Journal of Feline Medicine and Surgery (2004) **6**, 157–160

jfms

www.elsevier.com/locate/jfms

Metronidazole for the treatment of feline giardiasis

Andrea V. Scorza*, Michael R. Lappin

Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Veterinary Teaching Hospital, Colorado State University, 300 West Drake Road, Fort Collins, CO 80523, USA

Accepted 20 November 2003

Summary There are several drugs available for the treatment of giardiasis in cats, including metronidazole. The purpose of this study was to determine whether metronidazole benzoate administered at a dose of 25 mg/kg, orally, twice a day for 7 days lessens or eliminates *Giardia* cyst shedding in cats with chronic infection. Twenty-six, adult, laboratory-reared cats were used in this study. Sixteen cats had been inoculated orally with cysts of a human *Giardia* sp. isolate and had completed a *Giardia* vaccine study in one animal holding room. The other ten cats were infected with the same *Giardia* sp. presumably by contamination from the adjacent room where the *Giardia* vaccine study cats were located. From each cat, a fecal sample was collected within 1 week of the start of treatment and then every 2 to 4 days for 15 days after treatment was completed. Fecal samples were analyzed for the presence of *Giardia* cysts using a commercially available direct immunofluorescence test (IFA). Clinical signs of drug toxicity were not detected during the study.

Introduction

Giardia is a flagellate protozoan with worldwide distribution that causes significant gastrointestinal disease in a wide variety of vertebrates, including cats and people (Barr and Greene, 1998). Mammalian isolates are all currently classified as *Giardia lamblia*. Recently, two or three genotypes of *Giardia* sp. in people, two genotypes in dogs (Hopkins et al., 1997), and a genotype that may be unique to cats have been identified (Homan et al., 1998; Lu et al., 1998). *Giardia* infection can occur in healthy cats as well as cats with acute or chronic small bowel diarrhea with or without weight loss. Infection is common; in recent studies, *Giardia* sp. were detected in 5 of 206 (2.4%) of the adult cats tested in Colorado (Hill et al., 2000), 19 of 263 (7.2%) of the kittens tested in New York State (Spain et al., 2001), and 228 of 2234 (10.2%) of the cats tested in Germany (Barutzki, 2001).

Because some *Giardia* sp. are zoonotic, treatment is frequently considered for some healthy carriers as well as clinically ill cats. In the United States, there are several protocols that have been assessed for the treatment of giardiasis in cats. Administration of the drugs albendazole, fenbendazole, furazolidone and metronidazole as well as use of a *Giardia* vaccine as immunotherapy have all been assessed in small numbers of cats. Albendazole was ineffective in one group of cats (Barr et al., 1993) and was associated with bone marrow suppression (Stokol et al., 1997). Fenbendazole was shown to be safe when administered to healthy, adult, non-pregnant cats at a dosage five times higher than the approved dosage (Schwartz et al., 2000). However, when fenbendazole was administered to cats concurrently infected with *Giardia* sp. and *Cryptosporidium parvum*, only four out of eight cats stopped shedding *Giardia* cysts (Keith et al.,

* Corresponding author. Tel.: +1-970-491-4401; fax: +1-970-491-1275

E-mail address: vscorza@lamar.colostate.edu (A.V. Scorza).

1098-612X/04/$ - see front matter © 2003 ESFM and AAFP. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.jfms.2003.11.007

2003). Furazolidone causes inappetence and vomiting in many cats and efficacy data for the treatment of giardiasis in cats is minimal (Brightman and Slonka, 1976; Kirkpatrick and Lackzac, 1985). A vaccine containing inactivated *Giardia* sp. trophozoites developed for vaccination of kittens (Olson et al., 1996) was recently assessed as an immunotherapy in experimentally inoculated cats but there were no differences in cyst shedding between treated cats and control cats (Stein et al., 2003).

Metronidazole has been used frequently for the treatment of giardiasis in cats and people. However, the studies that have shown metronidazole to be effective in eliminating *Giardia* cyst shedding in naturally and experimentally infected cats only included small numbers of cats (Nesvadba, 1979; Shatto, 1981; Zimmer, 1987). In addition, gastrointestinal and central nervous system toxicity has been associated with metronidazole administration to cats (Caylor and Cassimatis, 2001).

The objectives of this study were to determine whether administration of metronidazole benzoate using one protocol lessens *Giardia* cyst shedding in cats and to clinically assess for toxicity.

