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Tissue Residues and Elimination of Sulphadimidine in Non-Starved and Starved Rabbits

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The tissue concentrations and kinetics of sulphadimidine (100 mg kg^{-1}; intravenous) has been studied in normal and starved rabbits by chemical assay method. The results indicate that, different concentrations of the drug were obtained in the various tissues (liver, heart, kidney brain and skeletal muscle) examined. The drug persisted in the brain and skeletal muscle of the animals up to 12 days after its administration. The starved rabbits maintained consistently higher concentrations of the drug in its tissues as compared to the fed ones. The half-life of the drug was shortest in the liver (5.63 and 6.11 h) of the non-starved and starved rabbits, respectively. The elimination rate constants were correspondingly higher in the liver (0.210 and 0.230 h), respectively for the non-starved and starved rabbits. The study therefore concludes that, acute starvation can raise the tissue concentrations of sulphadimidine in rabbits and the safe withdrawal time following the administration of the drug should be in excess of twelve days.

Key words: Concentrations, sulphadimidine, tissues, rabbits, starvation, administration

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INTRODUCTION

Sulphonamides were the first anti-infective agents to be put to use. Their therapeutic value was recognized in 1935 when it was demonstrated that the dye, Prontosil was effective in treating mice infected with streptococci (Okpako, 1991).

Despite the availability of other anti-microbial agents, sulphonamide has, continued to be relevant in clinical practices. Sulphadimidine is one of the most commonly used sulphonamide in veterinary medicine for prophylaxis and therapeutic purposes (Al-Nazawi and Homeida, 2005). Problems associated with the use of the drugs in food producing animals not only revolves about the detection of drug residues in tissues but also involves the detection of metabolites which may be of greater significance from public health standpoint than the parent or metabolized drug. For these reasons pharmacokinetic studies need to be conducted in a number of animal species to fully comprehend the differences that exist in the metabolic transformation and elimination of drugs (Mercer *et al*., 1998). Rabbits are gradually becoming a source of food protein in this environment and sulphadimidine is the commonest anti-infective agent in use. According to Kenyan Livestock Technologists Association, KELITA, most animal products found within the Kenyan market have an unacceptable high levels well above the recommended levels both at the Food Agricultural Organization (FAO), World Health Organization (WHO) and International organization for the Animal Health (OIE) (Neondo, 2002). This situation is the same in most developing countries.

The proper understanding and adequate database about the duration of certain antibiotics used in food animals will lead to the observation of appropriate withdrawal time. Also if a relationship could be established between tissue concentrations and plasma and/or urine concentrations of the drug, it could be possible to predict when the tissue concentrations in an animal had reached preset tolerance limits (Mercer *et al*., 1977). The disposition kinetics of sulphadimidine has been reported in various animal studies. Onyeyili *et al*. (1997) investigated the kinetics of the drug in domestic chickens and Rana *et al*. (1993) carried out his studies in pigs. The tissues residues of sulphadiazine, sulphadimidine and sulphquinoxaline were studied in healthy and *E. stiedai* infected rabbits (Atta *et al*., 1999). Cellarova *et al*. (2004) reported the influence of trimethoprim administration as a potentiator of sulphadimidine in the blood plasma of rabbits.

Most infective disorders usually treated with sulphadimidine are associated with loss of appetite, which may result in acute starvation. Starvation is associated with metabolic changes in the body and such metabolic dysfunctions are likely to affect the translocation of the drug in the body. The present study is therefore to determine the duration of stay of sulphadimidine in the various tissues of the rabbit following a single intravenous injection of the drug so as to suggest appropriate withdrawal time. The effect of acute starvation on the tissue profile of the drug will also be examined.

MATERIALS AND METHODS

This study was conducted in the department of Pharmacology, College of Health Sciences, Usmanu Danfodiyo University, Sokoto during the months of March and April 2005.

Eighteen healthy adult rabbits randomly selected were used for this study. They were kept in metal cages, fed and watered adequately for about two weeks before the commencement of the study. Their mean body weight was 1.48 kg.

Two of the animals were first slaughtered and used for preparing control tissues and tissue standards. The remaining sixteen was divided into two groups of eight rabbits each. Group one was treated with sulphadimidine 100 mg kg^{-1} intravenously while group two was starved for 48 h after which the eight rabbits were treated with the same dose of the drug as indicated above. Two animals from each group were sacrificed at 4, 8, 12 and 15 days post drug administration. Tissue samples were harvested from the liver, kidneys, heart, skeletal muscle of the thigh and the brain. The concentrations of sulphadimidine in the tissues were determined using the calorimetric assay method of Bratton *et al*. (1939).

Briefly, about 0.2 g of each tissue sample was taken, crushed into fine particles and mixed with 3.8 mL of distilled water. Trichloroacetic acid was added to coagulate the proteins. The filtrate was treated with ammonium sulphate and ethylenediamine dihydrochloride. The density of the resultant colour change observed was measured with spectrophotometer at 540 nM. The half-lives and the elimination constants of the drug were determined using standard procedures (Baggot, 1977). The mean value for the concentrations of the drug were calculated for each time period and the data between the non starved and starved groups were compared using paired student's t-test.

