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FULL PAPER

Pharmacology

Oral pharmacokinetics of sulfadiazine and sulfamonomethoxine in female Holstein milking cows

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ABSTRACT. The efficacy of orally administered drugs in cattle is thought to be slow because of the anatomical and physiological features of their forestomach. Thus, parenteral routes are mainly preferred to administer drugs. However, the effect of some drugs with unique physicochemical properties was promptly obtained even after oral administration in clinically ill cattle. Therefore, the present study aimed to investigate pharmacokinetically the usefulness of the oral route in cattle by comparing the oral pharmacokinetic properties of two sulfonamides with different physicochemical properties. Sulfadiazine (SDZ) and sulfamonomethoxine (SMM) were administered by intravenous and oral route to four female Holstein cows with a 4-weeks washout period. Blood samples were collected over time, and SDZ and SMM concentrations in plasma were analyzed by HPLC. Data obtained from the same animal after intravenous and oral administration were simultaneously analyzed with the one compartment model, and kinetic parameters were calculated. The T_{max} (mean ± SD) of SMM (2.75 ± 0.96 hr) was significantly achieved earlier than that of SDZ (5.00 ± 1.15 hr). Further, the mean absorption time of SMM (5.24 ± 0.69 hr) was significantly shorter than that of SDZ (5.92 ± 1.11 hr). Also, the half-life of absorption of SMM (3.91 ± 0.51 hr) was significantly shorter than that of SDZ (4.51 ± 0.82 hr). These data suggest that the absorption rates of highly unionized drugs (such as SMM) from the forestomach of cattle may be markedly higher than less unionized ones (such as SDZ).

KEYWORDS: cattle, oral administration, pharmacokinetics, sulfadiazine, sulfamonomethoxine

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The parenteral routes of drug administration are generally used to administer drugs in cattle. However, the intramuscular and subcutaneous routes often lead to local irritation and long withdrawal time due to the long residence of drugs at injection sites. Although this issue may be overcome by oral dosing, the absorption of drugs may be extremely slow because of the large forestomach, and thus, this route may not be appropriate for ruminants. Ruminants have unique anatomical and physiological stomachs [3]. The large volume compartments of their forestomach (rumen, reticulum, and omasum) range from 100 to 225 liter in large ruminants and 10–24 liter in small ruminants resulting in dilution of drugs and delaying its passage to small intestines where most absorption occurs [1, 4]. Elbadawy *et al*. [5, 6] found that the mean absorption times (MATs) of sulfamonomethoxine (SMM), sulfadiazine (SDZ), sulfanilamide, and sulfadimidine after oral administration to Shiba goats were very long (15, 13.2, 9.09, and 7.52 hr, respectively) and referred these long MATs to the slow gastric emptying in Shiba goats which delay the passage of drugs to small intestines. Further, the epithelial lining of the forestomach is lined by a keratinized stratified squamous epithelium which may also delay and limit the absorption of some drugs. Moreover, rumen microflora may inactivate some drugs through metabolic or chemical reactions [2, 10].

Although the main site of drug absorption after oral dosing is the small intestine, absorption of some drugs from the stomach may also be considerable and clinically useful. This occurs in the case of lipophilic drugs where their larger unionized fraction in the gastric

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fluid is efficiently absorbed from the stomach even though its a smaller effective surface area compared with the small intestines. In humans, extensive gastric absorption of lipophilic drugs such as salicylates, thiopental, aspirin, and antipyrine was reported before [9]. In ruminants, the absorption of more lipophilic drugs such as diclofenac (DF) was significantly faster (MAT: 6 hr) than the less lipophilic ones such as SMM (MAT: 15 hr) after oral administration to Shiba goats. In cattle, we previously reported a rapid antipyretic effect of DF in feverish dairy cows after its oral administration in a preliminary trial. Further, Sawaguchi *et al.* also detected rapid absorption of DF (MAT: 1.61 hr) after oral administration to cattle [13]. These findings suggest that DF, a more lipophilic drug, was considerably absorbed from the forestomach of ruminants. Therefore, the oral administration of DF may achieve appropriate efficacy as an antipyretic or analgesic, even in cattle.

