Pharmacokinetics and Metabolism of Diclofenac Sodium in Yucatan Miniature Pigs

Rebecca L. Oberle,[1,5] Helena Das,[2] Shekman L. Wong,[3] Keith K. H. Chan,[4] and Ronald J. Sawchuk[3]

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The pig has been suggested as an animal model in biomedical research because of its physiological similarity to man. Therefore, the pharmacokinetics and metabolism of diclofenac sodium (Voltaren) were studied in four Yucatan minipigs after intravenous administration of 25 and 50 mg and oral administration of 50 mg in a solution of 50 mL buffer, 50 mL water, and 200 mL water, and the results compared to historical data in man. The absolute bioavailability after oral administration of 50 mL buffer, 50 mL water, and 200 mL water solutions were 107, 97, and 109%, respectively, compared to approximately 50% in man. The total plasma clearance in minipigs was fivefold slower than in humans (57 ± 17 vs 252 ± 54 mL/hr/kg). The plasma levels of the metabolites 4'-hydroxy, 5-hydroxy, 3'-hydroxy, 4',5-dihydroxy, and 3'-hydroxy-4'-methoxy diclofenac were considerably lower in minipigs than in man after both iv and oral administration. These results suggest slower metabolism and/or enterohepatic recirculation of the parent drug in minipigs. The volume of distribution of the central compartment was 40% less in humans than in pigs (39 vs 67 mL/kg). The terminal half-lives of the parent drug were similar in pigs (2.4 hr) and humans (1.8 hr). The rate of oral drug absorption increased in the order of 50 mL aqueous, 200 mL aqueous, and 50 mL buffered solutions (K_a = 0.52 ± 0.11, 0.59 ± 0.13, and 1.2 ± 0.7 hr^{-1}, respectively). These trends are similar in man and suggest that both buffering and intake volume can affect diclofenac absorption. Possible reasons for these results include the pH-dependent solubility of this drug and the effect of volume on gastric emptying.

KEY WORDS: pharmacokinetics; metabolism; diclofenac; minipigs.

INTRODUCTION

Diclofenac sodium (Voltaren) is a nonsteroidal antiinflammatory drug used for the treatment of degenerative joint disease and other arthritic conditions. The drug has been marketed internationally since 1973 and is currently available in oral, parenteral, rectal and topical preparations. An oral enteric-coated tablet is the only formulation available commercially in the United States.

The pharmacokinetics and metabolism have been studied in various animal species after oral and intravenous administration (1–4). The metabolism of diclofenac sodium is highly species dependent. Humans and monkeys metabolize the drug mainly by hepatic hydroxylation and subsequent conjugation. The principal metabolite, 4'-hydroxy diclofenac, accounts for 20–30% of the dose excreted in the urine and 10–20% excreted in bile. Other metabolites, 5-hydroxy, 3'-hydroxy, 4',5-dihydroxy, and 3'-hydroxy-4'-methoxy diclofenac each account for 10–20% of the dose excreted in the urine and small amounts in the bile. After biliary elimination of the conjugates of these metabolites, intestinal hydrolysis does not regenerate the parent drug. In contrast, rats and dogs form mainly conjugates of unchanged diclofenac. These metabolites undergo varying degrees of intestinal hydrolysis, giving rise to enterohepatic recirculation of the parent drug. As the hydroxylated metabolites are markedly less toxic than the parent substance, the observed species differences in toxicity of diclofenac can be accounted for by species differences in its metabolism. Therefore, the dog is inadequate as an animal model for diclofenac disposition.

The dog has been widely used, with varying degrees of success, as a large animal model for studying pharmacokinetics (5–7). There is a considerable body of literature that suggests that the physiology of the pig resembles that of man and the pig may be a promising animal model for the study of human disease (8,9). Although knowledge is limited, continued study has demonstrated their usefulness in oral drug absorption and metabolism research (10–12). In addition, the recent breeding of the pig to a smaller size and the development of effective and gentle handling techniques have made the pig a more convenient and reasonable animal to use. The adaptability and docile nature of especially the Yucatan breed are conducive to utilizing them in experimental situations. The pig may serve as an alternate animal model for man, especially in the area of oral dosage-form development. Further evaluation of the minipig is necessary to determine the acceptability of this species for biopharmaceutical research in general. Extensive pharmacokinetic and disposition data after oral administration of selected dosage forms of diclofenac to various animal species are available and provide a good foundation for species comparison. Therefore, the pharmacokinetics and metabolism of diclofenac sodium were studied after intravenous and oral administration of various drug solutions to miniature pigs.

