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Oral absorption profiles of sulfonamides in Shiba goats: a comparison among sulfadimidine, sulfadiazine and sulfanilamide

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ABSTRACT. The oral pharmacokinetics of three sulfonamides, sulfadimidine (pKa 7.5), sulfadiazine (pKa 6.5) and sulfanilamide (pKa 10.5), with different rates of unionization in rumen juice, were compared in Shiba goats to clarify the relationship between drug absorption profiles after their oral administration as well as their degree of unionization in the rumen. Sulfonamides were administered either into the left jugular vein or orally to five male goats at doses of 10 mg/kg body weight, using a crossover design with at least a 3-week washout period. The T_{max} of sulfadimidine, sulfadiazine and sulfanilamide reached 2.0 ± 1.2, 6.0 ± 0.0, and 7.8 ± 1.6 hr, respectively, after their oral administration, and this was followed by their slow elimination due to a slow rate of drug absorption from the gastrointestinal tract. The MAT and $t_{1/2ka}$ of sulfadiazine (13.2 ± 2.0 and 10.9 ± 1.08 hr) were significantly longer than those of sulfanilamide (9.09 ± 1.67 and 7.46 ± 1.70 hr) and sulfadimidine (7.52 ± 0.85 and 5.17 ± 0.66 hr). These results suggest that the absorption rates of highly unionized drugs (such as sulfanilamide and sulfadimidine) from the forestomach of goats may be markedly higher than less unionized ones (such as sulfadiazine). The mean oral bioavailability of sulfadiazine was high (83.9 ± 17.0%), whereas those of sulfadimidine and sulfanilamide were low (44.9 ± 16.4% and 49.2 ± 2.11%, respectively).

KEY WORDS: goat, oral pharmacokinetic, sulfadiazine, sulfadimidine, sulfanilamide, unionization

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Oral dosing is generally considered to be inappropriate for ruminants due to their slow absorption of drugs. Therefore, intramuscular and subcutaneous injections are frequently used in cattle, sheep and goats. However, we previously reported the rapid antipyretic effect of diclofenac (DF) in dairy cows with infectious disease following its oral administration in a preliminary trial. This finding suggested the rapid absorption of DF from the gastrointestinal tract. Therefore, an oral administration route may be applicable for some drugs in ruminants, thereby avoiding tissue damage and the presence of local residues associated with drugs administered via IM and SC injections.

We previously examined the oral pharmacokinetics of DF and sulfamonomethoxine (SMM), which have different physicochemical properties, in Shiba goats, and found a marked difference in their mean absorption times (DF 6 hr and SMM 15 hr) [4]. Although this finding suggested that DF was mainly absorbed from the forestomach, the unionized fraction of SMM (pKa=6) was markedly higher than that of DF (pKa=4) in the rumen (pH=6.5). On the other hand, the partition coefficient of DF between octanol and water is approximately 8, while that of SMM is less than 1. Therefore, DF may be mainly absorbed from the forestomach because of its very high lipid solubility, thereby suggesting that the absorption of highly lipophilic drugs mainly occurs in the forestomach of ruminants.

Most drugs are generally considered to be absorbed from the gastrointestinal tract through a process of the passive diffusion of the unionized fraction across a lipid membrane after their oral administration [5, 11, 12]. Therefore, in addition to lipid solubility, the unionization or pKa of drugs is also an important factor for absorption from the forestomach. The main aim of the present study was to clarify the relationship between drug absorption profiles after their oral administration to goats as well as their degree of unionization in the rumen. To achieve this, the oral pharmacokinetic profiles of three sulfonamides; sulfadimidine (SDD), sulfadiazine (SDZ) and sulfanilamide (SA), were compared in Shiba goats, because they have different rates of unionization, but similar lipophilicities in the rumen.

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 Ethics Committee of the Faculty of Agriculture, Tokyo University of Agriculture and Technology (approval number 76/2013). Five clinically healthy male Shiba goats bred and maintained at Fuchu campus of Tokyo University of Agriculture and Technology, weighing 25–60 kg and aged 2–3 years, were used in this

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study. These goats were housed in pens at an ambient temperature and with good ventilation. Animals were fed hay cubes (#1A Cubes, Eckenberg Farms Inc., Mattawa, WA, U.S.A.) at 0.8 kg/head twice a day. Water and mineralized salt licks were available *ad libitum*.