The main purpose of the present study was to clarify more the relationship between oral absorption profiles of drugs and their physicochemical properties in ruminants. To achieve this goal, the oral pharmacokinetic profiles of two sulfonamides (SDZ and SMM) with different physicochemical properties were examined in Holstein cows after oral administration. Furthermore, we aimed to discuss pharmacokinetically the usefulness of oral administration of these drugs in cattle.

MATERIALS AND METHODS

Drugs and chemicals

SDZ was obtained from Sigma-Aldrich Corp. (St. Louis, MO, USA). The sodium salt of SMM was obtained from Meiji Seika Pharma Co., Ltd, Tokyo, Japan (Product name: Daimeton Soda). The physicochemical properties of SDZ [6] and SMM are shown in Table 1. The partition coefficients for SMM was measured according to previous reported method [6]. Sodium Hydroxide was obtained from Fujifilm Wako Pure Chemical Corp., Osaka, Japan. It was used to dissolve SDZ powder. For SMM, it was dissolved in sterilized distilled water before injection. All other solutions and chemicals used in the present investigation were of HPLC or analytical grade.

Animals

Four female Holstein milking cows (weight 585~655 kg, parity: 1.75 ± 1.5) which were reared on Fuji Animal Farm of Nippon Veterinary and Life Science University (Yamanashi, Japan), were used in the current study. They were fed twice a day individually. The total amount of feeding per head per day is below; 13 kg timothy hay, 3 kg alfalfa hay, 4 to 13 kg concentrate (16% DM CP), and 2.0 to 2.5 kg beet pulp. The concentrate was provided with an automatic concentrate feeder (Max Feeder HID, Orion, Nagano, Japan). The concentrate and beet pulp were provided according to each cow's milk yield. Water was available *ad libitum*. Healthy cows were defined as follows: none of the cows used in this study were diagnosed with clinical ketosis, hypocalcaemia, metritis, retained placenta, or displaced abomasum after normal parturition, as assessed by a veterinarian. All the experimental procedures complied with the Guidelines for the Care and Use of Animals established by Nippon Veterinary and Life Science University and all animal protocols were approved by the Institutional Animal Care and Use Committee (Nippon Veterinary and Life Science University [Tokyo, Japan], No. 28K-20). All animal experiments were performed in accordance with ARRIVE guidelines (https:// arriveguidelines. org).

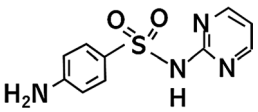
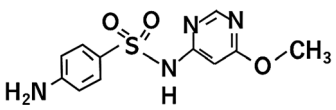
Preparation of sulfonamides for administration

For intravenous injection, 20% stock solutions of both SDZ and SMM were prepared in sterilized distilled water (DW). Eight mL of 8 N sodium hydroxide solution were used to help dissolve 20 g SDZ in 100 mL DW. These stock solutions of both sulfonamides were further diluted to 100 mg/mL DW before intravenous injection. For oral administration, a 6.67% of SDZ solution was prepared in DW by dissolving 40 g of SDZ in 600 mL DW including 20 mL of 8 N sodium hydroxide solution. For SMM, a 10% solution was prepared by dissolving 40 g of SMM in 400 mL DW. These stock solutions of both sulfonamides were further diluted to 40 mg/mL DW before oral administration.

Pharmacokinetic study

The intravenous and oral pharmacokinetics of SDZ and SMM were separately examined in the four cows using a crossover design with 4 weeks washout interval for each sulfonamide. At first, SDZ and/or SMM were administered into the right jugular vein at a dose of 5 mg/kg body weight (BW) where 5 mL of each sulfonamide solution per 100 kg of body weight were injected. Four weeks later, SDZ and/or SMM were administered intraruminally using a nasogastric catheter at doses of 10 mg/kg BW (25 mL of mixed

Table 1. Physical and chemical characteristics of sulfadiazine (SDZ) and sulfamonomethoxine (SMM)

Parameters	SDZ	SMM
Acid-base	acidic	acidic
pKa	6.5	6.0
Partition coefficient (*)	0.468 ± 0.049	1.72 ± 0.17
Chemical structure		

* Aparent partition coefficient between octanol and phosphate buffer at pH 6.5.

solution per 100 kg of body weight). Blood was sampled (5 mL) from the left jugular vein immediately before and 1, 2, 3, 4, 6, 8 hr post intravenous injection, and 1, 2, 4, 6, 8, 11, 24, and 31 hr post-oral administration of sulfonamides. Immediately after the blood sampling, the blood was placed in a test tube containing EDTA and centrifuged at 1,600 *g* for 15 min to separate the plasma. Plasma samples were kept at −20°C until analyzed. Four hr after blood sampling, the animals were given rice straws.

