Navicular Syndrome and the Clinical Use of Bisphosphonates in Equine Practice

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AAVME #495-35627

Disclaimer: The presenter is associated with Dechra Veterinary Products, LLC, the MAH of OSPHOS® (clodronate injection).

Overview

Basic Principles of Bisphosphonates
Bone Modeling & Remodeling: Navicular Syndrome
Equine Application of Bisphosphonates
Navicular Syndrome
Osphos® (clodronate injection)
Clinical Impact and Case Selection
Efficacy and Safety

Basic Principles of Bisphosphonates
Bisphosphonate Therapy

Class of drug that has been used in human medicine for over 30 years
Used for various diseases of abnormal bone metabolism
Animal models
Inhibit osteoclast bone resorption
Achieve positive calcium balance

How Bisphosphonates Work

Osteoblasts form bone and osteoclasts resorb bone
Normal bone balance between formation and resorption
Disordered bone tissue balance of osteoblasts and osteoclasts is disrupted
Bisphosphonates inhibit bone resorption by encouraging osteoclasts to undergo cell death and reduce bone breakdown

Bisphosphonates

Mechanism of Action
Bisphosphonates bind to calcium phosphate crystals
Accumulate at areas of high calcium deposition
Inhibit their formation and dissolution
Bisphosphonates inhibit osteoclast function
Reduce the number of active osteoclasts
Bisphosphonate Potency

Non-Nitrogenous Bisphosphonates
- Etidronate: 1
- Clodronate: 10
- Tiludronate: 10

Nitrogenous Bisphosphonates
- Pamidronate: 100
- Alaeronate: 1,000
- Risedronate: 5,000
- Ibandronate: 19,000
- Zoledronate: 20,000

Bone Modeling and Remodeling

Bone Development

Osteogenesis
- Osteo = Bone
- Genesis = New growth
- Modeling results in change in shape and size of bone and continues until adulthood as the skeleton matures.
- Remodeling is bone resorption and deposition in response to stress and repair of bony tissue.
The process of bone remodeling is under the influence of osteoclasts and osteoblasts.

Normal Bone Remodeling

Bone resorption process complete within ~ 3 weeks.
Bone formation process (including mineralization) takes ~ 3 months.
Osteoblast activity = Osteoclast activity
“Coupled” to work together
Amount of bone formed equals amount destroyed
No net loss or net gain of bone

Bone Disease

Osteoblast activity does not equal osteoclast activity; mechanism “uncoupled”
Osteoclasts become too aggressive; results in bone lysis = thinner, weaker bone
Osteoblasts get too aggressive; sclerosis occurs = thicker, less pliable bone
Bone Remodeling and Bisphosphonates

During times of chronic bone disease and repetitive stress, bone remodeling is accelerated.

Bisphosphonates regulate bone metabolism through inhibition of bone resorption via reduction of osteoclast activity.

Bisphosphonates help restore balance of osteoclast vs. osteoblast activity by reducing the activity of the osteoclasts.

Equine Application of Bisphosphonates

Nuclear Scintigraphy

Pyrophosphate (P-O-P) was linked to $^{99m}Tc$ in skeletal scintigraphy. Bisphosphonates (P-C-P) are analogs of pyrophosphate.
Peer-Reviewed Research


Navicular Syndrome

Bisphosphonates are applicable for the control of clinical signs associated with navicular syndrome in the horse.

FDA CVM approved bisphosphonates for the horse (2014)

- Osphos® (clodronate injection)
- Tildren® (tiludronate disodium)

Osphos is a registered trademark of Dechra Ltd.
Tildren is a registered trademark of Bimeda, Inc.
Navicular Syndrome

Navicular Syndrome – Definition
Chronic, intermittent forelimb lameness associated with pain arising from the navicular bone and closely related soft tissue structures including the collateral suspensory ligaments of the navicular bone, digital sesamoidean impar ligament, navicular bursa, and the deep digital flexor tendon.

Also known as:
Podotrochlear Apparatus Syndrome
Caudal Heel Pain

Factors Affecting the Navicular Bone
Normal forces acting on the navicular bone:
- Compression by deep digital flexor tendon
- Compressive forces downward from P2
- Tension from the supporting ligaments
- Ground forces

Navicular bone is constantly remodeling to adjust to changing workload
Navicular Syndrome - Signalment
~ 1/3 of all chronic forelimb lameness
Quarter Horse, Thoroughbreds, Appaloosas, Paints, & Warmbloods commonly affected
Typically between 4-15 years of age
No clear sex predilection
Western and English performance

Navicular Syndrome - Clinical Signs
Unilateral or bilateral forelimb (asymmetrical) lameness
Usually low-grade, slowly progressive
No consistent clinical picture, horse may:
- exhibit a short, choppy stride
- display toe in gait
- refuse to jump
- show intermittent weight shifting on front feet
- stumble
- display increased lameness the day after work
- have difficulty turning sharply and going downhill
- have difficulty moving on hard/rocky ground
- switch leg lameness while on hard ground or when crossing

