

Oral pharmacokinetics of the acidic drugs, diclofenac and sulfamonomethoxine in male Shiba goats

Mohamed ELBADAWY^{1,2)}, Takara SAKIYAMA¹⁾, Rania ABOHATAB³⁾, Kazuaki SASAKI¹⁾ and Minoru SHIMODA^{1)*}

¹⁾Laboratory of Veterinary Pharmacology, Department of Veterinary Medicine, Tokyo University of Agriculture and Technology, Fuchu, Tokyo 183–8509, Japan

²⁾Pharmacology Department, Faculty of Veterinary Medicine, Benha University, Moshtohor, Toukh, Elqaliobiya, 13736, Egypt

³⁾Forensic Medicine and Toxicology Department, Faculty of Veterinary Medicine, Suez Canal University, Ismailia, Egypt

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ABSTRACT. In the present study, we examined the oral pharmacokinetics of the acidic drugs, diclofenac (DF) and sulfamonomethoxine (SMM), which have different physicochemical properties, in Shiba goats. DF and SMM were intravenously and orally administered to 5 male goats using a crossover design. The T_{\max} of DF and SMM were reached 1.5 and 5.6 hr after they have been orally administered, respectively, and this was followed by their slow elimination. The elimination of both drugs was markedly faster after being intravenously rather than orally administered, which indicated flip-flop phenomena after the oral administration. The mean absorption times (MATs) of DF and SMM were 6 and 15 hr, respectively. This slow absorption may have been due to slow gastric emptying in goats. The large difference observed in MATs between DF and SMM may have been because DF, which is more lipophilic than SMM, was partly absorbed from the forestomach. Therefore, these results suggest that the absorption of highly lipophilic drugs from the forestomach may be markedly high in Shiba goats. In case of drugs whose elimination is quite fast, their efficacies may appear from the early stage after oral administration even in ruminants, because elimination rate is the determinant factor of T_{\max} in flip-flop phenomena. Such drugs may be used orally even in ruminants.

KEY WORDS: diclofenac, flip-flop phenomena, goat, oral pharmacokinetic, sulfamonomethoxine

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Oral dosing is generally considered to be inappropriate for ruminants, because of slow drug absorption and/or drug loss in the rumen. Therefore, intramuscular and subcutaneous injections are frequently used in cattle, sheep and goats. The slow drug absorption reported after the oral administration of drugs to ruminants may be due to the unique anatomical and physiological properties of the gastrointestinal tract. The forestomach (rumen, reticulum and omasum) is a large volume compartment with a capacity ranging between 100 and 225 l in cattle and 10–24 l in sheep and goats. This may result in the dilution of drugs and a long gastric emptying time [3]. Therefore, orally administered drugs may have a long residence time in the forestomach. The inner structure of the forestomach may also contribute to slow drug absorption; it is lined by a keratinized stratified squamous epithelium, which limits the absorption of drugs. Moreover, microflora in the rumen may inactivate some drugs through metabolic or chemical reactions [4].

Although it is well-known that drugs are mainly absorbed from the small intestine after oral dosing, the absorption of some drugs from the stomach may also be markedly high.

This has been demonstrated for salicylic acid [8], sulfaethi-dole and barbital [6], and metoprolol [9] in rats. Since the effective surface area of the stomach that actually contributes to drug absorption is small, the physicochemical properties of drugs may be important factors for their absorption from the stomach [28]. We also previously found the rapid antipyretic effects of DF in dairy cows with infectious disease following its oral administration in a preliminary trial. Moreover, sulfamethoxazole had a rapid appearance in the plasma of goats ($T_{\max} = 0.8 \pm 0.2$ hr) after its intraruminal administration [19]. These findings suggest that the absorption of some drugs from the forestomach of ruminants may be markedly high if they have appropriate lipid solubility and unionization in the rumen fluid. The main purpose of this study was to clarify the relationship between drug absorption profiles after their oral administration to ruminants and their physicochemical properties. To achieve this, the oral pharmacokinetic profiles of two weak acidic drugs, DF and sulfamonomethoxine (SMM), were examined in male Shiba goats.

