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

Whitfield CT, Schoonover MJ, Holbrook TC, Payton, ME, Sippel KM. Am J Vet Res. 2016 Feb;77(2):167-73. doi: 10.2460/ ajvr.77.2.167.

Abstract

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: Horses were randomly assigned to receive tiludronate (1 mg/kg), diluted in 5 L of isotonic electrolyte solution and delivered through a jugular vein catheter (systemic treatment group; n = 6), or tiludronate (0.1 mg/kg), diluted with saline (0.9% NaCl) solution to a total volume of 35 mL and delivered into the lateral digital vein of each forelimb with an IV regional limb perfusion (IVRLP) technique (IVRLP group; 6).

Mean peak vertical ground reaction force (pVGRF) measured with a stationary force plate and subjective lameness scores (SLSs) were recorded before (day -1) and at predetermined time points after tiludronate administration on day 0. Mean pVGRFs (standardized as percentage body weight of force) and mean SLSs for the most lame forelimb and for both forelimbs of horses in each group were compared with day -1 values to determine treatment effect.

RESULTS: Mean pVGRF for both forelimbs and for the most lame forelimbs of systemically treated horses were significantly increased on days 120 and 200, compared with day -1 results. No significant difference in mean pVGRF was observed for IVRLP-treated horses. The SLSs were not improved at any time point following systemic treatment and were improved only on day 120 following IVRLP.

CONCLUSIONS AND CLINICAL RELEVANCE: Tiludronate (1mg/kg, IV) as a single systemic treatment appeared to be beneficial for horses with NS, but no horses were judged as sound during the study period. Additional research on IVRLP with tiludronate is needed before this method can be recommended. (Am J Vet Res 2016;77:167-173).

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

Hunter BG, Duesterdieck-Zellmer KF, Larson MK., Peer J. 2015 Apr 28;3:e889. doi: 10.7717/peerj.889. eCollection 2015.

Abstract

Anecdotal accounts of tiludronate administration via intravenous regional limb perfusion (IVRLP) exist despite a lack of information regarding safety for synovial structures in the perfused area. The objective of this study was to determine whether tiludronate concentrations in synovial structures after IVRLP with low dose (0.5 mg, LDT) or high dose (50 mg, HDT) tiludronate remain below a value demonstrated *in vitro* to be safe for articular cartilage (<19,000 ng/ml), and to determine effects of tiludronate on synovial fluid cytology variables compared to saline perfused control limbs.

Using a randomized controlled experimental study design, horses received IVRLP with LDT (n = 6) or HDT (n = 6) in one forelimb and IVRLP with saline in the contralateral limb. Synovial fluid cytology variables and tiludronate concentrations were evaluated in navicular bursae (NB), and distal interphalangeal (DIP) and metacarpophalangeal (MCP) joints one week before and 30-45 min after IVRLP, and in DIP and MCP joints 24 h after IVRLP. Data were analyzed with 2-way rmANOVA ($p < 0.05$). Highest measured synovial fluid tiludronate concentrations occurred 30-45 min post-perfusion.

Mean tiludronate concentrations were lower in LDT limbs (MCP = 39.6 ± 14.3 ng/ml, DIP = 118.1 ± 66.6 ng/ml, NB = 82.1 ± 30.2 ng/ml) than in HDT limbs (MCP = 3,745.1 ± 1,536.6 ng/ml, DIP = 16,274.0 ± 5,460.2 ng/ml, NB = 6,049.3 ± 1,931.7 ng/ml). Tiludronate concentration was >19,000 ng/ml in DIP joints of two HDT limbs. Tiludronate was measurable only in synovial fluid from HDT limbs 24 h post-perfusion. There were no differences in synovial fluid cytology variables between control and treated limbs.

Conclusions: In some horses, IVRLP with HDT may result in synovial fluid concentrations of tiludronate that may have adverse effects on articular cartilage, based on in vitro data. IVRLP with LDT is unlikely to promote articular cartilage degradation. Further studies to determine a safe and effective dose for IVRLP with tiludronate are needed.

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

Duesterdieck-Zellmer KF, Moneta L, Ott JF, Larson, MK, Gorman EM, Hunter B, Löhr CV, Payton ME, Morré JT, Maier CS. PeerJ. 2014 Sep 4;2:e534. doi: 10.7717/peerj.534. eCollection 2014.

