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Corresponding author:
Manuela Schnyder;
Email: manuela.schnyder@uzh.ch

First report of apparent praziquantel resistance in *Dipylidium caninum* in Europe

Andreas W. Oehm[1], Anton Reiter[2], Angela Binz[3] and Manuela Schnyder[1]

[1]Institute of Parasitology, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland; [2]Independent scholar and [3]Tierklinik Aarau West, Oberentfelden, Switzerland

Abstract

Dipylidium caninum is a common tapeworm of dogs. Two cases of praziquantel resistance have been described in *D. caninum* in the United States. No further reports have been published to the authors' knowledge. Here, the case of a dog imported to Switzerland from Spain with a history of chronic excretion of tapeworm proglottids and unresponsiveness to praziquantel treatments is reported. Clinical signs were mild (restlessness, tenesmus, anal pruritus, squashy feces) and flea infestation could be ruled out. Infection with *D. caninum* was confirmed through morphological and genetic parasite identification. Different subsequently applied anthelmintic compounds and protocols, including epsiprantel, did not confer the desired effects. Proglottid shedding only stopped after oral mebendazole administration of 86.2 mg kg^{-1} body weight for 5 consecutive days. Clinical signs resolved and the dog remained coproscopically negative during a follow-up period of 10 months after the last treatment. This case represents the first reported apparent praziquantel and epsiprantel resistance in *D. caninum* in Europe. Treatment was extremely challenging especially due to the limited availability of efficacious alternative compounds.

Introduction

Dipylidium caninum (Cyclophyllidea, Dipylidiidae) is a common intestinal tapeworm of dogs with a worldwide distribution and with zoonotic potential (Gates and Nolan, 2009; Deplazes *et al*., 2021). Especially infants are prone to become infected after ingestion of infected fleas or lice (Elmonir *et al*., 2021) which act as intermediate hosts. In dogs, infections remain subclinical, or manifest with mild and unspecific clinical signs in most cases. Clinical signs may include anal pruritus causing an animal to rub its bottom along the ground, diarrhoea, weight loss, general restlessness or tenesmus (Wani *et al*., 2015; Saini *et al*., 2016). The primary drug of choice to combat infections with *D. caninum* in dogs is praziquantel (at a single dose of at least 5 mg kg^{-1} body weight (BW) *per os* (p.o.)) which usually shows high levels of efficacy (Schroeder *et al*., 2009; Saini *et al*., 2016; ESCCAP, 2021). Another effective treatment option includes epsiprantel (at least 5.5 mg kg^{-1} BW p.o.) (Corwin *et al*., 1989; ESCCAP, 2021).

To date, anthelmintic resistance in canine and feline parasites has been of minor relevance and rather confined to regions and limited in scope, whereas it is a considerable problem in livestock and horses (Raza *et al*., 2018; von Samson-Himmelstjerna *et al*., 2021). Recently, an increasing frequency of reports on multiple anthelmintic resistance of *Ancylostoma caninum* in dog kennels in North America has been addressed as a major concern (Marsh and Lakritz, 2023). Moreover, 2 cases of possible praziquantel resistance have been reported in *D. caninum*-infected dogs in the United States recently (Jesudoss Chelladurai *et al*., 2018; Loftus *et al*., 2022), emphasizing the importance of this matter in companion animals as well. In Europe, no cases of anthelmintic resistance in companion animals have been reported yet. This case represents the first description of clinical resistance to praziquantel in *D. caninum* in Europe.

Materials and methods

Case presentation

A male, mixed breed Can de Chira dog imported from Spain of approximately 10 months of age and weighing 16.7 kg was presented with a history of chronic excretion of tapeworm proglottids after arrival in Switzerland. The dog had been probably born in December 2021 around Monzón or Huesca (municipality of Aragon, Spain) and had been picked up from the street at the approximate age of 4 months together with other dogs of the same age. Subsequently, it had been kept at an animal shelter in Monzón. Clinical signs upon presentation were mild with general restlessness, tenesmus, slight anal pruritus and occasionally squashy feces. No evidence of flea infestation was present, and the dog had received treatment against ectoparasites (fluralaner, unknown dose) and helminths (praziquantel, febantel, pyrantel, unknown dose) before entering Switzerland. In Switzerland, the dog was presented to the primary veterinarian and treated orally with 5.9 mg kg^{-1} BW praziquantel, 5.9 mg kg^{-1} BW pyrantel, 18.0 mg kg^{-1} BW febantel (DrontalPlus®, Vétoquinol) twice within a period of 2 weeks as well as with 14.7 mg kg^{-1} BW fluralaner (Bravecto®, MSD Animal Health).