Chemicals and reagents: SDD was obtained from MP Biomedicals, LLC (Rue Geiler de Kaysersberg Illkirch Cedex, France). SDZ was obtained as a sodium salt from Sigma-Aldrich Corporation (St. Louis, MO, U.S.A.). SA was obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Sulfadimethoxine was obtained as a sodium salt from Daiichi Sankyo Pharmaceutical Co. (Tokyo, Japan). All other reagents and chemicals used in the present study were of HPLC or analytical grade and obtained commercially.

Experimental design

Pharmacokinetic study: Sulfonamides solutions (100 mg/m*l*) were prepared in sterilized distilled water. For SDZ, this was done by dissolving the sodium salt; the other two sulfonamides (SMZ and SA) were dissolved in water by adding a few drops of diluted (1N) sodium hydroxide solution. They were administered either into the left jugular vein or orally to five male goats at doses of 10 mg (0.1 m*l*)/kg body weight, using a crossover design with at least a 3-week washout period. The dose (10 mg/kg) was chosen for avoid unwanted effect (anorexia, diarrhea, etc.) to goats. Oral administration was carried out using a nasogastric catheter, which was flushed with 60 m*l* tap water after dosing. The interval between each study was at least three weeks. Blood (3 m*l*) was collected from the right jugular vein immediately prior to the treatments, 1, 2, 4, 6, 9, 12 and 24 hr after the intravenous injections, and 1, 2, 4, 6, 9, 12, 24, 32 and 48 hr after their oral administration. Plasma was separated by the centrifugation of blood at 1,600 *g* for 10 min and stored at −20°C until analyzed.

Stability of sulfonamides in the rumen juice: Two male Shiba goats of five goats used for a pharmacokinetic study were restrained, and nasal catheters were passed into the rumen. Thereafter, approximately 50 m*l* of rumen juice was aspirated through the catheter from each animal. The rumen juices (pH 6.5) of two goats were combined and processed for incubation immediately after its collection. Fifty microliters of the SDD, SDZ or SA solution (200 μg/m*l*) was added to 950 μl of the rumen fluid to give a final concentration of 10 μg/m*l* 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. The concentrations of sulfonamides were then measured by HPLC.

Octanol-buffer (pH 6.5) partitioning experiments: Octanol-buffer partitioning studies were performed using a shake flask method as recommended by the Organization for Economic Cooperation and Development (OECD) [9]. Before partitioning, the two solvents were mutually saturated at 25°C for 24 hr. Solutions of the three sulfonamides (10 μg/m*l*) were prepared in the octanol-saturated buffer. These solutions were then equilibrated at 25°C with an equivalent, double and half volume of buffer-saturated octanol. Two separating funnels were used in all three runs. Equilibration was achieved by hand shaking of the funnels (by rotation of the funnels through 180 degrees about its transverse axis approximately one hundred times in five min) allowing the trapped air to rise through the two phases. The funnels were then fixed vertically by racking until complete separation of the two phases. The buffer phase was collected and centrifuged at 1,600 *g* for 10 min at 25°C, and the supernatant octanol phase was discarded. The drug concentration in the buffer phase was then determined by HPLC, while that in the octanol phase was calculated from the difference between the initial and final concentrations in the buffer phase.

Drug assays

SDD, SDZ and SA concentrations were determined in plasma, rumen juice and buffer 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 10 min at 5°C. The obtained supernatant was filtered using a 0.45-μm HPLC filter. Fifty microliters of the filtrate was injected into the HPLC column.

