Pharmacokinetics, bioavailability and dosage regimen of sulphadimidine in camels (Camelus dromedarius) under hot, arid environmental conditions

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Vet. Res. 30 (1999) 39–47

Original article

Pharmacokinetics, bioavailability and dosage regimen of sulphadimidine in camels (*Camelus dromedarius*) under hot, arid environmental conditions

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(Received 15 May 1998; accepted 29 October 1998)

Abstract – A two-way crossover study was conducted in young Bikaneri camels (aged between 12 and 18 months) during the hot summer season to determine the bioavailability, pharmacokinetics and dosage regimens of sulphadimidine (SDM). A dose of 100 mg.kg^{-1} of SDM was used to study both the intravenous and oral pharmacokinetics of the drug. Analysis of the intravenous data according to a two-compartment pharmacokinetic model revealed that SDM was well distributed in the body ($Vd_{(area)}$: 0.862 L.kg^{-1}), had an overall body clearance of 0.035 ± 0.019 L.h^{-1}.kg^{-1} and the elimination of half-lives was in the range of 14.2 to 20.6 h. The mean maximum plasma SDM concentration following oral administration was 63.23 ± 2.33 µg.mL^{-1}, which was achieved 24 h after the oral administration. The mean bioavailability of SDM following oral administration was approximately 100 %. To achieve and maintain the therapeutically satisfactory plasma sulphadimidine levels of ≥ 50 µg.mL^{-1}, the optimum dosage regimen for camels following either intravenous or oral administration would be 110 mg.kg^{-1} as the priming dose and 69 mg.kg^{-1} as the maintenance dose, to be repeated at 24 h intervals. © Inra/Elsevier, Paris.

bioavailability / camel / dosage regimen / pharmacokinetics / sulphadimidine

Résumé – Pharmacocinétique, biodisponibilité et posologie de la sulphadimidine chez le chameau (*Camelus dromedarius*) dans un environnement chaud et aride. Une étude croisée double a été réalisée chez des jeunes chameaux Bikaneri (âgés de 12 à 18 mois) pendant la saison sèche d'été afin de déterminer la biodisponibilité, la pharmacocinétique et la posologie de la sulphadimidine (SDM). Une dose de 100 mg.kg^{-1} de SDM a été utilisée pour étudier la pharmacocinétique de la drogue administrée par voie orale ou intraveineuse. L'analyse des données obtenues après injection intraveineuse selon un modèle pharmacocinétique bi-compartimental révèle que la SDM été bien distribuée dans le

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corps ($Vd_{(area)}$: 0,862 $L.kg^{-1}$), a eu une clairance corporelle globale de 0,035 ± 0,019 $L.h^{-1}.kg^{-1}$ et les demi-vies d'élimination étaient réparties entre 14,2 et 20,6 h. La concentration maximale moyenne de SDM dans le plasma après administration orale a été 63,23 ± 2,33 $\mu g.mL^{-1}$; elle a été atteinte 24 h après l'administration orale. La biodisponibilité moyenne de la SDM près administration orale a été approximativement 100 %. Pour atteindre et maintenir des niveaux thérapeutiques satisfaisants de SDM dans le plasma supérieurs ou égaux à 50 $\mu g.mL^{-1}$, la posologie optimale après administration orale ou intraveineuse devrait être pour le chameau 110 $mg.kg^{-1}$ comme dose initiale et 69 $mg.kg^{-1}$ comme dose d'entretien administrée à 24 h d'intervalle. © Inra/Elsevier, Paris.

biodisponibilité / chameau / posologie / pharmacocinétique / sulphadimidine

1. INTRODUCTION

Sulphadimidine is one of the most extensively used drugs in veterinary medicine. In India, it is mainly used to treat coccidiosis and respiratory infections in camels. The pharmacokinetics and metabolism of sulphadimidine have been extensively investigated in the following ruminant species; cattle [16, 20, 24, 25], buffaloes [7, 29], sheep [30, 43], goats [35] and camels [14, 42]. All these studies indicate that a marked species difference exists in the metabolism and pharmacokinetics of sulphadimidine in animals, suggesting the importance of investigating the pharmacokinetic data in the animal species and environment in which the drug is clinically used. Furthermore, in view of the conflicting data available on the kinetics disposition of sulphadimidine in camels [14, 42], it was considered expedient to determine the pharmacokinetics of this drug, under the hot arid environment of the Great Thar desert of India, in order to determine an optimal dosage regimen for camels.

