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Safety of peroral sulfadimidine sodium treatment in chinchillas (*Chinchilla lanigera*)

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ABSTRACT

Safety of peroral sulfadimidine sodium (sulfamethazine) treatment was tested on two chinchilla (*Chinchilla lanigera*) groups. Sulfadimidine sodium was administered in drinking water to male chinchillas aged 5.5 to 7.5 months. Concentration of active ingredient in water was 960 and 1600 mg/l, respectively. During the initial five days the animals were drinking non-medicated water and, subsequently, over five consecutive days, water with sulfadimidine sodium. Sulfadimidine sodium, in concentrations of 960 and 1600 mg/l, did not influence the general health status of chinchillas or quality of faeces and body weight during and after the five-day treatment, nor did it influence the quality of fur, clearness of its colour and its density, which were unchanged immediately after the experiment and at 2.5 months post-treatment. This finding can be considered favourable for chinchilla breeders. Consumption of water with dissolved sulfadimidine, in relation to the non-medicated water intake, was reduced by 10% in group 960 mg/l ($P>0.05$), and by 24% in group 1600 mg/l ($P<0.01$). The average daily intake of sulfadimidine sodium in groups 960 mg/l and 1600 mg/l was 62.36 ± 4.37 mg/kg b.w./day and 89.66 ± 8.46 mg/kg b.w./day, respectively. These doses are in accordance with generally accepted doses for sulfadimidine sodium for the majority of animal species ranging from 50 to 100 mg/kg b.w./day. According to our results, the use of sulfadimidine sodium in drinking water can be recommended in both concentrations for treatment of bacterial infections in chinchillas, especially of gastro-intestinal, urinary and respiratory tract, if the microorganisms or protozoa are susceptible to this synthetic chemotherapeutic.

Key words: chinchilla (*Chinchilla lanigera*), sulfadimidine sodium, safety

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Introduction

The chinchilla (*Chinchilla lanigera*) is a domesticated species from the subfamily of hystricomorphic rodents originating from the South American Andes. In preclinical trials they are often used as otitis media model for evaluation of effects of antibiotics and non-steroidal anti-inflammatory drugs (DIVEN et al., 1995). Chinchillas are also kept as pets, but a vast majority of these animals are farmed for the purpose of obtaining good quality fur (BERDUX and BERDUX, 1959).

The available scientific and professional literature lists the following antimicrobial compounds for peroral treatment of chinchilla bacterial infections: tetracycline chloride, doxycycline, sulphonamides and their potentiated combinations with trimethoprim, chloramphenicol, neomycin and colistin sulphate, metronidazole, flumequine and enrofloxacin (COLLINS, 1995; TYNES, 1998; GÖEBEL, 1999; BURGMANN, 2000; GABRISCH and ZWART, 2001; FINK-GREMMELS et al., 2003).

However, for a very limited number of veterinary drugs, clinical trials on safety and efficacy are conducted in fur-bearing animals such as rabbits, and almost never in chinchillas. Most veterinary antimicrobial drugs do not possess marketing authorisation for exotic animals and these products are not subjected to any regulatory verification in respect of fur-bearing animals. Therefore, the final decisions regarding a patient's therapy are always the responsibility of the attending veterinarian.

Sulphonamides are synthetic compounds of a broad antimicrobial spectrum, which inhibit overgrowth and multiplication of numerous Gram-negative and Gram-positive bacterial species and some protozoa, for example, *Eimeria chinchillae*. These are bacteriostatic rather than bactericidal drugs and are mostly administered perorally since they are rapidly and thoroughly resorbed (BURGMANN, 2000). Clinically, they are used for treatment of alimentary and urinary tract infections, but they could also be used for prevention of soft tissue, respiratory and CNS infections (COLLINS, 1995; GÖEBEL, 1999; GABRISCH and ZWART, 2001; FINK-GREMMELS et al., 2003).

Sulfadimidine (= sulfamethazine) is, globally, the most used sulphonamide (BISHOP, 2001). The speed of its excretion from the organism is not uniform in different animal species, but generally it could be listed as a sulphonamide on the edge of short ($t_{1/2b}$ <8 h) and medium long ($t_{1/2b}$ = 8-24 h) half-life (LÖSCHER et al., 1999). There are no published pharmacokinetic parameters for sulfadimidine sodium in chinchillas.

