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Research Article
Comparative Pharmacokinetics of Intramuscular Sulphadimidine in Non-starved and Starved Grower Turkeys (*Meleagris gallopavo*)

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Abstract

Background: Sulphadimidine has maintained an active place in the armamentary of avian medicine. **Objective:** In view of this, comparative pharmacokinetic parameters were studied in starved and non-starved grower turkeys. **Methodology:** In a randomized parallel study, the pharmacokinetics of sulphadimidine sodium (100 mg kg^{-1} b.wt.) was obtained in non-starved healthy male and female grower turkeys (n = 20) and starved male and female grower turkeys (n = 20) after a single intramuscular administration. The mean peak serum concentrations of sulphadimidine were 99.42±3.81 μg mL^{-1} at 1.5 h in non-starved male turkeys and 127.68±10.37 μg mL^{-1} at 2 h in starved male turkeys, respectively. The mean elimination half-lives were 7.62±0.51 and 12.76±1.52 h in non-starved and starved male turkeys, respectively. **Results:** The mean peak serum concentrations of sulphadimidine were 99.42±3.81 μg mL^{-1} at 1.5 h in non-starved male turkeys and 127.68±10.37 μg mL^{-1} at 2 h in starved male turkeys, respectively. The mean elimination half-lives were 7.62±0.51 and 12.76±1.52 h in non-starved and starved male turkeys, respectively. The mean peak serum concentration of sulphadimidine at 2 h (86.70±6.46 μg mL^{-1}) in non-starved and 1.5 h (121.62±8.55 μg mL^{-1}) in starved female turkeys were recorded, respectively. The mean elimination half-lives were 9.99±1.31 and 14.39±1.52 h in non-starved and starved female turkeys, respectively. Based on target MIC of ≥50 μg mL^{-1} in serum, sulphadimidine was maintained above this level for 10 and 18 h in non-starved and starved male and female Turkeys, respectively. **Conclusion:** The study indicates that sulphadimidine sodium should be administered to anorexic male and female turkeys infected with coccidia and bacteria sensitive to sulphadimidine every 18 h interval. For prophylaxis, sulphadimidine can be administered intramuscular every 10 h interval.

Key words: Sulphadimidine, minimum inhibitory concentration, pharmacokinetics, starvation, sex

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Rapid human population growth and low protein intake are some of the major problems facing Nigerian population of about 174 million (PRB., 2013) and with over 70% of the population living on less than a dollar per day (Watts, 2006). Turkey production is an important profitable agricultural industry with a rising global demand for its products (Anandh *et al*., 2012). In order to boost productivity of turkeys, there is need to improve on therapeutic regimen of infectious diseases that affect turkeys.

Sulphadimidine, a systemic sulphonamide has attained an active place in the armamentary of antimicrobial drugs used in veterinary medicine (Saganuwan *et al*., 2003). It is useful against Gram positive and negative bacteria including nocardia, actinomyces, chlamydia, toxoplasma and coccidia (Prescott, 2000; Barragry, 1994). In poultry, it has been used for treating coccidiosis, infectious coryza, pullorum disease and fowl typhoid (Giguere *et al*., 2006). The disposition kinetics of sulphadimidine has been reported in cows (Nielsen and Rasmussen, 1977; Nouws *et al*., 1986a), sheep and goat (Nawaz and Khan, 1979), laying hen (Nouws *et al*., 1988), guinea fowl, domestic chicken and duck (Onyeyili *et al*., 1997), rabbit (Etuk *et al*., 2006), turkey poult (Heath *et al*., 1975), dogs (Saganuwan *et al*., 2003), broilers (Onyeyili *et al*., 2000), calves (Nouws *et al*., 1986b) and swine (Duffee *et al*.,1984).

Anorexia or loss of appetite which could be a sign of infection caused by both Gram positive and negative microorganisms as well as coccidia can lead to starvation. Although several studies on the pharmacokinetics of sulphadimidine have been carried out in various species of animals, there is no available information on the serum kinetics of intramuscular sulphadimidine in grower turkeys. Therefore, the present study was carried out with intent to providing basis for therapeutic regimen of sulphadimidine, following intramuscular administration in non-starved and starved male and female grower turkeys.

