Secnidazole for the treatment of giardiasis in naturally infected cats

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ABSTRACT

Giardia duodenalis causes enteric infections in humans and animals worldwide. Inefficiency of metronidazole is commonly reported in the veterinary clinic routine in the treatment of giardiasis in dogs and cats. The aim of this study was to evaluate the efficacy of secnidazole in the control of infection caused by G. duodenalis in naturally infected cats. For this purpose two experiments were carried out. In the first experiment seven cats were infected with G. duodenalis and treated orally with a single dose of secnidazole (30 mg kg\(^{-1}\)). In the second experiment a total of 16 cats were used, 11 naturally infected with G. duodenalis and five negative for the parasite. Animals were divided into three groups: group A (n=5) was composed of non-infected animals (negative control), group B (n=5) consisted of infected but untreated animals and group C (n=6) was composed by cats treated orally with a single dose of secnidazole (30 mg kg\(^{-1}\)). Hematological and biochemical parameters were evaluated before and after treatment. The first experiment reached 100% of efficacy because no cysts were found in the feces after treatment. However, doubts about intoxication and interference with hematological and biochemical parameters came to light. No side effects were observed, and the biochemical and hematological parameters of treated animals remained within physiological range, except for one feline which had elevation of liver enzymes. Based on these results, the utilization of secnidazole could be suggested for the treatment of giardiasis in cats. The main advantage of this treatment is that only a single dose is required, which is interesting in animals hard to handle like cats.

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1. Introduction

The flagellated protozoan Giardia duodenalis (syn. G. intestinalis, G. lamblia) commonly causes enteric infections in humans and animals worldwide [1,2]. Several genotypes have been identified, which may have different host species specificities [3,4]. G. duodenalis exists in two different forms, the trophozoite and the cyst. The trophozoite is motile and is found in the intestinal lumen, whereas the cyst is the transmissible form and is capable of prolonged survival in the environment [5]. Transmission occurs through ingestion of the cyst and once in the duodenum each cyst releases two trophozoites, which then attach to the intestinal epithelium [4].

Molecular and epidemiological studies showed that G. duodenalis is composed by at least seven genetically distinct assemblages, but morphologically identical (A to G). Moreover, assemblages C to G appear to have host-specific preferences [6,7]. Genotypes of assemblages A and B are known to infect humans, cattle and companion animals such as dogs and cats [8–10]. Assemblage F was detected in cats [11]. According to researchers, livestock are unlikely to be an important source of infection in humans, but the greatest risk of zoonotic transmission appears to be from companion animals such as dogs and cats [12]. However, the role of dogs and cats as a source of human giardiasis remains unclear [13], once several reports are divergent about the zoonotic potential.

Cats can be subclinical or have diarrhea due to malabsorption, malabsorption and increased motility in consequence of giardiasis [14]. In Brazil, this protozoan is widely distributed, parasitizing humans, domestic and wild animals [15,16]. The most severe cases of giardiasis occur in young or immunosuppressed animals [16]. Metronidazole and fenbendazole have been used in the treatment of feline and canine giardiasis [1,17,18]. All the studies which showed the efficacy of metronidazole in eliminating Giardia cysts in cats naturally and experimentally infected included only a small number of cats [19,20]. Moreover, drug resistance against giardiasis, especially to metronidazole and albendazole, has been reported elsewhere [21].

Inefficacy of metronidazole is commonly reported in veterinary routine when it is used in the treatment of giardiasis in dogs and cats (personal communication), and reinfection has been implicated as the
most common cause of treatment failure [22,23]. Thus, seeking for new therapeutic options, this study aimed to test the efficacy of secnidazole in the control of giardiasis in naturally infected cats.

2. Materials and methods

2.1. Experiment 1

Seven female cats aging between six and 12 months were used in this study. The animals were acquired to perform an experimental study in the Laboratory of Veterinary Parasitology of the Federal University of Santa Maria (UFSM), Brazil. When the animals arrived at the laboratory, three of them had diarrhea and dehydration. Thereafter, 1 g of fecal samples from each animal was examined by the zinc sulphate centrifugal flotation technique [24]. As a result, all animals showed high infection by cysts of *Giardia* (more than 300 cysts/slide).