Measurement of plasma sulfonamide concentration

The plasma SDZ and SMM concentrations were analyzed by a high-performance liquid chromatography (HPLC) method using a UV detector as previously described [4, 5]. Briefly, 100 µL of perchloric acid (0.5 M) was added to 100 µL of plasma sample, vortexed for 30 sec seconds, and then centrifuged at 20,000 *g* for two min at 5°C. The supernatant was collected and filtered by a 0.45-µm HPLC filter (Chromatodisc®, 4P, Kurabo Biomedical Industries, Ltd., Osaka, Japan). Fifty microliters of the filtrate were injected into the HPLC column. The peaks of SDZ and SMM in plasma samples were identified by comparing with the detection time of the standard substance, and the concentration was measured as follows:

$$\text{Concentration} = \frac{\text{SDZ (or SMM) sample area}}{\text{SDZ (or SMM) standard area}} \times \text{SDZ (or SMM) standard concentration (µg/mL)} \times 2 \quad \text{(Eq.1)}$$

The High-performance Liquid Chromatography (HPLC) system was from Shimadzu Corp., Kyoto, Japan, and involved an LC-10AD pump, an SPD-6A UV detector, an integrator (Chromatopac C-R7A plus) with a loop injector (Model 7125). The mobile phase was a mixture of 50 mM sodium acetate trihydrate (adjusted to pH 5.0 with 2N acetic acid) and acetonitrile (4:1, v/v). The mobile phase chemicals and solutions were bought from Fujifilm Wako Pure Chemical Corp., Osaka, Japan. Analytical separation of the drugs was performed using a reversed-phase C8 column (Mightysil RP-8 GP, 4.6 µm × 250 mm, Kanto Chemical Co., Tokyo, Japan). The flow rates were 1.0 mL/min, and the wavelength of the detector was set at 270 nm.

Pharmacokinetic analysis

The compartmental and non-compartmental analysis was applied to calculate the pharmacokinetic parameters. The obtained plasma concentration-time curves of SDZ and SMM following intravenous and oral administrations to cows fit well with the one-compartment model. Accordingly, the curves obtained after the intravenous injections (*PCiv* (*t*)) and those after their oral administration (*PCpo* (*t*)) were described by Eqs. 2 and 3, respectively.

$$PC_{iv}(t) = \frac{Dose}{V} e^{-k_{el} \cdot t} \quad \text{(Eq.2)}$$

$$PC_{po}(t) = \frac{Dose \cdot F}{V} \cdot \frac{ka}{ka - k_{el}} \left(e^{-k_{el} \cdot t} - e^{-ka \cdot t} \right) \quad \text{(Eq. 3)}$$

Where: *PC*=plasma drug concentration, *V*=volume of distribution, *F*=Bioavailability, *ka*=primary absorption rate constant, k_{el}=primary elimination rate constant, *t*=elapsed time after drug administration in hr. Both equations (Eq. 2, and 3) were simultaneously fit [6, 7] to the plasma concentration-time curves of SDZ and SMM after their intravenous injections and oral administrations to the same cattle, respectively, to compute pharmacokinetic parameters by the nonlinear least-squares method using the curve fitting program, MULTI [17]. Several pharmacokinetic parameters were calculated by a non-compartmental analysis [8]. The absorption half-life ($t_{1/2ka}$) and elimination half-life ($t_{1/2kel}$) was calculated as $\log_e 2/_{ka}$ and $\log_e 2/_{kel,}$ respectively. 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). The time of infinity was estimated by the terminal k_{el}, which was detected by the nonlinear least-square iterative technique based on four data points in the terminal portion of the concentration-time curve. The total body clearance (CL_{tot}=$Dose_{i.v.}/AUC_{i.v.}$), bioavailability (F=($Dose_{i.v.}$× $AUC_{p.o.}$) / ($Dose_{p.o.}$× $AUC_{i.v.}$) × 100), distribution volume at a steady state (V_{dss}=$Dose_{i.v}$ × $MRT_{i.v.}/AUC_{i.v.}$), mean residence time (MRT=AUMC/AUC), and mean absorption time (MAT=$MRT_{p.o}$–$MRT_{i.v.}$) were calculated by conventional equations as shown.

