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Sulfachloropyrazine disposition in *Eimeria tenella* infected chickens

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ABSTRACT

The control of coccidiosis in chickens is undertaken mainly by administration of anticoccidial drugs. Sulfachloropyrazine-sodium is still used as an effective coccidiocidal compound to treat poultry with clinical signs of coccidiosis. However, its disposition after three days treatment in *Eimeria tenella* infected chickens has not been well studied. Pharmacokinetics of sulfachlorpyrazine-sodium was investigated in healthy chickens and chickens experimentally infected with *E. tenella*. Serum and tissue concentrations were determined by HPLC-PDA analysis. The values of absorption half-life (17.24 ± 3.50 h) and time for achievement of maximal serum concentrations T_{max} (23.41 ± 3.78 h) of the sulfonamide were significantly higher in infected chickens. An accumulation index of 1.22 ± 0.13 was estimated and significantly higher serum concentrations were observed in *E. tenella* challenged animals. Significantly higher sulfachloropyrazine-sodium levels were found in the duodenum, caeca and the liver, which suggests that a longer withdrawn time could be expected in infected chickens after three days administration of the anticoccidial agent. The observed changes in sulfachloropyrazine disposition could be attributed to the alteration of the integrity of the intestines and decreased motility of the gastro-intestinal tract during the clinical coccidiosis.

Key words: chicken, cocidiosis, *Eimeria tenella*, pharmacokinetics, sulfachloropyrazine

Introduction

Coccidiosis is one of the major problems in poultry husbandry with significant economic impact on broiler chicken production (HAUG et al., 2008). The potential for clinical and subclinical coccidiosis is always a concern, since coccidial oocysts are present in broiler farms. Despite prophylactic feeding programs, which include administration of coccidiostatic drugs, it is occasionally necessary to apply cocidiocidal compounds to

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treat the coccidiosis (GUSSEM, 2007). Treatment with drinking water is more valuable in clinical cases of protozoal disease because water consumption is continued by the poultry. However, the range of available compounds is limited and includes mainly toltrazuril and sulfonamides (LACZAY et al., 1995).

Sulfonamides are relatively old synthetic antibacterial compounds but still effective in the treatment of caecal coccidiosis in poultry (LACZAY et al., 1995; CAMPBELL, 2008). They interfere with the synthesis of folic acid, which is required for deoxyribonucleic acid synthesis (GREIF et al., 2001). The equal or greater efficacy of sulfachlorpyrazine has been observed in *E. tenella* infected chickens in comparison to toltrazuril during the early stage of life cycle, or in the late stages of the parasite's development, respectively. Due to antibacterial activity, the sulfonamide drug prevents secondary bacterial infections which often occur after coccidiosis (YEQUANI and KORVER, 2008). Although sulfachloropyrazine was often used as a coccidiocidal drug in clinical cases, its disposition in infected poultry is not well described in the literature. The published data concern mainly pharmacokinetics after single intravenous and oral administration of the drug (LASHEV, 1998; KOINARSKI and LASHEV, 2006). Recently, LEBKOWSKA-WIERUSZEWSKA and KOWALSKI (2010) published residue depletion studies in healthy turkeys treated with sulfachloropyrazine. These investigations showed that sulfachloropyrazine has a long half-life and relatively high bioavailability. The drug was found at measurable concentrations in the edible tissues of turkeys eighteen days after the cessation of treatment. Delayed absorption rates have been observed in *Eimeria* infected chickens and turkeys (LASHEV, 1998). However, data are lacking about the pharmacokinetics of sulfachloropyrazine administered for three consecutive days to *E. tenella* infected chickens. Although a longer withdrawal time can be assumed in diseased animals on the basis of a single administration of the drug, there are no data about sulfachloropyrazine disposition after continuous treatment of infected chickens.

Therefore, the current study was designed to evaluate the pharmacokinetics of sulfachloropyrazine in *Eimeria tenella* infected chickens. The analysis of the serum and the tissue concentrations in the liver, the intestinal walls of the duodenum and caeca, was performed by the HPLC method. Additionally, the efficacy of the treatment was determined by registration of the oocyst index and lesion score.

