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COMPARATIVE EVALUATION OF THE APPLICATION OF MODERN ECTOPARASITICIDES

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Summary. Despite the success achieved in the control of parasitic animal diseases, there are still some issues that need to be scientifically sound. The issue of prevention and treatment of animals affected by ectoparasites is especially relevant. The study aimed to establish and experimentally confirm the effectiveness of innovative ectoparasiticides for dogs and cats for prevention and therapy in parasitic infections. Innovative antiparasitic drugs with the main active ingredient imidacloprid were used in the experiments: 'MegaStop for dogs' (drops for external use, spot application), 'Golden Defence for dogs spot-on', 'MegaStop for cats' (drops for external use, spot application), 'Golden Defence for cats spot-on'. Following the objectives of the study, we used visual and microscopic methods in accordance with existing practical manuals and current guidelines. According to the results of the research, a stable infection of experimental dogs with fleas was established at the mean intensity of 7.5 ± 2.0 parasite individuals per 10 cm^2 of animal skin, and otodectosis, sarcoptosis, and notoedrosis were diagnosed separately in some animals. Experimental cats were diagnosed with otodectosis, notoedrosis, sarcoptosis, demodicosis by clinical signs. Parasitism of fleas on the animal bodies was detected, and in one animal heartworm disease was diagnosed. The mean intensity of flea infection in cats ranged from 8 to 12 parasite individuals per 10 cm^2 of skin, and the mean intensity of mite infection was 2–3 mites in the field of view of the microscope. High activity of 'MegaStop for dogs', 'Golden Defence for dogs spot-on', 'MegaStop for cats', 'Golden Defence for cats spot-on' as agents with a broad spectrum of action against fleas (*Ctenocephalides* spp.), acariform mites (*Otodectes cynotis*, *Notoedres cati*, *Sarcoptes sapis*), mites of the genus *Demodex*; heartworm (effective against L3 and L4 larvae of *Dirofilaria immitis*) has been established

Keywords: antiparasitic drugs, dogs, cats, fleas, acariform mites, *Demodex* spp., microfilariae

Introduction. Despite the success achieved in the control of animal diseases, there are still many veterinary issues related to the control and prevention of infectious and parasitic pathologies (Pereira et al., 2016; Lappin et al., 2017; Paliy et al., 2020). The fight against ectoparasites of animals remains a particularly important issue today (Xhaxhiu et al., 2009; Colella et al., 2020).

Ectoparasites are not only pathogens of a particular group of diseases, but also carriers of viral, bacterial, protozoan, rickettsial diseases and mycoses of animals and humans (Spinage, 2012; Fong, 2017). The spread of ectoparasitosis among animals is facilitated by the uncontrolled increase in the number of stray animals on the streets (Becker et al., 2012; Szwabe and Blaszkowska, 2017; Otranto et al., 2017).

The most common ectoparasites of domestic animals are fleas (Siphonapteridae: *Ctenocephalus canis*) (Iannino et al., 2017). They can be mechanical and biological vectors of pathogens, as well as intermediate hosts of cestode *Dipylidium caninum* and filariasis of dogs *Dipetalonema reconditum* (Abdullah et al., 2019). Flea bites are painful, cause itching, inflammation of the skin, which causes weight loss in animals (Coşkun and Çetin, 2018). In young animals, there is progressive depletion, anemia. Puppies can die in the event of a high intensity of infection. Animals affected by fleas gnaw fur and injure the skin. The skin is covered with ulcers, hair falls out, the skin spreads an unpleasant odor (Bond et al., 2007; Farkas et al., 2009; Rust, 2017).

Scabies mites (*Otodectes cynotis*, *Notoedres cati*, *Sarcoptes sapis*, *Demodex* spp.) cause skin inflammation, sometimes severe itching, partial alopecia, irritability in animals, and decreased immunity (Moog et al., 2021). Animals affected by parasites grow poorly, do not gain weight with a good diet, have disorders of the digestive tract and respiratory system (Khalil et al., 2017; Arlian and Morgan, 2017).