Statistical analysis

The paired *t*-test was applied to analyze the difference in the calculated pharmacokinetic parameters (mean ± SD) of SDZ and SMM. Statistical software SPSS, version 16 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. When *P* values were ≤0.05, it is considered significant.

RESULTS

The semi-logarithmic plasma concentrations vs time obtained after a single intravenous injection and oral dosing of SDZ and SMM curves are depicted in Figs. 1 and 2, respectively. The solid lines in Figs. 1 and 2 show the theoretical values as calculated by Eqs. 2 and 3 with the pharmacokinetic parameters in Table 2. The lines fit well with the observed concentrations of SDZ and SMM. The mean ± SD of the corresponding pharmacokinetic parameter values are presented in Table 2. After oral dosing, the plasma concentrations of both sulfonamides were slowly elevated followed by slow elimination. Interestingly, after oral dosing of SDZ and SMM, the peak plasma concentration (C_{max}) of SMM was significantly faster (T_{max}=2.75 ± 0.96 hr) than that of SDZ (T_{max}=5.0 ± 1.015 hr) as shown in Table 2. Concurrently, the $t_{1/2ka}$ of SMM (3.91 ± 0.51 hr) was significantly shorter than that of SDZ (4.51 ± 0.82 hr). Also, the

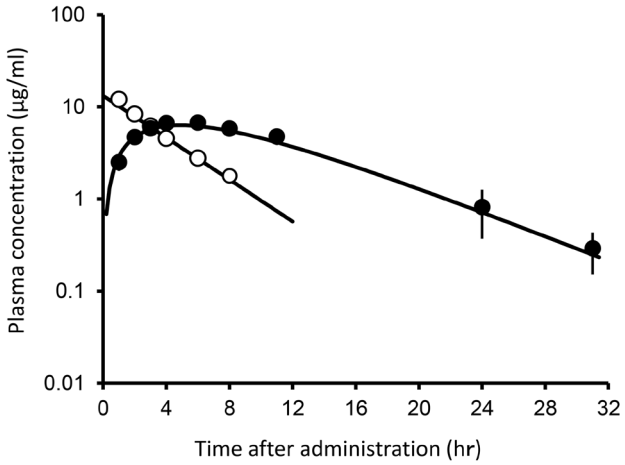


Fig. 1. Changes in plasma sulfadiazine concentration after intravenous administration of 5 mg/kg BW (opened circle) and oral administration of 10 mg/kg BW (closed circle). The points indicate the average of the measured values, and the vertical lines indicates the Standard Deviation. The solid lines are the calculated theoretical curves (n=4) using Eqs. 2 or 3 and pharmacokinetic parameters in Table 2.

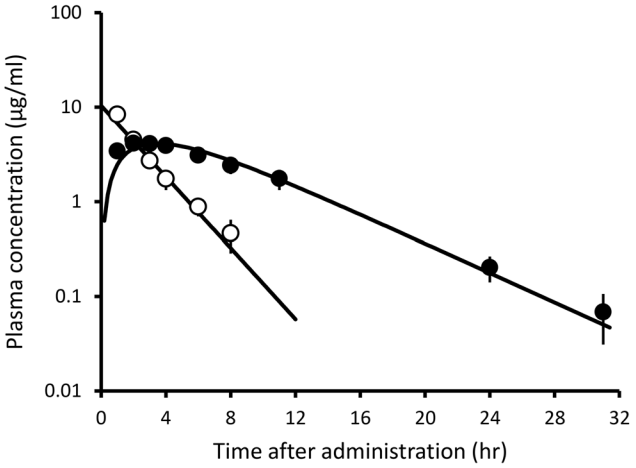


Fig. 2. Changes in plasma sulfamonomethoxine concentration after intravenous injection of 5 mg/kg BW (opened circle) and oral administration of 10 mg/kg BW (closed circle). The points indicate the average of the measured values, and the vertical lines indicates the Standard Deviation. The solid lines are the calculated theoretical curves (n=4) using Eqs. 2 or 3 and pharmacokinetic parameters in Table 2.

