

ORIGINAL ARTICLE

Pharmacokinetics of combination antiparasitic drug preparation for dogs and cats in the form of spot-on solution

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ABSTRACT

Objective: The object of the study was to examine the major pharmacokinetic parameters after a single application of a complex drug preparation for veterinary use based on fipronil, praziquantel, moxidectin, and pyriproxyfen in cats and dogs.

Materials and Methods: For dogs, the drug preparation was administered spot-on solution in the following dosage of active pharmaceutical substances: fipronil 27.0 mg/kg body weight (bwt), praziquantel 10.8 mg/kg bwt, moxidectin 6.75 mg/kg bwt, and pyriproxyfen 5.4 mg/kg bwt; for cats, the dosage was the following: fipronil 43.2 mg/kg bwt, praziquantel 17.28 mg/kg bwt, moxidectin 4.32 mg/kg bwt, and pyriproxyfen 8.64 mg/kg bwt. The blood samples were taken from dogs and cats. The principle of the method for determining praziquantel, trans-4-hydroxypraziquantel, pyriproxyfen, and fipronil in serum samples was chromatographed in a high-pressure liquid chromatograph with detection by means of a mass-spectrometric detector. The moxidectin content of the blood was detected by high-performance liquid chromatography.

Results: The drug preparation active substances: praziquantel, fipronil, and moxidectin are absorbed into the blood of dogs and cats. The penetration of praziquantel into the systemic circulation and further into organs and tissues was proved. After topical administration, moxidectin is absorbed and distributed systemically and is slowly removed from the plasma, which manifests itself in detectable concentrations of moxidectin in the blood for 1 month.

Conclusion: The present results of pharmacokinetic investigations may promote to the determination of effective therapy strategy and prophylaxis of parasitic diseases in dogs and cats.

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Introduction

For the treatment and prophylaxis of parasitosis of dogs and cats, veterinarian science is in need of harmless and effective antiparasitic veterinary drug preparations. Where possible, the finished dosage form should contain a combination of active ingredients, which can provide combined effect to minimize the number of the drug treatments and to reduce the time for extra treatments [1,2,3,4]. Consequently, it is necessary to carry out multifaceted pharmacol-toxicology investigations for proving the efficacy of the new combination drug, which should include the investigation of pharmacokinetics [5]. Pharmacokinetics data make it possible to appreciate the rate and efficiency of the drug preparation active pharmaceutical ingredients penetration processes, its

distribution in organs and tissues, targeting and quantitative evaluation of biotransformation processes, ways and rate of the drug preparation clearance. The findings are of fundamental importance in the creation, testing, and development of an optimal pharmacotherapy [6]. An additional point is that pharmacokinetic data have research and practical importance and contribute to a beneficial effect on the qualitative development of the medicinal product. It should be emphasized that pharmacokinetic parameters justify the therapeutic effectiveness of the drug preparation.

German company Neoterica GmbH in conjunction with and at the premises of Closed joint-stock company "Scientific-production company "Ekoprom" have developed complex antiparasitic veterinary drug preparation

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Inspector®Quadro. The veterinary medicine market is over-saturated with different drugs, however, the spot-on solution Inspector®Quadro based on fipronil, moxidectin, pyriproxyfen, and praziquantel is a new composition in veterinary medicine. Antiparasitic medication dosage form is a spot-on solution. The drug preparation has the following characteristics: for cats, the content of fipronil is 108.0 mg/ml, praziquantel—43.2 mg/ml, moxidectin—10.8 mg/ml, and pyriproxyfen—21.6 mg/ml (Inspector®Quadro K). The drug preparation intended for dogs includes fipronil at a rate of 108.0 mg/ml, praziquantel—43.2 mg/ml, moxidectin—27.0 mg/ml, and pyriproxyfen—21.6 mg/ml (Inspector®Quadro S). Tolerance of the drug preparation in increased curative dose was studied on binding species. In investigations, the negative influence of the drug preparation in the spot-on form on the bodies of cats and dogs was not found. This drug preparation is expected to be used as an antiparasitic drug preparation of a wide spectrum of action for veterinary use.