Sulfadimidin 32% injection solution (Veterina Ltd., Croatia) for parenteral and peroral administration is successfully used for therapy of horses, cows, calves, sheep, pigs, suckling pigs, dogs, cats and poultry, and for exotic animals such as rabbits, pigeons, parrots and other bird species (SAKAR and SAKAR, 1999). Since this compound is not registered for therapy of small monogastric herbivorous animals, in this work we evaluated safety and

possible side effects of sulfadimidine sodium in chinchillas, at concentrations of 960 and 1600 mg/l of drinking water.

Materials and methods

Experimental animals. Male South American chinchillas (*Chinchilla lanigera*) aged 5.5 to 7.5 months were used. Two groups, each comprising 6 animals, totalling 12 individuals in assay.

Chinchillas were kept in a stable measuring 10 x 15 x 3m (V. D. Farm, Virovitica, Croatia) They were divided in two groups, in cages bedded with white pine chips. Animals from one group (n = 6) had mutual access to a single water automated system. Animals were fed ad libitum with 'Complete diet for adult chinchillas' (Veterina Ltd., Croatia) and every individual was administered 5 g of following mix once daily: pelleted lucerne meal, sunflower seeds and oat grain in a weight ratio of 1:0.5:1. Microclimate conditions in the stable were adequate for age and category of animals: air temperature 16 ± 2 °C, average relative humidity 60%, and air exchange 2 - 2.5 x within one hour. Disinfection of stable and cages was conducted immediately prior to housing of chinchillas.

Experimental design. Sulfadimidin 32% solution (Veterina, Ltd., Croatia) contains 320 mg sulfadimidine sodium in 1 ml. In order to determine appropriate concentration of sulfadimidine sodium in drinking water, during the initial five days daily water intake was measured in each group, ranging from 60.5 - 89 ml/kg/day, and on average this was 71.99 ± 7.97 and 73.89 ± 10.43 ml/kg b.w./day. Based on these data, chinchillas were administered sulfadimidine sodium in drinking water, in concentrations of 960 and 1600 mg/l.

Intake of non-medicated, and later on medicated water, was measured daily between 7 and 8 p.m., feeders were filled, fresh water with and without medicine was offered and animals were also given 5 g of the above mentioned mix, which they soon consumed. Body weight of every chinchilla was measured immediately prior to commencement of the assay, and immediately after its end, which was on days -5 and 6 of the experiment.

All animals were monitored on a daily basis - behaviour, feed and water intake and the quantity and quality of faeces.

Statistics. Statistical evaluation of the data was performed using Statgraphic software version 4.0. For individual data the mean ± SD was calculated. Student's paired *t*-test was used to calculate significance. Differences from controls were considered significant at $P<0.05$ and $P<0.01$. Daily water intake and average dose of sulfadimidine sodium (mg/kg b.w./day) was calculated on the basis of body weight means measured on days 5 and 6 of the assay.

Results

Results of the experiment are presented in Table 2 and in Figures 1-4.

Body weight

Table 1. Body weight of chinchillas in groups I and II before and after administration of sulfadimidine sodium in drinking water in concentrations of 960 and 1600 mg/l

Group	Number of animals	Weight of a single animal (g) on day -5. ($\bar{X} \pm$ SD)	Weight of a single animal (g) on day 6. ($\bar{X} \pm$ SD)	P
I. 960 mg/l	6	545.2 ± 53.4	546.7 ± 55.5	n.s.
II. 1600 mg/l	6	517.7 ± 34.7	527.7 ± 31.1	n.s.

n.s. = not significant (P > 0.05)

Water intake

According to the results of the average body weight of single chinchillas in the two groups, determined immediately before administration of non-medicated water (day -5) and immediately after the end of treatment with medicated water containing sulfadimidine sodium (day 6), it can be concluded that the five-day application of this drug did not influence body weight adversely. In group 960 mg/l, body weight remained almost equal to the weight at the beginning of the trial, while chinchillas in group 1600 mg/l increased their weight by 10 g. However, these changes were not at the significance level of 5% (P>0.05, Table 1). Results on water intake before and during administration of sulfadimidine in drinking water indicate that chinchillas in group 960 mg/l decreased water consumption from 71.99 ± 7.97 ml/kg b.w./day to 64.95 ± 4.54 ml/kg b.w./day which, on average, is 10% less (Table 2), but this change was not significant (P>0.05). Conversely, by administration

