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Research Submission

Differential Pharmacokinetics of Diclofenac Potassium for Oral Solution vs Immediate-Release Tablets From a Randomized Trial: Effect of Fed and Fasting Conditions

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Objective.—To compare the pharmacokinetics of, and food effect on, diclofenac potassium delivered as an oral solution vs an immediate-release tablet.

Background.—Diclofenac potassium for oral solution is the only nonsteroidal anti-inflammatory drug approved as monotherapy for the acute treatment of migraine attacks with or without aura in adults 18 years of age or older. It is formulated with potassium bicarbonate as a buffering agent to raise the pH and consequently increase the aqueous solubility of diclofenac in the acidic environment of the stomach following oral administration. The dosage is 50 mg of powdered diclofenac potassium dissolved in 1 to 2 ounces (30 to 60 mL) of water prior to administration, with dosing time in relation to food intake not specified – this was the case for the pivotal efficacy and safety trials in subjects with acute migraine attacks in which the primary endpoints were achieved. For acute treatment of migraine attacks, rapid onset of pain relief is desirable and is likely related to a rapid appearance of an effective concentration of the drug in the systemic circulation. The rate at which an orally administered drug reaches the blood is affected by both its formulation and the presence of food in the stomach. The present study was designed to investigate the pharmacokinetics of 2 formulations of diclofenac potassium, an immediate-release tablet and an oral solution, and to ascertain the effect of food.

Methods.—This was an open-label, randomized, single-center, crossover trial in healthy volunteers. Subjects were randomized using computer-generated list to 1:1:1:1 ratio. They received a single 50-mg dose of diclofenac potassium in 4 sequences (ABCD, BADC, CDBA, and DCAB) during each of the 4 treatment periods. The 4 treatments were: A, oral solution fasting; B, tablet fasting; C, oral solution fed; and D, tablet fed. There was a ≥7-day washout period between dosing. Blood samples for pharmacokinetic analysis were taken for up to 12 hours post-dose and analyzed for diclofenac concentrations. Pharmacokinetic parameters, including peak concentration (C_{max}), time to C_{max} (t_{max}), area under the concentration-time curve (AUC) from time 0 to last measurable concentration (AUC_t), and extrapolation to infinity (AUC_∞) were obtained using non-compartmental analysis. Comparative assessments for C_{max} and AUC were performed between the solution and tablet under fed and fasting conditions and between fed and fasting states for both formulations. *Bioequivalent exposure* was defined as the geometric mean ratio and its 90% confidence interval falling within 80.0-125.0% for C_{max} and AUC. Adverse events (AEs) were monitored throughout the trial.

Results.—Sixty-one percent of the 36 randomized subjects were male, 91.7% were Caucasian, and the mean (standard deviation [SD]) age was 31.9 (7.6) years. Thirty-three (91.7%) subjects completed all 4 treatments.

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***Solution vs Tablet.*—When taken under fed conditions, the oral solution resulted in an approximately 80% faster median t_{max} (0.17 vs 1.25 hours, $P = .00015$) and a 21% lower C_{max} (mean ± SD, ng/mL: 506 ± 305 vs 835 ± 449, $P = .00061$) compared with the tablet. AUC values were similar between the 2 formulations. When taken under fasting conditions, the oral solution exhibited a 50% faster median t_{max} (0.25 vs 0.50 hours, $P = .00035$) to achieve a 77% higher C_{max} (mean ± SD, ng/mL: 1620 ± 538 vs 1160 ± 452, $P = .00032$) compared with the tablet. AUC_t and AUC_∞ were similar between the 2 formulations.**

***Fed vs fasting.*—When taken under fed conditions, the oral solution resulted in a similar median t_{max} (0.17 vs 0.25 hours, $P = .185$) and 64% lower C_{max} (mean ± SD, ng/mL: 506 ± 305 vs 1620 ± 538, $P < .00001$) compared with fasting conditions. In comparison, the tablets under fed conditions resulted in a statistically significantly delayed median t_{max} (1.25 vs 0.50, $P = .00143$) and ~30% lower C_{max} (mean ± SD, ng/mL: 835 ± 449 vs 1160 ± 452, $P = .00377$). AUC values were similar between fed and fasting conditions for both formulations.**

Twelve subjects (33%) experienced ≥1 treatment-emergent AE during the study. All AEs were mild and resolved without treatment; none resulted in study discontinuation. More treatment-emergent AEs were reported in subjects receiving the tablet compared with the solution formulation (20.0% vs 11.8 % in fasting and 17.1% vs 8.6% in fed conditions).