Along with ectoparasites, pets can be affected by pathogens of endoparasitic diseases, which requires appropriate attention in the prevention and control of them (Jones and Garcia, 2019; Paliy et al., 2021a).

Successful control of invasive animal diseases is possible only in the presence of highly effective veterinary drugs (Pink et al., 2005; Paliy et al., 2021d). The market in Ukraine is provided with expensive imported veterinary drugs. Recommendations for their use are often developed without taking into account the current epizootic situation, animal resistance and environmental impact of local factors.

Providing animal owners with the necessary range of effective and inexpensive means of combating ectoparasite diseases, in convenient forms — the path to well-being for these diseases (Woods and Williams, 2007; Mukherjee et al., 2016).

The therapeutic efficacy of chemotherapeutic agents for the treatment of invasions depends primarily on the chemical activity of the active substance. However, it has been found that the pharmaceutical form and technology

of manufacture of drugs, their physical condition, properties of constituent components, application methods are also important (Mäser et al., 2012; Paliy et al., 2021c).

Antiparasitic drugs belong to different classes of compounds. They are usually effective against a narrow range of pathogens, which encourages pet owners to use dozens of drugs for the treatment and prevention which are not perfect in action on the animal and are dangerous in environmental terms. Therefore, specialists have always been interested in the possibility of creating and using drugs with a broad spectrum of action (Martin and Robertson, 2010; Paliy et al., 2021b).

In recent years, manufacturers have proposed several tools that are used for therapeutic and prophylactic purposes in animal ectoparasitosis at all stages of parasite development and prevention and treatment of helminthiasis (Rajput et al., 2006).

The effectiveness of the drug can be estimated by the spectrum of its action. In addition, the effectiveness of the drug is characterized by improving the clinical condition of sick animals, the speed of their recovery, tolerance to the drug, the manifestation of adverse reactions (Geary, Conder and Bishop, 2004; Molento, 2009).

Thus, timely diagnosis, treatment and prevention of ectoparasitosis among homeless and domestic animals, especially in cities, are of great sanitary and epidemiological importance (Wall, 2007).

The aim of the study was to establish and experimentally confirm the effectiveness of innovative ectoparasiticides for dogs and cats for prophylactic and therapeutic purposes in parasitic infections.

Material and methods. Studies to determine the effectiveness of insecticides on dogs and cats were conducted in the Laboratory of Veterinary Sanitation and Parasitology of the NSC 'Institute of Experimental and Clinical Veterinary Medicine' and at the animal shelter (Balakliia, Kharkiv Region).

Innovative antiparasitic drugs were used in the experiments:

— 'MegaStop for dogs' (drops for external use, spot application) (Ukraine). 1 ml of the drug contains active substances: imidacloprid — 100 mg, ivermectin — 25 mg; excipients: N-methylpyrrolidone, dimethyl sulfoxide, PEG-400;

— 'Golden Defence for dogs spot-on' (Ukraine). The drug contains active substances: imidacloprid — 12%, moxidectin — 3%; excipients: benzyl alcohol, H-methyl pyrrolidone, caprylic triglyceride, PEG-400;

— 'MegaStop for cats' (drops for external use, spot application) (Ukraine). 1 ml of the drug contains active substances: imidacloprid — 100 mg, ivermectin — 10 mg; excipients: N-methyl pyrrolidone, dimethyl sulfoxide, PEG-400;

— 'Golden Defence for cats spot-on' (Ukraine). The drug contains active substances: imidacloprid — 11%, moxidectin — 1.2%; Excipients: benzyl alcohol, H-methyl pyrrolidone, caprylic triglyceride, PEG-400.

Research scheme:

— clinical examination of animals in the shelter, establishment of a preliminary diagnosis, sampling of ectoparasites and skin scrapings for laboratory examination, continuous clinical monitoring of the physiological condition of experimental animals;

— microscopic studies of samples to determine of pathogens of parasitic diseases in the biological material, their identification, determination of mean intensity of infection in dogs and cats;

— formation of experimental and control groups of animals;

— application of drugs externally, individually, directly on the skin, keeping animals in the shelter, taking samples of scrapes for laboratory testing 5, 10, 30, and 45 days after the last application of the drug. Determination of the effectiveness of the drug.