MATERIALS AND METHODS

Animals: All animals were maintained in accordance with the recommendations of the ‘Guide for the Care and Use of Laboratory Animals’ approved by the Faculty of Agriculture, Tokyo University of Agriculture and Technology. Five clinically healthy male Shiba goats, weighing 25–43 kg and aged 2–3 years, were used in this study. These goats were housed in pens at an ambient temperature and with good ventilation.

*CORRESPONDENCE TO: SHIMODA, M., Laboratory of Veterinary Pharmacology, Department of Veterinary Medicine, Tokyo University of Agriculture and Technology, Fuchu, Tokyo 183–8509, Japan.
e-mail: ms@cc.tuat.ac.jp

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Animals were fed hay cubes (#1A Cubes[®], Eckenberg farms Inc., Mattawa, WA, U.S.A.) at 600 g/head twice a day, and water was available *ad libitum*.

Reagents and chemicals: The sodium salt of DF and flufenamic acid (FA) were obtained from Sigma-Aldrich Corporation (St. Louis, MO, U.S.A.). SMM and sulfadimethoxine were obtained as a sodium salt from Daiichi Pharmaceutical Company (Tokyo, Japan). All other reagents and chemicals used in this study were of HPLC or analytical grade.

Experimental design

Pharmacokinetic study: DF or SMM was dissolved in sterilized distilled water for injection and administered either into the left jugular vein or orally to 5 male Shiba goats at doses of 1.0 and 10 mg/kg, respectively, using a crossover design with at least a 3-week washout period. In case of the oral administration of these drugs, drug solutions were given with 3 hay cubes. The SMM study was started 3 weeks after the DF study. Blood (3 ml) was collected from the right jugular vein immediately prior to the treatment and 0.5, 1, 2, 3, 4, 6, 9, 12 and 24 hr after dosing. Plasma was separated by the centrifugation of blood at 1,600 g for 10 min and stored at -20°C until analysis.

Stability of DF and SMM in the rumen juice: Two male Shiba goats were restrained, and nasal catheters were passed into the rumen. Thereafter, 40 ml of rumen fluid was aspirated through the catheter and processed for incubation immediately after its collection. Fifty microliters of DF or SMM solutions (200 $\mu\text{g/ml}$) was added to 950 μl of the rumen fluid to give a final concentration of 10 $\mu\text{g/ml}$ of the incubation mixture. Five samples of each drug were prepared and incubated in a thermostatic shaking water bath at 39°C for 24 hr under anaerobic conditions. After the incubation, the concentrations of DF and SMM were measured by HPLC.

Drug assays

Diclofenac: DF concentrations in the plasma and rumen juice were determined by HPLC with UV-detection, as described previously [1] with some modifications. Briefly, 100 μl of FA solution (10 $\mu\text{g/ml}$) was added as an internal standard to 500 μl of the plasma or rumen juice sample, followed by the addition of 200 μl of phosphoric acid (0.15 M). Subsequently, 4 ml of diethyl ether was added to the mixture and shaken for 3 min. The sample was centrifuged at 3,000 g for 10 min at 5°C . The obtained supernatant (organic layer) was transferred into a pear shaped flask and evaporated to dryness by an evaporator (Rotavapor[®] R-114, Shibata Scientific Technology, Ltd., Tokyo, Japan) at 30°C . The residue was reconstituted in 200 μl of the mobile phase and filtered using a 0.45- μm HPLC filter (Chromatodisc[®], 4P, Kurabo Biomedical Industries, Ltd., Osaka, Japan). Fifty microliters of the filtrate was injected into the HPLC column.