Navicular Syndrome - Diagnostic Tools
Multiple test necessary for accurate diagnosis
- History & Physical examination
- Lameness evaluation and gait analysis
- Motion analysis software
- Hoof pressure response
- Nerve and synovial/bursal analgesia
- Radiography
- Other imaging modalities
- Ultrasound
- Nuclear scintigraphy
- Computed tomography (CT)
- Magnetic resonance imaging (MRI)
Navicular Syndrome – Diagnosis

Radiographic changes involve a wide range of remodeling & degenerative changes

- Enlarged synovial fossae
- Cyst-like lesion

Reference radiographs

Navicular Syndrome – Diagnosis

Standing MRI images courtesy of Hallmarq

Navicular Syndrome - Medical Management/Treatment

Multimodal treatment is most effective and includes:
- Rest and Rehabilitation
- Corrective trimming and shoeing
- Medical therapy
  - Systemic anti-inflammatories
  - Vasodilators
  - Intrarticular medications
  - Non-nitrogenous bisphosphonates
- Extracorporeal shock wave therapy
- Surgical Treatment (palliative therapy)
  - Palmar digital neurectomy
  - Navicular bursoscopy
OSPHOS® (clodronate injection)

OSPHOS® (clodronate injection)

FDA Approved non-nitrogenous bisphosphonate for use in horses
For control of clinical signs associated with navicular syndrome
4 years of age and older
Osphos is the ONLY intramuscular option
Ready to use injection
Dosage: 1.8 mg/kg up to a maximum dose of 900 mg per horse; divide into 3 sites
Proven efficacy and safety
Option to re-administer q3-6 months

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

OSPHOS® Clinical Field Study 7,8
Title/Objective: Evaluation of the clinical efficacy of OSPHOS for the control of the clinical signs associated with navicular syndrome in horses
Multi-site, double-masked, placebo-controlled
3:1 ratio (Osphos:NaCl)
Investigators: United States and Europe
Rob Boswell, DVM, PA- Florida
David Kolb, DVM - Wisconsin
John Johnson, DVM, MS, DACVS - Texas
Suess Shoeemaker, DVM, DACVS - New York
Bradley King, DVM - Indiana
Michael Frevel, DVM - Germany


7,8
**OSPHOS® Clinical Field Study 7,8**

**Overall Treatment Successes**

Defined as improvement of at least AAEP lameness grade

<table>
<thead>
<tr>
<th>Study Day</th>
<th>OSPHOS</th>
<th>Saline Control</th>
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<tbody>
<tr>
<td>28</td>
<td>67.4%</td>
<td>20.7%</td>
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<tr>
<td>56</td>
<td>74.7%</td>
<td>3.3%</td>
</tr>
<tr>
<td>280</td>
<td>65.4%</td>
<td>None evaluated*</td>
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</tbody>
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Day 56 Improvement of Lameness Grades (raw data from Osphos clinical efficacy trial)

- One grade ‒ 16 horses
- Two grades ‒ 45 horses
- Three grades ‒ 8 horses

* Compassionate use was allowed after Day 56 evaluation

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**Excerpts from the Clodronate Roundtable & Use of Bisphosphonate Therapy in Equine Practice**

**Event Date: May 14, 2019**

**Objective:**

To aggregate cross-disciplinary opinions and experiences from leading equine experts on the use of bisphosphonates in horses

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**Panelists**

[Panelists' images and names]
Clinical Impact

FDA approved in 2014 to control the clinical signs of navicular syndrome in horses. A non-nitrogenous bisphosphonate drug—has changed the way in which equine practitioners manage sports medicine. Another tool in their toolbox. More targeted approach. Increased client education and partnership.

"[Clodronate] gives us another tool in our tool box to address some of these issues that have potentially been refractory to other treatment modalities. In my practice it is just part of our day to day. We are asking changes, were changes, looking at foaling. It’s a part of the holistic approach."

- Sarah le Jeune, DVM, DACVS, DACVS/SMR

"Clodronate has really opened up a great conversation with our clients and the ability to have a collaborative discussion, let’s think about your horse, how do we treat your horse—long-term management and looking at all the wholeness rather than just give a drug or just do an injection."

- Richard Markell, DVM, MRCVS, MBA
Case Selection

Clinical picture (history, PE, lameness work-up)
Diagnostic anesthesia
Radiographic and/or MRI evidence of Bone Changes
Evaluate for Concurrent Soft Tissue Injury
Risk vs Benefit (Precautions/Contraindications)

What is your case selection criteria?

Case Selection

Based upon MRI findings I believe that the most responsive bone changes, such as those associated with the navicular bone or the hindlimb, are only phalanx, rather than soft tissue issues, are a good place for OSPHOS to be used.

- Myra Barrett, DVM, DACVR

I agree, I see a lot of significant improvement when OSPHOS is used to treat bone changes: “I think up until this point there hasn’t been a really good solution that was reliable as far as helping with the presumptive pain part of the bone changes (osteo) I’m seeing.”