METHODS

Animals

Four healthy male miniature swine of the Yucatan strain were obtained from Charles River Inc. (Wilmington, MA). The animals were individually housed in pens with rubber-coated metal mesh gratings, at a temperature of 68–70°F and approximately 50% relative humidity. The animals were exposed to automated 12-hr lighting cycles. They were fed once daily with minipig chow (Purina Mills) and given water ad libitum. The animals were 1–2 years in age and ranged in weight from 19 to 40 kg (mean weight, 29 kg) at the time of

[1] Basic Pharmaceutics Research, Ciba-Geigy Corporation, Ardsley, New York 10502.
[2] Present address: School of Veterinary Medicine Cornell University, Ithaca, New York 14853.
[3] Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455.
[4] Clinical Pharmacokinetics and Disposition, Ciba-Geigy Corporation, Ardsley, New York 10502.
[5] To whom correspondence should be addressed.

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the studies. The animals were individually conditioned with regard to handling, restraint, and dosing.

For the collection of blood and intravenous administration of diclofenac sodium, catheters were prepared and placed surgically in the carotid artery and internal jugular vein according to a previously described procedure (13). Catheters were flushed daily with 20 mL of sterile normal saline. Between uses, catheters were filled with heparin (1000 U/mL) and plugged with an obturator.

Study Design

Pharmacokinetic studies were initiated at least 3 weeks after surgery. At least 1 week was allowed between studies. Pigs were fasted for 24 hr prior to all studies. Meals were given at 4 hr postdosing. Water was restricted 1 hr prior to and 2 hr after initiating all studies; otherwise, water was allowed ad libitum.

Intravenous infusions of diclofenac sodium in normal saline, yielding doses of either 25 or 50 mg, were performed in four pigs. Constant-rate infusions were carried out for 20 min at a flow rate of 1.2 mL/min. Blood samples were collected arterially at 0, 5, 10, 15, 20, 25, 30, 35, 40, 55, 70, 85, 110, 140, 170, 200, 230, 260, 290, 320, 350, 380, 500, 620, and 740 min and 24 hr after initiating the infusion.

Fifty milligrams of diclofenac sodium was administered as a buffered solution (0.02 *M* phosphate buffer, pH 7.4) of 50 mL via oral intubation in three pigs. On separate occasions in each pig, an unbuffered solution of diclofenac sodium was administered with either 50 or 200 mL of water to determine the effect of pH (buffering) and coadministered volume on the plasma level profile. Blood samples were drawn at 0, 5, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 240, 270, 300, 360, 420, 480, 600, and 720 min and 24 hr postdosing.

Drug and Metabolite Assays

All blood samples were centrifuged at 2000 rpm and plasma was removed and stored at −70°C until analysis. The parent drug was measured in all samples. The metabolites, 3′-hydroxy-4′-methoxy, 4′,5-dihydroxy, 3′-hydroxy, 4′-hydroxy, and 5-hydroxy diclofenac, were determined in plasma samples from 25-mg intravenous infusion and the oral 50-mg buffered solution studies in two pigs.

Plasma samples were analyzed for the presence of the parent drug according to a previously published high-performance liquid chromatographic (HPLC) method for which precision, accuracy, sensitivity, and linearity had been established previously (14). The concentrations of drug in plasma were calculated from calibration curves constructed on each occasion. Coefficients of variation ranged from 1.5 to 4.2% over a 0.025–5.0 μg/mL concentration range. Quality-control plasma standards were prepared at the start of these studies and assayed with each run. Plasma samples were analyzed for the major human hydroxy metabolites according to a gradient HPLC method. Plasma samples (1 mL) were spiked with internal standard (200 μL, 0.01 μg/mL indomethacin and 200 μL, 0.1 μg/mL 3-chlorobenzoic acid), 0.25 mL of 2.5 *N* H_3PO_4 and 15 mL of (5:95%, v:v) tertiary butyl alcohol:dichloromethane. After shaking and centrifuging, the upper layer was aspirated and disgarded. The organic layer was then evaporated to dryness at 45°C. The residue was reconstituted with 100 μL of (55:45%, v:v) methanol and mobile-phase buffer [0.01 *M* $(NH_4)HPO_4$, pH 2.6], and 10 μL was then injected in duplicate onto the HPLC. The lower limit of quantitation of the metabolites was 50 ng/mL.

Pharmacokinetic Analysis

Pharmacokinetic analysis utilized standard methods of data treatment. Inspection of semilogarithmic plots of the postinfusion drug plasma level-versus-time curves indicated that they could be described by a biexponential equation. Initial estimates of parameters were obtained by standard stripping techniques. These estimates, together with all plasma-level data and the appropriate equations, were used as input for regression analysis using the program PCNONLIN (15). The secondary parameters A and B have been corrected for the infusion time and are reported as parameters for a corresponding bolus intravenous injection. All plasma-level data were weighted according to $1/C^2$, where C is the plasma level of diclofenac. The volume of distribution of the central compartment (V_c) was calculated as the intravenous dose divided by the sum of A and B.

