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The Effect of Short Term Starvation on the Plasma Kinetics of Sulphadimidine in Rabbits

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Abstract: A comparative plasma kinetics of sulphadimidine (100 mg kg^{-1}, intravenous) studied by chemical assay in non-starved and starved rabbits has shown that; the mean peak plasma concentrations of the drug (101.70±5.74 μg mL^{-1}) was higher in the starved than the non-starved animals (72.45±6.22 μg mL^{-1}). The volume of distribution of the drug ($V_d\beta$) and the total body clearance (CL) were significantly reduced after deprivation of food for 48 h in the animals. Equally, the elimination rate constant (β = 0.078 h^{-1}) was higher in the non-starved than in the starved rabbits (β = 0.052 h^{-1}). The study therefore concludes that, short term starvation has significantly increased the plasma concentrations and altered the kinetic profile of sulphadimidine following intravenous administration in rabbits. Thus, this factor should be considered when administering the drug to avoid dose dependent toxicity.

Key words: Sulphadimidine, starvation, rabbits, elimination, plasma, concentration

INTRODUCTION

Sulphadimidine has proven to be clinically useful since its introduction in both human and veterinary medicine as therapeutic agent for a wide range of microbial diseases (Bywater, 1982; Bevill, 1991; Grshame-smith and Arouson, 1992). The disposition kinetics of this drug has been reported in various animal studies (Nielsen and Rassmussen, 1979; Onyeyili *et al*., 1997). Onyeyili *et al.* (2000) investigated the effect of starvation on the kinetic profile of sulphadimidine in broiler chickens.

Anorexia or loss of appetite for food which may result in acute starvation is a prominent feature of some protozoan and bacterial infections and this fact should be an important consideration in the use of this drug since loss of appetite and/or absence of food in take could affect sulphadimidine metabolism and elimination.

Despite the extensive use of this antibiotics in this environment, there has been limited information on the kinetic profile of the drug in animals, thus the current research effort is to address this.

MATERIALS AND METHODS

This study was conducted in the Department of Pharmacology, College of Health Sciences, Usmanu Danfodiyo University, Sokoto in February 2005.

Animal and treatment: Eight adult rabbits of both sexes weighing between 1.2 to 1.8 kg were used for this study. The animals were purchased locally, kept singly in cages, watered freely and fed with rabbit pellets and vegetable for a forth night before the commencement of the experiments.

At the beginning, the rabbits were dosed intravenously with sulphadimidine (100 mg kg^{-1} body weight) and blood samples collected from contralateral veins into vials containing EDTA as anticoagulant. The blood samples were collected at 15 min before the drug treatment, then 0.25, 0.50. 1.0, 3.0, 6.0, 12, 24, 36, 48 and 72 h after the drug administration. The collected samples were immediately centrifuged and the separated plasma was stored at –20°C pending the determination of sulphadimidine concentrations.

The same set of the animals was reused for the second phase of the study but after a period of four weeks. This time, they were given only drinking water but no food for 48 h before the administration of the drug. Sulphadimidine was then administered intravenously at the same dose and blood samples collected and processed as indicated above.

Determination of sulphadimidine from plasma: The determination of free (direct reacting) sulphadimidine in blood samples was done using the modified chemical assay method described by Bratton *et al.* (1939)

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and later used by Onyeyili *et al.* (1997) to determine the sulphadimidine concentration in the plasma samples of chicken. Briefly, in the modification: 0.2 mL of the plasma was mixed with 3.8 mL of distill water. The mixture was treated with 1.0 mL of 20% trichloroacetic acid. The supernatant obtained was further mixed with 0.1% sodium nitrite, ammonium sulphate and 0.5% N-(1-naphthy1) ethylene diamine dihydrochloride. The optical density of the resultant colour changes was measured using spectrophotometer at 540 nm. The following formula was then adopted in calculating the concentrations of sulphadimine in the plasma.

$$\text{Concentration of drug (D)} = \frac{\text{Conc. of standard} \times \text{optical density of D}}{\text{Optical density of standard}}$$

Where, D, is the concentration of drug in the unknown sample and the Standard prepared by serial dilution of a known concentration of the original drug in plasma.

