Serum disappearance and urinary excretion of sulfamethoxypyridazine in goats

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La pharmacocinétique et l'excrétion urinaire de la sulfaméthoxypyridazine ont été déterminées sur des chèvres après une injection unique par voie intraveineuse à la dose de 100 mg/kg de poids vif. Un modèle ouvert à deux compartiments apparaît comme le mieux adapté pour décrire la cinétique de l'élimination du produit. Sa distribution et son élimination au stade de la demi-vie ont été de 0,10 ± 0,03 et de 6,28 ± 0,44 h, respectivement. Les valeurs du volume apparent de la distribution à l'état stable et la clearance corporelle totale ont été égales à 0,39 ± 0,02 l/kg et 0,73 ± 0,06 ml/kg/min respectivement. Le taux d'acétylation était bas, car situé entre 4,49 ± 1,96 et 25,07 ± 6,31 p. 100 du produit total dans le sérum avec une moyenne totale de 11,99 ± 1,66 p. 100. L'excrétion urinaire cumulée a été très basse, car seuls 2,97 ± 0,50 p. 100 de la dose totale administrée se sont retrouvés dans l'urine pendant 24 h. La posologie chez la chèvre serait de 37,00 et 27,15 mg/kg de poids vif comme dose d'attaque et dose d'entretien respectivement, à renouveler à 12 h d'intervalle par voie intraveineuse, afin d'obtenir le taux bactériostatique supérieur ou égal à 25 µg/ml.

Mots clés : Caprin - Sulfonamide - Sérologie - Miction - Inde.

INTRODUCTION

This study is a part of an applied research project to recommend an efficient sulfonamide which does not require frequent administration in goats, at least not earlier than 12 hours, a period under which it would be practically unfeasible in field conditions.

Sulfamethoxypyridazine (SMPd), a long acting sulfonamide, is gaining wide acceptance in the armament of antimicrobial therapy in veterinary medicine. Studies on the blood/plasma levels and/or blood disposition of SMPd in different species of animals namely sheep (8, 15), calves and cattle (4, 14, 15), buffalo calves (13), swine (5, 7) and dogs and horses (15) and the data on its urinary excretion in sheep (8), pigs (7) and buffalo calves (13) revealed inter-species variation in the degree of acetylation, pharmacokinetic profile and urinary excretion. The optimal therapeutic regimen should be based on the kinetic data obtained in the particular animal species and the environment in which the drug is to be clinically used. Data are available on the pharmacokinetics of a number of sulfonamides in goats (11, 12, 16). However, such informations on the disposition kinetics and urinary excretion of SMPd are apparently lacking in goats. This investigation was undertaken to determine the disposition kinetics, suitable dosage regimen and urinary excretion of SMPd in this species.

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MATERIALS AND METHODS

Animals

The experiments were carried out in nine adult female Gaddi goats weighing between 12.5 and 19.5 kg. They were fed locally available green tree leaves, concentrate and mineral mixture. Water was provided *ad libitum*. The studies were conducted in two phases:

Pharmacokinetic studies

SMPd (25% solution)* was administered intravenously (IV) to four animals at the dose rate of 100 mg/kg body weight. Blood samples (4 ml each) were drawn from the contralateral jugular vein at 2.5, 5, 10, 20 and 40 min and 1, 1.5, 2, 4, 6, 8, 12, 24, 48 and 72 post injection hour. Serum was separated and stored at -20°C until analysis.

Urinary excretion

Urinary excretion studies were conducted in five goats following a single IV dose of 50 mg/kg body weight. The animals were kept in metabolic cages of standard size. With the help of urine collecting bags, the total volume of urine voided during 0-3, 3-6, 6-9, 9-12 and 12-24 h was collected and recorded. An aliquot was taken, centrifuged and stored at -20°C until analysed for SMPd.

Assay of sulfamethoxypyridazine

The concentration of free and acetylated SMPd in serum and urine samples was determined spectrophotometrically (3). The acetylated SMPd was estimated

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after acid hydrolysis with 0.5 N HCl for 1 h. The percentage of acetylation was calculated by the following formula:

$$\% \text{ of acetylation} = \frac{N_4}{S+N_4} \times 100$$

where N_4 and S are the concentrations of acetylated and free SMPd, respectively.

