

Fig. 11A.

Tildren[®] and Tiludronic Acid: A Clinical Update

Kent Allen, DVM, Cert. ISELP
Virginia Equine Imaging

Fig. 14A.

Fig. 15A.



What is a Bisphosphonate?

- Can be nitrogenous or non-nitrogenous
 - Tildren is non-nitrogenous
- Molecule binds to calcium in bone
- Osteoclasts absorb it
- Molecule is metabolized and competes with ATP → apoptosis
- Causes apoptosis of osteoclasts
 - Osteoblastic activity is partially directed by osteoclast activity → indirectly decreases osteoblast activity if abnormal
- Anti-inflammatory
 - Decreases nitric oxide and cytokine release from macrophages
 - Inhibits secretion of IL-1 from cartilage and synovium

What is a Bisphosphonate?

- Potency of common bisphosphonates
 - Etidronate 1
 - Clodronate – 10 Equine
 - Tiludronate 10 – Equine
 - Pamidronate 100 – Human
 - Risendronate 2000 – Human
 - Zoledronate 20000 – Human

List of available bisphosphonates according to side chains and relative potency.

Bisphosphonates in Medical Practice. Reiner Bartl et al. Springer.Com

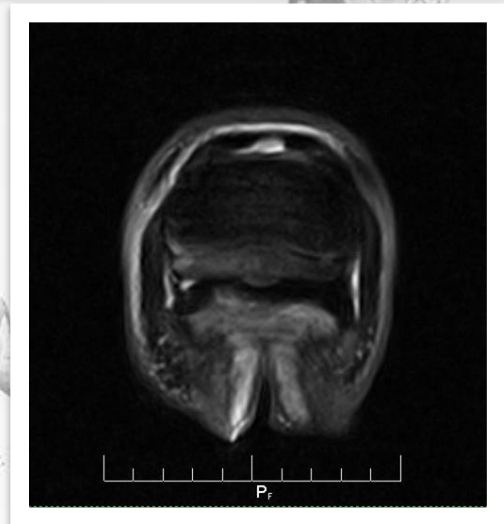
Tildren® Administration

- Overall Purpose in Horses
 - Stop bone remodeling to decrease pain
- Dose – 1mg/kg (0.45mg/lb)
- Reconstitute in 1L of saline (0.45% NaCl)
- Administer via slow intravenous infusion (60-90 minutes)
- Side Effects:
 - Colic 41%
 - Hematoma 9%
 - PUPD 5%
 - Increased creatinine/BUN in horses treated with NSAIDs 32%
 - No evidence of renal toxicity when given to healthy horses
 - Anecdotal reports of kidney failure

Clinical Use

How we use Tildren® :

- 500mg dose intravenous over 60-90 minutes
- Uses:
 - Navicular Edema/Remodeling
 - Arthritis (hocks, back, etc.)
 - Enthesiopathy
 - Suspensory
 - Collateral Ligaments etc.
 - Bone Contusion



FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-420

TILDREN

tiludronate disodium

Powder for injection

Horse

FDA Approval Study – Improve navicular pain

- 1mg/kg IV over 90 minutes
- Followed 204 cases, 136 treated and 68 controls, for two months
- 64% overall success rate ($p=0.0479$)
 - Improved lameness grade by 1 level or more
- In healthy horses, risk of renal damage is low
 - Increased creatinine/BUN in horses treated with NSAIDs 32%
- 44% of horses developed mild colic symptoms

Review of VEI Records

- 1062 doses given to 818 horses between 2006 and 2015
- 760 horses treated at VEI
- 373 horses with consistent follow up
 - 263 horses out of 373 considered successes (70%)
 - Improved at least one grade in lameness, or back pain
- 254/260 returned to previous level of work
- 188/263 horses did not need second dose to improve
 - 135 lameness, 34 back pain, 50 other axial skeleton pain
- **228 (86.6%) of successful cases did not need 2nd dose within 12 months**

Hock Arthritis

Tiludronate infusion in the treatment of bone spavin:
A double blind placebo-controlled trial