MATERIALS AND METHODS

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. Sample size (10-12 turkeys) was adopted according to a method described by Saganuwan (2012). Forty turkeys of both sexes and 12 weeks old, weighing 1.57±0.2 kg were used for the study. Twenty healthy male grower turkeys were randomly divided into 2 groups of 10 each in a parallel design. The first group was administered sulphadimidine (non-starved) and the second group was starved for 48 h before administration of sulphadimidine. In a similar manner, 20 healthy female grower turkeys were also randomly selected and assigned into two groups of ten each. The first group (non-starved) was administered sulphadimidine and the second group was starved for 48 h before administration of sulphadimidine. All the animals were raised on deep litter system and acclimatized for two weeks prior to experimentation. They were fed Growers Mash® and water was provided *ad libitum*. The animals were handled according to the international guiding principle for biomedical research involving animals (CIOMS., 1985) and as approved by Ethical Committee, College of Veterinary Medicine, University of Agriculture, Makurdi, Nigeria.

Drug administration and sampling: Sulphadimidine sodium (33.3%) produced by Kepro, Holland was used for the study at a dose of 100 mg kg^{-1} b.wt. All the turkeys were administered sulphadimidine (100 mg kg^{-1}) intramuscularly via breast muscle. Blood sample (1 mL) was collected from the right jugular vein of each turkey into plain sample bottle.

Fifteen minutes before drug administration, control blood samples were collected from the right jugular vein and thereafter at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 24, 48, 72 and 96 h using a 23G disposable needle and 2 mL syringe. The samples collected were immediately centrifuged at 5000 revolution per minute (rpm) for 5 min and the serum obtained using a micropipette into cryogenic vials and stored at -20°C for analysis.

Assay of serum sulphadimidine: Free sulphadimidine in serum was determined using spectrophotometer (Bratton and Marshall, 1939; Salinas *et al*., 1990). For the analysis of serum sulphadimidine, 3.8 mL of distilled water was mixed with 0.2 mL of serum and treated with 1 mL of 20% trichloroacetic acid. After thorough mixing, the samples were allowed to stand for 10 min and 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 of 0.5% ammonium sulphamate and mixed. The samples were allowed to stand for 2 min before adding 0.2 mL of 0.5% N-(1-naphthyl) ethylene diammine dihydrochloride. The samples were mixed and the optical density of the resulting color determined using a spectrophotometer at 540 nm wavelength.

The linear calibration curve of sulphadimidine in serum, with the range of 1-10 μg mL^{-1} was obtained by plotting percentage absorbance against drug concentration. The

correlation coefficient (R^2) was greater than 0.93. The limit of detection (LOD) is 0.05 μg mL^{-1} and the limit of quantification (LOQ) is 1.0 μg mL^{-1}. The concentration of sulphadimidine in serum was calculated using the formula below:

$$\text{Concentration of drug} = \frac{\text{Concentration of standard} \times \text{Optical density of drug}}{\text{Optical density of standard}}$$

Calculation of pharmacokinetic parameters: The pharmacokinetic parameters for individual animals were calculated using established pharmacokinetic equations (Aguiyi *et al*., 1996; Baggot, 2001; Bauer, 2006).

Statistical analysis: The data on serum kinetics and pharmacokinetic parameters were presented in graphical and tabular form, respectively. Serum concentrations and pharmacokinetic parameters were presented as Mean±Standard Error of Mean (SEM). Test for significance between the parameters in respect of non-starved and starved turkeys were performed using student's t test paired at 5% level of significance, $p<0.05$ (Gravetter and Wallnau, 2004).

RESULTS

After intramuscular administration of sulphadimidine (100 mg kg^{-1} b.wt.) to non-starved and starved male domestic grower turkeys, serum concentrations of free sulphadimidine were determined and plotted against time.

A mean serum concentration of sulphadimidine of 58.36±4.53 μg mL^{-1} was obtained in non-starved male turkeys, while 66.84±4.08 μg mL^{-1} of sulphadimidine was obtained in starved male turkeys at 0.25 h. These serum concentrations increased until a peak concentration of 99.42±3.81 μg mL^{-1} was reached at 1.5 h in non-starved turkeys, while in starved turkeys, a peak concentration of 127.68±10.37 μg mL^{-1} was obtained at 2 h. The peak serum concentration subsequently decreased and at 96 h post sulphadimidine administration serum concentrations were 1.12±0.25 and 2.28±0.40, respectively in non-starved and starved male turkeys. The pharmacokinetic evaluation of the drug indicated that the data fit a two compartment open model (Fig. 1).