RESULTS

The results indicate that, measurable levels of the drug were obtained in the various tissues of the animals examined four days after administration of a single bolus of sulphadimidine at 100 mg kg^{-1} body weight intravenously (Table 1). The tissue concentrations of the drug in the liver, brain, heart, kidney and skeletal

Table 1: Suphadimidine concentrations in the various tissues (μg g^{-1}) of the non-starved and starved rabbits

	Liver		Kidney		S/muscle		Heart		Brain	
Time (Days)	NSR	SR	NSR	SR	NSR	SR	NSR	SR	NSR	SR
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
4	2.07	2.83	1.40	1.87	0.20	0.27	0.28	0.32	0.047	0.073
8	0.30	0.53	0.063	0.181	0.20	0.26	0.01	0.07	0.033	0.038
12	0.00	0.00	0.00	0.00	0.18	0.21	0.00	0.00	0.015	0.028
15	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

NSR = Non-Starved Rabbits; SR = Starved Rabbits; Average Values based on two observations

Table 2: The half-lives and elimination rate constants of sulphadimidine in the various tissues of the rabbits

	Half-lives (h)		Elimination rate constant	
Tissues	NSR	SR	NSR	SR
Liver	5.63	6.11	0.210	0.230
Kidney	7.31	7.88	0.035	0.036
Brain	12.82	12.78	0.013	0.013
Heart	6.79	7.01	0.180	0.180
Skeletal Muscle	15.11	16.31	0.010	0.011

NSR = Non Starved Rabbits; SR = Starved Rabbits

muscle were higher in the starved that in non-starved rabbits (Table 1). Peaks concentrations of the drug in the tissues examined were recorded on the forth day, thereafter the concentrations declined gradually until no detection could be made after 12 days. The liver has the highest concentrations of the drug; 2.07 and 2.83 μg g^{-1} the non starved and starved rabbits, respectively. The lowest tissue concentrations of (0.047 and 0.073 μg g^{-1}) for non-starved and starved rabbits, respectively were recorded in the brain. Sulphadimidine was detected in the skeletal muscle and brain of the animals up to day 12 and only for 8 days in heart, liver and kidney post drug administration. The concentrations of the drug in the heart and skeletal muscle (0.28 and 0.20 μg g^{-1}), respectively were not significantly different at four hours after the drug administration but after 8 h the drug could no longer be detected in the heart while it lasted up to 12 h in the skeletal muscle. This finding was collaborated by a higher elimination rate constant (0.18 vs 0.01) calculated for the heart.

The half-life of the drug was shortest in the liver (5.63 and 6.11 h) of the non-starved and starved rabbits, respectively. The elimination rate constants were correspondingly higher in the liver (0.210 and 0.230 h), respectively for the non-starved and starved rabbits (Table 2).

DISCUSSION

The distribution of sulphadimidine after intravenous administration of a single dose (100 g kg^{-1}) to the various tissues examined was not uniform in both the starved and non-starved rabbits. The tissues sampled in diminishing order of sulphadimidine concentrations were, liver (2.07 μg g^{-1}), kidney (1.40 μg g^{-1}) heart (0.28 μg g^{-1}), skeletal muscle (0.20 μg g^{-1}) and brain (0.047 μg g^{-1}) in the non-starved rabbits. The values were increased but the order maintained after starvation. This agrees with the findings of Onyeyili *et al.* (2000) in starved and non-starved broiler chicken. Sharma *et al.* (1975) did observe that, a constant relationship do exist between plasma and tissue drug concentrations. The high plasma concentration of sulphadimidine recorded after the acute starvation in the animals might have been responsible for the corresponding increase in tissue concentrations.

The data in Table 1 also indicates that, the liver and the kidneys have the highest concentrations of tissue sulphadimidine. This agrees with the findings of Onyeyili *et al.* (1997) in guinea fowl and domestic chickens; that sulphadimidine was concentrated most in the livers of these animals. The enzymes involved in acetylation of sulphadimidine, has been shown to be located within the liver (Bevill, 1991). Earlier it was reported that sulphadimidine is eliminated at the renal glomerulus by active proximal tubular secretion (Bioson and Keng, 1995). This may be responsible for the high level of the drug in the tissue.

The study also indicates that, the drug could be detected in the skeletal muscle and brain of the rabbits up to 12 days post drug administration but practically undetectable after 8 days in the liver, heart and kidney. This put the safe withdrawal period of sulphadimidine in rabbits in excess of twelve days. This time limit was longer than the excess of seven days withdrawal period after treatment with sulphadimidine in domestic chickens recommended by Onyeyili *et al.* (1997). In an earlier study Rana *et al.* (1993) reported a withdrawal period of 7 days not to be adequate after treatment of pigs with sulphaquinoxaline. Roundaut and Garmier (2002) has also reported the withdrawal period of sulphadimidine from eggs laid by chickens given oral sulphadimidine and sulphadimethoxine to be 12-20 days. Also Atta *et al.* (1999) reported that no residues of sulphadimidine could be detected in the tissues of rabbit after 7 days. But in rabbits infected with Eimeria Stiedai, the drug persisted in the tissues beyond 7 days. The researcher in the last study administered 0.5 g L^{-1} of the drug through drinking

water while in the present study, 100 mg kg^{-1} of the drug was administered intravenously. It has been reported that, the bioavailability of any drug depends on the route of administration and the dose administered (English, 1961). The increase in the duration of stay in the rabbit tissues recorded in the present studies might be as a result of the intravenous treatment, which ensures 100% bioavailability of the drug.

This study therefore concludes that, although acute starvation did not alter the pattern of sulphadimidine distribution in the various tissues examined in the rabbits, it however elevates the tissue concentrations of the drug and the minimum withdrawal time after the use of the drug should be in excess of twelve days.

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