Navicular Syndrome and Clinical Application of Bisphosphonates in Equine Practice

Presenters:
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Disclaimer: These presenters are associated with Dechra Veterinary Products, the MAH of Osphos® (Clodronate Injection)

Overview
Basic Principles of Bisphosphonates
Bone Modeling and Remodeling
Equine Application of Bisphosphonates
Navicular Syndrome
Efficacy of Clodronate in Navicular Syndrome

Basic Principles of Bisphosphonates

Class of drug that has been used in human medicine for over 30 years ¹
• used for various diseases of abnormal bone metabolism

   • Animal models
   • Inhibit osteoclast bone resorption
   • Achieve positive Ca²⁺ balance


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

Human Uses
Osteoporosis
Geriatric, glucocorticoid, tumor, transplant, immobilization, or pregnancy induced
Paget’s Disease
Osteogenesis Imperfecta
Hypercalcemia
Skeletal Metastases of Breast Cancer

Bisphosphonates

Mechanism of Action

Bisphosphonates bind to CaP crystals
Accumulate at areas of high calcium deposition
Inhibit their formation and dissolution
Bisphosphonates inhibit osteoclast function
reduces the number of active osteoclasts

Bisphosphonate Potency

List of available BPs according to side chains and relative potency
Table 3.1 (pg 35) Bisphosphonates in Medical practice

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Potency</th>
</tr>
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<tbody>
<tr>
<td>Etidronate</td>
<td>1</td>
</tr>
<tr>
<td>Clodronate</td>
<td>10</td>
</tr>
<tr>
<td>Tiludronate</td>
<td>10</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>100</td>
</tr>
<tr>
<td>Aledronate</td>
<td>1,000</td>
</tr>
<tr>
<td>Risedronate</td>
<td>5,000</td>
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<tr>
<td>Ibandronate</td>
<td>10,000</td>
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<tr>
<td>Zoledronate</td>
<td>20,000</td>
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Bone Histology

Bone cells
Osteoblast
Osteocytes
Osteoclasts
Osteochondral progenitor cells

Woven Bone – collagen fibers randomly oriented
Lamellar Bone – mature bone in sheets
Cancellous bone (spongy) contain trabeculae less bone matrix and more space
Compact bone – dense more bone matrix and less space

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 bone

Bone Remodeling

The process of bone remodeling is under the influence of osteoclasts and osteoblasts

[Diagram of bone remodeling]
Bone Remodeling
1. Activation: abnormal stress to bone sensed by osteocytes, who send signals to start process
2. Resorption: osteoclasts dissolve bone mineral and digest the osteoid
3. Reversal: during this phase bone resorption transitions to bone formation
4. Bone formation: osteoblasts make new bone (osteoid) until the resorption cavity is filled
5. Mineralization: osteoblasts promote calcification of osteoid & mineralized bone is created

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 & 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 Tc, in skeletal scintigraphy
BP’s (P-C-P) are analogs of pyrophosphate

Image courtesy of Furlong Equine & Associates
Navicular Syndrome

Applicable for the control of clinical signs associated with navicular syndrome in the horse

FDA CVM – approved bisphosphonates for equine (2014)

Osphos® (clodronate injection)

Tildren® (tiludronate injection)

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, distal sesamoidean impar ligament, navicular bursa, and the deep digital flexor tendon. Also known as: podotroclar apparatus syndrome and caudal heel pain

Factors Affecting the Navicular Bone

Normal forces acting on the navicular bone:
- Compression by DDFT
- Compressive forces downward from P2
- Tension from the supporting ligaments
- Ground forces

Navicular bone is constantly remodeling to adjust to changing work loads

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 (Geldings)

Western and English performance

Navicular Syndrome-Biomechanical Forces

Abnormal mechanical forces lead to continual pressure and stress

- extreme physiological loads applied to a foot with normal conformation
- normal loads applied to a foot with abnormal conformation

Excessive stress alters bone metabolism and results in an abnormal rate of bone remodeling
Navicular Syndrome-Diagnostic Tools

<table>
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<tr>
<th>History</th>
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<tr>
<td>Physical exam</td>
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<tr>
<td>Lameness evaluation and gait analysis</td>
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<tr>
<td>Hoof pressure response</td>
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<tr>
<td>Nerve and intraarticular/bursal analgesia</td>
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<tr>
<td>Radiography</td>
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<tr>
<td>Other imaging modalities</td>
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<tr>
<td>Ultrasound</td>
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<tr>
<td>Nuclear scintigraphy</td>
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<tr>
<td>Computed tomography (CT)</td>
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<tr>
<td>Magnetic resonance imaging (MRI)</td>
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Navicular Syndrome-Diagnostic Radiography

- Enlarged synovial fossae
- Cyst-like lesion

Navicular Syndrome-Diagnostic MRI

Standing MRI images courtesy of Hallmarq

Navicular Syndrome-Traditional Management

- Rest and rehabilitation
- Corrective trimming and shoeing
- Medical therapy
  - Systemic anti-inflammatories
  - Vasodilators
  - Intraarticular or bursal injections
  - Extracorporeal shock wave therapy
- Surgical treatment
  - Palmar digital neurectomy
  - Navicular burrosopy

Efficacy of Osphos® (clodronate injection) for Navicular Syndrome

OSPHOS® Clinical Field Study

**Title/Objective:**
Evaluation of the clinical efficacy of OSPHOS for the control of the clinical signs associated with navicular syndrome in horses

**Investigators:** United States & Europe
- US: Rob Boswell, FL; David Kolb, WI; John Janicek, TX; Stuart Shoemaker, ID; Bradley King, IN
- EUR: Michael Frevel, Germany

Source: FDA.gov/Osphos Freedom of Information
OSPHOS® Clinical Field Study

Multi-site, double masked, placebo-controlled
3:1 ratio (Osphos:Na+Cl-)

Inclusion Criteria:
- grade 2 lameness (AAEP Lameness Scale)
- positive response to PDN blocks
- radiographic evidence of mild to moderate navicular bone changes

Exclusion Criteria:
- severe bony or soft tissue radiographic abnormalities
- rear-limb lameness
- ancillary therapies
- no shoeing changes

OSPHOS® Fair and Balance

Adverse reactions associated with the administration of OSPHOS included discomfort, nervousness, pawing, colic, lip licking, yawning, head shaking, injection site swelling, and hives.

No horses were terminated from the study as a result of an adverse event

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

Concurrent use of NSAIDs is strongly cautioned against

Bisphosphonates may be associated with GI and renal toxicity in individual patients

Should not be used in pregnant or lactating mares, or mares used for breeding

OSPHOS has not been evaluated in horses less than 4 years of age

OSPHOS® Conclusion

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 at least 6 months of improvement from a one-time 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" 5

References


