



### **Bisphosphonates in equine orthopaedics – what is the evidence?**

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Bisphosphonates are thought to be the most potent inhibitors of bone resorption clinically available to humans.<sup>1</sup> They have the basic chemical structure of two phosphate groups linked to a carbon atom and are divided into two categories based on the components of their side chains: nitrogen-containing and non-nitrogenous. The nitrogen-containing bisphosphonates are more potent than the non-nitrogenous class.<sup>2</sup>

Non-nitrogenous bisphosphonates act on osteoclasts through intracellular accumulation of cytotoxic ATP leading to the apoptosis of osteoclast.<sup>3</sup> Moreover, they have been shown to have anti-inflammatory properties by decreasing the amount of nitric oxid and cytokines released from activated macrophages,<sup>4</sup> as well as by inhibiting the activity of matrix metalloproteinases.<sup>5</sup>

The USA recently approved 2 non-nitrogenous members of the bisphosphonates drug family, clodronate (Osphos) and tiludronate (Tildren), whereas nitrogenous bisphosphonates are not yet licensed in the horse. Osphos is administered intramuscularly at a dose of 1.53 mg/kg, while Tildren is given as an intravenous infusion at a dose of 1 mg/kg diluted in 0.9% NaCl over 90 minutes. In one study, the effect of tiludronate on cartilage explants was investigated: whereas lower tiludronate concentrations had some chondroprotective effects, high concentrations were detrimental to equine articular cartilage, suggesting that intra-articularly administration of tiludronate to horses may be detrimental.<sup>6</sup>

The most common side effects of bisphosphonates in horses are colic and mild symptoms related to the central nervous system. Bisphosphonates also have the potential for nephrotoxicity. High or frequent doses of bisphosphonates can cause bone fragility.

Current evidence for the use of bisphosphonates in the horse comes from equine studies which investigated the administration of tiludronate for the treatment of chronic back soreness,<sup>7</sup> lowed hock osteoarthritis<sup>8</sup> and navicular disease.<sup>9</sup> All these studies yielded favourable results from blinded analysis, although in all cases only clinical signs were the main determinant of success. Therefore it is questionable, if at least some of the positive changes seen may have been due to pain-relieving or anti-inflammatory effects of tiludronate, rather than a direct effect on bone density, which was not assessed.

Development subchondral cystic lesions (SCLs) secrete proinflammatory prostaglandin E2, nitric oxid and MMPs, which result in pain and recruitment of osteoclasts, resulting in cyst expansion.<sup>10</sup> Although there would be a theoretical rationale for use of bisphosphonates in SCLs, because of their antiresorptive and anti-inflammatory effect,<sup>11</sup> there are no studies investigating the effect of these drugs on lameness of horses suffering from SCLs.

Licensed bisphosphonates are only labelled for horses older than 4 years. One study have shown that bone remodelling biomarkers, which are increased in healthy, trained juvenile horses, were decreased after the administration of tiludronate.<sup>12</sup>

In conclusion, bisphosphonates may be useful in the treatment of specific orthopaedic conditions in the adult horse, whereas insufficient evidence for efficacy or long-term safety exists to support their use in young horses.



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