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ORIGINAL ARTICLE

The use of preparative forms of amitraz in ectoparasitic dermatoses of animals

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Ectoparasitic diseases of domestic animals are an urgent problem of modern veterinary medicine. Mite-borne dermatitis acquires the greatest epizootological, epidemiological and social significance. According to the results of the conducted researches it has been established that the etiological factors of parasitic dermatoses in domestic animals are the mites *Otodectes cynotis*, *Sarcoptes canis*, *Demodex canis*, *Notoedres cati*, *Demodex cati* and *Psoroptes cuniculi*. According to the results of the laboratory study, the prevalence of mite infestation among stray dogs is 66.7%, the mean intensity of invasion is 2.3 ticks in the field of view of the microscope, and among cats the prevalence of mite infestation is 75.0% with the mean intensity of infestation 3.0 ticks in the field of view of the microscope. The study of scrapings from the ears of rabbits revealed Psoroptes cuniculi mites, and the prevalence of the infection was 11.4% at the mean intensity of 3.0 mites in the field of view of the microscope. According to the results of the research it was established that the preparative forms of amitraz (drug No 1 with amitraz content of 2.0 mg/ml and drug No. 2 with amitraz content of 3.0 mg/ml) exhibit high acarinocidal properties and can be used to treat animals (dogs, cats, rabbits) with otodectosis, sarcoptosis, psoroptosis, notohedrosis, demodecosis.

Keywords: Otodectosis, sarcoptosis, notohedrosis, demodecosis, amitrazine, dogs, cats, rabbits.

Introduction

Parasitic diseases of both farm and domestic animals occupy a significant place in the structure of overall morbidity. This is due to a number of factors, the main of which are a fairly high stability and survival of parasite development stages in the environment, diversity of their populations, high fertility and rapid adaptation to living conditions, etc. (Wells et al., 2018; Paliy et al., 2019; Bogach et al., 2020; 2021).

Among domestic animals and poultry among the whole spectrum of parasitic pathologies, the main place is occupied by ectoparasitosis, which has mass character and is characterized by contagiousness (Paliy et al., 2018b; Murillo et al., 2020). For dogs and cats, mite dermatitis, which include otodectosis, sarcoptosis, notohedrosis, and demodecosis, are most dangerous (Malik et al., 2006; Yang & Huang, 2016).

The most common etiological agent of otitis externa in domestic animals is the ear mite *Otodectes cynotis*. It is a common parasite in areas with a Mediterranean semi-arid climate (Fanelli et al., 2020). The prevalence of otodectosis (38%) among foxes in northwestern Iceland was found (Gunnarsson et al., 1991).

Of particular note is sarcoptic mange due to the fact that it is a zoonotic disease that is easily transmitted to humans (Bandi & Saikumar, 2013).

An urgent problem is the skin ectoparasitic disease of cats caused by *Notoedres cati*, a mite belonging to the family *Sarcoptidae*. The disease occurs in cats, sometimes in other mammals and humans (Leone, 2007).

All skin diseases caused by *Demodex* mites fall under the term demodecosis, which can be an etiological factor in various dermatoses. Demodex infection usually remains asymptomatic and can play a pathogenic role only at high densities, as well as due to the body's immune imbalance (Rather & Hassan, 2014).

Surveyed stray cats were affected by *Otodectes cynotis* mites (15.8%), *Notoedres cati* mites (2.35%), *Cheyletiella blakei* mites (2.05%), *Ctenocephalides felis* fleas (24.3%) and *Felicola subrostratus* lice (0.59%). Significantly higher prevalence of ectoparasites was observed in long-haired breeds of animals (Lefkaditis et al., 2015).

High rates of ectoparasite infection in domestic animals pose a risk of spreading infections of epidemiological and epizootiological significance (Salant et al., 2014; Tomás et al., 2018).

Mite-borne skin lesions are quite common in rabbits (Harcourt-Brown, 2002; Sheinberg et al., 2012). The mites *Psoroptes cuniculi* are of particular epizootiological importance, they cause psoroptosis (Panigrahi et al., 2016). *Psoroptes cuniculi* was found to survive for 4-21 days at a relative humidity of 20% to 99% and a temperature from 5 to 30°C (Arlian et al., 1981).

