

Effects of Piroxicam on Pharmacokinetics of Sulphadimidine in West African Dwarf Male and Female Goats (*Capra hircus*)

Emmanuel AI, Saganuwan SA* and Onyeyili PA

Department of Veterinary Physiology, Pharmacology and Biochemistry, College of Veterinary Medicine, University of Agriculture, Benue State, Nigeria

*Corresponding address: Saganuwan Alhaji Saganuwan, Department of Veterinary Physiology, Pharmacology and Biochemistry, College of Veterinary Medicine, University of Agriculture, P. M. B 2373, Makurdi, Benue State, Nigeria, Tel: +2347039309400, +2348027444269; E-mail: pharn_saga2006@yahoo.com

Received date: June 19, 2017; Accepted date: July 26, 2017; Published date: July 31, 2017

Copyright: © 2017 Emmanuel AI, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Sulphadimidine is used in the treatment of susceptible enteric bacteria that could cause enteritis and since piroxicam is a potent anti-inflammatory agent, it is co-administered with sulphadimidine intramuscularly. In view of this, effects of piroxicam on the pharmacokinetics of sulphadimidine were studied in West African Dwarf (WAD) goats. Twenty goats of both sexes, aged 1-year-old and weighing 10.4 ± 1.3 kg were divided into two groups of 10 each (5 males; 5 females) were administered 100 mg/kg body weight of sulphadimidine via right thigh muscle, whereas piroxicam (5 mg/kg) was administered to WAD goats (5 males; 5 females). Blood samples were collected over a range of time (0-192 hrs) and analyzed for presence of sulphadimidine. The results showed significant increase ($p < 0.05$) in time maximum ($T_{max} = 1.90 \pm 0.45$ hr), elimination half-life ($T_{1/2\beta} = 9.13 \pm 1.26$ hr) and mean residence time (13.51 ± 1.90 hr) in male goats administered sulphadimidine/piroxicam as compared to T_{max} (1.10 ± 0.29 hr), $T_{1/2\beta}$ (7.24 ± 0.59 hr) and MRT (10.54 ± 0.92 hr) of male goats administered sulphadimidine alone. However, WAD goats showed significant increase ($P < 0.05$) in time maximum ($T_{max} = 1.50 \pm 0.22$ hr), volume of distribution area ($V_{darea} = 3.94 \pm 0.55$ L/kg), elimination half-life ($T_{1/2\beta} = 8.72 \pm 0.84$ hr) and mean residence time (MRT = 12.77 ± 1.90 hr) in female goats administered sulphadimidine with piroxicam as compared to T_{max} (0.90 ± 0.18 hr), V_{darea} (3.39 ± 0.38 l/kg), $T_{1/2\beta}$ (70.68 ± 0.72 hr) and MRT (11.25 ± 1.11 hr) of female goats administered sulphadimidine alone. Co-administration of piroxicam with sulphadimidine may delay elimination of sulphadimidine, prolong its therapeutic effect and withdrawal period in West African Dwarf goats.

Keywords: Piroxicam; Sulphadimidine; Pharmacokinetics; West African dwarf goats

Introduction

Sulphadimidine has proven to be clinically useful since its introduction in veterinary medicine as therapeutic agent for a wide range of microbial diseases, including chlamydia, actinomycosis, toxoplasmosis and coccidiosis. Sulphadimidine is 79% bound to plasma proteins with a half-life of 3.88 to 15.4 hrs and has particularly large percentage (60-90%) excretion as acetylated derivatives. The disposition kinetics of sulphadimidine has been reported in cows, sheep and goat, hen, guinea fowl, domestic chicken and duck, rabbit, turkey poult, grower turkey, dog, broilers, Calves and Swine [1-19].

Non-steroidal Anti-inflammatory Drugs (NSAIDs) are commonly used in animals to reduce pain, fever and inflammation and in the treatment of different clinical conditions such as rheumatoid disorders, osteoarthritis, foot rot and mastitis [20-23]. Piroxicam, is bound to plasma proteins, and has a half-life of 50 hrs and excreted in urine and faeces [24]. It could antagonize the release of prolactin leading to improved fertility, offers neuroprotection in cerebral ischemia which may be positively correlated with lipid solubility at high doses [25-27]. But sex dependent metabolism of the drug appears to be a major determinant of sex related differences in piroxicam pharmacokinetics [28]. The chronic effect of piroxicam is attributed to its chemical transformation [29]. So the risk of bioequivalence is very low. The pharmacokinetics of piroxicam has been reported in rats [28,30-32].

West African Dwarf (WAD) goats (*Capra hircus*) are believed to be the wild Bezoar goat. It is endowed with capacity to resist trypanosome, gastrointestinal nematode, produce wool, milk, improved carcass yield leading to more than 90% of the overall household keeping goats in Nigeria [33-35]. The meat of WAD goats is preferred to other animal meats most especially in the North-Central and South-Eastern Nigeria, because of its flavour, tenderness and palatability [36,37]. It commands higher market price than beef on marriage, religious rites and are insurance against crop failure, a good medium for friendship and peace [38-40].

Piroxicam has higher binding capacity to albumin (91%) and could interfere with the pharmacokinetics of sulphadimidine with albumin binding capacity (79%). In view of the above, effects of piroxicam on the pharmacokinetics of sulphadimidine were studied in male and female West African Dwarf goats.