Materials and methods

Animals

Twenty-six laboratory-reared, mixed sex cats between 1 and 2 years of age were purchased from a commercial breeder. Sixteen cats were housed in one animal holding room (Stein et al., 2003) and the other 10 cats (Scorza et al., 2003) were located in an adjacent room. The cats were housed in individual cages, were fed a commercial feline diet at libitum, and were observed daily for attitude, stool consistency, and signs of drug toxicity including neurological disorders, lethargy, anorexia, vomiting, diarrhea and hepatoxicity. The protocol used in this study was reviewed and approved by the Colorado State University Animal Care and Use Committee in accordance with federal regulations. The cats were adopted to private homes after the completion of the study.

Experimental design

Each of the 26 cats treated in this study were known to be chronically infected with a human *Giardia* sp. isolate. Sixteen cats were housed in one animal holding room and had been inoculated orally with 10^6 cysts 10 months before being treated in this study. They had been persistently infected since that time, and had been either control cats or had failed treatment with *Giardia* vaccine given as immunotherapy (Stein et al., 2003).

The other 10 cats were infected with *C. parvum* 16 months previously (Scorza et al., 2003). By retrospective evaluation of stored feces, it was determined that the *C. parvum*-infected cats had been infected with *Giardia* sp. for approximately 5 months prior to use in this study. These 10 cats were presumed to have been accidentally exposed to *Giardia* sp. from the adjacent room where the other 16 cats were housed. The two groups of cats were infected by the same *Giardia* sp. isolate as determined by comparison of a sequence analysis of the GDH locus (Homan et al., 1998). These 10 cats had either not been treated for *Giardia* sp. infection or had failed treatment with fenbendazole, administered at 50 mg/kg, PO, daily for 5 days (Keith et al., 2003).

Metronidazole benzoate (PCCA, Houston, Texas) was administered to all 26 cats at 25 mg/kg, PO, q12hr for 7 days. A liquid formulation was used with a final concentration of 25 mg/ml of base which is equivalent to 40 mg of benzoate. From each cat, a fecal sample was collected within 1 week of the start of treatment and then every 2 to 4 days for 15 days after treatment was completed. The fecal samples were analyzed for the presence of *Giardia* cysts by use of a commercially available direct immunofluorescence assay (IFA; Merifluor *Cryptosporidium/Giardia*, Meridian Diagnostics, Cincinnati, OH, USA).

Results

In the 3 month period prior to treatment in this study, all of the cats were positive for *Giardia* sp. cysts by IFA in at least two of four fecal samples tested; the majority of the cats were positive in the last four fecal samples. All the cats in the study were positive for *Giardia* cysts within 1 week of the administration of metronidazole benzoate. Clinical signs of drug toxicity, including neurologic disorders, lethargy, anorexia, vomiting and diarrhea were not detected in any of the cats during or after treatment. All 26 cats were negative for *Giardia* cysts by IFA in the three fecal samples collected within the 15-day post-treatment period.

Discussion

Because all 26 cats treated here had been shedding *Giardia* cysts for five to 10 months (Keith et al., 2003; Stein et al., 2003), including the fecal sample collected within 1 week prior to treatment, we believed that the cats can be considered to be

chronically infected. Thus, it is likely that the failure to document a single cyst in any sample from any of 26 cats within 15 days of treatment with metronidazole benzoate indicates a treatment response, not spontaneous resolution of cyst shedding. It would have been optimal to have included an untreated control group in this study, but because each cat had persistently shed *Giardia* cysts for months, to lessen the need for more infected cats, and to attempt to clear the infection so the cats could be adopted, all were treated. It also may have been optimal to monitor for cyst shedding for longer periods of time. However, because the prepatent period for *Giardia* sp. cyst shedding in dogs and cats is approximately 2 weeks and the organism is extremely infectious, it is impossible to determine whether positive samples detected after that time are a repeat infection or a failure to eliminate infection. Thus, most *Giardia* treatment studies are discontinued within 1 week of completing the treatment period (Barr et al., 1994, 1998).

Our results correlate with previous reports that showed metronidazole to be effective in lessening or eliminating *Giardia* sp. cyst shedding when administered to individual cats; in some studies duration of parasitological follow up was not stated (Nesvadba, 1979; Shatto, 1981; Zimmer, 1987). In another study, metronidazole eliminated *Giardia* sp. cyst shedding by two naturally infected and two experimentally infected cats for four or five weeks post-treatment (Kirkpatrick and Farrell, 1984). In that study, a modified $ZnSO_4$ flotation technique was used to assess for presence of *Giardia* sp. cysts in feces. Administration of metronidazole at the dose of 22 mg/kg twice a day for 5 weeks, eliminated cyst shedding as detected by $ZnSO_4$ flotation in seven naturally infected cats; the diarrhea either ceased or was markedly diminished (Zimmer, 1987). In the study described here, we could not determine whether the administration of metronidazole lessened the clinical signs of giardiasis, since none of the cats had diarrhea.