Calculation of pharmacokinetic constants: Pharmacokinetic analysis was performed by standard procedures (Baggot, 1977) and Instat 3 software was used for non-linear regression analysis. Two-compartment open model was confirmed using a log linear plot of drug concentration in plasma against time and least squares analysis linear regression. The following pharmacokinetic parameters and constants were determined. Zero time intercept distribution phase (A), Zero time intercept elimination phase (B), concentration of drug at zero time (Cp°), area under the concentration-time curve (AUC), elimination rate constant (β), total body clearance (CL), Volume of distribution ($V_d\beta$), elimination half-life ($t_{½}\beta$). These parameters were calculated according to standard procedures (Gilbaldi *et al.*, 1969; Gilbaldi and Perrier, 1982).

Statistical analysis: The result of the disposition study were expressed as mean±SD. Tests for significance between parameters in respect of non starved and starved rabbits were performed using student's paired t-test. And the null hypothesis was rejected at 5% level of probability. All the data were analyzed using Instat 3 software.

RESULTS

The data presented in Table 1 indicates that, following intravenous administration of sulphadimidine (100 mg kg^{-1}) to non-starved and starved rabbits, measurable blood levels of the drug were observed for 72 h in both group of experimental animals. The Table 1 also shows that the mean value of drug concentration for starved rabbits were higher than the mean values for non starved rabbits at the respective time intervals. Mean peak plasma concentrations of 72.45±6.22 and 101.70±5.74 μg mL^{-1} were achieved at 0.25 h post drug administration in non-starved and starved rabbits, respectively. Thereafter the plasma concentrations of the drug declined gradually until the minimum concentrations

Table 1: Mean Sulphadiminine concentrations (μg mL^{-1}) in the non-starved and starved rabbits

Time (h)	Non-starved rabbits concentration (μg mL^{-1})	Starved rabbits concentration (μg mL^{-1})
0	0.00±0.00	0.00±0.00
0.25	72.45±6.22	101.70±5.74
0.5	50.20±4.96	83.10±4.84
1	44.22±3.81	70.74±3.88
2	35.66±2.99	57.40±3.80
3	33.54±2.06	52.50±2.72
6	28.12±1.36	44.78±2.60
12	16.54±1.96	31.62±2.46
36	2.16±0.31	8.46±1.68
48	1.02±0.09	4.92±0.90
72	0.16±0.04	1.32±0.64

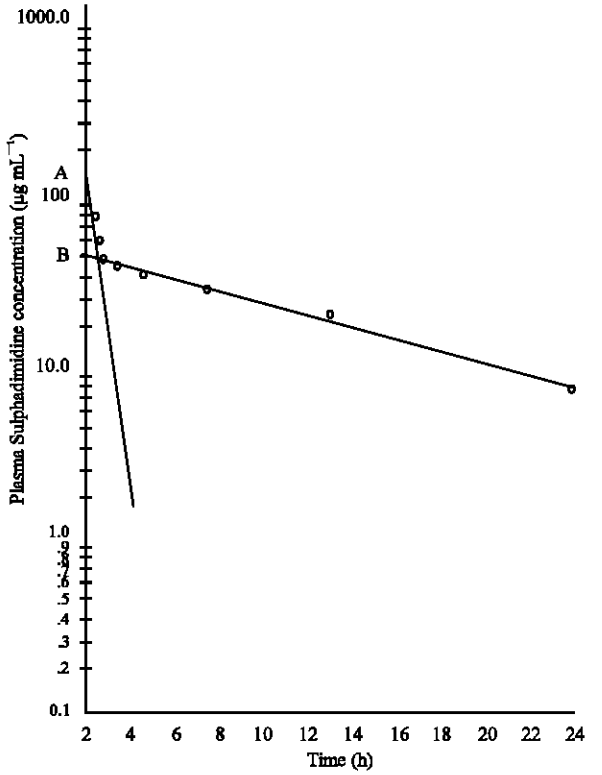

Fig. 1: The plasma concentration-time profile for sulphadimidine following a single intravenous injection of the drug (100 mg kg^{-1}) to non-starved rabbits

Table 2: Pharmacokinetic parameters obtained from the study in starved and non-starved rabbits