Materials and Methods

Drugs

Sulphadimidine sodium (33.3 mg/ml) produced by kepro, Holland was used for the study at a single dose of 100 mg/kg body weight and Piroxicam (0.5%) produced by Hanbet, Shandong China was used for the study at a single dose of 5 mg/kg body weight.

Experimental animals and design

This study was conducted in the Department of Veterinary Physiology, Pharmacology and Biochemistry laboratory, College of

Veterinary Medicine, University of Agriculture Makurdi. Twenty healthy goats of both sexes, aged 1-year-old, weighing 10.4 ± 1.3 kg were randomly selected and assigned into two groups of ten each. The goats were fed corn offal and fresh grass; clean water was provided ad libitum. All the animals were handled according to international guiding principle for biomedical research involving animals (CIOMS and ICLAS, 2012) and approved by the appropriate animal care review committee of the University of Agriculture, Makurdi, Nigeria.

Drug administration and sampling

Twenty goats were divided into two groups of 10 each (5 males; 5 females) were used. The first group was administered sulphadimidine im (100 mg/kg body weight) alone, and the second group was administered 100 mg/kg of sulphadimidine and 5 mg/kg of piroxicam via right and left thigh muscle respectively.

Pre-treatment blood samples were collected from the jugular vein into EDTA bottles using 23G needle and 5 ml syringe which served as control, 10 min before drug administration and thereafter at 0.08, 0.16, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 72, 96, 120, 144, 168, and 192 hrs for sulphadimidine assay. The blood samples collected were centrifuged at 5000 rpm and the plasma obtained using a micropipette into cryogenic vials and stored at -20°C for analysis.

Assay of plasma sulphadimidine

Free sulphadimidine in plasma was determined according to the method of Bratton and Marshall and modified by Salinas et al. [41,42]. For the analysis of plasma sulphadimidine, 3.8 ml of distilled water was mixed with 0.2 ml of plasma and treated with 1 ml of 20% trichloroacetic acid. After thorough mixing, the samples were allowed to stand for 10 min. They were centrifuged at 3000 rpm for 10 min. To 2 ml of clear supernatant, 0.1 ml of 0.1% sodium nitrate was added and mixed. The mixtures were allowed to stand for 3 min followed by addition of 0.2 ml 0.5% ammonium sulphamate and mixed. The samples were allowed to stand for 2 min before adding 0.2 ml 0.5% N-(1-naphthyl) ethylene diammine dihydrochloride. The samples were mixed and the optical density of the resulting color determined at 540 nm wavelength using a spectrophotometer. The minimum detection limit of the assay was $0.05 \mu\text{g/ml}$. The linear calibration curve of sulphadimidine in plasma within the range of 1-10 $\mu\text{g/ml}$ was obtained by plotting percentage absorbance against drug concentration. The correlation coefficient (R^2) was greater than 0.93. The concentration of sulphadimidine in plasma was calculated using the formula below:

$$\text{Concentration of the drug (D)} = \frac{\text{Concentration of Standard} \times \text{Optical Density of Drug}}{\text{Optical Density of Standard}}$$

Calculation of pharmacokinetic parameters

The pharmacokinetic parameters for individual animals were calculated using established pharmacokinetic equations [43-47].

Statistical analysis

The data on plasma kinetics and pharmacokinetic parameters of sulphadimidine administered and co-administered with piroxicam were presented in graphical and tabular form respectively. Plasma concentrations and pharmacokinetic parameters were presented as

mean \pm Standard Error of Mean (SEM). Test for significance between the parameters in respect of male and female WAD goats administered sulphadimidine at 100 mg/kg body weight and sulphadimidine (100 mg/kg) co-administered with piroxicam (5 mg/kg) were performed using paired samples Student's t test at 5% level of significance [48].

