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Disposition of sulphonamides in food-producing animals: disposition of sulphathiazole in tissues, urine, and plasma of cattle following intravenous administration

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Plasma, urine and tissue concentrations of sulphathiazole were determined at various times following intravenous administration to fifteen cattle. The averaged plasma and urine data were consistent with a two-compartment pharmacokinetic model with a half-life of elimination of 1.3 h and a total volume of distribution of 0.41 l/kg body weight. Sulphathiazole was eliminated by excretion of unchanged drug into urine (48%) and by formation of acetylated and polar metabolites. The averaged data obtained from eight selected tissue sites were consistent with the two-compartment pharmacokinetic model presented and confirmed that residues of sulphathiazole in edible tissue can be predicted from serum and urine concentrations of the drug.

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INTRODUCTION

The regulatory, analytical and medical problems caused by residues of antibacterial drugs in the edible tissues of food-producing animals have been reviewed elsewhere (Bevill, Sharma, Meachum, Wozniak, Bourne & Dittert, 1977). Detection of drug residues prior to slaughter offers the possibility of a solution of these problems more effective than current post-slaughter testing programs. Preslaughter tests for drug residues would be feasible if tissue drug concentrations could be estimated from drug concentrations in plasma. If the pharmacokinetics of the drug were known, it would also be possible to predict the time required for tissue residues to decline to a sufficiently low level to allow the animal to be slaughtered for meat.

The validity of using a pharmacokinetic model to define the relationship between plasma, urine and tissue concentrations of sulphathiazole in sheep has been established (Bevill, Koritz, Dittert & Bourne, 1977). The purpose of this study was to develop a similar model for the disposition of sulphathiazole in cattle.

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MATERIALS AND METHODS

Animals. Seventeen heifers of mixed breeding were obtained from local sources two months prior to the initiation of the study. During this acclimation period and the subsequent treatment period, they were limit-fed a balanced ration containing 11% protein with hay and water provided *ad libitum*. At body weights of 177–338 kg (6–12 months of age), the animals were randomly assigned to five treatment groups of three animals each and a control group of two animals. They were placed in individual metabolism cages and fitted with urinary retention catheters (Bardex, C. R. Bard Inc., Murray Hill, N.J.), size 24 French gauge, 48 h prior to treatment.

Drug Administration and Sample Collection. Sodium sulphathiazole (72 mg/kg) (Holmes Serum Co., lot No. 8483), as a 12.5% solution in sterile distilled water, was administered by rapid infusion into the right jugular vein of each animal. Animals were slaughtered in groups of three at 2, 4, 8, 16 and 24 h after dosing. Two untreated control animals were slaughtered at the end of the study.

Heparinized blood samples (10 ml) from the left jugular vein and urine samples were collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 16, and 24 h following drug administration from each remaining animal. Plasma was obtained by centrifugation and stored at 4 °C until assayed. The total volume of urine excreted during each sampling period was recorded and aliquots were stored at −10 °C until assayed.

Samples of liver, kidney, heart, leg muscle, shoulder muscle, loin muscle, body fat and omental fat were obtained from each animal at slaughter. The samples were cut into 1 cm cubes, frozen in liquid nitrogen, reduced to a powder in a blender, and stored in plastic-lined containers at −10 °C until assayed.

Analytical Methods. Plasma and tissue samples were analysed for sulphathiazole and urine samples for sulphathiazole, acetylsulphathiazole, and polar metabolites (Bevill *et al.*, 1977).

RESULTS AND DISCUSSION

The average plasma concentrations and rates of urinary excretion of sulphathiazole determined at various times following intravenous administration of the drug are shown in Fig. 1. Sulphathiazole was rapdily eliminated from plasma reaching 5 mg% (50 μg/ml) (a minimum therapeutically effective concentration) in 2 h and 0.1 mg% (1 μg/ml) (approximate limit of detection) in 12 h. The average cumulative amounts of sulphathiazole and its acetylated and polar metabolites excreted into urine are presented in Fig. 2. Approximately 48% of the dose was excreted as unchanged sulphathiazole, 18% as acetylsulphathiazole and 2% as polar metabolites. Concentrations of sulphathiazole in tissues collected at slaughter are reported in Table I.