Materials and methods

Drug. Sulfachloropyrazine-sodium monohydratum (Sudachim, Ltd., Sofia, Part. No 20070415) was used for oral (p.o.) treatment. The drug was administered as a water solution according to the manufacturers' instructions at a concentration of 0.03%. The medicated water was prepared *ex tempore* and was supplied *ad libitum*. The treatment aimed for a dose of sulfachloropyrazine 70 mg/kg b.m./day. Water consumption was

registered, as well as the body weight of the chickens, and the received daily dose was calculated to be 70 mg/kgb.m./day.

Animals. Broiler chickens from both sexes (Plymouth Rock × Cornish, n 127) were included in the experiment. They were obtained from a commercial poultry farm immediately after hatching. The chickens were housed under identical conditions, according to the requirements of the species (Bulgarian Regulation No. 15/03 Feb 2006 for minimum requirements for the protection and welfare of experimental animals). They had free access to standard commercial feed (without antibiotics and coccidiostats) and water. The animals were reared in cages, on a grilled floor and under conditions excluding an additional invasion of *Eimeria* spp. The birds were regularly examined during the experiment. They were free of cocidiosis and infectious disease during the acclimatization period and before the experimental infection. The experimental animals were divided into three groups at the age of 14 days. The chickens were of body weight between 214 and 305 g at that age.

Study design and treatment. The first group of 50 chickens was housed separately in order to prevent any *Eimeria* infection. They served as healthy controls. Ten chickens remained untreated. The remaining 40 animals received sulfachloropyrazine-sodium via drinking water for 3 consecutive days. The treatment started at the age of 21 days, thereby healthy and infected animals were treated at an identical age. The chickens were of body weight between 367 and 529 g. Water consumption was registered and the recalculated dose received did not differ from the target dose of 70 mg/kg b.m./day. The blood samples (0.8 mL) were taken from the v. brachialis. They were collected in tubes without an anticoagulant prior to treatment and at 1, 2, 4, 6, 24, 50, 54, 74, 76, 78 and 80 hours after the start of the treatment. Six samples were taken at each time interval during the first 24 hours from different animals and five samples per each time interval until the end of the experiment. Serum was collected after centrifugation at 1800g for 15 min and stored at -30 °C prior to analyses. The liver, duodenum, caeca and caecal content were collected 50, 54, 74, 76, 78 and 80 h after the start of the treatment. Five animals were euthanized by cervical dislocation at each time interval to obtain the tissue samples. Serum and tissue samples were also taken from healthy untreated animals for control blank samples and for the preparation of standard curves, for HPLC analysis of drug concentrations.

The second (n = 50) and the third (n = 27) groups consisted of infected chickens. They were infected with *E. tenella* at the age of 15 days. The chickens from the *second group* were treated with sulfachloropyrazine-sodium via drinking water for 3 consecutive days. The treatment started at the age of 21 days, 6 days after the infection and after the first clinical signs of coccidiosis. The animals ingested 67 mg/kg sulfachlorpyrazine-sodium, almost equal to the target dose of 70 mg/kg. Serum and tissue samples were collected in the same manner and at the same time intervals as described for healthy treated animals.

In order to determine parasitological parameters, samples from the caecum were taken on the second (n = 6), third (n = 8) and forth (n = 20) days after the start of the treatment. Tissue samples from these animals were also used for determination of the concentrations of sulfachloropyrazine in the duodenum, caecum, caecal content and liver.

The animals from the *third group* remain untreated until the end of the experiment. Tissue samples for parasitological observation from these animals were taken seven days after infection (n = 6) as well as on the eighth (n = 8) and ninth (n = 8) days after the challenge with *E. tenella*. The dead animals (n = 21) from both infected groups (second and third groups) were subjected to pathological examination.