2. MATERIALS AND METHODS

2.1. Animals

Experiments were conducted on six clinically healthy male camels (*Camelus dromedarius*) of the Bikaneri breed, aged between 12 and 18 months and weighing 125 to 156 kg, in the months of May and June when stable temperature during the day was 43 to 45 °C, at the National Research Centre on Camels, Bikaner, India. The animals were maintained on khejri (*Prosopis cineraria*) and pala (*Zizyphus nummularia*). Water was provided ad libitum.

2.2. Drug administration

Sodium sulphadimidine (33.3 %) available as an injectable preparatoin (Indian Drugs and Pharmaceuticals Limited, Hyderabad, India) was administered in the left jugular vein of animals at a dose rate of 100 $mg.kg^{-1}$ body weight. For oral administration, an aqueous solution of sulphadimidine containing 100 mg of sodium sulphadimidine per milliliter was prepared from a pure crystalline sulphadimidine base by dissolving it in warm, sterile, distilled water to which a sufficient amount of 5 N sodium hydroxide was added to permit its dissolution. The camels were dosed via a stomach tube with sulphadimidine solution at a dose of 100 mg of sodium sulphadimidine per kg body weight. The stomach tube was flushed with isotonic saline solution after use.

2.3. Collection of samples

Blood samples (5–7 mL) were drawn from the right jugular vein into heparinized tubes just before (0 h) and at 0.17, 0.34, 0.67, 1, 2, 3, 4, 6, 9, 12, 24, 36, 48, 60 and 72 h after intravenous administration and at 0, 1, 2, 3, 4, 6, 9, 12, 24, 36, 48, 60 and 72 h after oral administration of sulphadimidine sodium. Plasma was separated by centrifugation (at 1 500 *g* for 10 min) within 20 min of sample collection and stored at –20 °C until analysed.

2.4. Experimental design

Camels were randomly allotted to two groups of three animals each. Administration of the drug to the animals was made according to a two-way crossover design with a washout period of 21 days between subsequent administrations.

2.5. Drug analysis

Drug analysis was carried out according to the diazotizing and coupling method [11] within 3 days of sample collection. The concentration of total sulphadimidine (SDM) was measured on the same samples after acid hydrolysis with 0.5 mL of 4N HCl in 10 mL of sample at 100 °C for 1 h. The concentration of ^{4}N-acetylated SDM was calculated as the difference between the concentration of SDM before and after acid hydrolysis and was expressed as a percentage of the total. The minimum detection limit of the assay was 1.0 $\mu g.mL^{-1}$. The standard curve of sulphadimidine in camel plasma was linear between 2.5 and 80 $\mu g.mL^{-1}$. The correlation coefficient (r) was greater than 0.98.

2.6. Pharmacokinetic analysis

Pharmacokinetic analysis of sulphadimidine concentration–time data was performed, using a computer program for non-linear regression analysis, MULTI [41]. Data points were weighed according to the equation

$$W_i = 1/Y_i^2$$

where W_i is the weight, Y_i is the fitted value of the ith observation. After intravenous administration, plasma concentration of sulphadimidine from individual camels was fitted to the general polyexponential equation

$$C_t(P) = \sum_{i=1}^{n} Y_i e^{-\lambda_i t}$$

where $C_t(P)$ represents plasma sulphadimidine concentration at time t, Y_i is the coefficient of the ith exponential term and λ_i is the exponent of the ith exponential term. Initial pharmacokinetic variable estimates were obtained using the linear regression method. The number of exponents needed for each data set was determined by applying Akaike's information criterion [40]. The sulphadimidine plasma concentration versus time points following intravenous administration were best fitted to a two-compartment open model

$$C_t(P)_{iv} = Y_1 e^{-\lambda_1 t} + Y_2 e^{-\lambda_2 t}$$

where $C_t(P)_{iv}$ is the plasma concentration at time t, Y_1 and Y_2 are zero-time intercepts, λ_1 is the distribution rate constant and λ_2 is the elimination rate constant.

Plasma concentration versus time data after oral administration were best fitted to a one-compartment open model with a first order adsorption rate

$$C_t(P)_{oral} = Y_2^{-Kt} - Y_1 e^{-K_a t}$$

where $C_t(P)_{oral}$ is the plasma concentration at time t, after oral administration, Y_2 and Y_1 are zero-time intercepts, k_a is the absorption rate constant and k is the elimination rate constant.