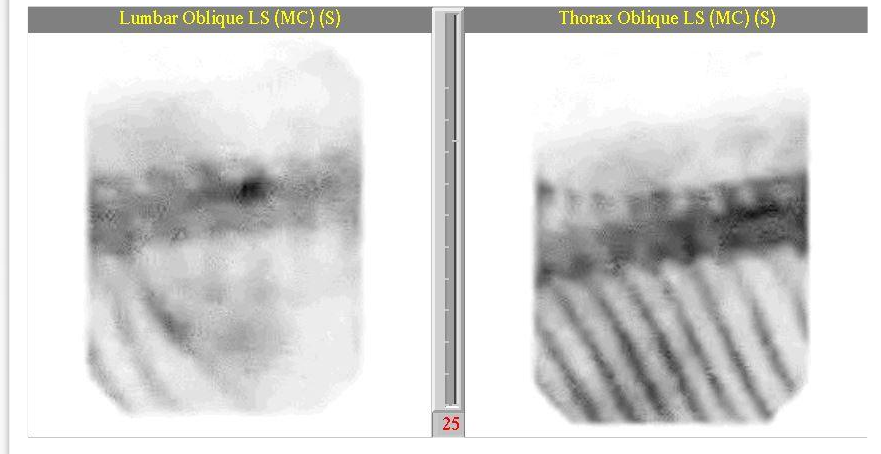
M. R. GOUGH*, D. THIBAUD† and R. K. W. SMITH‡

- Reduce bone pain and speed of remodeling
- VEI Data:
 - 33 horses with lameness from hock arthritis
 - 25 horses returned to work (75%)
 - 8 horses did not return to work
 - 3 for hock pain (9%), 5 for other reasons(15%)
- Study by Gough:
 - Treated horses had decreased periarticular osteophytes and tended to have less subchondral bone thickening on 60 day recheck radiographs
 - 42 horses received treatment and 60% had improved lameness score by 2 or more grades by 60 days



Back Pain

- VEI Data:
 - Tildren® combined with shockwave: 69% of horses have improved back pain, and 58% had back pain resolve for >1 year
 - Given to horses that failed other treatments primarily
 - Shockwave alone: 83% improved back pain, 34% resolved for >1 year
- Study by Coudry:
 - 77% of all horses treated that were evaluated at 60 days were reported improved by owners, which was significantly higher than non-treated (22%, $p=0.011$)
 - Flexion of back at trot and canter work improved in all treated horses



Efficacy of tiludronate in the treatment of horses with signs of pain associated with osteoarthritic lesions of the thoracolumbar vertebral column

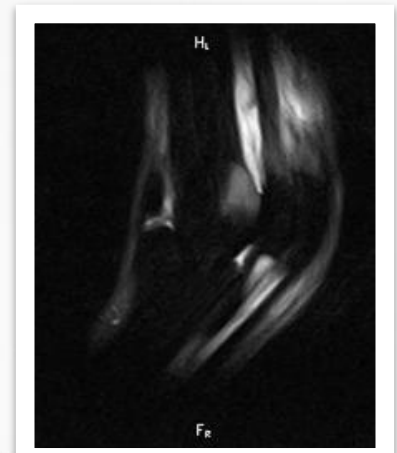
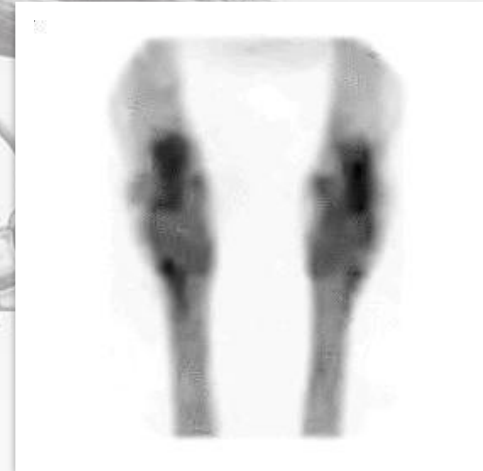
Virginie Coudry, DVM; Dominique Thibaud, DVM; Barbara Riccio, DVM; Fabrice Audigié, DVM, PhD;
David Didierlaurent, MSc; Jean-Marie Denoix, DVM, PhD

Enthesiopathies and Bone Contusion

- No formal data yet
- Suspensory enthesiopathy, collateral ligament enthesiopathy, muscle attachment injuries
- Traumatic or repetitive bone concussion
- Study by Mizobe:
 - 3 of 4 horses returned to racing and had improved signal (decreased edema) on recheck MRI
 - 4th horse did not complete protocol

Signal changes in standing magnetic resonance imaging of osseous injury at the origin of the suspensory ligament in four Thoroughbred racehorses under tiludronic acid treatment

Fumiaki MIZOBE^{1*}, Motoi NOMURA¹, Tomohiro KATO¹, Yasuo NAMBO² and Kazutaka YAMADA³



Other Recent Research

• Cartilage

- IA dose of 50mg Tildren® reaches concentrations of 1,900 mg/L
- In vitro, exposure of arthritic cartilage to concentrations >1,900mg/L and normal cartilage to > 19 mg/L may be detrimental to joint health
- Tildren concentrations in the joint of less than 1.9mg/L should decrease proteoglycan degradation and cartilage apoptosis in cartilage → beneficial
- Aim for dose between 0.19 and 1.9mg/L in the joint for cartilage effects. Effects on subchondral bone are unknown.