Pharmacokinetic analysis

The serum SMPd concentrations against different time intervals from individual goat were analysed by using the curve-stripping (CSTRIP), which determines whether data can best be described by mono-, bi- or triexponential equations, and the nonlinear least square regression (SASNONLIN) computer programmes. After fitting the data to a suitable biexponential equation, other pharmacokinetic parameters were determined as described by BAGGOT (1) and GIBALDI and PERRIER (6).

Dosage regimen

On the basis of *in vitro* minimum inhibitory concentrations (MIC) of ≥ 25 µg/ml in respect of majority of the microorganisms (9) and the disposition kinetic data, the dosage regimen were calculated by using the equation as described by NOTARI (10).

RESULTS

The data on serum concentrations (mean ± SEM) of free and the N_4-acetyl-metabolite of SMPd as a function of time in goats are presented in table I. The peak serum concentration of 414.37 ± 23.94 µg/ml observed at 2.5 min declined rapidly to 312.15 µg/ml at 10 min. Thereafter, the blood level was reduced gradually to 33.51 µg/ml at 24 h and traces of the drug could be detected in blood up to 72 h.

No definite pattern of acetylation could be appreciated during the first 6 h, thereafter the percentage of acetylation increased up to 12 h and decreased 12 h onward (table I). The values of acetylation ranged between 4.49 to 25.07 percent at 2.5 min to 12 h with an overall mean of 11.99 ± 1.66 percent during 24 post injection hour.

Different pharmacokinetic variables describing the distribution and elimination of SMPd in goats are presented in Table II. The distribution and elimination half life values were 0.10 ± 0.03 and 6.28 ± 0.44 h, respectively.

Parameters determined :

A, α, $t_{1/2}(\alpha)$: intercept, rate constant and half life during the distribution phase, respectively

TABLE I Mean concentrations (µg/ml) of free SMPd and the percentage of N_4-acetyl SMPd following single intravenous administration (100 mg/kg body weight) in goats.

Time (h)	Serum concentration	
	[a] Free SMPd	[b] N_4-acetyl SMPd
0.04	414.37 ± 23.94	4.49 ± 1.96
0.08	360.92 ± 20.70	8.52 ± 3.09
0.16	312.15 ± 18.88	7.21 ± 2.98
0.33	270.60 ± 18.18	5.66 ± 1.03
0.66	247.47 ± 15.39	12.34 ± 3.34
1.00	232.65 ± 16.31	9.22 ± 0.79
1.50	211.85 ± 18.43	11.49 ± 1.36
2.00	192.18 ± 8.56	9.74 ± 0.96
4.00	160.30 ± 8.33	13.79 ± 4.63
6.00	125.06 ± 9.33	13.10 ± 5.35
8.00	105.62 ± 11.43	22.58 ± 9.58
12.00	66.40 ± 8.80	25.07 ± 6.31
24.00	33.51 ± 4.59	12.63 ± 3.58

[a] : mean ± SEM of four animals ; [b] : mean ± SEM of three animals.

B, ß, $t_{1/2}(ß)$: intercept, rate constant and half life during the elimination phase, respectively

CP_0 : expected theoretical drug concentration at time zero

Kel : rate constant of elimination from central compartment

K_{12}, K_{21}: rate constants of transfer of drug from central to peripheral and pheripheral to central compartments, respectively

V_c, Vd_{ss} : apparent volume of central compartment and apparent volume of distribution at steady state, respectively

Cl_B : the total body clearance

f_c : fraction of the drug present in the central compartment

T/C: ratio of drug concentration between tissue and central compartment

AUC : area under the concentration - time curve

MRT : mean residence time.

Table III presents the data (mean ± SEM) on urinary excretion of free and N_4-acetyl derivative of SMPd after a single IV dose of 50 mg/kg body weight. Urinary excretion of this drug was almost negligible as only 2.97 ± 0.50 percent of the total administered dose was excreted in urine (free + N_4-acetyl-metabolite) during 24 h. However, the acetylated metabolite increased from 7.39 ± 2.28 percent at 3 h to 27.63 ± 7.16 percent by 24.

TABLE III Urinary excretion of sulfamethoxypyridazine and the N_4-acetyl-sulfamethoxypyridazine in goats following a single intravenous administration (50 mg/kg).