The two-compartment pharmacokinetic model provided simultaneous estimates of the extrapolated zero-time drug concentrations (Y_1 and Y_2), initial concentration as sum of Y_1 and Y_2 (C_0), hybrid rate constants (λ_1 and λ_2), the apparent volume of distribution [$Vd_{(area)}$], the total body clearance (CL_B) and the area under the plasma concentration–time curve [$AUC_{(0-\infty)}$]. The first order rate constants for the drug elimination from the central compartment (K_{el}), and for the drug transfer from the central compartment to the peripheral compartment and back (K_{12} and K_{21}), and the drug fraction in the central compartment (Fc) were calculated by standard procedures [5]. The one-compartment model with a first order absorption provided hybrid rate constants (K_a and K), the elimination half-life ($t_{1/2K}$), and the area under the plasma concentration–time curve [$AUC_{(0-\infty)}$]. Peak plasma concentration (C_{max}) and peak time (T_{max}) were reported as observed values.

Bioavailibility (F) was calculated by the formula:

$$F = \frac{AUC_{oral}}{AUC_{iv}} \times \frac{Dose_{i.v.}}{Dose_{oral}} \times 100$$

2.7. Dosage regimen

The suitable dosage regimens were calculated using standard formulae [6, 8].

2.8. Statistical analysis

Data are presented as mean ± SEM. For plasma half-lives, harmonic means were calculated and their SEM values were calculated using a jackknife technique [19]. Values of half-lives and areas under curves between the two experiments were compared using analysis of variance (ANOVA). The 0.05 level for probability was used to judge significant differences [31].

3. RESULTS

The mean plasma concentrations of sulphadimidine determined at different time intervals following intravenous and oral administration of 100 mg.kg^{-1} body weight are shown in *figure 1*. Pharmacokinetic parameters were obtained from each animal individually and are summarized in *table I* as mean ± SEM of six animals.

After intravenous administration, initial sulphadimidine concentration was 281.40 ± 4.91 μg.mL^{-1} measured at 0.17 h. The concentration declined rapidly to 100.60 ± 2.80 μg.mL^{-1} after 3 h, after which the drug concentrations in plasma decreased slowly. At 72 h, mean drug concentration levels were still above the detection limit (6.50 ±

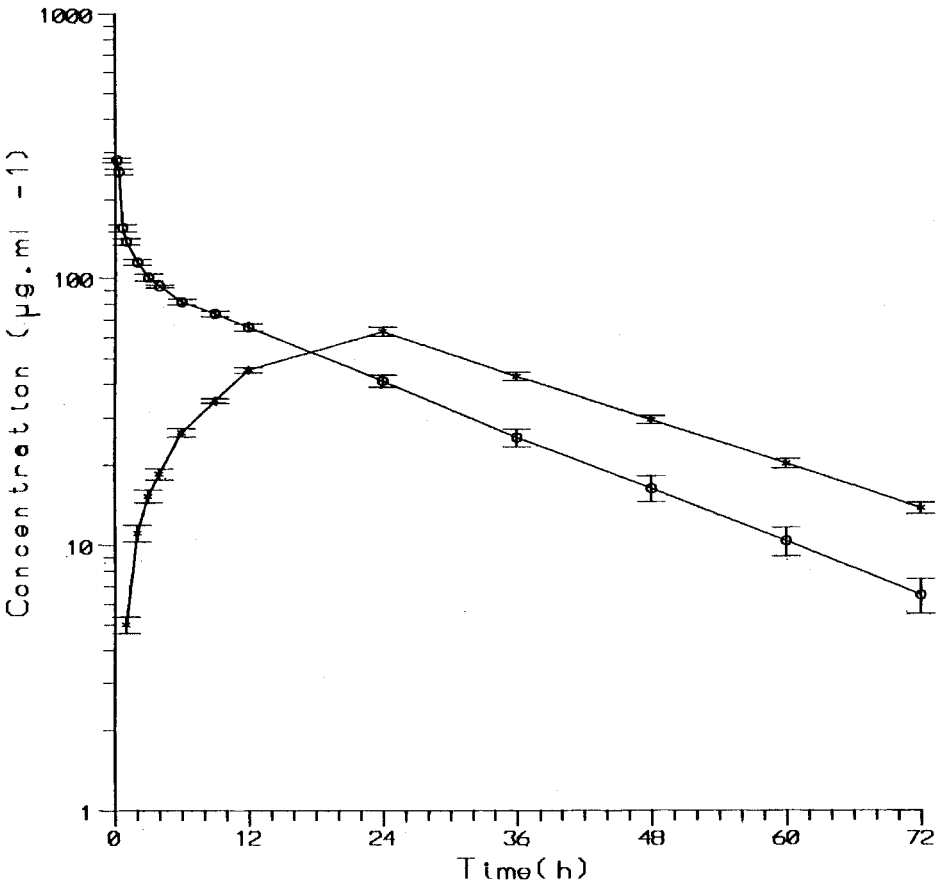

Figure 1. Mean plasma concentration–time profile (± SE) of sulphadimidine following intravenous (Φ) and oral (✳) administration of sulphadimidine sodium at 100 mg.kg^{-1} body weight to six camels.