Semi-logarithmic plots of the averaged data for the elimination of sulphathiazole from plasma and its excretion into urine versus time (Fig. 1) were biexponential with similar shapes suggesting that the overall elimination of the drug in cattle could be described by a linear two-compartment pharmacokinetic model (Gibaldi & Perrier, 1975). With the addition of urinary excretion data for sulphathiazole, acetylsulphathiazole and polar metabolites and the assumption that the elimination of metabolies from the central compartment was first order, the two-compartment model in Fig. 3 was proposed to describe the disposition of sulphathiazole in cattle. As all of the dose was not recovered in the urine, the 'lost' fraction (32%) was included to represent miscellaneous extrarenal routes of excretion, most probably biliary.

To determine if the proposed two-compartment model gave the best fit to the data, one- and three-component models were fitted to the averaged plasma and urine data. It was determined that the two-compartment model was significantly better than the one-compartment model ($P = 0.002$), but the two-compartment model was not significantly better than the three-compartment model ($P > 0.1$) as determined by F test (Boxenbaum, Riegelman & Elashoff, 1974). The two-compartment model was therefore retained as the simplest model to best fit the averaged plasma and urine data.

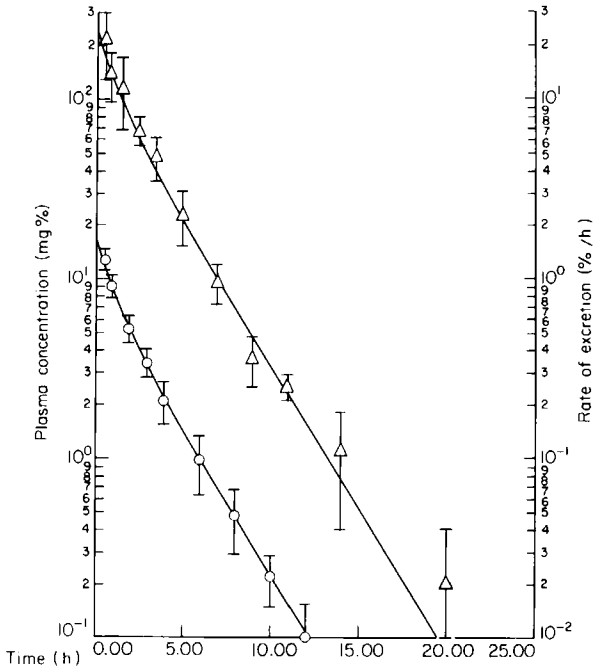

FIG. 1. Semi-logarithmic plot of average plasma sulfathiazole concentration (○) and average rate of urinary excretion of unchanged sulfathiazole (△) versus time following intravenous administration to cattle. The points were experimentally determined (± 1 standard deviation) and lines were calculated using the pharmacokinetic model (Fig. 3) and the values of the parameters presented in Table II.

