-ENVA.

Pathological bone remodelling, tiludronate's speciality.

Different cases of bone remodelling affect a specific area (subchondral bone or not), or the entire skeleton (loss of bone density following immobilisation). The different complaints can be classified as follows:

Articular problems		Loss of bone density following immobilisation
Arthropathies and subchondral lesions	Non subchondral bone lesions	
• Hocks (bone spavin)* • Fetlocks • Thoracolumbar vertebral column* • Juvenile osteoarticular lesions (subchondral cysts and osteo-chondrosis).	• Navicular syndrome* • Phalangeal or metacarpo/meta-tarsophalangeal exostosis • Enthesiopathies of the suspensory ligament.	• Entire skeleton*

** Proven efficacy of tiludronate*

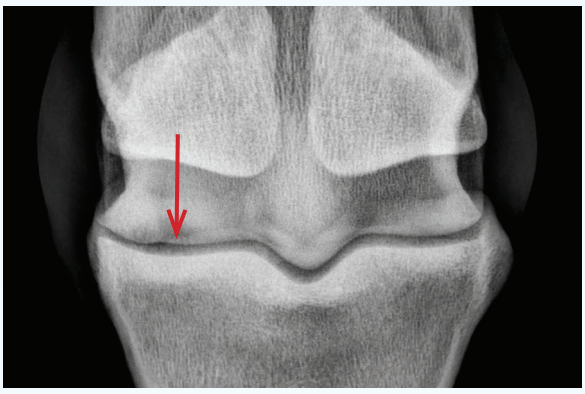
A benefit of Tiludronate has been clearly demonstrated on at least 3 different osteo-articular diseases.

Studies have proven Tiludronate's efficacy in several of these equine disease processes which makes this molecule the only bisphosphonate with demonstrated benefits in at least 3 osteo-articular diseases in the horse:

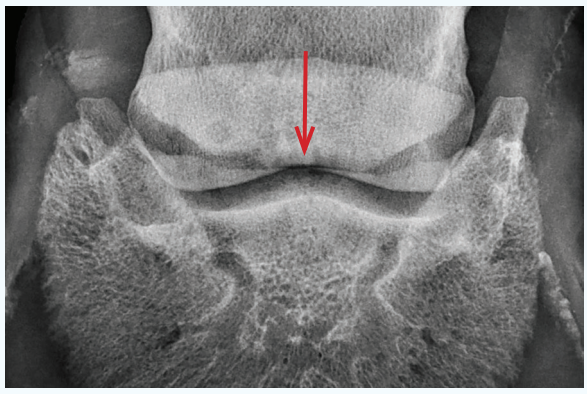
- arthropathies with subchondral bone disease such as bone spavin (1) and thoracolumbar vertebral column abnormalities (3).

- Navicular syndrome (2-8) as an osseous abnormality that does not have a subchondral bone involvement.

- Generalized demineralisation occurring in the immobilized horse as demonstrated by measurement of the CTX-1 marker (marker of bone resorption) (4)



Medial subchondral bone cyst, fetlock joint (dorsopalmar view)
Courtesy of CIRALE-ENVA.



Navicular disease (severe osseous form, upright dorsopalmar view)
Courtesy of CIRALE-ENVA.

4 methods of administration of Tiludronate evaluated in the horse.

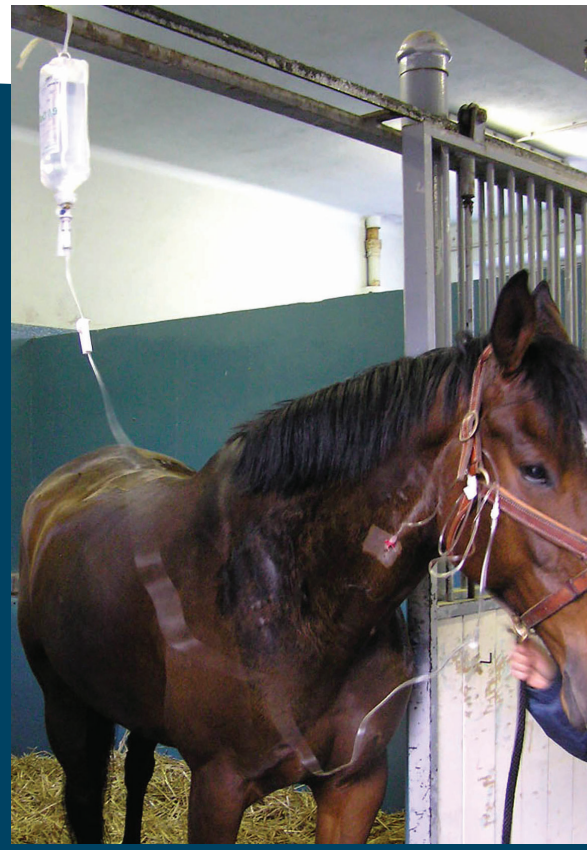
– Systemic intravenous administration **(jugular vein)**

- Either as a single administration in 0.9% NaCl over a 60 - 90 minute period (1)
- Or as daily slow injection over 10 consecutive days (2).

– Intravenous regional **perfusion was evaluated for lack** of deleterious effects on cartilage. The efficacy of this technique remains empirical at the moment and necessitates further scientific evaluation (7-8).

– Intra-articular tiludronate administration is not recommended based on published scientific data that demonstrates side-effects on cartilage.

The summary of these studies is available in a synthetic document « Bibliographie Tiludronate », Audevard 2016



Intravenous perfusion of a horse
Source : CIRALE-ENVA.