Flea prophylaxis with fluralaner was pursued every 12 weeks as recommended by the manufacturer. Subsequently, proglottid excretion ceased, but re-started in an unchanged manner 3 weeks after the last treatment with praziquantel/pyrantel/febantel. Hence, the dog received a single dose of 0.7 mg kg^{-1} BW milbemycinoxime and 7.4 mg kg^{-1} BW praziquantel (Milbemax®, Elanco Animal Health). Proglottid shedding continued and fenbendazole (Panacur®, MSD Animal Health) was administered orally for 5 consecutive days at a dose of 44 mg kg^{-1} BW. For 4 days, proglottid shedding ceased, and 0.7 mg kg^{-1} BW milbemycinoxime and 7.4 mg kg^{-1} BW praziquantel (Milbemax®, Elanco Animal Health) were administered orally twice within 2 weeks. Excretion of proglottids continued and 0.7 mg kg^{-1} BW milbemycinoxime and 7.4 mg kg^{-1} BW praziquantel (Milbemax®, Elanco Animal Health) were administered orally once a week for a period of 4 weeks, yet excretion of cestode segments persisted.

Investigations

The presence of eggs/proglottids was examined *via* the adhesive tape method (Deplazes *et al.*, 2021) and proglottids were also directly collected from the surface of the fecal samples. Furthermore, a combined sedimentation–flotation using saturated sodium chloride solution with a specific weight of 1.2 g cm^{-3} was performed on fecal samples (Deplazes *et al.*, 2021). Proglottids were assessed microscopically and egg packets were pressed out from the proglottids in squash preparations. A multiplex polymerase chain reaction (PCR) targeting the mitochondrially encoded 12S ribosomal RNA of non-*Echinococcus* cestodes [267 base pairs (bp)] (Trachsel *et al.*, 2007) was carried out to molecularly confirm the microscopic diagnosis.

Treatments and follow-up

The patient received 31.1 mg kg^{-1} BW pyrantel and 12.0 mg kg^{-1} BW epsiprantel (Dosalid®, Zoetis) in the first place. Next, 50.3 mg kg^{-1} BW mebendazole (Lendue Maxi®, Teknofarma S.r.l.) were administered on 5 consecutive days. Subsequently, 6.0 mg kg^{-1} BW praziquantel, 6.0 mg kg^{-1} pyrantel and 24.0 mg kg^{-1} oxantel (Dolpac 10®, Vétoquinol) were initiated for a total of 6 days. One month after the last treatment with Dolpac 10®, a second round of mebendazole (Lendue Maxi®, Teknofarma S.r.l.) was administered for 5 days, this time at an increased dose of 86.2 mg kg^{-1}. Contemporaneously, the animal owner daily recorded the development of proglottid excretion.

All the compounds mentioned in this section are not commercially available in Switzerland and were purchased in Portugal, Italy or at an international pharmacy after considering the regulations of off-label use in veterinary medicine in Switzerland and following the Swiss compendium of veterinary medicinal products (Tierarzneimittelkompendium CliniPharm, www.vetpharm.uzh.ch). The extension from 3 to 5 days of mebendazole treatment was derived from Miro *et al.* (2007). A detailed temporal pattern of anthelmintic treatments and proglottid excretion is compiled in Table 1.