The value of absorption phase (A = 50.14±5.44 μg mL^{-1}), concentration maximum (C_{max} = 103.06±2.80 μg mL^{-1}),

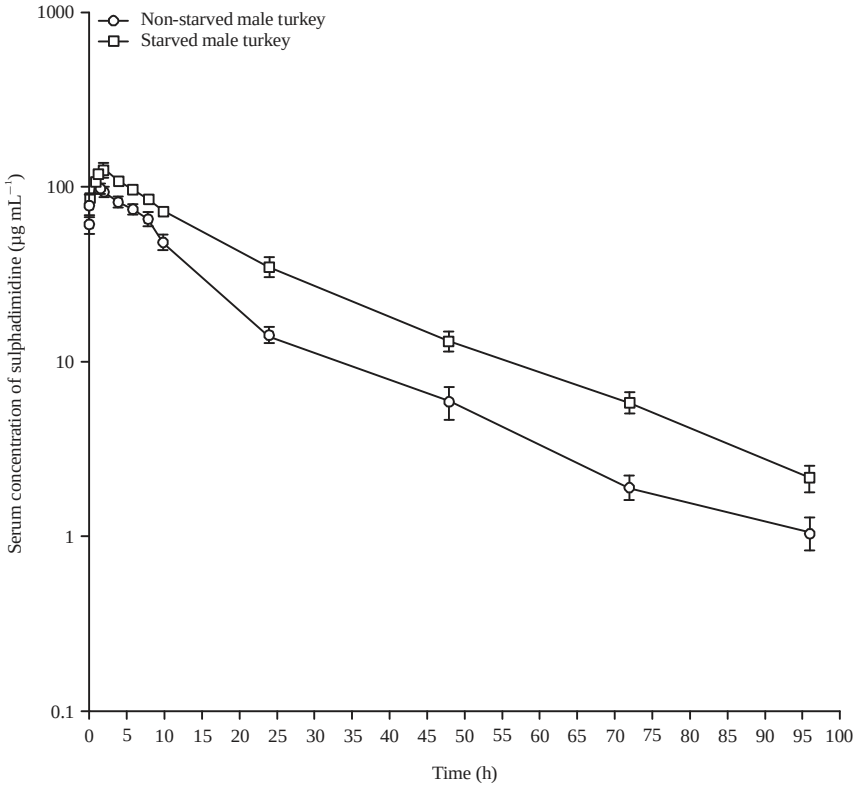

Fig. 1: Mean serum concentration-time curve of sulphadimidine (100 mg kg^{-1}) following a single intramuscular administration to non-starved and starved male domestic grower turkeys, *Meleagris gallopavo* (n = 10)

time of maximum drug concentration (T_{max} = 1.40±0.10 h), absorption half-life ($T_{1/2\alpha}$ = 1.60±0.36 h), elimination rate constant (β = 0.095±0.01 h^{-1}), elimination half-life ($T_{1/2\beta}$ = 7.62±0.51 h), mean residence time (MRT = 10.96±0.74 h), area under the curve from 0-96 h (AUC_{0-96} = 1.60±0.10 mg L^{-1} h^{-1}), area under the curve from zero to infinity ($AUC_{0-\infty}$ = 1.61±0.10 mg L^{-1} h^{-1}) and area under moment curve (AUMC = 17.76±1.80 mg L^{-1}) were significantly lower ($p<0.05$) in non-starved male turkeys in comaparison with A (61.64±4.94 μg mL^{-1}), C_{max} (131.38±9.74 μg mL^{-1}), T_{max} (1.85±0.08 h), $T_{1/2\alpha}$ (2.45±0.31 h), β (0.062±0.01 h^{-1}), $T_{1/2\beta}$ (12.76±1.52 h^{-1}), MRT (18.18±2.09 h), AUC_{0-96} (2.65±0.20 mg L^{-1} h^{-1}), $AUC_{0-\infty}$ (2.70±0.21 mg L^{-1} h^{-1}) and AUMC (50.72±8.37 mg L^{-1}) of the starved male turkeys, respectively. However the absorption rate constant (α = 0.61±0.10 h^{-1}), body clearance (Cl_b = 0.12±0.01 L kg^{-1} h^{-1}), volume of peripheral compartment (V_t = 0.48±0.08 L kg^{-1}), volume of central compartment (V_c = 1.72±0.05 L kg^{-1}) and elimination rate constant from central compartment to outside (K_{10} = 2.50±1.71 h^{-1}), elimination rate constant from central compartment to peripheral compartment (K_{12} = 2.58±1.81 h^{-1}), elimination rate constant from peripheral compartment to central compartment (K_{21} = 0.48±0.39 h^{-1}) of non-starved male grower turkeys were significantly higher ($p<0.05$) than α (0.33±0.04 h^{-1}), Cl_b (0.071±0.000 L kg^{-1} h^{-1}), V_t (0.12±0.02 L kg^{-1}), V_c (1.43±0.11 L kg^{-1}), K_{10} (0.47±0.02 h^{-1}), K_{12} (0.32±0.47 h^{-1}) and K_{21} (0.05±0.03 h^{-1}) of the starved male grower turkeys, respectively. But there was no significant difference ($p>0.05$) in the Vd (area), B and MAT between starved male and non-starved male turkeys (Table 1).