Abstract

To determine effects of intraarticularly administered tiludronate on articular cartilage in vivo, eight healthy horses were injected once with tiludronate (low dose tiludronate [LDT] 0.017 mg, n = 4; high dose tiludronate [HDT] 50 mg, n = 4) into one middle carpal joint and with saline into the contralateral joint. Arthrocentesis of both middle carpal joints was performed pre-treatment, and 10 min, 24 h, 48 h, 7 and 14 days after treatment.

Synovial nucleated cell counts and total solids, tiludronate, sulfated glycosaminoglycan (sGAG), chondroitin sulfate 846 epitope (CS-846, a measure of aggrecan synthesis), and collagen type II cleavage neoepitope (C2C) concentrations were determined. Histologic analysis of joint tissues and sGAG quantitation in cartilage was performed at 14 days in HDT horses.

Data were analyzed by repeated measures non-parametric ANOVA and Wilcoxon signed-rank test. High dose tiludronate administration produced synovial fluid tiludronate concentrations of 2,677,500 ng/mL, exceeding concentrations that were safe for cartilage in vitro, and LDT administration produced synovial fluid concentrations of 1,353 ng/mL, remaining below concentrations considered potentially detrimental to cartilage.

With HDT, synovial fluid total solids concentration was higher at 24 h and 7 days and sGAG concentration was higher at 48 h, compared to control joints. Synovial fluid CS-846 concentration was increased over pre-treatment values in HDT control but not in HDT treated joints at 24 and 48 h.

All joints (HDT and LDT control and treated) showed a temporary decrease in synovial fluid C2C concentration, compared to pre-treatment values. Histologic features of articular cartilage and synovial membrane did not differ between HDT treated and control joints.

High dose tiludronate treatment caused a transient increase in synovial total solids and temporarily increased proteoglycan degradation in cartilage. Although clinical significance of these changes are questionable, as they did not result in articular cartilage damage, further investigation of the safety of intraarticular HDT in a larger number of horses is warranted.

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

Duesterdieck-Zellmer KF, Driscoll N, Ott JF., Am J Vet Res. 2012 Oct;73(10):1530-9.

Abstract

OBJECTIVE: To determine concentration-dependent effects of tiludronate on cartilage explants incubated with or without recombinant equine interleukin-1β (rEq IL-1).

SAMPLE: Articular cartilage explants from the femorotibial joints of 3 young adult horses.

PROCEDURES: Cartilage explants were incubated with 1 of 6 concentrations (0, 0.19, 1.9, 19, 190, or 1,900 mg/L) of tiludronate and with or without rEq IL-1 (0.01 ng/mL) for 96 hours. Prostaglandin E(2) (PGE(2)) concentrations in culture medium and explant digests were analyzed via PGE(2) enzyme immunoassay.

Sulfated glycosaminoglycan (sGAG) concentrations in culture medium were quantified via 1,9-dimethylmethylene blue assay. Chondrocyte apoptosis in paraffin embedded explant sections was measured via terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling assay. Relative gene expression of matrix metalloproteinases (MMPs), interleukin (IL)-6, and IL-8 was determined via the comparative cycle threshold method.

RESULTS: rEq IL-1 increased PGE(2) concentration, sGAG release from explants, chondrocyte apoptosis, and MMP gene expression. Lower tiludronate concentrations reduced rEq IL-1-induced sGAG release and chondrocyte apoptosis, whereas the higher tiludronate concentrations increased sGAG release and chondrocyte apoptosis. At the highest tiludronate concentration evaluated, IL-8 gene expression was increased independent of whether rEq IL-1 was present.

CONCLUSIONS AND CLINICAL RELEVANCE: Tiludronate had biphasic concentration-dependent effects on cartilage explants that were independent of PGE(2) secretion or MMP gene expression. Low tiludronate concentrations had some chondroprotective effects, whereas high tiludronate concentrations were detrimental to equine articular cartilage. Administration of tiludronate intra-articularly to horses may be detrimental, dependent on the dose used. In vivo studies are needed before intraarticular tiludronate administration to horses can be recommended.

Tiludronate infusion in the treatment of bone spavin: a double blind placebo-controlled trial."

Gough MR, Thibaud D, Smith RK., Equine Vet J. 2010 Jul;42(5):381-7

Abstract

REASONS FOR PERFORMING STUDY: Tiludronate regulates bone remodelling through a decrease of the resorptive process and should therefore ameliorate the remodelling processes active in osteo-arthritis of the distal tarsal joints ('bone spavin') and alleviate pain associated with abnormal bone lysis.