Table I. Pharmacokinetic parameters of sodium sulphadimidine (100 mg·kg^{-1} bw) after intravenous and oral administration to six camels.

Kinetic parameters	Mean ± SEM	Range
Intravenous		
C_o (μg.mL^{-1})	372.10 ± 5.33	349.26–385.75
Y_1 (μg.mL^{-1})	262.03 ± 6.43	239.73–282.56
Y_2 (μg.mL^{-1})	110.01 ± 2.13	103.18–118.65
λ_1 (h^{-1})	2.19 ± 0.07	1.94–2.43
λ_2 (h^{-1})	0.041 ± 0.002	0.034–0.049
K_{el} (h^{-1})	0.130 ± 0.006	0.113–0.147
K_{12} (h^{-1})	1.42 ± 0.06	1.24–1.66
K_{21} (h^{-1})	0.68 ± 0.03	0.60–0.77
$t_{1/2}\lambda_1$ (h)	0.32 ± 0.01	0.28–0.36
$t_{1/2}\lambda_2$ (h)	16.96 ± 0.98	14.21–20.62
$Vd_{(area)}$ (L.kg^{-1})	0.862 ± 0.017	0.798–0.925
Vd_{ss} (L.kg^{-1})	0.823 ± 0.017	0.760–0.887
CL_B (L.h^{-1}.kg^{-1})	0.035 ± 0.019	0.029–0.042
AUC (μg.mL^{-1}.h^{-1})	2 885.32 ± 151.25	2 377.97–3 388.48
FC (ratio)	0.31 ± 0.01	0.28–0.34
Oral		
C_{max} (μg.mL^{-1})	63.23 ± 2.33	57.00–70.50
T_{max} (h)	24.00 ± 0.00	–
K (h^{-1})	0.040 ± 0.001	0.038–0.044
K_a (h^{-1})	0.059 ± 0.002	0.055–0.066
$t_{1/2ka}$ (h)	11.73 ± 0.34	10.43–12.49
$t_{1/2k}$ (h)	17.29 ± 0.36	15.79–18.29
$AUC_{(o-\infty)}$ (μg.mL^{-1}.h^{-1})	2 868.08 ± 84.74	2 559.82–3 079.94
F (%)	99.70 ± 4.10	88.20–116.00

0.97 μg.mL^{-1}). The minimum therapeutic concentration, ≥ 50 μg.mL^{-1} of drug was maintained up to 12 h.

Following oral administration the plasma concentration reached its peak value (C_{max}) (63.23 ± 2.33 μg.mL^{-1}) at 24 h, and the minimum therapeutic concentration (≥ 50 μg.mL^{-1}) of the drug was maintained up to 24 h. The mean oral bioavailability of the drug was 99.7 %. The concentration of ^{4}N-acetylated SDM varied from 2.8 to 3.7 % of the corresponding total sulphadimidine concentration in the plasma after administration of the drug by either route. Taking 12 and 24 h as convenient dosage intervals (τ), with minimum therapeutic plasma concentration [C_∞^{min}] at 50 μg.mL^{-1} and using the values of λ_2 and $Vd_{(area)}$ of *table I*, the dosage regimens for sulphadimidine were computed and are presented in *table II*.

Table II. Calculated dosage regimen of sulphadimidine sodium in camels required to maintain a minimum therapeutic concentration of drug ≥ 50 μg.mL^{-1}.

Parameter		Dosage interval (h)	
		12	24
D^* (mg.kg^{-1})	I.V.	67.25 ± 1.84	110.19 ± 5.84
	P.O.	67.55 ± 1.84	110.73 ± 5.85
D^m (mg.kg^{-1})	I.V.	26.10 ± 1.80	69.04 ± 5.98
	P.O.	26.20 ± 1.80	69.36 ± 6.00
C_{∞}^{max} (μg.mL^{-1})	P	212.64 ± 3.77	215.19 ± 4.88
	M	81.83 ± 2.35	134.22 ± 7.68
C_{∞}^{AV} (μg.mL^{-1})	P	159.40 ± 4.34	130.60 ± 6.90
	M	61.64 ± 0.96	81.15 ± 2.68

C_{∞}^{max} = maximum steady-state concentration of drug; C_{∞}^{AV} = average steady-state concentration of drug; D^* = priming dose; D^m = maintenance dose; P = plasma drug concentration after priming dose; M = plasma drug concentration after maintenance dose.