Combination of moxidectin and praziquantel included in the drug preparation provides a broad spectrum of its anthelmintic effects on nematodes and cestodes parasitizing dogs and cats [7].

Moxidectin is included in the drug preparation as an active component, which is a macrocyclic lactone from the class of milbemycins. Moxidectin retains activity in the body for a long time, therefore, it is often used for the manufacture of prolonged antiparasitic drug preparations. Moxidectin has more pronounced anthelmintic and acaricidal properties than insecticidal ones [8].

For the first time, macrocyclic lactones were used in the process of protection against *Dirofilaria*. It is necessary to administer the drug preparation for every month to eradicate larvae of the three and four phase [9].

Praziquantel is a compound of pyrazine isochinoline group; it is active against mature and immature cestodes [10]. The mechanism of its action is based on inducing the disintegration of the tegument and inhibition of fumarate reductase, persistent depolarization of helminth muscle cells, disturbance of energy metabolism, which causes paralysis and death of cestodes. Praziquantel undergoes biotransformation in the liver with the formation of hydroxylated metabolites, mainly the active metabolite *trans*-4-hydroxypraziquantel [11].

When applied to the skin of animals, fipronil and pyriproxyfen are accumulated in the epidermis, hair follicle, and sebaceous glands of the skin and have a prolonged contact insectoacaricide and repellent effect [12,13]. Fipronil blocks gamma-aminobutyric acid (GABA)-dependent parasite receptors, disrupts neurotransmission, which ultimately leads to akinesia and death of arthropods [14]. Fipronil has no impact on GABA-receptors of mammals. Pyriproxyfen disrupts chitin synthesis and larvae

molting process, prevents the development of complete chrysalides, and causes the death of insects at preimaginal phases of development, which leads to the end of the ectoparasites population replenishment.

In connection with the foregoing, the relevance and expediency of studying the pharmacokinetics of the new antiparasitic veterinary drug preparation in spot-on form are quite evident. The purpose of the study was to examine the major pharmacokinetic parameters after a single application of a complex medicinal drug preparation for veterinary use based on fipronil, praziquantel, moxidectin, and pyriproxyfen in cats and dogs.

Materials and Methods

Ethical approval

The study was approved by the Federal Scientific Center of the Russian Academy of Sciences (No. 2018/03/FSC VIEV RAS). The research work was carried out on animals and it is complied with the national regulations [15] and the institutional policies relating to the care and use of target animals. The investigations were conducted in conformity with the international regulations [16].

Experimental groups

In total, 12 animals were selected. In the experiment, 1–1.5-year-old outbred dogs with a body weight of 16.0, 10.2, 22.5, 21.5, 16.2, and 11.1 kg and 2–3-year-old outbred cats with a body weight of 3.0, 2.0, 2.12, 2.7, 3.0, and 2.6 kg participated. Dogs and cats were kept in standard conditions of Breeding Kennel BANO “Eco” (Moscow) in containers on standard complete feeding [17]. The access to water was free. The conditions of keeping the animals met the established requirements [18]. During 30 days before the beginning of the experiment, the animals were not taking any chemotherapeutic drug preparations and they were healthy as well.

The product was applied to animals once by the spot-on method at the rate of 0.25 ml per 1 kg of body weight of a dog and 0.4 ml per 1 kg of body weight of a cat. For the accurate dosage, the animals were weighted.

Animal blood sampling was carried before (0 h) and 1, 2, 3, 6, 9, 12, 18, 24, 48, 96, 168, 240, 360, 480, 600, and 720 h after the application of the product. Additionally, blood sampling of dogs was carried after 40 days (960 h) after the application of the product. The blood was taken into polyethylene tubes without anticoagulant; the serum was separated and frozen until the time of the research.