Noncompartmental pharmacokinetic parameters from oral plasma level-versus-time data were determined. $C_{max(1)}$ was the earliest peak plasma level and $C_{max(2)}$ was the second peak drug concentration in plasma. $T_{max(1)}$ was the time at which $C_{max(1)}$ occurred and $T_{max(2)}$ was the time at which $C_{max(2)}$ occurred. The terminal rate constant was determined by linear regression analysis of the log-linear terminal phase of the plasma concentration–time profile. At least three points were used in the determination and the correlation coefficient values had to be greater than 0.95 for the estimate to be accepted. $AUC_{(0-inf)}$ was determined as the area under the plasma concentration–time curve up to the last measured time point, calculated by the linear trapezoidal rule, plus any residual area, which was calculated as the concentration at the last time point, divided by the terminal rate constant. Absolute bioavailability (F_{abs}) was calculated as the ratio of the $AUC_{(0-inf)}$ of the oral to that of the intravenous plasma concentration–time profile times the ratio of the intravenous to the oral dose. Total plasma clearance (Cl) was calculated as the intravenous dose divided by the $AUC_{(0-inf)}$. For the species comparison of the data, Cl and V_c were normalized for body weight.

Individual oral absorption parameters were also determined by the Loo–Riegelman method using individual micro-rate constants, K_{12}, k_{21}, and k_{10}, obtained from nonlinear least-squares regression of the 50-mg intravenous data (16).

Statistics

The differences in the pharmacokinetic parameters of diclofenac sodium after intravenous and oral administration of various intravenous doses and oral solutions were compared by an ANOVA test at the $P = 0.05$ level.

RESULTS

Intravenous Infusions

Examples of individual plasma level profiles together

with the fit of the data after 25- and 50-mg intravenous doses are given in Fig. 1. Plasma-level data were adequately fit by nonlinear least-squares regression analysis to a two-compartment model with zero-order infusion. Mean values ± standard deviations of the pharmacokinetic parameters together with the coefficients of determination, r^2 values, and the randomness of the weighted residuals were examined to determine the goodness of fit.

Pharmacokinetic parameters are given in Table I. The concentrations at the end of the infusion (20 min) were 8.4 ± 0.3 and 16.4 ± 1.6 μg/mL for the 25- and 50-mg intravenous doses, respectively. The mean terminal half-life (2.4 ± 0.3 hr) and plasma clearance (1.5 ± 0.25 L/hr) were independent of dose in the range of 25–50 mg. Mean $AUC_{(0-inf)}$ values were 18.3 ± 2.9 and 35.5 ± 4.8 μg*hr/mL for the 25- and 50-mg intravenous doses, respectively, indicating dose proportionality over the dose range studied.

Oral Solutions

Diclofenac sodium, 50 mg, was administered in (A) 50 mL of buffer, (B) 50 mL of water, and (C) 200 mL of water. Individual plasma-level profiles in a representative pig are given in Fig. 2. Mean pharmacokinetic parameters are given in Table II. Mean $C_{max(1)}$ values for 50 mL buffer, 50 mL aqueous, and 200 mL aqueous solution doses were 9.1 ± 2.0, 5.3 ± 0.9, and 6.3 ± 1.7 μg/mL, respectively. $C_{max(1)}$ values were not statistically different from each other. All plasma level curves in 50 mL buffer, 50 mL aqueous, and 200 mL aqueous solution doses exhibited double peaks. Mean terminal half-life values after oral treatments were not statistically different from each other or from the mean intravenous terminal half-life of 2.4 hr. Individual Loo–Riegelman plots from a representative pig are given in Fig. 3. The rate of absorption appeared first order in the initial portion of the fraction remaining to be absorbed-versus-time plots. For the 200-mL aqueous dose, curves appeared biphasic. The half-lives for initial absorption were 34.3 ± 11.3, 81.8 ± 10.7, and 70.8 ± 16.2 min for the 50 mL buffer, 50 mL water, and 200 mL water treatments, respectively.

Metabolites

Plasma samples from 25-mg intravenous and 50-mg oral buffered solution studies were assayed for the presence of 3′-hydroxy-4′-methoxy, 4′,5-dihydroxy, 3′-hydroxy, 4′-hydroxy, and 5-hydroxy diclofenac. The individual plasma-level profiles of the 4′-hydroxy metabolite are given in Fig. 4. Levels of the other metabolites were below the lower limit of quantitation (50 ng/mL). Comparison of C_{max} and $AUC_{(0-inf)}$ of the metabolites between minipigs and man is given in Table III.