Time interval (h)	Percentage of the total drug excreted		Total time (h)	Cumulative excretion of SMPd as the percentage of total dose administered		
	F	N_4		F	T	N_4
0-3	92.61 ± 2.28	7.39 ± 2.28	3	0.19 ± 0.06	0.21 ± 0.007	0.02 ± 0.01
3-6	90.34 ± 4.10	9.66 ± 4.10	6	0.39 ± 0.09	0.44 ± 0.10	0.05 ± 0.01
6-9	88.07 ± 5.04	11.93 ± 5.04	9	0.59 ± 0.17	0.66 ± 0.17	0.07 ± 0.02
9-12	86.27 ± 6.64	13.73 ± 6.64	12	1.14 ± 0.35	1.42 ± 0.48	0.27 ± 0.17
12-24	72.37 ± 7.10	27.63 ± 7.16	24	2.15 ± 0.57	2.97 ± 0.50	0.82 ± 0.15

F = free ; T = total ; N_4 = acetyl-SMPd.
Data expressed are mean ± SE of 5 goats.

TABLE II Pharmacokinetic parameters for sulfamethoxypyridazine after a single IV administration (100 mg/kg) in goats (n = 4).

Parameters	Units	Mean ± SE
A	µg/ml	266.12 ± 54.57
α	h^{-1}	10.77 ± 4.63
$t_{\frac{1}{2}}(\alpha)$	h	0.10 ± 0.03
B	µg/ml	253.75 ± 10.79
β	h^{-1}	0.11 ± 0.008
$t_{\frac{1}{2}}(\beta)$	h	6.28 ± 0.44
CP_0	µg/ml	519.88 ± 73.20
Kel	h^{-1}	0.22 ± 0.02
K_{12}	h^{-1}	5.56 ± 2.79
K_{21}	h^{-1}	5.09 ± 1.84
K_{12}/K_{21}	Ratio	0.96 ± 0.13
V_c	l/kg	0.20 ± 0.02
Vd_{ss}	l/kg	0.39 ± 0.02
Cl_B	ml/kg/min	0.73 ± 0.06
f_c	—	0.50 ± 0.03
T/C	—	0.99 ± 0.13
AUC	µg/ml . min	149 699.50 ± 13 324.3
MRT	h	8.92 ± 0.25

Caption: see part "Results"

DISCUSSION

Following a single intravenous administration of SMPd, therapeutic concentrations (≥ 25 µg/ml) were detected in serum up to 24 h. Apparently no data are available on the metabolism of SMPd in goats, however, hydroxylation and glucoronidation have been suggested as the major metabolic pathways for sulfadimidine, and acetylation plays a minor role (11). Further, goats have been recognized as poor and slow acetylators of sulfadimidine (12, 16).

The present studies on the acetylated metabolite in blood and urine suggest that Gaddi goats are slow and poor acetylators of SMPd similar to that reported for swine (5). Calves on the contrary are fast but also poor acetylators (4) and there is no acetylation in dogs (15).

Evaluation of the disposition kinetic data on SMPd revealed that biexponential equation was best suited to describe the pharmacokinetics of this drug in goats as for several other sulfonamides in this species (12, 16). The distribution half life (0.10 ± 0.03 h) of this drug in goats suggested that this drug is distributed in the body at a much faster rate compared to other sulfonamides - sulfacetamide (0.18 ± 0.04 h), sulfadimidine (0.24 - 0.80 h) and sulfanilamide (0.23 ± 0.03 h), respectively (12). The values of apparent volume of distribution (Vd_{ss}; 0.39 ± 0.02 l/kg) reflected slight to moderate degree of penetration of the drug into body fluids and tissues of goats. Almost similar values for the distribution volume have been reported for sulfadimidine, sulfadoxine, sulfamethoxydiazine (16). But higher values of Vd for sulfanilamide, sulfasomidine, sulfadimethoxine and sulfamoxole and on the contrary lower Vd values for sulfamonomethoxine and sulfafurazole have been observed in goats (12, 16).

SMPd is distributed almost equally between the central and tissue compartments as reflected by the values of certain pharmacokinetic parameters (T/C -0.99 ± 0.13; K_{12}/K_{21} -0.96 ± 0.13 ; f_c-0.50 ± 0.03) and suggested that the disappearance of parent compound from the blood and tissues occurs at similar rates as reported by BEVILL for other sulfonamides in cattle, sheep and swine (2).

