Rapid absorption of diclofenac and acetaminophen after their oral administration to cattle

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ABSTRACT. The oral pharmacokinetics of diclofenac (DF) were evaluated in cattle by analyzing plasma concentration-time data after its intravenous and oral administration in order to propose the oral administration of DF as effective route to avoid long withdraw period. DF was intravenously and orally administered at 1 mg/kg to cattle using a crossover design with a 4-week washout period. Plasma concentrations of DF were determined by a HPLC analysis. The mean absorption time (MAT) and absorption half-life ($t_{1/2ka}$) were 1.61 ± 0.61 and 1.51 ± 0.38 hr, respectively, and bioavailability was nearly 100%. The oral pharmacokinetics of acetaminophen (AAP) were also evaluated in cattle. Plasma concentrations of AAP were determined by a HPLC analysis. MAT and $t_{1/2ka}$ were 2.85 ± 0.93 and 1.53 ± 0.28 hr, respectively, and bioavailability was approximately 70%. In conclusion, the results of the present study indicate that DF and AAP are rapidly absorbed from the forestomach of cattle. Therefore, the appropriate efficacies of these drugs may be achieved via their oral administration, even in cattle.
KEY WORDS: acetaminophen, cattle, diclofenac, oral absorption, pharmacokinetics

An intravenous, intramuscular or subcutaneous injection is typically employed as the administration route of drugs in cattle. However, the intramuscular and subcutaneous routes often lead to a long withdrawal time due to their long residues at injection sites. Although this issue may be overcome by oral administration, the oral absorption of drugs may be extremely slow because of the large forestomach, and thus, this route may not be appropriate for cattle and other ruminants.

The main drug absorption site in many animal species after oral administration is the upper small intestine. The forestomach of cattle is a large volume compartment with a capacity ranging between 100 and 225 l [2]. This large volume may result in slow gastric emptying and thus the markedly slower absorption of drugs after their oral administration than that in monogastric animal species. Elbadawy *et al.* [7] reported that the mean absorption time (MAT) of sulphamonomethoxine was very long (approximately 15 hr) following its oral administration to Shiba goats, which are relatively small ruminants, and concluded that this long MAT may be the result of slow gastric emptying.

On the other hand, some drugs may be absorbed not only from the small intestine, but also the stomach. When lipid-soluble drugs exist in an unionized form in gastric fluid, they may be absorbed in large amounts from the stomach even though the effective surface area of this organ, which contributes to drug absorption, is markedly smaller than that of the small intestine. This has also been demonstrated in rats for salicylic acid [4], sulphaethidole and barbital [3], and metoprolol [5]. The extensive absorption of drugs, such as salicylic acid, aspirin, thiopental, secobarbital and antipyrine [11], from the stomach has also been reported in humans. Elbadawy *et al.* [7] found that, after it oral administration to Shiba goats, the absorption of diclofenac (DF; MAT of approximately 6 hr) was markedly faster than that of sulphamonomethoxine (MAT of approximately 15 hr). This finding suggests that DF is rapidly absorbed from the forestomach.

DF is a highly lipid-soluble drug. It has a high partition coefficient between octanol and buffer solution at pH 6.5, which corresponds to that of rumen juice [8]. This property may facilitate the rapid diffusion of DF from rumen juice to the membranes of the forestomach. Therefore, the oral administration of DF may achieve appropriate efficacy as an antipyretic or analgesic, even in cattle.

In a preliminary study, we examined the antipyretic effects of DF after its oral administration to cattle with infectious disease and found a relatively rapid decrease in the body temperature of most cattle examined. Since this finding suggested the rapid absorption of DF after its oral administration, we examined its pharmacokinetics following its oral and intravenous administration to cattle in order to clarify oral absorption profiles. As a reference, we also examined the oral pharmacokinetic profiles of acetaminophen (AAP). Although the lipid solubility of AAP is less than that of DF, it is still rapidly absorbed from the small intestine of humans

[9] and other animal species, such as dogs [23] and rats [20]. Therefore, it may be absorbed from the forestomach, because the pH of rumen juice is similar to that of intestinal fluid. In addition, a previous study indicated that AAP was absorbed rapidly after its oral administration to Shiba goats [8].