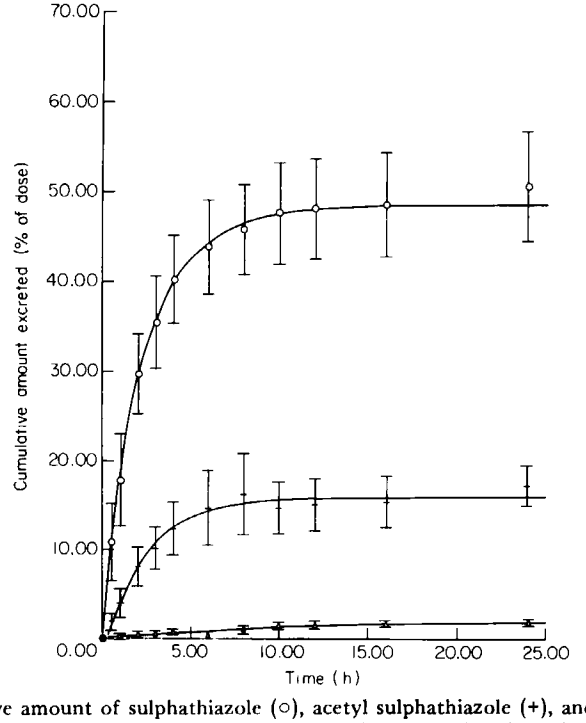

FIG. 2. Plot of cumulative amount of sulphathiazole (○), acetyl sulphathiazole (+), and polar metabolite (△) excreted in urine versus time following intravenous administration to cattle. The points were experimentally determined (± 1 standard deviation) and the lines were calculated using the pharmacokinetic model (Fig. 3) and the values of the parameters presented in Table II.

TABLE I. Average concentrations of sulphathiazole in tissues of cattle at various times following intravenous administration at 72 mg/kg.

Time after dosing (h)	Average Tissue Concentration (ppm±SD)							
	Kidney	Heart	Leg Muscle	Shoulder Muscle	Loin Muscle	Body Fat	Omental Fat	Liver
2.0	269 ±46	24 ±2.8	28 ±3.3	26 ±4.4	20 ±2.2	21 ±7.2	9.3 ±2.4	28 ±2.9
4.0	94 ±30	12 ±2.3	8.8 ±1.4	9.7 ±3.1	8.1 ±2.2	4.8 ±2.1	2.5 ±0.6	11 ±2.4
8.0	26 ±10	3.4 ±1.5	2.9 ±1.1	3.0 ±1.1	2.7 ±1.0	2.0 ±0.7	1.0 ±0.4	4.5 ±1.0
16.0	2.9 ±0.5	0.2 ±0.1	0.3 ±0.1	0.2 ±0.2	0.3 ±0.1	0.2 ±0.1	ns*	0.4 ±0.1
24.0	0.4 ±0.2	ns	0.1 ±0.1	ns	ns	ns	ns	0.2 ±0.1

*ns, not significant ($P < 0.01$).

Initial estimates of the rate constants in Fig. 3 were determined (Bourne, Bevill, Sharma, Gural & Dittert, 1977) to serve together with the averaged plasma and urine data as input into an iterative least-squares computation using the SAAM-23 program (Berman & Weiss, 1968) on a digital computer (IBM 370/165) to fit the model parameters to the data. The calculated 'best fit' values of the parameters are reported in Table II. The overall elimination rate constant, $k_{el} = k_{MISC} + k_{SU} + k_{SA} + k_{SP}$ (Figure 3) was 0.549 h^{-1} (half-life 1.3 h). The apparent total volume of distribution was 0.414 l/kg body weight with the central volume (0.334 l/kg body weight) approximately four times larger than the peripheral volume (0.0795 l/kg body weight).

The parameters based on average data (Table II) and the model in Fig. 3 were used to generate the solid lines in Figs 1 and 2 to illustrate the close agreement between the model and data. In each figure, the points are the averaged value for the remaining animals at each sample time with one standard deviation indicated by error bars.

The variability of the pharmacokinetic parameters within the cattle population was estimated by fitting the models in Figs 3 and 4 to the plasma and urine data from individual animals. The elimination of the drug from the plasma into the urine of eight of the

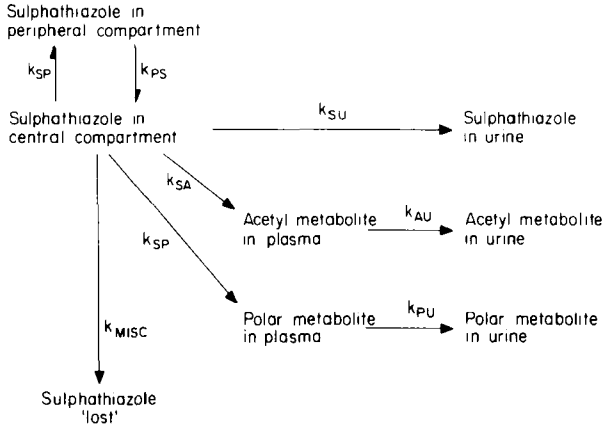

FIG. 3. Two-compartment model of sulphathiazole pharmacokinetics in cattle.