Results

Based on gross morphological features of the proglottids (size of ~12 mm × 3 mm, mature genital organs, double genital pores slightly behind the middle of the lateral margins of each proglottid) and the eggs (capsulated and clustered in packets of 120–200 μm, with hexacanth embryo), *D. caninum* was diagnosed (Deplazes *et al.*, 2021) (Fig. 1). PCR confirmed an infection with *D. caninum*: a DNA segment of 259 bp was successfully sequenced and nucleotide basic local alignment search tool (BLAST) against the nucleotide collection of GenBank showed an identity of 98.07% (254/259 bp) with *D. caninum* from a canine host (accession number MH182479.1) (Jesudoss Chelladurai *et al.*, 2018). After epsiprantel/pyrantel (Dosalid®, Zoetis) treatment, proglottid shedding continued in an unchanged manner (Table 1). Mebendazole at a dose of 50.3 mg kg^{-1} BW for 5 consecutive days reduced the quantity of the excreted tapeworm segments. These were not superficially located on the feces anymore but mixed within the fecal matter. Moreover, the proglottids appeared macerated and without motility. Re-appearance on the surface, however, occurred 2 weeks after the final administration of mebendazole. The combination praziquantel/pyrantel/oxantel (Dolpac 10®, Vétoquinol) did not stop the excretion of tapeworm segments. Eventually, proglottid shedding stopped from the second day of treatment with mebendazole 86.2 mg kg^{-1} BW (Table 1) and clinical signs (general restlessness, tenesmus, slight anal pruritus, occasionally squashy feces) resolved. Moreover, the shedding of proglottids stopped and the dog remained coproscopically negative for a follow-up period of 10 months.

Discussion

This case represents the first written report of apparent praziquantel resistance in *D. caninum* in Europe. During the investigations for potential alternative anthelmintic treatments, further oral reports from veterinary parasitologists of Italy and Spain were mentioned to the authors (M. Schnyder, personal communication 2023). To confirm that the infection was indeed caused by *D. caninum*, a combination of traditional parasitological and genetic methods was implemented.

Anthelmintic resistance is defined as the ability of helminth parasites to survive the administration of a certain previously effective drug (Prichard *et al.*, 1980; Sangster *et al.*, 2018). According to the VICH (Veterinary International Conference on Harmonization) guidelines (VICH, 2000, 2001), efficacy is described as a reduction of ⩾90% of *D. caninum* scolices in controlled terminal studies. In the current case resistance may be suspected by the fact that multiple doses of praziquantel at the standard label treatment of 5 mg kg^{-1} BW (Schmid *et al.*, 2010) did not stop the continuous excretion of proglottids. Investigating the above-mentioned threshold for a drug to be considered efficacious in a controlled study would have required experimental infections: several factors (i.e. deriving from the individual dog, or being related to the environment, etc.) may in fact influence the presence and quantity of proglottids in feces. Therefore, the absence of proglottids in this case did not allow to finally conclude on the efficacy of an anthelmintic agent, still, this represented the goal for the animal owner. Consequently, in the context of the current case, it was not possible to establish the resistance of the isolate by experimental infection of laboratory animals to further fathom the nature of this resistance, comparable to Jesudoss Chelladurai *et al.* (2018). The efficacy of anthelmintic treatment in the here reported case was instead continuously assessed by documenting the presence and quantity of proglottids excreted in feces, by final determination of the absence of eggs in feces, and by the adhesive tape method. Accordingly, the isolate was not eliminated by the administration of praziquantel at the label dose of 5 mg kg^{-1} BW (Lloyd and Gemmell, 1992; Altreuther *et al.*, 2009, Schroeder *et al.*, 2009) nor by fenbendazole at a dosage of 44 mg kg^{-1} BW (Burke and Roberson, 1978) nor by epsiprantel (combined with pyrantel) at a dose of 12.0 mg kg^{-1} BW, i.e. more than twice as high as the recommended dose of 5.5 mg kg^{-1} BW (Corwin *et al.*, 1989). Interestingly, oral administration of praziquantel/pyrantel/febantel twice within a

Table 1. Observed proglottid shedding and administered medications after antiparasitic treatments with pyrantel, febantel, milbemycinoxime, fenbendazole and fluralaner, and unsuccessful treatments with praziquantel administered to a dog infected with *Dipylidium caninum.* Proglottid shedding stopped for at least 10 months after the last mebendazole administration