Table 2. Absolute and relative water consumption of groups I and II before and after administration of sulfadimidine sodium, and average daily dosage intake

Group	Non-medicated water intake during a 5-day period ($\bar{X} \pm$ SD)	%	Concentration of sulfadimidine sodium in drinking water	Medicated water intake during a 5-day period ($\bar{X} \pm$ SD)	%	P
I	71.99 ± 7.97 ml/kg b.w./day	100	960 mg/l	64.95 ± 4.54 ml/kg b.w./day	90	n.s.
II	73.89 ± 10.44 ml/kg b.w./day	100	1600 mg/l	56.06 ± 5.29 ml/kg b.w./day	76	< 0.01

of higher concentrations of sulfadimidine sodium to group II (1600 mg/l), average daily intake of water decreased from 73.89 ± 10.44 ml/kg b.w./day to 56.06 ± 5.29 ml/kg b.w./day, i.e. it decreased by 24% (Table 2). These changes were at the significance level of 1% ($P<0.01$, Table 2).

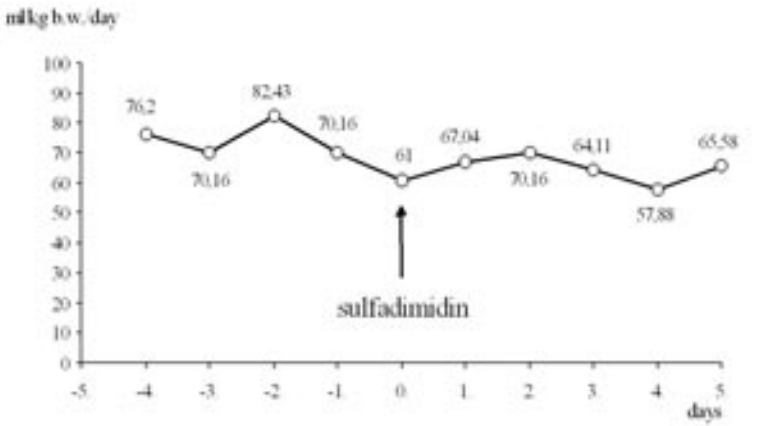

Fig. 1. Average daily water intake (ml/kg b.w.) of male chinchillas in group I before and during administration of sulfadimidine sodium in water in a concentration of 960 mg/l

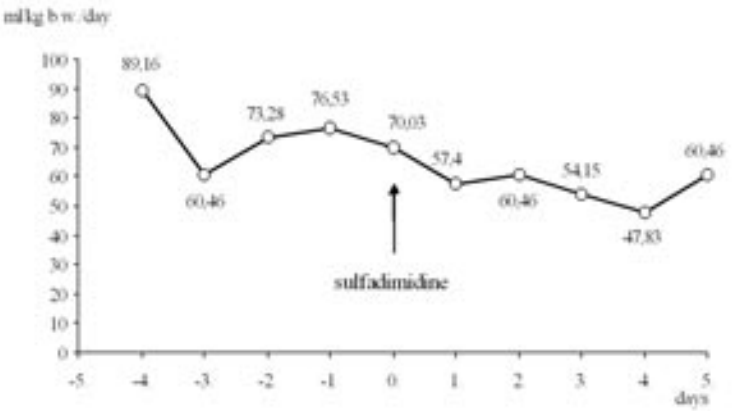

Fig. 2. Average daily water intake (ml/kg b.w.) in male chinchillas of group II before and during administration of sulfadimidine sodium in water in a concentration of 1600 mg/l

Monitoring of intaken quantities of active ingredient in group I, which drank 960 mg sulfadimidine sodium/l, showed that chinchillas had an average intake of 62.36 ± 4.37 mg sulfadimidine sodium/kg b.w./day (Table 3, Fig. 3). Group II, which drank 1600 mg sulfadimidine sodium/l, intook an average dose of 89.66 ± 8.46 mg sulfadimidine sodium/kg b.w./day (Table 3, Fig. 4). The increase of sulfadimidine sodium concentration in drinking water from 960 to 1600 mg/l increased the daily intake of the drug by more than 40%, although animals in group II consumed 24% less water than group I animals (Table 2).

