PILOT STUDY: PHARMACOKINETICS OF ORAL AND TOPICAL MOXIDECTIN IN THE RETICULATED GIRAFFE (*GIRAFFA CAMELOPARDALIS*)

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PILOT STUDY: PHARMACOKINETICS OF ORAL AND TOPICAL MOXIDECTIN IN THE RETICULATED GIRAFFE (*GIRAFFA CAMELOPARDALIS*)

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Abstract: The objective of this study was to obtain an estimate of the pharmacokinetic parameters of moxidectin administered at a dosage of 1 mg/kg orally and topically to healthy adult giraffe (*Giraffa camelopardalis*). The maximum plasma concentration (C_{MAX}) of moxidectin after oral and topical administration was 69.2 ± 4.6 and 18.6 ± 16.1 ng/ml ($P = 0.045$), respectively. The areas under the plasma curve (AUC), a measure of total drug exposure, was 532.0 ± 232.3 and 209.1 ± 180.0 day*ng/ml ($P = 0.308$) for the oral and topical administrations, respectively. These data suggest moxidectin achieves higher peak plasma concentrations following oral administration compared with topical (transdermal) administration using the cattle pour-on formulation. Additionally, the percent coefficient of variation, a measure of variability, was smaller for the oral formulation (C_{MAX} %CV = 7%; AUC %CV = 44%) compared with the topical formulation (C_{MAX} %CV = 86%; AUC %CV = 86%). The smaller variability suggests that oral administration of moxidectin produces more predictable and less variable drug absorption than topical administration in giraffe and is the preferred route of administration.

Key words: Anthelmintic resistance, *Giraffa camelopardalis*, Giraffe, *Haemonchus contortus*, Moxidectin, Pharmacokinetics.

BRIEF COMMUNICATION

Parasite resistance with the nematode *Haemonchus contortus* is a significant cause of morbidity and mortality in captive giraffe (*Giraffa camelopardalis*).[6–8] Anthelmintic drug resistance has been documented in giraffe using larval development assays and may be developing because of improper dosing.[5,6,8–10,16] Assessing the pharmacokinetic profile of antiparasitic drugs, specifically moxidectin, is essential to evaluate plasma kinetic levels, bioavailability, and mean residence time of these drugs. If effective doses can be achieved, parasite resistance in giraffe can be minimized. Moxidectin is a relatively safe, second-generation macrocyclic lactone with good efficacy against nematodes, especially *H. contortus*, although this may vary depending on parasite resistance patterns. The cattle pour-on formulation (Cydectin®, Boehringer Ingelheim Vetmedica, St. Joseph, Missouri 64506, USA) is ideal for zoo and wildlife species because it allows for minimal handling and prevents rejection of bad-tasting oral formulations. Although moxidectin pharmacokinetics have been established in domestic ruminants, these profiles can be highly variable among species.[1,3,4] Moxidectin pharmacokinetics have been minimally evaluated in zoo and wildlife species, including camels and wombats.[2,12]

This pharmacokinetic study of moxidectin in giraffe investigated the best dosage and administration route in giraffe by comparing oral and topical administration. Appropriate use of anthelmintic drugs will decrease parasite resistance and contribute to improving the health care of captive giraffe.

Four healthy adult giraffes, including one female and three males, ranging in weight from 596 to 920 kg, participated in this pilot study, which was approved by the institutional animal care and use committees at Lion Country Safari and Kansas State University. The giraffes were considered healthy based on visual examination and routine bloodwork. All giraffes were trained for voluntary blood draws from the jugular vein and to accept an oral syringe filled with medication using operant conditioning with banana food rewards. Three giraffes were included in the final data set due to reluctance to venipuncture by one individual (female). Prior to the onset of this research project, the giraffes were not given any

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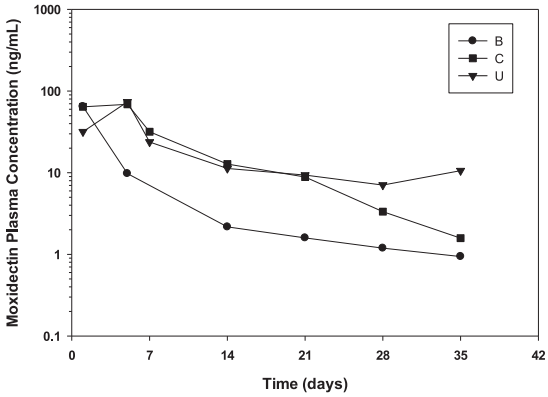

Figure 1. Plasma profile of oral moxidectin 1 mg/kg in healthy adult giraffe. Letters B, C, and U each represent an individual giraffe.