Calculation of pharmacokinetic parameters was conducted in the program PK Solver (approximation in the approach of a single-chamber suction model) [19].

Determination of praziquantel, trans-4-hydroxypraziquantel, pyriproxyfen, and fipronil in the blood serum sample of dogs and cats

The principle of method consisted of the chromatographic procedure by means of a high-pressure liquid chromatograph with a diol column of blood serum extracts obtained after solid-phase extraction of the analytes followed by the detection by a mass spectrometric detector in the positive ionization mode of the electrospray. Processing of accessed data was carried out by means of program "MassHunter Workstation Software LC/MS Data Acquisition Triple Quadrupole Version B.06.00".

Equipment

Laboratory weigh-scales Shinko Denshi ViBRA HTR-220 CE (discretization 0.0001 g). High-pressure liquid chromatography "Agilent 1290" with Mass Spectrometry detector Agilent 6430 (QQQ), chromatographic column of hydrophilic interaction Kromasil 60-5-HILIC, 2.1 × 100 mm (\emptyset of sorbing agent is 5 μ m). Sedimentator Vortexer Micro-spin FV-2400 BioSan. Shaker-mixer Eppendorf Thermomixer compact AG 22331. Sonication bath PSB 5735-05; sedimentator Eppendorf 5418; airvoid manifold VacMaster with aerotonometer; concentrating cartridges for solid-phase extraction Waters Oasis WCX (\emptyset of sorbing agent is 30 μ m, weight of sorbing agent is 60 mg).

Preparation of the equipment for work

Mass spectrometric conditions

Ionization method: Electrospray is in positive mode (ESI+); temperature of ionization: 300°C; gas flow 11 l/min; pressure of nebulizer: 25 psi; voltage: \pm 4,000 V. For assay of praziquantel, trans-4-hydroxypraziquantel, pyriproxyfen, and fipronil by multiple reaction monitoring (MRM) method, the investigation of ions disintegration under the action of bombarding flow of nitrogen molecules with subsequent resolution of the decomposition products (MS/MS method).

Mobile phase consisted of two components: component A is a 0.1 % solution of formic acid in water; component B is a 0.1 % solution of formic acid in acetonitrile. Ratio of components A:B = 10:90. The chromatograph was switched on and set up according to the attached instructions.

Metrological certification of the method was conducted according to Boulanger et al. [20] and Eipstein [21] by the content of analytes in blood serum. Detection limit (LOD) of praziquantel is 1.9 ng/ml, of trans-4-hydroxypraziquantel is 0.5 ng/ml, of pyriproxyfen is 0.3 ng/ml, and fipronil is 5.2 ng/ml. Limit of quantification (LOQ) of praziquantel is 6.2 ng/ml, of trans-4-hydroxypraziquantel is 1.7 ng/ml, of pyriproxyfen is 1.0 ng/ml, and of fipronil is 15.7 ng/ml. The given method was linear within the range of calibration

($R > 0.99$) and showed fine repeatability and accuracy. The method allowed to identify analytes in model samples and specimens of cat and dog blood serum.

Determination of moxidectin in specimens of blood serum

The method is based on the determination of moxidectin by HPLC method in accordance with methodological instructive regulations 4.1.1821-03 [22] with pre-column modification of N-methylimidazole as well as trifluoroacetic anhydride and followed by detection by fluorescence. To control of the reaction running, ivermectin was added as the internal standard. The assay was conducted by the external standard method.

Equipment

Chromatograph Shimadzu Prominence LC20 with fluorometric detector RF-20Axs, column for reverse phase HPLC Kromasil C18 150 × 4.6 mm (granulation of sorbing agent is 5 μ m) and shielding pre-column Kromasil C18, electronic laboratory weigh-scales HTR.