Pharmacokinetic parameters	Non starved rabbits	Starved rabbits
Cp° (μg mL^{-1})	115.00	*140.00
Elimination rate constant (β) HR^{-1}	0.078	*0.052
Elimination half-life ($t_{½}β$) HR	8.89	*13.33
Volume of distribution ($V_dβ$) L kg^{-1}	2.66	*1.99
Clearance (CL) L kg^{-1} HR	0.18	*0.10
AUC (HR μg L^{-1})	6.39	*13.54

* = $p<0.05$ student's t-test

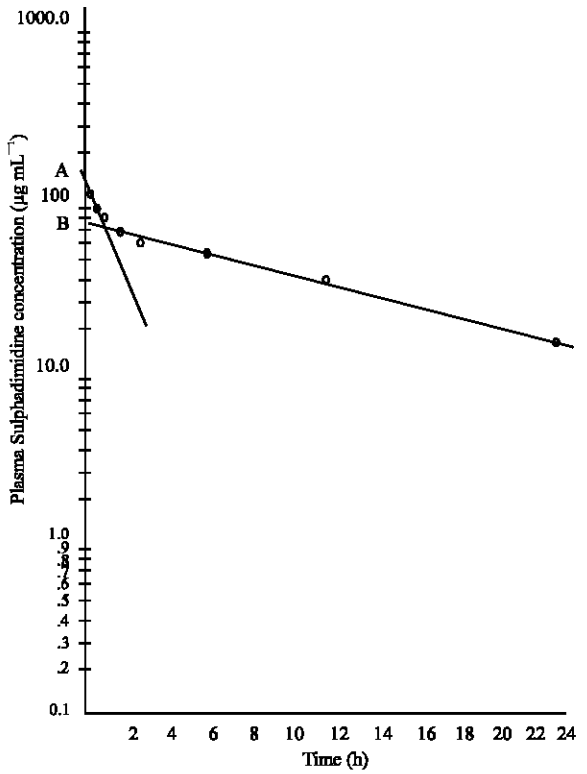

Fig. 2: The plasma concentration-time profile for sulphadimidine following a single intravenous injection of the drug (100 mg kg^{-1}) to starved rabbits

of 0.16±0.04 and 1.32±0.64 μg mL^{-1} for the non-starved and starved animals, respectively were recorded after 72 h.

The disposition kinetic evaluation of sulphadimidine suggests that, the data should best fit a two compartment open model (Fig. 1 and 2). The zero time concentration (Cp°) was calculated to be 115 μg mL^{-1}, with volume of distribution ($V_dβ$), elimination half-life ($t_{½}β$) and elimination rate constant (β) of 2.26 L kg^{-1}, 8.89 and 0.078 h^{-1}, respectively in the non-starved rabbits. But after the food deprivation for 48 hours, the zero time concentration became 140 μg mL^{-1}, with volume of distribution, elimination half-life and elimination rate constant being, 1.99 L kg^{-1}, 13.33 and 0.052 h^{-1}, respectively (Table 2).

The area under the curve (AUC) and total body Clearance were 6.93 and 0.18 L kg^{-1} h, respectively. The corresponding values after starvation were 13.54 and 0.10 L kg^{-1} h, respectively.

DISCUSSION

The two compartment open model (Fig. 1 and 2) adopted for the description of the pharmacokinetic profile of sulphadimidine in this study is in line with the reports of Onyeyili *et al.* (2000) in starved and non starved broiler chickens and that of Nawaz (1980) in dogs. But it differs with the one compartment model exhibited by the drug in guinea fowls, domestic chickens and ducks (Onyeyili *et al.*, 1997); sheep, goats (Nawaz and Nawaz, 1983). The kinetic profile of a particular drug may differ from one animal to another or even among the different species of the same animals (Nisson-Ehle *et al.*, 1960). This further underlined the need to study the kinetic profile of any drug in use very widely.

There was a significant increase ($p<0.05$) in the zero time plasma concentration of sulphadimidine coupled with a reduction in the volume of distribution after the acute starvation.