The HPLC system (Shimadzu Corporation, Kyoto, Japan) consisted of a pump (LC-10AD), a UV detector (SPD-6A),

an integrator (Chromatopac C-R7A plus) and a loop injector (Model 7125). The mobile phase was a mixture of 0.1 M acetate buffer (pH 6.3) and acetonitrile (65:35, v/v). Analytical separation was accomplished by using a reversed-phase ODS column (TSK-gel ODS-120T[®], 4.6 $\mu\text{m} \times 250$ mm, TOSOH Co., Tokyo, Japan). The flow rate was 1 ml/min. The wavelength of the detector was 278 nm. The recovery from plasma samples was $106.1 \pm 2.8\%$ at 1 $\mu\text{g/ml}$ ($n=5$), while that from rumen juice samples was $110.3 \pm 8.5\%$ at 10 $\mu\text{g/ml}$ ($n=5$). The inter-day CV values ranged from 0.83 to 3.72% for plasma samples and from 3.11 to 14.1% for rumen juice samples ($n=5$, 3 times).

Sulfamonomethoxine: SMM concentrations were determined in the plasma and rumen juice samples by HPLC with UV-detection. Two hundred microliters of perchloric acid (0.5 M) was added to 200 μl of the plasma sample. The mixture was vortexed for 30 sec and then centrifuged at 20,000 g for 5 min at 5°C . The obtained supernatant was filtered using the 0.45- μm HPLC filter. Fifty microliters of the filtrate was injected into the HPLC column.

In the case of rumen juice samples, SMM concentrations were determined after extraction with ethyl acetate. After being incubated for 24 hr, 100 μl of sulfadimethoxine solution (10 $\mu\text{g/ml}$) was added as an internal standard to the rumen juice samples. Subsequently, 5 ml of ethyl acetate was added. The mixture was vortexed for 30 sec and then centrifuged at 3,000 g for 10 min at 5°C . The obtained supernatant was transferred into a pear shaped flask and evaporated to dryness at 30°C . The residue was reconstituted in 200 μl of the mobile phase and filtered using the 0.45- μm HPLC filter. Fifty microliters of the filtrate was injected into the HPLC column.

The mobile phase was a mixture of 50 mM acetate buffer (pH 5) and acetonitrile (75:25, v/v). Analytical separation was accomplished using a reversed-phase C₈ column (Mightysil RP-8 GP[®], 4.6 $\mu\text{m} \times 250$ mm, Kanto Chemical Co., Tokyo, Japan). The flow rate was 1.0 ml/min. The wavelength of the detector was 270 nm. The recovery from plasma samples was $101.7 \pm 4.34\%$ at 1 $\mu\text{g/ml}$ ($n=5$), while that from rumen juice samples was $99.4 \pm 4.2\%$ at 10 $\mu\text{g/ml}$. The inter-day CV values ranged from 3.23 to 5.82% for plasma samples and from 3.39 to 4.67% for rumen juice samples ($n=5$, 3 times).

Pharmacokinetic analysis: The plasma concentration-time curves of DF after the intravenous injection fit well with the two compartment model. Therefore, the curves obtained after the intravenous injection ($C_{p_{iv}}(t)$) and oral administration ($C_{p_{po}}(t)$) were described by Eqs. 1 and 2, respectively.

$$C_{p_{iv}}(t) = \frac{\text{Dose}}{V} \left\{ \frac{\alpha - k_{21}}{\alpha - \beta} \cdot e^{-\alpha \cdot t} + \frac{k_{21} - \beta}{\alpha - \beta} \cdot e^{-\beta \cdot t} \right\} \quad (\text{Eq.1})$$

$$C_{p_{po}}(t) = \frac{\text{Dose} \cdot F \cdot k_a}{V} \left\{ \begin{aligned} &\frac{k_{21} - \alpha}{(k_a - \alpha)(\beta - \alpha)} \cdot e^{-\alpha \cdot t} \\ &+ \frac{k_{21} - \beta}{(k_a - \beta)(\alpha - \beta)} \cdot e^{-\beta \cdot t} \\ &+ \frac{k_{21} - k_a}{(\alpha - k_a)(\beta - k_a)} \cdot e^{-k_a \cdot t} \end{aligned} \right\} \quad (\text{Eq.2})$$