Concentration-dependent effects of tiludronate on equine articular cartilage explants incubated with and without interleukin-1 β

Katja F. Duesterdieck-Zellmer, Dr med vet, PhD; Nellie Driscoll, DVM; Jesse F. Ott, BS

Effects of low and high dose intraarticular tiludronate on synovial fluid and clinical variables in healthy horses—a preliminary investigation

Katja F. Duesterdieck-Zellmer¹, Lindsey Moneta², Jesse F. Ott¹, Maureen K. Larson¹, Elena M. Gorman³, Barbara Hunter¹, Christiane V. Löhr³, Mark E. Payton⁴, Jeffrey T. Morré³ and Claudia S. Maier³

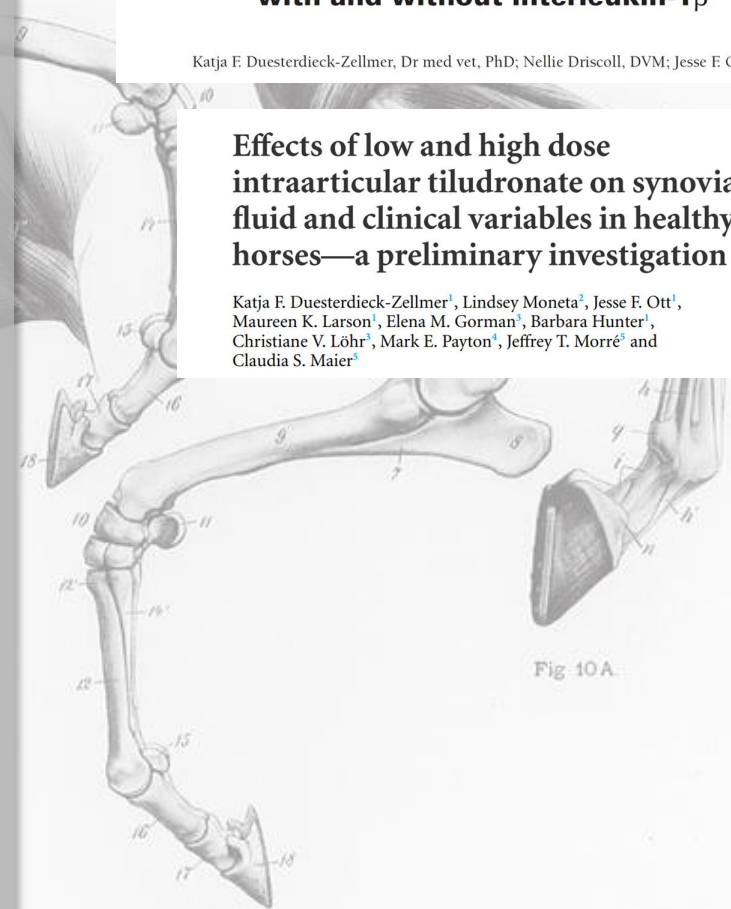


Fig. 15A.

Other Recent Research

- Cartilage

- 50mg dose in middle carpal joints increased indicators of inflammation (higher total solids, sGAGs, lower aggrecan synthesis) where dose of 0.017mg did not, but no obvious damage to cartilage was seen

- Via regional limb perfusion, received 0.5mg Tildren[®] or 50mg Tildren[®] in the left forelimb

- Reached concentrations >30,000 ng/mL in two coffin joints in high dose group
- Low dose coffin joint 449.6 ng/mL = 0.449mg/L
- 30,000ng/mL = 30mg/L

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Tiludronate concentrations and cytologic findings in synovial fluid after intravenous regional limb perfusion with tiludronate in horses

Barbara G. Hunter¹, Katja F. Duesterdieck-Zellmer and Maureen K. Larson

Aim for dose between 0.19 and 1.9mg/L

Other Recent Research

- Regional Limb Perfusion
 - 1mg/kg IV systemic dose vs. 0.1mg/kg RLP dose
 - Measured lameness with force plate
 - Ground reaction force improved through 200 days for horses treated systemically, but there was no change for horses treated via regional limb perfusion
- No advantage to regional limb perfusion

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Quantitative assessment of two methods of tiludronate administration for the treatment of lameness caused by navicular syndrome in horses

Chase T. Whitfield DVM, MS
Mike J. Schoonover DVM, MS
Todd C. Holbrook DVM
Mark E. Payton PhD
Kate M. Sippel DVM

OBJECTIVE

To determine effects of 2 tiludronate administration protocols on measures of lameness in horses with navicular syndrome (NS).