The terminal half life of SMPd (6.28 ± 0.44 h) was almost similar to that of sulfadoxine (6.44 ± 0.99 h), sulfanilamide (7.73 ± 1.36 h) and sulfamoxole (4.47 - 5.92 h) but it was shorter than the $t_{1/2}(\beta)$ values for sulfadimethoxine (8.58 ± 1.55 h) and sulfadimidine slow eliminators (8.48 - 9.55 h). Compared to SMPd, sulfamonomethoxine (1.25 ± 0.34 h), sulfacetamide (1.88 ± 0.19 h), sulfafurazole (1.57 ± 0.06 h), sulfasomidine (2.13 ± 1.12 h), sulfadimidine fast eliminators (2.40 - 4.11 h) and sulfamethoxydiazine (4.26 ± 0.60 h) have comparatively shorter $t_{1/2}(\beta)$ in goats (11, 12, 16). Compared to other species, half life of SMPd in goats was almost equal to that of 7 h in sheep (8) and

cows (14) but shorter than that of 10.2 h in pigs (7). Therefore, results of present investigations in goats suggest that there are interspecies differences in the disposition kinetic profile of drugs and hence warrant the importance of data generation in all the species of animals.

CONCLUSION

Ultimate objective of the present studies was to compute a suitable dosage regimen of SMPd for field conditions. Based on the results, the priming and maintenance doses of sulfamethoxypyridazine would be 37.0 and 27.15 mg/kg body weight respectively, to be repeated at 12 h interval to achieve and maintain the optimum bacteriostatic level of ≥ 25 µg/ml.

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Pharmacokinetics and urinary excretion of sulfamethoxypyridazine were determined in goats following single intravenous administration (100 mg/kg body weight). The disposition kinetics of sulfamethoxypyridazine could be best described by a 2-compartment open model. The distribution and elimination half life of the drug were 0.10 ± 0.03 and 6.28 ± 0.44 h, respectively. The values of apparent volume of distribution at steady state and total body clearance were found to be 0.39 ± 0.02 l/kg and 0.73 ± 0.06 ml/kg/min, respectively. The degree of acetylation was low as it ranged between 4.49 ± 1.96 to 25.07 ± 6.31 % of the total drug in serum with an overall mean of 11.99 ± 1.66 %. Cumulative urinary excretion of sulfamethoxypyridazine was very low as only 2.97 ± 0.50 % of the total administered dose was excreted in urine during 24 h. The dosage regimen in goats would be 37.00 and 27.15 mg/kg body weight as the priming and maintenance doses respectively, to be repeated at 12 h intervals by intravenous route to achieve the bacteriostatic level of ≥ 25 µg/ml.

Key words: Goat - Sulfonamide - Urination - Serology - India.

GARG (S.K.), UPPAL (R.P.), RIVIERE (J.E.). Desaparición sérica y excreción urinaria de la sulfametoxipiridazina en cabras. *Revue Élev. Méd. vét. Pays trop.*, 1994, **47** (2) : 215-218

Se determinaron la farmacocinética y la excreción urinaria de la sulfametoxipiridazina en cabras, luego de una administración intravenosa única (100 mg/kg de peso vivo). La cinética de disposición de la sulfametoxipiridazina puede describirse con un modelo abierto de dos fases. La vida media de distribución y de eliminación del medicamento fue de 0,10 ± 0,03 y 6,28 ± 0,44 h respectivamente. Los valores de volumen aparente de distribución en estado estable y liberación corpórea total fueron de 0,39 ± 0,02 l/kg y 0,73 ± 0,06 ml/kg/min respectivamente. El grado de acetilación fue bajo, entre 4,49 ± 1,96 y 25,07 ± 6,31 por ciento del total del medicamento en el suero, con un promedio general de 11,99 ± 1,66 por ciento. La tasa de excreción urinaria acumulativa de la sulfametoxipiridazina fue muy baja, sólo 2,97 ± 0,50 por ciento de la dosis total administrada se excretaron en la orina durante 24 h. Las dosis iniciales y de mantenimiento en cabras pueden ser de 37,00 y 27,15 mg/kg de peso vivo respectivamente, a ser repetidas cada 12 h por vía intravenosa, esto con el fin de alcanzar un nivel bacteriostático de ≥ 25 µg/ml.

Palabras clave : Caprino - Sulfonamida - Micción - Serología - India.