In the case of rumen juice samples, SDD, SDZ and SA concentrations were determined after extraction with ethyl acetate. After being incubated for 24 hr, 50 μl of the internal standard (200 μg/m*l*) was added to the rumen juice samples. The internal standards used in the present study were sulfadimethoxine, SA and SDZ for SDD, SDZ and SA, respectively. Subsequently, five milliliters of ethyl acetate was then added. The mixtures were vortexed for 30 sec and then centrifuged at 3,000 *g* for 10 min at 5°C. The obtained supernatants were transferred into pear-shaped flasks and evaporated to dryness at 30°C. The residue was reconstituted in 500 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 phases used were a mixture of 50 mM acetate buffer (pH 5) and acetonitrile (75:25, v/v) for SDD, a mixture of 50 mM acetate buffer (pH 4) and acetonitrile (75:25, v/v) for SDZ, and a mixture of 50 mM acetate buffer (pH 5) and acetonitrile (80:20, v/v) for SA. Analytical separation was accomplished using a reversed-phase C_8 column (Mightysil RP-8 GP, 4.6 μm × 250 mm, Kanto Chemical Co., Tokyo, Japan). The flow rates were 0.8 m*l*/min. The wavelength of the detector was 270 nm.

The recoveries of SDD, SDZ and SA from plasma samples at 1 μg/m*l* (n=5) were 109.2 ± 2.00%, 87.9 ± 1.52% and 95.0 ± 1.75%, while those from rumen juice samples at 10 μg/m*l* (n=5) were 83.5 ± 2.06%, 84.3 ± 2.09% and 88.1 ± 2.35%, respectively. The inter-day CV values for plasma samples ranged from 1.67 to 2.14% for SDD, 0.63 to 3.84% for SDZ and from 1.21 to 2.29% for SA, while those for rumen juice samples ranged from 1.86 to 2.79% for SDD, 1.96 to 5.24% for SDZ and 1.61 to 3.57% for SA (n=5, 3 times).

Statistical analysis

Data were expressed as the mean ± standard deviation. Pharmacokinetic parameters relating to oral drug absorption

were statistically analyzed. Differences in the mean values between groups were analyzed by Scheffé's multiple comparison test after a one-way ANOVA single factor test. Equal variances among the groups were confirmed by the Bartlett test. Differences were considered significant when $P<0.05$.

Pharmacokinetic analysis

The plasma concentration-time curves of SDD, SDZ and SA after their intravenous administration fit well with the one compartment model. Therefore, the curves obtained after the intravenous injections ($Cp_{iv}(t)$) and those after their oral administration ($Cp_{po}(t)$) were described by Eqs. 1 and 2, respectively.

$$Cp_{iv}(t) = \frac{Dose}{V} e^{-k_{el} \cdot t} \quad \text{(Eq.1)}$$

$$Cp_{po}(t) = \frac{Dose \cdot F}{V} \cdot \frac{ka}{ka - k_{el}} (e^{-k_{el} \cdot t} - e^{-ka \cdot t}) \quad \text{(Eq.2)}$$

Equations 1 and 2 were simultaneously fit to the plasma concentration-time curves after the intravenous injections and oral administration to the same goats, respectively, in order to calculate pharmacokinetic parameters by the non-linear least-squares method using the curve fitting program, MULTI [15].

Several pharmacokinetic parameters were calculated by a 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 (F), mean residence time (MRT), mean absorption time (MAT), elimination half-life ($t_{1/2kel}$) and distribution volume at a steady state (V_{dss}) were calculated by conventional methods.

RESULTS

The plasma concentrations against time curves obtained after a single intravenous or oral dosing of SDD, SDZ or SA are shown in Fig. 1. The plasma concentrations of SDD, SDZ and SA rapidly increased and peaked at 2.0, 6.0 and 7.8 hr (Table 1), respectively, after their oral administration, and this was followed by their slow elimination. On the other hand, their plasma concentrations decreased rapidly after the intravenous injections with markedly shorter half-lives (Table 1), indicating a flip-flop phenomenon after the oral administration of the three drugs.