MATERIALS AND METHODS

Animals: Ten castrated male Holsteins (1.5−2 years old, 600−810 kg), which were fattened in Hitachi farm (Ibaraki Town, Japan), were used in this study. They were given rice straw at 0.5 kg/head and mixed feed (Beef Up®, Meiji Feed Co., Ltd., Tokyo, Japan) at 5.5 kg/head twice a day. Water was given *ad libitum*. Animal care was conducted 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.

Chemicals: The sodium salt of DF and flufenamic acid were obtained from Sigma-Aldrich Corporation (St. Louis, MO, U.S.A.). AAP was obtained from Wako Pure Chemical (Osaka, Japan). All other reagents and chemicals used in this study were of HPLC or analytical grade.

Experimental design

Pharmacokinetic study: The intravenous and oral pharmacokinetics of DF were examined in 5 animals using a crossover design. DF was administered at 1 mg/kg. There was an approximately 4-week interval between the first and second legs of the study. In the case of intravenous injections, DF was dissolved in a mixture of injectable distilled water and DMSO (99:1, v/v) at 40°C, and its concentration was then adjusted to 50 mg/ml. The temperature of the drug solution was maintained at 36–38°C before being injected into the right jugular vein. In the case of oral administration, the drug was dissolved in distilled water at 2.5 mg/ml and administered orally using a nasogastric catheter. Blood samples (5 ml) were collected from the left jugular vein immediately prior to and 0.5, 1, 2, 3, 4, 6, 8 and 10 hr following the intravenous injection of DF, and 1, 2, 4, 7, 10, 24 and 32 hr after its oral administration. Immediately after the blood sampling, the blood was placed in a test tube containing EDTA and centrifuged to separate the plasma. After blood sampling at 4 hr, the animals were given rice straw.

The intravenous and oral pharmacokinetics of AAP were examined in another 5 cattle using a crossover design with a 4-week washout period. AAP was administered at 10 mg/ kg. AAP was dissolved in propylene glycol at 40°C. The solution was diluted with injectable distilled water, and its concentration was adjusted to 50 mg/ml. The solution was injected into the right jugular vein or administered orally using a nasogastric catheter. Blood samples (5 ml) were collected from the left jugular vein immediately prior to and 1, 2, 3, 4, 6 and 8 hr following the intravenous injection of AAP, and 1, 2, 4, 7 and 10 hr after its oral administration.

Blood samples were centrifuged at 1,600 × *g* for 10 min, and the plasma obtained was stored at −20°C until the HPLC analysis.

Stability test: Since the oral bioavailability of DF was complete and, thus indicated good stability in the rumen juice of cattle, the stability of only AAP was determined in rumen juice as described previously [8]. Briefly, approximately 100 ml of rumen fluid was collected from two cattle using a catheter, pooled and then processed for an incubation immediately after its collection. Two hundred microliters of the drug solution (1 mg/ml) was added to 1.8 ml of rumen juice to give a final concentration of 100 μg/ml in the incubation mixture. The mixture was incubated in a thermostatic shaking water bath at 39°C for 24 hr under anaerobic conditions. The incubated mixture was then centrifuged at 20,000 × *g* for 10 min, and the supernatant was collected. The supernatant obtained was stored at −20°C until the HPLC analysis.

Determination of drugs

DF concentrations: DF concentrations in the plasma were determined by HPLC with UV detection, as described previously [7]. Briefly, 100 μl of flufenamic acid solution (10 μg/ml) was added as an internal standard to 500 μl of the plasma 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* at 5°C for 10 min. The supernatant obtained (organic layer) was 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), UV detector (SPD-6A), integrator (Chromatopac C-R7A plus) and loop injector (Model 7125). The mobile phase was a mixture of 0.1 M sodium acetate (pH 6.3) and acetonitrile (65:35, v/v). Analytical separation was accomplished using a reversed-phase ODS column (TSK-gel ODS-120T®, 4.6 μm × 250 mm, TOSOH Co., Tokyo, Japan). The flow rate was 1 ml/min. The wavelength of the detector was 278 nm. Recovery from plasma samples was 100 ± 2.20% at 1 μg/ml (n=5).