Munsey *et al.* (1993) had demonstrated that acute starvation stimulates amino acid transport across the apical plasma membrane of the enterocytes by inducing specific carrier units in isolated enterocytes. The total serum proteins and albumin concentrations are known to increase during acute water deprivation (Hassan, 1989). Acute starvation may be associated with a reduction in the total body water because food consumption is intrinsically related with the demand for water (Little *et al.*, 1976). Thus, the initial increase in plasma albumin as a result of acute starvation could enhanced drug protein binding; raised the plasma concentrations of the drug and delay the elimination of the drug from the body. This position was further collaborated with a significantly high value of elimination half-life and decreased drug clearance recorded after food deprivation in the same study. Onyeyili *et al.* (2000) had earlier reported that, the plasma concentrations of sulphadimidine increased significantly after a short term food deprivation in chicken.

This study has shown that, acute starvation can result in a significant increase in the plasma concentration of sulphadimidine in rabbits; the clearance of the drug may be reduced thereby increasing the risk of dose dependent toxicity of the drug. These findings may suggest the need to reduce the dosage or frequency of dosing in a patient if regular food intake has been stalled for a reasonable time.

REFERENCES

Baggot, J.D., 1977. Principles of Drug Disposition in Domestic Animals. W.B. Saunders Company, Philadelphia.

Bevill, R.J., 1991. Sulphanamids. In: Veterinary Pharmacology and Therapeutics. Editors, N.H. Both and L.E. McDonald, IOWA University Press.

Bratton, A.C., E.K. Marshal, D. Babbit and A.R. Henderson, 1939. A new coupling component for sulphanilamide determination. J. Biol. Chem., 128: 537-550.

Bywater, R.J., 1982. Sulphadimidines. In: Veterinary Applied Pharmacology and Therapeutics. 4th Edn., Bailliere Tindal, London, pp: 422.

Gibaldi, M., 1977. Pharmacokinetic consideration of drug concentrations in plasma. In: Textbook of Biopharmaceutics and clinical pharmacokinetics. 2nd Edn., LEA and FABIGER, Philadephia, pp: 3.

Gibaldi, M. and D. Perier, 1982. Methods of residuals. Pharmacokinetics, 15: 433-444.

Grshame-Smith, D.G. and K.J. Arouson, 1992. Sulphonamides. In: Oxford Textbooks of Clinical Medicine and Drug Therapy 2nd Edn. Oxford University Press, Oxford, pp: 690.

Hassan, G.E.A., 1989. Physiological responses of Anglo-Nubian and Baladi goats and their cross breeds to water deprivation under subtropical conditions. Livestock Prod. Sci., 22: 295-304.

Little, W., B.E. Sansom., R. Mandon and W.M. Allen, 1976. Effects of restricting the water intake of diary cows upon their milk yield, body weight and composition. Anim. Prod., 22: 329-339.

Munsey, T., R.E. Grigg, A. Mccrpack, H.W. Symonds and C.J. Bowmer, 1996. Binding of Sulphadimidine to pig plasma proteins. J. Vet. Pharmacol. Ther., 19: 135 -141.

Nawaz, M., 1980. Pharmacokinetics and dosage of sulphadimidine in dogs. J. Vet. Med., 27: 75-80.

Nawaz, M. and R. Nawaz, 1983. Pharmacokinetics and urinary excretion of sulphadimidine in sheep during summer and winter. Vet. Records., 12: 379-381.

Nielsen, P. and F. Rassmussen, 1979. Half-life, apparent volume of distribution and protein binding for some sulfonamides in cows. Res. Vet. Sci., 2: 205-211.

Nilsson-Ehle, P., T. Yosikawa and C. Oka, 1960. Quantification of antibiotics using HPLC. Tetracycline. Antimicrobial Agents and Chemotherapy, 9: 745-760.

Onyeyili, P.A., G.O. Egwu, O.A. Apampa and J. Ameh, 1997. Elimination of sulphadimidine from edible tissues and blood of guinea fowls, domestic chickens and ducks. Bulletin of Animal Health and Production in Africa, 45: 225-229.

Onyeyili, P.A., O.O. Ogundele and S. Sanni, 2000. Effect of starvation on the elimination kinetics of sulphadimidine in Broiler chickens. Nig. J. Exp. Applied Biol., 1: 25-28.