Experimental infection. Eimeria tenella strain was isolated from naturally invaded chickens and enriched via transmission through susceptible birds. A 0.4 mL volume of *E. tenella* culture containing 8×10^4 sporulated oocysts was instilled into the crop of each chicken. The animals were infected at the age of 15 days. Clinical signs of infection were seen in most animals within 6 days after inoculation. Mortality rate, lesion score and oocyst index were registered. Lesion scoring is the numerical ranking of gross lesions caused by coccidia. A score of 0 was set when lesions were not determined; a score of 1 if mild lesions were observed; a score of 2 for moderate lesions; 3 for severe lesions and 4 when extremely severe lesions were recorded (JOHNSON and REID, 1970).

Sulfachlorpyrazine concentrations in serum and tissues. Analytical work was performed in the Central Scientific Laboratory, Trakia University. The serum concentrations of sulfachloropyrazine were determined using the HPLC method with minor modifications (KOWALSKI et al., 2009). KOWALSKI et al. (2009) showed that this analytical method has high specificity and sensitivity and adequate precision and accuracy. Briefly, 2 mL acetonitrile was added to serum samples (200 μL). The samples were centrifuged for 5 min at 339 ×*g*. The organic phase was collected and was evaporated in a vacuum evaporator at 40°C. The residue was dissolved in 200 μL of demineralized Milli-Q-water. Extraction of the antibacterial compound from tissues was performed according to the method cited. A 20 μL aliquot was injected into the HPLC system comprising a Hypersil Spherisorb ODS-2 (C18)-150 × 4.6 mm 5 μM column, a Surveyor LC Pump Plus and Surveyor PDA detector and Surveyor Autosampler Plus (Thermo Fisher Scientific Inc., USA). The samples and standard solutions were monitored at a wavelength of 270 nm. The mobile phase consisted of acetonitrile in aqueous solution (25:75, v/v) of potassium dihydrogenophosphate (0.02 M) in water. The pH of the phosphate buffer was adjusted to 2.7 with phosphoric acid (85%). The flow rate was 1.4 mL/min. Peak area integrations were measured by the ChromQuest Chromatography Data System (Thermo Fisher Scientific Inc., USA). Standard dilutions of sulfachloropyrazine-sodium were prepared in the serum and tissues obtained from untreated chickens at concentrations of 100, 50, 10, 5, 1, 0.5 and 0.2 μg/mL and subjected to HPLC analysis.

Sulfadiazine sodium was used as an internal standard. The internal standard was added to each sample, including standard solutions, at a concentration of 1 mg/mL. The peak area ratio of sulfachloropyrazine-sodium to the internal standard was used for construction of the standard curves. The standard curve was linear over the range of the tested concentrations (r = 0.999). The intra-assay and the inter-assay coefficients of variation (CV) were 2.32 and 11.21, respectively. The limit of detection was 0.2 μg/mL and the limit of quantification was 0.5 μg/mL. Experiments with spiked tissue samples demonstrated that the overall recovery rate in the liver exceeded >77% and in the other tissue specimens it exceeded >65%.

Pharmacokinetic analysis. Pharmacokinetic analysis of the data was performed using a non-compartmental model, steady state mode (WinNonlin 5.0.1., Pharsight Corporation, 800 West El Camino Real, Mountain View, CA, USA). The area under the serum-concentration-time curve (AUC) was calculated by the method of trapezoids, between the times 0 and 80 h. Maximum serum concentration (C_{max}) and the time to reach C_{max} (T_{max}) were taken directly from the observed data, average (C_{avg}) and minimum (C_{min}) serum concentrations were calculated. Mean residence time (MRT) was also calculated. Additionally, data were analyzed by the one-compartmental model (Model 3 from WinNonlin library). Absorption (k_{01}) and elimination (β) rate constants, and respective half-lives were calculated on the basis of simulated serum concentrations for three consecutive days. C_{max} and T_{max} were also predicted with the performed simulations. Pharmacokinetic parameters were calculated by the naive pooling approach. The individual concentrations measured at each time interval were grouped and then time-concentration curves were analyzed for six animals.

Statistical analyses. The pharmacokinetic parameters of sulfachlorpyrazine were presented as mean ± SD. They were computed with the Statistica 6.1 computer program (Statistica for Windows, StatSoft, Inc., USA, 1984-2002). Mann-Whitney test was used for statistical evaluation of differences between healthy and infected animals. Level of significance $P<0.05$ was considered as significant.

