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Pharmacokinetics and urinary excretion of sulfadiazine in buffalo calves

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Summary — Pharmacokinetics and urinary excretion of sulfadiazine were determined in buffalo calves following single oral administration (150 mg/kg). Kinetic evaluation of plasma levels was performed using a 2-compartment model. The absorption half-life and elimination half-life were 3.41 ± 0.63 and 13.75 ± 1.94 h, respectively. Based on this study, an optimal dosage regimen of sulfadiazine in buffalo calves would be 165 mg/kg, followed by 75 mg/kg at 12-h intervals. Sulfadiazine was mainly excreted in the urine as free amine, while the percentage of acetylated sulfadiazine was comparatively low.

kinetics / sulfadiazine / buffalo calf / urinary excretion

Résumé — Pharmacocinétique et excrétion urinaire de la sulfadiazine chez les veaux de buffles. La pharmacocinétique et l'excrétion urinaire de la sulfadiazine ont été déterminées chez les veaux de buffles après l'administration par voie orale d'une dose unique de sulfadiazine de 150 mg/kg. L'évaluation cinétique de la concentration dans le plasma a été réalisée selon un modèle bicompartmental. La demi-vie d'absorption et la demi-vie d'élimination ont été respectivement $3,41 \pm 0,63$ et $13,75 \pm 1,94$ h. Deux injections (165 mg/kg), à 12 h d'intervalle, devraient constituer d'après cette étude une posologie optimale de sulfadiazine chez les veaux de buffles. La sulfadiazine a été principalement excrétée dans l'urine sous forme d'amine libre tandis qu'on notait un pourcentage relativement faible de sulfadiazine acétylée.

cinétique / sulfadiazine / veau de buffle / excrétion urinaire

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INTRODUCTION

The pharmacokinetics and excretion of different sulfonamides have been described in various species of animals (Silvestri *et al*, 1967; Baggot, 1977; Nielson and Rasmussen, 1977). In veterinary practice, sulfadiazine is frequently used in the treatment of infections caused by *Streptococci*, *Staphylococci*, *Salmonella*, *E coli* and *Pasteurella* (Bevill, 1982). Earlier studies have shown that the optimal therapeutic regimen should only be based on the kinetic data obtained in the particular animal species and the environment in which the drug is to be clinically used. Further, it is also essential to determine the extent of acetylation of sulfonamides, as acetylated sulfonamides have no antibacterial activity and are more toxic than their parent compound. This investigation was therefore designed to determine the disposition kinetics of sulfadiazine and its suitable dosage regimen and urinary excretion in buffalo calves in a tropical environment.

MATERIALS AND METHODS

Animals and treatment

Six clinically healthy buffalo calves weighing 80–100 kg were used in the present study. The animals were acclimatized for 2 weeks in the departmental animal house before the start of the experiment. The animals were maintained under identical feeding conditions. Sulfadiazine was administered orally at a dose rate of 150 mg/kg body weight.

Collection of samples and analysis

Before administration of the test drug, blood samples were collected from the contralateral

jugular vein in the heparinized glass centrifuge tubes at 0.5, 1, 2, 3, 4, 6, 9, 12, 24 and 48 h after administration. Plasma was separated after centrifugation at 3 000 rpm for 15 min at the room temperature. The day temperature of the animal house was recorded that 37–40 °C during the experimental stage. Urine samples were collected for assay at 3, 6, 12, 24 and 48 h after administration of the drug. All the samples were stored at –20 °C until analysis.

The samples were analysed spectrophotometrically by the method of Bratton and Marshall (1939) for the free and acetylated sulfadiazine. The acetylated sulfadiazine was estimated after acid hydrolysis with 0.5 N HCl for 1 h.

The percentage of acetylation was calculated by the following formula:

$$\% \text{ of acetylation} = \frac{N^4}{N^4 + S} \times 100$$

where N^4 and S are concentrations of acetylated and free sulfadiazine respectively.

Pharmacokinetic analysis

The plasma sulfadiazine concentration – time were fitted separately for each animal by a 2-exponential equation using a computer program (Tallarida and Murray, 1987). Various pharmacokinetic parameters were determined as described by Gibaldi and Perrier (1982) and using a computer program (Tallarida and Murray, 1987). The dosage regimen for sulfadiazine was calculated as described by Notari (1980).

RESULTS

The sulfadiazine plasma concentration against time at different time intervals is presented in table I. The maximal level of free sulfadiazine was observed to be 35.7 µg/ml at 12 h, which decreased to 5.4 µg/ml at 48 h. A concentration around the minimum inhibitory concentration (40 µg/ml) which is effective against most of the organisms sensitive to this sulfonamide.

Table I. Plasma concentrations ($\mu\text{g/ml}$) of sulfadiazine in buffalo calves following its single oral administration (150 mg/kg).

Time (h)	Free	Acetylated	Total	Acetylation (%)
0.5	4.0 ± 1.1	1.6 ± 0.35	5.6 ± 1.3	28.6
1	5.2 ± 1.4	1.2 ± 0.42	6.4 ± 1.7	18.7
2	8.1 ± 1.9	2.0 ± 0.53	10.1 ± 1.2	19.8
3	12.2 ± 1.2	2.1 ± 0.60	14.3 ± 1.9	14.7
4	15.5 ± 1.6	3.4 ± 0.78	18.9 ± 2.5	17.9
6	20.8 ± 2.1	3.9 ± 0.85	24.7 ± 2.9	15.8
9	29.2 ± 5.4	8.0 ± 1.64	37.2 ± 3.4	21.5
12	35.7 ± 3.7	7.4 ± 1.35	43.1 ± 3.9	17.2
24	18.1 ± 2.1	4.8 ± 0.92	22.9 ± 2.8	20.9
48	5.4 ± 0.8	1.7 ± 0.45	7.1 ± 0.7	23.9

Values are mean \pm SEM of 6 animals.

mid was not attained at any time interval. The drug was found to be acetylated in the range of 14.7–28.6%.