TABLE II. Values of the parameters of the pharmacokinetic models describing sulphathiazole disposition in cattle (Schemes I and II)

nal ber	$V_{central}$	$V_{peripheral}$	V_{total}	k_{el}	k_{SU}	k_{SA}	k_{SP}	k_{MISC}	k_{AU}	k_{PU}	k_{CP}
	0.402	–	0.402	0.509	0.244	0.0616	0.0063	0.197	6.31	0.738	–
	0.522	–	0.522	0.474	0.236	0.105	0.0107	0.122	0.632	0.433	–
	0.331	–	0.331	0.533	0.240	0.118	0.0071	0.168	0.808	0.665	
	0.431	–	0.430	0.444	0.214	0.0783	0.0061	0.146	1.45	0.248	–
	0.390	–	0.390	0.361	0.162	0.0633	0.0084	0.128	2.33	0.0899	–
	0.469	–	0.469	0.412	0.172	0.107	0.0462	0.0869	1.03	0.0130	–
	0.369	–	0.369	0.440	0.186	0.0447	0.0027	0.207	2.24	0.915	–
	0.434	–	0.434	0.473	0.238	0.0809	0.0077	0.146	0.567	0.0467	–
	0.328	0.066	0.394	0.568	0.243	0.106	0.0073	0.212	0.663	3.90	0.0932
	0.304	0.269	0.573	0.546	0.324	0.0985	0.0115	0.118	2.33	0.325	0.0873
	0.300	1.103	1.403	0.571	0.298	0.0839	0.0083	0.181	0.724	0.307	0.155
	0.389		0.520	0.485	0.232	0.086	0.011	0.156	1.74	0.698	0.112
*	0.071		0.301	0.067	0.049	0.023	0.012	0.041	1.68	1.10	0.37
aged†	0.334	0.0795	0.414	0.549	0.266	0.088	0.011	0.185	1.92	0.15	0.169

', volume of distribution, l/kg; k, rate constant, h^{-1}; *Average and standard deviation of values from fitting Fig. 3 or 4 to animals 4–15 o
al 12. †Results from fitting Fig. 4 to averaged plasma and urine data.

animals was monoexponential and was therefore best described by the one compartment model (Gibaldi & Perrier, 1975) (Fig. 4). This result indicated that in these animals the peripheral compartment was essentially contained within the central compartment. Individual data from three animals were best described by the two-compartment model in Fig. 3.

Insufficient data were available from the three animals slaughtered at 2 h post-dosing for modelling. Animal No. 12, slaughtered at 16 h post-dosing, was excluded from pharmacokinetic analysis because crystallization of the drug in its urinary tract interfered with normal drug elimination. The mean of the individual elimination rate constants was $0.485 \pm 0.067\ h^{-1}$ (half-life 1.43 ± 0.20 h) and the mean volume of the central compartment was 0.389 ± 0.071 l/kg body weight. These values compare favourably with those obtained from the averaged plasma and urine data (Table II).

The relatively large central compartment appeared to indicate that a number of extravascular tissues were in rapid equilibrium with plasma. When averaged tissue concentrations of sulphathiazole were plotted with model-predicted concentrations of sulphathiazole in the central and peripheral compartments (Fig. 5), the elimination phases were approximately parallel. Furthermore, linear regression analysis of the average plasma concentrations of sulphathiazole or its urinary excretion rates versus tissue drug concentrations gave very high correlation coefficients (Table III). This direct proportionality between sulphathiazole concentrations in plasma or outputs in urine and tissue residues of the drug makes it possible to use plasma and/or