Materials and Methods

The study aimed to establish and experimentally confirm the effectiveness of amitrazine formulations by use for prophylactic and therapeutic purposes in animal ectoparasitic infections.

For research two veterinary drugs with the active substance amitraz were used:

- Drug number 1: transparent oily liquid, colorless or yellowish color with a specific specific odor of the components. 1 ml of the drug contains the active substance amitraz-3.0 mg and excipients (decamethoxine, dimethyl sulfoxide, polyethylene glycol 400).
- Drug number 2: oily yellowish liquid with a specific odor. 1 ml of the drug contains the active substance amitraz-2.0 mg and excipients (dimethyl sulfoxide, PEG-400).

In the asymmetric unit of the title compound {systematic name: N'-(2,4-di-methyl-phen-yl)-N-[N-(2,4-di-methyl-phen-yl) carbox-imido-yl]-N-methyl-methanimidamide}, $C_{19}H_23N_3$, which is a formamidine pesticide, there are two independent and conformationally similar mol-ecules, with the dihedral angle between the mean planes of the 2,4-di-methylbenzene rings in each mol-ecule being 41.63 (6) and 42.09 (5). The crystal structure is stabilized by a C-H···N hydrogen bond, as well as weak inter-molecular C-H···π and π-π inter-actions [ring centroid separation=3.7409 (15) Å], giving one-dimensional chains extending down the b direction (Lee et al., 2013).

Amitraz is a contact acaricide of the amidine group, active against sarcoptiform mites: *Otodectes cynotis, Notoedres* spp., *Sarcoptes* spp., *Psoroptes cuniculi* and thrombidiform mites *Demodex* spp. The mechanism of its action is the effect on octopamine receptors of arthropods, which causes impaired motor activity, paralysis and death of parasites (Varma et al., 2013). Amitraz is effective against populations of mites resistant to chlorine and phosphoorganic insecticides, penetrates and is deposited in the epidermis, hair follicles, sebaceous and sweat glands. Due to the presence of decamethoxine, the drug has antimicrobial action, active against gram-positive and gram-negative microorganisms, fungi (Moyano et al., 2019; National Center for Biotechnology Information, 2021).

Auxiliary components of the drugs promote the penetration of the active substance into the localization of parasites, reduce inflammation, activate the healing of damaged tissues, relieve pain and itching.

In the treatment of otodectosis, the external auditory canal was previously cleaned of superficial crusts and scabs using a cotton gauze swab soaked in the drug. Then instilled in each ear 2-3 drops of the drug, folded the auricle in half and lightly massaged at the base for even distribution. The drug must be injected into both ears, even if one is affected. Treatment was performed once a day until the disappearance of clinical signs of the disease (5-8 treatments).

In the treatment of notohedrosis, sarcoptosis, demodecosis, the drug was applied in a thin layer on pre-cleansed affected areas of the skin with a cotton gauze swab at the rate of 0.5 ml per 1 kg of body weight, evenly distributed from the periphery to the center with capture healthy border skin at least 1 cm. Treatment was performed once a day every 2-3 days until the disappearance of clinical signs of the disease. Animals with large areas of skin lesions were treated in two steps with an interval of one day, applying the drug first on one half of the affected surface of the torso, and then on the other.

To prevent licking of the drug, the animals wore a muzzle or protective collar, which was removed after complete drying of the drug.

Pregnant and lactating females, puppies and kittens under 3 months of age, as well as patients with infectious diseases, recovering and debilitated animals were not treated. Chihuahua and Spitz dogs, as well as animals with diabetes, hypothermia and heart disease, were not treated.

We did not allow the drug to get into the eyes, mucous membranes, mouth. Animals were not treated with the drug in very hot weather.

When working with drugs, we followed the basic rules of hygiene and safety adopted when working with veterinary drugs.

Animals were treated with protective rubber gloves to avoid contact with the hands.

For research at the previous stage, a clinical examination of both homeless and sheltered animals (dogs (n=14), cats (n=12)) and rabbits (n=10) kept on the experimental base of the National Scientific Center "Institute of Experimental and Clinical Veterinary Medicine" was conducted. Samples of ectoparasites were taken from animal skin, microscopic examinations of samples were performed to determine and identify the causative agents of ectoparasitic diseases, and the prevalence was determined. After that, experimental groups of animals were formed, in which antiparasitic drugs were used. The animals were constantly monitored and their physiological state was monitored. Sampling of animals for laboratory testing was performed 5, 10 and 30 days after treatment. Extensive efficacy of the drug was determined.

