Orally Administered Sub-Antimicrobial Doxycycline Attains Synovial Fluid Levels Capable of Inhibiting Matrix Metalloproteinases 3 and 13

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This study confirms that intragastric administration of low-dose doxycycline results in measurable synovial-fluid doxycycline concentrations; this may decrease cartilage catabolism through inhibition of matrix metalloproteinases and may slow the progression of osteoarthritis. Authors' addresses: Department of Clinical Sciences, Cornell University, Ithaca, NY 14853 (Watts, Schnabel, Fortier); and Department of Molecular Biomedical Sciences, North Carolina State University, College of Veterinary Medicine, 4700 Hillsborough Street, Raleigh, NC 27606 (Papich); e-mail: ashleedvm@gmail.com. © 2007 AAEP.

1. Introduction
Tetracyclines have been used to alleviate symptoms and slow the progression of osteoarthritis (OA). In vitro studies indicate that doxycycline at concentrations of 0.0462 μg/ml significantly decreases matrix metalloproteinases (MMPs) 3 and MMP-13 gene expression in synoviocytes treated with either interleukin-1 or MMP-13. The purpose of this study was to determine if low-dose doxycycline administered orally could achieve anti-MMP concentrations in synovial fluid and plasma.

Six healthy adult horses without evidence of joint disease or lameness received doxycycline at one-half the reported anti-microbial dose (5 mg/kg every 12 h through nasogastric intubation). Venous-blood and synovial-fluid samples were collected into heparin tubes immediately before doxycycline administration at t = 0 h; then, samples were collected at t = 0.25, 0.5, 1, 12, 24, 48, and 72 h. Doxycycline concentrations were measured using high-performance liquid chromatography (HPLC).

Doxycycline concentration in the plasma of all horses was >0.2146 μg/ml by t = 0.5 h, and the mean at t = 0.5 h was 0.2550 ± 0.0228 μg/ml. At time points after t = 12 h, the concentration was 0.1018 ± 0.0193 μg/ml, which is below reported minimum inhibitory concentration (MIC) (0.25 μg/ml) for doxycycline susceptible bacteria. Synovial-fluid concentrations of doxycycline in all horses were >0.1227 μg/ml by t = 1 h, and the mean at t = 1 h was 0.1943 ± 0.0279 μg/ml. At time points after t = 1 h, the synovial concentration was 0.2153 ± 0.0180 μg/ml.
This study confirms that intragastric administration of low-dose doxycycline results in measurable synovial-fluid doxycycline concentrations that may decrease cartilage catabolism through inhibition of MMPs and slow the progression of OA. However, further in vivo studies are warranted to determine if MMP activity is inhibited in vivo and to fully elucidate a medication protocol.

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Footnote

aDoxycycline 100 mg tablets, Vetessa Pharmaceutical, 10460 NW 37th Terrace, Doral, FL 33178.