4. DISCUSSION

In the present investigation the pharmacokinetics of sulphadimidine in camels is best described by a two-compartment open model as recorded previously for crossbred calves, cows, buffaloes, sheep, goats and dogs [12, 20–22, 27, 29, 30, 43]. This is in contrast to the one-compartment model [14] and three-compartment open model [42] used previously to describe the pharmacokinetics of this drug in camels. The difference in the choice of pharmacokinetic models used to describe pharmacokinetics of sulphadimidine in these studies appears to be due to the difference in the frequency of blood sampling in the initial phase of the experiment and the sensitivity of analytical methods employed for the estimation of plasma drug concentration.

The value of $Vd_{(area)}$, 0.862 ± 0.02 L.kg^{-1} obtained in the present investigation compares well with an earlier reported value of 0.73 ± 0.108 L.kg^{-1} in camels [42]. This value is, however, much higher than they reported for sulphadimidine in cows (0.44 ± 0.02 L.kg^{-1} [24]); sheep (0.474 ± 0.012 L.kg^{-1} [43]; 0.60 ± 0.10 L.kg^{-1} [30]; 0.410 ± 0.07 L.kg^{-1} [12]); goats (0.316 ± 0.007 L.kg^{-1} [14]) and pigs (0.547 ± 0.611 L.kg^{-1} [13]) indicating that sulphadimidine is more extensively distributed in fluids and tissues of camels than in cows, sheep, goats and pigs. On the contrary, much higher values of $Vd_{(area)}$ for sulphadimidine had been reported for lactating buffaloes, 1.23 ± 0.07 L.kg^{-1} [29]. The higher values of K_{12} versus K_{21} further indicated that the rate of transfer of sulphadimidine from the central to the peripheral compartment was faster than its transfer in the opposite direction. Moreover, only 31 % of the drug was available for elimination in the central compartment (Fc; 0.31 ± 0.01) following its intravenous administration to camels.

The elimination half-life of sulphadimidine in camels as established in the present study (16.96 ± 0.98 h) or reported previously, 13.2 ± 4.1 h [42], 8.7 to 16.5 h [17] compares well with the half-life of this drug described in monogastric animals, namely pigs, 16.0 h [34], 15.17 to 18.74 h [13] and dogs, 16.2 ± 5.7 h [27]. Much shorter half-

lives of sulphadimidine have, however, been reported for other ruminant species such as cows, 11.3 h [24], young buffaloes, 9.4 h [3], sheep, 4.72 ± 0.26 h [14] and goats, 4.00 ± 0.24 h [22], 2.77 ± 0.22 h [14]. Large variations in the half-life of sulphadimidine in camels may, in part, be attributed to differences in the age, sex, breed of camels and the environmental conditions in which these studies were conducted. The present investigation was conducted in young male camels (12–18 months of age) of the Bikaneri breed as opposed to earlier studies where old males of 3–5 years of age [14] and old females of 4–5 years of age [42] of different breeds were used. Furthermore, the present investigation was conducted during summer when the environmental temperature was very high and daytime temperature ranged between 43 and 45 °C. It is well known in other species that sulphadimidine clearance is urine flow dependent [25, 42]. Renal function is greatly reduced in camels during the summer [38]. In the heat of the summer, the glomerular filtration rate, plasma flow rate and urine flow rate in camels is reduced by 75 % (from 0.81 $mL.min^{-1}.kg^{-1}$ to 0.23 $mL.min^{-1}.kg^{-1}$), 72 % (from 5.5 $mL.min^{-1}.kg^{-1}$ to 1.5 $mL.min^{-1}.kg^{-1}$) and over 50 % (from 3.3 $mL.min^{-1}$ to 0.7 $mL.min^{-1}$), respectively [39]. The increased levels of aldosterone and antidiuretic hormone (ADH) in the summer account for the increased retention of salt and water in the body of the camel [28]. Furthermore, the glomerular filtration rate (GFR) in the camel is 0.6 $mL.kg^{-1}.min^{-1}$ [37], which is much smaller than reported for cattle, sheep and goats [5, 9, 26]. The nephron in camels is twice as long as that in cows or goats [1]. As a result, most of the water filtered through the glomerulus is reabsorbed in the kidney via long loops of Henle leading to significantly reduced urine flow; the urine flow in normal circumstances being only 3.3 $mL.kg^{-1}.day^{-1}$ [38] as compared to 10–40 $mL.kg^{-1}.day^{-1}$ in sheep and goats and 17–45 $mL.kg^{-1}.day^{-1}$ in cattle [33]. This may lead to extensive reabsorption of sulphadimidine from renal tubular fluid into the systemic circulation. Apart from urine, sulphonamides are also excreted in large amounts into ruminal juice via salivary secretion [3]. Since the nature of camel saliva is highly alkaline, pH 8.06–8.32 [10] and that large volume of parotid saliva (30 $L.day^{-1}$) is continuously secreted [15], a considerably large amount of sulphadimidine (pK_a 7.3) is likely to be excreted into ruminal fluid via this route. Ruminal epithelium is bi-directionally permeable to several drugs including sulphonamides [4]. The transport of drugs across the ruminal epithelium is affected by a concentration gradient, plasma protein binding, anatomical differences [18] and lipid solubility [23]. Once the non-ionized fraction of sulphadimidine had diffused into the rumen, it may be trapped at a pH lower than that of plasma [5]. This drug may be reabsorbed, however, later as it is passed down the gastrointestinal tract. The inherent water recirculation mechanism in camels [38] may increase recycling of sulphadimidine in the system thus affecting its rate and mode of excretion from the body. Species variations with regard to rate and the pattern of metabolism are known to influence the pharmacokinetic behaviour of sulphonamides in animals [23, 36]. The dependence of the half-lives of the drug on the rate of metabolism was also supported in the present study by the presence of relatively small amounts of ^{4}N-acetyl SDM (2.8–3.7 %) in camels versus that recorded for cows (15 %), sheep (6–11 %), goats (8 %) and pigs (25 %) [36]. The activities of some drug metabolizing enzymes such as mixed-function mono-oxygenases and conjugating enzymes are lower in camels than in sheep and goats [2].