ANIMALS

12 horses with bilateral forelimb NS.

PROCEDURES

Summary

- Supportive data to use Tildren® for treatment of:
 - Navicular pain
 - Osteoarthritic changes in the back and neck
 - Hock osteoarthritis
 - Possibly suspensory ligament injury
 - Prevent bone loss in lay-up and immobilization situations
- Route of Administration
 - Best documented results with systemic administration
 - Possible damaging effects at 50mg intra-articular and with regional limb perfusions
 - Use your tools appropriately
- More Research to be Done
 - Concentrations present in joints and subchondral bone following systemic administration vs. other routes

References

- Coudry et al. Efficacy of tiludronate in the treatment of horses with signs of pain associated with osteoarthritis lesions of the thoracolumbar vertebral column. AJVR (2007) Vol. 68, No. 3, 329-337
- Duesterdieck et al. Effects of low and high dose intraarticular tiludronate on synovial fluid and clinical variables in healthy horses – a preliminary investigation. Peer J (2014) DOI 10.7717/peerj.534
- Delguste et al. Pharmacological effects of tiludronate in horses after long-term immobilization. Bone (2007) Vol.41, 414-421
- Duesterdieck-Zellmer et al. Concentration-dependent effects of tiludronate on equine articular cartilage explants incubated with and without interleukin-1B. AJVR (2012) Vol. 73, No. 10, 1530-1539
- Gough et al. Tiludronate infusion in the treatment of bone spavin: A double blind placebo-controlled trial. Equine Vet J (2010) Vol. 42, No. 5, 381-387
- FDA. Freedom of Information Summary, Original New Animal Drug Application, NADA 141-420 Tildren, February 13, 2014
- Hunter et al. Tiludronate concentrations and cytologic findings in synovial fluid after intravenous regional limb perfusion with tiludronate in horses. Peer J (2015) DOI 10.7717/peerj.889
- Mizobe et al. Signal changes in standing magnetic resonance imaging of osseus injury at the origin of the suspensory ligament in four Thoroughbred racehorses under tiludronic acid treatment. J. Equine Sci (2017) Vol. 28, No. 3, 87-97
- Whitfield et al. Quantitative assessment of two methods of tiludronate administration for the treatment of lameness caused by navicular syndrome in horses. AJVR (2016) Vol. 77, No.2, 167-173

Thank you.



Tildren® Administration

- Routes of Administration
 - Recommended
 - Intravenous
 - Other
 - Regional Limb Perfusion
 - Intra-articular



Fig. 16.

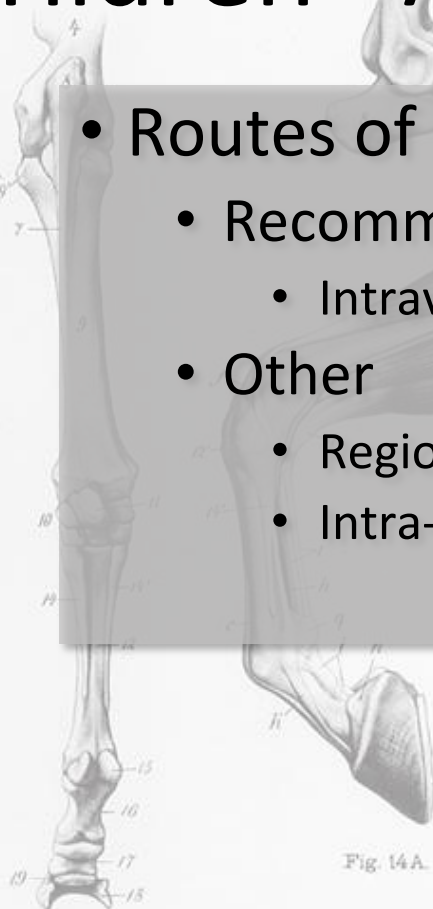


Fig. 17.