Table 2. Comparison of sulfadiazine (SDZ) and sulfamonomethoxine (SMM) oral pharmacokinetics in Holstein cows (n=4) after their intravenous (5 mg/kg BW) and oral administration (10 mg/kg BW)

Parameters	Units	SDZ Mean ± SD	SMM Mean ± SD
k_a	hr^{-1}	0.158 ± 0.029	0.179 ± 0.023*
$t_{1/2ka}$	hr	4.51 ± 0.82	3.91 ± 0.51*
k_{el}	hr^{-1}	0.262 ± 0.027	0.433 ± 0.058*
$t_{1/2kel}$	hr	2.66 ± 0.25	1.62 ± 0.24*
C_{max}	μg/mL	7.01 ± 0.50	4.29 ± 0.32*
T_{max}	hr	5.00 ± 1.15	2.75 ± 0.96*
F	%	85.7 ± 2.7	89.5 ± 7.3
MAT	hr	5.92 ± 1.11	5.24 ± 0.69*
$MRT_{i.v.}$	hr	3.69 ± 0.32	2.21 ± 0.31*
$MRT_{p.o.}$	hr	9.61 ± 1.27	7.45 ± 0.66*
$AUC_{i.v.}$	μg/hr/mL	52.0 ± 6.5	25.1 ± 3.0*
$AUC_{p.o.}$	μg/hr/mL	98.5 ± 13.1	45.6 ± 6.0*
CL_{tot}	L/hr/kg	0.0973 ± 0.0118	0.202 ± 0.023*
V_{dss}	L/kg	0.357 ± 0.027	0.445 ± 0.081

ka=primary absorption rate constant; $t_{1/2ka}$=absorption half-life; k_{el}=primary elimination rate constant; $t_{1/2kel}$=elimination half-life; C_{max}=maximum blood concentration; T_{max}=time to maximum plasma concentration; F=oral bioavailability percentage; MAT=Mean absorption time; $MRT_{i.v.}$=average residence time during intravenous administration; $MRT_{p.o.}$=average residence time during oral administration; $AUC_{i.v.}$=area under the plasma concentration-time curve after intravenous injection; $AUC_{p.o.}$=area under the plasma concentration-time curve after oral administration; CL_{tot}=total body clearance; V_{dss}=distribution volume at steady state.

MAT of SMM (5.24 ± 0. 69 hr) was significantly shorter than that of SDZ (5.92 ± 1.11 hr). The bioavailability of both sulfonamides after oral dosing was more than 85%.

However, after their intravenous injection of both sulfonamides, the plasma concentrations declined faster with markedly shorter half-lives, indicating a flip-flop phenomenon. The $t_{1/2kel}$ of SMM was significantly shorter (1.62 ± 0.24 hr) than that of SDZ (2.66 ± 0.25 hr), which was 1.70 times longer than that of SMM as shown in Table 2. The CL_{tot} of SMM (0.202 ± 0.023 L/hr/kg) was significantly higher than that of SDZ (0.0973 ± 0.0118 L/hr/kg).

DISCUSSION

Oral absorption of drugs is usually unpredictable in ruminants and may exhibit markedly different disposition profiles than in monogastric species. These differences have been attributed to the unique structural and functional style of the gastrointestinal organs in ruminants [1]. Also, the physicochemical properties of drugs affect their oral pharmacokinetics in ruminants [4–6]. Recent studies showed that drugs with appropriate physicochemical properties could be suitable for oral administration to ruminant animals and could be therapeutically effective.

In the present study, we demonstrated the oral absorption profiles of two physicochemically different sulfonamides, SMM and SDZ, in cattle. After oral administration, SMM showed a faster and more appropriate absorption profile than SDZ as indicated by the pharmacokinetic parameters in Table 2. The average values of T_{max} and $t_{1/2ka}$ for SMM were 2.75 and 3.91 hr, respectively, and were significantly shorter than those of SDZ (T_{max} and $t_{1/2ka}$ for SDZ were 5.00 and 4.51 hr, respectively, Table 2). This faster absorption of SMM may be attributed to its marked absorption from the forestomach of cows due to its higher lipophilicity than SDZ (Table 1). The partition coefficient is the dissolution rate in an organic solvent such as octanol and a buffer solution such as water. The higher the partition coefficient value, the higher the lipid solubility and the faster the absorption of drugs [14]. The octanol/buffer (pH=6.5, corresponding with the pH of rumen juice) partition coefficients of SMM and SDZ were 1.72 and 0.468, respectively (Table 1). Therefore, SMM may have been more absorbed than SDZ from the forestomach of cows, because of its higher lipophilicity compared to SDZ.