Following P.O. administration, the peak plasma concentration of drug (C_{max}) was much lower in camels (*table I*) than reported for sheep administered sulphadimidine at the same dose level, 160 ± 43 $\mu g.mL^{-1}$ [12]. The time to reach peak concentration (T_{max}) in camels (24 h) was, however, much longer than reported for sheep (5.7 ± 1.8 h). But

when the same sheep were given calfspan®, a sustained-release preparation of sulphadimidine, orally at a dose of 39 $mg.kg^{-1}$, the T_{max} was achieved after a much longer time (14.8 ± 12.9 h). The mean bioavailabilities of the oral sulphadimidine solution and calfspan® preparation in sheep were recorded to be 58.3 and 52.5 %, respectively [12] as compared to 99.70 ± 4.10 % recorded for camels in this study. The long absorption half-life, $t_{1/2Ka}$; 11.73 ± 0.34 h, coupled with high oral bioavailability of 99.70 ± 4.1 % (88.20–116 %) indicated that sulphadimidine is slowly but completely absorbed after oral administration in camels. Based on the bioavailability and resulting plasma concentrations, it was concluded that the oral route is an efficient means of sulphadimidine administration in camels.

Since the activities of the drug metabolizing enzymes and water turnover rate in camels is low it may affect the pharmacokinetics of other drugs as well, especially those drugs which are excreted primarily through the kidney, with a danger of intoxication. To prevent, sulphadimidine accumulation in the body, a dosage interval of 24 h is advisable. To achieve and maintain the therapeutically satisfactory plasma sulphadimidine levels of ≥ 50 $\mu g.mL^{-1}$ [32], the optimum dosage regimens for camels following either intravenous or oral administration would be 110 $mg.kg^{-1}$ as the priming dose and 69 $mg.kg^{-1}$ as the maintenance dose, to be repeated at 24 h intervals. Though the method of drug analysis used in the present investigation is less sensitive than the HPLC method used by some other investigators [14, 42], the calculated dosage regimen of SDM for camels remained unchanged as they are based on rather high MIC values (≥ 50 $\mu g.mL^{-1}$).

ACKNOWLEDGEMENT

The senior author is extremely thankful to Dr N.D. Khanna, Project Director, National Research Centre on Camel (NRCC), Jodbeer, Bikaner for providing necessary research facilities to carry out this investigation at his farm. The help given by Indian Drugs and Pharmaceuticals Ltd. (IDPL), Hyderabad, India, in the form of a free gift of pure sulphadimidine powder is also fully acknowledged.

REFERENCES

[1] Abdalla M.A., Abdalla O., Morphometric observations on the kidney of the camel (*Camelus dromedarius*). J. Anat. 129 (1977) 45–50.