Preparation of the equipment for work

The chromatograph was switched on and set up according to the attached instructions. Metrological evaluation of the procedure was carried out in accordance with Boulanger et al. [20] and Eipstein [21] by the content of moxidectin in serum. The calculated LOD and LOQ values of moxidectin in serum are 0.2 and 0.6 ng/ml, respectively. The proposed method was linear in the range 1–100 ng/ml ($R > 0.99$) and showed good repeatability and accuracy. The method allowed to identify moxidectin in model samples and serum samples.

In our work, the results of the content of praziquantel, trans-4-hydroxypraziquantel, pyriproxyfen, fipronil, and moxidectin are given with rounding up to tenths; unit of measurement is ng/ml.

Results and Discussion

Studying of pharmacokinetic parameters of praziquantel, trans-4-hydroxypraziquantel, pyriproxyfen and fipronil in the blood serum of dogs and cats

Calculations of pharmacokinetic parameters are shown in Table 1 and in Figure 1a–d. After an hour, praziquantel is determined in dog blood only in two animals out of six. Dynamics of praziquantel distribution was characterized by a slow increase of concentration with the maximum after 48 h ($C_{av} = 30.0$ ng/ml). Further, the level of praziquantel decreased very smoothly reaching the method determination limit after 30 days (720 h).

Trans-4-hydroxypraziquantel in dog blood serum was determined in trace amounts starting from 3 h after the

Table 1. Pharmacokinetic parameters of praziquantel and fipronil in dogs and cats blood.

Parameter	Pharmacokinetic parameters of praziquantel in the blood of dogs		Pharmacokinetic parameters of praziquantel in the blood of cats		Pharmacokinetic parameters of fipronil in the blood of dogs		Pharmacokinetic parameters of fipronil in the blood of cats	
	Average	RSD (%)	Average	RSD (%)	Average	RSD (%)	Average	RSD (%)
K_{el} , h^{-1}	2.19×10^{-3}	33.4	6.13×10^{-3}	54.5	2.22×10^{-3}	101.3	4.81×10^{-3}	62.63
C_{max} , ng/ml	25.7	22.4	38.7	18.1	69.4	36.4	56.2	20.5
AUC_{0-inf} , ng/ml*h	12,755	18.0	8,909	45.7	64,950	78.4	15,407	44.0
$AUC_{(0-T)}$, ng/ml*h	9,199	15.2	7,857	35.5	28,296	32.6	10,721	37
$AUMC_{0-inf}$, ng/ml*h ²	6.63×10^6	46.0	2.41×10^6	92.2	8.39×10^7	118.7	5.11×10^6	83
MRT, h	504	31.1	224	56.1	926	76.1	284	54.9
T_{max} , h	18	50.0	19	29.0	63	43.3	10	77.8
T_{half} , h	347	31.7	152	58.4	627	78.8	195	55.9
V_d , ml/kg body weight	6.9	42.8	1.04	27.2	6.7	66.7	1.9	42.2
Cl, ml/kg body weight/h	1.43×10^{-2}	40.3	5.77×10^{-3}	40.9	1.14×10^{-2}	84.77	8.54×10^{-3}	48.3

RSD = relative standard deviation, K_{el} = elimination constant (elimination rate), C_{max} = value of maximum concentration of the drug preparation substance, AUC = area under curve, area under curve of the drug preparation substance in blood, $AUMC$ = area under multiplication curve, area under the first moment versus time curve, MRT = mean residence time, T_{max} = time-to-peak concentration of drug preparation substance, T_{half} = elimination half-life of drug preparation substance, V_d = apparent volume of distribution, Cl = drug preparation clearance from the system.