Shedding of *Giardia* cysts by cats may fluctuate from undetectable to concentrations to >1,000,000 cysts/g of feces (Kirkpatrick and Farrell, 1984). The IFA used in the present study is thought to be one of the most sensitive tests for the diagnosis of giardiasis (Deng and Cliver, 1999); in preliminary studies in our laboratory, the threshold of detection in spiked feline fecal samples ranges between 60 and 110 *Giardia* cysts per gram of feces. In another study of cats infected with the human *Giardia* sp. strain used in this study, the IFA was more sensitive and specific than $ZnSO_4$ flotation and comparable to an antigen detection technique when used on refrigerated samples (Lappin et al., 2002). However, it cannot be determined with absolute certainty whether administration of metronidazole benzoate eliminated infection or just inhibited cyst shedding to undetectable limits. We purposely chose not to euthanas the cats to confirm or deny the presence of the organism in the intestinal tract. Recently it was reported that polymerase chain reaction (PCR) was more sensitive when compared with microscopy and ELISA in cat feces infected with giardiasis (McGlade et al., 2003). PCR should be considered for use in future *Giardia* sp. treatment studies.

There are two formulations of metronidazole available for oral administration; metronidazole benzoate was used here. Products containing metronidazole benzoate are commercially available in some countries and the drug is available for formulation in the United States. Metronidazole USP induces salivation and inappetence when administered orally to some cats (Groman, 2000). In contrast, metronidazole benzoate is very well tolerated by cats, as seen in this report. Whether the two formulations have equivalent activity against *Giardia* sp. in cats has not been determined. The protozoal toxicity of metronidazole is from short-lived intermediates or free radicals that produce damage by interacting with DNA and possibly other molecules (Lindsay and Blagburn, 2001). The recommended dose of metronidazole in cats is between 10 and 60 mg/kg body weight per day (Lindsay and Blagburn, 2001). Vomiting, inappetence, hepatotoxicity and rarely, central nervous toxicity can occur with metronidazole therapy (Caylor and Cassimatis, 2001). Neurological toxicity may develop following either chronic therapy or acute high doses (Caylor and Cassimatis, 2001). Even though central nervous toxicity is rare, clinicians should be aware of the potential complications associated with the use of metronidazole. The results of this study suggest that administration of metronidazole to cats at 25 mg/kg, PO, q12hr for 7 days is unlikely to cause toxicity.

Many different *Giardia* sp. strains had been identified; cats in this study were infected with a human isolate. To our knowledge, there have not been studies assessing sensitivity of different *Giardia* sp. strains to different drugs in cats. It is possible that the strain that we used in this study was very sensitive to metronidazole. Treatment failures are common in humans and other animals with giardiasis; reinfection, inadequate drug levels, inmunosuppression, drug resistance, and sequestration of the organism in the gall-bladder or

pancreatic ducts are all proposed reasons (Nash et al., 2001). To further assess the effect of different *Giardia* sp. strains on treatment results, case control treatment studies of naturally infected and experimentally infected cats will be needed. It is likely that no drug will be universally effective for the treatment of giardiasis. Therefore, in clinical practice, the drug and protocol used here should be adjusted for each individual patient having considered all options for treatment.

Acknowledgements

The authors would like to thank the following people for their help in collecting samples and animal care; Dr Carey Keith, Melissa Brewer, and Jennifer Hawley.

References

Barr, S.C., Bowman, D.D., Heller, R.L., Erb, H.N., 1993. Efficacy of albendazole against *Giardia* sp. in dogs and cats. Proceedings of the American Asssociation of Veterinary Parasitologists, July 17–20, pp. 56.

Barr, S.C., Bowman, D.D., Heller, R.L., 1994. Efficacy of fenbendazole against giardiasis in dogs. American Journal of Veterinary Research 55, 988–990.

Barr, S.C., Bowman, D.D., Frongillo, M.R., Joseph, S.L., 1998. Efficacy of a drug combination of praziquantel, pyrantel pamoate, and febantel against giardiasis in dogs. American Journal of Veterinary Research 59, 1134–1136.

Barr, S.C., 1998, in: Greene, C.E. (Ed.), Infectious Diseases of the Dog and Cat; Enteric Protozoal Infections, second ed. Philadelphia, WB Saunders, pp. 482–491.

Barutzki, D., 2001. Contribution of Bayer Animal Health at the 18th International Conference of the WAAVP. August 26–30 Stresa, Italy. Prevalence of *Giardia* spp. in Dogs and Cats in Germany, pp. 24–25.

Brightman, A.H., Slonka, G.F., 1976. A review of five clinical cases of giardiasis in cats. Journal of the American Hospital Association 12, 492–497.