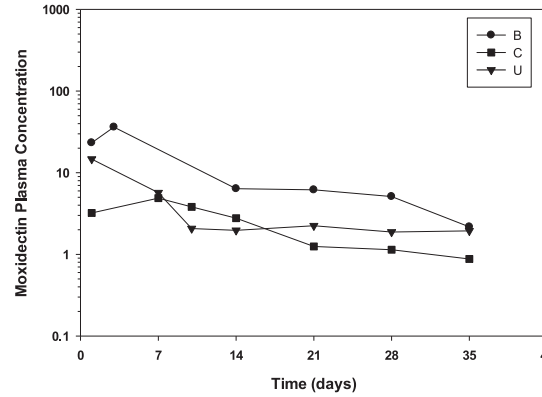

Figure 2. Plasma profile of topical (transdermal) moxidectin in 1 mg/kg in healthy adult giraffe. Letters B, C, and U each represent an individual giraffe.

antiparasitic medication for 60 days. Weights on each individual giraffe were obtained.

Giraffe were administered moxidectin (Quest® 2% Equine Oral Gel, Zoetis, Kalamazoo, Michigan 49007, USA; 1 mg/kg, p.o., once) or moxidectin pour-on formulation for cattle (Cydectin®, Boehringer Ingelheim Vetmedica; 1 mg/kg, topically along the dorsum, once) in a randomized crossover with at least 90 days between treatments. The skin of the giraffes was not prepared in any way prior to topical administration of the moxidectin. Blood samples, 9 ml/time point, were scheduled to be obtained on days 0, 1, 3, 5, 7, 14, 21, 28, and 35, but all samples were not collected in all animals due to nonparticipation by the giraffe (Figs. 1 and 2). There were a total of 27 plasma samples used for analysis. Blood samples were centrifuged for 10 min at 3,000 *g*, and plasma was separated and stored frozen (–20°C) until the end of the crossover. Samples were then shipped on ice in a styrofoam cooler to the analytical laboratory where they were stored at –70°C until analysis. Plasma concentrations were determined with high-pressure liquid chromatography (Shimadzu Prominence, Shimadzu Scientific Instruments, Columbia, Maryland 20588, USA) and mass spectrometry (API 3000, Applied Biosystems, Foster City, California 94404, USA). The qualifying ion for moxidectin was 640.36 and the quantifying ion was 528.30 with a 400-ms dwell time. Moxidectin samples and plasma standards, in bovine plasma, were prepared by adding 1 ml plasma to 1 ml 4% phosphoric acid in water, and then solid phase extraction was performed. The extraction cartridges (Bond Elut C18, 3 mL, Agilent Technologies, Santa Clara, California 95050, USA) were conditioned with 2 ml methanol, followed by 2 ml deionized water. The plasma sample/phosphoric acid mixture was added, and the cartridges were then washed with 2 ml 5% methanol in water. The samples were eluted with 2 ml methanol and evaporated to dryness in a heated water bath (40°C) under an air stream for 30 min, after which they were reconstituted with 0.15 ml 40% ammonium acetate buffer, 10 mM, pH 5.0, in 60% acetonitrile. The injection volume was 0.1 ml. The standard curve was linear from 0.5 to 100 ng/ml and accepted if the measured values were within 15% of the actual values and the correlation coefficient was at least 0.99. The mobile phase consisted of (A) acetonitrile and (B) ammonium acetate buffer, 10 mM, pH 5.0. A gradient was used starting at 60% A from 0 to 1 min and a linear gradient to 90% A at 3.5 min and then back to 60% A at 4.5 min, with a total run time of 5.5 min and using a C8 column (Supelco Discovery C8, Sigma Chemicals, St. Louis, Missouri 63101, USA); achieved separation was maintained at 40°C. The accuracy of the assay was 98 ± 7% of the actual concentrations determined on replicates of five at each of the following concentrations: 0.5, 5, and 50 ng/ml. The coefficient of variation was 7%, determined on replicates of five at each of the following concentrations: 0.5, 5, and 50 ng/ml. Noncompartmental pharmacokinetic analysis was conducted with computer software (WinNonlin 5.2, Pharsight Corporation, Mountain View, California 94035, USA). Statistical comparisons of the pharmacokinetic parameters were made with computer software (Sigma Stat 3.11, Systat Software, Inc., San Jose, California 95002, USA) using a paired *t*-test.