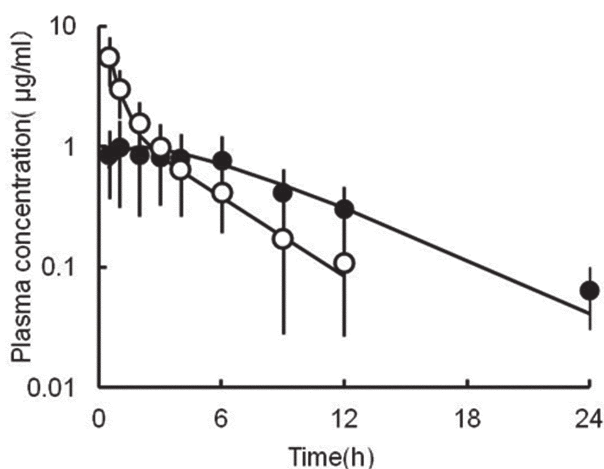


Fig. 1. Plasma concentration-time curves of diclofenac (1.0 mg/kg body weight) after its single intravenous (opened circle) and oral administration (closed circle) to male Shiba goats. Each point and vertical bar represent the mean and standard deviation, respectively (n=5). Each line was calculated by Eqs. 1 or 2 using pharmacokinetic parameters in Table 1.

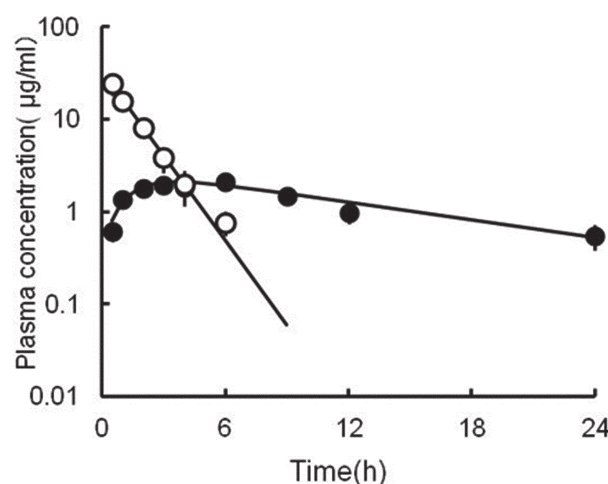


Fig. 2. Plasma concentration-time curves of sulfamonomethoxine (10 mg/kg body weight) after its single intravenous (opened circle) and oral administration (closed circle) to male Shiba goats. Each point and vertical bar represent the mean and standard deviation, respectively (n=5). Each line was calculated by Eqs. 3 or 4 using pharmacokinetic parameters in Table 2.

Equations 1 and 2 were simultaneously fit to the plasma concentration-time curves of DF after it was intravenously and orally administered to the same goats, respectively, in order to calculate pharmacokinetic parameters by the non-linear least squares method using the curve fitting program, MULTI [26].

On the other hand, the plasma concentration-time curves of SMM after it was intravenously administered fit well with the one compartment model. Therefore, the curves obtained after the intravenous injection ($Cp_{iv}(t)$) and those after the oral administration ($Cp_{po}(t)$) were described by Eqs. 3 and 4, respectively.

$$Cp_{iv}(t) = \frac{Dose}{V} e^{-k_{el} \cdot t} \quad (\text{Eq.3})$$

$$Cp_{po}(t) = \frac{Dose \cdot F}{V} \cdot \frac{k_a}{k_a - k_{el}} (e^{-k_{el} \cdot t} - e^{-k_a \cdot t}) \quad (\text{Eq.4})$$

Equations 3 and 4 were simultaneously fit to the plasma concentration-time curves after the intravenous injection and oral administration to the same goats, respectively.

Several pharmacokinetic parameters were calculated by non-compartmental analysis. The area under the concentration versus time curve (AUC) was calculated by the trapezoidal method (from time zero to the last sampling time) and integration (from the last sampling time to infinity). Total body clearance (CL_{tot}), bioavailability, mean residence time (MRT), mean absorption time (MAT) and the distribution volume at a steady state (V_{dss}) were calculated by conventional methods.