Once diagnosed the disease, the cats were weighed and housed in individual cages in an experimental room with controlled temperature and humidity (25 °C; 70% U.R.). They were fed with commercial chow and water ad libitum. At the same day, the cats received a single oral dose (1 mL) of 30 mg kg\(^{-1}\) secnidazole diluted in water. The cats were daily monitored for clinical signs of drug toxicity and clinical alterations after the administration of the drug. For the evaluation of drug efficacy, feces were re-examined at days 6, 7 and 8 post-treatment.

2.2. Experiment 2

The experiment 2 was designed to clarify some doubts remaining from experiment 1, such as: (1) is secnidazole toxic to cats and responsible for the clinical signs observed in four cats of experiment 1? (2) is the dose able to change hepatic and renal functions? (3) does secnidazole cause alterations in the hemogram of cats? and (4) is the dose administered really effective in the treatment of giardiasis in felines?

To address this issue, fecal samples were collected from female adult cats belonging to a cattery of UFSM. Samples (1 g) were processed by the zinc sulphate centrifugal flotation technique [24]. Eleven positive cats (more than 30 cysts of *Giardia* per gram of feces) were used in this study, as well as five cats as negative controls. Cats were divided into three groups. Group A (n = 5) consisted on cats negative for giardiasis by fecal flotation (negative controls), group B (n = 5) consisted on cats positive for giardiasis by fecal flotation but not treated (positive controls) and group C (n = 6) consisted on cats positive for giardiasis by fecal flotation and treated with a single dose of secnidazole (30 mg kg\(^{-1}\)).

Cats were weighed and housed in individual cages in an experimental room with controlled temperature and humidity (25 °C; 70% U.R., respectively). They were fed with commercial diet and water ad libitum. Hematological and biochemical parameters were analyzed at days 0 and 5, after anesthesia with midazolam (0.3 mg kg\(^{-1}\)) and ketamine (1.0 mg kg\(^{-1}\)). Approximately 1 mL of blood was stored in tubes containing anticoagulant (EDTA) for analysis of hemogram and 3 mL of blood was stored in tubes without anticoagulant to obtain serum, which was used for evaluation of hepatic and renal functions.

Erythrocyte count, hematocrit, hemoglobin concentration, mean corpuscular volume, mean corpuscular hemoglobin concentration and total leukocyte count were evaluated. Hematocrit and hematometric indexes were evaluated as previously described [25]. Erythrocyte and leukocyte count and hemoglobin concentration were determined using an electronic counter. Serum activity of alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT) and the levels of creatinine and urea were evaluated in a semi-automatic analyzer (TP Analyzer Plus®, Thermoplate-China) using commercial kits (Labtest® Diagnóstica S.A., Lagoa Santa, MG, Brazil). Tests were carried out in duplicates. For the evaluation of drug efficacy, feces were re-examined at days 6, 7 and 8 post-treatment.

The results were submitted to analysis of variance (ANOVA) followed by the Tukey test. Significance level was set at P < 0.05. Statistical analysis was carried out vertically and horizontally to hematological and biochemical parameters.

3. Results

3.1. Experiment 1

Five of seven cats showed high salivation rates during approximately 5 min after drug administration. The four most debilitated cats presented apathy and did not eat during the first 48 h post-treatment. After this period, no clinical alterations were observed. *Giardia* spp. cysts were not observed in the feces of all cats by microscopic examination after fecal flotation at days 6, 7 and 8 post-treatment. Episodes of diarrhea were not more observed after the eighth day of treatment. Therefore, the therapeutic protocol used obtained 100% of effectiveness.

3.2. Experiment 2

Six of six cats showed high salivation rates during approximately 3 min after drug administration. No clinical signs were observed in the cats treated with secnidazole. *Giardia* spp. cysts were not observed in the feces of all cats by microscopic examination after fecal flotation at days 6, 7 and 8 post-treatment (Table 1). Therefore, the therapeutic protocol used obtained 100% of efficacy. Cats from group B maintained the elimination of the parasite cysts in feces during the experimental period (Table 1).

The hematological parameters remained within normal limits in all cats before and after treatment (Table 2). The therapeutic protocol used did not affect renal function in all treated cats (groups A and C), as well as the hepatic function in the majority of animals (10/11) (Table 3). Only one cat from group C had increased levels of ALT and GGT post-treatment. ALT increased from 61 to 250 U/L and GGT from 2.56 to 7.2 U/L. Despite this increase, no clinical changes were observed.