Dosage intake

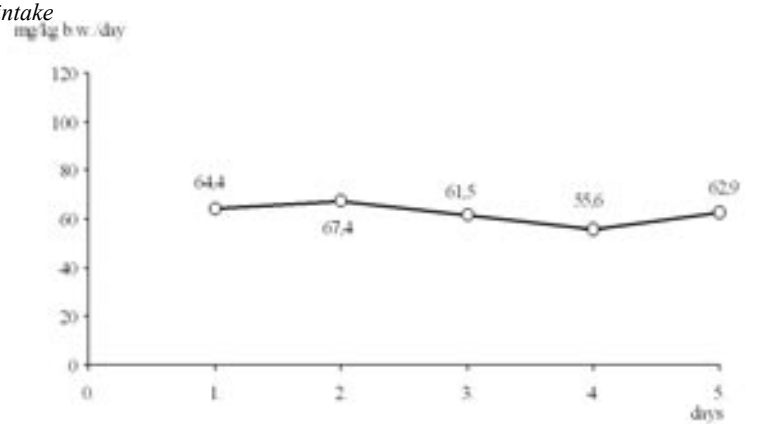

Fig. 3. Peroral intake of sulfadimidine sodium (mg/kg b.w./day) during five-day treatment of chinchillas in group I in a concentration of 960 mg/l in drinking water

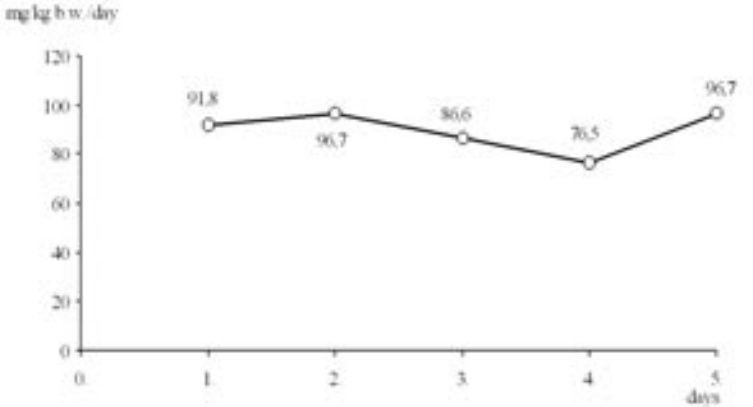

Fig. 4. Peroral intake of sulfadimidine sodium (mg/kg b.w./day) during five-day treatment of chinchillas in group II in a concentration of 1600 mg/l in drinking water

Table 3. Daily dosage of sulfadimidine sodium during five-day treatment of chinchillas

Group	Concentration of sulfadimidine sodium in drinking water	Dose of sulfadimidine sodium during a 5-day treatment ($\bar{X} \pm$ SD)
I	960 mg/l	62.36 ± 4.37 mg/kg b.w./day
II	1600 mg/l	89.66 ± 8.46 mg/kg b.w./day

n.s. = not significant ($P > 0.05$)

Discussion

In veterinary praxis there is a growing need for the correct housing, feeding and treatment of small mammals such as rabbits, rodents, fur-bearing animals and exotic species of birds, reptiles, etc. Bacterial infections of these animal species are relatively frequent and antimicrobial treatment is often required (KRAFT, 1994; GÖEBEL, 1999; GABRISCH and ZWART, 2001). For only a very small number of veterinary drugs approved for application in large, and for some companion animals, have proper clinical assays been conducted to assess their use in fur-bearing animals.

Relatively few papers in the available scientific and professional literature list doses of sulphonamides and their combinations with trimethoprim for treatment of chinchillas and related rodents (COLLINS, 1995; ROSENTHAL, 1998; BURGMANN, 2000; BISHOP, 2001; GABRISCH and ZWART, 2001; FINK-GREMMELS et al., 2003). Dosage recommendations for certain animal species, mentioned in the literature, are often based on the experience of the breeder, or on the basis of very few controlled clinical trials. Therefore, it should be considered that the majority of recommendations for treatment of fur-bearing animals could be regarded merely as basic instructions, while a veterinarian is always responsible for extra-label usage of drugs.