As shown in Table 1, a pharmacokinetic analysis revealed the different absorption profiles of the three sulfonamides in Shiba goats after their oral administration. The MAT and $t_{1/2ka}$ of SDZ were significantly longer than those of SDD and SA. The order of MAT values was different from that of the unionized fraction at pH 6.5 (SA >SDD >SDZ, see Table 2) and was also different from that of partition coefficients at pH 6.5 (SDD >SDZ >SA, see Table 2). The oral bioavail-

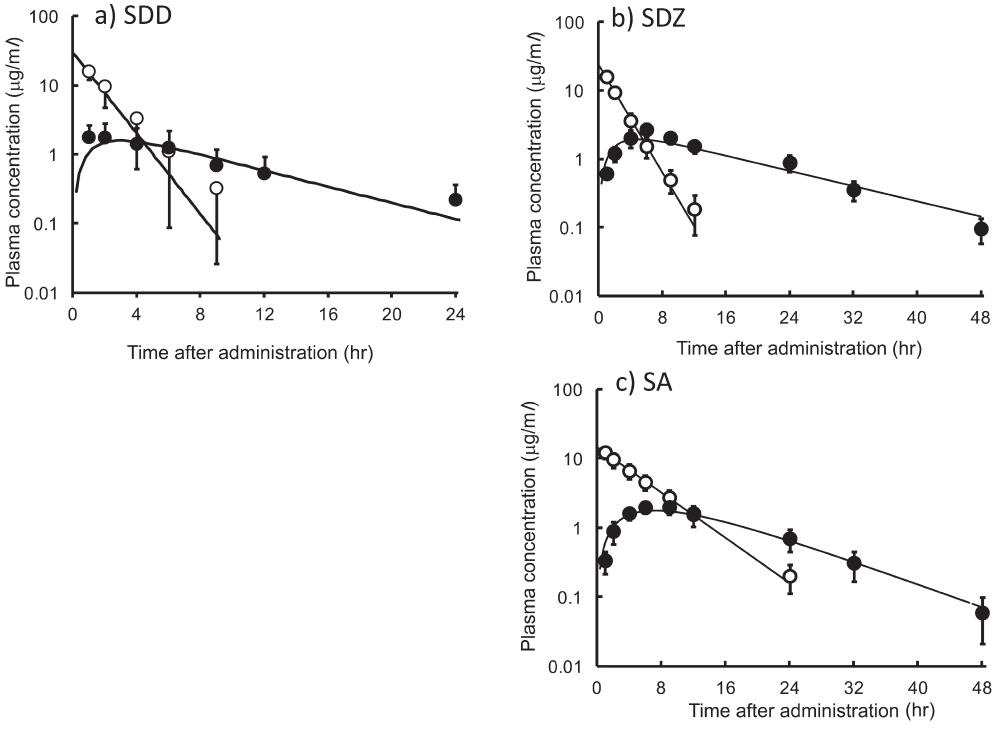

Fig. 1. Plasma concentration-time curves of a) sulfadimidine (SDD), b) sulfadiazine (SDZ) and c) sulfanilamide (SA) after their single intravenous (opened circles) and oral administration (closed circles) to Shiba goats at a dose of 10 mg/kg body weight. Each point and vertical bar represent the mean and standard deviation, respectively (n=5). Each line was calculated by Eq. 1 or 2 using the pharmacokinetic parameters in Table 1.

Table 1. Pharmacokinetic parameters of sulfadimidine, sulfadiazine and sulfanilamide in Shiba goats (n=5) after their intravenous and oral administration at 10 mg/kg body weight

Parameter	Unit	Sulfadimidine	Sulfadiazine	Sulfanilamide
ka	hr^{-1}	0.136 ± 0.017 [b,c)]	0.064 ± 0.006[a,c)]	0.097 ± 0.023[a,b)]
$t_{1/2ka}$	hr	5.17 ± 0.663[b)]	10.9 ± 1.08[a,c)]	7.46 ± 1.70[b)]
k_{el}	hr^{-1}	0.728 ± 0.357	0.454 ± 0.073	0.188 ± 0.016
$t_{1/2kel}$	hr	1.09 ± 0.378	1.56 ± 0.274	3.71 ± 0.340
C_{max}	μg/ml	2.14 ± 1.05	2.70 ± 0.568	2.08 ± 0.379
T_{max}	hr	2.00 ± 1.23	6.00 ± 0.00	7.80 ± 1.64
F	%	41.6 ± 14.9	79.8 ± 13.0	48.1 ± 1.79
F*	%	44.9 ± 16.4	83.9 ± 17.0	49.2 ± 2.11
MAT	hr	7.52 ± 0.850[b)]	13.2 ± 2.02[a,c)]	9.09 ± 1.67[b)]
$MRT_{i.v.}$	hr	1.61 ± 0.564	2.13 ± 0.337	5.33 ± 0.396
$MRT_{p.o.}$	hr	9.13 ± 1.02	15.3 ± 1.93	14.4 ± 1.98
$AUC_{i.v.}$	μg·hr/ml	55.2 ± 31.3	55.0 ± 4.74	81.3 ± 19.9
$AUC_{p.o.}$	μg·hr/ml	22.5 ± 13.3	46.0 ± 9.18	39.8 ± 8.95
CL	l/hr/kg	0.311 ± 0.329	0.183 ± 0.016	0.129 ± 0.031
V_{dss}	l/kg	0.374 ± 0.207	0.386 ± 0.033	0.683 ± 0.144