Table I. Mean (±SE) Pharmacokinetic Parameters After Intravenous Administration of Diclofenac Sodium to Miniature Pigs (n = 4)

Parameter	25 mg	50 mg
$AUC_{(0-inf)}$ (μg*hr/mL)	18.3 ± 2.9	35.5 ± 4.8
$t_{1/2,\beta}$ (hr)	2.4 ± 0.40	2.4 ± 0.25
V_c (L)	1.8 ± 0.18	1.9 ± 0.32
Cl (L/hr)	1.5 ± 0.25	1.5 ± 0.25
k_{10} (hr^{-1})	1.0 ± 0.04	0.7 ± 0.06
k_{12} (hr^{-1})	4.4 ± 2.2	2.1 ± 0.51
k_{21} (hr^{-1})	2.5 ± 0.76	1.6 ± 0.37

DISCUSSION

Marked species differences in the metabolism of diclofenac have been observed between dogs and man (1–4,18). The parent drug is subject to enterohepatic recirculation in the dog but not in man. As a result, the plasma levels of unchanged drug maintain higher values for longer periods and diclofenac is more toxic in the dog compared to man. Consequently, a better animal model is needed for the study of diclofenac pharmacokinetics and disposition.

Previous results have demonstrated the value of minipigs in metabolism studies. The cytochrome P-450 levels and mixed-function oxygenase activity in pigs are similar to those in man (10,11). As a result, the metabolic pattern of various compounds is comparable between the two species (19–21).

The absorption, pharmacokinetics, and disposition of diclofenac in miniswine are different from those in man. A comparison of the pharmacokinetic parameters in pigs and humans (17) is given in Table IV. The terminal half-life values

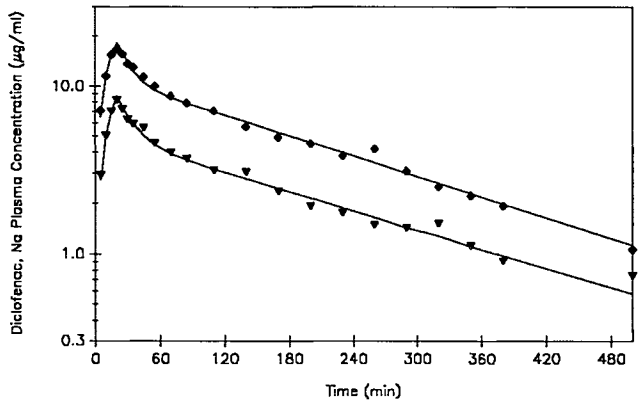

Fig. 1. Individual plasma-level profiles of diclofenac sodium and fit of the data after 25 (inverted triangles) and 50 mg (diamonds) intravenous infusions to minipig 3.

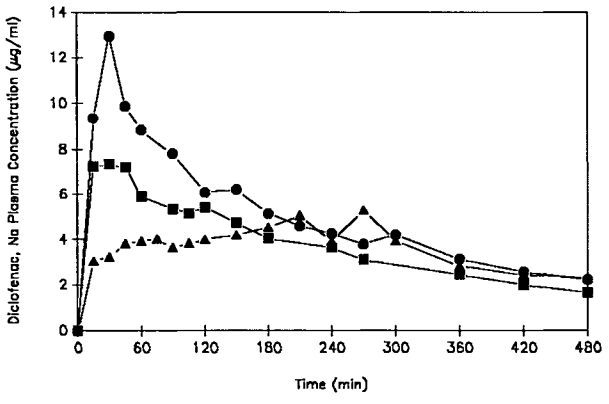

Fig. 2. Individual plasma-level profiles of diclofenac sodium after oral administration of 50 mg as a 50-mL buffered solution (circles), 50-mL aqueous solution (triangles), and 200-mL aqueous solution (squares) to minipig 1.

Table II. Mean (±SE) Pharmacokinetic Parameters After Oral Administration of 50 mg Diclofenac Sodium Solution to Miniature Pigs (n = 3)

Parameter	Treatment		
	50 mL buffered	50 mL aqueous	200 mL aqueous
$C_{max(1)}$ (μg/mL)	9.1 ± 2.0	5.3 ± 0.9	6.3 ± 1.7
$C_{max(21)}$ (μg/mL)	5.7 ± 0.8	5.2 ± 0.6	5.6 ± 0.9
$T_{max(1)}$ (hr)[a]	0.75	0.75	0.5
$T_{max(2)}$ (hr)[a]	2.5	3.0	2.5
$t_{1/2,\beta}$ (hr)	2.4 ± 0.5	2.5 ± 0.5	3.4 ± 0.8
$AUC_{(0-inf)}$ (μg*hr/mL)	35.6 ± 7.8	33.2 ± 3.5	34.3 ± 4.8
F_{abs}	1.07 ± 0.05	0.97 ± 0.08	1.09 ± 0.2