Conclusions.—Diclofenac potassium oral solution and tablet formulations produced statistically significantly different C_{max} and t_{max} but similar AUC under fed and fasting conditions. Fed conditions produced significantly lower C_{max} for both formulations and profoundly delayed t_{max} for the tablet, but had no effect on t_{max} for the solution formulation. These data provide insights into the importance of an earlier and greater exposure to diclofenac arising from the solution formulation than the tablet, which may account for the superiority in the onset and sustained pain reduction for the solution than the tablet formulation observed in the double-blind, efficacy/safety study in migraine patients conducted in Europe.

Key words: diclofenac potassium, liquid formulation, rate of absorption, pharmacokinetics, migraine treatment, nonsteroidal anti-inflammatory medication

Abbreviations: AE adverse event, AUC area under the concentration-time curve, BMI body mass index, C_{max} peak concentration, CNS central nervous system, FDA Food and Drug Administration, GI gastrointestinal, NSAID nonsteroidal anti-inflammatory drug, t_{max} time to peak concentration

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Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that has been in clinical use for many years, particularly for the treatment of inflammatory and degenerative rheumatic diseases, and the pain resulting from minor soft tissue injuries.[1-3] It is also effective in treating other painful non-rheumatic and inflammatory conditions, such as dysmenorrhea and post-operative pain.[4,5] The mechanism of action for its anti-inflammatory, anti-nociceptive, and anti-pyretic effects is not completely understood but likely arises from inhibition of cyclooxygenase, an early component of the arachidonic acid cascade, resulting in reduced formation of prostaglandins, thromboxanes, and prostacyclin.[5]

Diclofenac, either as free acid or potassium and sodium salts, is available in a number of formulations for topical and oral administration.[6-8] Oral formulations of diclofenac include immediate-release and extended-release tablet or capsule formulations.[7-10] Voltaren XR® is an example of an extended-release diclofenac sodium tablet.[7] Immediate-release formulations include Cataflam®,[8] a tablet formulation of diclofenac potassium; Zipsor®,[9] a liquid-filled gel capsule formulation of diclofenac potassium; and Zorvolex®,[10] a capsule formulation of diclofenac free acid. The immediate-release diclofenac products have been used for the treatment of mild-to-moderate pain associated with various conditions including primary dysmenorrhea, osteoarthritis, and bunionectomy.[6-10] The usual daily dose for diclofenac potassium and sodium is 100-200 mg, given in divided doses.

The tolerability profile of diclofenac is well established, as wide experience has been gained with the drug in clinical practice. Approximately 10% of patients treated with diclofenac experience adverse events (AEs) that are usually mild and transient. As with other NSAIDs in its class, gastrointestinal (GI) problems are the most frequent side effects, followed by minor central nervous system (CNS) symptoms, allergic or local reactions, and transient elevations of serum transaminases.[6-10]

Following oral administration, diclofenac is completely absorbed, with an absolute bioavailability (ie, the ratio of area under the concentration-time curve

[AUC] following an oral vs intravenous administration at the same dose) of approximately 60%, independent of formulations and fed or fasting conditions.[6-10] A complete absorption is due to its high permeability throughout the entire intestinal epithelial membrane (from duodenum to colon), as it has a relative high oil-to-water partition coefficient (4.4).[11,12] The less than 100% absolute bioavailability (ie, ~60%) is due to its first pass metabolism by cytochrome P450 2C9.[6-10]

Key differences among various oral formulations are the peak plasma concentration (C_{max}) and time to C_{max} (t_{max}). For example, t_{max} spans from 0.5 hour to 5 hours.[6-10] One critical formulation factor contributing to a rapid t_{max} is diclofenac being in a soluble state prior to oral administration. For example, the t_{max} from the liquid-filled capsule is 0.5 hour whereas the immediate-release tablet is 1.0 hour.[8,9] These data would suggest that a solution formulation may achieve an even quicker t_{max}, thereby a more rapid onset of action.