Table 1. Pharmacokinetic parameters (range) of moxidectin after oral and topical (transdermal) administration of 1 mg/kg to three animals per treatment.

Parameter	Units	Oral	Topical
C_{MAX}	ng/ml	65–74	5–36
T_{MAX}	day	1–5	1–7
AUC	day*ng/ml	265–691	81–415
MRT	day	4.9–11.1	9.0–12.6

P value determined using a paired *t*-test comparing oral and topical pharmacokinetic parameters. C_{MAX}, maximum plasma concentration; T_{MAX}, time to C_{MAX}; AUC, area under the plasma curve from 0 to last measured time point (35 days); MRT, mean residence time from 0 to last measured time point (35 days).

The pharmacokinetics of oral and topical (transdermal) moxidectin in giraffe are presented in Table 1, and the plasma profiles are presented in Figures 1 and 2. The maximum plasma concentration was significantly higher ($P = 0.045$) after oral moxidectin compared with topical moxidectin (Table 1). There was no significant difference in the area under the plasma curve (AUC; from time 0 to 35 days), mean residence time (from time 0 to 35 days), or time to maximum plasma concentration. The percent coefficient of variation was larger in the topical group compared with the oral group for C_{MAX}, T_{MAX}, and AUC, suggesting greater variability in rate and extent of absorption following topical administration. The terminal half-life was not estimated due to excessive extrapolation and increasing plasma concentrations at day 35 in two-thirds of the animals. The statistical power was low (<0.8) for each parameter due to the small number of study subjects.

Although therapeutic doses of moxidectin in giraffe were not evaluated in this study, moxidectin research in cattle and horses demonstrates that therapeutic doses reach a C_{MAX} of 33.5 ± 12.0 to 42.8 ± 3.8 ng/ml and 30.1 ng/ml in cattle (*Bos taurus*) and horses (*Equus caballus*), respectively.[3,13–15] Therefore, a surrogate target of 30 ng/ml was used for the mean C_{MAX} in giraffes. The oral doses exceeded 30 ng/ml for a C_{MAX}, but the topical doses did not. The oral dose of 1 mg/kg achieved a higher and more consistent C_{MAX} than the topical doses. If drug efficacy and subsequently a minimized selection of drug resistant organisms is achieved by achieving a higher C_{MAX} (i.e., concentration-dependent effects), then the oral route would be a better option in giraffes. Despite including only three animals, the pattern of absorption indicates oral administration of 1 mg/kg moxidectin produces higher maximum plasma concentrations and less variable pharmacokinetic parameters than topical (transdermal) administration and is therefore the preferred route of administration.

Efficacy of moxidectin was not assessed in this study. However, anecdotal evidence suggests that oral administration of moxidectin in giraffe results in a greater and more reliable decrease in fecal egg count than topical administration (Hammond, pers.comm.). Oral administration may have advantages against gastrointestinal parasites because unabsorbed drug could directly interact with the parasite, increasing drug exposure and potential efficacy.[11] However, giraffes may be averse to the taste of moxidectin, making oral administration difficult.

Although relatively easy to administer, topical moxidectin efficacy could be affected by application challenges or the possibility that the drug is removed before adequate absorption, such as due to rain or the animal rubbing or licking the site. Self-grooming can increase the animal's absorption. Conversely, in a herd setting, conspecifics may be exposed to the drug through grooming and decrease the absorption of the drug by the target animal.

Future studies could evaluate the pharmacokinetics of injectable moxidectin in giraffe, but this was beyond the scope of this study. A disadvantage of the injectable formulation is that a large volume must be administered due to the concentration of the drug and the large size of giraffes. Additionally, the giraffes in the current study were not trained for hand injection of medication, and the large volume of drug needed would make darting the medication difficult. Comparing moxidectin levels in feces to those in plasma would also be beneficial in future studies.