Results

The result showed male goats to have increased time maximum ($T_{\text{max}}=1.90 \pm 0.45$ hr), absorption rate constant ($\alpha=0.72 \pm 0.08$ hr), elimination half-life ($t_{1/2\beta}=9.13 \pm 1.26$ hr), mean residence time ($\text{MRT}=13.51 \pm 1.90$ hr), mean absorption time ($\text{MAT}=2.93 \pm 0.40$ hr), area under moment curve ($\text{AUMC}=67.12 \pm 16.60$ mg.hr 2/l) and volume of distribution to central compartment ($V_c=7.73 \pm 3.51$ l/kg) in goats administered sulphadimidine/piroxicam as compared to ($T_{\text{max}}=1.10 \pm 0.29$ hr), ($\alpha=0.58 \pm 0.02$ hr), ($t_{1/2\beta}=7.24 \pm 0.59$ hr), ($\text{MRT}=10.54 \pm 0.92$ hr), ($\text{MAT}=1.72 \pm 0.058$ hr), ($\text{AUMC} = 37.37 \pm 10.58$ mg.hr 2/l) and ($V_c = 6.32 \pm 2.70$ l/kg) of goats administered sulphadimidine respectively. However elimination intercept ($B=1.36 \pm 0.83 \mu\text{g/ml}$), concentration maximum ($C_{\text{max}}=244.08 \pm 10.11 \mu\text{g/ml}$), volume of distribution area ($V_{\text{darea}}=2.88 \pm 0.20$ l/kg), absorption half-life ($t_{1/2\alpha}=1.03 \pm 0.17$ hr), body clearance ($\text{Cl}_b=0.23 \pm 0.03$ l/kg/hr) and elimination rate constant from central compartment to peripheral compartment ($K_{12}=0.37 \pm 0.085$ hr $^{-1}$) were significantly lower ($P<0.05$) in goats administered sulphadimidine/piroxicam, in comparison with B ($13.91 \pm 4.30 \mu\text{g/ml}$), C_{max} ($262.42 \pm 29.13 \mu\text{g/ml}$), V_{darea} (3.91 ± 0.76 l/kg), $t_{1/2\alpha}$ (1.90 ± 0.007 hr), Cl_b (0.39 ± 0.094 l/kg/hr) and K_{12} (0.52 ± 0.09 hr $^{-1}$) of male goats administered sulphadimidine. Other parameters such as absorption intercept (A), elimination rate constant (β), area under curve from zero to 192 hrs (AUC_{0-92} hr), area under curve from zero to infinity ($\text{AUC}_{0-\infty}$), volume of distribution in peripheral compartment (V_{ext}), elimination rate constant from central compartment to outside (K_{10}) and elimination rate constant from peripheral to central compartment (K_{21}) did not increase significantly ($P>0.05$) between the groups administered sulphadimidine and sulphadimidine/piroxicam (Table 1). The pharmacokinetic evaluation of sulphadimidine in male goats indicated that the data fit a two compartment open model.

Female goats showed significant increase ($P<0.05$) in elimination intercept ($B=25.68 \pm 17.32 \mu\text{g/ml}$), time maximum ($T_{\text{max}}=1.50 \pm 0.22$ hr), volume of distribution area ($V_{\text{darea}}=3.94 \pm 0.55$ l/kg), elimination half-life ($T_{1/2\beta}=8.72 \pm 0.84$ hr), mean residence time ($\text{MRT}=12.77 \pm 1.90$ hr), and volume of distribution steady state ($V_{\text{ss}}=41.99 \pm 3.00$ mg/l) in female goats administered sulphadimidine with piroxicam as compared with B ($11.74 \pm 9.73 \mu\text{g/ml}$), T_{max} (0.90 ± 0.18 hr), V_{darea} (3.39 ± 0.38 l/kg), $t_{1/2\beta}$ (70.68 ± 0.72 hr), MRT (11.25 ± 1.11 hr) and V_{ss} (14.98 ± 5.24 mg/l) of the female West African dwarf goats administered sulphadimidine alone. However, concentration maximum ($C_{\text{max}}=236.32 \pm 16.80 \mu\text{g/ml}$) decreased significantly ($P<0.05$) in the goats administered sulphadimidine/piroxicam as compared to the goats administered sulphadimidine ($C_{\text{max}}=243.02 \pm 16.45 \mu\text{g/ml}$) respectively. Other pharmacokinetic parameters investigated did not increase significantly ($p>0.05$) between goats administered sulphadimidine and sulphadimidine/piroxicam (Table 2). The pharmacokinetic evaluation of the sulphadimidine in female goats indicated that the data fit a two compartment open model.

Kinetic parameters	Sulphadimidine alone	Sulphadimidine/piroxicam	P-value
A (µg/ml)	98.14 ± 36.02	72.29 ± 18.42	P>0.05
B (µg/ml)	13.91 ± 4.30	1.36 ± 0.83	P<0.05
C _{max} (µg/ml)	262.42 ± 29.13	244.08 ± 10.11	P<0.05
T _{max} (hr)	1.10 ± 0.29	1.90 ± 0.45	P<0.05
Vd (area) (L/kg)	3.91 ± 0.76	2.88 ± 0.20	P<0.05
α (1/h)	0.58 ± 0.02	0.72 ± 0.08	P<0.05
β (1/h)	0.098 ± 0.007	0.084 ± 0.014	P>0.05
T _{1/2α} (hr)	1.90 ± 0.088	1.03 ± 0.17	P<0.05
T _{1/2β} (hr)	7.24 ± 0.59	9.13 ± 1.26	P<0.05
Clb (L/kg/hr)	0.39 ± 0.094	0.23 ± 0.031	P<0.05
MRT (hr)	10.54 ± 0.92	13.51 ± 1.90	P<0.05
MAT (hr)	1.72 ± 0.058	2.93 ± 0.40	P<0.05
AUC ₀₋₉₆ (mg/l/hr)	3.33 ± 0.68	4.62 ± 0.65	P>0.05
AUC _{0-∞} (mg/l/hr)	3.34 ± 0.69	4.65 ± 0.65	P>0.05
AUMC (mg.hr 2/l)	37.37 ± 10.58	67.12 ± 16.60	P<0.05
V _{ss} (mg/l)	13.79 ± 3.68	26.31 ± 9.30	P<0.05
V _c (L/kg)	6.32 ± 2.70	7.73 ± 3.51	P>0.05
K ₁₀	0.0014 ± 0.0006	0.00061 ± 0.00022	P>0.05
K ₁₂	0.52 ± 0.09	0.37 ± 0.085	P<0.05