RESULTS

The plasma concentrations of DF and SMM rapidly increased and peaked 1–2 hr and 5–6 hr after being orally administered, respectively, followed by their slow elimination. On the other hand, plasma concentrations decreased rapidly after the intravenous injection with relatively short half-lives (3.05 ± 1.13 hr for DF and 1.00 ± 0.11 hr for SMM), indicating flip-flop phenomena after the oral administration of both drugs (Figs. 1 and 2). As shown in Tables 1 and 2, a pharmacokinetic analysis indicated the slow absorption of both drugs in male Shiba goats. The calculated MATs of DF and SMM were approximately 6 and 15 hr, respectively. The absorption half-life ($t_{1/2ka}$) of DF was slightly longer than its elimination half-life ($t_{1/2\beta}$). On the other hand, the $t_{1/2ka}$ of SMM was markedly longer than its $t_{1/2kel}$ (approximately 10 times). The bioavailabilities of both drugs were more than 70%, as listed in Tables 1 and 2.

Since the bioavailabilities of DF and SMM were incomplete, we evaluated the stability of both drugs in the rumen juice collected from male Shiba goats. The recovery from rumen juice samples was completed after a 24-hr incubation and was $104.8 \pm 11.9\%$ for DF and $99.4 \pm 2.85\%$ for SMM.

DISCUSSION

In the present study, we examined the absorption profiles of DF and SMM after their oral administration to male Shiba goats. The results of a pharmacokinetic analysis revealed the slow absorption of both drugs. The MAT values obtained were long (6 hr for DF and 15 hr for SMM). The oral pharmacokinetic profiles of DF and SMM have been clarified in several animal species. The absorption rate constant values

Table 1. Pharmacokinetic parameters of DF in male Shiba goats determined after single intravenous and oral administration of 1 mg/kg body weight

Parameter	Mean \pm SD (n=5)
k_a (hr^{-1})	0.194 ± 0.073
C_{\max} ($\mu\text{g}/\text{ml}$)	1.12 ± 0.58
T_{\max} (hr)	1.51 ± 1.41
α (hr^{-1})	2.09 ± 0.97
β (hr^{-1})	0.250 ± 0.078
$t_{1/2ka}$ (hr)	4.13 ± 1.94
$t_{1/2\beta}$ (hr)	3.05 ± 1.13
$\text{AUC}_{i.v.}$ ($\mu\text{g}\cdot\text{hr}/\text{ml}$)	14.7 ± 6.2
$\text{AUC}_{p.o.}$ ($\mu\text{g}\cdot\text{hr}/\text{ml}$)	10.4 ± 4.0
CL ($\text{l}/\text{hr}/\text{kg}$)	0.0784 ± 0.0309
F (%)	75.4 ± 24.0
F* (%)	73.9 ± 20.2
$\text{MRT}_{i.v.}$ (hr)	2.38 ± 1.01
$\text{MRT}_{p.o.}$ (hr)	8.42 ± 2.15
MAT (hr)	6.05 ± 2.74
V_{dss} (l/kg)	0.181 ± 0.102

k_a = absorption rate constant; C_{\max} = maximum plasma concentration; T_{\max} = time to maximum plasma concentration; α = first-order rate constant associated with the distribution phase; β = first-order rate constant associated with the elimination phase; $t_{1/2ka}$ = absorption half-life; $t_{1/2\beta}$ = elimination half-life; $\text{AUC}_{i.v.}$ = area under the plasma concentration–time curve after i.v. injection; $\text{AUC}_{p.o.}$ = area under the plasma concentration–time curve after oral administration; CL = total body clearance; F = bioavailability calculated by compartmental analysis; F* = bioavailability calculated by non-compartmental analysis; $\text{MRT}_{i.v.}$ = mean residence time after i.v. injection; $\text{MRT}_{p.o.}$ = mean residence time after p.o. administration; MAT = mean absorption time; V_{dss} = volume of distribution at a steady state.