A mean serum concentration of sulphadimidine was obtained in non-starved (50.42±6.12 μg mL^{-1}) and starved (69.72±7.56 μg mL^{-1}) female grower turkeys at 0.25 h, respectively. These serum concentrations increased until a peak concentration of 86.70±6.46 μg mL^{-1} was reached at 2 h in non-starved female turkeys, while in starved female turkeys, a peak concentration of 121.62±8.55 μg mL^{-1} was obtained at 1.5 h. The peak serum concentration subsequently decreased from 96 h to 1.12±0.25 and 2.28±0.40 μg mL^{-1} in non-starved and starved female turkeys, respectively. The pharmacokinetic evaluation of the drug indicated that the data fit a two compartment open model (Fig. 2).

The value of absorption intercept (A = 45.48±5.71 μg mL^{-1}), elimination intercept (B = 1.89±1.06 μg mL^{-1}), concentration maximum (C_{max} = 91.91±6.58 μg mL^{-1}),

Table 1: Pharmacokinetic parameters of sulphadimidine in non-starved and starved male domestic grower turkey (*Meleagridis gallopova*) following intramuscular treatment at 100 mg kg^{-1} b.wt. (n = 10)

Kinetic parameters	Non-starved male grower turkey	Starved male grower turkey
A (μg mL^{-1})	50.140±5.44	61.640±4.94[b]
B (μg mL^{-1})	2.930±2.56	4.680±4.42
C_{max} (μg mL^{-1})	103.060±2.80	131.380±9.74[b]
T_{max} (h)	1.400±0.10	1.850±0.08[b]
V_d (area) (L kg^{-1})	1.240±0.10	1.240±0.13
α (1 h^{-1})	0.610±0.10	0.330±0.04[c]
β (1 h^{-1})	0.095±0.01	0.062±0.01[c]
$T_{1/2\alpha}$ (h)	1.600±0.36	2.450±0.31[b]
$T_{1/2\beta}$ (h)	7.620±0.51	12.760±1.52[b]
CL_b (L kg^{-1} h^{-1})	0.120±0.010	0.071±0.00[c]
MRT (h)	10.960±0.74	18.180±2.09[b]
MAT (h)	2.440±0.54	3.530±0.45
AUC_{0-96} (mg L^{-1} h^{-1})	1.600±0.10	2.650±0.20[b]
$AUC_{0-\infty}$ (mg L^{-1} h^{-1})	1.610±0.10	2.700±0.21[b]
AUMC (mg h^2 L^{-1})	17.760±1.80	50.720±8.37[b]
V_t (L kg^{-1})	0.480±0.08	0.120±0.02[c]
V_c (L kg^{-1})	1.720±0.05	1.430±0.11[c]
K_{10} (1 h^{-1})	2.500±1.71	0.470±0.02[c]
K_{12} (1 h^{-1})	2.580±1.81	0.320±0.47[c]
K_{21} (1 h^{-1})	0.480±0.39	0.050±0.03[c]