A: Absorption phase; B: Elimination phase; C_{max}: Peak concentration; T_{max}: Peak time; Vd(area): Volume of distribution area; α: Absorption rate constant; β: Elimination rate constant; t_{1/2α}: Absorption half-life; t_{1/2β}: Elimination half-life; Clb: Clearance; MRT: Mean residence time; MAT: Mean absorption time; AUC₀₋₉₆: Area under the curve zero to 96 h; AUC_{0-∞}: Area under the curve zero to infinity; AUMC: Area under the moment curve; V_{ss}: Volume of distribution steady state; V_c: Volume of distribution central compartment; K₁₀: Elimination rate constant from central compartment to outside; K₁₂: Elimination rate constant from central compartment to peripheral compartment

Table 1: Pharmacokinetic parameters of sulphadimidine in male WAD goats following intramuscular treatment with sulphadimidine alone (100 mg/kg) body weight and sulphadimidine (100 mg/kg) co-administered with piroxicam (5 mg/kg).

Discussion

The lower elimination intercept (B), Volume of distribution (Vd), Concentration maximum (C_{max}), time of maximum drug concentration (T_{max}), absorption half-life (t_{1/2α}, elimination half-life (t_{1/2β}), body clearance (Clb) and distribution from central compartment to peripheral compartment (K₁₂) in WAD goats administered sulphadimidine/piroxicam in comparison with the goats administered sulphadimidine, show that piroxicam and sulphadimidine compete for same binding site, albumin [49]. However, the increased T_{max}, α, t_{1/2β}, MAT, AUMC and V_{ss} of goats administered sulphadimidine/piroxicam in comparison with sulphadimidine show that piroxicam can increase bioavailability of sulphadimidine in goats. The C_{max} of sulphadimidine was higher in the goats administered sulphadimidine alone (C_{max}=262.42 ± 29.13 µg/ml) than in the goats administered sulphadimidine/piroxicam (C_{max}=244.08 ± 0.11 µg/ml) but lower in the non-starved guinea fowl (52.5 ± 2.62 µg/ml) administered intramuscular sulphadimidine [50].

But the elimination half-life (T_{1/2β}=9.13 ± 1.26 hr) of goats administered sulphadimidine/piroxicam is higher than that of non-starved guinea fowl (7.2 ± 2.6 hr) administered intramuscular sulphadimidine at the same dose rate. However the elimination half-life of sulphadimidine in the two groups of goats (t_{1/2β}=7.24 ± 0.59; 9.13 ± 1.26 hr) is lower than that of dog, 16.80 ± 3.9 hr, 16.00 ± 0.00 hr, camel (13.20 ± 0.00 hr), horse, 13.00 ± 0.00 hr, 9.80 ± 0.00 hr, 11.40 ± 2.26 hr, cattle, 11.2 ± 0.43 hr, pigs, 11.9 ± 0.7 hr, 11.05 ± 2.76 hr, 13.00 ± 0.00 hr, but similar to that of buffalo 7.69 ± 2.39 hr, 9.38 ± 0.00 hr) and higher than that of sheep (2.9 ± 0.7 hr, 4.75 ± 0.00 hr, 4.00 ± 0.00 hr), rabbit (3.00 ± 0.00 hr) and chickens, 3.00 ± 0.00 hr and male turkeys, 7.62 ± 0.51. Interspecies comparisons of sulphadimidine disposition have been considered in connection with the influence of variations in metabolic rate in relation to body weight and glomerular filtration rate [7,8,15,18,50-59].

Kinetic parameter	Sulphadimidine alone	Sulphadimidine/piroxicam	P-value
A (µg/ml)	106.86 ± 20.54	109.34 ± 20.04	P>0.05
B (µg/ml)	11.74 ± 9.73	25.68 ± 17.32	P<0.05
C _{max} (µg/ml)	243.02 ± 16.45	236.32 ± 16.80	P<0.05
T _{max} (hr)	0.90 ± 0.18	1.50 ± 0.22	P<0.05
Vd (area) (L/kg)	3.39 ± 0.38	3.94 ± 0.55	P<0.05
α (1/h)	0.54 ± 0.10	0.46 ± 0.04	P>0.05
β (1/h)	0.09 ± 0.008	0.082 ± 0.08	P>0.05
T _{1/2α} (hr)	1.58 ± 0.37	1.53 ± 0.14	P>0.05
T _{1/2β} (hr)	7.68 ± 0.72	8.72 ± 0.84	P<0.05
Clb (L/kg/hr)	0.29 ± 0.032	0.30 ± 0.019	P>0.05
MRT (hr)	11.25 ± 1.11	12.77 ± 1.19	P>0.05
MAT (hr)	2.28 ± 0.51	2.09 ± 0.28	P>0.05
AUC ₀₋₁₉₂ (mg/L/hr)	3.45 ± 0.53	3.36 ± 0.31	P>0.05
AUC _{0-∞} (mg/L/hr)	3.46 ± 0.53	3.38 ± 0.31	P>0.05
AUMC (mg.hr 2/l)	39.27 ± 6.86	40.09 ± 4.94	P>0.05
V _{ss} (mg/l)	14.98 ± 5.24	41.99 ± 3.00	P>0.05
V _c (L/kg)	2.77 ± 0.60	3.15 ± 0.69	P>0.05
K ₁₀	0.00050 ± 0.00011	0.00052 ± 0.00017	P>0.05
K ₁₂	0.53 ± 0.09	0.51 ± 0.06	P>0.05