Similarly, in Shiba goats (a small ruminant animal), we previously demonstrated a faster absorption of a more lipophilic drug as DF (pKa=4 [11]) than a less lipophilic one, SMM (pKa=6 [12]) from the forestomach after oral dosing [5]. The MAT of DF (6.05 hr) in that study was less than half of SMM (15.1 hr) [5]. Although SMM was more unionized than DF in rumen juice based on pKa values, the faster absorption of DF was attributed to its higher lipophilicity [5]. Moreover, in another study in Shiba goats [6], we also reported different oral absorption profiles among three sulfonamides (SDZ, sulfadimidine, and sulfanilamide) with different physicochemical properties [15]. In that study, the T_{max}, $t_{1/2ka}$, and MAT for SDZ (pKa (fraction unionized)=6.5 (50%)) were 6.00, 10.9, and 13.2 hr, respectively; for sulfadimidine (pKa (fraction unionized)=7.5 (90%)) were 2.00, 5.17, and 7.52 hr, respectively; and for sulfanilamide (pKa (fraction unionized=10.5 (99.9%)) were 7.8, 7.46, and 9.09 hr, respectively [6].

When lipid solubility is the nearly similar, the degree of unionization is another determinant factor for the rate of absorption of drugs from the forestomach of ruminants [5, 6]. This has been the case for the sulfadimidine and SMM in Shiba goats [5, 6]. The MAT of sulfadimidine (7.52 hr) was reported less than half that of SMM (15.1 hr), whereas the partition coefficients of octanol/buffer (pH=6.5) were nearly similar; that of sulfadimidine was 1.96, and that of SMM was 1.72. However, the percentage of the unionized fraction in the rumen juice (pH 6.5) was different (approximately 90% for sulfadimidine and 30% for SMM). Therefore, sulfadimidine may have been more absorbed than SMM from the forestomach, because of its markedly higher unionization in the rumen juice. These data suggest that drugs with high unionization are also largely absorbed from the forestomach of ruminants.

The plasma concentration curves of SMM and SDZ shown in Figs. 1 and 2 revealed a flip-flop phenomenon. This phenomenon occurs when the k_a is smaller than the k_{el}. Thus, the slope of terminal log-linear phase after oral giving reflects the k_a of a drug. As shown in Table 2, the k_a values of SMM and SDZ were smaller their k_{el} values. When oral pharmacokinetic profile shows flip-flop phenomenon, the T_{max} value depends greatly on the elimination rate of drug. The $t_{1/2kel}$ of SMM (1.62 hr) was shorter than SDZ (2.66 hr). Therefore, the elimination of SMM in cows may have been fast enough to achieve C_{max} more rapidly (T_{max}=2.75 hr) than SDZ (T_{max}=5 hr) after their oral administration. This finding suggests that, even in ruminant animals, the oral administration may be appropriate for rapidly eliminated drugs if they are not subjected to an extensive first-pass effect in the liver and are stable in lumen juice. Based on their chemical structure, most sulfonamides are stable against hydrolysis or reduction in the rumen. This was shown in previous studies, in which there was no degradation for SMM, SDZ, sulfadimidine, sulfamethoxydiazine, sulfathiazole, or sulfamoxole found in ruminal juice [5, 6, 16].

In conclusion, the results of the present study suggest that drugs with appropriate physicochemical properties such as high lipophilicity and unionization state in rumen juice possess the potential to be rapidly absorbed from the forestomach of cows. Further, the efficacy of drugs that are eliminated quickly can be achieved rapidly after oral administration, even in ruminants, because the k_{el} from the body is the determinant factor for T_{max} in flip-flop phenomena. Such drugs can achieve fast therapeutic effects if it is stable in rumen juice and can withstand the first-pass effect of liver. Therefore, these drugs can be administered orally to ruminants and thus, we can avoid the local reactions as muscle damage and long withdrawal time after parenteral administrations of some drugs. Treatment by oral administration, rather than by injection by veterinarians, will be more convenient for veterinarians and farmers.

CONFLICT OF INTEREST. The authors have not stated any conflicts of interest.

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