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SPECIAL REPORT

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WHAT WE KNOW ABOUT BISPHOSPHONATES FOR HORSES

For years, equine veterinarians relied on drugs, corrective shoeing, and surgery to help horses suffering from navicular syndrome to minimize discomfort and disease progression.

Also known as podotrochlosis, navicular syndrome is the degeneration of the navicular bone nestled near the coffin bone near the rear of the horse's foot, along with its associated structures. Management of this disease changed significantly in 2014 when the U.S. Food and Drug Administration approved bisphosphonates for treatment. Despite the availability of this newer treatment option, success rates—in terms of improvement in lameness grade—hovered around the 67% mark, leaving many horses in continued pain.

Recently, Texas A&M researchers reviewed the current body of knowledge surrounding bisphosphonates and their use in horses. Their goal, they wrote, was to "discuss the current understanding of the strengths and weaknesses of BPs [bisphosphonates] in equine veterinary medicine and highlight the future utility of these potentially highly beneficial drugs."

BISPHOSPHONATE BASICS

We spoke with Larry J. Suva, PhD, professor and department head of Veterinary Physiology and Pharmacology in the university's College of Veterinary Medicine and Biomedical Sciences, who defined bisphosphonates as a class of phosphorus-containing chemical compounds that inhibit bone resorption.

"Bone resorption is part of normal bone turnover to maintain a healthy musculoskeletal system that supports the horse's current athletic demands," he said. "Two major types of cells are involved in bone turnover: osteoblasts that lay down new bone and osteoclasts that essentially remove bone."

BISPHOSPHONATES:
A class of phosphorus-containing chemical compounds that inhibit bone resorption.

The rationale for wanting to stop bone resorption is to increase navicular bone strength.

"The idea may be that bone mass increases with decreased bone resorption, hence the navicular bone should be stronger," Suva said.

Two types of bisphosphonates exist: those that do and those that do not contain nitrogen. In horses, only two bisphosphonates, both non-nitrogenous—tiludronate and clodronate—are FDA-approved. They function differently than nitrogen-containing bisphosphonates; however, both forms inhibit bone resorption, leading to increased bone mass and strength because osteoblasts continue to form bone.

"Interestingly, despite increased bone mass and strength being the obvious goals of bisphosphonate administration in horses, few studies have actually examined the effect of tiludronate or clodronate on those parameters," said Suva.

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Bisphosphonates used according to FDA-approved guidelines do appear beneficial for adult horses with navicular syndrome.

Instead of looking at serum biochemical markers of bone turnover or, more importantly, bone density, researchers on most equine studies have used improvement in lameness grade as the endpoint. One research group did examine serum markers of bone turnover in bisphosphonate-treated horses, including two proteins found in bone: osteocalcin (a marker of bone formation) and C-terminal collagen-I telopeptide (a marker of bone resorption). They noticed no change in either marker, as would be expected if bone treatment decreased turnover yet lameness was significantly reduced.

However, in another study using horses casted on one leg, researchers found an increase in serum markers of bone turnover. This was expected because disuse results in increased bone resorption to adapt to decreased weight-bearing. After administering tiludronate, the investigators saw a significant reduction in markers of bone turnover.

"This latter report is one of the only studies demonstrating an anti-resorptive effect of bisphosphonates in horses," Suva said, adding, "These data also suggest alternative mechanisms of action of bisphosphonates to explain the improvement in lameness."

Examples of such mechanisms that have not yet been proven include anti-inflammatory properties, decreased activity of enzymes that contribute to bone turnover, and altered growth factor effects.

"Even though we do not have all the data we wish for, bisphosphonates used according to FDA approval guidelines in animals 4 years of age or older do appear beneficial for horses with navicular syndrome," Suva said. "The concern is related to bisphosphonates being used off-label for various other conditions in horses."

OFF-LABEL USE

Veterinarians sometimes administer tiludronate or clodronate to horses with chronic back soreness, osteoarthritis of the lower hock joint (bone spavin), and chronic lameness due to other causes.

Larry J. Suva, PhD, suggests three ways the veterinary community can help pinpoint the exact role and optimal use of bisphosphonates in horses:

1. Push for more research and clinical trials, especially those focusing on long-term use and safety that measure bone markers and bone density;
2. Offer more continuing education opportunities to keep the equine community abreast of the latest information on bisphosphonates; and
3. Understand the rationale and potential mechanisms for bisphosphonate usage because, based on available data, bisphosphonates' positive effects might be more connected to non-bone-related effects rather than inhibiting bone resorption.

"While not illegal, off-label use of bisphosphonates may or may not be effective and may potentially be harmful to the horse," said Suva. "We simply do not have enough data to support widespread recommendations for off-label use."

In addition, veterinarians have administered some nitrogen-containing bisphosphonates to horses, such as zoledronic acid.

Suva said that in a 2013 pharmacology study, researchers gave a single zoledronic acid dose (0.057 mg/kg, intravenous) via a 30-minute infusion. The infusion produced sustained decreases in total serum calcium (at seven days), as expected for such a potent bisphosphonate. It appears that zoledronic acid inhibits bone resorption and is safe in healthy adult horses, he said, noting further studies evaluating potential benefits of zoledronic acid in horses with orthopedic conditions are warranted.

CONCERNS TO CONSIDER

Some adverse effects identified in humans, where bisphosphonate use is far more widespread (in osteoporosis and cancer patients), include osteonecrosis (abnormal breakdown of the bone) of the jaw and atypical femoral (thighbone) fractures. These are very rare events, said Suva, often following long-term use of more potent nitrogen-containing bisphosphonates.

Current manufacturer recommendations are to use FDA-approved bisphosphonates according to label instructions. In studies conducted to garner FDA approval in 4-year-old horses with navicular syndrome, researchers did find a significant beneficial effect.

"With the rampant bisphosphonate use in the equine industry, it is important to recognize and follow the approved use of these powerful molecules," said Suva.

The article, "Bisphosphonate use in the horse: what is good and what is not," was co-authored by Alexis Mitchell, Ashlee Watts, and Frank Ebertino, all from Texas A&M University's College of Veterinary Medicine and Biomedical Sciences.