The studies used laboratory glassware, a microscope, a refrigerator, Petri dishes, slides and coverslips, reagents for microscopic examinations (glycerin), sodium hydroxide, skin scrapings from the studied animals (dogs, cats, rabbits).

In order to take samples for the diagnosis of otodectosis, sarcoptosis, demodecosis and notohedrosis, the animals were fixed in a supine position. For otodectosis, scrapings from animals were taken from the inner surface of the ear with a blunt scalpel on the border of healthy and affected areas of skin. Scrapes were made deep to the treasure (no more than 0.5 cm^3), skin peels were placed in a tightly closed test tubes and labeled.

In other cases (sarcoptosis, demodecosis) animals were fixed in a supine position. Examination of the skin of the animals started with the head. Then examined the neck, back, sides, abdomen and limbs. With a blunt scalpel from 2-3 places on the border of healthy and affected area of skin, before the appearance of capillary blood, deep, up to 0.5 cm^3, scrapings of skin were selected and placed in test tubes. The tubes were closed with a stopper. A label was affixed to each test tube.

The selected material was examined no later than 72 hours after scraping. The material was examined by mortal methods (detection of dead mites) and biotic methods (detection of live mites, larvae and eggs).

The skin scrapers were placed on a glass slide. 4-5 drops of 10% alkali solution were applied to the slide with the sampled material. After 5-10 minutes, it was covered with a cover glass and examined under a microscope at a magnification of at least × 150. The presence in the field of view of a large number of the preimaginal stages of mites (eggs, larvae and nymphs) indicates the degree of arachnosis. The type of mites was determined by reference book (Vodianov, 2009).

In accordance with the objectives the studies were conducted by visual and microscopic methods (Galat et al., 2009; Mathison & Pritt, 2014).

The Prevalence Of Invasion (PI) was determined in relation to the number of infected animals to the total number of animals, expressed as a percentage. The Mean Intensity (MI) was determined by counting ectoparasites in scrapings from the skin of sick animals. Extensive Efficacy (EE) of the drugs was calculated by the number of treated animals in the percentage that were completely free of parasites.

Animal experiments were performed in accordance with modern requirements of bioethics following existing recommendations (Festing & Wilkinson, 2007; Kabene & Baadel, 2019).

Results and Discussion

As a result of a clinical examination of dogs and cats in the shelter, as well as homeless animals, individuals with skin and ear lesions were found. There was redness, inflammation of the skin, a well-marked itching reflex, papules, scales, visible places of alopecia were found on the skin. The skin is rough, cracked. The animals were exhausted. Anxiety was noted in rabbits, the animals shook their heads, scratched their ears and thus damaged their skin. The skin of the external auditory canal is covered with a layer of brown exudate.

For laboratory research, 40 scrape samples were taken (24 samples from dogs, 16 samples from cats, 12 samples from rabbits) (Table 1).

Table 1. Determination of prevalence and mean intensity of infection in animals

Parasite Species	Prevalence, %	Mean Intensity, Mites In Sight
	Dogs	
Otodectes cynotis	25.0	3.3
Sarcoptes canis	25.0	2.3
Demodex canis	16.7	1.3
	Cats	
Otodectes cynotis	37.5	3.5
Notoedres cati	25.0	2.0
Demodex cati	12.5	3.5
	Rabbits	
Psoroptes cuniculi	11.4	3.0

According to the results of laboratory research, it was found that the prevalence of mite infestation among dogs is 66.7%, with a mean intensity of mite infestation of 2.3 mites in the field of view of the microscope; among cats, the prevalence of mite infestation is 75.0%, with a mean intensity of 3.0 mites in the field of view of the microscope.

According to the results of the examination of rabbits, ten ones showed signs of damage to the skin of the ears. In the study of scrapings from the ears of rabbits we revealed mites *Psoroptes cuniculi*, with PI 11.4% at the mean intensity-3.0 mites in the field of view of the microscope.