Diclofenac potassium for oral solution (Cambia®) was developed with such an aim. Although diclofenac had been approved for the treatment of pain arising from various conditions, diclofenac potassium for oral solution is the first diclofenac-containing drug product and the only steroidal anti-inflammatory preparation approved by the Food and Drug Administration (FDA) as a monotherapy for the treatment of migraine in the United States.[13]

Migraine is a chronic, often debilitating disorder, affecting both the central and peripheral nervous systems, characterized by severe head pain and often associated with nausea, photophobia, and phonophobia.[14-18] Many neurogenic factors are involved in the activation of trigeminal nociceptors in the meninges that transmit signals to the trigeminal ganglion and into the pons. This in turn leads to a cascade of events in the brain stem, thalamus, and cortex leading to the headache.[14-18] Dampening or preventing the initial stimulation and the resulting downstream cascade of these events is believed to be critical to achieving rapid and sustained pain relief. To attain this result, the rapid appearance of drug at sufficient levels at the appropriate site of action is critical. This was the driving force behind the development of alternate triptan formulations (eg, subcutaneous injections and nasal spray) that provided more rapid time to peak concentration.[19-21]

The oral solution formulation of diclofenac potassium is packaged as a buffered powder that is dissolved in 30-60 mL of water prior to dosing.[13] We hypothesized that diclofenac potassium buffered powder for solution would provide a more rapid rate of absorption compared with the non-buffered diclofenac potassium in an immediate-release tablet formulation. This is because, as a weak acid, with a pK_a of ~4, diclofenac is largely insoluble in the acidic stomach environment.[12] The buffering agent, potassium bicarbonate, raises the pH of the resulting dosing solution, providing buffering capacity when the solution enters the stomach. This allows diclofenac to be maintained in a soluble state that is optimum for a rapid absorption in the upper small intestine and rapid attainment of C_{max}.[22,23] Furthermore, by delivering diclofenac potassium as a dissolved powder, the oral solution also precludes the time required for a tablet or capsule to disintegrate, disperse, and dissolve in stomach fluids.[24] Thus, compared with a tablet, the oral solution delivers diclofenac potassium in a state that is ready for absorption, resulting in more rapid and consistent absorption compared with tablets.[22-26] This in turn may lead to not only a more rapid onset of effect but also quicker interruption of the migraine cascade that leads to persistent pain.[22-26]

The primary objectives of the trial were to compare the pharmacokinetics of diclofenac potassium in solution to that of a tablet form of the same dose of the medication under fed and fasting conditions, as well as to investigate the effect of food on the pharmacokinetics of both formulations.

DESIGN AND METHODS

Subject Selection.—Healthy male and female subjects (18-45 years old) were selected from the adult population in the general geographic area of the clinical research unit in Quebec, Canada. Women of childbearing potential had to be using a medically acceptable form of birth control for the duration of the study and must have had a negative serum pregnancy test at screening. The key eligibility criteria

include a body mass index (BMI) within the range of 18-30 kg/m^2, normal 12-lead electrocardiogram, and no significant disease or abnormal clinical laboratory values as determined by medical history, physical exam, and laboratory evaluations at screening visits or on admission to the clinical research unit. The study was approved by an Institutional Review Board and written informed consent was obtained prior to screening and conducted in accordance with Good Clinical Practice and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines.

Study Design and Treatments.—This was an open-label, single-center, randomized, 4-way crossover study. Using a computer-generated randomization list, subjects were randomized in a 1:1:1:1 ratio to 1 of 4 treatment sequences (ABCD, BADC, CDBA, or DCAB). The randomization was balanced for sequence (4 sequences) and period (4 periods). The 4 treatments were: A, oral solution 50 mg × 1 fasting; B, tablet 50 mg × 1 fasting; C, oral solution 50 mg × 1 fed; and D, tablet 50 mg × 1 fed. The oral solution 50 mg (lot# CO60123A) and tablet 50 mg (lot# C5J0075) were supplied to the clinical study site by the sponsor. The study was performed in the single clinical research unit (Anapharm, Quebec, Canada) between February 16, 2006 and April 20, 2006. The study conduct, data management, and medical monitoring were provided by Clinical Pharmacology Services, a division of Pharmanet (Kennett Square, PA, USA). The study was not registered at clinicaltrials.gov.

Study Drug Administration.—During each treatment, subjects were confined to the clinical research unit from the day before dosing until 12 hours following dosing on day 1. For the fed conditions, a standard FDA defined high-fat, high-calorie breakfast (ie, ~800-1000 calories; 50% of which is from fat) was used; for the fasting condition, subjects were instructed to avoid food for approximately 10 hours prior to the dosing. Both the oral solution and the tablet were taken with 240 mL of room-temperature water. Under all circumstances, subjects were not allowed any oral fluids for 1 hour post-dose or any food until 4 hours post-dose. There was a 7-day washout period between treatments.

