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Antihelminthic effects of active substances moxidectin and praziquantel

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A comprehensive approach to conducting preventive and therapeutic measures involves studying the resistance of parasites to anthelmintic drugs synthesis of new preparations of a wide range of action. The purpose of the study was to compare the effectiveness of the effect of antiparasitic drugs of various dosage forms with the exact content of agents on dogs and cats. The surveyed dogs and cats that come to the shelter for pets were diagnosed by mono- and mixing of helminthiasis. The eggs of helminths (*Dipylidium caninum, Ancylostoma caninum, Toxocara canis, Toxascaris leonina, Trichuris vulpis, Uncinaria stenocephala* and *Dipylidium caninum, Toxocara mystax, Toxascaris leonina,* and *Trichuris vulpis)* induced in the samples of feces from sick dogs and cats, respectively. There is a contamination of dogs and cats with microfilariae. We proved that the most contaminated eggs of helminth objects in indoor premises are gender and inventory. Antiparasitic agents containing moxidectin and praziquantel there are effective anthelminthic during cestodes, nematodes, trematodes, and mixed invasions of dogs and cats, regardless of the form of release (tablets, suspension) in a dose corresponding to the therapeutic concentration of 0.25 mg moxidectin and 5 mg of praziquantel on 1 kg body weight of the animal.
Keywords: invasion, moxidectin, praziquantel, dogs, cats, rooms.

Introduction

The modern anti-episotic measures in parasitic animal diseases include continuous monitoring and predicting outbreaks of invasive diseases, their diagnosis, and treatment (Sharma et al., 2015; Momčilović et al., 2019). This program has a special meaning in the dilution and maintenance of domestic animals (Dysko et al., 2002; Stull et al., 2013).

To date, the role and importance of pets for people have changed somewhat. For most animals in the megalopolis, guarding the premises and fishing rodents is not the main one, and their social function is becoming increasingly important (Hajek & König, 2020; Koyasu et al., 2020; Menchetti et al., 2020). However, there are several risks of infection for humans with causative agents of zoonotic infections from animals through some household trends (direct contact, random bites) (Damborg et al., 2016; Iannino et al., 2018).

In order to minimize the risks of infection of people and ensuring the epizootological well-being of animals, it is necessary to comply with the recommendations on the responsible maintenance of domestic animals, including modern hygiene practice, breeding, feeding, content and mental and physical problems, relevant animal biology (Overgaauw et al., 2020).

Despite the success achieved in the fight against animal diseases and today, there is an acute issue of diagnosis, treatment, and prevention of helminthiasis (Paliy et al., 2021c), reserving environmental objects in order to destroy exogenous steps of parasite development (Paliy et al., 2020a; 2020c). The uncontrolled increase in the number of homeless animals on the streets causes widespread pollution of the environment with exogenous forms of helminths, in turn, causes the spread of invasive diseases among pets (Otranto et al., 2019; Paliy et al., 2019).

Thus, it is reported to a significant role of helminthous invasion among domestic carnivorous animals (dogs, cats) compared to other diseases (Capelli et al., 2018; Anvari et al., 2019). Numerous studies have found that extensively domestic carnivores with toxocarosis, toxascariosis, ancylostomosis, echinococcosis, dipilidiosis, and teniosis in various climatic and landscape-geographical regions is 50-100% (Capelli et al., 2018).
According to its biology, the parasites of animals differ within one species. However, they all harm the host organism (Råberg et al., 2009; Modis, 2012). The most widespread causative agents of helminthiases of dogs and cats in the world of cestodes (*Dipylidium caninum, Taenia pisiformis, T. hydatigera, Hydatigera taeiniaeformis, Echinococcus granulosus, Multiceps multicept, E. multilocularis*) and nematods (*Ancylostoma caninum, Uncinaria stenocephala, Toxocara canis, Toxascaris leonina, Toxocara mystax*) (Cholewiński et al., 2015; Otranto et al., 2019). Mixed helminthiases of carnivorous make up a significant part of all cases of parasitic diseases. Therefore, their therapy is constantly relevant (Khasnis et al., 2005; de Azevedo et al., 2009; Paliy et al., 2021a).
Given the considerable sanitary, epidemiological, and epizootological importance of helminths, the leading importance acquires timely diagnosis and liquidation of parasitic animal diseases (Saini et al., 2016; Paliy et al., 2018) by applying modern, highly efficient drugs (Woods et al., 2011; Monzote, 2014; Paliy et al., 2020b). Today, the pharmaceutical industry is focused on expanding the spectrum of anti-helminth drugs and improving existing drugs (Geary et al., 2004; McKerrow & Lipinski, 2017; Arion et al., 2018).
For drugs that are used in parasitic animal diseases, sufficiently high demands are put forward; first of all, they must be adequate, non-toxic, and have a wide range of action (Monzote, 2014; Shkromada et al., 2019). The active substance of any anti-helminth preparations has a spectrum of biological action and effectiveness for some pathogens (Geary & Thompson, 2003; Rana & Misra-Bhattacharya, 2013).
A comprehensive approach to preventive and therapeutic measures provides for studying the resistance of parasites to anthelmintic drugs, synthesizing new drugs of a wide range of effects, and high-quality disinfection of premises.