— daily clinical examination of the health of the experimental animals throughout the experiment.

Experimental animals: the study involved 18 purebred dogs of different ages with a body weight from 3 to 20 kg, 16 purebred cats of different ages. Animals were kept in typical aviaries at an air temperature of 24.0 ± 1.5°C, relative humidity 40–70%, air movement 0.2–0.5 m/s. Animals were fed according to the ration approved by the shelter.

In accordance with the objectives, the study was conducted by visual and microscopic methods in accordance with practical guidelines (Vasil'kova, 1955; Yuskiv, 1998; Halat et al., 2009).

Intravital diagnosis of ectoparasitosis was performed and the number of ectoparasites was determined. Identification of ectoparasitic pathogens was performed by microscopic method. The mean intensity was determined by counting ectoparasites per 10 cm^2 area of the animal's skin. Intravital diagnosis of helminthiasis was also performed. For this faeces and blood samples were taken. Identification of pathogens was performed by microscopic method (Kuzmin, 1998). The mean intensity was determined by counting the number of helminth eggs in 1 g of feces and the number of microfilariae in the blood smear.

Sick dogs were divided into two groups, which were separately applied the drug 'MegaStop for dogs' (drops for external use, spot application) (n = 10) and the drug 'Golden Defence for dogs spot-on' (n = 8). Clinical examination of animals was performed before, during, and after treatment. The external examination included an assessment of the general appearance, condition of the skin and coat, measurement of body temperature, pulse and respiratory rate, examination of eyes, mouth, and ears, palpation of the skin and peripheral lymph nodes.

From cats diagnosed with ectoparasitic infection we formed experimental groups: Group 1 (n = 4) — fleas, demodicosis; Group 2 (n = 2) — fleas, otodectosis, notoedrosis, sarcoptosis; Group 3 (n = 2) — fleas, heartworm disease (*Dirofilaria immitis* larvae stage L3 and L4); Group 4 (n = 6) — fleas, demodicosis; Group 5 (n = 2) — fleas, otodectosis, sarcoptosis.

In 5th, 10th, 20th, and 30thday after treatment, the results of studies were recorded on the basis of examinations of treated animals, counting of live ectoparasites on them and determined the prevalence and effectiveness of the drug after treatment.

To collect ectoparasites from animal skin, they were fixed in a supine position. Examination of the skin of the animals began with the head. Then we examined the neck, back, sides, abdomen, and limbs. The fur was parted and combed during the inspection. We examined first with the naked eye, and then — with a magnifying glass.

Detected ectoparasites were removed from the skin of animals with tweezers or by hand in a rubber glove. Removed ectoparasites were placed in a glass vessel filled with Barbagalo liquid (3% aqueous formalin solution in saline) or 70% ethanol.

Some ectoparasites were delivered alive to the laboratory in test tubes or containers with moist filter paper inside. The strips of filter paper were moistened with boiled water. Tubes and jars were covered with a layer of cloth and tied. A label was to each test tube and jar.

When sampling for acariform mites, scrapings from animals were taken both from the affected areas and from the inner surface of the ear with a blunt scalpel on the border of healthy and affected areas of skin. The skin was scraped until capillary bleeding was observed (no more than 0.5 cm^3), skin peels were placed in a tightly closed test tube and labeled.

The selected material was examined no later than 72 h after scraping. The material was studied by mortal methods (detection of dead mites) and biotic methods (detection of live mites, larvae, and eggs) (Vodianov, Lutsuk and Tolokonnikov, 2009).

The diagnosis of heartworm disease was established by microscopic examination for the detection of microfilariae in a thick drop of peripheral blood and serum (modified Knott method), by enriched smear method, by cytological examination of punctures obtained from pseudotumor and ulcerative lesions of the skin and soft tissues, as well as ascitic fluid. In addition, a test was performed for antibodies produced in response to the presence of L4, immature and mature helminths.

To examine dust and debris from the enclosures where the treated animals were kept, a sample weighing 30 g was placed in a cylinder or conical flask, filled with water and mixed thoroughly. The particles that surfaced were removed and the water was carefully drained, leaving a sediment. The sediment was mixed with 20 parts of saturated salt solution and precipitated for 20 min.