Experimental animals were administered the drugs individually, after that the prevalence of the invasion (%) and the mean intensity of the invasion (mites in the field of view of the microscope) were determined (Table 2, 3, 4).

Table 2. The results of the study of skin scrapings from dogs with acarosis after treatment with experimental drugs

Parasite Species	Before Treatment		After Treatment							
	PI, %	Mean Intensity	5th day		10th day		20th day		30th day	
			PI, %	MI	PI, %	MI	PI, %	MI	PI, %	MI
			Drug No.1 (n=7)							
O. cynotis	100	3.3	100	2.3	50	1.3	0	0	0	0

D. canis	100	1.3	100	1.0	100	1.0	100	1.0	0	0
S. canis	100	2.3	100	2.3	50	1.3	0	0	0	0
drug No 2 (n=7)										
O. cynotis	100	3.3	100	2.3	100	1.3	0	0	0	0
D. canis	100	1.3	100	1.0	100	1.0	100	1.0	100	1.0
S. canis	100	2.3	100	2.3	50	1.3	50	1.0	0	0

According to the results presented in Table 2, it is seen that after the use of experimental drugs in dogs there was a gradual decrease in both the prevalence and mean intensity of the invasion by mites. The use of drug No 1 caused the release of animals from *O. cynotis* and *S. canis* on the 20th day, but for *D. canis* the drug showed 100% effectiveness only after 20 days of the experiment. Under the action of the drug No 2, complete release of animals from *O. cynotis* and *S. canis* was observed on days 20 and 30, respectively. At that, *D. canis* mites were detected on treated dogs even after 30 days of the experiment. In this case, completely cure the affected animals from demodicosis was possible by applying the test drug for 40 days.

Table 3. The results of a study of skin scrapings from Cats with acarosis after treatment with experimental drugs

Parasite Species	**Before Treatment**		**After Treatment**							
	PI, %	**Mean Intensity**	**5th day**		**10th day**		**20th day**		**30th day**	
			PI, %	**MI**	**PI, %**	**MI**	**PI, %**	**MI**	**PI, %**	**MI**
drug No 1 (n=6)										
D. cati	100	3.5	100	3.0	100	2.5	100	1.0	0	0
O. cynotis	100	3.5	100	2.0	50	1,0	0	0	0	0
N. cati	100	2.0	100	2.0	50	1,3	0	0	0	0
drug No 2 (n=6)										
D. cati	100	3.5	100	3.0	100	2.5	100	1.0	0	0
O. cynotis	100	3.5	100	2.0	100	1.0	0	0	0	0
N. cati	100	2.0	100	2.0	50	1.3	0	0	0	0

In the treatment of cats affected by tick-borne dermatitis, it was found that the drug No 1 completely destroys *O. cynotis* and *N. cati* after 10 days, and *D. cati*-after 20 days of application. Similar results were obtained with the use of the drug No. 2.

Table 4. The results of the study of skin scrapings from rabbits with acarosis after treatment with experimental drugs

Parasite Species	**Before Treatment**		**After Treatment**							
	PI, %	**Mean Intensity**	**5th day**		**10th day**		**20th day**		**30th day**	
			PI, %	**MI**	**PI, %**	**MI**	**PI, %**	**MI**	**PI, %**	**MI**
Drug No.1 (n=5)										
P. cuniculi	100	3.0	100	2.0	50	1.0	0	0	0	0
Drug No.2 (n=5)										
P. cuniculi	100	3.0	100	2.0	50	2.0	50	1.0	0	0

Analysis of the results presented in Table 4 shows that the use of the drug 1 caused a therapeutic effect in psoroptosis of rabbits after 10 days, while the drug 2 was effective after 20 days of the experiment.

Extensive Efficacy (EE) of drugs with an active substance amitraz in industrial trials in animals with demodecosis, otodectosis and sarcoptosis was 100%.

Extensive Efficacy (EE) of drugs in industrial trials in rabbits with psoraptosis was 100%.

During treatment and during clinical observation of experimental and control animals, no complications or changes in clinical condition were observed after drug administration. In our opinion, the slightly lower efficacy of drug № 2 compared to drug № 1 can be associated with different content of active substance in the drugs.