[a] Median.

were similar in pigs and humans (humans, 1.8 hr; pigs, 2.4 hr). However, total plasma clearance in pigs was fivefold lower than in humans (57 ± 17 mL/hr/kg vs 252 ± 54 mL/hr/kg). Differences in the $AUC_{(0-inf)}$ values are reflected in the slower clearance and higher volume of distribution in the pig. The twofold difference in oral bioavailability between the two species is due to the lack of first-pass metabolism in the pig. The volume of distribution of the central compartment after adjustment for body weight was 40% less in humans than in pigs (39 vs 67 mL/kg), after 50 mg iv. The lower clearance in pigs relative to man may be due to slower metabolism and/or the presence of enterohepatic recirculation of the parent drug in pigs.

In the current study, the metabolism of diclofenac was studied by measurement of the major human metabolites in the plasma after both 25-mg iv and 50-mg oral buffered solution studies. In man, the metabolite-to-parent C_{max} ratios were approximately 0.2 for 4′-hydroxy metabolite and approximately 0.05 each for 5-hydroxy, 3′-hydroxy, 4′,5-dihydroxy, and 3′-hydroxy-4′-methoxy diclofenac after oral administration (Table III) (22). In the minipig, the plasma levels of these metabolites were considerably lower than in man after both iv and oral administration (Fig. 4). The 4′-hydroxy was the only metabolite detected and it accounted for a negligible amount of the parent drug after oral dosing. No other metabolites were detected by the current assay method, which has a lower limit of quantitation of 50 ng/mL. The absence of measured metabolites is consistent with the lower clearance and higher plasma levels of the parent drug observed in the pig relative to man.

In man, the absolute bioavailability of diclofenac after oral administration of enteric-coated tablets (50 mg) was 54 ± 2% (17). This is due to a considerable hepatic first-pass metabolism, whereas oral absorption into the portal circulation is complete. In pigs, the mean absolute bioavailabilities for the oral buffered solution (50 mL), unbuffered solution (50 mL), and unbuffered solution (200 mL) were 1.07, 0.97, and 1.09, respectively, and suggestive of little first-pass metabolism.

In man, absorption of the drug from oral solution is extremely rapid, with peak concentrations being reached within 5–10 min after administration of a buffered aqueous solution to healthy, fasted subjects (23). When the drug is given as an unbuffered aqueous solution to man, rapid absorption also occurs, but the absorption rate is variable; Multiple peaks are frequently observed in the resulting plasma level profiles (23,24). Differences in the plasma-level profiles of diclofenac sodium between oral administration of buffered versus unbuffered solutions in man may be attributed to the significant pH-dependent solubility of the drug. Diclofenac is a weak acid, with a pK_a of 4.0 (18) and an octanol:pH 7.4 buffer partition coefficient of 13.4 (25). Diclofenac sodium is poorly soluble in acidic medium and ap-

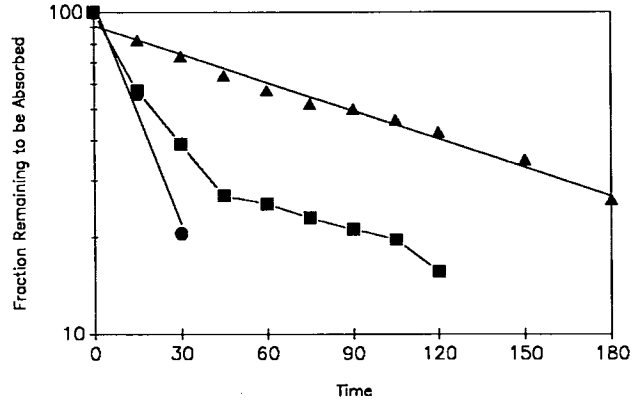

Fig. 3. Individual Loo–Reigelman absorption profiles after oral administration of diclofenac sodium, 50 mg, as a 50-mL buffered solution (circles), 50-mL aqueous solution (triangles), and 200-mL aqueous solution (squares) to minipig 1.

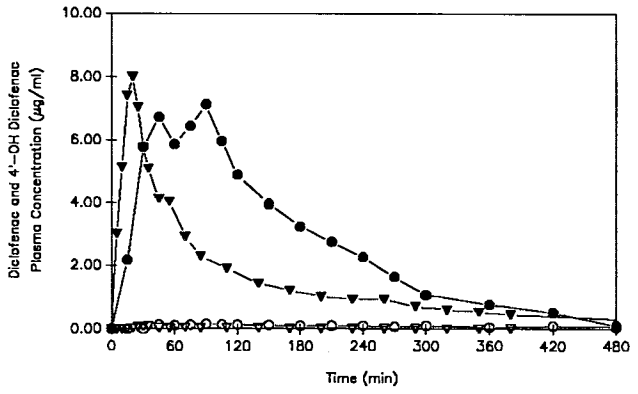

Fig. 4. Plasma-level profiles of diclofenac (filled symbols) and 4′-hydroxy diclofenac (open symbols) after intravenous administration of 25 mg (inverted triangles) and oral administration of 50 mg as a 50-mL buffered solution (circles) to minipig 2.