Pharmacokinetic Assessment.—Blood samples (~4 mL) for determination of diclofenac plasma concentrations were obtained pre-dose, and at 5, 10, 15, 20, 30, 40, 50 minutes, and at 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, and 12 hours post-dose. Blood samples were collected in EDTA K_2 tubes and the plasma fraction was separated within 1 hour by centrifugation at 1500 × *g* (~2000 rpm) for 10 minutes at 4-8°C. Plasma samples were kept at –20°C before analysis by a validated high-performance liquid chromatography method coupled with mass spectrometer detector.

Safety Assessment.—Safety was assessed by monitoring AEs, vital signs (blood pressure, respiratory rate, pulse, and oral body temperature), clinical laboratory parameters, and physical examination.

Statistical Methods for Pharmacokinetic and Safety Data Analysis and Determination of Sample Size.—*Pharmacokinetic Parameters and Statistical Methods.*—Pharmacokinetic parameters, including peak plasma concentration (C_{max}) and time to reach C_{max} (t_{max}), AUC and elimination half-life ($t_{1/2}$), were obtained based on individual plasma concentration time data using WinNonlin (version 4.1; Pharsight Incorp., Mountain View, CA, USA).

Pharmacokinetic parameters were summarized using descriptive statistics. A 2-sample 2-tailed *t*-test was used for the comparison of pharmacokinetic parameters between formulations and between fed and fasting conditions for the same formulation. A *P* value of ≤.05 was considered statistically significant with no adjustment for multiple comparisons.

For the bioequivalence assessments, a mixed-effects analysis of covariance model was used with sequence, period, and treatment variables in the model (SAS version 8.2; Cary, NC, USA) for the following treatment pairs: solution vs tablet under fed and fasting conditions, and fed vs fasting for both formulations. For both AUC and C_{max}, point estimates (least squares [LS] mean) for treatment differences as well as the 90% confidence interval (CI) were calculated on the log-transformed data and then exponentiated to provide estimates of, and CI for, the geometric mean ratios. The residual variance from the mixed model was used to calculate the 90% CI for the difference between the treatments under same fed or

Table 1.—Demographic and Other Baseline Characteristics

Demographic	Treatment Sequence ABCD (n = 9)	BADC (n = 9)	CDBA (n = 9)	DCAB (n = 9)	ALL (n = 36)
Age, mean ± SD, years	34.3 ± 8.1	34.2 ± 6.3	30.2 ± 7.2	28.9 ± 8.5	31.9 ± 7.6
BMI (kg/m^2)	26.5 ± 3.2	23.7 ± 1.8	25.6 ± 1.8	23.4 ± 3.0	24.8 ± 2.8
Ethnicity, n (%)					
Not Hispanic or Latino	8 (88.9)	9 (100)	9 (100)	8 (88.9)	34 (94.4)
Hispanic or Latino	1 (11.1)	0	0	1 (11.1)	2 (5.6)
Race, n (%)					
White	8 (88.9)	9 (100)	8 (88.9)	8 (88.9)	33 (91.7)
Other	1 (11.1)	0	0	1 (11.1)	2 (5.6)
Black, or African American	0	0	1 (11.1)	0	1 (11.1)
Gender, n (%)					
Male	6 (66.7)	7 (77.8)	4 (44.4)	5 (55.6)	22 (61.1)
Female	3 (33.3)	2 (22.2)	5 (55.6)	4 (44.4)	14 (38.9)

BMI = body mass index.

fasting conditions and between fed and fasting conditions for the same treatment. *Bioequivalent exposure* was defined as the geometric mean ratio and its 90% CI falling within 80.0-125.0% for both C_{max} and AUC.

Safety Data Analysis.—All safety data were listed for subjects who received ≥1 dose of any study medication. AEs were coded using the MedDRA (version 9). Treatment-emergent AEs (any AEs occurred post the start of study drug administration) and treatment-related (ie, AEs were possibly or probably related to study drug) AEs were summarized by treatment and severity. Other safety parameters were summarized by treatment period using descriptive statistics.

Sample Size Determination.—We expected that the solution and tablet formulations of diclofenac potassium would not be equivalent in the rate (t_{max} and C_{max}) but in the extent (overall AUC) of absorption. Therefore, the trial was powered to detect possible difference in AUC between the 2 formulations. It was expected that a sample size of 33 subjects would provide 80% power to confirm equivalence in AUC between the 2 treatments for a crossover design. The assumptions included an inter-individual coefficent of variation (CV) of 28% in AUC, as previously reported, and the observed geometric mean ratio of AUC within 0.95 and 1.05. A sample of 36 subjects was enrolled to allow for possible early discontinuations.