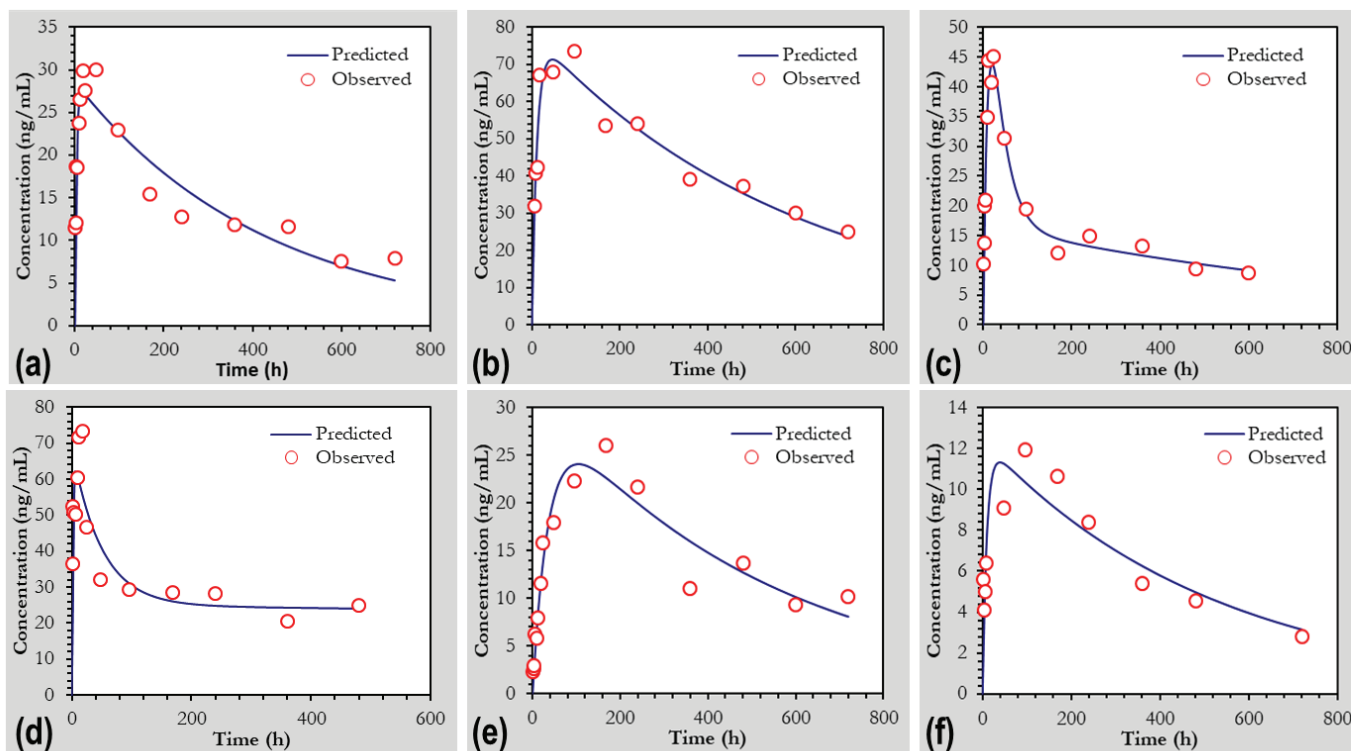


Figure 1. Dynamic pattern of concentration of different antiparasitic drugs in blood serum of dogs and cats; (a) praziquantel in dogs, (b) fipronil in dogs, (c) praziquantel in cats, (d) fipronil in cats, (e) moxidectin in dogs, and (f) moxidectin in cats.

drug preparation application. The maximum concentration of *trans*-4-hydroxypraziquantel is achieved after 18 h ($C_{av} = 11.6$ ng/ml) followed by a gradual decrease of concentration below the determination limit after 10 days (240 h).

In cat blood, praziquantel was determined starting from the first hour after the application of the drug preparation. Pharmacokinetics of praziquantel in the bodies of cats was similar to the pharmacokinetics of dogs: concentration increased slowly and the maximum was reached faster, after 24 h ($C_{av} = 45.0$ ng/ml). Average maximum concentration of praziquantel in cat blood was higher than in dog blood. Excretion of praziquantel from the bodies of cats occurred somewhat faster, however, it was also characterized by a very smooth decrease of concentration up to the method determination limit after 25 days (600 h).