Table III. Comparison of Plasma Levels of Diclofenac Metabolites Between Man and Minipig

Diclofenac metabolite	Ratio[a]	Human[23]	Miniswine
Parent drug	$AUC_{(0-inf)}$	1.0	1.0
	C_{max}	1.0	1.0
4'-Hydroxy	$AUC_{(0-inf)}$	0.51	—
	C_{max}	0.18	0.019
5-Hydroxy	$AUC_{(0-inf)}$	0.12	ND[b]
	C_{max}	0.05	
3'-Hydroxy	$AUC_{(0-inf)}$	0.23	ND
	C_{max}	0.05	
4',5-Dihydroxy	$AUC_{(0-inf)}$	0.29	ND
	C_{max}	0.05	
3'-Hydroxy-4'-methoxy	$AUC_{(0-inf)}$	11.1	ND
	C_{max}	0.03	

[a] Data are expressed as the ratio of either $AUC_{(0-inf)}$ or C_{max} of the metabolite to the parent drug. Oral doses were 100 mg in humans and 50 mg in miniswine.
[b] Not detected.

proximately 1000-fold more soluble in basic medium (0.003 and 13 mg/mL in simulated gastric and intestinal fluids, respectively). This suggests that regional pH differences and variability are important factors influencing the absorption of the drug, although this has not been verified experimentally in man. In the case of an unbuffered solution, the drug may precipitate in the low pH environment of the stomach. Dissolution of the drug and subsequent absorption would then depend on gastric emptying to the small intestine where the pH is higher. This dependence would probably result in erratic absorption since gastric emptying is highly variable in man. Administration of drug as a buffered solution may minimize the effect of or prevent this series of events.

Diclofenac sodium was administered as various solutions to study the effect of pH (buffering) and dose volume on diclofenac absorption and to compare to similar studies in man. Absorption of diclofenac in pigs was faster from a buffered solution of 50 mL than from an unbuffered solution of 50 mL ($k_a^{buffered} = 1.2 \pm 0.7\ hr^{-1}$; $k_a^{unbuffered} = 0.52 \pm 0.11\ hr^{-1}$) (Fig. 3). The rates were not statistically different. There was no statistical difference in C_{max} or T_{max} between treatments, although trends in the data were worth noting. The mean $C_{max(1)}$ for the buffered solution was 9.1 μg/mL, 1.7 times greater than the mean $C_{max(1)}$ for the unbuffered solution (50 mL), 5.3 μg/mL. The median $T_{max(1)}$ for both treatments was 0.75 hr. The secondary peak was less noticeable after the buffered solution. The same relative difference was found after administration of buffered and unbuffered solutions to man (24).

Secondary peaks were observed in the plasma-level curves after administration of both buffered and unbuffered solutions to pigs (Figs. 2 and 4). The presence of double peaks may be due to the pH-dependent solubility of this drug but, unlike in man, may be confounded by the possible enterohepatic recirculation of the parent compound since double peaks were also observed after intravenous administration in pigs but not in man. Variability in stomach pH has been found in the pig and may also contribute to the variability in drug absorption (26).

Median T_{max} values in pigs were greater than those in man (5–10 min) for all oral solution treatments (Table II). This may be due to the fact that gastric emptying is reportedly slower in pigs than in man (8,9,27).

An unbuffered solution was administered with volumes of 50 and 200 mL to study the effect of dosing volume on the plasma level profiles. Studies in man have shown that 200 mL empties statistically faster than 50 mL, with a first-order gastric emptying rate constant of 0.1 min^{-1} for 50 mL and 0.134 min^{-1} for 200 mL (28). For drugs whose absorption is greatly dependent on the rate of gastric emptying, the coadministered volume, among other factors, would be expected to influence the absorption rate and, for drugs that are rapidly eliminated, subsequent plasma drug levels. A number of studies of a variety of drugs have reported differences in the plasma-level profiles between those administered with small and those with large volumes of water (29,30). In this study, the mean absorption rate of diclofenac from unbuffered solution (200 mL) tended to be faster than with the unbuffered solution (50 mL), but a statistical difference was not reached between the two treatments. Further physiological and pharamcokinetic studies in a larger number of pigs would be needed to determine the effect of pH and coadministered volume on the plasma-level profiles of diclofenac after administration to pigs. The results of the current study, though limited, were similar to those in man and suggest that both buffering and increased intake volume could increase the absorption rate of diclofenac. As in man, these factors had no effect on the extent of bioavailability.