There were no changes during the course of the study or changes in the planned analyses.

RESULTS

Demographic and Baseline Characteristics.— Thirty-six subjects met the entry criteria and were enrolled into the study; all were randomized to a treatment sequence. Of the 36 subjects, 33 (91.7%) completed all 4 treatments. Subjects 001, 011, and 036 discontinued the study after completing 3 (all 4 but solution fasting), 1 (ie, solution fasting), and 3 (all 4 but tablet fasting) treatments, respectively, due to reasons unrelated to the study drugs. Thirty-five (97%) subjects were included in the pharmacokinetic (PK) and bioequivalence analysis because subject 011 discontinued after completing only 1 treatment period, thus excluded from the pharmacokinetic analysis. All subjects were included in the safety analysis. Detailed demographic and other baseline characteristics are listed in Table 1.

Pharmacokinetics.—Plasma concentrations of diclofenac under both fed and fasting conditions are presented in Figure 1. Pharmacokinetic parameters are presented in Table 2. There are no missing data/variables from subjects who completed ≥2 of the 4 treatments.

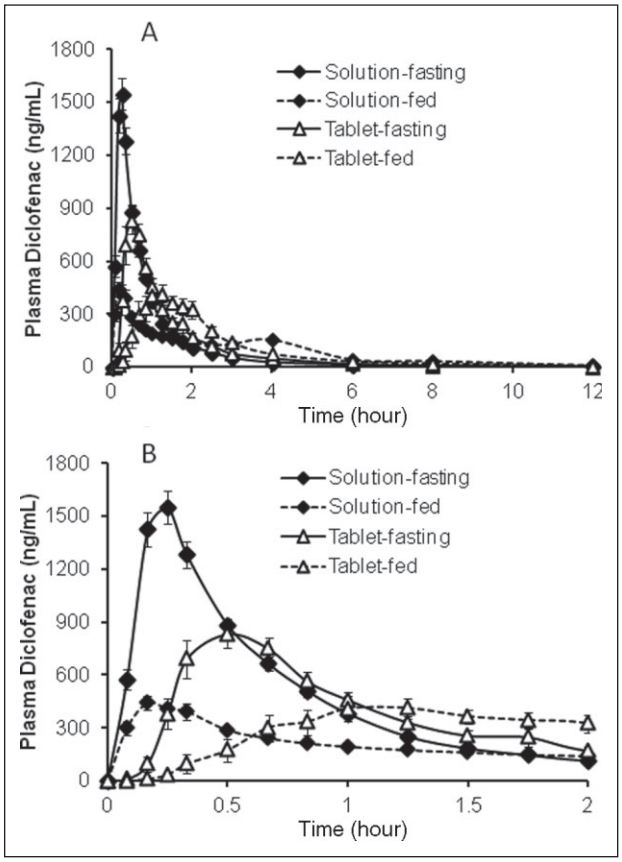

Fig 1.—Plasma concentration (mean ± standard deviation [SD]) of diclofenac following administration of a single oral 50-mg dose as a solution or tablet, under fasting and fed conditions in healthy subjects. (A) 0-12 hours profile. (B) 0-2 hour expanded to show details.

Solution vs Tablet.—When taken under fed conditions, the oral solution resulted in an approximately 80% faster median t_{max} (0.17 vs 1.25 hours; $P = .00015$) and a 21% lower mean C_{max} compared with the tablet (506 vs 835; $P = .00061$). AUC values were similar between the 2 formulations. When taken under fasting conditions, the oral solution exhibited a 50% faster median t_{max} than the tablet (0.25 vs 0.50; $P = .00035$) to achieve a 77% higher mean C_{max} compared with the tablet (1620 vs 1160 ng/mL, $P = .00032$). AUC_t and AUC_∞ were similar between the 2 formulations.

Fed vs Fasting.—When taken under fed conditions, the oral solution resulted in a similar median t_{max} (0.17 vs 0.25 hours; $P = .185$) and 64% lower mean C_{max} (506 vs 1620 ng/mL, $P < .00001$) compared with fasting conditions. In comparison, the tablet resulted in a significantly more delayed median t_{max} (1.25 vs 0.50 hours; $P = .00143$) and ~30% lower mean C_{max} (835 vs 1160 ng/mL, $P = .00377$) under fed conditions when compared with the fasting conditions. AUC values were similar between fed and fasting conditions for both formulations.

