Bisphosphonate Medication in the Horse

Introduction

Bisphosphonates were discovered in the 19th century for purposes of water softening. In the 1960's scientific research focused on their effect on bone metabolism. In human medicine, bisphosphonates are used primarily for the treatment of osteoporosis, pelvic and vertebral fracture prevention, Paget's disease, and multiple other problems such as bone tumors.

Bisphosphonates are known to be very potent inhibitors of osteoclastic activity in bone by encouraging osteoclasts to undergo apoptosis (programmed cell death). They can decrease bone resorption without affecting osteoblasts in their bone formation hence restoring the balance of bone remodeling.

Chemical Structure and Action

Bisphosphonates are divided into two classes, based on their molecular structure and mechanism of action: Nitrogen-containing and non-Nitrogen-containing bisphosphonates.

The bisphosphonate molecules consist of a central carbon atom with a phosphate group on either side. The central carbon atom is also attached to two side chains: a short side chain, which is always a hydroxyl group in N-containing bisphosphonates; and a long side chain which contains the N-atom. The long side chain determines the chemical properties of the molecule and distinguishes individual types of bisphosphonates.

A particular chemical structure of the two phosphate groups, the hydroxyl short side chain, acts as a 'bone hook' to precisely target and rapidly attach to hydroxyapatite of mineral bone. Once localized within the bone, the long side chain of the molecule determines the biological activity and the ability of the drug to interact with specific molecular targets.

Osteoclasts resorb the molecule during their osteoclastic activity, and after ingestion, apoptosis is induced of the osteoclasts. Besides apoptosis, bisphosphonates also have an effect on osteoclast recruitment, differentiation from mononuclear precursors and resorptive capacity of active osteoclasts.

There are also multiple reports on the effects of bisphosphonates on chemokine expression as well as their anti-inflammatory effects.

After administration (IV, IM or in human medicine PO), the molecules are very quickly absorbed by the targeted tissues, within 48 hours (zoledronate 100% within 4-8 hours) or are excreted by renal clearance.

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Tiludronate

One of the first bisphosphonates successfully used in equine medicine was Tiludronate. It was initially studied for use in navicular disease (Denoix et al., 2003). In navicular disease, mechanical overloading influences the normal bone remodeling process. Normally there is a cycle of a rapid bone resorption phase (taking weeks), followed by a longer bone formation phase (taking months). Ostblom et al. have shown that in horses with navicular disease, this ratio is increased from 0.51 to 0.10 in normal navicular bones, caused by a significant increase in osteoclastic resorption. Under these circumstances the resorption is not followed by bone formation, eventually leading to navicular bone degeneration and pain.

In horses, Tiludronate has been shown to have significant influences on the balance between bone resorption and formation, by demonstrating a significant increase in bone mineral density in an equine osteoporosis model (Delguste et al.).
Denoix et al. have shown significant improvement in lameness scores in horses treated with 1.0 mg/kg Tiludronate once daily for ten days compared to a lower dose or placebo.
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Similar positive results were found in a placebo-controlled study performed by Gough et al. In this study 60% of treated horses showed an average improvement in 2 lameness grades at day 120 after treatment (based on a 0-10 lameness scale).

In the treatment of osteoarthritic changes of the thoracolumbar spine, a significant improvement in thoracolumbar mobility was found in comparison with a placebo-treated group of horses. In 3 out of 22 treated animals, repeated treatment was performed at four weeks after initial treatment because of lack of response after the first treatment. 2 of the three horses who received this repeated treatment also improved. This phenomenon was also observed in the navicular disease study: 10-20% of non-responders after 4-6 weeks who are given a second treatment can still improve after this repeated treatment.

Concerning the dosage regime: in a pharmacokinetic and dynamic treatment study, Delguste et al, have shown complete bioequivalence of both treatment regimens: 10 days consecutive 0.1 mg/kg tiludronate IV vs. a single 1 mg/kg IV continuous rate infusion.

Clodronate

Clodronate is an FDA approved and EU-registered non-Nitrogenous Bisphosphonates for use in navicular disease and bone spavin. There are no articles published with pharmacokinetic and dynamic data on this drug. The only study regarding its clinical efficacy is a study carried out on behalf of DECHRA (distributor of OSPHOS) itself, and therefore results are not peer-reviewed or free of conflicts of interest by the researchers.