Materials and methods

The purpose of the study was to compare the effectiveness of antiparasitic drugs of a different dosage form containing the same active ingredients on dogs and cats of different ages and breeds. In experiments, preparations of domestic production were used:
preparation No. 1 – tablets from white to milk color, 1 tablet (0.25 g) contains active substances: moxidectin – 2.5 mg and praziquantel – 50 mg auxiliary substances: starch, calcium stearate, flavoring, lactose.
preparation No. 2 – is a suspension from white to gray with a specific odor of components, 1 ml of the drug contains active substances: moxidectin – 0.5 mg and praziquantel – 10 mg. Auxiliary substances: xanthan gum, potassium sorbet, bentonite, glycerin, and purified water.
Moxidectin is a semi-synthetic compound of milbemycin groups (macrocyclic lactones), active concerning larvae and adult nematodes. It increases the permeability of the membranes for chlorine ions, suppresses the electrical activity of helminths nerve cells, and causes innervation violation, paralysis, and parasite death (Milton et al., 2020). Moxidectin is quickly absorbed in the gastrointestinal tract, penetrates the systemic bloodstream, and is distributed in the organs and tissues of the animal organism, especially focusing in adipose tissue; excreted mainly with feces (Cobb & Boeckh, 2009).
Praziquantel – Pyrazicohinolin derivative acts on most types of cestodes and trematodes at all stages of development. The mechanism of action lies in depolarization of neuromuscular ganglia, violation of the transportation of glucose and microtubular function in cestodes and trematodes, which leads to paralysis and death of parasites and contributes to their excretion from the animal organism (Cioli & Pica-Mattoccia, 2003; Doenhoff et al., 2008). Praziquantel is quickly absorbed from the gastrointestinal tract, reaching the maximum concentration in the blood plasma after 1-3 hours, and is distributed in the organs and tissues of the animal organism. In part, it is released back into the intestinal lumen, which makes it effective against parasites in the intestinal wall. It is almost completely metabolized in the liver and is excreted within 24 hours, mainly with the urine (Zwang & Olliaro, 2014).
Preparations were used with prophylactic and therapeutic purposes in helminths invasion of pets.
Clinical studies of the drug on dogs and cats to study the therapeutic effect were carried out in the following directions: clinical examination of animals, establishing a preliminary diagnosis, taking diseases of feces for laboratory research, continuous clinical observation of the physiological state of experimental animals; microscopic tests of samples by definition in biological material of pathogens of helminthiasis, their identification, establishing the extensiveness of invasion in dogs and cats; the formation of experimental and control groups of animals; the introduction of drugs, individually, the content of animals, taking samples of feces for a laboratory study after 5, 10, 15 days and 1 month after the last use of drugs; daily clinical examination of the health status of experimental animals during the entire experiment.
Experimental animals: dogs (n=12) of various breeds, with different weight of cats' body (n=22) of various rocks with different body weights.
Venue: The work was performed in the laboratory of veterinary sanitation and the parasitology of the National Scientific Center "Institute of Experimental and Clinical Veterinary Medicine" and in the animal shelter "The Society for the Protection of Animals "Friendship" (Balakley, region Kharkiv).
During the studies, laboratory dishes, microscopes, refrigerators, centrifuge, Petri dishes, substantive and coating glasses, reagents for microscopic studies (glycerin, Lugol solution, sodium chloride are used. Following the tasks assigned, the experiments were carried out by applying visual and microscopic research methods (Robinson & Dalton, 2009; Sepulveda & Kinsella, 2013; Jiménez et al., 2016; Idris et al., 2019).
The intensity of invasion was determined by counting the number of eggs of helminths in 1 g of feces.