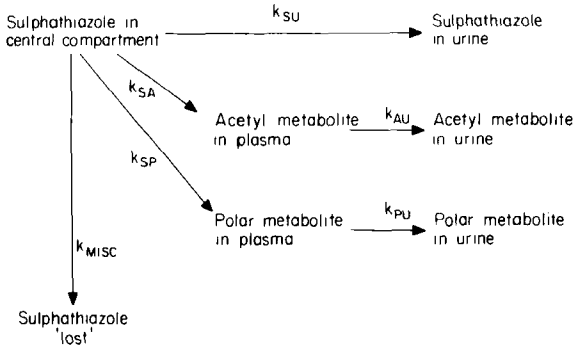

FIG. 4. One-compartment model of sulphathiazole pharmacokinetics in cattle.

TABLE III. Linear regression analysis of average plasma sulphathiazole concentration and excretion rate of unchanged sulphathiazole versus the sulphathiazole concentration in various tissues following intravenous administration of sulphathiazole to cattle at 72 mg/kg.

Time after dosing (h)	Average plasma concentration mg/100 ml	Average excretion rate % dose/h	Concentration in Tissues (ppm)				
			Kidney	Liver	Heart	Muscle	Fat
2.0	5.3	9.3	269	28	24	25	15
4.0	2.1	3.9	94	11	12	8.9	3.7
8.0	0.5	0.7	26	4.5	3.4	2.9	1.5
16.0	0.1	0.1	2.9	0.4	0.2	0.3	0.1
r (between plasma and tissue concentrations)			0.999	0.997	0.996	0.999	0.985
r (between excretion rate and tissue concentrations)			0.995	0.994	0.997	0.995	0.977

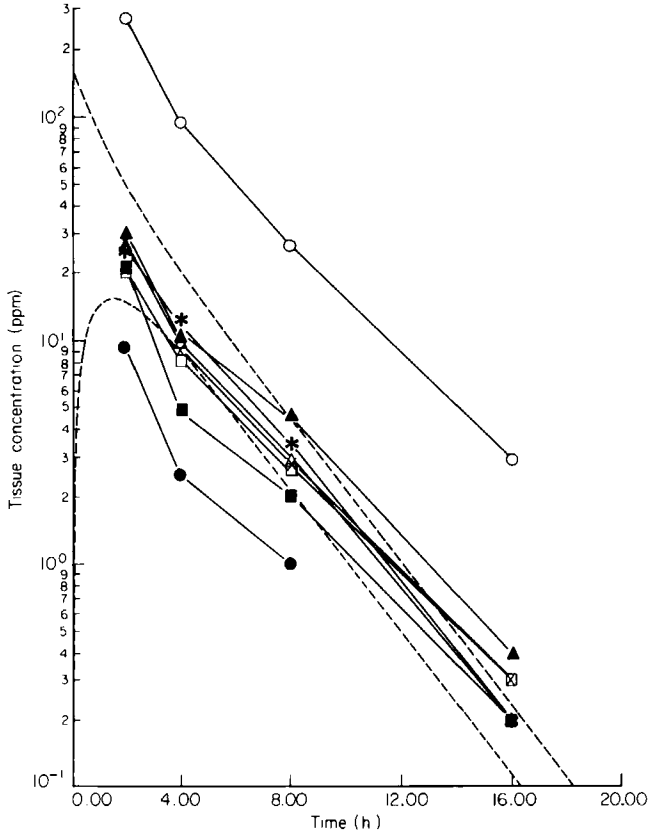

FIG. 5. Semi-logarithmic plot of sulphathiazole concentration in various tissues versus time following intravenous administration to cattle. The points (with solid connecting lines) were experimentally determined in kidney (○), heart (*), liver (▲), loin muscle (□), leg muscle (x), shoulder muscle (△), body fat (■), and omental fat (●) tissue. The upper and lower dashed lines represent sulphathiazole concentrations in the central and peripheral compartments, respectively, calculated using the pharmacokinetic model (Fig. 3) and the values of the parameters presented in Table II.

urine analyses prior to slaughter to confirm that sulphathiazole residues in edible tissues are below the acceptable limit or to predict the time required for this to occur.

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