Caylor, K.B., Cassimatis, M.K., 2001. Metronidazole neurotoxicosis in two cats. Journal of the American Hospital Association 37, 258–262.

Deng, M.Q., Cliver, D.O., 1999. Improved immunofluoresce assay for the detection of *Giardia* and *Cryptosporidium* from asymptomatic adult cervine animals. Parasitology Research 85, 733–736.

Groman, R., 2000. Metronidazole. Compendium on Continuing Education for the Practicing Veterinarian 22, 1104–1107.

Hill, S.L., Cheney, J.M., Taton-Allen, G.F., Reif, J.S., Bruns, C., Lappin, M.R., 2000. Prevalence of enteric zoonoses in cats. Journal of American Veterinary Medical Association 216, 687–692.

Homan, W.L., Gilsing, M., Bentala, H., Limper, L., van Knapen, F., 1998. Characterization of *Giardia duodenalis* by polymerase-chain-reaction fingerprinting. Parasitology Research 84, 707–714.

Hopkins, R.M., Meloni, B.P., Groth, D.M., Wetherall, J.D., Reynoldson, J.K., Thompson, R.C.A., 1997. Ribosomal RNA sequencing reveals differences between the genotypes of *Giardia* isolates recovered from humans and dogs living in the same locality. Journal of Parasitology 83, 44–51.

Keith, C.L., Radecki, S.V., Lappin, M.R., 2003. Evaluation of fenbendazole for treatment of *Giardia* infection in cats concurrently infected with *Cryptosporidium parvum*. American Journal of Veterinary Research 64, 1027–1029.

Kirkpatrick, C.E., Farrell, J.P., 1984. Feline giardiasis: observations on natural and induced infections, 45, 2182–2188.

Kirkpatrick, C.E., Lackzac, J.P., 1985. Giardiasis in a cattery. Journal of American Veterinary Medicine Association 187, 161–162.

Lappin, M.R., Jensen, W.A., Taton-Allen, G., 2002. Comparison of Zn SO_4 centrifugation, a fecal antigen assay, and an immunofluorescent antigen assay for diagnosis of giardiasis in cats. Journal of Veterinary Internal Medicine 16, 345. Abstract.

Lindsay, D.S., Blagburn, B.L., 2001, in: Adams, H.R. (Ed.), Veterinary Pharmacology and Therapeutics, eighth ed. Ames, Iowa, Iowa State University Press, pp. 993–994.

Lu, S.Q., Baruch, A.C., Adam, R.D., 1998. Molecular comparison of *Giardia lamblia* isolates. International Journal of Parasitology 28, 1341–1345.

McGlade, T.R., Robertson, I.D., Elliot, A.D., Thompson, R.C.A., 2003. High prevalence of Giardia detected in cats by PCR. Veterinary Parasitology 110, 197–205.

Nash, T.E., Ohl, C.A., Thomas, E., Subramanian, G., Keiser, P., Moore, T.A., 2001. Treatment of patients with refractory giardiasis. Clinical Infectious Diseases 33, 22–28.

Nesvadba, V.J., 1979. Giardiasis in a cat. Kleintier-Praxis 24, 177–179.

Olson, M.E., Morck, D.W., Ceri, H., 1996. The efficacy of a *Giardia lamblia* vaccine in kittens. Canadian Journal of Veterinary Research 60, 249–256.

Schwartz, R.D., Donogue, A.R., Baggs, R.B., Clark, T., Partington, C., 2000. Evaluation of the safety of fenbendazole in cats. Journal of American Veterinary Research 61, 330–332.

Scorza, A.V., Brewer, M.M., Lappin, M.R., 2003. Polymerase chain reaction for the detection of *Cryptosporidium* spp. in cat feces. Journal of Parasitology 89, 423–426.

Shatto, N.L., 1981. Feline giardiasis (a case report). Veterinary Medicine & Small Animal Clinician 76, 1297–1298.

Spain, C.V., Scarlett, J.M., Wade, S.E., McDonough, P., 2001. Prevalence of enteric zoonotic agents in cats less than 1 year old in Central New York State. Journal of Veterinary Internal Medicine 15, 33–38.

Stein, J.E., Radecki, S., Lappin, M.R., 2003. Efficacy of *Giardia* vaccination for treatment of giardiasis in cats. Journal of the American Veterinary Medical Association 222, 1548–1551.

Stokol, T., Randolph, J.F., Nachbar, S., Rodi, C., Barr, S.C., 1997. Development of bone marrow toxicosis after albendazole administration in a dog and cat. Journal of the American Veterinary Medical Association 210, 1753–1756.

Zimmer, J.F., 1987. Treatment of feline giardiasis with metronidazole. Cornell Veterinary 77, 383–388.