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

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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 regimen 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(ave): 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

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corps (Vd\textsubscript{area} : 0,862 L.kg\textsuperscript{-1}), a eu une clairance corporelle globale de 0,035 ± 0,019 L.h\textsuperscript{-1}.kg\textsuperscript{-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\textsuperscript{-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\textsuperscript{-1}, la posologie optimale après administration orale ou intraveineuse devrait être pour le chameau 110 mg.kg\textsuperscript{-1} comme dose initiale et 69 mg.kg\textsuperscript{-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 preparation (Indian Drugs and Pharmaceuticals Limited, Hyderabad, India) was administered in the left jugular vein of animals at a dose rate of 100 mg.kg\textsuperscript{-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 4N-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 µg.mL⁻¹. The standard curve of sulphadimidine in camel plasma was linear between 2.5 and 80 µg.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

\[ C_i(P) = \sum_{i=1}^{n} Y_i e^{-\lambda_i t} \]

where \( C_i(P) \) represents plasma sulphadimidine concentration at time \( t \), \( Y_i \) is the coefficient of the ith exponential term and \( \lambda_i \) 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

\[ C_i(P)_{iv} = Y_1 e^{-\lambda_1 t} + Y_2 e^{-\lambda_2 t} \]

where \( C_i(P)_{iv} \) is the plasma concentration at time \( t \), \( Y_1 \) and \( Y_2 \) are zero-time intercepts, \( \lambda_1 \) is the distribution rate constant and \( \lambda_2 \) 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

\[ C_i(P)_{oral} = Y_2 -K_4t - Y_1 e^{-K_4 t} \]

where \( C_i(P)_{oral} \) is the plasma concentration at time \( t \), after oral administration, \( Y_2 \) and \( Y_1 \) are zero-time intercepts, \( K_4 \) 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 (\( \lambda_1 \) and \( \lambda_2 \)), the apparent volume of distribution (\( Vd_{(oral)} \)), the total body clearance (\( CL_B \)) and the area under the plasma concentration–time curve [AUC(\( p_{\text{oral}} \)]. The first order rate constants for the drug elimination from the central compartment (\( K_{12} \)) 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 (\( F_c \)) 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 (\( t_{1/2} \)), and the area under the plasma concentration–time curve [AUC(\( p_{\text{oral}} \)]. Peak plasma concentration (\( C_{\text{max}} \)) and peak time (\( T_{\text{max}} \)) were reported as observed values.

Bioavailability (\( F \)) was calculated by the formula:

\[ F = \frac{AUC_{\text{oral}}}{AUC_{iv}} \times \frac{\text{Dose}_{iv}}{\text{Dose}_{oral}} \times 100 \]

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 (△) and oral (■) administration of sulphadimidine sodium at 100 mg.kg⁻¹ body weight to six camels.
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 \( (C_{\text{max}}) \) \((63.23 \pm 2.33 \mu g.mL^{-1}) \) at 24 h, and the minimum therapeutic concentration \((≥ 50 \mu g.mL^{-1})\) 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 \((\tau)\), with minimum therapeutic plasma concentration \([C_{\text{min}}]\) at 50 μg.mL⁻¹ and using the values of \(\lambda_2\) and \(V_{d_{\text{area}}}\) of table I, the dosage regimens for sulphadimidine were computed and are presented in table II.
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 $V_d^{\text{area}} = 0.862 \pm 0.02 \text{ L.kg}^{-1}$ obtained in the present investigation compares well with an earlier reported value of $0.73 \pm 0.108 \text{ L.kg}^{-1}$ in camels [42]. This value is, however, much higher than they reported for sulphadimidine in cows ($0.44 \pm 0.02 \text{ L.kg}^{-1}$ [24]); sheep ($0.474 \pm 0.012 \text{ L.kg}^{-1}$ [43]; $0.60 \pm 0.10 \text{ L.kg}^{-1}$ [30]; $0.410 \pm 0.07 \text{ L.kg}^{-1}$ [12]); goats ($0.316 \pm 0.007 \text{ L.kg}^{-1}$ [14]) and pigs ($0.547 \pm 0.611 \text{ L.kg}^{-1}$ [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 $V_d^{\text{area}}$ for sulphadimidine had been reported for lactating buffaloes, $1.23 \pm 0.07 \text{ L.kg}^{-1}$ [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 ($F_c = 0.31 \pm 0.01$) following its intravenous administration to camels.

The elimination half-life of sulphadimidine in camels as established in the present study ($16.96 \pm 0.98$ h) or reported previously, $13.2 \pm 4.1$ 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, $16.2 \pm 5.7$ h [27]. Much shorter half-

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$C_{\infty}^{\text{max}}$ = maximum steady-state concentration of drug; $C_{AV}^{\text{max}}$ = average steady-state concentration of drug; $D'$ = priming dose; $D''$ = maintenance dose; $P$ = plasma drug concentration after priming dose; $M$ = plasma drug concentration after maintenance dose.
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 (pKₐ 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 ⁴N-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 1) than reported for sheep administered sulphadimidine at the same dose level, 160 ± 43 µg.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, t1/2Ka; 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 µg.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 µg.mL⁻¹).

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