Results

Clear clinical signs of caecal cocidiosis appeared within six days after the experimental infection with *E. tenella*. Gross pathological changes such as erosions of the mucosa, blood in the intestinal lumen as well as enlargement of the intestinal size were observed in the caecum. The lesion score and the oocyst index in the treated animals were lower and reached zero at the end of the treatment. In contrast, these parameters in untreated animals were one and twenty at the end of the experiment, respectively. Body weight of the healthy and uninfected chickens before the challenge with *E. tenella* was 258.63 ± 36.04 g. At the end of the experiment, the body weight of the infected animals was

significantly lower in comparison to healthy and to infected and treated animals. The last group of animals did not reach the body weight of healthy chickens (Table 1). The mortality of untreated and treated groups was 44% and 18%, respectively.

Table 1. Changes of the body weight, lesion score and oocyst index in *Eimeria tenella* infected chickens

Group	Body weight at the end of experiment (24 days old)	Seven days after infection (22 days old)		Eight days after infection (23 days old)		Ninth days after infections (24 days old)	
		LS	Oocyst number (OI)	LS	Oocyst number (OI)	LS	Oocyst number (OI)
Healthy (n = 50)	592.90 ± 78.94[a]	0	0	0	0	0	0
Infected (n = 27)	396.64 ± 103.57[b]	3	22.5 ×10^6 (40)	1.5	15 ×10^6 (40)	1	10 ×10^6 (20)
Infected and treated (n = 50)	504.15 ± 93.36[c]	1.6	12.2 ×10^6 (40)	0.6	6.0 ×10^6 (20)	0	Single oocysts (0)

a, b, c - statistically significant differences at $P<0.05$ between healthy, infected and infected and treated animals; LS - lesion score; OI - oocyst index.

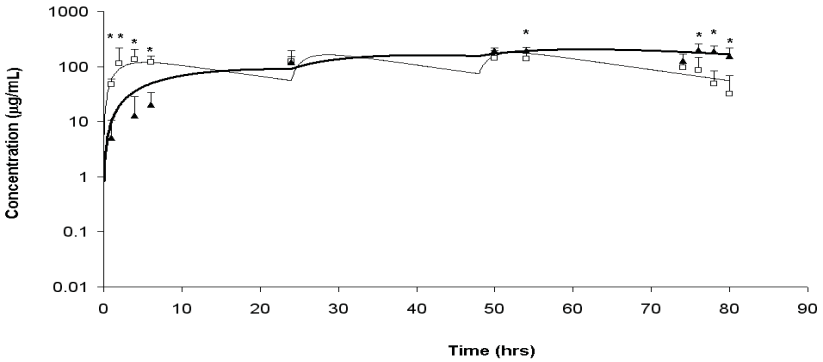

Fig. 1. Predicted (lines) and observed (dots) serum concentrations of sulfachlorpyrazine-sodium after administration for three consecutive days via drinking water at a dose rate of (70 mg/kg) in healthy (n = 40) and *E. tenella* infected (n = 50) chickens. Thick line and triangles show data for infected poultry and thin line and squares - data for healthy animals.

Serum concentrations of sulfachlorpyrazine are shown on Fig. 1. Pharmacokinetic parameters of healthy and infected animals are presented in Tables 2 and 3. After simulation of the serum concentrations with one-compartmental method of analysis, significantly lower value of absorption rate constant and higher values of respective half-live as well as predicted T_{max} were observed in infected animals. Predicted C_{max} values for first hours after treatment based on simulated serum concentrations were insignificantly lower in infected animals. In contrast, the observed C_{max}, and the calculated C_{avg} and C_{min} values during the three days treatment period were significantly higher in infected animals. Similar changes were found in the values of the concentrations measured in the liver, intestinal walls and caecal content (Fig. 2). The other parameters were not significantly changed.