Trans-4-hydroxypraziquantel in cat blood serum is determined in trace quantities. The maximum concentration of *trans*-4-hydroxypraziquantel was achieved after 12 h ($C_{av} = 8.4$ ng/ml) followed by a gradual decrease of concentration below the determination limit after 7 days (168 h).

Pyriproxyfen in dog blood serum is determined in trace amounts. Concentrations of analyte varied within the limits 1–6 ng/ml for 2–600 h after application; after 720 h (30 days), the level that exceeded the method determination limit was noted only in one animal. Pyriproxyfen in cat blood serum is determined in trace quantities. The maximum concentration of pyriproxyfen is achieved after 12 h ($C_{av} = 12.8$ ng/ml) followed by a gradual decrease of concentration below the determination limit after 20–25 days (480–600 h).

For *trans*-4-hydroxypraziquantel and pyriproxyfen, calculations of pharmacokinetic parameters were not conducted, because these substances were found in traces that did not allow to conduct processing of the data received. For *trans*-4-hydroxypraziquantel, these results are connected with submicrogram of praziquantel in the drug preparation dose. Taking into account, lower anthelmintic activity of metabolites compared with starter compound, pharmacokinetic parameters of *trans*-4-hydroxypraziquantel can be neglected in the present experiment.

Low concentration of pyriproxyfen in animal blood serum is connected with the fact that it is the substance of external activity. It is known that it does not penetrate the blood but accumulates in the epidermis [23]. Thus, the effectiveness of pyriproxyfen is not due to its presence in the systemic circulation, and therefore, the calculation of its pharmacokinetic parameters for this method of use is not of clinical significance.

Fipronil pharmacokinetics was characterized by a significant individual variability of concentrations. The

maximum concentration of fipronil is achieved after 96 h ($C_{av} = 73.6$ ng/ml) followed by a gradual decrease of concentration below the determination limit after 25 days (600 h). Quantitative content of fipronil in the blood of cats was characterized by a significant individual variability of concentrations, especially on the first day of the research. The maximum concentration of fipronil was achieved after 18 h ($C_{av} = 73.3$ ng/ml) followed by a gradual decrease of concentration below the determination limit after 20–25 days (480–600 h).

The mean residence time of praziquantel (MRT) in the blood of dogs was 504 h, in the blood of cats—224 h; the mean residence time of fipronil in the blood of dogs was 926 h, in the blood of cats—284 h. Deposition of one or another active ingredient leads to increasing of apparent volume of distribution. The apparent volume of distribution of praziquantel (V_d) in dogs was 6.9 ml/kg bwt, in cats—1.04 ml/kg bwt. The apparent volume of distribution of fipronil in dogs was 6.7 ml/kg bwt, in cats—1.9 ml/kg bwt. Taking into account, pharmacokinetic parameters of praziquantel and fipronil in dogs and cats, it can be noted that praziquantel and fipronil excrete 2.3 and 3.3 times slower in dogs than in cats, respectively.

According to Gupta and Milatovic [24] data, the prolonged period of half excretion of fipronil in blood 150–245 h can reflect the slow release of its metabolites from body fat.

A study of the pharmacokinetics of praziquantel in dogs was mentioned in the work of Gutiérrez et al. [25]. A transdermic drug preparation was applied to dogs in a dosage of praziquantel of 14.5 mg/kg bwt. Blood samples were selected before application and after 1, 2, 4, 6, 12, 24, and 48 h. The results were as follows: $C_{max} = 56.0 \pm 15$ ng/ml; $T_{max} = 5.0 \pm 1.1$ h.

The pharmacokinetics was studied in case of subcutaneous administration of complex drug preparation based on aversectin C_1 and praziquantel to dogs (0.5 mg/kg bwt based on aversectin C_1 and 5.0 mg/kg bwt based on praziquantel). Praziquantel was found after half an hour post injection, and after 1 h, its maximum concentration was noticed. The drug preparation was not found in the blood of dogs after 72 h [26].