4. Discussion

Secnidazole is a commercialized drug for the treatment of giardiasis in humans. It has the advantage to be administered in a single dose with sound curative effects. Children treated with a single dose of secnidazole (30 mg kg\(^{-1}\)) achieved 98% [26] and 78.1% [27] of cure. Researchers, in a comparative study between secnidazole and metronidazole [28]. When metronidazole was used in a single dose, its curative rate was reduced to 54% [29,30]. On the other hand, a single dose of secnidazole reaches the same response achieved with multiple dosage regimens of metronidazole or tinidazole [26,28].

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of <em>Giardia duodenalis</em> cysts</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: n = 5</td>
<td>Before treatment: 97.8 (±43.7)</td>
</tr>
<tr>
<td>B: n = 5</td>
<td>After treatment: 103.1 (±51.9)</td>
</tr>
</tbody>
</table>

Comparison among groups: Means followed by same letters in the same column were not statistically different from each other (Tukey test).
In the present study, the curative efficacy of secnidazole in cats infected by *G. duodenalis* was 100%. Similar efficacy of this drug was observed in a comparative study with metronidazole (97%), fenbendazole (98%) and secnidazole (100%) in mice naturally infected by *G. muris* [31]. Studies involving treatment with secnidazole in cats with giardiasis have not been performed yet, although some veterinarians in southern Brazil have been using this drug in a single dose of 30 mg kg⁻¹ for dogs and cats, achieving good curative rates (personal communication). The main reason for the limited use of secnidazole in the treatment of feline giardiasis is because it is not commercially available for veterinary therapy.

Metronidazole has been used frequently in the treatment of giardiasis in humans and cats. An experimental study showed that metronidazole benzoxide (25 mg kg⁻¹ orally twice a day for 7 days) was able to eliminate *Giardia* cyst shedding in cats with chronic infection [32]. The metronidazole is in the nitromidazole class of agents. Once the drug enters the parasite it becomes activated by the nitro group and binds covalently to DNA molecules, producing a more sensitive assay than the fecal flotation technique [36,37]. Good curative efficacy in cats experimentally infected with different *Giardia* species was obtained by researchers [13] when using a combination product containing febantel, pyrantel and praziquantel for 5 days. The combination febantel–praziquantel–pyrantel can also be used to treat dogs with giardiasis, but according to the authors bathing and changing the environment after treatment may be more important in preventing recurrence than duration of treatment with or without vaccination with a commercial *Giardia* vaccine [33].

Salivation was observed in the cats after drug administration but the symptom was observed only for 3–5 min. Loss of appetite and apathy observed in four animals of experiment 1 are likely to be consequence of giardiasis, since these alterations were observed only in debilitated animals, with dehydration and diarrhea. In Experiment 2, the treated cats did not show any clinical signs other than the short period of salivation after drug administration, and their liver and kidney functions were within normal range. Moreover, ALT, GGT, urea and creatinine remained within normal physiological ranges in the majority of the animals. The animal with increased ALT and GGT levels was the only one of the experiment 2 which showed high infection by *G. duodenalis* associated with diarrhea. According to researchers, secnidazole may interfere with the results of several biochemical analysis, such as the determination of liver transaminases (AST and ALT) activities and triglycerides [34], being this information also mentioned in the leaflet of the drug. Another important feature of secnidazole lies in the fact that the dose administered in the cats did not interfere with hematological parameters. Therefore, since neither clinical signs nor alterations were observed in the hematological and biochemical assays, it is possible to suggest secnidazole may be an additional drug for treatment of giardiasis in cats.

Absence of *Giardia* cysts does not guarantee that the infection was eliminated. Peaks of cyst shedding occur sporadically rather than cyclically, from undetectable to concentrations above 1,000,000 cysts/gram of feces, and the duration between any two given peaks is generally from 2 to 7 days [35]. Immunofluorescence and PCR are more sensitive assays than the fecal flotation technique [36,37]. Notwithstanding, animals of Experiment 1 showed health improvement and absence of diarrhea after treatment.

At the end of the experiment, five cats from group B were successfully treated with the same protocol of those from group C. Therefore, a total of 18 cats were treated in this study with 100% of efficacy for the protozoan. Based on these results, it is concluded that the secnidazole-based protocol is effective in cats naturally infected by *G. duodenalis*. However, this product is only commercialized for human medicine usage, and from now on it is expected that the industry of veterinary products may consider the commercial production of this medicine for veterinary therapeutic, which would help in the treatment of giardiasis in domestic cats, that are particularly difficult to treat. Despite the promising results achieved with secnidazole further studies with lower doses and different age groups are required, mainly as attempting to dosage reduction and evaluating its effectiveness.