Due to the widespread prevalence of parasitosis (Paliy et al., 2018c), the control of ectoparasites in animals remains an urgent task of modern veterinary medicine (Packianathan et al., 2020; Paliy et al., 2021c).

Amitraz is a formamidine group of compounds used in many countries around the world as an agricultural pesticide and ectoparasiticide (Mueller et al., 2020; Shilpakar et al., 2020). Poisoning by this substance is a rather rare phenomenon, and treatment has a favorable prognosis (Dhooria & Agarwal, 2016).

It has been shown that a combination of amitraz (150 mg/ml) with pyriprole (125 mg/ml) and metaflumizone (150 mg/ml) can be proposed in a leishmaniasis prevention program (Thomas et al., 2008).

The efficacy of 10% imidacloprid/1% moxidectin against *O. cynotis* has been reported to be 90% on day 9 and 100% on day 16 after administration to sick cats (Ahn et al., 2013; Huang & Lien, 2013).

Fluralaner is highly effective against *O. cynotis* mites when applied topically to cats and orally or topically to dogs (Taenzler et al., 2017). Fluralaner completely kills fleas and ear mites and is 100% effective against both parasites up to 84 days after treatment (Bosco et al., 2019). Highly effective against *O. cynotis* invasions in cats is a single topical application of a fixed combination of fluralaner and moxidectin (Taenzler et al., 2018), as well as a single oral administration of afoxolaner in the minimum recommended dose (Carithers et al., 2016).

One oral dose of sarolaner is effective in controlling otodecosis in naturally infected cats (Ribeiro Campos et al., 2021).
Multiple regressive analysis showed that the survival time of mites is affected by temperature fluctuations. Thus, the survival rate of parasites decreases linearly with increasing average temperature. This basic understanding of out-of-host survival suggests that places where infected animals lived must be disinfected or left free at least 12 days before settling (Otranto et al., 2004).
NexGard® and NexGard Spectra®, administered twice a month, provide effective and safe treatment against sarcoptic mange in dogs (Hampel et al., 2018; Tielemans et al., 2021).
Ivermectin subcutaneously at a dose of 200-400 μg/kg is effective in the treatment of animals with sarcoptosis (Lu et al., 2018; Rowe et al., 2019).
One average dose of doramectin at a dose of approximately 290 micrograms per kg is sufficient to control notohedral scabies in cats (Delucchi & Castro, 2000).
The combination of fipronil and ivermectin has been used successfully in the treatment of rabbits affected by psoroptosis (Cutler, 1998; Elhawary et al., 2017). The combined use of vitamins significantly improves the clinical condition of animals (Singh et al., 2012). Selamectin is effective in the natural invasion of rabbits with *P. cuniculi* and *S. scabiei* (Kurtdede et al., 2007). A single subcutaneous injection of eprinomectin at a dose of 200-300 μg/kg body weight of the animal is recommended (Pan et al., 2006).
The use of amitraz as an active substance in acaricides is a scientifically ground step, which is confirmed by a number of scientific experiments.
Despite the success in controlling parasitic animal diseases, the development and large-scale testing of complex antiparasitic drugs containing various active substances and excipients remains relevant (Woods & Williams, 2007; Woods et al., 2011; Shkromada et al., 2019; Paliy et al.., 2020b; 2021a; 2021b).
In the prevention and control of animal diseases of various etiologies, along with specific drugs, it is necessary to carry out a set of veterinary and sanitary measures through the use of various disinfectants (Paliy et al., 2018a; 2020a; 2020c).

Conclusion

Studies have shown that the etiological factors of parasitic dermatoses in domestic animals are *Otodectes cynotis*, *Sarcoptes canis*, *Demodex canis*, *Notoedres cati*, *Demodex cati* and *Psoroptes cuniculi*. The prealence of mite infestation in dogs and cats is 66.7% and 75.0% with a mean intensity of mite infestation of 2.3 and 3.0 mites in the field of view of the microscope, respectively. The prevalence of *P. cuniculi* rabbit infestation was 11.4% at a mean intensity of 3.0 mites in the field of view of the microscope. According to the results of the research it is established that the preparative forms of amitraz (2-3 mg/ml) show high acarinocidal properties and can be used for the treatment of animals (dogs, cats, rabbits) with otodectosis, sarcoptosis, psoroptosis, notohedrosis, demodecosis.

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