Later, a sample (three drops) was removed from the surface of the flotation film with a wire loop, placed on a glass slide, covered with a cover glass and examined under a microscope

Prevalence (P) was defined as the ratio of the number of infected animals to the number of examined animals, expressed as a percentage:

$$P = \frac{X}{Y} \times 100,$$

where: X — number of animals with detected ectoparasites, microfilariae;
Y — total number of animals.

The mean intensity (MI) was determined by the number of ectoparasites per 10 cm^2 of animal skin, the number of nymphs and adults in skin scrapings, microfilariae in blood smears.

Effectiveness (E) of the drug was calculated by the number of treated animals in the percentage that were completely free of parasites.

To determine the acaricidal action of 'MegaStop for cats' and 'Golden Defence for cats spot-on' against fleas, two experimental and one control groups of fleas from cats were formed. Experimental groups of fleas were treated separately with the studied agents, the control group was not treated. The experiments were performed in glasses of 250 cm^3. Fleas were immobilized by carbon dioxide. The drug was applied on fleas using a microsyringe. The glasses were covered with gauze and rubber rings. The glasses were left at a temperature of 20–25°C indoors.

Determination of 'knockdown effect' in fleas in each glass was performed after 6, 12, and 24 h.

Experiments on animals were conducted following the recommendations of the 'European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes' (CE, 1986) and Council Directive 86/609/EEC (CEC, 1986), and in accordance with Art. 26 of the Law of Ukraine No. 3447-IV of 21.02.2006 'About protection of animals from cruel treatment' (VRU, 2006) and basic bioethical principles (Simmonds, 2017).

The research program was reviewed and approved by the Bioethics Commission of the National Scientific Center 'Institute of Experimental and Clinical Veterinary Medicine' in the current order.

Results and discussions. As a result of a clinical examination of sick dogs, redness, inflammation of the skin, a well-marked itching reflex, papules and scales were found. Visible areas of alopecia. The skin in the affected areas was rough and cracked. The animals were exhausted.

The results of laboratory studies of biological material selected from dogs are given in Table 1.

Visual examination revealed persistent flea infection in all dogs, demodicosis was detected in two dogs along with fleas, otodectosis was detected in two animals, sarcoptosis in two dogs, and notoedrosis in one animal. The mean intensity of flea infection in dogs was 7.5 ± 2.0 individuals per 10 cm^2 of animal skin area.

A clinical examination of 16 cats kept in an animal shelter revealed that fleas parasitized on all animals, and the inner surfaces of the ears were affected. Animals were constantly itching, combing their ears, sitting with their heads down.

Table 1 — Prevalence and mean intensity of parasite infection in dogs (n = 18)

Species of parasites	P, %	MI
Ectoparasites		
Ctenocephalus canis	100.0	7.5 ± 2.0 per 10 cm^2
Sarcoptes canis	11.1	4.5 in sight
Otodectes cynotis	16.7	3.3 in sight
Notoedres cati	9.7	1.2 in sight
Demodex canis	11.1	3.5 in sight
Endoparasites		
Dipylidium caninum	100.0	13.1 ± 1.0
Ancylostoma caninum	50.0	3.5 ± 1.5
Toxocaris leonina	10.0	3.5 ± 2.5
Toxocara canis	100.0	3.5 ± 1.5
Toxocaris leonina	20.0	2.5 ± 1.5
Dirofilaria spp.	11.1	2.5 ± 1.5 in a smear

In 6 cats, purulent exudate is secreted from the ears. According to clinical signs, otodectosis (*O. cynotis*), notoedrosis (*N. cati*), sarcoptosis (*S. canis*), demodicosis, fleas (*C. felis*) were preliminarly diagnosed.

One animal was diagnosed with cough and dyspnea, as well as non-food vomiting. This gave us a reason to establish a preliminary diagnosis of heartworm disease. Cat fleas (*C. felis*) and mites (*O. cynotis*, *N. cati*, *S. canis, Demodex* spp.) were found in cats.