Table IV. Comparison of Diclofenac Sodium Pharmacokinetics Between Man and Minipig[a]

	Human		Minipig	
	iv[17]	Oral[23]	iv	Oral
Cl (mL/hr/kg)	252 ± 54		57 ± 17	
C_{max} (μg/mL)		2.4 ± 1.0		9.1 ± 2.0
T_{max} (hr)[b]		0.25		0.75
$AUC_{(0-inf)}$ (μg*hr/mL)	3.3 ± 0.7	1.4 ± 0.6	35.5 ± 4.8	35.6 ± 6.7
F_{abs}		0.42 ± 0.27		1.07 ± 0.05
V_c (mL/kg)	39.0 ± 20.0		66.7 ± 5.8	

[a] All intravenous and oral doses were 50 mg. The oral dose was administered as a buffered solution in both pig and man. The mean weights of the human subjects were 62.3 kg (17) and 88.4 (23) kg and the mean weight of the minipigs was 28.9 kg.
[b] Median values.

When choosing an animal model, the ability to predict a correlation of pharmacokinetics between man and the animal is desired. Results of the current study suggest that the pig would not be appropriate in this regard. In particular, the pharmacokinetics and metabolism of diclofenac in minipigs were not similar to man. The plasma levels of diclofenac were higher in miniswine than humans for equivalent intravenous and oral doses. Total plasma clearance of diclofenac in pigs was fivefold slower than in humans. In the minipig, the plasma levels of the hydroxydiclofenac metabolites were considerably lower than in man after both intravenous and oral administration. The 4′-hydroxy metabolite was the only metabolite detected. In pigs, the absolute bioavailability was approximately 100% compared to approximately 55% in man. On the other hand, relative differences between oral drug absorption from buffered and unbuffered solutions were similar between pig and man. Although the physiology of the pig is reportedly similar to man, the basis of knowledge on relevant gastrointestinal physiology is lacking and more studies tailored specifically to the interests of pharmaceutical scientists are needed.