	Number of proglottids		
	Assessment time		
Date	Morning	Afternoon/evening	Anthelmintic treatments (compounds, dose, commercial name, company, country of origin)
16/02/2023	Not observed	1	
17/02/2023	9	0	
18/02/2023	10	0	
19/02/2023	1	3	
20/02/2023	13	0	
21/02/2023	5	0	
22/02/2023	16	1	
23/02/2023	0	>20	
24/02/2023	8	0	
25/02/2023	8	0	
26/02/2023	>16	9	
27/02/2023	12	6	Epsiprantel, 12.0 mg kg^{-1} BW/Pyrantel 31.1 mg kg^{-1} BW p.o. (Dosalid®, Zoetis, Portugal)
28/02/2023	1	0	
01/03/2023	4	0	
02/03/2023	9	2	
03/03/2023	5	0	
04/03/2023	15	0	
05/03/2023	21	Not observed	
06/03/2023	13	0	Mebendazole 50.3 mg kg^{-1} BW p.o. (Lendue Maxi®, Teknofarma S.r.l., Italy)
07/03/2023	>7[a]	0	Mebendazole 50.3 mg kg^{-1} BW p.o.
08/03/2023	0	0	Mebendazole 50.3 mg kg^{-1} BW p.o.
09/03/2023	0	0	Mebendazole 50.3 mg kg^{-1} BW p.o.
10/03/2023	0	0	Mebendazole 50.3 mg kg^{-1} BW p.o.
23/03/2023	1	0	
24/03/2023	0	0	
25/03/2023	1	0	
26/03/2023	1	0	
27/03/2023	3	0	
28/03/2023	2	0	
29/03/2023	2	0	
30/03/2023	2	0	
01/04/2023	0	0	
02/04/2023	0	0	
03/04/2023	0	0	
04/04/2023	8	0	Praziquantel 6.0 mg kg^{-1} BW Pyrantel 6.0 mg kg^{-1} BW Oxantel 24.0 mg kg^{-1} p.o. (Dolpac 10®, Vétoquinol, international pharmacy)
05/04/2023	5	5	Praziquantel 6.0 mg kg^{-1} BW Pyrantel 6.0 mg kg^{-1} BW Oxantel 24.0 mg kg^{-1} p.o.
06/04/2023	2	2	Praziquantel 6.0 mg kg^{-1} BW Pyrantel 6.0 mg kg^{-1} BW Oxantel 24.0 mg kg^{-1} p.o.
07/04/2023	2	0	

(*Continued*)

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Table 1. (*Continued.*)

Date	Number of proglottids — Assessment time — Morning	Afternoon/evening	Anthelmintic treatments (compounds, dose, commercial name, company, country of origin)
			Praziquantel 6.0 mg kg^{-1} BW Pyrantel 6.0 mg kg^{-1} BW Oxantel 24.0 mg kg^{-1} p.o.
08/04/2023	4	1	Praziquantel 6.0 mg kg^{-1} BW Pyrantel 6.0 mg kg^{-1} BW Oxantel 24.0 mg kg^{-1} p.o.
09/04/2023	8	0	Praziquantel 6.0 mg kg^{-1} BW Pyrantel 6.0 mg kg^{-1} BW Oxantel 24.0 mg kg^{-1} p.o.
10/04/2023	0	0	
11/04/2023	20	0	
12/04/2023	0	0	
13/04/2023	0	0	
14/04/2023	6	0	
15/04/2023	7	0	
16/04/2023	9	0	
17/04/2023	4	4	
18/04/2023	9	0	
19/04/2023	28	0	
22/04/2023	9	0	
23/04/2023	5	0	
24/04/2023	10	0	
25/04/2023	15	0	
26/04/2023	1	0	
27/04/2023	10	0	
28/04/2023	2	0	
29/04/2023	10	0	
30/04/2023	11	0	
01/05/2023	10	0	
02/05/2023	1	0	
03/05/2023	8	0	
04/05/2023	8	0	
05/05/2023	7	0	
06/05/2023	5	0	
07/05/2023	5	0	
08/05/2023	8	0	
09/05/2023	6	0	
10/05/2023	3	0	
11/05/2023	5	0	Mebendazole 86.2 mg kg^{-1} BW p.o. (Lendue Maxi®, Teknofarma S.r.l., Italy)
12/05/2023	0	0	Mebendazole 86.2 mg kg^{-1} BW p.o.
13/05/2023	0	0	Mebendazole 86.2 mg kg^{-1} BW p.o.
14/05/2023	0	0	Mebendazole 86.2 mg kg^{-1} BW p.o.
15/05/2023	0	0	Mebendazole 86.2 mg kg^{-1} BW p.o.
16/05/2023	0	0	Mebendazole 28.7 mg kg^{-1} BW p.o.

[a]At his point, proglottids were not superficially located on the feces, but rather mixed within the fecal matter and they seem macerated without motility.