Injection solution Sulfadimidin 32% (Veterina Ltd., Croatia), for peroral and parenteral administration, is not registered for use in chinchillas, although its active substance, sulfadimidine sodium, is recommended for treatment of these and other related rodents (BURGMANN, 2000; BISHOP, 2001). Therefore, clinical trials on safety and eventual side-effects were conducted. Concentration of sulfadimidine sodium in drinking water for treatment of birds and fur-bearing animals, is most often 1000 mg/l, i.e. animals are administered 0.1% solution of this sulphonamide (COLLINS, 1995). Some authors list higher concentrations, ranging from 1000 to 5000 mg/l (BURGMANN, 2000). On the other hand, doses expressed on body weight range from 50 up to 100 mg/kg/day for i.v., i.m., s.c., and p.o. application (LÖSCHER et al., 1999). It is well known that many species of small monogastric herbivores are not to be treated with most β-lactame drugs, macrolides, lincosamides and other related antimicrobials because of possible enterocolitis and lethal clostridiotoxicosis (CARMAN and EVANS, 1984; ROSENTHAL, 1998; GÖEBEL, 1999; BURGMANN, 2000; BISHOP, 2001).

Doses of sulfadimidine sodium administered via drinking water can be regarded as sufficient, as the generally accepted dose of sulfadimidine sodium for most animal species ranges from 50 to 100 mg/kg/day (LÖSCHER et al., 1999), while for guinea pigs, for example, it ranges from 75 to 100 mg/kg/day (FINK-GREMMELS et al., 2003). Daily doses of sulfadimidine sodium in the monitored period were relatively uniform, which implies the good palatability of this antimicrobial drug for chinchillas. Minuscule daily dose aberrations are also an indicator that through the permanent peroral intake of medicated water, sulfadimidine concentrations in blood and tissues most probably remain sufficient, which is an essential condition for successful antimicrobial treatment.

According to the conducted assay, administration of sulfadimidine sodium can be recommended in drinking water in both concentrations: 960 and 1600 mg/l for treatment of chinchilla bacterial infections, particularly of gastro-intestinal, urinary and respiratory system, in circumstances when microorganisms sensitive to this synthetic chemotherapeutic have been isolated. A finding that sulfadimidine sodium did not affect the quality of the fur, and that its colour and density remained unchanged before and immediately after the assay, as well as 2.5 months later, is particularly important for fur-bearing animal farming.

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SAKAR, D., A. PREVENDAR CRNIĆ, D. JANIĆ, T. SAKAR: Neškodljivost peroralne primjene sulfadimidin natrija u činčila (*Chinchilla lanigera*). Vet. arhiv 75, 283-291, 2005.

SAŽETAK

U pokusu je provjerena sigurnost peroralne primjene sulfadimidin natrija (= sulfametazin) u dvije skupine činčila (*Chinchilla lanigera*). Sulfadimidin natrij davan je činčilama muškog spola u dobi od 5,5 do 7,5 mjeseci u vodi za piće u koncentraciji aktivne tvari od 960 mg/l i 1600 mg/l. Životinje su tijekom 5 dana pile vodu bez lijeka, a potom im je 5 uzastopnih dana davana voda sa sulfadimidinom. Koncentracije sulfadimidin natrija od 960 i 1600 mg/l nisu tijekom petodnevnog davanja utjecale na opće zdravstveno stanje, kvalitetu izmeta i tjelesnu masu činčila. Sulfadimidin nije utjecao na kakvoću krzna odnosno na njegovu boju i gustoću 2,5 mjeseca nakon davanja. Potrošnja vode s otopljenim lijekom u skupini koja je dobivala 960 mg/l umanjila se u odnosu na potrošnju vode bez lijeka za 10% ($P > 0,05$), a u skupini koja je dobivala 1600 mg/l za 24% ($P < 0,01$). Peroralnim davanjem otopine sulfadimidin natrija u koncentracijama od 960 i 1600 mg/l postignut je prosječni dnevni unos ovog antimikrobnog lijeka od $62,36 \pm 4,37$ i $89,66 \pm 8,46$ mg/kg t.m. Navedene doze u suglasju su s opće prihvaćenim dnevnim dozama sulfadimidina za većinu životinjskih vrsta od 50 do 100 mg/kg t.m. Na temelju postignutih rezultata može se preporučiti primjena sulfadimidin natrija u vodi za piće u obje navedene koncentracije za liječenje bakterijskih infekcija činčila i to prije svega onih probavnog, mokraćnog i dišnog sustava, a u okolnostima kada su izdvojeni mikroorganizmi ili protozoi osjetljivi na ovaj sintetski kemoterapeutik.

Ključne riječi: činčila (*Chinchilla lanigera*), sulfadimidin natrij, sigurnost primjene