Studying of pharmacokinetic parameters of moxidectin in the blood serum of dogs and cats

Calculations of pharmacokinetic parameters are shown in Table 2 and in Figure 1e,f. In the blood of dogs, moxidectin was detected in most animals starting from 3 h after application; after 1 h, trace quantities of analyte (2.3 ng/ml) were noted only in one dog, after 2 h, moxidectin was noted in two animals, also in small amounts. After the skin application, moxidectin was gradually accumulating in the blood, reaching the maximum after 7 days (168 h)

Table 2. Pharmacokinetic parameters of moxidectin in the blood of dogs and cats.

Parameter	Pharmacokinetic parameters of moxidectin in the blood of dogs.		Pharmacokinetic parameters of moxidectin in the blood of cats.	
	Average	RSD, %	Average	RSD, %
K_{el} , h ⁻¹	2.61×10^{-3}	58.91	5.34×10^{-3}	44.10
C_{max} , ng/ml	25.3	23.71	13.6	58.1
AUC _{0-inf} , ng/ml*h	15,264	36.26	4,876	103.2
AUC _(0-T) , ng/ml*h	10,808	25.86	4,377	101
AUMC _{0-inf} , ng/ml*h ²	9.10×10^6	67.37	1.63×10^6	130
MRT, h	537	42.80	275	46.5
T_{max} , h	107	26.81	68	93.1
T_{half} , h	342	48.03	160	55.1
V_d , ml/kg body weight	3.5	38.01	0.8	65.5
Cl, ml/kg body weight/h	8.91×10^{-3}	77.29	3.60×10^{-3}	49.4

RSD = relative standard deviation, K_{el} = elimination constant (elimination rate), C_{max} = value of maximum concentration of the drug preparation substance, AUC = area under curve, area under curve of the drug preparation substance in blood, AUMC = area under multiplication curve, area under the first moment versus time curve, MRT = mean residence time, T_{max} = time-to-peak concentration of drug preparation substance, T_{half} = elimination half-life of drug preparation substance, V_d = apparent volume of distribution, Cl = drug preparation clearance from the system.

(C_{av} = 26.0 ng/ml) followed by a slow decrease of the concentration up to 10.0 ng/ml after 30 days (720 h).

In the blood of cats, during the first 9 h after application, there was a significant variability of individual values. Small concentrations of moxidectin were reported in some animals (2–3 from the group) while in others the level of the analyte was below the method determination limit. Starting only from 12 h, in the blood of all cats, moxidectin was registered in the determined concentrations. The maximum concentration of moxidectin was achieved after 96 h (C_{av} = 11.9 ng/ml) followed by a gradual decrease of concentration up to 2.8 ng/ml after 30 days (720 h). The results obtained confirm the presence of moxidectin in the blood of dogs and cats during 1 month after the application of the product in the determined concentrations.

In addition, the content of moxidectin in the blood of dogs was examined after 40 days (960 h) after a single application of the drug preparation. After 40 days (960 h) after a single application of drug preparation Inspector®Quadro, the concentration of moxidectin in the blood serum of dogs was within the range of 5.1–8.4 ng/ml. The average concentration was 6.1 ng/ml.

After local administration, moxidectin is absorbed and distributed systematically and is slowly excreted from the blood plasma, which is manifested in detectable concentrations of moxidectin in the blood for 1 month. Our investigations showed quite a high level of AUC that indicates good tissue distribution of the investigated compound.

The MRT in the blood of dogs was 537 h, in the blood of cats—275 h. The apparent volume of distribution of moxidectin (V_d) in dogs was 3.5 ml/kg bwt, in cats—0.8 ml/

kg bwt. Moxidectin is excreted two times slower from dog bodies than from cat bodies.

