Bone and Bisphosphonates

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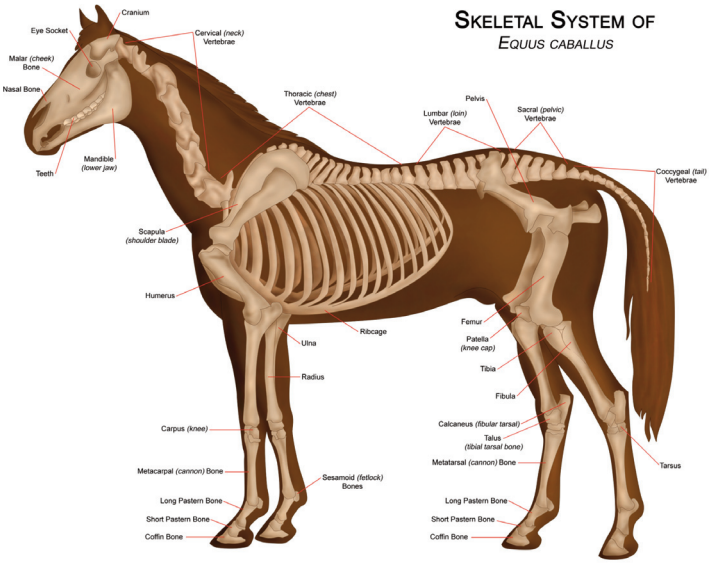
Bone is a very dynamic and metabolically active tissue. This metabolic activity supports a continual turnover of bone that is essential for its function of supporting the horse's body through a wide range of activities. Exercise is an essential ingredient for the development of a robust skeleton through bone remodeling. Remarkably, bone is both strong and pliable. This apparent contradiction occurs as a result of a critical balance between the mineral (calcium) and organic (collagen and chondroitin sulfate) components of bone. An increase in mineral content can make the bone stronger, but may also make the bone increasingly brittle as the high mineral content displaces organic components making the bone less pliable.

The forces that bones experience, in the form of exercise, largely determine the balance of mineral and organic content. There are two types of cell within bone that balance the "teeter-totter" of bone turnover. These cells, osteoblasts and osteoclasts, are the gatekeepers of bone turnover and essential for bone remodeling. Osteoblasts are the builders of bone – easy to remember as the B's go together. These cells synthesize new bone. Osteoclasts resorb bone to enable osteoblasts lay down new bone matrix where it is needed. Bone remodeling requires time and the bone to be conditioned to withstand the forces placed upon it. For example, research has demonstrated that intermittent short bursts of fast exercise allowed the shins of young racehorses to remodel more appropriately than with daily slower work, resulting in a significantly lower incidence of bucked shins.

Recently, two drugs new to the equine veterinary field have been licensed by the FDA. These bisphosphonate drugs are named Tildren® (tiludronate) and Osphos® (clodronate). Both of these drugs are older generation bisphosphonates, but newer, more potent 'family members' are emerging. This class of drug has been used in recent decades in post-menopausal women with osteoporosis and younger patients with very severe bone diseases to stop bone resorption.



Bisphosphonates are drugs that mimic the substances cells need to make energy. After administration they are rapidly excreted from the body through the kidney. A fraction of the drug becomes tightly adhered to the vast mineral component of bone. These molecules lodge there unchanged for several months to years. Osteoclasts absorb the attached bisphosphonate molecules as they resorb bone matrix as part of the natural remodeling and turnover process. The absorbance of bisphosphonate results in the death of the osteoclasts – thus debilitating one arm of the bone turnover and remodeling process for months to years.

In elderly women with the crippling disease of osteoporosis and cancer patients with erosive metastatic bone tumors, bisphosphonates have provided significant relief by reducing bone resorption. However, over time the side effects of these drugs that have been noted have led physicians to prescribe them less liberally.

Side effects include atypical long bone fractures, jaw necrosis, atrial fibrillation, and kidney disease. The unusual long bone fractures, mostly of the femur, have caused grave concern in the medical profession as some have been life threatening. These fractures have been attributed to abnormal bone density and pliability as a result of bisphosphonate inhibition of the normal bone turnover process. The other major side effect seen in bisphosphonate patients has been profound jaw necrosis, many times being noted some considerable time after the drug was administered. These patients have suffered with dramatic and seemingly unstoppable loss of jaw bone tissue and the teeth residing in it. The finding of an unexpectedly high incidence of atrial fibrillation in bisphosphonate patients is equally of concern, if less common.
The mechanism of this side effect is also poorly understood, but off target activity of bisphosphonates cannot be ruled–in, or ruled-without further research. Bisphosphonates are excreted by the kidney. Like many drugs excreted by the kidney, bisphosphonates can cause kidney damage. Life-threatening or extremely painful diseases that have few effective treatment options, can mean that the risk of unpleasant side effects must be accepted. However, these severe side-effects have led to more circumspect use of bisphosphonates in the human medical field.

In horses, tiludronate has been explored as a drug to modify pain and bone pathology related to navicular syndrome. The research was performed on horses four years and older and suggested that some horses may have experienced relief at the higher dose used in the study. No research has been performed looking at the effects of these drugs on younger horses or racehorses in training. Recently, bisphosphonates have gained some 'off-label' use in younger horses for sesamoiditis. Given the duration that bisphosphonates remain present in the bone, administration at this early age has the potential to subvert the essential bone remodeling that must occur during training.

Disarming one side of the delicate balance of bone turnover and remodeling could have far reaching consequences on racehorses long after the drug's administration. From our present, very limited understanding of bisphosphonates we do not know how safe they are in the short-, medium-, and long term for young horses or the racehorse population. Physiologically, bones need both osteoblastic and osteoclastic cell activity to attain the dynamic and delicate balance of mineral density and pliability necessary for healthy, training adapted bones.

FDA approval of any drug can be a welcome event, however, the specific details of the licensure and the appropriate clinical application always require careful consideration. Bisphosphonates have been approved for use in humans for decades, and analysis of cumulative data has refined their clinical application. At the present time the short, medium, and long term effect of bisphosphonates on the skeleton of racing age horses is undetermined. It is critically important that the ramifications of these drugs in racing age horses are understood to prevent their use from becoming the horse's nemesis.

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