[b]Data of starved male grower turkeys are significantly higher than those of non-starved male turkeys, [c]Data of starved male turkeys are significantly lower than those of non-starved turkeys and student's t-test paired ($p<0.05$)

elimination half-life ($T_{1/2\beta}$ = 9.99±1.31 h), mean residence time (MRT = 14.40±1.80 h), area under curve from 0-96 h (AUC_{0-96} = 1.57±0.15 mg L^{-1} h^{-1}), area under curve from zero to infinity ($AUC_{0-\infty}$ = 1.58±0.15 mg L^{-1} h^{-1}), area under moment curve (AUMC = 23.62±3.96 mg L^{-1}) and elimination rate constant from peripheral compartment to central compartment (K_{21} = 0.06±0.02) were significantly lower ($p<0.05$) in non-starved female grower turkeys in comparison with A (62.22±8.87 μg mL^{-1}), B (5.03±0.66 μg mL^{-1}), C_{max} (128.04±6.97 μg mL^{-1}), $T_{1/2\beta}$ (14.39±1.52 h), MRT (20.41±2.08 h), AUC_{0-96} (2.64±0.31 mg L^{-1} kg^{-1}), $AUC_{0-\infty}$ (2.72±0.34 mg L^{-1} kg^{-1}), AUMC (57.89±1.18 mg L^{-1}) and K_{21} (0.96±1.05) of the starved female grower turkeys, respectively. However the elimination rate constant (β = 0.08±0.01 h), body clearance (Cl_b = 0.10±0.01 h), volume of distribution of peripheral compartment (V_t = 0.28±0.16 L kg^{-1}), volume of distribution of central compartment (V_c = 1.62±0.11 L kg^{-1}), elimination rate constant from central compartment to outside (K_{10} = 1.06±1.04) were significantly higher ($p<0.05$) in the non-starved female grower turkeys as compared with β (0.05±0.01), Cl_b (0.06±0.01 L kg^{-1}), V_t (0.07±0.02 L kg^{-1}), V_c (1.07±0.08 L kg^{-1}) and K_{10} (0.07±0.02) of the starved female grower turkeys, respectively. Other parameters such as time maximum (T_{max}), volume of distribution (Vd area), absorption rate constant (α), absorption half-life ($T_{1/2\alpha}$), Mean

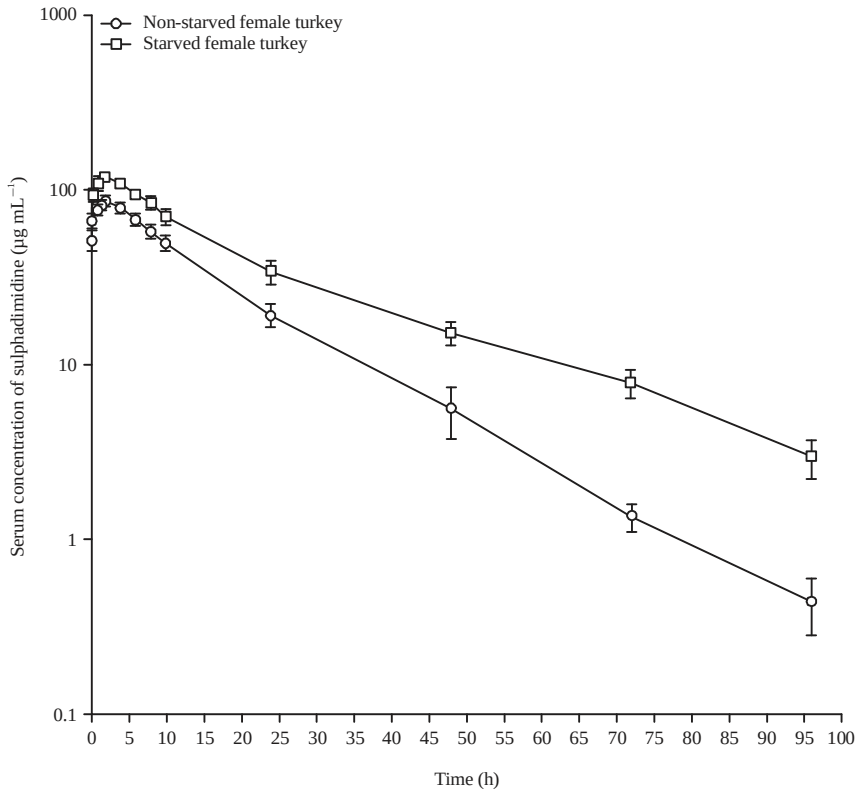

Fig. 2: Mean serum concentration-time curve of sulphadimidine (100 mg kg^{-1}) following a single intramuscular administration to non-starved female grower turkeys, *Meleagris gallopavo* (n = 10)