The various disposition kinetic parameters are summarized in table II. The half-life of sulfadiazine was 13.75 h. The value of absorption rate constant (K_a) was low (0.203 h^{-1}). The C_{max} value was $41.91 \mu\text{g/ml}$ in plasma which was attained in 9.13 h (t_{max}). The total area under the plasma concentration curve (AUC) was $953.5 \mu\text{g}\cdot\text{h ml}^{-1}$. The calculated optimal dosage regimen of sulfadiazine in buffalo calves in the present study would be a priming dose of 165.3 mg/kg (for use in practice: 165 mg/kg) and maintenance dose of 74.9 mg/kg (for use: 75 mg/kg) with a dosage interval of 12 h to attain the minimum therapeutic level during the course of therapy.

The urinary excretion of sulfadiazine as total, free and acetylated amine is presented in table III. During the first 3 h the urine concentration of free sulfadiazine was $64 \mu\text{g/ml}$. The highest level of free sulfadiazine was $1\ 215 \mu\text{g/ml}$ 6–12 h post drug ad-

Table II. Kinetic parameter estimates for the 2-compartment model of sulfadiazine in the plasma after a single oral administration (150 mg/kg in buffalo calves).

Parameters	Unit	Values (mean \pm SEM)
K_a	h^{-1}	0.203 ± 0.038
$t_{1/2} K_a$	h	3.414 ± 0.634
K_{el}	h^{-1}	0.0504 ± 0.008
$t_{1/2} K_{el}$	h	13.75 ± 1.94
C_{max}	$\mu\text{g/ml}$	41.91 ± 8.92
t_{max}	h	9.13 ± 1.07
AUC	$\mu\text{g}\cdot\text{h/ml}$	953.5 ± 87.4
D^p	mg/kg	165.3 ± 9.4
D^*	mg/kg	74.9 ± 6.2
τ	h	12

K_a , $t_{1/2} K_a$: slope and half-life during the absorption phase, respectively; K_{el} , $t_{1/2} K_{el}$: slope and half-life during the elimination phase, respectively; C_{max} , t_{max} : calculated maximum plasma concentration and time when the drug concentration is highest in plasma, respectively; AUC: area under the curve; D^p : priming dose; D^* : maintenance dose; τ : dosage interval.

Table III. Urinary levels ($\mu\text{g/ml}$) of sulfadiazine in buffalo calves following its single oral administration (150 mg/kg).

Time (h)	Free	Acetylated	Total	Acetylation (%)
0-3	64.0 \pm 8.4	8.5 \pm 2.1	72.5 \pm 7.6	11.72
3-6	446.0 \pm 67.5	65.4 \pm 11.4	511.4 \pm 81.2	12.79
6-12	1215.0 \pm 141.8	166.8 \pm 20.7	1381.8 \pm 176.9	12.07
12-24	1171.8 \pm 127.4	510.2 \pm 67.8	1682.0 \pm 204.1	30.33
24-48	480.5 \pm 52.3	225.2 \pm 28.3	705.7 \pm 97.3	31.91

Values are mean \pm SEM of 6 animals.

ministration. The drug was acetylated in the urine in the range of 11.7–31.9%

DISCUSSION

Sulfonamides are bacteriostatic agents; the plasma concentration during the course of therapy should therefore not fall below a certain effective plasma concentration. However, in the present investigation a concentration around the minimum effective concentration (40 $\mu\text{g/ml}$) was not achieved at any time following oral administration of sulfadiazine in buffalo calves as analysed by the spectrophotometric method of Bratton and Marshall (1939). Moreover, sulfadiazine was slowly absorbed in the blood after oral administration in buffalo calves (absorption rate constant, K_a : 0.203 h^{-1}). The elimination half-life of sulfadiazine in buffalo calves as established in this study was 2.5-fold longer than that reported in cows after a single intravenous infusion of sulfadiazine (Atef *et al*, 1979) and 3-fold longer than that reported in poultry (Reddy *et al*, 1988).

Sulfonamides are acetylated at the N^4 position by the enzyme system *N*-acetyltransferase and acetyl co-enzyme A (Marshall *et al*, 1937). Sulfadiazine in plas-

ma was acetylated in the range of 14.7–28.6%. A comparatively low extent of acetylation of sulfadiazine suggests its safe use in buffalo calves without risk of toxicity.

On the basis of the kinetic data obtained during this investigation, the optimal dosage regimen of sulfadiazine in buffalo calves is suggested to be a priming dose of 165 mg/kg followed by maintenance dose of 75 mg/kg with a 12-h dosage interval which is nearly comparable to the dosage of sulfonamides prescribed to treat the mild to severe bacterial infections in cattle (Bevill, 1982). Thus the results of the present study revealed marked species differences in the kinetic behaviour of sulfadiazine. This emphasizes the need for determining the optimal therapeutic regimens on the basis of kinetic parameters in the particular environment as determined in the present study.

The higher urinary levels of sulfadiazine in buffalo calves suggest its lower reabsorption from the renal tubules. These results are in agreement with those reported by Singh and Ahmad (1977). Reabsorption of a drug from tubules into blood occurs through passive diffusion which is governed by lipid solubility and unionized fraction of the drug. The urine of herbivores is alkaline in reaction. Therefore sulfadiazine

(pK_a 6.48) in an alkaline medium will remain in an almost ionized state, unfavourable to its reabsorption.

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