for DF were previously shown to be $0.5\text{--}1.2 \text{ hr}^{-1}$ in pigs [17], 0.5 hr^{-1} in rabbits [2] and 0.38 min^{-1} in rats [18]. These values were markedly higher than those obtained from the male Shiba goats in the present study (0.19 hr^{-1}). The absorption of SMM was shown to be fast in pigs [13] as well as horses and humans [5]. The obtained k_a values (1.8 hr^{-1} in pigs and 0.023 min^{-1} in horses) were markedly higher than those obtained from the male Shiba goats in the present study (0.07 hr^{-1}). Since the absorption of drugs from the small intestines is generally fast, gastric emptying is the determining factor for drug absorption after the oral administration of drugs [10, 21]. Markedly higher k_a values were obtained for SMM in pigs and DF in rats after their intraduodenal administration than after their oral administration [11, 18]. This may also have been the case for the male Shiba goats used in the present study. Therefore, the slow absorption rate of DF and SMM in the male Shiba goats may be due to their long residence time in the forestomach.

Although a pharmacokinetic analysis indicated the slow absorption of DF and SMM after their oral administration to goats, the C_{\max} of both drugs achieved rapidly (T_{\max} of DF and SMM were 1.5 and 5.6 hr, respectively). In addition, the plasma concentration–time curves shown in Figs. 1 and 2 revealed the flip-flop phenomena. These phenomena occur when the absorption rate constant is smaller than the elimina-

Table 2. Pharmacokinetic parameters of SMM in male Shiba goats determined after single intravenous and oral administration of 10 mg/kg body weight

Parameter	Mean \pm SD (n=5)
k_a (hr^{-1})	0.0737 ± 0.0296
C_{\max} ($\mu\text{g}/\text{ml}$)	2.15 ± 0.29
T_{\max} (hr)	5.60 ± 2.30
k_{el} (hr^{-1})	0.703 ± 0.084
$t_{1/2ka}$ (hr)	10.5 ± 3.6
$t_{1/2kel}$ (hr)	1.00 ± 0.11
$\text{AUC}_{i.v.}$ ($\mu\text{g}\cdot\text{hr}/\text{ml}$)	49.9 ± 11.3
$\text{AUC}_{p.o.}$ ($\mu\text{g}\cdot\text{hr}/\text{ml}$)	37.5 ± 6.7
CL ($\text{l}/\text{hr}/\text{kg}$)	0.212 ± 0.067
F (%)	79.3 ± 16.5
F* (%)	77.1 ± 14.8
$\text{MRT}_{i.v.}$ (hr)	1.49 ± 0.19
$\text{MRT}_{p.o.}$ (hr)	16.6 ± 4.6
MAT (hr)	15.1 ± 4.7
V_{dss} (l/kg)	0.321 ± 0.134

k_a = absorption rate constant; C_{\max} = maximum plasma concentration; T_{\max} = time to maximum plasma concentration; k_{el} = elimination rate constant; $t_{1/2ka}$ = absorption half-life; $t_{1/2kel}$ = elimination half-life; $\text{AUC}_{i.v.}$ = area under the plasma concentration–time curve after i.v. injection; $\text{AUC}_{p.o.}$ = area under the plasma concentration–time curve after oral administration; CL = total body clearance; F = bioavailability calculated by compartmental analysis; F* = bioavailability calculated by non-compartmental analysis; $\text{MRT}_{i.v.}$ = mean residence time after i.v. injection; $\text{MRT}_{p.o.}$ = mean residence time after p.o. administration; MAT = mean absorption time; V_{dss} = volume of distribution at a steady state.

tion rate constant [27]; therefore, the slope of the terminal log-linear phase after the oral administration of a drug reflects the absorption rate constant. When oral pharmacokinetics exhibits these phenomena, the determining factor of T_{\max} is function of the drug elimination rate constant, and the faster elimination results in the shorter T_{\max} . The elimination half-lives ($t_{1/2\beta}$ or $t_{1/2kel}$) obtained for both DF and SMM were relatively shorter (Tables 1 and 2). Therefore, the elimination of DF and SMM in male Shiba goats may have been fast enough to achieve C_{\max} rapidly after their oral administration. This result suggests that, even in ruminants, an oral route may be suitable for drugs that have a fast elimination if they are not subjected to an extensive first-pass effect in the liver.