AAP concentration: AAP concentrations in plasma, rumen juice and buffer samples were determined by HPLC with UV detection, as described previously [8]. Briefly, 200 μl of perchloric acid (0.15 M) was added to 200 μl of the plasma or rumen juice samples and stirred. The mixtures were centrifuged at 20,000 × *g* for 10 min. The supernatants were obtained and filtered using a 0.45-μm HPLC filter (Chromatodisc®, 4P, Kurabo Biomedical Industries). Fifty microliters of the filtrate was injected into the HPLC column.

The mobile phase was a mixture of 0.1 M acetate buffer (pH 4) and acetonitrile (90:10, v/v). Triethylamine was added to the mobile phase at 150 μl/l. Analytical separation was accomplished using the ODS column (TSK-gel ODS-120T®, 4.6 μm×250 mm, TOSOH Co., Tokyo, Japan). The flow rate was 1 ml/min. The wavelength of the detector was 248 nm. Sample preparation and analyses were conducted at room temperature. AAP was found to be accurately resolved

as a single sharp peak with a retention time of 5–6 min. The recovery of AAP from plasma samples was 92.1 ± 1.2% at 1 μg/ml (mean ± SD, n=5), while that from rumen juice samples was 100.0 ± 1.9% at 100 μg/ml (mean ± SD, n=5).

Pharmacokinetic analysis

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

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

$$Cp_{po}(t) = \frac{Dose \cdot F \cdot k_a}{V}\left\{\begin{array}{l}\frac{k_{21} - \alpha}{(k_a - \alpha)(\beta - \alpha)}\cdot e^{-\alpha \cdot t}\\[2mm] +\frac{k_{21} - \beta}{(k_a - \beta)(\alpha - \beta)}\cdot e^{-\beta \cdot t}\\[2mm] +\frac{k_{21} - k_a}{(\alpha - k_a)(\beta - k_a)}\cdot e^{-k_a \cdot t}\end{array}\right\}\text{(Eq. 2)}$$

In Eq. 2, F is bioavailability.

Eqs. 1 and 2 were simultaneously fit to the plasma concentration-time curves of DF or AAP after it was intravenously and orally administered to the same cattle, respectively, in order to calculate pharmacokinetic parameters by the non-linear least-squares method using the curve fitting program, MULTI [22]. The absorption half-life ($t_{1/2ka}$) was calculated as $\log_e 2/ka$.

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) and the distribution volume at a steady state (V_{dss}) were calculated by conventional methods.

RESULTS

The plasma concentrations of DF rapidly increased and peaked 2 hr after its oral administration. Thereafter, they decreased with the slope similar to that in the elimination phase after the intravenous injection (Fig. 1). The plasma concentration-time profiles of AAP were similar to those of DF (Fig. 2). The flip-flop phenomenon was not observed after the oral administration of either drug.

The solid lines in Figs. 1 and 2 show the theoretical values calculated by Eqs. 1 and 2 with the pharmacokinetic parameters in Table 1. The lines fit well with the observed concentrations of DF and AAP.

As shown in Table 1, pharmacokinetic parameters related to oral absorption indicated the rapid absorption of DF; MAT and $t_{1/2ka}$ were less than 2 hr (1.61 ± 0.61 hr and 1.51 ± 0.38
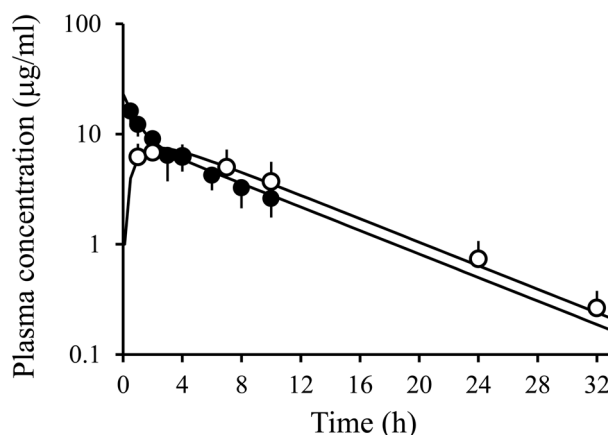