Each value represents mean ± SD (n=5). a) significantly different from sulfadimidine, b) significantly different from sulfadiazine, c) significantly different from sulfanilamide. ka=absorption rate constant; $t_{1/2ka}$=half-life of absorption; k_{el}=elimination rate constant; $t_{1/2kel}$=half-life of elimination; C_{max}=maximum plasma concentration; T_{max}=time to maximum plasma concentration; F=bioavailability calculated by a compartmental analysis; F*=bioavailability calculated by a non-compartmental analysis; MAT=apparent mean absorption time; $MRT_{i.v.}$=mean residence time after an i.v. injection; $MRT_{p.o.}$=mean residence time after p.o. administration; $AUC_{i.v.}$=area under the plasma concentration–time curve after an i.v. injection; $AUC_{p.o.}$=area under the plasma concentration–time curve after oral administration; CL=total body clearance; V_{dss}=volume of distribution at a steady state.

abilities of SDD and SA were less than 50% and lower than that of SDZ.

The recovery of sulfonamides from rumen juice samples after a 24-hr incubation was 88.6 ± 4.61% for SDD, 89.9 ± 3.61% for SDZ and 76.5 ± 4.85% for SA. These values were markedly higher than those for bioavailability, suggesting that SDD and SA were exposed to the extensive 'first-pass' effect of the liver.

DISCUSSION

Oral drug absorption is generally more complex and unpredictable in ruminants and may exhibit markedly different kinetics from those in monogastric species, and these differences have been attributed to the unique anatomical and physiological features of the gastrointestinal tract in ruminants. The forestomach (rumen, reticulum and omasum) is a large volume compartment (100–225 l in cattle and 10–24 l in sheep and goats), which may result in the dilution and long residence time of drugs in the forestomach [1]. Furthermore, the inner structure of the forestomach is lined by a keratinized stratified squamous epithelium, which may also contribute to the slow absorption of drugs. We previously reported the marked absorption of diclofenac from the forestomach of Shiba goats after its oral administration and suggested that this may have been due to the high lipid solubility of the drug [4]. Therefore, we herein examined the absorption profiles of SDD, SDZ and SA, which have different pKa, but similar lipophilicities (Table 2) after their oral administration to Shiba goats.

Marked differences were observed in the oral absorption profiles of the three sulfonamides. The absorption rate of SDZ from the forestomach of goats may have been markedly slower, because of its longer MAT and $t_{1/2ka}$ than those of SDD and SA. The pKa values of SDZ, SDD and SA were previously reported to be 6.5, 7.5 and 10.5, respectively [8, 13], suggesting that 50% of SDZ molecules are unionized, SDD molecules mainly exist in an unionized form (90%), and SA molecules are mainly unionized (more than 99.9%) in the rumen juice because its pH value was 6.5 in this study, as has been reported previously [3, 6]. Therefore, the slow absorption rate of SDZ from the forestomach may have been due to its lower degree of unionization than SDD and SA in the rumen juice.