Table 2. Pharmacokinetic parameters of sulfachlorpyrazine at a dosage of 70 mg/kg b.m. after oral (p.o.) administration in healthy (n 40) and infected with *E. tenella* (n = 50) chickens, mean ± SD

Pharmacokinetic parameters	Units	Sulfachlorpyrazine, (p.o., 70 mg/kg b.m.)	
		Healthy animals	Infected animals
One-compartmental analysis			
k_{01}	h^{-1}	0.68 ± 0.51	0.04 ± 0.01*
$t_{1/201}$	h	2.12 ± 2.45	17.24 ± 3.50*
β	h^{-1}	0.06 ± 0.03	0.04 ± 0.01
$t_{1/2\beta}$	h	14.71 ± 5.22	17.31 ± 3.45
$C_{max\ (predicted)}$	$\mu g.mL^{-1}$	117.36 ± 17.32	90.91 ± 9.09
$T_{max\ (predicted)}$	h	5.28 ± 2.51	23.41 ± 3.78*
Non-compartmental analysis			
$C_{max\ (obserevd)}$	$\mu g.mL^{-1}$	164.18 ± 38.46	210.38 ± 16.65*
$T_{max\ (obserevd)}$	h	51.60 ± 2.19	52.0 ± 2.19
C_{min}	$\mu g.mL^{-1}$	113.36 ± 24.74	172.99 ± 13.47*
C_{avg}	$\mu g.mL^{-1}$	120.04 ± 34.05	176.17 ± 18.91*
MRT	h	15.90 ± 2.89	28.12 ± 8.64
$AUC_{0\text{-}80h}$	$\mu g.h.mL^{-1}$	2972.24 ± 1298.01	4855.95 ± 1948.27
Accumulation index		1.09 ± 0.13	1.22 ± 0.13

k_{01} - absorption rate constant; $t_{1/201}$ - absorption half-live; β - elimination rate constant; $t_{1/2\beta}$ - terminal elimination half-life; C_{max} - maximum serum levels; t_{max} - time of C_{max}; C_{avg} - average serum concentration; C_{min} - minimum serum concentration; $AUC_{0\text{-}\infty}$ - area under the serum concentration-time curves from 0 h to ∞; $AUC_{0\text{-}80h}$ - area under the serum concentration-time curves from 0 h to 24 h; MRT - mean residence time; * - statistically significant differences at $P<0.05$

Table 3. Concentrations (mean ± SD) of sulfachlorpyrazine in the intestinal tissues from duodenum and caeca, the content of caeca and the liver.

Pharmacokinetic parameters	Units	Sulfachlorpyrazine, (p.o., 70 mg/kg b.m.)	
		Healthy animals (n = 30)	Infected animals (n = 28)
Caeca			
C_{max}	$\mu g.g^{-1}$	92.75 ± 8.73	176.92 ± 33.31*
C_{min}	$\mu g.g^{-1}$	56.06 ± 24.03	119.23 ± 26.03*
C_{avg}	$\mu g.g^{-1}$	68.82 ± 13.81	123.07 ± 26.54*
Accumulation index		1.48 ± 0.30	4.95 ± 3.10*
Withdrawal time	h	243.17	683.82
Content of caecum			
C_{max}	$\mu g.g^{-1}$	124.44 ± 81.23	277.92 ± 198.36
C_{min}	$\mu g.g^{-1}$	98.69 ± 83.98	171.92 ± 161.20
C_{avg}	$\mu g.g^{-1}$	100.10 ± 49.60	210.94 ± 0.00
Accumulation index		1.13 ± 0.24	1.94
Duodenum			
C_{max}	$\mu g.g^{-1}$	68.85 ± 17.02	125.71 ± 16.35*
C_{min}	$\mu g.g^{-1}$	41.29 ± 15.01	90.35 ± 7.69*
C_{avg}	$\mu g.g^{-1}$	48.90 ± 15.80	103.56 ± 12.08*
Accumulation index		1.54 ± 0.39	3.11 ± 1.36*
Withdrawal time	h	229.70	481.72
Liver			
C_{max}	$\mu g.g^{-1}$	73.03 ± 7.75	159.95 ± 50.60*
C_{min}	$\mu g.g^{-1}$	50.31 ± 18.20	105.07 ± 25.49*
C_{avg}	$\mu g.g^{-1}$	57.68 ± 17.59	107.72 ± 12.56*
Accumulation index		1.57 ± 0.46	3.65 ± 2.52
Withdrawal time	h	250.90	424.18