The bioequivalence evaluations of C_{max} and AUC_∞ values showed that the geometric mean ratios and 90% CI for the solution-to-tablet comparison were 61% (50.83-72.36) for C_{max} and 104% (98.05-110.55) for AUC_∞ under fed conditions, and 145%

Table 2.—Pharmacokinetics of Diclofenac Following a Single Oral Administration of 50-mg Dose

	Solution Formulation		Tablet Formulation	
Parameters†	Fasting (n = 34)	Fed (n = 35)	Fasting (n = 34)	Fed (n = 35)
t_{max} (hours)	0.25 (0.17-0.67)‡	0.17 (0.08-4.00)‡	0.50 (0.25-4.00)	1.25 (0.33-8.00)§
C_{max} (ng/mL)	1620 ± 538‡	506 ± 305‡§	1160 ± 452	835 ± 449§
AUC_{0-t} (ng·h/mL)	1240 ± 298	1050 ± 250	1080 ± 269	1060 ± 252
$AUC_{0-\infty}$ (ng·h/mL)	1250 ± 306	1080 ± 245	1100 ± 272	1070 ± 258
$t_{1/2}$ (hours)	1.35 ± 0.40	2.15 ± 0.94	1.29 ± 0.37	1.56 ± 0.55

†All parameters were expressed as mean ± SD, except for t_{max} where median (range) were presented. A 2-sample 2-sided t-test was used to test the differences without adjustment for multiple comparisons and a P value of ≤.05 was considered to be statistically significant.
‡Statistically significant difference was observed between the solution and the tablet under the same fed or fasting conditions.
§Statistically significant difference was observed between the fed and fasting conditions for the same formulation (solution or tablet).

Table 3.—Incidence of the Treatment-Related AEs

MedDRA System Organ Class	Solution Formulation		Tablet Formulation	
n (%)	Fasting-Treatment A (n = 34)	Fed-Treatment C (n = 35)	Fasting-Treatment B (n = 35)	Fed-Treatment D (n = 35)
Investigations	2 (5.7)	0	2 (5.7)	2 (5.7)
Red blood cells urine positive	1 (2.9)	0	1 (2.9)	1 (2.9)
Bleeding time prolonged	0	0	1 (2.9)	1 (2.9)
Protein urine positive	1 (2.9)	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	1 (2.9)
Pruritus	0	0	0	1 (2.9)
Vascular disorders	0	0	0	1 (2.9)
Hot flash	0	0	0	1 (2.9)

(121.12-174.48) for C_{max} and 113% (107.10-120.21) for AUC_{∞} under fasting conditions. AUC_t exhibited similar results. The observations were similar for the fed-to-fasting comparison in C_{max} and AUC for either formulation: the geometric mean ratios and 90% CI for the fed-to-fasting comparison were 28% (23.63-33.92) for C_{max} and 88% (82.94-93.75) for AUC_{∞} for the solution and 67% (56.20-80.28) for C_{max} and 97% (91.22-102.26) for AUC_{∞} for the tablet. Based on FDA criteria (ie, the geometric mean ratio and its 90% CI falling within 80.0-125.0%), bioequivalence was achieved for both formulations for AUC values regardless of fed or fasting conditions, but not for C_{max} values under either fed or fasting conditions.

Safety.—All AEs were mild or moderate, and none was serious or resulted in study discontinuation. Of the 36 subjects who received ≥1 dose of the study drug, 12 (33.3%) experienced at least 1 treatment-emergent AE during the study. Treatment-emergent AEs were experienced by 3 subjects (8.6%) following solution fed, 6 subjects (17.2%) following tablet fed, 4 subjects (11.8%) following solution fasting, and 7 subjects (20%) following tablet fasting. Across all treatments, the most commonly reported treatment-emergent AEs (n/%) were i.v. catheter site pain (4/11.1%), presence of red blood cells in urine (3/8.3%), decrease in heart rate (2/5.6%), and prolongation of bleeding time (2/5.6%).

Treatment-related AEs were reported for 4 subjects (11%). These included 2 (5.6%) subjects reported that they "bled longer than usual," which was coded as prolonged bleeding time. However, since coagulation tests were not performed as part of the safety assessments, these observations could not be independently confirmed. Other treatment-related AEs were protein in urine, blood in urine, hot flushes, and pruritus. The summary of treatment-related AEs is provided in Table 3.