With experienced animals, two groups were formed, 6 dogs and 11 cats each, and created identical conditions of detention and content. Drug No. 1 was used individually orally, in the morning hours of feeding with a small amount of feed or was injected into the root of the language at the rate of 1 tablet by 10 kg of body weight of the animal (which corresponds to the therapeutic concentration of 0.25 mg of moxidectin and 5 mg of praziquantel per 1 kg of mass bodies of the animal). Drug No. 2 was used individually orally, in the morning hours of feeding with a small amount of feed or was injected into the root of the tongue with a syringe dispenser at the rate of 0.5 ml of the drug per 1 kg of body weight of the animal (which corresponds to the therapeutic concentration of 0.25 mg moxidectin and 5 mg of praziquantel per 1 kg of body weight of the animal). With therapeutic purpose, the determination of animals was performed twice with an interval of 10-14 days.

Preparations of animals were injected individually in doses corresponding to animal species and mass.

Accounting for research results were carried out after 5, 10, 15, and 30 days after treatment while considering the clinical state of animals, the presence of helminth eggs in feces samples. We determined the change in the extensiveness of the invasion after the use of drugs.

The study of feces samples for the presence of helminth eggs was carried out in a native smear, flotation method according to Fulleborne, and precipitation according to GOST26283 (ST SEV 2647-80) using a light microscope for an increase (×100). The detected eggs of helminths were identified by increasing (×400).

Along with this flotation method, it was investigated by flushed from places where exporting animals were kept (samples were taken from dishes, walls, and gender). The extensiveness of invasion was determined concerning the number of positive samples of feces, in which helminth eggs were revealed to the total number of samples multiplied by 100.

It should be noted that the Balaclesky District of the Kharkiv region of Ukraine is disadvantaged by Dirofilaria of animals and people. Therefore, there was a selection of blood samples from dogs and cats for parasitological studies. The blood test for the presence of microfilariae was carried out by direct microscopy of a drop of fresh blood under a slight increase in the microscope (×10) – the easiest, convenient and fast method of diagnosis of Dirofilaria. The movable parasite larvae are noticeable by their active movement between erythrocytes. Also used concentration methods of research (modified KNOTT method). The KNOTT test discovers all the microfilariae available in the blood regardless of the genus and species (it may not only represent the kind of Dirofilaria). The method is as follows: 10 ml of 2.0% solution of formalin was added to 1 ml of venous blood. This solution was well stirred and centrifuged at 1500 across./min for 5 minutes. The supernatant was removed, and the precipitate was mixed with an equal volume of methylene blue in dilution 1:1000 and left for staining for 5 minutes. The microscopy of the sediment was performed to identify fixed microfilariae (Knott, 1939; Weil & Ramzy, 2007). The microscopic identification of the larvae Dirofilaria L1 was performed in a native blood smear and serum. Several milliliters of venous blood from the animal was poured into the test tube to explore the serum. When blood is coagulated, microfilariae migrate to serum. Blood serum with clot was settled in a tube for 2 hours. After that, a parser pipette was taken by several droplets of the serum from the bottom of the test tube or the scene on the border of the serum and the blood bunch. These drops were placed on the slide, covered with a cover, and investigated under a slight increase in the microscope for the presence of moving microfilaria (Chungpivat & Taweethavonsawat, 2008).

The extent efficiency (EE) of drugs was calculated from the number of treated animals in percent.

The statistical processing of the results of studies was carried out by determining the average arithmetic (M), the statistical error of the average arithmetic (m).