The intensity of flea infection ranged from 8 to 12 fleas per 10 cm^3 of skin area. The prevalence was 100%. The mean intensity of mite infection was 2–3 mites in the field of view of the microscope. One animal was diagnosed with heartworm disease — 1–2 microfilariae in a smear.

The result of determining the rate of the 'knockdown effect' of fleas under the action of the veterinary drug 'MegaStop for cats' and 'Golden Defence for cats spot-on' with topical application is given in Table 2.

Table 2 — Effectiveness of drugs with topical application

Species of parasites	Number of parasites	'Knockdown effect', after		
		6 h	12 h	24 h
'MegaStop for cats'				
C. felis	10	9	1	–
'Golden Defence for cats'				
C. felis	10	8	2	–
Control				
C. felis	10	–	–	–

The 'knockdown effect' in all fleas began 6 h after exposure, and 12 h later there was a complete 'knockdown' of all experimental fleas.

Subsequently experimental groups of animals were applied with veterinary drugs individually, point wise according to the instructions.

Thus, from the 2nd to the 7th day after treatment, dead fleas were found on treated dogs. On day 10, no fleas were found on the animal bodies. On the 30th day after the application of the drugs, fleas were not detected on the animal bodies (Tables 3, 4).

Table 3 — Insecticidal action of 'MegaStop for dogs' and 'Golden Defence spot-on for dogs' against fleas on dogs

Group of animals	Before treatment		After treatment, day							
			5		10		15		30	
	P, %	MI, average	P, %	MI	P, %	MI	P, %	MI	P, %	MI
Experimental group I (n = 10)	100	8.25	20	2.5	0	0	0	0	0	0
Experimental group II (n = 8)	100	7.75	12.5	2.0	0	0	0	0	0	0

Table 4 — Results of the study of skin scrapings from dogs with acarosis after treatment with 'MegaStop for dogs' and 'Golden Defence for dogs spot-on'

Group of animals	Before treatment		After treatment, day							
			5		10		20		30	
	P, %	MI, average	P, %	MI	P, %	MI	P, %	MI	P, %	MI
Experimental group I (n = 10)	100	3.8	20	2.5	10	1.5	10	0.5	0	0
Experimental group II (n = 8)	100	3.75	12.5	2,0	0	0	0	0	0	0

Effectiveness of 'MegaStop for dogs' and 'Golden Defence for dogs spot-on' in industrial trials for flea infection of dogs was 100%.

Effectiveness of 'MegaStop for dogs' and 'Golden Defence for dogs spot-on' in industrial trials in dogs with demodicosis, otodectosis, notoedrosis, and sarcoptosis was 100%.

The results of determining the therapeutic efficacy of the studied drugs in cats are presented in Table 5.

According to the results of studies on the use of 'MegaStop for cats' and 'Golden Defence for cats spot-on' against ectoparasites of animals, it has been found that on the 2nd day after application of the drug on animals dead fleas were detected. Dead ectoparasites on animals were detected up to the 7th day, and on the 10th day, fleas were not observed on the bodies of animals.

No fleas were detected on the animal bodies during observation for 60 days.

When using drugs against otodectosis, notoedrosis, sarcoptosis, demodicosis, one mite was detected in the field of view of the microscopeafter the first treatment, after the second treatment, mites were not detected.

Table 5 — Effectiveness of the drug against pathogens of parasitic diseases

Group of animals	Species of ectoparasites	Before treatment		After treatment
		P, %	MI	E, %
Experimental group 1 (n = 4)	*C. felis*, *Demodex* spp.	100	8–12 2–3	100 (not found)
Experimental group 2 (n = 2)	*C. felis*, *O. cynotis*, *N. cati*, *S. canis*	100	8–12 2–3	100 (not found)
Experimental group 3 (n = 2)	*C. felis*, *D. immitis*	100	8–11 1–2	100 (not found)
Experimental group 4 (n = 6)	*C. felis*, *Demodex* spp.	100	8–11 2–3	100 (not found)
Experimental group 5 (n = 2)	*C. felis*, *O. cynotis*, *S. canis*	100	8–11 2–3	100 (not found)

No complications or changes in animal clinical status were observed during treatment and during clinical observation of experimental and control animals.