Fig. 1. Plasma concentration-time curves of DF after its single intravenous (closed circles) and oral administration (open circles) to cattle at 1 mg/kg. Each concentration is represented by the mean ± SD (n=5). The lines represent theoretical values calculated by Eqs. 1 and 2 using the pharmacokinetic parameters in Table 1.
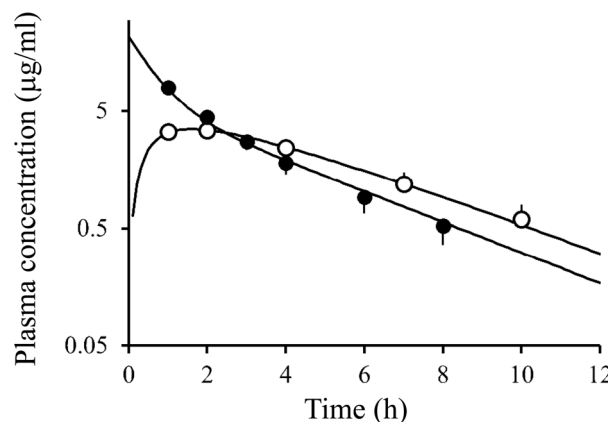

Fig. 2. Plasma concentration-time curves of AAP after its single intravenous (closed circles) and oral administration (open circles) to cattle at 10 mg/kg. Each concentration is represented by the mean ± SD (n=5). The lines represent theoretical values calculated by Eqs. 1 and 2 using the pharmacokinetic parameters in Table 1.

hr, respectively). These values of AAP were similar to those of DF, as is clearly shown in Table 1, indicating rapid oral absorption. The oral bioavailability of DF was nearly 100%, whereas that of AAP was approximately 70%. CL of DF and AAP was 0.0121 ± 0.0032 l/hr/kg and 0.310 ± 0.460 l/hr/kg, respectively. V_{dss} of DF and AAP was 0.0859 ± 0.0271 l/kg and 0.686 ± 0.143 l/kg, respectively.

The stability test of AAP in rumen juice showed that the recovery of AAP from rumen juice after a 24-hr incubation was 96.0 ± 1.5% (mean ± SD, n=5). Since the bioavailability of DF was almost complete, its stability was not examined in the present study.

Table 1. Pharmacokinetic parameters of DF and AAP in male cattle determined after their single intravenous and oral administration

Parameter	DF (1 mg/kg)	AAP (10 mg/kg)
k_a (hr^{-1})	0.481 ± 0.109	0.472 ± 0.106
C_{max} ($\mu g/ml$)	6.93 ± 2.60	3.45 ± 0.38
T_{max} (hr)	2.00 ± 1.22	1.40 ± 0.55
α (hr^{-1})	1.18 ± 0.48	1.57 ± 0.94
β (hr^{-1})	0.123 ± 0.013	0.282 ± 0.096
$t_{1/2ka}$ (hr)	1.51 ± 0.38	1.53 ± 0.28
$t_{1/2\beta}$ (hr)	5.69 ± 0.55	2.41 ± 0.58
$AUC_{i.v.}$ ($\mu g \cdot hr /ml$)	83.4 ± 20.4	31.7 ± 4.7
$AUC_{p.o.}$ ($\mu g \cdot hr /ml$)	90.1 ± 37.5	21.5 ± 3.7
CL ($l/hr/kg$)	0.0121 ± 0.0032	0.310 ± 0.460
F (%)	95.4 ± 24.8	70.1 ± 10.6
F* (%)	102 ± 26	64.1 ± 9.59
$MRT_{i.v.}$ (hr)	7.09 ± 0.86	2.22 ± 0.37
$MRT_{p.o.}$ (hr)	8.70 ± 0.67	4.70 ± 0.93
MAT (hr)	1.61 ± 0.61	2.85 ± 0.93
V_{dss} (l/kg)	0.0859 ± 0.0271	0.686 ± 0.143

Each value represents the mean ± SD (n=5). 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; $AUC_{i.v.}$=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; F=bioavailability calculated by a compartmental analysis; F*=bioavailability calculated by a non-compartmental analysis; $MRT_{i.v.}$=mean residence time after an i.v. injection; $MRT_{p.o.}$= mean residence time after p.o administration; MAT=mean absorption time; V_{dss}=volume of distribution at a steady state.