- Josh Zacharias, DVM, DACVS, DACVSMR
Case Selection

"The age of the horse matters, as does the work the horse has been doing."
- Steven Colburn, DVM

Clinical Efficacy

Short-term Outcomes
Long-term Outcomes
Rehabilitation and return to work protocols
Re-dosing decision based upon clinical findings

What do you expect short-term?
"So the improvement, if we talk about heel pain [...] we're looking for an increase or an improvement in their lameness grades. And for me, it's not unusual for those to improve at least 2 lameness grades. I mean, I kind of expect that."

- Chris Ray, DVM, DACVS

What do you expect long-term?

"[Bisphosphonates have been a game changer in navicular disease. I can now manage much better than I could 10 or 15 years ago. It has also allowed me now to] have some more effective tools in conjunction with the other tools I'm using. So that's how it worked for me."

- Kent Allen, DVM
The horse should look better after 14 days and should be good after 4 weeks; the treatment approach always needs to be multimodal.

I don't like to rest horses unless they're very lame (similar to the human side). I've changed my management approach to a package that is more aggressive as the horses are out of commission for less time.

Marc Koene, DVM

I think we need to be careful and thoughtful as really the medical necessity of NSAIDs is uncertain in a routine re-dosing and I don't believe in preemptive or preventative medications.

Richard Markell, DVM, MRCVS, MBA

Safety
For horses 4 years and older
Reproductive considerations
Gastrointestinal signs
Renal toxicity
NSAIDs Contraindicated
OSPHOS® Specific Safety Info

In field studies, the most common side effects reported were signs of discomfort or nervousness, cramping, pawing, and/or colic within 2 hours post-treatment.
- Majority of horses clinical signs resolved within 10-15 minutes of hand walking.

NSAIDs should not be used concurrently with OSPHOS.
- Horses should be well-hydrated prior to and after the administration of OSPHOS.
- Water intake and urine output should be monitored for 3-5 days post-treatment; any changes from baseline should elicit further evaluation.

OSPHOS should not be used in pregnant or lactating mares, or mares intended for breeding.

Use of OSPHOS in patients with conditions affecting renal function, mineral or electrolyte homeostasis is not recommended.

What safety considerations do you have?

Safety

Nitrogenous ≠ Non-Nitrogenous

Judicious Use

Long Term Safety Considerations

Richbourg HA, Mitchell CF, Gillett AN. (2018) Tiludronate and clodronate do not affect bone structure or remodeling kinetics over a 60 day randomized trial. BMC Veterinary Research. 14:105-115.
"And that safety factor, I think, is important in bringing up the conversation about nitrogenous bisphosphonates. [...] and the nitrogenous have a very different pathway of pharmacology. They are around for a long, long time, years and years. They can create issues that we're not aware of and the safety data has not been done on these nitrogenous ones. [...] The caution with the nitrogenous ones is real and imminent and should be discussed."

- Richard Markell, DVM, MRCVS, MBA

"I was actually pretty happy with the findings. It means that we can use clodronate, that we know is very effective in keeping horses with navicular syndrome in work and able to perform with and for their owners, without the risk that we see in people of a type fracture."

- Ashlee Watts, PhD, DVM, DACVS
So, we looked at two time points on density just to see if there was a change due to the influence of [clodronate] treatment...that didn't show. And there was not a big of the treatment...When you look at the data...from the clodronate safety study...I think I look at is that it was not only proven safe at the recommended dose, but it has a very wide safety margin.

Chris Kawcak, PhD, DVM, DACVS, DACVSMR

OSPHOS® (clodronate injection) Summary

The application of bisphosphonates in equine practice is due to the body of evidence for efficacy and safety in navicular syndrome.

At least 2/3 of horses experienced a minimum of 6 months of improvement from a single intramuscular dose.

“Improvement produced by clodronate was apparent by Day 28...and was in the absence of any ancillary treatment that could have confounded the result.”
Key Points

Bisphosphonates have become a useful pharmaceutical application in veterinary medicine.

Understanding bone modeling and remodeling has become crucial in applying bisphosphonates in equine practice.

A multimodal approach to treating navicular syndrome is essential for a successful outcome and bisphosphonates have become an integral tool in that approach.

References

OSPHOS® (clodronate injection)
Fair & Balance Statement

As with all drugs, side effects may occur. In field studies and post-approval experience the most common side effects reported were signs of discomfort, nervousness, and colic. Other signs reported were renal insufficiency/failure, anorexia, lethargy, hypercalcemia, behavioral disorders, hyperkalemia, hyperactivity, recumbency, hyperthermia, injection site reactions, muscle tremor, uricaemia, hyperglycemia, and fracture. In some cases, death has been reported as an outcome of these adverse events. The safe use of OSPHOS has not been evaluated in horses less than 4 years of age or breeding horses. OSPHOS should not be used in pregnant or lactating mares, or mares intended for breeding. NSAIDs should not be used concurrently with OSPHOS. Concurrent use of NSAIDs with OSPHOS may increase the risk of renal toxicity and acute renal failure. Use of OSPHOS in patients with conditions affecting renal function or mineral or electrolyte homeostasis is not recommended. Refer to the prescribing information for complete details or visit www.dechra-us.com.