Experiments conducted on animals do not contradict international bioethics standards (materials of the IV European Convention on the Protection of Vertebles Animals used for experimental and other purposes (Strasbourg, 1985) (Council Directive 86/609 /EEC).

Results and discussion

As a result of a clinical examination of sick dogs and cats, we registered animal weight loss, digestive disorders, soft wool. With satisfactory feeding, animals did not gain weight; young individuals did not grow. We took the feces from these animals for laboratory testing (Table 1). In the room where the animals were kept, we made the flushes to study contamination with exogenous forms of helminths.

Table 1. Determination of the extensiveness and intensity of helminths invasion (qualitative and quantitative composition) in dogs (n=12) and cats (n=22)

Species of helminths	Extensiveness invasion (EI), %	Intensity invasion (II), number eggs in 1 g feces
	Dogs	
Dipylidium caninum	50	132±10
Ancylostoma caninum	8.3	77±20
Toxocara canis	41.7	35±10
Toxascaris leonina	8.3	38±25
Trichuris vulpis	16.7	15±10
Uncinaria stenocephala	16.7	15±10
	Cats	
Dipylidium caninum	36.4	105±5
Toxocara mystax	54.5	30±15
Toxascaris leonina	9.1	25±15
Trichuris vulpis	4.5	15±10

In parallel, the sampling of blood samples from dogs and cats for parasitological studies for the presence of microfilariae was taken (Table 2).

According to the study results (Table 1), *Dipylidium caninum* monoinvasion we found in 3 dogs, 25% of the invasive, the *Toxocara canis* monoinvasion we also found in 2 dogs, it is 16.7%. Monoinvasion microfilarias detected in 1 dog – 8.3%. Mixinvasion helminths we found in 6 animals, which is 50%. *Dipylidium caninum* mono-invasions were discovered only in 2 cats, 9.1%, and Toxocara mystax – 6 animals, 27.3%. Monoinvasion microfilariae from cats we not found. Invasion two types of helminths we found in 10 animals, 45.5%, three species of 4 animals – 18.2%. So, the mixing of cats occurred at 13.7% more often. The greatest extensiveness of invasion in dogs was Cestoda *Dipylidium caninum* – 50% with the intensity of invasion 132±10 eggs in 1 g of feces, in cat's Nematoda *Toxocara mystax* – 54.5% for II – 30±15 eggs in 1 g of feces.

Table 2. Determination of extensiveness and intensity of Microfilaria invasion in dogs (n=12) and cats (n=22)

Species of animal	Number of blood samples examined	Number of positive samples	*Dirofilaria* spp.	
			EI, %	II, the average number of microfilariae in blood smear
dogs	12	4	33.3	6.5±1.5
cats	22	4	18.2	4.5±0.5

In addition to studying samples of biological material from animals, the level of contamination of objects in the shelter for pets with helminths eggs was determined (Table 3).

Table 3. Determination of extensiveness and intensity of contamination with exogenous forms of helminths in premises by animal maintenance

Test object	Extensiveness invasion (EI), %	Intensity invasion (II), number eggs in 1 sample
	Dogs	
Dishes	–	–
Wall	–	–
Floor	100	2.5±0.5
Cleaning equipment	100	4.5±2.5
	Cats	
Dishes	–	–
Wall	–	–
Floor	10	1.0±0.5
Cat tray	60	1.5±0.5
Cleaning equipment	100	3.5±0.5

Note: "–" – there is no contamination with exogenous forms of helminths.

According to the results of the studies (Table 3), it was found that the most contaminated helminths eggs in the dog maintenance rooms are floor and equipment, and in the cat maintenance room – equipment and trays with different intensity of invasion.

The study of the therapeutic effectiveness of the test preparations in dog and cat helminthiasis after their treatment is shown in Tables 4 & 5.

Table 4. Study of the therapeutic effectiveness of the studied drugs on dogs

Before treatment		After treatment							
		5 day		10 day		15 day		30 day	
EI, %	II, average	EI, %	II	EI, %	II	EI, %	II	EI,%	II
				preparation No. 1 (n=6)					
100	35.6	16.7	2.5	8.3	2.5	0	0	0	0
				preparation No. 2 (n=6)					
100	35.8	16.7	2.0	8.3	2.0	0	0	0	0

After the use of drugs in dogs, increased individual sensitivity was not noted.