OBJECTIVE: To confirm the efficacy of tiludronate, administered as a single infusion at a dose of 1 mg/kg bwt, in the treatment of bone spavin in the horse.

METHODS: A double blind placebo controlled trial on108 clinical cases of bone spavin was under-taken. The lameness score of the lamest limb was assessed following distal tarsal analgesia of the contralateral limb and followed-up using the same procedure throughout the study. Bone spavin in the lamest limb was confirmed by distal tarsal analgesia and radiography. Horses were treated at Day 0 and reassessed 60 days later after controlled exercise. A second nonblinded treatment was given to unresponsive horses and all horses were re-examined at Day 120. Exercise levels were recorded at each examination.

RESULTS: Eighty-seven horses completed the trial as per the protocol. The tiludronate horses were significantly less lame than the placebo horses (P = 0.0318). Horses treated at Day 60 with tiludronate showed further improvement in lameness at Day 120 (P = 0.0096 and P = 0.0034 for horses treated with tiludronate and placebo at Day 0, respectively). The only significant difference in radiographic findings between tiludronate and placebo was for presence of periarticular osteophytes (P = 0.006).

CONCLUSIONS: Tiludronate treatment is proven to be effective in bone spavin in horses in association with a controlled exercise programme.

CLINICAL RELEVANCE: Tiludronate in combination with controlled exercise offers an alternate medical treatment for bone spavin.

"Comparative pharmacokinetics of two intravenous administration regimens of tiludronate in healthy adult horses and effects on the bone resorption marker CTX-1."

Delguste C, Amory H, Guyonnet J, Thibaud D, Garnero P, Detilleux J, Lepage OM, Doucet M.
J Vet Pharmacol Ther. 2008 Apr;31(2):108-16

Abstract

Bioavailability and pharmacological effects of tiludronate were compared when administered as an intravenous (i.v.) bolus at a dosage of 0.1 mg/kg body weight (b.w.) once daily for 10 consecutive days (group 1, n =6) and as a single constant rate infusion (CRI) at a total dose of 1 mg/kg b.w. (group 2, n = 6) in healthy adult horses. Tiludronate and carboxy-terminal cross-linking telopeptide of type I collagen (CTX-1) were measured in plasma and urine.

There was no statistically significant difference in area under the curve (AUC) and clearance (Cl) between the two groups. Bioavailability of the CRI was 103% (not significantly different) that of the 10 daily i.v. bolus doses. Cumulative urine tiludronate excretion could not be compared between groups because of poor sensitivity of the assay in urine.

Plasma and urine CTX-1 levels were not different between groups throughout the study. However, interindividual variations were greater in group 1 than in group 2. A significant decrease in CTX-1 levels was observed in plasma after the first administration in group 1, but not in urine; while in group 2, a significant decrease in CTX-1 concentrations was observed after treatment in both plasma and urine.

In conclusion, both dosage regimens of tiludronate produced similar plasma exposure and pharmacological effects in adult healthy horses.

"Pharmacological effects of tiludronate in horses after long-term immobilization."

Delguste C, Amory H, Doucet M, Piccot-Crézollet C, Thibaud D, Garnero P, Detilleux J, Lepage OM. Bone. 2007 Sep;41(3):414-21. Epub 2007 May 23.

Abstract

INTRODUCTION: Tiludronate, a bisphosphonate, has recently been introduced in veterinary medicine to treat orthopedic conditions in the horse. This study was designed to evaluate its effects on biochemical biomarkers of bone metabolism and on bone density and structure in an experimental model of disuse osteoporosis induced by cast application in horses.

METHODS: Two groups of eight horses were immobilized during 8 weeks. The first group (P-group) received a placebo, and the second group (T-group) received tiludronate 1 mg/kg by slow IV infusion. Both treatments were administered twice, 28 days apart. Immobilization consisted of stall rest with the left forelimb packed in a fiberglass cast.

It was followed by a 4-week remobilization period and an 8-week standardized training protocol. One biomarker of bone resorption, the C-telopeptides of type I collagen cross-links (CTX-1) and one biomarker of bone formation, the bone isoenzyme of alkaline phosphatase (bone ALP), were assessed. Metacarpus III (MCIII) bone mineral density (BMD) and speed of sound (SOS) were evaluated respectively by dual energy X-ray absorptiometry (DEXA) and quantitative ultrasonography (QUS). Lameness was regularly assessed during the remobilization and training periods. Group- and time-related effects were tested by analysis of variance on repeated measurements.