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REFERENCES

1. W. Reiss, H. Stierlin, P. Degan, J. W. Faigle, A. Gerardin, J. Moppert, A. Sallmann, K. Schmid, A. Schweizer, M. Sulc, W. Theobald, and J. Wagner. Pharmacokinetics and metabolism of the anti-inflammatory agent Voltaren. *Scand. J. Rheumatol. Suppl.* 22:17–29 (1978).
2. W. Reiss, H. Stierlin, J. W. Faigle, *et al.* The pharmacokinetics of diclofenac in animals and man. In F. J. Wagenhauser (ed.), *Voltaren, a New Nonsteroidal Antirheumatic Agent (Diclofenac)*; Proc. VIII Congr. Rheumatol., Helsinki, 1975, pp. 19–28.
3. H. Stierlin, J. W. Faigle, A. Sallmann, *et al.* Biotransformation of diclofenac sodium (Voltaren) in animals and man I. Isolation and identification of principal metabolites. *Xenobiotica* 9:601–610 (1979).
4. H. Stierlin and J. W. Faigle. Biotransformation of diclofenac sodium (Voltaren) in animals and man. II. Quantitative determination of the unchanged drug and principal phenolic metabolites in urine and bile. *Xenobiotica* 9:611–621 (1980).
5. W. A. Cressman and D. Sumner. The dog as a quantitative model for evaluation of non-disintegrating sustained-release tablets. *J. Pharm. Sci.* 60:132–134 (1971).
6. W. Crouthamel and A. C. Sarapu. *Animal Models for Oral Drug Delivery in Man: In Situ and in Vivo Approaches*, Am. Pharm. Assoc., Washington, DC, 1980.
7. J. B. Dressman. Comparison of canine and human gastrointestinal physiology. *Pharm. Res.* 3:123–131 (1986).
8. W. G. Pond and K. A. Houpt. *The Biology of the Pig*, Comstock, Ithaca, NY, 1978.
9. M. E. Tumbleson (ed.). *Swine in Biomedical Research*, Plenum Press, New York, 1985.
10. H. Souhaili-El Amri, A. M. Batt, and G. Siest. Comparison of cytochrome P-450 content and activities in liver microsomes of seven animal species, including man. *Xenobiotica* 16:351–358 (1986).
11. C. L. Litterest, T. E. Gram, E. G. Mimnaugh, P. Leber, D. Emmerling, and R. I. Freudental. A comprehensive study of *in vitro* drug metabolism in several laboratory species. *Drug Metab. Disp.* 4:203–207 (1976).
12. E. Harboe, C. Larsen, M. Johansen, and H. P. Olesen. Macromolecular prodrugs. XIV. Absorption characteristics of naproxen after oral administration of a dextran T70-naproxen ester prodrug in pigs. *Int. J. Pharm.* 53:157–165 (1989).
13. J. M. Terris, T. V. Martin, and R. C. Simmonds. Metabolism unit, confinement unit and placement of indwelling catheters for use with swine. In M. E. Tumbleson (ed.), *Swine in Biomedical Research, Vol. 1*, Plenum Press, New York, 1985, pp. 111–121.
14. K. Chan, K. Vyas, and K. Wnuck. A rapid and sensitive method for the determination of diclofenac sodium in plasma by high-performance liquid chromatography. *Anal. Lett.* 15;1649–1663 (1982).
15. Statistical Consultants, Inc. PCNONLIN and NONLIN: Systems for the statistical analysis on nonlinear models. *Am. Stat.* 40:52 (1986).
16. J. C. K. Loo and S. Riegelman. New method for calculating the intrinsic absorption rate of drugs. *J. Pharm. Sci.* 57:918–928 (1968).
17. J. V. Willis, M. J. Kendall, R. M. Flinn, D. P. Thornhill, and P. G. Welling. The pharmacokinetics of diclofenac sodium following intravenous and oral administration. *Eur. J. Clin. Pharmacol.* 16:405–410 (1979).
18. W. Reiss, H. Stierlin, J. W. Faigle, V. P. Gerger, A. Gerardin, K. Schmid, M. Sulc, J. Wagner, and W. P. Theobald. Kinetik und biotransformation von diclofenac in tier und mensch. *Therapiewoche* 26:18 (1976).
19. J. O. Peggins, T. F. McMahon, W. P. Beierschmitt, and M. Weiner. Comparison of hepatic and renal metabolism of acetaminophen in male and female miniature swine. *Drug Metab. Disp.* 15:270–273 (1987).
20. C. L. Litterst, T. E. Gram, E. G. Mimnaugh, P. Leber, D. Emmerling, and R. I. Freudenthal. A comprehensive study of in vitro drug metabolism in several laboratory species. *Drug Metab. Disp.* 4:203–207 (1976).
21. J. O. Peggins, L. A. Shipley, and M. Weiner. Characterization of age-related changes in hepatic drug metabolism in miniature swine. *Drug Metab. Disp.* 12:379–381 (1984).
22. P. H. Degen, W. Dieterle, W. Schneider, W. Theobald, and U. Sinterhauf. Pharmacokinetics of diclofenac and five metabolites after single doses in healthy volunteers and after repeated doses in patients. *Xenobiotica* 18:1449–1455 (1988).
23. H. S. H. Lau, K. Chan, L. Y. Shum, S. Adair, H. Ross, H. Eyring, D. Guase, and V. John. Dose-proportionality of diclofenac sodium (Voltaren) in man. *Pharm. Res.* 6:S-194 (1989).
24. N. Vidon, A. Pfeiffer, J. Godbillon, M. Rongier, S. Gandon, J. Hirtz, J. J. Bernier, and J. P. Dubois. Evaluation of the gastric absorption and emptying of drugs under various pH conditions using a simple intubation method: Application to diclofenac. *Br. J. Clin. Pharmacol.* 28:121–124 (1989).
25. R. Menase, P. R. Hedwall, J. Kraetz, C. Pericin. L. Riesterer, A. Sallmann, R. Ziel, and R. Jagnes. Pharmacological properties of diclofenac sodium and its metabolites. *Scand. J. Rheumatol. Suppl.* 22:5–16 (1978).
26. R. L. Oberle and H. Das. Pharmacokinetics of diclofenac sodium (Voltaren) in Yucatan miniswine. *Pharm. Res.* 7:S-237 (1990).
27. M. Hossain, W. Abramowitz, B. J. Watrous, G. J. Szpunar, and J. W. Ayres. Gastrointestinal transit of non-disintegrating, nonerodible oral dosage forms in pig. *Pharm. Res.* 7:1099–1012 (1990).
28. R. L. Oberle, T. S. Chen, C. Lloyd, J. L. Barnett, C. Owyang, J. Meyer, and G. L. Amidon. The influence of interdigestive migrating myoelectric complex on the gastric emptying of liquids. *Gastroenterology* 99:1275–1282 (1990).
29. P. G. Welling. Effect of food on bioavailability of drugs. *Pharm. Int.* 1:14–17 (1980).
30. W. S. Nimmo. Gastric emptying and drug absorption. *Pharm. Int.* 1:221–223 (1980).