The presence of segments of *Dipylidium caninum* was revealed for ten days. After using anthelmintic drugs in dogs, the extensiveness of invasion decreased by 83.3%. Mean infection intensity decreased by 65.3% and 72.4%, respectively, to mean

infection intensity before treatment. From 10 days to 30 days of observation in animal feces, helminths eggs were not found; therefore, the extent efficiency of the drugs is 100%.

Table 5. Study of the therapeutic effectiveness of the studied drugs on cats

Before treatment		After treatment							
EI, %	II, average	5 day		10 day		15 day		30 day	
		EI, %	II	EI, %	II	EI, %	II	EI, %	II
preparation No. 1 (n=11)									
100	6.80	4.5	0.5	0	0	0	0	0	0
preparation No. 2 (n=11)									
100	6.75	4.5	0.5	0	0	0	0	0	0

After using drugs in four cats, hypersalivation was observed, which disappeared after 15 minutes, and then they were noted for drowsiness, lack of appetite; the animals did not approach food but drank much water during the first day. Deviation of sexually mature forms of helminths with feces was observed in animals from day 2 to 6; no complications or changes in the clinical condition of experimental animals were observed from 2 days onwards. The extensiveness of invasion in cats decreased by 95.5% after using anthelmintic drugs. The average invasion intensity decreased by 63.7% and 63.6%, respectively, to the average intensity of invasion before processing. From 10 days to 30 days, observations in the animal feces have not detected helminths eggs; therefore, the extent efficiency of drugs is 100%.

The summary of the results was established that the extension of the studied drugs in the determination of dogs and cats during mono and mixing of helminths was 100%. The study of the samples of flushes from the animal enclosures for the presence of exogenous forms of helminths is presented in Table 6.

Table 6. Determination of extensiveness and intensity of contamination with exogenous forms of helminths in premises by animal maintenance

Object	Before treatment of animals		After treatment of animals					
			5 day		10 day		30 day	
	EI, %	II	EI, %	II	EI, %	II	EI, %	II
			Dogs					
floor	100	2.5±0.5	100	1.5±1.0	0	0	0	0
cleaning equipment	100	4.5±2.5	100	2.5±2.0	0	0	0	0
			Cats					
floor	10	1.0±0.5	5	1.0±0.5	0	0	0	0
cat tray	60	1.5±0.5	30	1.5±1.0	0	0	0	0
ceaning equipment	100	3.5±0.5	50	1.5±1.0	0	0	0	0

As can be seen from Table 6, the 5th day after deworming of contamination with exogenous forms of helminth in the rooms where animals are kept is reduced, and no exogenous forms of helminths were found in the rooms for experimental and control animals from 10 to 30 days. Reducing the contamination by exogenous forms of helminths in the premises, where they contained cats, passed more intensively. In our opinion, this is because cats were quickly freed from sexually mature forms of helminths, and they also lack manifestations of coprophagy. Animals found microfilariae in blood strokes were processed twice with an interval of 10 days, but rare microfilariae detected up to 15 days in the smears; for 30 days, microfilariae in the blood did not detect (Table 7).

In April, the animals were injected once with drugs. In April, May, and early June, there was no microfilaria in blood samples of experimental and control animals. Summarizing the results is determined that the extent efficiency (EE) of research drugs in treating and preventing dirofilariasis is 100%.

Angiostrongylus vasorum did not reveal in our studies, as the area of this pathogen is Western Europe (United Kingdom, Ireland, France, Spain), infection *Ancylostoma tubaeforme* is inherent in the wild species of the Feline family. Invasion *Echinococcus granulosis* and *Echinococcus multilocularis*, *Taenia* spp. they are found among shepherds and service dogs, which are fed the waste of slaughter of animals. Invasion of trematodes (*Opisthorchis* spp.) was not found in dogs and cats since these helminthiases are characteristic of animals living near reservoirs and eating fish. Invasion by cestodes (*Mesocestoides* spp.) is

found in carnivores and can move in wildlife and catches small vertebrates. In dogs and cats in Europe and Ukraine, invasion is more common in rural areas, where animals are infected by invasive rodents (Crosbie et al., 2000).