Table 2: Pharmacokinetic parameters of sulphadimidine in non-starved and starved female grower turkeys (*Meleagris gallopavo*) following intramuscular treatment at 100 mg kg^{-1} b.wt. (n = 10)

Kinetic parameters	Non starved female turkeys (µg mL^{-1})	Starved female turkeys (µg mL^{-1})
A (µg mL^{-1})	45.48±5.71	62.22±8.82[e]
B (µg mL^{-1})	1.89±1.06	5.03±0.66[e]
C_{max} (µg mL^{-1})	91.91±6.58	128.04±6.97[e]
T_{max} (h)	2.00±0.36	1.70±0.28
V_d (area) (L kg^{-1})	1.34±0.18	1.09±0.11
α (1 h^{-1})	0.44±0.08	0.44±0.08
β (1 h^{-1})	0.08±0.01	0.053±0.01[f]
$T_{1/2\alpha}$ (h)	2.22±0.56	2.10±0.38
$T_{1/2\beta}$ (h)	9.99±1.31	14.39±1.52[f]
CL_b (L kg^{-1} h^{-1})	0.10±0.01	0.06±0.01[f]
MRT (h)	14.40±1.80	20.41±2.08[e]
MAT (h)	3.20±0.80	3.03±0.54
AUC_{0-96} (mg L^{-1} h^{-1})	1.57±0.15	2.64±0.31[e]
$AUC_{0-\infty}$ (mg L^{-1} h^{-1})	1.58±0.15	2.72±0.34[e]
AUMC (mg h^2 L^{-1})	23.62±3.96	57.89±1.18[e]
V_t (L kg^{-1})	0.28±0.16	0.02±0.07[f]
V_c (L kg^{-1})	1.62±0.11	1.07±0.08[f]
K_{10}	1.06±1.04	0.07±0.02[f]
K_{12}	1.12±0.95	1.27±1.14
K_{21}	0.06±0.02	0.96±1.05[e]

[e]Data of starved female turkeys significantly higher than those of non-starved female turkeys, [f]Data of starved female turkeys significantly lower than those of non-starved female turkeys and $p<0.05$, student's t-test paired

Absorption Time (MAT) and elimination constant from central to peripheral compartment (K_{12}) were not significantly different ($p>0.05$) between starved and non-starved female grower turkeys (Table 2).

DISCUSSION

The results presented in Fig. 1, showed that intramuscular administration of sulphadimidine at 100 mg kg^{-1} b.wt., resulted in measurable blood levels of sulphadimidine for 96 h in both non-starved and starved male domestic grower turkeys. The result also indicated that sulphadimidine was eliminated from the serum of turkeys in a biphasic process when administered intramuscularly to non-starved and starved male grower turkeys. This disagrees with the findings in guinea fowls, domestic chickens and ducks (Onyeyili *et al*., 1997). The higher absorption intercept (A), concentration maximum (C_{max}), time of maximum drug concentration (T_{max}), absorption half-life ($t_{1/2\alpha}$), elimination half-life ($t_{1/2\beta}$), Mean Residence Time (MRT), area under the curve from 0-96 h (AUC_{0-96}), area under the curve from zero to infinity ($AUC_{0-\infty}$) and Area Under Moment Curve (AUMC) in starved male turkeys in comparison with non-starved male turkeys