To the authors' knowledge, this is the first moxidectin pharmacokinetic study performed in giraffe and suggests that oral moxidectin administered at a dosage of 1 mg/kg is preferable to topical (transdermal) administration in giraffe.

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LITERATURE CITED

1. Alvinerie M, Escudero E, Sutra JF, Eeckhoutte C, Galtier P. The pharmacokinetics of moxidectin after

oral and subcutaneous administration to sheep. Vet Res. 1998;29:113–118.

2. Death CE, Taggart DA, Williams DB, Milne R, Schultz DJ, Holyoake C, Warren KS. Pharmacokinetics of moxidectin in the southern hairy-nosed wombat (*Lasiorhinus latifrons*). J Wildl Dis. 2011;47(3):643–649.

3. Dupuy, J, Sutra JF, Alvinerie M. Pharmacokinetic assessment of moxidectin long-acting formulation in cattle. Vet Parasit. 2007;147:252–257.

4. Escudero E, Carceles CM, Diaz MS, Sutra JF, Galtier P, Alvinerie M. Pharmacokinetics of moxidectin and doramectin in goats. Res Vet Sci. 1999;67:177–181.

5. Fleming SA, Craig E, Kaplan RM, Miller JE, Navarre C, Rings, M. Antihelminthic resistance of gastrointestinal parasites in small ruminants. J Vet Intern Med. 2006;20:435–444.

6. Garretson PD, Hammond EE, Craig TM, Holman PJ. Anthelmintic resistant *Haemonchus contortus* in a giraffe (*Giraffa camelopardalis*) in Florida. J Zoo Wildl Med. 2009;40(1):131–139.

7. Goosens, E, Dorny P, Boomker J, Vercammer F, Vercruysse J. A 12 month survey of the gastrointestinal helminthes of antelopes, gazelles, and giraffids kept at two zoos in Belgium.

8. Hammond, EE, Craig TM, Kinney A, Miller JE. Integrated parasite management in a herd of captive giraffe (*Giraffa camelopardalis*). In: Proc Am Assoc Zoo Vet/Assoc Rept Amphib Vet Joint Annu Meet; 2008. p. 129–130.

9. Isaza, R, Courtney CH, Kollias GV. The prevalence of benzimidazole resistant trichostrongylid nematodes in antelope collections in Florida. J. Zoo Wildl Med. 1995;26:260–264.

10. Isaza, R, Courtney CH, Kollias GV. Survey of parasite control programs used in captive wild ruminants. Zoo Biol. 2005;9(5):385–392.

11. Miller, JA, Oehler DD, Scholl PJ. Moxidectin: pharmacokinetics and activity against hornflies (Diptera:Muscidae) and trichostrongyle nematode egg production. Vet Parasit. 1994;53:133–143.

12. Oukessou M, Berrag B, Alvinerie M. A comparative kinetic study of ivermectin and moxidectin in lactating camels (*Camelus dromedaries*). Vet Parasitol. 1999;83(2):151–159.

13. Perez R, Cabezas I, Garcia M, Rubilar L, Sutra JF, Galtier P, Alvinerie M. Comparison of the pharmacokinetics of moxidectin (Equest) and ivermectin (Eqvalan) in horses. J Vet Pharmacol Ther. 1999;22: 174–180.

14. Whang EM, Bauer C, Kollmann D, Burger HJ. Efficacy of two formulations ('injectable' and 'pour on') of moxidectin against gastrointestinal nematode infections in grazing cattle. Vet Parasit. 1994;51:271–281.

15. Yazwinski TA, Williams JC, Smith LL, Tucker C, Loyacano AF, Derosa A, Peterson P, Bruer DJ, Delay RL. Dose determination of the persistent activity of moxidectin long-acting injectable formulations against various nematode species in cattle. Vet Parasit. 2006;137:273–285.

16. Young KE, Jensen JM, Craig TM. Evaluation of anthelmintic activity in captive wild ruminants by fecal egg reduction tests and larval development assay. J Zoo Wildl Med. 2000;31(3):348–352.

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