

Effect of Albendazole on the kinetics of Sulphadimidine in West African Dwarf (WAD) Goats following Intramuscular Administration



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Abstract

Cases of mixed infections requiring the use of antimicrobials and anthelmintics are common in veterinary medicine. In view of this, the effect of albendazole on the kinetics of sulphadimidine was studied in eight WAD goats of 1-2 years old with 12.44 ± 0.83 kg mean body weight separated into two groups of four animals each. Sulphadimidine sodium (33.3%) and albendazole (2.5%) were administered intramuscularly at a dose of 100 and 15 mg/kg body weight, respectively. The elimination half-life (5.86 ± 0.59 h) was significantly lower ($p < 0.05$) in the sulphadimidine treated group as compared to the half-life of sulphadimidine/albendazole treated group respectively. However, volume of distribution (Vd) (9.76 ± 1.03 L/kg) and total body clearance (Cl) (1.21 ± 0.22 L/kg/h) were significantly higher ($p < 0.05$) in sulphadimidine treated group as compared to Vd (7.31 ± 0.80 L/kg) and Cl (0.67 ± 0.06 L/kg/h) of the sulphadimidine/albendazole treated group, respectively. Hence albendazole could increase elimination half-life of sulphadimidine, invariably increasing the duration of sulphadimidine antimicrobial activity.

Keywords: Pharmacokinetic; Sulphadimidine; African Dwarf goat; Albendazole; Half-life

Abbreviations: TCA: Trichloroacetic Acid; WAD: West African Dwarf; ICLAS: International Council for Laboratory Animal Science; LOD: Limit of Detection; LOQ: Limit of Quantification

Introduction

Albendazole is extensively used in the treatment of gastrointestinal helminthosis. It has activity against liver flukes, lungworm and migrating larvae with low levels of toxicity in animals [1]. Albendazole inhibit the assembly of microtubule in the sensitive nematode, whereas its metabolite albendazole sulfoxide is responsible for anthelmintic activity [2,3]. Sulphadimidine, a synthetic antimicrobial drug is widely used in the treatment of animal diseases caused by micro-organisms including norcardia, actinomyces, toxoplasma and coccidiosis [4,5]. Low cost and effectiveness are responsible for its widespread use [6]. The kinetics of sulphadimidine has been studied in several species of animals including cattle, goat, sheep, broilers, turkey, guinea fowl, domestic chicken, duck, rabbits and dogs [7-12]. Sulphadimidine is used in combination with albendazole in the treatment of infections caused by microorganisms sensitive to sulphadimidine

and when there is a concurrent diagnosis of helminthosis. Literature reviews have shown no information on the possible interaction between the combination of both drugs. In view of the above, the effect of albendazole on the pharmacokinetics of sulphadimidine was studied in West African Dwarf goats.

Materials

The materials used during the research are Trichloroacetic acid (TCA) manufactured by (Guangdong, China), sodium nitrite (Kermel, China), sulphamic acid (BDH Chemicals, England), 8-OH quinoline (Sinopharm, China), sodium hydroxide (Qualikems, India), distilled water, sulphadimidine sodium (Shijiazhuang Guanghua Pharma. Co, Ltd. China), albendazole (Shijiazhuang Guanghua Pharma. Co, Ltd. China), uv spectrophotometer, vortex mixer, test tubes and test tube rack, measuring cylinder, weighing scale, spatula, lithium heparin tubes, needle and syringes (2 ml).

Animals

This study was carried out in the laboratory of Veterinary Pharmacology and Toxicology, College of Veterinary Medicine, Federal University of Agriculture, Makurdi. The West African Dwarf (WAD) goats were purchased from local breeders in Makurdi metropolis. The goats were screened for the presence of endo and ectoparasites and stabilized for two weeks prior to experimentation. Concentrate and water were provided ad libitum. All the animals were handled according to the international guiding principle for biomedical research involving animals [International Council for Laboratory Animal Science [ICLAS] and Council for International Organization of Medical Sciences (CIOMS), [13] as permitted by the College of Veterinary Medicine, Federal University of Agriculture, Makurdi, Ethical Committee.