A comparison of the MAT of SDD in the present study with that of SMM in our previous study on Shiba goats [4] revealed that the MAT of SDD (7.52 ± 0.85 hr) was less than half that of SMM (15.1 ± 4.7 hr), whereas the partition coefficients of octanol and the buffer (pH=6.5) were nearly

Table 2. Physicochemical parameters and MAT of sulfadimidine, sulfadiazine and sulfanilamide

Sulfonamides	pKa (f_u)	P	P*	MAT (hr)
Sulfadimidine	7.5 (90%)	1.96 ± 0.162	2.16	7.52 ± 0.85
Sulfadiazine	6.5 (50%)	0.468 ± 0.049	0.935	13.2 ± 2.02
Sulfanilamide	10.5 (99.9%)	0.257 ± 0.047	0.257	9.09 ± 1.67

f_u: unionized fractions (calculated at pH 6.5), pKa: referred from references 8 and 13, P: partition coefficient between octanol and phosphate buffer at pH 6.5, P*: intrinsic partition coefficient calculated from the apparent partition coefficient and pKa in the table, MAT: mean absorption time in the present study.

similar; that of SDD was 1.96 ± 0.16 (Table 2), and that of SMM was 1.72 ± 0.17 (determined by the method used in the present study). However, the percentage of the unionized fraction in the rumen juice (pH 6.5) was different (approximately 90% for SDD and 30% for SMM). Therefore, SDD may have been absorbed more from the forestomach than SMM, because of its markedly higher unionization in the rumen juice, suggesting that drugs with high unionization are largely absorbed from the forestomach of ruminants.

No significant differences were observed in the MAT between SDD and SA (Table 1), and may have been because of the nearly similar degree of unionization of both drugs in the forestomach (Table 2). Therefore, the degree of unionization may be an important factor for the absorption of drugs from the forestomach after their oral administration.

The plasma concentration curves of three sulfonamides shown in Fig.1 revealed at the flip-flop phenomena. These flip-flop kinetics occur when the absorption rate constant (ka) is smaller than the elimination rate constant (k_{el}), and therefore, the slope of the terminal log-linear phase after oral administration of a drug reflects the absorption rate constant. As listed in Table 1, ka values of three drugs were smaller than k_{el} values in the same way. When oral pharmacokinetics exhibits flip-flop phenomena, the determining factor of T_{max} is function of the drug elimination results in the shorter T_{max}. The elimination half-life (1.09 hr) of SDD was shorter than half-lives (1.56 and 3.71 hr) of other two drugs (SDZ and SA).Therefore, the elimination of SDD in shiba goat may have been fast enough to acheve C_{max} more rapidly (2.00 hr of T_{max}) than SDZ or SA after their oral administration.

The slow absorption kinetics of three sulfonamides after their oral administration to male Shiba goats were shown in this study. The oral pharmacokinetic profiles of SDD in pigs were reported [7]. The absorption of SDD was shown to be fast in monogastric animal. The obtained k_a values (0.498 hr^{-1} in pigs) were markedly higher than those obtained from the Shiba goats in the present study (0.136 hr^{-1}). The slow absorption rate of sulfanomaides in the Shiba goats may be due to their long residence time in the forestomach.

We suggested that the lower bioavailability (44.9% as F*) of SDD after oral administration was mainly due to the considerable 'first-pass' effect in the liver because of its fast elimination rate (0.728 hr^{-1} as k_{el}). The oral bioavailability of SDD was low (26.4%) in dwarf goats and attributed this to a consequence of the marked hepatic 'first-pass' effect as reported previously [14]. It was also found that the oral bioavailability of a SDD solution was low (58.3%) in sheep [2]. Another study also suggested that the low bioavailability of sulfamethoxazole after its oral administration to goats was most likely due to the hepatic 'first-pass' effect [10]. On the other hand, although the slow elimination of SA (0.188 hr^{-1}) couldn't explain the low oral bioavailability, the low stability (76.5%) of SA in rumen juice might explain the low bioavailavility of SA after its oral administration. These findings may support our suggestion regarding the incomplete bioavailability of SDD and SA in the present study.

In conclusion, the results of the present study suggest that drugs that are highly unionized in rumen juice as well as highly lipophilic may be mainly absorbed from the forestomach of goats, indicating that an oral route is suitable for such drugs, even in ruminants.

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