RESULTS: A rapid, transient and significant decrease in CTX-1 concentration was seen after each treatment in the T-group only. No significant differences between groups were seen in the evolution of bone ALP activity. At the end of the experiment, the loss of MCIII BMD measured by DEXA in the immobilized limb was significantly less in the T-group than in the P-group. The MCIII SOS measured by QUS did not significantly vary within or between groups throughout the study.

DISCUSSION AND CONCLUSIONS: tiludronate was found to significantly reduce bone resorption during immobilization, as well as to prevent long-term osteopenia in the immobilized limb. treat orthopedic conditions in the horse. This study was Disuse osteopenia did not affect the lateral superficial cortex of MCIII.

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

Coudry V, Thibaud D, Riccio B, Audigié F, Didierlaurent, D, Denoix JM. Am J Vet Res. 2007 Mar;68(3):329-37.

Abstract

OBJECTIVE: To evaluate the efficacy of tiludronate for the treatment of horses with signs of pain associated with lesions of the thoracolumbar vertebral column.

ANIMALS: 29 horses with clinical manifestations of pain associated with lesions of the thoracolumbar vertebral column and abnormal radiographic findings indicative of osteoarthritis of the articular process-es-synovial intervertebral joints.

PROCEDURES: Horses were initially examined in accordance with a standardized protocol, which included radiographic, ultrasonographic, and scintigraphic examinations. Fifteen horses were randomly assigned to receive tiludronate (1 mg/kg, IV, as a slow-rate infusion), and 14 horses received a control substance (day 0). Horses were monitored for the subsequent 120 days. Clinical evaluations were performed on days 60 and 120. Horses that had no evidence of clinical improvement on day 60 were administered tiludronate. Statistical analyses were performed to compare efficacy at day 60, improvement of dorsal flexibility at day 120, and dorsal flexibility before and 60 days after administration of tiludronate.

RESULTS: Horses treated with tiludronate had significant improvement in dorsal flexibility between days 0 and 60, compared with control horses. Clinical improvement in dorsal flexibility was still evident at day 120. The percentage of positive responses was higher in the tiludronate group at 60 days.

CONCLUSIONS AND CLINICAL RELEVANCE:
Tiludronate had efficacy in the treatment of horses with signs of pain induced by osteoarticular lesions of the thoracolumbar vertebral column, causing a significant improvement in dorsal flexibility. Tiludronate may offer a treatment option for the management of horses with intervertebral lesions and the associated pain.

"Tiludronate as a new therapeutic agent in the treatment of navicular disease: a double-blind placebo-controlled clinical trial."

Denoix JM, Thibaud D, Riccio B., Equine Vet J. 2003 Jun;35(4):407-13.

Abstract

REASONS FOR PERFORMING STUDY: Bisphosphonates, such as tiludronate, are used to normalise bone metabolism via inhibition of bone resorption. Areas of increased bone resorption and formation are typical lesions in a diseased navicular bone.

OBJECTIVES: To determine if bone remodelling changes occurring in navicular disease may be corrected with therapies regulating bone metabolism.

METHODS: We designed a double-blind, placebo-controlled clinical trial to compare 2 doses of tiludronate, 0.5 mg/kg and 1 mg/kg bwt administered via daily i.v. injections over 10 days for the treatment of navicular disease.

Seventy-three horses, split into 2 subpopulations of recent and chronic cases, were enrolled to be followed-up over 6 months. Of these, 33 recent and 17 chronic cases meeting the selection criteria were maintained in the final efficacy analyses. Clinical examinations were videorecorded and reviewed blindly by an independent expert.

RESULTS: Horses treated with the higher dose showed optimal improvement of lameness and return to normal level of activity 2-6 months post treatment. The more recent the onset of clinical signs at the time of treatment, the greater the efficacy. The treatment did not modify the response to extension and flexion tests. The lower dose failed to significantly improve the condition.

CONCLUSIONS: Tiludronate efficacy is demonstrated in the treatment of navicular disease at the dose of 1 mg/kg bwt.

POTENTIAL RELEVANCE: Our results support the clinical relevance of bone remodelling changes in the outcome of navicular disease.