Experimental design and drug administration

Eight (8) WAD goats of 1- 2 years old that weighed 12.44 ± 0.83 kg mean weight were separated into two groups of four animals, consisting of two males and female each. Sulphadimidine sodium (33.3%) and albendazole (2.5%) were administered at doses of 100 and 15 mg/kg body weight respectively. Sulphadimidine was administered on the right gluteal muscle to goats. The goats in group 2 also received albendazole suspension orally at the same time.

Collection blood sample

Blood sample (2.0 ml) was collected through the left jugular vein of each goat prior to sulphadimidine administration and at 15, 30, 45 min and 1, 2, 4, 6, 8, 10, 12, 24, 48 hr. The samples collected into heparinized tubes using 23 G disposable needle and 2 ml syringe were centrifuged at 3000 rpm for 10 min. The plasma was obtained and stored at -20°C until analysed.

Determination of sulphadimidine in plasma

Concentration of sulphadimidine in plasma was determined by a modified chemical assay method described by Nagaraja et al. [14]. The method is based on the diazotization of sulphadimidine and coupling with 8-OH quinoline in alkaline media to yield red colored products with absorption maxima at 500 nm. To 0.4 ml of plasma in a 5 ml glass test tube, 2 ml of distilled water was added, followed by 0.6 ml of 20% trichloroacetic acid. The resulting solution was mixed using a vortex mixer and centrifuged for 5 min. To the clear supernatant (2.5 ml) 0.15 ml of 1.0% sodium nitrite was added, mixed and allowed to stand for 5 min. Thereafter, 0.25 ml of 2.0% sulphamic acid was added, mixed and allowed to stand for 5 min. This was followed by addition of 0.2 ml of 0.5% 8-OH quinoline. The resulting solution was mixed and allowed to stand for 5 min, followed by addition of 0.2 ml of 20% sodium hydroxide. The resulting solution was mixed, and the absorbance read using a UV-spectrophotometer (spectrum lab 23A, 340- 1000

nm) at a wavelength of 500 nm. The linear calibration curve of sulphadimidine in plasma within the range of 1.25-20.0 $\mu\text{g/ml}$ was obtained by plotting absorbance on y-axis against time on x-axis with linear regression showed $R^2=0.998$. The limit of detection (LOD) and limit of quantification (LOQ) of sulphadimidine in plasma were 0.08 and 0.24 $\mu\text{g/ml}$ respectively. The intra-day and inter-day precision were 0.50 and 0.80 % respectively.

Calculation of pharmacokinetic parameters

The pharmacokinetic parameters for individual animals were calculated using established kinetic equations [2,15,16] and pharmacokinetic software (Kinetica 5.0, Thermo Fischer Scientific). Micro constants (α , β) were determined from all the plotted graphs obtained from the generated data. Statistical analysis. The data on plasma kinetics and pharmacokinetic parameters were presented in graphical and tabular form respectively. Plasma concentrations and pharmacokinetic parameters were presented as Average \pm Standard Error of Mean (SEM) and analyzed Graph Pad Prism 6.03 for windows at 5% level of significance.