Effectiveness of 'MegaStop for cats' and 'Golden Defence for cats spot-on' when used to treat cats with ectoparasites (fleas, scabies mites) is 100%. The results of the study of bedding samples from aviaries where treated animals were kept for the presence of larvae and adults of ectoparasites are presented in Table 6.

Table 6 — The results of analyzes of bedding samples from aviaries for the presence of larvae and adults of ectoparasites

Test method	Number of larvae and adults of ectoparasites in the bedding	
	Before treatment	On the 10th day after treatment
Flotation	14.5 ± 1.5	not found

As can be seen from Table 6, after treatment of animals on the 10th day in the bedding larvae and adults of ectoparasites were not found.

The results of determining the effectiveness of the studied drugs in heartworm disease are presented in Table 7.

As can be seen from Table 7, after treatment of animals for 20 days in the studied smears from sick animals microfilariae were not detected.

No complications or changes in animal clinical status were observed during treatment and during clinical observation of experimental and control animals.

Table 7 — The results of blood tests in dogs after treatment with 'MegaStop for dogs' and 'Golden Defence for dogs spot-on' in heartworm disease

Group of animals	Before treatment		After treatment, day							
			5		10		20		30	
	P, %	MI, average	P, %	MI	P, %	MI	P, %	MI	P, %	MI
Experimental group I	100	2.5±1.5 in a smear	100	2.0	100	1.0	0	0	0	0
Experimental group II	100	2.5±1.5 in a smear	100	2.0	100	1.0	0	0	0	0
Negative control	0	0	0	0	0	0	0	0	0	0

The use of veterinary drugs for the prevention and control of parasitic animal diseases has integrated into practical veterinary medicine. This is due to the widespread of parasitic pathogens in the environment (Paliy et al., 2019; Bogach et al., 2020). According to the epizootic situation and the type of disease, various manufacturers have proposed to use many drugs. However, their effectiveness is not always satisfactory, and new drugs must undergo extensive pre-clinical and clinical trials. Common drugs in the control of animal ectoparasites are the drugs with the active substance imidacloprid (Larsen, Siggurdsson and Mencke, 2005). Thus, after 3 months of imidacloprid use, the number of fleas in domestic animals decreased by 99.5% (Dryden, Denenberg and Bunch, 2000). The use of Seresto® collars significantly reduces the risk of infection of cats with *Bartonella* spp. (Greco et al., 2019) and also has a high (> 98.2%) efficacy against flea in cats during an 8-month study (Dryden et al., 2016). Imidacloprid collars are 95% effective against fleas and 99% effective against their larvae for 8 months. In addition, the stable acaricidal effectiveness of this tool for 8 months is 100% (Stanneck et al., 2012). Therefore, our results are consistent with the results of other researchers on the high anti-parasitic efficacy of drugs with the active substance imidacloprid.

Conclusions. On the basis of the conducted researches, preparations 'MegaStop for dogs' (drops for external use, point drawing), 'Golden Defence for dogs spot-on', 'MegaStop for cats' (drops for external use, point drawing), 'Golden Defence for cats spot-on' have been found to be well tolerated by animals and give no side effects or changes in the clinical status of the animals.

Clinical studies have shown high activity of 'MegaStop for dogs', 'Golden Defence for dogs spot-on', 'MegaStop for cats', 'Golden Defence for cats spot-on' as veterinary drugs with a broad spectrum of action against fleas (*Ctenocephalides* spp.), acariform mites (*Otodectes cynotis*, *Notoedres cati*, *Sarcoptes sapis*), mites of the genus *Demodex*; heartworms (effective against L3 and L4 stage larvae of *Dirofilaria immitis*).

According to the results of research, it has been established that veterinary drugs 'MegaStop for dogs', 'Golden Defence for dogs spot-on', 'MegaStop for cats', 'Golden Defence for cats spot-on' can be used for prevention and treatment of pets affected by fleas, acariform mites, *Demodex* mites, heartworms.

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