DISCUSSION

In the present study, we demonstrated that the oral absorption of DF was rapid, even in cattle. After its oral administration, the average value of T_{max} was 2 hr, and those of MAT and $t_{1/2ka}$ were less than 2 hr. This rapid absorption may be due to extensive absorption from the forestomach.

Ehsani-Kheradgerdi *et al.* [6] examined the pharmacokinetics of AAP after its abomasal administration to Holstein-Friesian heifers. They demonstrated that T_{max} was 80 min. This value was mainly determined by the abomasal emptying rate, because AAP is hardly absorbed from stomach juice in abomasum under low pH conditions, but is extensively absorbed from small intestinal fluid under markedly higher pH conditions in other animal species [9, 20, 23]. The T_{max} value of DF after its oral administration to cattle was similar to that of AAP after its abomasal administration. The residence time of drugs in the forestomach must be markedly longer than that in abomasum, if they are not extensively absorbed from the forestomach. Therefore, DF may have mainly been absorbed from the forestomach in cattle following its oral administration, and this may have been due to its high lipid solubility, as suggested in Shiba goats by Elbadawy *et al.* [7].

In the present study, the oral pharmacokinetics of AAP were also examined in cattle. The results obtained suggested no significant difference in absorption rates between DF and AAP, because the T_{max}, MAT and k_a of APP were similar to those of DF (Table 1). Therefore, AAP may also have been absorbed rapidly from the forestomach of cattle. The oral pharmacokinetics of AAP have been examined in order to evaluate gastric emptying profiles in monogastric animal species. The reported values for T_{max} were similar to those obtained in the present study: 0.5–1 hr in humans [13, 18], 0.5–3 hr in dogs [12] and 1–3.5 hr in pigs [19], which appears to support our suggestion that AAP was rapidly absorbed from the forestomach of cattle.

Since most drugs are absorbed from the gastrointestinal tract through a lipid barrier by passive diffusion, lipid solubility is an important factor for oral absorption. The apparent lipid solubility of AAP in rumen juice is markedly weaker than that of DF. The partition coefficients of DF and AAP between octanol and pH 6.5 buffer solution were previously reported to be 91.8 and 2.07, respectively [8]. Since a pH value of 6.5 is typically observed in rumen juice from cattle, the marked differences in their absorption rates from the forestomach may be due to the large difference observed in the partition coefficient between DF and AAP. However, the results of the present study suggest that both drugs were absorbed from the forestomach at a similar rate after their oral administration. This result may be explained as follows; the smaller molecular size of AAP (151.17) than that of DF (296.15) as well as its lipid solubility may enable its rapid absorption from the forestomach in cattle, as suggested in Shiba goats by Elbadawy *et al.* [8]. Morishita *et al.* already suggested that physicochemical factors including molecular size affected the absorption of sulfonomides in rats [16].

The oral pharmacokinetic profiles of DF obtained in the present study suggest that its appropriate efficacy as an antipyretic is obtained via its oral administration, even in cattle, because these profiles were similar to those in other animal species, such as humans, dogs and pigs. The values of T_{max} have been reported to be 0.6–2.5 hr in humans [10, 14, 21], 1 −2 hr in dogs [1] and 0.75 hr in pigs [17]. These values are similar to 2 hr in cattle. Therefore, rapid efficacy may even be obtained in cattle.

To date, only the intramuscular use of DF has been approved for cattle in the EU. When DF is intramuscularly injected into cattle, its elimination half-life is approximately 30 hr [15], which is markedly longer than that after its oral administration (5.69 hr in Table 1). This long half-life is due to its slow absorption from the injection site. Slow absorption may require higher doses to obtain appropriate efficacy than rapid absorption to achieve effective concentrations. As a result, a longer withdrawal time may be required. The withdrawal time of DF is long in cattle (15 days), but may be shortened by its oral administration due to its markedly shorter half-life and faster absorption via this route. Therefore, oral administration may be better than intramuscular injections of DF in cattle. The lowering dose of DF by oral administration for cattle might be useful to reduce the environmental impacts and the effect on wild animals.

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