DISCUSSION

The objectives of this study were to compare the pharmacokinetics of diclofenac administered as an oral solution formulation and as a tablet formulation, and to determine the effect of the fed and fasting conditions on the pharmacokinetics. Consistent with the literature, we observed no differences in total exposure to diclofenac as measured by AUC (from time 0 to last measurable concentration or to infinity) between the 2 formulations under fed and fasting conditions, suggesting that neither the dosage form nor presence of food in the stomach affects the extent of availability of diclofenac.[6-10]

However, as expected, the solution formulation displayed a 50% shorter time to reach a ~70% higher C_{max} compared with the tablet formulation under fasting conditions. Concentrations as high as ~500 ng/mL of diclofenac in the blood were observed even at 5 minutes post-dose for the solution formulation. In contrast, a similar concentration was observed around 30 minutes post-dose for the tablet formulation. Moreover, a high-fat, high-calorie meal did not

affect the t_{max} for the solution but statistically significantly delayed it for the tablet compared with the fasting conditions. This finding is consistent with data from a study of unbuffered enteric-coated diclofenac sodium tablets.[27] A much-delayed t_{max} was observed following a single-dose, oral administration under fed conditions: 2.5-12 hours under fed conditions vs 1.5-2.8 hours under fasting conditions.[27] Consequently, the bioequivalence analysis in the current study demonstrated that the solution and tablet formulations did not produce equivalent systemic exposures under either fasting or fed conditions, mainly due to a clinically meaningful difference in the peak concentrations; thus, they are not interchangeable.[13]

The higher rate of absorption of diclofenac from the solution than the tablet formulation under fasting conditions observed in the present study is consistent with results from earlier studies, which showed a similar median t_{max} of 10 to 15 minutes observed for the solution as oppose to 46 to 53 minutes observed for the tablet.[25-27] This more rapid rate of absorption of diclofenac from the solution compared with the tablet likely reflects the additional processing required by the tablet before diclofenac can be absorbed through the epithelial membrane of the intestine. Diclofenac must first be liberated from the tablet "package" through being broken down into smaller solid particles by gastric muscle activity, and subsequently dissolve in GI fluids. By virtue of being dissolved in water at the time of administration, the solution bypasses these steps, which in part accounts for faster absorption.

Moreover, potassium bicarbonate in the solution formulation raises the pH of the water into which diclofenac potassium is completely dissolved before dosing. The buffer also helps to retain diclofenac potassium in the solution in the acidic stomach environment following oral administration.[12] Solubility of diclofenac in such a buffered solution may be less susceptible to the change in pH of the GI tract compared with the tablet formulation without such buffering agent.[22,23,25]

It is known that solubility of diclofenac in aqueous medium is affected by the pH of the environment, the formulation itself (eg, solution vs tablet), and the GI tract.[12] The lower the pH such as in the stomach (pH 1-3), the lower the aqueous solubility diclofenac has. As pH increases (ie, becomes more basic as in the small intestine, pH 6.8-7.4 to colon, pH ~7.8), diclofenac becomes more ionized and thereby has a higher solubility. As observed in previous studies, formulation without such buffering agent exhibited a lower and less consistent solubility in the stomach, and thus slower and variable absorption.[22,23,25]

Furthermore, consistent with the role of potassium bicarbonate, previous studies demonstrated that, under fasting conditions, the rate of absorption of diclofenac was fastest for the buffered solution (t_{max}, ~15 minutes), followed by a buffered tablet (t_{max}, ~30 minutes), and then the non-buffered tablet (t_{max}, 60 minutes).[26] This may also partially explain why in the current study the fed condition did not affect t_{max} for the buffered solution but statistically significantly delayed it for the regular tablet.

The association of an earlier plasma peak concentration with an earlier onset of pain relief was observed for sumatriptan. A review of pharmacokinetics and efficacy for sumatriptan subcutaneous injection vs oral tablet showed that the earlier time to peak resulting from the subcutaneous injection was associated in turn with a quicker onset of pain free/relief compared with the tablet formulation.[19,20] Likewise, the more rapid absorption of diclofenac from the solution than from the tablet suggests that the solution may likely provide patients a more rapid onset of pain relief.

Indeed, this was observed in the study by Diener et al,[28] which was a randomized, double-blind, double-dummy, crossover, phase 3 trial conducted in Europe. The trial compared a single dose of 50 mg diclofenac potassium as a solution, tablet, and placebo for the acute treatment of migraine attacks.