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Figure 1. Eggs clustered in packets with hexacanth embryos typical for *Dipylidium caninum*.

period of 2 weeks induced a 3-week suspension of proglottid excretion, suggesting some efficacy. The administration of praziquantel/pyrantel/oxantel had previously been successful in *D. caninum* infections (Grandemange *et al.*, 2007; Jesudoss Chelladurai *et al.*, 2018) and it was hypothesized that oxantel would exert a synergistic effect with the other compounds due to differences in drug action (Martin *et al.*, 2004; Jesudoss Chelladurai *et al.*, 2018). Yet, no reduction in the excretion of proglottids was noticed. In contrast, with mebendazole at the dosage of 50.3 mg kg^{-1} BW for 5 days, a clear reduction of the number of proglottids on fecal samples was observed, but single proglottids were also present after the last day of treatment. Previous studies have indicated an efficacy of oral mebendazole against cestodes (Vanparijs and Thienpont, 1973; Genchi *et al.*, 1990). Side-effects of mebendazole such as vomiting and diarrhoea can occur already when therapeutic doses are administered. Moreover, the compound has been associated with hepatotoxicity visible as icterus, depression or anorexia and side-effects commonly occur 1 day until 2 weeks after administration (Polzin *et al.*, 1981; Swanson and Breider, 1982). In the current case, the dog was closely monitored, and no side-effects of any kind were observed even when mebendazole was given at the increased dose. A thorough surveillance of dogs being treated with this compound seems reasonable, especially if administered off-label. As mebendazole had at least induced an apparent reduction of the number of excreted proglottids, it was decided to increase the dose to 86.2 mg kg^{-1} BW. This eventually turned out to be effective after the failure of multiple agents as well as mebendazole at a lower dose. However, it cannot be excluded that shedding of proglottids stopped due to reaching of the natural lifetime of the parasite (Jesudoss Chelladurai *et al.*, 2018). Yet, the macroscopic appearance of the proglottids and their motility evidently changed after initiation of mebendazole administration supporting the resistance of this *D. caninum* isolate to previous anthelmintic treatments and rather ruling out the potential natural termination of infection.

One aspect to consider was the potential of flea infestation as a source of continuous reinfection of the patient. Consequently, the inability to eliminate the parasite could have been mistakenly interpreted as anthelmintic resistance with only temporary elimination of the infection. Yet, reinfection due to continued flea infestation of the dog appeared extremely unlikely as the dog was repeatedly treated against ectoparasites and in accordance with the information provided by the manufacturer the treatments were still exerting their flea-insecticidal activity during the investigations and their follow-up. Moreover, the owners implemented intensive environmental surveillance for potential presence of fleas as well as environmental decontamination, although indications of flea infestation were absent. Flea absence is further corroborated by the fact that the dog remained negative for a follow-up period of more than 3 months after the last anthelmintic treatment as well as for an extended follow-up period of at least 10 months.

Owner compliance is an obviously relevant aspect in the context of suspected drug resistance when the administration of anthelmintics is delegated to the pet owner. This may include anthelmintics that are not administered in the right dose or frequency (Jesudoss Chelladurai *et al.*, 2018) or if the animal, unobserved, expels orally administered drugs. In the present case, owner compliance, involvement, and engagement were exceptionally high and due to the background of the owner as a medical practitioner, correct observation of the case, meticulous documentation as well as appropriate administration of medications were ensured.

Infections with *D. caninum* in humans are rare, associated with mild clinical signs such as discomfort or gastrointestinal disturbances (Taylor and Zitzmann, 2011; Portokalidou *et al.*, 2018), and mainly limited to cases where flea infestations and oral ingestion of fleas are present, e.g. in infants (Chappell *et al.*, 1990; Molina *et al.*, 2003; Jesudoss Chelladurai *et al.*, 2018). Given the interconnectedness of human and animal health, the emergence of anthelmintic resistance in *D. caninum* could pose a minimal risk to human health as well.

Conclusions

Future investigations are necessary to understand the extent of potential anthelmintic resistance present in *D. caninum* infecting dogs and cats, and the mechanisms involved to confer this resistance. Importantly, notifying the occurrence of similar cases with pharmacovigilance authorities will contribute to better data collection. Major challenges are represented by the limited availability of alternative effective compounds and their restricted availability depending on the country.

Data availability statement. All data have been presented and/or are available on request from the authors.

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Ethical standards. Informed and written consent for the anthelmintic treatments and the coproscopic analyses was obtained from the animal owner.

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