indicate that starvation can affect metabolism of drugs and may result in accumulation of the drug in the body with resultant toxic effects (Bevil, 1982; Bywater, 1982). The C_{max} of starved (C_{max} = 131.38±9.74 μg mL^{-1}) and non-starved (C_{max} = 103.06±2.80 μg mL^{-1}) male turkeys are higher than the reported values of the non-starved guinea fowl (52.5±2.62 μg mL^{-1}) administered intramuscular sulphadimidine (Onyeyili *et al*., 1995). The elimination half-life of sulphadimidine in starved male turkeys in this study was higher than that obtained for the non-starved male turkeys. The elimination half-life ($t_{1/2\beta}$ = 7.62±0.51 h) of non-starved male turkeys in the present study is comparably similar to that of non-starved guinea fowl (7.2±2.6 h) administered intramuscular sulphadimidine at the same dose level (Onyeyili *et al*., 1995). However the elimination half-life of sulphadimidine in starved male turkeys ($t_{1/2\beta}$ = 12.76±1.52 h) is lower than that of dog 16.80±3.9 and 16.00±0.00 h (Saganuwan *et al*., 2003; Nawaz, 1980), similar to that of camel 13.20±0.00 h (Younan *et al*., 1989), pigs 13.00±0.00 h (Vree and Hekster, 1985) but higher than that of buffalo 7.69±2.39 and 9.38±0.00 h (Lashev and Pashov, 1992; Atef *et al*., 1981), goat 2.9±0.7, 4.75±0.00 and 4.00±0.00 h (Nouws *et al*., 1986b; Abdullahi and Baggot, 1988; Nawaz and Khan, 1979), rabbit 3.00±0.00 h (Yuan and Fung, 1990) and chickens 3.00±0.00 h (Geertsma *et al*., 1987), respectively. 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 (Nouws *et al*., 1986b).

The higher elimination half-life of sulphadimidine in starved male turkeys compared to non-starved male turkeys may be an indication that the drug is more retained in the body with higher level of distribution in various body fluids and tissues. The value of elimination rate constant (0.095±0.01 h^{-1}) in the non-starved male turkeys in this study is comparable with that of non-starved guinea fowls (0.096±0.02 h^{-1}) administered intramuscular sulphadimidine (Onyeyili *et al*., 1995) suggesting that the two species of birds may have similar way of eliminating sulphadimidine from their bodies. Elimination is known to be a function of the rate of metabolism and/or excretion (Baggot, 2001). It is obvious that starvation (or anorexia from a clinical point of view) lowers metabolic rate in animals. 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 (Nouws *et al*., 1988). In poultry, both hydroxylation and acetylation are relatively important pathways for metabolism of sulphadimidine, but approximately 57% of the administered dose is unaccounted for (Nouws *et al*., 1986b). The decrease in absorption rate constant, elimination rate constant, volume of distribution in central compartment, elimination rate constant from central compartment to outside (K_{10}), elimination rate constant from central compartment to peripheral compartment (K_{12}) and elimination rate constant from peripheral compartment to the central compartment (K_{21}) show that the rate of absorption of sulphadimidine and its concentration in the central compartment and peripheral compartment are low. This may be as a result of depletion of body protein which is the biological fuel of last result (Caloin, 2004) and the physiological switch from lipid-dominated catabolism to protein-dominated catabolism which occur only when an animal's lipid level reach some critical threshold (Jenni *et al*., 2000).

Sex variation is another factor that affects the pharmacokinetic behavior of a drug in animals. In the present study, sulphadimidine kinetics is best described by two compartment open model in female turkeys. This is at variance with findings in turkey poults (Heath *et al*., 1975), guinea fowls, domestic chicken and ducks (Onyeyili *et al*., 1997), sheep and goats (Nawaz and Khan, 1979) and buffaloes (Atef *et al*., 1981) where the drug was eliminated by one compartment model. This may be due to variation in the sex and route of administration. However the findings of this study are in agreement with the findings in dogs (Saganuwan *et al*., 2003; Nawaz, 1980), broiler chicken (Onyeyili *et al*., 2000), cows (Nielsen and Rasmussen, 1977) and buffaloes (Atef *et al*., 1981) indicating that the kinetic profile of a drug may differ from one species of animal to another or even among the same species of animals (Nilsson-Ehle *et al*., 1976). The elimination constant and elimination half-life of sulphadimidine in the female turkeys were significantly decreased ($p<0.05$) by starvation translating to significantly increased C_{max} (128.04±6.97 μg mL^{-1}) of the starved female turkeys in comparison with C_{max} (91.91±6.58 μg mL^{-1}) of non-starved female turkeys. Birds when deprived of food employ various behavioural, physiological and structural responses to reduce metabolism, which prolongs the period in which energy reserves can cover metabolism. Such behavioural responses include a reduction in spontaneous activity and a lowering in the body temperature. Although in later stages of food deprivation in which starvation commences, activity may increase as food-searching is activated. Gastrointestinal tract undergoes marked atrophy when digestive processes are curtailed and digestive functions are restored soon after feeding and these transitions appear to occur at low metabolic costs (Wang *et al*., 2006). This further underlines the need to study the kinetic profile of any drug that is widely used both in feeding and non-feeding conditions.