A: Absorption phase; B: Elimination phase; C_{max}: Peak concentration; T_{max}: Peak time; Vd(area): Volume of distribution area; α: Absorption rate constant; β: Elimination rate constant; t_{1/2α}: Absorption half-life; t_{1/2β}: Elimination half-life; Clb: Clearance; MRT: Mean residence time; MAT: Mean absorption time; AUC₀₋₉₆: Area under the curve zero to 96 h; AUC_{0-∞}: Area under the curve zero to infinity; AUMC: Area under the moment curve; V_{ss}: Volume of distribution steady state; V_c: Volume of distribution central compartment; K₁₀: Elimination rate constant from central compartment to outside; K₁₂: Elimination rate constant from central compartment to peripheral compartment.

Table 2: Pharmacokinetic parameters of sulphadimidine in female WAD goats following intramuscular treatment with sulphadimidine alone at 100 mg/kg body weight and sulphadimidine (100 mg/kg) co-administered with piroxicam (5 mg/kg).

The lower elimination half-life in group administered sulphadimidine is suggestive of higher level of distribution in various body fluids and tissues. But the value of elimination rate constant ($0.098 \pm 0.07 \text{ hr}^{-1}$) in the WAD goats administered sulphadimidine in this study is comparable with that of non-starved guinea fowls ($0.096 \pm 0.02 \text{ hr}^{-1}$) administered intramuscular sulphadimidine [50] suggesting that two different species of animals may have similar way of eliminating sulphadimidine from their bodies. Sulphadimidine has been documented to be more rapidly eliminated after injection faster than oral sulphadimidine mixed with feed or drinking water [60]. The renal clearance of metabolites of sulphadimidine was reported to be 10 times greater than that of sulphadimidine as a parent drug indicating that its metabolites are excreted faster than the parent drug [9].

Once pseudo-distribution equilibrium has been established; the rate of decline in plasma concentration is reduced and determined mainly by the elimination of the drug from the central compartment [46].

The half-lives of the majority of drugs including sulphadimidine which are used as the therapeutic agents in humans and domestic

animals are independent of dose administered, since their overall elimination obeys first order kinetics (i.e. exponential) which implies that a constant fraction of the drug present in the body is eliminated per unit of time. However, the higher the absorption rate constant ($0.72 \pm 0.08 \text{ hr}$) observed in WAD goats administered sulphadimidine/piroxicam in comparison with β ($0.58 \pm 0.02 \text{ hr}$) of goats administered sulphadimidine, may suggest that piroxicam can delay the absorption of intramuscular sulphadimidine. But an estimate of the absorption rate of a drug from a particular dosage form is given by the time at which the peak is reached on the plasma concentration versus time curve, plotted in arithmetic coordinates. Absorption continues after the peak plasma concentration has been reached [46]. However, the decrease in elimination intercept (B), C_{max}, Vd, t_{1/2β}, Clb, and K₁₂ show that the rate of absorption of sulphadimidine and its concentration in the central compartment and peripheral compartment can be affected by co-administration of piroxicam. This may be as a result of depletion of body protein which is the biological fuel of last result [60,61].

The pharmacokinetic behavior of sulphadimidine in the West African dwarf goats under the present study is best described by two compartment open model. This is at variance with findings in turkey poult [12], guinea fowl, domestic chicken and duck [10], sheep, goat and buffaloes [51] where the drug was eliminated by one compartment model. This may be due to variation in the species and co-administration of two drugs and route of administration. However, our findings are in agreement with the findings in dogs, broiler chicken, Cows and buffaloes indicating that the kinetic profile of a drug may differ from one animal to another or even among the same species of animals [7,15,16,51,56,62]. The higher increased intercept (B), T_{max} , Vd, $t_{1/2\beta}$ and Vss of the goats administered sulphadimidine/piroxicam in comparison with the values of goats administered sulphadimidine show that piroxicam can decrease time maximum, volume of distribution, half-life and volume of distribution, steady state of sulphadimidine in goats. However, the increased T_{max} and decreased C_{max} of sulphadimidine in the goats administered sulphadimidine/piroxicam show that the lower the concentration, the higher the time maximum. However, the volume of distribution ($Vd=3.94 \pm 0.55$ L/kg) is higher in the goats administered sulphadimidine/piroxicam as compared with the goats administered sulphadimidine (3.39 ± 0.38 L/kg). However, Vd values are lower in guinea-fowl (1.29 ± 0.47 L/kg), chicken 1.08 ± 0.06 L/kg, dog 0.68 ± 0.12 L/kg and sheep 0.6 ± 0.11 L/kg [10,15,54,63]. The more extensive distribution of sulphadimidine in West African dwarf goats may be suggestive of slower elimination of the drug in the animals as shown by low rate of elimination from central compartment to outside. The greater the volume of distribution, the longer the half-life and the slower the drug eliminated from the body [16]. The elimination half-life of the WAD goats administered sulphadimidine ($t_{1/2\beta}=7.68 \pm 0.72$ hr) and sulphadimidine/piroxicam ($t_{1/2\beta}=8.72 \pm 0.84$ hr) are lower than the elimination half-life of starved broiler chicken ($t_{1/2\beta}=11.60 \pm 0.72$ hr), ducks ($t_{1/2\beta}=9.0 \pm 0.9$ hr) sheep, 3.93 ± 0.61 hr, 4.50 ± 0.3 hr, 4.5 hr, 4.0 hr, 3.28 hr (54,18,64,8,65), but higher than that of guinea fowl ($t_{1/2\beta}=6.0 \pm 0.9$ hr), domestic chicken, $t_{1/2\beta}=6.2 \pm 0.8$ hr, cow, 11.30 hr, 11.08 ± 2.68 hr, 14.5 hr, 10.53 hr administered intravenous sulphadimidine. However, Silvestri et al. reported elimination half-life (8 hr) of sulphadimidine in cow [7,10,54,64-67].