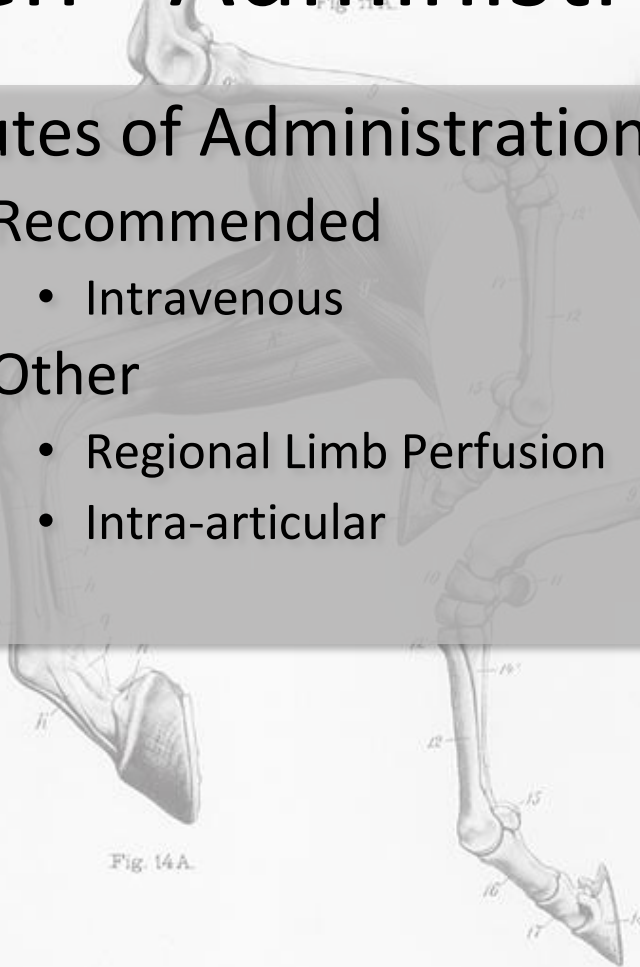


Fig. 14A.

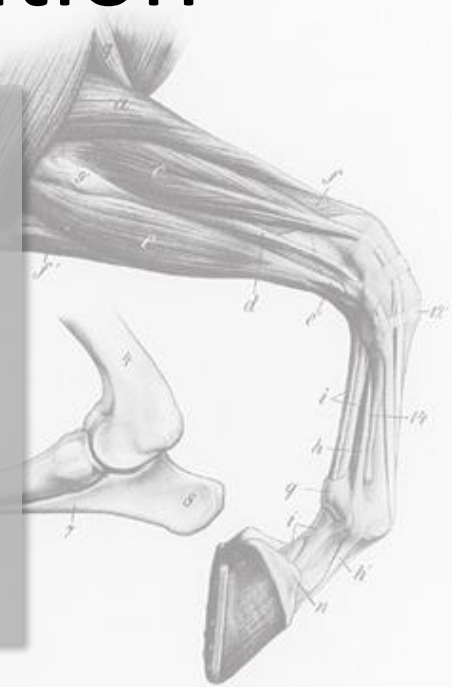


Fig. 10A.

Concentration-dependent effects of tiludronate on equine articular cartilage explants incubated with and without interleukin-1 β

Katja F. Duesterdieck-Zellmer, Dr med vet, PhD; Nellie Driscoll, DVM; Jesse F. Ott, BS

- Anecdotal IA treatment with 50mg (~1,900 mg/L if put in joint with 26mL synovial volume)
- Stifle cartilage explants in tissue culture
 - Simulated normal healthy joint cartilage, and arthritic cartilage by incubating with IL-1
 - Incubated with Tildren concentrations in powers of 10 from 0.19 mg/L to 1,900 mg/L
- Chondroprotective
 - Decreased sGAG release from arthritic cartilage at concentrations less than or equal to 190mg/L, and healthy cartilage less than or equal to 19 mg/L
 - Decreased chondrocyte apoptosis in arthritic cartilage at concentrations less than or equal to 190mg/L, and healthy cartilage less than or equal to 0.19mg/L
- Chondrodestructive
 - Increased sGAG release from arthritic cartilage at concentrations greater than 1,900 mg/L, and healthy cartilage greater than 19 mg/L
 - Increased chondrocyte apoptosis in arthritic cartilage at concentrations greater than 190mg/L, and healthy cartilage greater than 19 mg/L