The volume of distribution area (Vd_{area}) relates the drug concentration in the plasma to the total amount of drug in the body after distribution equilibrium has been reached. But in the present study the Vd_{area} of sulphadimidine was slightly lower in starved female turkeys (1.09±0.11 L kg^{-1}) in comparison with non-starved female turkeys (1.34±0.18 L kg^{-1}), guinea fowl (1.29±0.47 L kg^{-1}) but higher than that of chicken 1.08±0.06 L kg^{-1} (Onyeyili *et al*., 1997) and sheep 0.6±0.11 L kg^{-1} (Srivastava and Rampal, 1990). The more extensive distribution of sulphadimidine in starved and non-starved female grower turkeys may be suggestive of slower elimination of the drug in turkeys 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 (Onyeyili *et al*., 2000). In the present study, the absorption half-life was not significantly different between starved (2.10±0.38 h) and non-starved (2.22±0.56 h) female turkeys. The elimination half-life and elimination rate constant of non-starved female turkeys ($T_{1/2\beta}$ = 9.99±1.31 and β = 0.08±0.01 h^{-1}) are comparatively similar to the elimination half-life and elimination rate constant of starved broiler chicken ($T_{1/2\beta}$ = 11.60±0.72 and β = 0.06±0.02 h^{-1}) and ducks ($T_{1/2\beta}$ = 9.0±0.9 and β = 0.077±0.008 h^{-1}) but lower than that of guinea fowl ($T_{1/2\beta}$ = 6.0±0.9 and β = 0.110±0.02 h^{-1}) and domestic chicken ($T_{1/2\beta}$ = 6.2±0.8 and β = 0.100±0.008 h^{-1}) (Onyeyili *et al*., 1997). The elimination half-life of female non-starved grower turkeys (9.99 h) in the present study was slightly higher than the previously reported value (8.9 h) in female turkey poults (Heath *et al*., 1975), sheep 4.5, 4.0 and 3.28 h (Lashev and Pashov, 1992; Srivastava and Rampal, 1990), goat 3.88±0.93 h (Lashev and Pashov, 1992) and higher in cow 14.5 and 10.53 h (Malik and Srivastava, 1986; Bengtsson *et al*., 1989) administered intravenous sulphadimidine. However the elimination half-life is 8 h in cow (Silvestri *et al*., 1967).

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 (Lashev and Pashov, 1992). This probably is valid also for the differences in the half-lives of sulphadimidine in cattle (Malik and Srivastava, 1986; Silvestri *et al*., 1967). However, interspecies variations in half-lives 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 of sulphadimidine and body weight, before a decision is made as to the extent the available pharmacokinetic data are of relevance in the prediction of an appropriate dosage regimen (Lashev and Pashov, 1992). The higher body clearance, mean resident time, area under the curve 0-96 h, area under the curve zero to infinity, area under the moment curve and volume of distribution of central compartment of starved in comparison with non starved turkeys may be related to the rate and 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 renal excretion of metabolites and parent substance (Nouws *et al*., 1986a, b).

CONCLUSION

The ultimate objective of a satisfactory dosage regimen is to maintain the serum drug level above Minimum Inhibitory Concentration (MIC) during treatment period. For sulphonamides the MIC was reported to be 50 μg mL^{-1}. Sulphadimidine administered under the present study appeared in the serum of non-starved and starved male and female turkeys above 50 μg mL^{-1} of MIC, 18 and 10 h, respectively. It is therefore being suggested that sulphadimidine sodium should be administered to anorexic male and female turkeys infected with coccidia and bacteria sensitive to sulphadimidine every 18 h interval. For prophylaxis, sulphadimidine can be administered intramuscular every 10 h interval.

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