**Ethics committee**

The study was approved by the Committee of Ethics and Animal Welfare of the Rural Science Center of the Federal University of Santa Maria (CCR/UFSM), no 11/2011 in accordance with existing legislation

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**Table 2**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A before treatment</th>
<th>Group A after treatment</th>
<th>Group B before treatment</th>
<th>Group B after treatment</th>
<th>Group C before treatment</th>
<th>Group C after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>29.6 (± 2.01)</td>
<td>33.6 (± 3.1)</td>
<td>28.6 (± 1.5)</td>
<td>29.0 (± 1.2)</td>
<td>32.2 (± 3.90)</td>
<td>32.4 (± 4.40)</td>
</tr>
<tr>
<td>Erythrocytes (10¹²/μL)</td>
<td>5.85 (± 0.46)</td>
<td>6.20 (± 0.30)</td>
<td>6.2 (± 0.48)</td>
<td>5.58 (± 0.4)</td>
<td>6.50 (± 0.68)</td>
<td>6.16 (± 0.76)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.8 (± 0.60)</td>
<td>10.9 (± 1.01)</td>
<td>9.0 (± 0.36)</td>
<td>9.2 (± 0.45)</td>
<td>10.0 (± 1.16)</td>
<td>10.2 (± 1.47)</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>50.7 (± 1.3)</td>
<td>46.6 (± 4.1)</td>
<td>48.2 (± 1.7)</td>
<td>51.9 (± 1.9)</td>
<td>47.3 (± 3.1)</td>
<td>45.5 (± 2.7)</td>
</tr>
<tr>
<td>MCHC (X%)</td>
<td>33.2 (± 0.5)</td>
<td>33.5 (± 0.71)</td>
<td>31.4 (± 0.4)</td>
<td>31.0 (± 0.3)</td>
<td>32.1 (± 0.09)</td>
<td>31.4 (± 0.17)</td>
</tr>
<tr>
<td>Leukocytes (10³/μL)</td>
<td>9.4 (± 2.7)</td>
<td>13.2 (± 0.9)</td>
<td>10.2 (± 4.4)</td>
<td>12.6 (± 3.7)</td>
<td>9.5 (± 4.2)</td>
<td>12.5 (± 2.1)</td>
</tr>
</tbody>
</table>

No statistical difference with the hematological parameters was observed among groups or before and after treatment.

**Table 3**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A before treatment</th>
<th>Group A after treatment</th>
<th>Group B before treatment</th>
<th>Group B after treatment</th>
<th>Group C before treatment</th>
<th>Group C after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (U/L)</td>
<td>54.3 (± 11.7)</td>
<td>79.6 (± 26.7)</td>
<td>69.5 (± 17.1)</td>
<td>76.0 (± 30.1)</td>
<td>62.5 (± 17.0)</td>
<td>92.6 (± 76.1)</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>4.1 (± 1.7)</td>
<td>4.0 (± 1.5)</td>
<td>3.1 (± 0.7)</td>
<td>2.4 (± 0.9)</td>
<td>3.8 (± 2.7)</td>
<td>4.5 (± 3.4)</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>38.4 (± 12.4)</td>
<td>62.1 (± 13.0)</td>
<td>48.0 (± 5.1)</td>
<td>71.9 (± 15.1)</td>
<td>45.5 (± 5.7)</td>
<td>48.6 (± 6.5)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.0 (± 0.11)</td>
<td>1.3 (± 0.12)</td>
<td>1.5 (± 0.3)</td>
<td>1.0 (± 0.2)</td>
<td>1.28 (± 1.14)</td>
<td>1.3 (± 0.25)</td>
</tr>
</tbody>
</table>

No statistical difference with the hematological parameters was observed among groups or before and after treatment. *The high standard deviation observed after treatment in Group C is due to increased ALT and GGT levels in one cat. ALT increased from 61 to 250 U/L and GGT from 2.56 to 7.2 U/L.*

Please cite this article as: Da Silva AS, et al, Secnidazole for the treatment of giardiasis in naturally infected cats, Parasitol Int (2011), doi:10.1016/j.parint.2011.06.024
and the Ethical Principles published by the Brazilian College of Animal Experiments (COBEA).

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