There are considerable within-species and inter-species variations in half-life which are likely to be due in part, to the method applied in the corresponding investigations [54]. However, interspecies variations in half-life not related to size could be introduced by other factors. It could be assumed that these differences also illustrate the need for analyses of correlation between the half-life and body weight of sulphadimidine, before a decision is made as to the extent the available pharmacokinetic data are of relevance in the prediction of an appropriate dosage regimen [54]. Lack of significant difference in body clearance, mean resident time, area under the curve zero to 96 hr, area under the curve zero to infinity, area under the moment curve and volume of distribution of central compartment of goats administered sulphadimidine/piroxicam in comparison with sulphadimidine may connote that piroxicam can not affect these parameters in female West African Dwarf goats. The observation may not affect extent of metabolism, rate of renal clearance of the drug and the acetylation-deacetylation equilibrium which govern the elimination half-life of sulphadimidine and its persistence in the body, hence sulphadimidine is eliminated by an extensive biotransformation and by renal excretion of metabolites and parent substance [17,18]. The ultimate objective of a satisfactory dosage regimen is to maintain the plasma drug level above minimum inhibitory concentration (MIC) during treatment period.

For sulphonamides the MIC was reported to be $50 \mu\text{g/ml}$ [1,4]. Concentration of sulphadimidine in the goats administered Sulphadimidine and sulphadimidine/piroxicam under the present study appeared above $50 \mu\text{g/ml}$ of MIC, 7 and 9 hr respectively.

Conclusion

Co-administration of piroxicam with sulphadimidine delay elimination of sulphadimidine invariably prolonging its therapeutic effect but may prolong withdrawal period of sulphadimidine in West African Dwarf goats. Hence the tissues may pose threat of Stevens-Johnsons syndrome to susceptible humans.

Acknowledgement

Dr. Agbo Joseph Odeh is acknowledged for typing and sending of the manuscript. Funding-The research was funded by the authors. The authors declare no conflict of interest.

References

1. Bywater RJ (1982) Veterinary Applied Pharmacology and Therapeutics (4th edn.). Bailliere Tindal, London.
2. Bevil RF (1991) Sulphonamides. In: Booth NH and McDonald LE (eds.) Veterinary Pharmacology and Therapeutics (6th edn.). Iowa State University Press, Ames, Iowa, pp:785-795.
3. Grahame-smith DG, Aronson KJ (1992) Oxford textbooks of clinical medicine and drug therapy (2nd edn.). Oxford University Press, Oxford.
4. Bevil JD (1982) Sulphonamide. In: Booth NH and McDonald LE (eds.) Jones Veterinary Pharmacology and Therapeutics. Kalyani Publications, New Delhi, India pp: 717-726.
5. Prescott JF (2000) Antimicrobial therapy in veterinary medicine. 3rd Blackwell, Iowa.
6. Baggot JD (2001) The physiological basis of veterinary clinical pharmacology. Blackwell Science, Oxford, UK.
7. Niel0073en, Rasmussen F (1977) Half-life, volume of distribution and protein binding for some sulphonamides in cows. Vet Res Sci 22: 205-208.
8. Nawaz M, Khan FH (1979) Pharmacokinetics of and urinary excretion of sulphadimidine in sheep and goats. J Vet Pharmacol Thera 2: 129-132.
9. Nouws JFM, Geertsma MF, Grondel JL, Aerts MML, Vree TB, et al. (1988) Plasma disposition and renal clearance of sulphadimidine and its metabolites in laying hens. Res Vet Sci 44: 202-207.
10. Onyeyili PA, Egbu GO, Apampa OA, Ameh J (1997) Elimination of sulphadimidine from edible tissues and blood of guinea fowl, domestic chickens and ducks. Bull. Afri Ani Hlth Prod 45: 225-229.
11. Etuk EU, Umarudeen AM, Onyeyili PA, Elsa TA (2006) Effect of short term starvation on the plasma kinetics of sulphadimidine in rabbits. Intl J Pharmacol 2: 331-334.
12. Heath GE, Kline DA, Bames CJ, Showalter DH (1975) Elimination of sulphamethazine from edible tissues, blood, urine and feces of turkey poult Amer J Vet Res 36: 913-197.
13. Agbo JO, Saganuwan SA, Onyeyili PA (2016) Tissue distribution of sulphadimidine sodium in non-starved and starved grower turkeys (Meleagris gallopavo). Intl J Pharmacol Toxicol 4: 154-158.
14. Agbo JO, Saganuwan SA, Onyeyili PA (2016) Comparative pharmacokinetics of intramuscular sulphadimidine in non-starved and starved male and female grower turkeys. J Pharmacol Toxicol 11: 11-19.
15. Elsa SA, Mahammad AT (2003) Disposition kinetics of sulphadimidine in Nigerian mongrel dogs. J Sci Ind Stud 1: 35-38.
16. Onyeyili PA, Ogundele OO, Sanni S (2000) Effect of starvation on the elimination kinetics of sulphadimidine in Broiler chickens. Nig J Experi Appl Biol 1: 25-28.
17. Nouws JFM, Vree TB, Baakman M, Driessens F, Breukink HJ, et al. (1986) Age and dose dependency in the plasma disposition and the renal