Results

The pharmacokinetic parameters of sulphadimidine in WAD goats administered sulphadimidine alone and sulphadimidine with albendazole is shown in Table 1. Concentrations of sulphadimidine free amine were detected for a period of 48 h. The kinetic disposition of sulphadimidine indicated that the data best fitted a two compartmental open model (Figure 1). There was significant difference ($p<0.05$) between absorption rate constant α ($0.24\pm 0.05/\text{h}$), absorption half-life ($T_{1/2\alpha}$) (3.10 ± 0.57 h), mean absorption time (MAT) (4.98 ± 0.44 h), elimination half-life ($T_{1/2\beta}$) (5.86 ± 0.59 h), volume of distribution (V_d) (9.76 ± 1.03 L/kg), total body clearance (Cl) (1.21 ± 0.22 L/kg/h), mean residence time (MRT) (8.22 ± 0.78 h), area under the curve from zero to 48 h (AUC_{0-48}) (1132.77 ± 91.71 $\mu\text{g/ml.h}$), area under the curve from zero to infinity ($\text{AUC}_{0-\infty}$) (1141.99 ± 90.51 $\mu\text{g/ml.h}$) and area under the moment curve (AUMC) (8795.26 ± 1666.89 $\mu\text{g/ml.h}^2$) in the sulphadimidine treated group as compared to the α ($0.76\pm 0.08/\text{h}$), $T_{1/2\alpha}$ (0.93 ± 0.10 h), MAT (1.34 ± 0.14 h), $T_{1/2\beta}$ (7.42 ± 0.41 h), V_d (7.31 ± 0.80 L/kg), Cl (0.67 ± 0.06 L/kg/h), MRT (11.52 ± 0.30 h), AUC_{0-48} (1766.16 $\mu\text{g/ml.h}$), $\text{AUC}_{0-\infty}$ (1788.98 $\mu\text{g/ml.h}$), and AUMC (18322.59 ± 1749.40) of the WAD goats administered sulphadimidine and albendazole treated group (Table 1). Data are presented as mean \pm SEM; a= significantly higher; b = significantly lower; $p<0.05$. C_{max} = maximum concentration; T_{max} = time of maximum concentration; α = absorption rate constant; $T_{1/2\alpha}$ = absorption half-life; β = elimination rate constant; $T_{1/2\beta}$ = elimination half-life; V_d = volume of distribution; Cl= total body clearance; MRT= mean residence time; AUC_{0-t} = area under the plasma concentration vs time curve from 0 to 48 h; $\text{AUC}_{0-\infty}$ = area under the plasma concentration vs time curve from 0 to infinite; AUMC= Area under the moment curve.

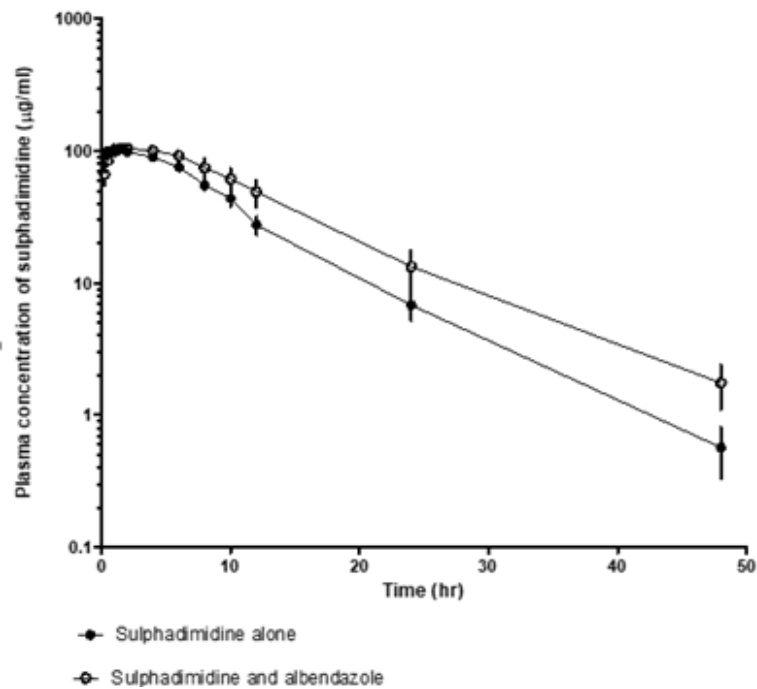


Figure 1: Mean plasma concentrations of sulphadimidine ($\mu\text{g/ml}$) in WAD goats following intramuscular treatment with sulphadimidine (100 mg/kg) alone and sulphadimidine (100 mg/kg) co-administered with albendazole (15 mg/kg) ($n=4$).

Kinetic parameters	Sulphadimidine	Sulphadimidine/ Albendazole
Cmax ($\mu\text{g/ml}$)	106.91 \pm 3.55	106.03 \pm 3.10
Tmax (h)	1.12 \pm 0.24	2.12 \pm 0.65
α (1/h)	0.24 \pm 0.05	0.76 \pm 0.08 ^a
$T_{1/2\alpha}$ (h)	3.10 \pm 0.57	0.93 \pm 0.10 ^b
MAT (h)	4.98 \pm 0.44	1.34 \pm 0.14 ^b
β (1/h)	0.12 \pm 0.02	0.09 \pm 0.01
$T_{1/2\beta}$ (h)	5.86 \pm 0.59	7.42 \pm 0.41 ^a
Vd (L/kg)	9.76 \pm 1.03	7.31 \pm 0.80 ^b
Cl (L/kg/h)	1.21 \pm 0.22	0.67 \pm 0.06 ^b
MRT (h)	8.22 \pm 0.78	11.52 \pm 0.30 ^a
AUC ₀₋₄₈ ($\mu\text{g/ml.h}$)	1132.77 \pm 91.71	1766.16 \pm 51.06 ^a
AUC _{0-∞} ($\mu\text{g/ml.h}$)	1141.99 \pm 90.51	1788.98 \pm 48.81 ^a
AUMC($\mu\text{g/ml.h}^2$)	8795.26 \pm 1666.89	18322.59 \pm 1747.40 ^a