Pharmacokinetics of moxidectin in the case of different ways of administrations have been studied on rats, sheep, cattle, horses, pigs, camels, cats, and dogs [27,28]. In the investigations of Arisov et al. [28] on studying the pharmacokinetics of an oral drug preparation based on moxidectin and praziquantel, a long-term retention of moxidectin in cat and dog blood was noted. The concentration of this analyte decreased progressively starting from 600 h (25 days) up to lower than the detectable level. Pharmacokinetics in the case of oral use of moxidectin for dogs in a dose of 250 mcg/kg bwt have been studied. Sampling was conducted starting from 0.5 day to 56 days after treatment. Moxidectin peak concentration in plasma was (C_{max}) 234.0 ± 64.3 ng/ml [27].

Pharmacokinetics of moxidectin in cattle have been studied. After subcutaneous administration of 0.2 mg/kg bwt of moxidectin, C_{max} was 60.0 mcg/kg bwt in blood serum. In the investigations of Arisov et al. [29] on studying of Inspector®Quadro for dogs and Inspector®Quadro for cats, the therapeutic efficacy in enteric nematodes and cestodes showed 100% result. The obtained pharmacokinetic data conform to the presented above investigations.

On the grounds of reference data and in-house investigations, it is possible to deduce that pharmacokinetics of medications largely depends on lots of factors, particularly on the way of administration, drug preparation, physical and chemical properties, on a combination of additive agents, animal species, age, and sex. Additive agents in all cases of their application affect the “drug preparation-macrorganism” system [30].

Inspector®Quadro as an additive agent contains diethylene glycol monoethyl ether, N-methylpyrrolidone, butylhydroxyanisole, and butylhydroxytoluene. Diethylene glycol monoethyl ether is used as a solvent. Besides, diethylene glycol monoethyl ether possesses high conducting characters due to its capability to dissolve dermal and lipid barrier. Present additive component provides pre-dosed delivery of drug preparation active pharmaceutical ingredients through the skin deep into the tissues [31]. Prosperous combination of active and additive components in drug preparation Inspector®Quadro and knowledge of pharmacokinetics parameters of this pharmacologic composition allows to assure effective and safe pharmacotherapy of domestic animals (dogs and cats).

Conclusion

Pharmacokinetics of active pharmacological ingredients of complex drug preparation Inspector®Quadro in the blood serum of dogs and cats was studied. The findings indicate that praziquantel, fipronil, and moxidectin are absorbed into the blood of both species of animals. Detected concentrations of praziquantel are being found in the blood of carnivores for 25–30 days after a single skin application, which confirms that the antiparasitic effect of the drug preparation on cestodes parasitizing the small intestine of dogs and cats. Our studies confirm that the absorption of praziquantel into the systemic circulation and further into organs and tissues. In addition, trace amounts of the metabolite praziquantel were found in the blood. By the end of the experiment (30 days), moxidectin was found in animal blood serum that suggests its potential antiparasitic action against nematodes and their larvae (dirofilaria) as well as ectoparasites during at least 1 month after the drug preparation administration. Pyriproxyfen is practically not absorbed into the blood. The investigation permitted to establish only trace quantities of pyriproxyfen congenial to the method detection limit. At the same time, the presence of this component in the blood does not have therapeutic implication because pyriproxyfen possesses contact action against ectoparasites. It should also be noted that in general, the absorption of the drug preparation into the blood and the achievement of its maximum concentration in animals is different. In cats, the time of the maximum concentration of active components is reached much earlier than in dogs, which may be due to a more intensive metabolism in this species of animals. The present results of pharmacokinetic investigations may promote to the determination of effective therapy strategy and prophylaxis of parasitic diseases in dogs and cats.

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Conflict of Interest

Authors declared that there is no conflict of interest.

Author Contribution

AMV designed the study, interpreted the data, and drafted the manuscript. IEN carried out the research work and prepared the manuscript. AGB compared analyzed data and critical checking of this manuscript. AMV, IEN, and AGB final acknowledgment of the version to be published.

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