[2] Ali B.H., El-Sheikh H.A., Drug metabolism in camels, in: Allen W.R., Higgins A.J., Maybew I.G., Snow D.H., Wada J.F. (Eds.), Proceedings of the First International Camel Conference, R. and W. Publishers (New Market) Ltd, Suffok, UK, 1992, pp. 318–321.

[3] Atef M. Salem A., Al-Samarral S.A., Zafar S.A., Ruminal and salivary concentrations of some sulfonamides in cows and their effect on rumen flora, Res. Vet. Sci. 27 (1979) 9–14.

[4] Austin F.H., Absorption, distribution and excretion of sulphonamides in ruminants, Fed. Proc. 26 (1967) 1001–1005.

[5] Baggot J.D., The Basis of Veterinary Clinical Pharmacology, W.B. Saunders, Philadelphia, USA, 1977.

[6] Baggot J.D., Davis L.E., Reuning R.H., The disposition kinetics of amphetamine in the ruminant animal, Arch. Int. Pharmacodyn. Ther. 202 (1973) 17–27.

[7] Balakrishnarao D., Honnegowda, Narayana K., The effect of phenylbutazone on the blood plasma concentration and pharmacokinetics of sulphadimidine in buffalo calves (*Bubalus bubalis*), Indian Vet. J. 67 (1990) 920–923.

[8] Benet L.Z., Mitchell J.R.., Lewis B.S., Pharmacokinetics: the dynamics of drug absorption, distribution and elimination in: Gillman A.G., Rall T.W., Nies A.S., Taylor P. (Eds.), The Pharmacological Basis of Therapeutics, Pergmon Press, New York, 1990, pp. 3–32.

[9] Benlamlih S., Depomyers H., Changes in endogenous urea recycling and the handling of renal urea in pregnant and lactating Sardi sheep kept on a constant feeding level, Reprod. Nutr. Dev. 30 (1989) 227–235.

[10] Bhatia J.S., Ghosal A.K. Studies on fermentation in the camel (*Camelus dromedarius*), in: Allen W.R., Higgins A.J., Maybew I.G., Snow D.H., Wada J.F. (Eds.), Proceedings of the First International Camel Conference, R. and W. Publishers (New Market) Ltd, Suffok, UK, 1992, pp. 271–274.

[11] Bratton A.C., Marshall E.K., A new coupling component for sulphanilamide determination, J. Biol. Chem. 128 (1939) 537–550.

[12] Bulgin M.S., Lane V.M., Archer T.E., Baggot J.D., Craigmill A.L., Pharmacokinetics, safety and tissue residue of sustained release sul-

phamethazine in sheep, J. Vet. Pharmacol. Ther. 14 (1991) 36–45.

[13] Duffee N.E., Bevill R.F., Thurmon J.C., Luther H.G., Nelson D.E., Hacker F.E., Pharmacokinetics of sulphamethazine in male, female and castrated male swine, J. Vet. Pharmacol. Ther. 7 (1984) 203–211.

[14] El-Sheikh H.A., Ali B.H., Homeida A.M., Hassan T., Hapke H.J., Pharmacokinetics of antipyrine and sulphadimidine (sulphamethazine) in camels, sheep and goats, J. Vet. Pharmacol. Ther. 14 (1991) 269–275.

[15] Engelhardt W.V., Abbas A.M., Mousa H.M., Lechner-Doll M., Comparative digestive physiology of the forestomach in Camelids, in: Allen W.R., Higgins A.J., Maybew I.G., Snow D.H., Wada J.F. (Eds.), Proceedings of the First International Camel Conference, R. and W. Publishers (New Market) Ltd, Suffok, UK, 1992, pp. 263–270.

[16] Garg S.K., Pharmacokinetics and dosage regimen of sulphadimethylpyrimidine in male and female calves, Indian Vet. J. 67 (1990) 607–610.

[17] Ibrahim W.Y., Nouws J.F.M., Homeida A.M., Ali H.M., Pharmacokinetics and metabolism of sulphadimidine in the camel, in: Allen W.R., Higgins A.J., Maybew I.G., Snow D.H., Wada J.F. (Eds.), Proceedings of the First International Camel Conference, R. and W. Publishers (New market) Ltd, Suffok, UK, 1992, pp. 419.

[18] Jenkins W.L., Davis L.E., An approach for the study of drug distribution across ruminal epithelium in-vivo, J. South Afr. Vet. Med. Assoc. 41 (1970) 325–327.

[19] Lam F.C., Hung C.T., Perrier D.G., Estimation of variance for harmonic mean half-lives, J. Pharm. Sci. 74 (1985) 229–231.