C_{max} - maximum serum levels; C_{avg} - average serum concentration; C_{min} - minimum serum concentration; .* - statistically significant differences at $P<0.05$

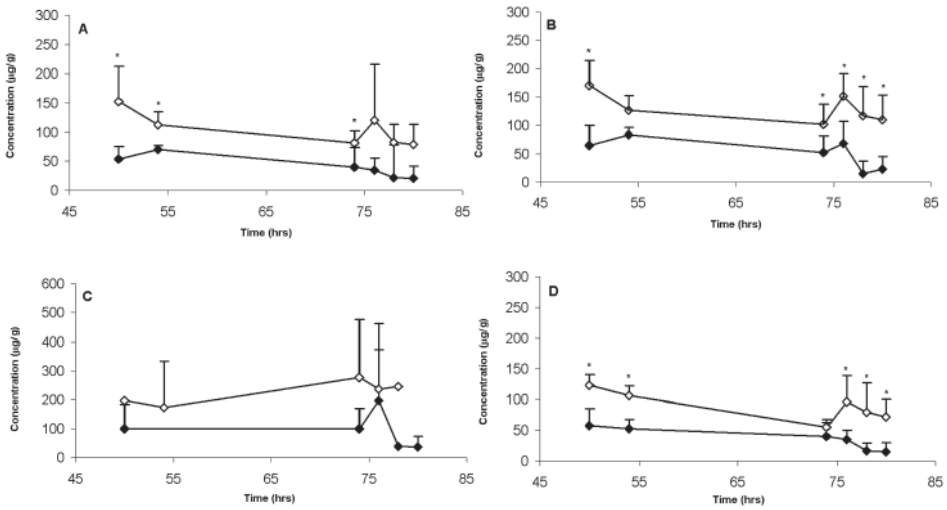

Fig. 2. Observed concentrations of sulfachlorpyrazine-sodium in the liver (A), caeca (B), content in the caeca (C) and duodenum (D) after administration of the drug for three consecutive days via drinking water at a dose rate of (70 mg/kg) in healthy (n = 40) and *E. tenella* infected (n = 50) chickens. ◊ - data for infected poultry; ♦ - data for healthy animals. * - statistically significant difference at P<0.05.

Discussion

Antibacterial and cocidiocidal effect of sulfachlorpyrazine have been well described in the literature. The efficacy of the sulfonamide drug against the oocysts at different stages of development was compared with other anticocidial drugs in many investigations (LACZAY et al., 1995; SIDDIKI et al., 2008; ILIE et al., 2009). Although this drug is used many years, its pharmacokinetics, including the disposition in the target tissues of *Eimeria spp.* infected chickens is not well described. Most of the publications contain data about the sulfachlorpyrazine disposition after single oral administration (HARITOVA and LASHEV, 2002; KOINARSKI and LASHEV, 2006). Therefore, in our study we described sulfachlorpyrazine pharmacokinetics in chickens experimentally infected with *E. tenella* and treated with the drug for three consecutive days via the drinking water.

The experimental infection with *E. tenella* in our study resulted in significant injuries in the mucosa of the caeca up to day six post infection. The observed changes, expressed by the determination of the lesion score and oocyst index, were indicative for *E. tenella* infection. At the end of the treatment, the efficacy of therapy with sulfachlorpyrazine was manifested by lesion score and oocyst index equal to zero. Significant differences

in the body weight between the group of healthy, the group of infected and the group of infected and treated chickens were in line with the reported changes that occurs due to coccidiosis (KETTUNEN et al., 2001; NODEH et al., 2008). Sulfachlorpyrazine treatment allowed normalization of weight gains due to improvement of the integrity and function of the intestinal mucosa. Mean mortality rate of almost 30% allow us to perform the planned experiment with high resemblance of clinical trial. The group of healthy and infected animals consumed amount of water that ensure achievement of nearly equal dose of sulfachlorpyrazine in both groups.