Table 1: Plasma kinetic parameters of sulphadimidine in WAD goats following intramuscular treatment with sulphadimidine (100 mg/kg) alone and sulphadimidine (100 mg/kg) co-administered with albendazole (15 mg/kg) ($n=4$).

Discussion

The pharmacokinetic parameters of sulphadimidine and sulphadimidine in combination with albendazole best fit a two-compartment open model (Figure 1). Our findings agree with the report of Akogwu et al. [7], indicating that intramuscular sulphadimidine obeys first order kinetics in WAD goats. Sulphadimidine has also been reported to follow a two-compartment open model in turkey poults, cows, dogs and buffaloes [10, 17-19]. However, our findings are at variance with the observation in guinea fowls and turkey poults where the disposition kinetics of sulphadimidine was described by mono-exponential decline in plasma levels of the drug with passage of time after administration. The higher absorption rate constant observed in the sulphadimidine/albendazole group shows that albendazole can increase absorption of sulphadimidine. Our findings agree with the report of Saganwan [20] indicating that disposition kinetics of albendazole is dependent on the volume of distribution and could be antagonistic. Metabolites of albendazole could display different disposition kinetics [20] The elimination half-life of sulphadimidine in the WAD goats administered sulphadimidine and albendazole concurrently is higher than the reported values in sheep (4.72 ± 0.26 h) [8] and Nubian goat (4.13 h) [21] and similar to the value reported in WAD goat (7.24 ± 0.59 h) [7]. However, the elimination half-life of sulphadimidine with albendazole is lower than that of cattle (9.46 ± 0.93 h, 8.32 ± 0.96 h) [22] and sheep (9.51 h) [23]. This may be due to the differences in species, route of administration and analytical method employed. This also indicates that kinetics of sulphadimidine differ from one animal to another even among the same animal species [24].

The volume of distribution in animals administered sulphadimidine alone (9.76 ± 1.03 L/kg) and those treated with the combination of sulphadimidine and albendazole (7.31 ± 0.80 L/kg) showed that sulphadimidine has high volume of distribution in WAD goats. These volumes of distributions were higher than those of the dog (0.68 ± 0.12 L/kg), sheep (0.6 ± 0.11 L/kg), guinea fowl (1.29 ± 0.47 L/kg), ducks (2.33 ± 0.36 L/kg) and WAD goat (3.39 ± 0.38 L/kg) [7,11,18,25]. Concurrent administration of sulphadimidine and albendazole decreased the volume of distribution and increased plasma concentrations of sulphadimidine as seen [26,27] (Figure 1). Total body clearance is known to reflect the elimination of drug from the body [20]. The higher the drug concentration in the plasma, the faster the drugs are eliminated as observed in the present study. Treatment with sulphadimidine alone decreased AUC of the drug as compared with that of sulphadimidine/albendazole, signifying that albendazole can decrease disposition kinetics of sulphadimidine.

Conclusion

Albendazole decreased absorption half-life, mean absorption time, volume of distribution and total clearance of sulphadimidine in WAD goats. On the contrary, albendazole increased absorption

rate constant, elimination half-life, mean residence time, area under curve and area under moment curve of sulphadimidine. Hence administration of intramuscular sulphadimidine and albendazole should be done carefully to avoid crystalluria. Administration of albendazole in combination with sulphadimidine significantly altered the kinetic parameters of sulphadimidine in WAD goats. The combination increased the sulphadimidine concentrations in plasma above the minimal inhibitory concentration for several hours when compared to that of sulphadimidine treatment alone. This implies a synergistic interaction between the two drugs.

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