[20] Malik J.K., Srivastava A.K., Pharmacokinetics and dosage of sulphadimidine in crossbred calves, Acta. Vet. Hung. 35 (1987) 291–296.

[21] Nawaz M., Pharmacokinetics and urinary excretion of sulphadimidine in sheep during summer and winter, Vet. Rec. 112 (1983) 379–381.

[22] Nawaz M., Khan F.H., Pharmacokinetics and urinary excretion of sulphadimidine in sheep and goats, I. Vet. Pharmacol. Ther. 2 (1979) 129–132.

[23] Nielsen P., Rasmussen F., Influence of age on half-life of trimethoprim and sulphadoxine in goats, Acta Pharmacol. Toxicol. 38 (1976) 113–116.

[24] Nielsen P., Rasmussen F., Half-life, apparent volume of distribution and protein binding of some sulphonamides in cows, Res. Vet. Sci. 22 (1977) 205–208.

[25] Nouws J.F.M., Vree T.B., Baakman M., Driessen F., Breukink H.J., Mevius D., Age and dosage dependency in the plasma disposition and renal clearance of sulphamethazine and its N_4-acetyl and hydroxy metabolites in calves and cows, Am. J. Vet. Res. 47 (1986) 642–649.

[26] Olsson K., Benlamlih S., Dahlborn K., Fyhrquist F., Effects of water deprivation and hyperhydration in pregnant and lactating goats, Acta Physiol. Scan. (1982) 1–370.

[27] Riffat S., Nawaz M., Zia-Ur-Rehman., Pharmacokinetics of sulphadimidine in normal and febrile dogs, J. Vet. Pharmacol. Ther. 5 (1982) 131–135.

[28] Siebert B.D., Macfarlane W.V., Water turnover and renal function of dromedaries in the desert, Physiol. Zool. 44 (1971) 225–240.

[29] Singh M.K., Jayachandran C., Roy C.P., Banerjee N.C., Pharmacokinetics and distribution of sulphadimidine in plasma, milk and uterine fluid of female buffaloes, Vet. Res. Commun. 12 (1988) 41–46.

[30] Srivastava A.K., Rampal S., Disposition kinetics and dosage regimens of sulhamethazine in sheep (*Ovis aries*), Br. Vet. J. 146 (1990) 239–242.

[31] Steel R.G.D., Torrie J.H., Principles and Procedure of Statistics: A Biometric Approach, 2nd ed., McGraw Hill Book Company, New York, 1980.

[32] Stowe C.M., Sisodia C.S., The pharmacological properties of sulphadimethoxine in dairy cattle, Am. J. Vet. Res. 24 (1963) 525–535.

[33] Swenson M.J., Duke's Physiology of Domestic Animals, Cornell University Press, London, 1977.

[34] Tschudi P., Elimination, Plasmaproteinbindung and Dosierung einiger Sulfonamide. III. Untersuchungen beim Schwein, Zentrabl. Veterinaei Med. 20 (1973) 155–165.

[35] Van Gogh H., Pharmacokinetics of nine sulphonamides in goats, J. Vet. Pharmacol. Ther. 3 (1980) 69–81.

[36] Vree T.B., Hekster Y.A., Pharmacokinetics of sulphonamides revisited, Antibiot. Chemother. 34 (1985) 1–208.

[37] Wilson R.T., The Camel, The Print House Pte Ltd, Singapore, 1984.

[38] Yagil R.F., The Desert Camel, Comparative Physiological Adaptation, Karger Ltd, Basal, 1985.

[39] Yagil R.F., Berlyne G.M., Glomerular filtration rate and urine concentration in the camel in dehydration, Renal Physiol. 1 (1978) 104–112.

[40] Yamaoka K., Nakagawa T., Uno T., Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations, J. Pharmacokinet. Biopharm. 6 (1978) 165–175.

[41] Yamaoka K., Tanigawara Y., Nakagawa T., Uno T., A pharmacokinetic analysis program (MULTI) for microcomputer, J. Pharmacobio-Dyn. 4 (1981) 879–885.

[42] Younan W., Nouws J.F.M., Homeida A.M., Vree T.B., Degan M., Pharmacokinetic and metabolism of sulphadimidine in camel, J. Vet. Pharmacol. Ther. 12 (1989) 327–329.

[43] Youssef S.A.H., El-Gendi A.Y.I., El-Sayed M.G.A., Atef M., Abdelsalam S.A., Some pharmacokinetic and biochemical aspects of sulphadiazine and sulphadimidine in ewes, J. Vet. Pharmacol. Ther. 4 (1981) 173–182.