Bisphosphonate use in equine musculoskeletal disorders

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Bisphosphonates have received much attention in recent years for their therapeutic potential in treating resorptive bone conditions in the equine patient. Orthopedic disease remains one of the most common performance limiting issues in the equine industry. In regard to western performance horses, distal tarsal osteoarthritis and navicular syndrome are common causes of lameness. Both disease processes can be characterized by bone resorption. The use of bisphosphonates in equine practice stems from the marked response to treatment observed in bone resorptive diseases in human medicine where bisphosphonates have been used since the 1960’s. There are two classes of bisphosphonates, non-nitrogenous and nitrogenous. Both work by binding to circulating calcium and other divalent metal ions, then bind to bone mineral, specifically hydroxyapatite crystals, at areas of active remodeling. Here they act directly on osteoclasts causing decrease recruitment, activity and lifespan of these cells. Non-nitrogenous bisphosphonates specifically work by inducing osteoclastic apoptosis by forming non-hydrolysable ATP analogs that gather in the cytosol interfering with cellular functions. An additional benefit of non-nitrogenous bisphosphonates is there anti-inflammatory properties. They work on monocytes to inhibit pro-inflammatory cytokines and nitric oxide release. Nitrogenous bisphosphonates, considered to be more potent than non-nitrogenous bisphosphonates, contain an additional nitrogen attached to their basic structure. They work by inhibiting enzymes in the mevalonate pathway associated with cholesterol synthesis eventually inducting osteocyte apoptosis. Bisphosphonates in general have been used to treat a number of bone resorptive conditions in humans including Paget’s disease, osteoporosis, malignant metastatic bone disease and hypercalcemia of malignancy. Potential side effects noted following bisphosphonate treatment in humans include hypocalcemia, osteonecrosis, atrial fibrillation and severe musculoskeletal pain.

There are currently two available bisphosphonates labeled for use in horses, tiludroante (Tildren®) and clondrionate (Osphos®). Both are classified as non-nitrogenous bisphosphonates. Tiludronate has been investigated for the treatment of navicular syndrome, distal tarsal osteoarthritis and thoracolumbar osteoarthritis. One study published evaluated the efficacy of tiludronate on lameness in horses caused by navicular syndrome. The authors concluded that horses responded best to treatment with a systemic dose of 1 mg/kg. Additionally, horses treated within 6 months of diagnosis responded more favorably to treatment (Denoix, 2003). Another study focused on horses with lameness in horses caused by distal tarsal osteoarthritis (bone spavin). This study found that horses treated with a systemic dose of 1 mg/kg were significantly less lame that placebo treated horses at 60 and 120 days post treatment (Gouch, 2010). A third study using tiludronate focused on pain in horses associated with thoracolumbar osteoarthritis. This study concluded that tiludronate treated horses had significant improvement in dorsal flexibility compared to controls (Coudry, 2007). These studies outline the potential benefit of tiludronate administered systemically in the treatment of equine orthopedic conditions. Tiludronate
given via a regional limb perfusion (RLP) is also used commonly in equine practice for the treatment of bone resorptive lesions in the horse, with anecdotal reports of improved lameness. The doses and regimens used are variable and inconsistent. There is one scientific report of the use of tiludronate via RLP used in conjunction with extracorporeal shockwave therapy to treat dorsal metacarpal disease in the horse (Carpenter, 2012). RLP of tiludronate at 0.1 mg/kg has been shown to not significantly alter measured synovial fluid parameters of the navicular bursa, distal interphalangeal and metacarpophalangeal joints in treated horses (Hunter, 2014). Potential benefits of the use of tiludronate via RLP include reduced cost and safety as compared to systemic administration. There are reports of transient hypocalcemia, colic and acute renal failure associated with the systemic administration (1 mg/kg) of tiludronate in horses.

Recently available to the market is the intramuscular bisphosphonate clondronate (Osphos®), approved for treatment of navicular syndrome in horses. Clinical trials showed that approximately 75% of the horses improved in their lameness score following treatment with clondronate and 65% maintained their level of improvement through six months. Colic is reported to be the most common side effect following administration.

A Zoledronate is a nitrogenous bisphosphonate that has been evaluated in the horse for the treatment of bone fragility. This disease, most commonly seen in horses in California, perpetuates as a progressive systemic osteopenia of the axial skeleton and proximal appendicular skeleton. A study evaluating this drug reported clinical improvement and decreased scintigraphic uptake 6 months following treatment.

Based on these reports, there appear to be beneficial effects of bisphosphonates in the treatment of equine musculoskeletal disorders. Additional research is needed to determine their appropriate use and further therapeutic benefits.

References


Tildren®, package insert.

Osphos®, package insert