Clinical efficacy in the horse: lameness improvement occurs rapidly and is still visible at 6 months.

Numerous studies on Tiludronate have been carried out in the horse; They have clearly demonstrated a clinical improvement in treated horses. Lameness improvement becomes rapidly visible and is still measurable 6 months after administration (2).

FAQ'S

Is there a withdrawal time for tiludronate?

Reevaluated to 1 month by the LCH (Racing and Fédération Française d'Equitation (FFE) competitions) in July 2016 and at 28 days by the FEI in October 2016.

The 'Laboratoire des Courses Hippiques (LCH)' has recently put into place a detection method that applies to all bisphosphonates (11-12). In view of the necessity to treat certain horses as well as maintain equity between racing and FFE participants, it has become necessary to introduce a framework for each molecule dependent on its specific characteristics.

A study was carried out by the LCH in 2016 in order to further evaluate tiludronate's pharmacokinetics following administration to horses presenting for pathological bone remodelling. Following this work, withdrawal time has been set to 1 month.

It is therefore not recommended to administer tiludronate less than 1 month prior to a race or FFE competition.

After the 1st of July 2017, countries following EHSLC or LCH rules will align themselves on tiludronate doping time. It is recommended to contact the competent relevant authorities prior to competing abroad.

Tiludronate is on the FEI controlled substance list. The proposed detection time is 28 days (October 2016). As a reminder, the FEI specifies that the prohibited substance list includes substances that have a similar chemical structure or biological effect to molecules listed, therefore all bisphosphonates.

Is it possible to use tiludronate in fractures?

The subacute stage is the preferred period of administration.

In fracture cases, the bone undergoes natural physiological bone remodelling in order to repair the lesion. Although this is a normal, non-pathological process, the remodelling could be influenced by tiludronate usage. Current studies do not draw clear conclusions in regards to the potential effects of bisphosphonates in fracture repair.

However it should be kept in mind that fracture repair requires a period of immobilization. This in itself leads to bone remodelling independent of the remodelling that leads to fracture repair and incurs generalised loss of bone density.

Tiludronate has been proven to be efficacious in such circumstances and it's utilisation in immobilized horses has been validated (4).

In view of these elements and in the absence of studies in fracture repair in the horse, it would appear preferable not to administer tiludronate in the acute phase of fracture repair but at a slightly later stage as a palliative to bone density loss due to immobilisation.

Is it possible to use tiludronate in young horses and pregnant or lactating mares?

In the absence of studies, benefit versus risk should be evaluated.

The effects of tiludronate have not been studied in horses under 3 years of age. During growth, bone metabolism is active and bone remodelling plays an obvious important role during this time. In the absence of studies, it is not possible to determine if tiludronate would have a negative impact in the growing horse.

In the same way, the effects of tiludronate after administration to the pregnant or lactating mare have not been evaluated. In the absence of data, it is not possible to know whether or not tiludronate would have a negative impact on the foetus or the foal, whose bone development is of course paramount.

Is it possible to administer tiludronate on the day of examination after scintigraphy?

A delay of 2-3 weeks advised.

Bone scintigraphy is often used as a diagnostic tool prior to tiludronate administration. It should be noted that all bisphosphonates have a similar mode of action. Receptors for medronate or DPD and tiludronate onto hydroxyapatite crystals are the same. In order to avoid that these molecules compete with one another, a 2-3 week delay between administrations of the 2 molecules is recommended.

Bone remodelling and pathological bone remodelling.

Bone remodelling is a physiological process that is essential to the maintenance of osseous framework.

Bone remodelling is a complex interaction between osteoclasts and osteoblasts, a calcified extracellular matrix and a large number of regulating factors (hormones, cytokines and growth factors). In addition, it can also be described as being a fragile balance between 2 types of complementary cell types. Remodelling occurs in a continuous fashion in order to maintain mechanical bone properties as well as its ability to adapt to strain.

Pathological bone remodelling is caused by an increase in osteoclasts activity which leads to bone resorption despite the compensatory increase in osteoblasts activity.

Certain situations (such as excessive strains due to work, age, genetic predisposition or nutrition) can lead to an imbalance in the remodelling process and a loss of bone density. This imbalance is mainly due to the excessive recruitment of osteoclasts, cells responsible for matrix degradation. In response, the bone attempts to compensate this destruction by osteoblast intervention. These cells, play the role of builders and contribute to the mineralisation of the bone matrix by facilitating deposits of hydroxyapatite crystals. Although bone destruction appears to predominate in these cases, the affected areas also show a strong osseous synthesis activity.

Many diseases incur pathological bone remodelling.

In addition to conventional imaging techniques, increase usage of scintigraphy over the last few years has highlighted many cases of abnormal bone remodelling in the horse.

Articular problems		Loss of bone density following immobilisation
Arthropathies and subchondral lesions	Non subchondral bone lesions	
• Hocks (bone spavin) • Fetlocks • Thoracolumbar vertebral column • Juvenile osteoarticular lesions (subchondral cysts and osteo-chondrosis).	• Navicular syndrome • Phalangeal or metacarpo/meta-tarsophalangeal exostosis • Enthesiopathies of the suspensory ligament.	Elevation in CTX-1 marker (increased resorption marker) occurs rapidly after a period of immobilization.

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LABORATOIRES
AUDEVARD
Veterinary Expertise & Guarantees

42/46 rue Médéric
92110 Clichy - France

info@audevard.com
audevard.com