- clearance of sulfamethazine and its N4-acetyl and hydroxyl metabolites in calves and cows. *Am J Vet Res* 205: 171-183.
18. Nouws JFM, Vree TB, Aerts R, Grodel J (1986) Pharmacokinetics and residues of sulphadimidine, its N4-acetyl and hydroxyl metabolites in food producing animals. *Archiv Für Lebensmittelhygiene* 37: 57-84.
19. Duffee NE, Berill RF, Thurmon JC, Luther HG, Nielsen DE, et al. (1984) Pharmacokinetics of sulphadimidine in male, female and castrated male swine. *J Vet Pharmacol Ther* 7: 203-211.
20. Deleforge JE, Thomas JL, Divot JL, Bireme B (1994) A field evaluation of the efficacy of tolfenamic acid and oxytetracycline in the treatment of bovine respiratory disease. *J Vet Pharmacol Ther* 17: 43-47.
21. Godson DL, Campos M, Attah-poku SK, Redmond MJ, Cordeiro DM, et al. (1996) Serum heptoglobin as an indicator of the acute phase responder in bovine respiratory disease. *Vet Immunol Immunopathol* 51: 277-292.
22. Huskisson EC, Ghozlan R, Kurthen R, Degner FL, Bluhmki ER (1996) A long term study to evaluate the safety and efficacy of meloxicam therapy in patients with rheumatoid arthritis. *Rheumatol Br J* 35: 29-34.
23. Daniel LS, Regina MB, Timothy H (2004) Cyclooxygenase isozymes: The biology of prostaglandin synthesis and inhibition. *Pharmacol Rev* 56: 387-437.
24. Brayfield A (2004) *Matindale: the complete drug reference*. Pharmaceutical press, London, UK.
25. Saganuwan SA, Agbaji OA (2015) Toxicological effects of piroxicam. *J Exper Neurosci* 10: 121-128.
26. Bhattacharya P, Pandey AK, Paul S, Patnaik R (2014) Alleviation of glutamate mediated neuronal insult by piroxicam in rodent model of focal cerebral ischemia: a possible mechanism of GABA agonism. *J Physiol Biochem* 70: 901-13.
27. Saganuwan SA (2016) Physicochemical and structure-activity properties of piroxicam- a mini review. *Comp Clin Pathol* 25: 1-5.
28. Roskos LK, Boudinot FD (2006) Effect of dose and sex on the pharmacokinetics of piroxicam in the rat. *Biopharm Drug Dispos* 11: 215-225.
29. Frank I, Grimme S, Peyerin Hof SD (1996) Quantum chemical investigations of the thermal and photo-induced protein transfer reactions of 2-(2,4'-clinitrobenzyl) pyridine. *J Chem Phys* 91: 5694-5700.
30. Park CW, Ma KW, Jang SW, Son M, Kang MJ (2014) Comparison of piroxicam pharmacokinetics and anti-inflammatory effect in rats after intra-articular and intramuscular administration. *Biomol Thera* 22, 260-266.
31. Saidu SA, Fada AM (1989) Influence of cimetidine on the Pharmacokinetics of piroxicam in rat and man. *Arzneimittel-Forschung* 39: 790-792.
32. Tagilati CA, Kimura E, Northenberg MS, Santos SR, Oga S (1999) Pharmacokinetic profile and adverse gastric effect of zinc-piroxicam in rats. *Gen Pharmacol* 33: 67-71.
33. Chiejina SN, Behnke JM (2011) The unique resistance and resilience of the Nigerian West African Dwarf goats to gastrointestinal nematode infection. *Parasites and Vector* 4: 1-10.
34. Ifut OJ, Inyang VA, Udosi IS, Ekpo MI (2011) Carcass yield of West African Dwarf goat fed mixed forages and brewers' spent grain. *Nig J Agric Food Environ* 7: 77-79.
35. Ukpabi UH, Emerole CO, Ezeh CI (2000) Comparative of Strategic goat marketing in Umahia regional market in Nigeria, Preceeding of 25th Annual Conference of Nigerian Society for Animal Production pp: 364-365.
36. Odeyinka SM (2000) Feeding behavior and diet selection by West African Dwarf goats. *Arch Tierz Dummerst* 43: 57-61.
37. Idiong NB, Orok EJ (2008) Acceptability of some fodder plants by West African Dwarf goats. *J Agric Techno Bus Appl Sci* 1: 33-37.
38. Idiong NB, Udome GN (2008) Sex influence on performance of West African Dwarf goats. *Elect J Agri Environ Agri Food Chem* 10: 2350-2355.
39. Gefu JO, Audu IF, Alawa BI, Magaji SO (1994) Characteristics of small holder sheep and goat management practices in South East Nigeria. *Nig J Anim Prod* 21: 127-135.
40. Mattewman RW (1980) Small ruminant production in the humid tropical zone of Southern Nigeria. *Trop Anim Hlth Prod* 1: 234-242.