A marked difference was observed in the oral absorption profiles of DF and SMM. The MAT of DF was less than half that of SMM in the present study. This result suggests that absorption of DF from the forestomach of male Shiba goats may have been markedly high. The pH value of the rumen juice in this study was 6.4, as has been reported previously [11]. Furthermore, the pKa of DF is 4 [20], suggesting that negligible DF molecules exist as an unionized form (0.1–1%) in the contents of the rumen. On the other hand, the pKa of SMM is 6 [14, 16, 23], which suggests that 10–50% of SMM molecules exist as an unionized form. These findings indicate that SMM is more suitable for absorption from the forestomach of goats. However, the partition coefficient between octanol and water (pH 7) is different. That of DF is

approximately 8, whereas that of SMM is less than 1. Therefore, DF may have been absorbed from the forestomach, because of its extremely high lipid solubility.

In the present study, Eqs. 1 and 2 or Eqs. 3 and 4 were simultaneously fit to intravenous and oral plasma concentration-time data from the same goats, respectively, in order to calculate pharmacokinetic parameters. Data obtained from intravenous and oral administration routes are typically independently analyzed. Therefore, it is not uncommon to obtain different values for the same parameter, such as the elimination rate constant, even though both data are obtained from the same individuals. This difference may result in inaccuracies in the absorption rate constants obtained. In order to avoid this problem, we adopted a simultaneous analysis. As a result, we obtained a good fit between the observed points and theoretical curves in the cases of DF and SMM, as shown in Figs. 1 and 2. Therefore, we considered the absorption rate constants obtained to be reliable.

Although the oral bioavailabilities of DF and SMM were incomplete (Tables 1 and 2), both drugs were stable in the rumen juice in the *in vitro* spiked test, which indicated that both drugs were subjected to the first-pass effect in the liver. Previous studies demonstrated that DF had good gastrointestinal tolerability [15] and underwent first-pass metabolism [7, 12, 22].

Most sulphonamides are unlikely to undergo degradation in the rumen juice. Weijkamp *et al.* [24] reported that sulfamethoxydiazine, sulfathiazole, sulfadimidine and sulfamoxole were stable in the rumen juice of dwarf goats during anaerobic incubation at 39°C. A previous study also suggested that the low bioavailability of sulfamethoxazole after its oral administration to goats was most likely due to the first-pass effect in the liver [19].

The present study was done using 5 male Shiba goats. Witkamp *et al.* [25] suggested that female dwarf goats have higher hydroxylation capacity for sulfamethazine than males. They found that CL values of the sulfonamide in females were 3.5 times higher than males after intravenous injection. They also indicated that this higher capacity is due to lower testosterone levels in females. These facts may suggest that female Shiba goats have higher hydroxylation capacity for SMM than males. Since acetylated metabolites of SMM were not found in plasma, SMM may be biotransformed mainly into hydroxylated metabolites in Shiba goats, like sulfamethazine in dwarf goats. Female Shiba goats, therefore, may show lower bioavailability due to higher first-pass effect in the liver and shorter T_{\max} due to faster elimination after its oral administration, compared with males in the present study.

In conclusion, gastric emptying may be the determining factor for drug absorption after the oral administration of drugs to male Shiba goats. The absorption of highly lipophilic drugs from the forestomach may be markedly high in ruminants. In the case of drugs whose elimination is fast, their efficacies may appear from the early stage after their oral administration, even in ruminants, because the elimination rate from the body is the determining factor for T_{\max} in flip-flop phenomena.

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