Table 7. Study of the therapeutic effectiveness of investigated preparations on animal invasion Microfilaria

Groups of animals	Before treatment		After treatment							
	EI, %	II, average	5 day		15 day		30 day		45 day	
			EI, %	II	EI, %	II	EI, %	II	EI, %	II
				Dogs						
preparation No. 1 (n=2)	100	6.80	50	0.5	25	0.5	0	0	0	0
negative the control	0	0	0	0	0	0	0	0	0	0
preparation No. 2 (n=2)	100	6.80	50	0.5	25	0.5	0	0	0	0
negative the control	0	0	0	0	0	0	0	0	0	0
				Cats						
preparation No. 1 (n=2)	100	6.75	50	0.5	25	0.5	0	0	0	0
negative the control	0	0	0	0	0	0	0	0	0	0
preparation No. 2 (n=2)	100	6.75	50	0.5	25	0.5	0	0	0	0
negative the control	0	0	0	0	0	0	0	0	0	0

According to foreign authors of praziquantel, it has an influential effect against these pathogens (Schimmel et al., 2009; Shepherd et al., 2018; Vienažindienė et al., 2018). Along with this, other researchers have also established the high therapeutic efficacy of drugs developed based on moxidectin and praziquantel in nematodes and cestodes of dogs and cats of different age groups (Arisov et al. 2015; 2016). It has also been established that these drugs are used when used in double and five times an increased therapeutic dose for seven days do not show a negative effect on the general condition of animals, their physiological status and behavior, do not change the morphological composition of blood and physicochemical indicators of urine (Arisov et al., 2015). It was registered that the combination of moxidectin and albendazole exceeds the action of only one moxidectin (Keller et al., 2020). It has been proven that moxidectin is safe and well-tolerated by humans when used in a dose of 3 mg to 36 mg (Cotreau et al., 2003). In addition to the planned and forced deworming of domestic animals, veterinary and sanitary measures to combat ectoparasites of animals are necessary (Taylor, 2001; Pereira et al., 2016; Paliy et al., 2021c), disinfection (Rodan & Sparkes, 2012; Sykes & Weese, 2014; Paliy et al., 2020a) and the eradication of synanthropic rodents (Leirs et al., 2001; Mikhail & Hasan, 2016; Paliy et al., 2021b).

Conclusions

Are diagnosed for a dog which contains in an animal's shelter as mono- and mixed invasions by helminths *Dipylidium caninum, Ancylostoma caninum, Toxocara canis, Toxascaris leonina, Trichuris vulpis, Uncinaria stenocephala* in the extensiveness of an invasion from 8.3 to 50% and intensity of an invasion from 3 to 50% and intensity of invasion from 15±10 to 132±10 eggs of helminths in 1 g of feces. Cats are diagnosed with *Dipylidium caninum, Toxocara mystax, Toxascaris Leonina, Toxocara mystax, Toxascaris leonina, Trichuris vulpis* on the extensiveness of invasion from 4.5 to 36.4% and intensity of invasion from 15±10 to 105±5 eggs of helminths in 1 g of feces. Infection of dogs and cats by microfilariae with an invasion intensity of 33.3% and 18.2%, respectively, was established. The objects most contaminated with helminths eggs in pet premises are floor and inventory in pollution intensity from 2.5±0.5 to 4.5±2.5 eggs of helminths in 1 sample.

We established that antiparasitic agents containing moxidectin and praziquantel in their composition are effective antihelminthics during cestodes, nematodes, trematodes, and mixed invasions of dogs and cats independently of the dosage form (tablets, suspension). The test drugs may be administered to the animal to deworm individually orally, during the morning feeding hours with a small amount of fodder, or forced on the root of the tongue is administered at a dose corresponding to a therapeutic concentration of 0.25 mg of moxidectin and 5 mg of praziquantel per 1 kg of animal body weight.

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