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- Tildren® did not affect expression of MMPs or PGE2 known to increase expression in arthritis
- Did not affect expression of IL-6
- Only affected IL-8 expression in arthritic cartilage at concentrations of 1,900mg/L
- Other known actions of Tildren® :
 - Downregulate proteoglycan degrading proteases at concentrations of 19 to 190mg/L
 - Decrease apoptosis in osteoblasts and osteocytes in concentration dependent manner
 - Binds to connexin 43 hemichannels which activates pro-survival pathways
 - Same channel exists in articular chondrocytes

Overall Summary

- Exposure of arthritic cartilage to concentrations greater than 1,900mg/L and normal cartilage to greater than 19 mg/L may be detrimental to joint health
- Tildren® concentrations in the joint of less than 1.9mg/L should decrease proteoglycan degradation and cartilage apoptosis in cartilage independent of PGE and MMP production
- Aim for dose between 0.19 and 1.9mg/L in the joint for cartilage effects. Effects on subchondral bone are unknown.

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Claudia S. Maier⁵

- High dose of IA Tildren® of 50mg in 6mL saline given or low dose of 0.017mg in 1mL saline injected in middle carpal joint on one leg, blinded
- More subjective effusion in high dose joints
- Tildren® not detectable in low dose joints after 24 hours, but was detectable in two weeks in high dose joints
- No change in cell counts or histologic score for cartilage or synovium for high versus low dose at two weeks
 - Includes sGAG content and percent apoptotic chondrocytes
- Higher total solids and sGAGs in joint fluids in high dose joints vs. low dose, and lower CS-846 (indicator of aggrecan synthesis) in high dose joints
- Overall – High dose increased indicators of inflammation, but no obvious damage to cartilage seen on histology
 - Evaluated at 14 days, more time?

Tiludronate concentrations and cytologic findings in synovial fluid after intravenous regional limb perfusion with tiludronate in horses

Barbara G. Hunter*, Katja F. Duesterdieck-Zellmer and Maureen K. Larson

- 6 horses, received 0.5mg Tildren® or 50mg Tildren® in the left forelimb, double blinded
- Administered via regional limb perfusion with 50mL saline
- 24 hours after treatment, limbs that received higher dose were lamer
- Synovial samples taken from coffin and fetlock joints and navicular bursas of both forelimbs
- No change in synovial fluid solids or cell counts
- Tildren® was detectable in synovial fluid of non-treated limbs immediately after tourniquet removal
- In low dose limbs, was not detectable after 24 hours, but was detectable in both limbs of high dose group at 24 hours
- Reached concentrations >30,000 ng/mL in two coffin joints in high dose group
 - Low dose coffin joint 449.6 ng/mL 30,000ng/mL = 30mg/L
- Highest concentrations reached in coffin joints ← navicular bursa ← fetlock joint
- Concentration high enough to induce apoptosis of osteoblasts?

Quantitative assessment of two methods of tiludronate administration for the treatment of lameness caused by navicular syndrome in horses

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ANIMALS

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PROCEDURES

- Horses with navicular changes treated with 1mg/kg systemic treatment or 0.1mg/kg via regional limb perfusion in forelegs
- Radiographs before and after treatment
 - No change in radiographs over 200 days
- Ground reaction force in both front legs measured before and after treatment throughout 200 days
 - Increased (improved) ground reaction force at day 120 and 200 in both front legs and the lamest leg in the systemic treated horses
 - No significant change in RLP horses
- Day 120 lameness score improved for regional limb horses for both legs, and day 60 and 120 on the lamest leg
 - Improved for systemic horses but not statistically significant

Pharmacological effects of tiludronate in horses after long-term immobilization☆

C. Delguste^{a,*}, H. Amory^a, M. Doucet^b, C. Piccot-Crézollet^c, D. Thibaud^d, P. Garnero^e, J. Detilleux^a, O.M. Lepage^c

- Measured bone density, CTX-1 (marker of bone resorption) and ALP (marker of bone formation) in 4-8 year old racehorses placed in casts for 56 days, then reintroduced to work
- Followed treated and untreated controls for 140 days
- There was a significant decrease in bone mass in untreated horses over 140 days
 - Bone density not significantly changed over 56 days in treated horses, but bone density decreased to day 140 in treated horses,
- CTX-1 stayed above baseline until day 42 in non-treated horses
- CTX-1 decreased in both groups when reintroduced to work (stop bone resorption)
- ALP decreased in both groups by day 7 of immobilization
 - Tildren® did not affect ALP or bone formation
- Treatment prevented long-term bone loss in treated horses
 - Affect on bone-healing for fractures?
 - Better for casted ligament or tendon injuries?