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Numerous reports (e.g., Nancollas et al.) show that clodronate has the lowest hydroxyapatite affinity of all bisphosphonates (even lower than the less potent etidronate). In human medicine, treatment with clodronate is usually orally with a onceor twice per week administration. Because of this frequent human dosage regimen, the OSPHOS equine dosage regimen of once per 3-6 months is questionable.

There have been no published equine studies showing any effect of clodronate on biomarkers (e.g., CTX-1 levels) of bone resorption or bone mineral density studies.

Concerning safety, side-effects were seen in 28 out of 111 horses, varying from colic to mild discomfort. Clinical results are reported by the manufacturer to be comparable to Tiludronate-administration when Clodronate is given in a 1.4 mg/kg IM dosage.

Zoledronate

Zoledronate is known to be the most potent bisphosphonate available in medicine. It belongs to the Nitrogen-containing bisphosphonate class. Its potency comparative to clodronate and tiludronate is 1000 times higher.

Two studies in horses have shown impressive results concerning its clinical efficacy as well as its pharmacokinetic and dynamic properties.

A study from Katzman et al. has shown that 9 out of 10 horses with silicate-intoxication induced osteoporosis completely recovered after treatment with zoledronate infusions.

Pharmacokinetic and dynamic data from Nieto et al. also showed fascinating results. The efficacy of zoledronate is assessed by measuring a biomarker which is released systemically when bone mineral is resorbed (CTX-1). If bisphosphonates are still active, the levels of this biomarker are decreased.
Nieto et al. have shown suppression of CTX-1 levels for at least one year. In the treatment of menopause-related osteoporosis, clinical efficacy in women on average lasts for 3-5 years with zoledronate. This is very high in comparison to the known biological duration of action of Tiludronate (4-6 months in 80-90% of treated horses and 4-6 weeks in 10-20% of treated animals). Next, to this, no significant side-effects were noted in all ten treated animals.

Even though no clinical studies regarding other potential skeletal disorders have been performed, zoledronate appears to be the most superior bisphosphonate of all, with the highest amount of osteoclastic inhibition and the longest duration of action.
In contrast to Clodronate IM and Tiludronate IV, side -effects of administration are very rare.

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Can biphosphonates potentially cause fractures?

Because of their effect on bone modelling, concerns have been made of their negative influence on fracture repair by possibly causing a microfracture to develop into a full crack. However, a long-term study in a beagle dog model that simulated fracture repair has demonstrated that ibandronate treatment did not adversely affect normal bone healing. Studies of repair processes after creating drill-hole defects in dogs also showed no impairment with ibandronate. Besides this: the enormous preventive effect of fracture occurrence in osteoporosis far outweighs the potential rare incidence of a bisphosphonate induced fracture.

Literature

Coudry et al. 2007, AJVR, 68(3) Efficacy of tiludronate in the treatment of horses with signs of pain associated with osteoarthritic lesions of the thoracolumbar vertebral column

Delguste et al., 2007, Bone, 41(3), 414-421 Pharmacological effects of tiludronate in horses after long-term immobilisation

Denoix, et al., 2003, EVJ, 35(4), 407-413 Tiludronate as a new therapeutic agent in the treatment of navicular disease: a double-blind placebo-controlled clinical trial

Gough et al., 2010, EVJ, 42(5), 381-387, Tiludronate infusion in the treatment of bone spavin: A double-blind placebo-controlled trial

Graham and Russel, 2007, Pediatrics, 119 Suppl 2, Biphosphonates: mode of action and pharmacology

Katzman et al., 2012, JAVMA, 240, 1323-1328 Use of zoledronate for treatment of a bone fragility disorder in the horse

Nancollas et al., 2006, Bone, 38(5), 617-627, Novel insights into actions of bisphosphonates on bone: Differences in interactions with hydroxyapatite

Nieto et al., 2013, AJVR, 74(4), 550-556, Pharmacokinetics, pharmacodynamics and safety of zoledronic acid in horses

Ostblom et al., 1989, EVJ, 21, 431-433 Navicular bone disease: a comparative histomorphometric study