41. Bratton AC, Marshall EK. 1939. A new coupling component of sulphonamide determination. *J Biochem* 128: 537- 550.
42. Salinas F, Mansilla E, Nevado JJB (1990) Derivative spectrophotometric determination of sulphonamides by Bratton-Marshall reaction. *Analytica Chemica Acta* 233: 289-294.
43. Saganuwan SA (2012) *Principles of pharmacological calculations*. Ahmadu Bello University Press, Zaria.
44. Aliu YO (2007) *Veterinary pharmacology (1st edn.)*. Tamazzan Publishing Company Limited, Zaria.
45. Bauer LA (2006) *Clinical pharmacokinetics (1st edn.)*. McGraw-Hill, NY, USA.
46. Baggot JD (1978) Some aspects of clinical pharmacokinetics in veterinary medicine. *II J Vet Pharmacol Ther* 1: 111-118.
47. Aguiyi JC, Gyang SS, Odutola AA (1996) *A text book of basic clinical pharmacokinetics (1st edn.)*. Chucks Press, Jos.
48. Gravetter FJ, Wallnau LB (2004) *Statistics for the behavioral sciences (6th edn.)*. Thomson Wadsworth Belmonth, USA.
49. Trnavska Z, Trnavsky K, Zinay D (1984) Binding of Piroxicam to synovial fluids and plasma proteins in patients with rheumatoid arthritis. *Euro J Clin Pharmacol* 26: 457-461.
50. Onyeyili PA, Ameh JA, Egwu GO, Aliyu MM, Bukar F (1995) Pharmacokinetics of sulphadimidine following various routes of administration. *Biosci Res Com* 8: 241-244.
51. Nawaz M (1980) Pharmacokinetics and dosage of sulphadimidine in dogs. *J Vet Med* 26: 75-80.
52. Younan W, Nouws JFM, Homeid AM, Vree TB, Degen M (1989) Pharmacokinetics and metabolism of sulphadimidine in the camel. *J Vet Pharmacol Ther* 3: 327-329.
53. Austin FH, Kelly WR (1966) Sulphamethylphen-azole-a new long acting sulphamide 11. Some Pharmacodynamic aspects in dogs, pigs, and horses. *Vet Rec* 78: 192-196.
54. Lashev LD, Pashov DA (1992) Interspecies variation in plasma half-life of ampicillin, amoxicillin sulphadimidine and sulphacetamide related to variation in body mass. *Res Vet Sci* 53: 160-164.
55. Vree TB, Hekster YA (1985) Pharmacokinetics of sulphonamides revisited. *Antibio Chemother* 34: 1-208.
56. Atef MM, El-sayed MCA, Ramadan A (1981) Pharmacokinetics of some sulphonamides in buffaloes. *Zbl Vet Med* 28: 122-130.
57. Abdullahi AS, Baggot JD (1988) The effect of food deprivation on the rate of sulphamethazine elimination in goats. *Vet Res Comm* 12: 441-446.
58. Zhong HY, Fung KF (1990) Pharmacokinetics of sulphadimidine and its N4-acetyl metabolites in healthy and diseased rabbits infected with *Pasteurella multocida*. *J Vet Pharmacol Thera* 13: 192-197.
59. Geertsma MF, Nouws JFM, Grondel JL, Aerts ML, Vree TB, et al. (1987) Residues of sulphadimidine and its metabolites in eggs following oral sulphadimidine medication of hens. *Vet Quart* 1: 67-75
60. Botsoglou NA, Fletouris DJ (2001) Drug residues in foods pharmacology: food safety and analysis. Marcel Dekker, NY, USA.
61. Caloin M (2004) Modeling of lipid and protein depletion during total starvation. *Am J Physiol* 287: 790-798.
62. Nilsson EP, Yosikawa T, Oka C (1960) Quantification of antibiotics using HPLC tetracycline. *Antimicrob Agents Chemother* 9: 745-760.
63. Srivastava AK, Rampal S (1990) Disposition kinetics and dosage regimen of sulphamethazine in sheep (*Ovis aries*). *Br Vet J* 146: 239-242.
64. Nouws JF, Mevius D, Vree TB, Degen M (1989) Pharmacokinetics and renal clearance of sulphadimidine, sulphamerazine and sulphadiazine and their N4-acetyl and hydroxyl metabolites in pigs. *Vet Quart* 11: 78-86.

-
65. Malik JK, Srivastava AK (1987) Pharmacokinetics and dosage of sulphadimidine in cross-breed calves. Acta Vet Hung 3: 291-296.
66. Bengtsson B, Franklin A, Luthman J, Jacobson SO (1989) Concentrations of sulphadimidine, oxytetracycline and penicillin G in serum, synovial fluid and tissue cage fluid after parenteral administration to calves. J Vet Pharmacol Thera 12: 37-45.
67. Silvestri R, Magnificu F, Gladstein G (1967) Long acting sulphonamides in cattle: a case study of pharmacological properties. Am J Vet Res 28: 1983-1999.