According to our results, pharmacokinetics of sulfachlorpyrazine is significantly affected by the clinical and biochemical changes during coccidiosis in chicken. The rate of the absorption of the drug was significantly decreased in infected animals. Although higher water consumption was expected in the infected chickens, severe increase in total mucosal thickness, a decrease in villus height, damage of the epithelial cells and decreased motility of the gastro-intestinal tract, altogether cause slow and incomplete absorption and later achievement of maximum concentrations in the serum during the first 24 hours of the treatment. The elimination half-life and MRT were not significantly affected by the disease. Similar changes were observed in previous studies with *E. tenella* infected chickens and turkeys (LASHEV, 1998). More interestingly, differences in the value of T_{max} between healthy and infected chickens disappeared during the course of the treatment but significant changes in serum concentrations were observed. Although MRT was insignificantly longer and accumulation index was insignificantly higher, the measured C_{max}, and calculated C_{avg} and C_{min} were significantly increased in the infected animals. Slower absorption and elimination rates resulted in higher accumulation of sulfachlorpyrazine in the serum and tissues of the infected group of animals. Almost double concentrations and accumulation was found in the intestinal wall of the caeca and of the duodenum, and in the liver. Significantly higher concentrations in the intestinal content during the course of the treatment could be attributed to the decreased motility of the intestines and increased feed passage time. Decrease in pH of the infected area of intestines also can contribute to the trapping of the drug molecules (KETTUNEN et al., 2001; NODEH et al., 2008). Together with impaired integrity of the intestines, the measured concentrations in the content of the caeca contribute to higher penetration of the drug in the intestinal cells and to the higher absorption. Although *E. tenella* infection is strongly localized in the caeca, clinical, pathological and biochemical changes are generalized and liver and kidney function is affected which can have impact on the duration of the withdrawal time (GEORGIEVA et al., 2010). Our rough estimations on the basis of mean concentrations show that the withdrawal time in infected animals treated with sulfachlorpyrazine for three days is longer in comparison to the healthy chickens.

In conclusion, our study shows that pathological changes in *E. tenella* infected chickens contribute to slower absorption and elimination rate of sulfachlorpyrazine which resulted in higher accumulation of the drug in the body. Altogether these changes suggest that the achieved concentrations in the infected tissues such as caeca significantly contribute to the efficacy of the treatment. On the basis of the analyzed data, a longer withdrawal time can be expected in infected animals.

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SAŽETAK

Kontrola kokcidioze u pilića pretežito se provodi primjenom protukokcidijskih lijekova (kokcidiostatika). Natrijev sulfaklorpirazin se još uvijek rabi kao učinkovit kokcidiocidni sastojak za liječenje peradi s kliničkim znakovima kokcidioze. Ipak, njegova raspodjela nakon tri dana liječenja nije dovoljno istražena u pilića zaraženih vrstom *Eimeria tenella*. Farmakokinetika natrijeva sulfaklorpirazina u ovom je radu istražena u zdravih i pokusno invadiranih pilića parazitom *E. tenella*. Njegove koncentracije u serumu i tkivima bile su određivane metodom HPLC-PDA. Vrijednosti poluvremena apsorpcije (17,24 ± 3,50 h) i vremena za postizanje najvećih koncentracija u serumu T_{max} (23,41 ± 3,78 h) bile su značajno veće u zaraženih pilića. Procijenjeni akumulacijski indeks bio je 1,22 ± 0,13, a značajno veće serumske koncentracije bile su ustanovljene u zaraženih životinja. Značajno veće razine sulfaklorpirazina bile su dokazane u dvanaesniku, slijepim crijevima i jetri što govori da se može očekivati duže vrijeme izlučivanja u zaraženih pilića nakon trodnevne primjene antikokcidijske tvari. Ustanovljene promjene u raspodjeli sulfaklorpirazina mogu se pripisati promjeni integriteta crijeva i smanjenom motilitetu želučano-crijevnog sustava kod kliničke kokcidioze.

Ključne riječi: pilići, kokcidioza, *Eimeria tenella*, farmakokinetika, sulfaklorpirazin