The results demonstrated that onset of analgesic effect was 15 minutes for the solution vs 60 minutes for the tablet formulation, which is consistent with t_{max} for the solution (10 minutes, fed and 15 minutes, fasting) vs the tablet (75 minutes, fed and 30 minutes, fasting). Moreover, the phase 3 study[28] showed that the solution was statistically significantly more effective in pain intensity reduction than the tablet between 15 and 90 minutes post-dose. To better

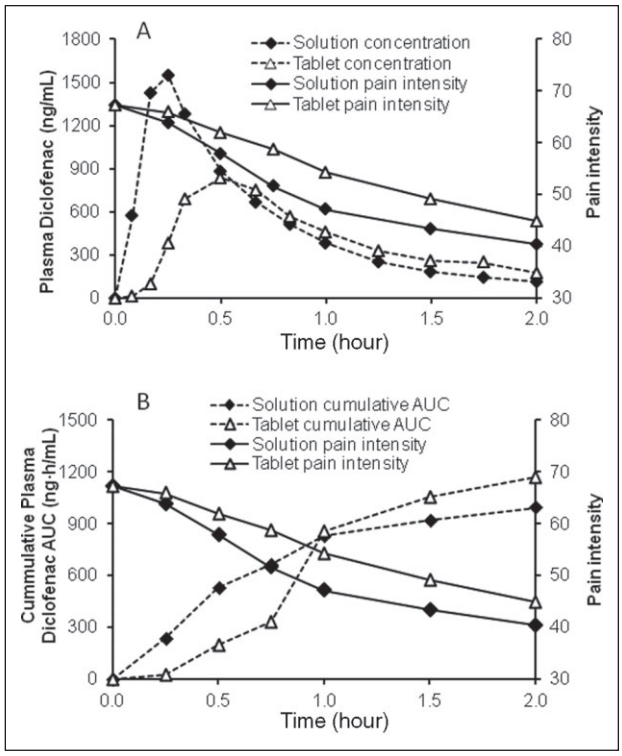

Fig 2.—Relationship between plasma concentration (A) and cumulative AUC (B) vs efficacy measured by change in pain intensity from baseline over time for the oral solution and tablet formulations. Pharmacokinetic data were from the present studies in healthy volunteers under fasting conditions following a single dose of 50 mg diclofenac potassium. The efficacy data were from the phase 3 study comparing the solution vs the tablet formulation for treating a single migraine attack with a 50-mg dose.[28] Note the efficacy data are from a separate study.[28]

understand the pharmacokinetic–pharmacodynamic relationship of diclofenac for the treatment of acute migraine attack, we compared the pharmacokinetic (as concentration or cumulative AUC)–pharmacodynamic (as the reduction of pain intensity) profiles between the solution and the tablet (Fig. 2). However, it is important to note that the pharmacokinetic and pharmacodynamic data are from 2 separate studies. The former were in healthy volunteers, the majority of whom were males, and the latter in migraine patients, the majority of whom were females. Our results demonstrated no sex effect of diclofenac pharmacokinetics for either formulation under both fed and fasting conditions. For example, for the solution formulation under fasting conditions, expressed as mean ± SD (13 females and 22 males) values for AUC: 1322 ± 305 vs 1211 ± 306 (P = .315), C_{max}: 1815 ± 626 vs 1496 ± 450 (P = .094), and t_{max}: 0.28 ± 0.13 vs 0.27 ± 0.09 (P = .817). Moreover, some studies have shown a slower rate of absorption of drugs in migraine compared with non-migraine healthy subjects.[29,30] Yet, it is reasonable to assume that diclofenac concentrations/pharmacokinetics in migraine subjects might not be affected meaningfully by slow GI motility based on the great association between t_{max} in healthy volunteers and onset of analgesic effect in migraine patients for both dosage forms. Aside from absorption, factors that affect metabolism and excretion of diclofenac could have contributed to the difference in pharmacokinetics between the 2 populations. Elimination of diclofenac is mainly mediated via hepatic P450 2C9 metabolism followed by renal elimination. No study has shown altered CYP2C9 or renal function due to migraine. Taken together, pharmacokinetics of both diclofenac formulations under the fed and fasting conditions from the present study likely represent that in migraine subjects.

The pharmacokinetic–pharmacodynamic profiles (Fig. 2) indicated that the difference in pain intensity reduction between the solution and the tablet lagged behind the difference in exposure to diclofenac as concentration (Fig. 2A) or cumulative AUC (Fig. 2B) between the 2 formulations. The apparent lag time between the exposure to diclofenac and efficacy in this case suggests a delay in the equilibrium between the drug in the systemic circulation and at the site of action for migraine pain relief, which is mainly mediated by receptors in the CNS and possibly the meninges as well.[14,19] The sustained superiority in reduction of pain intensity of the solution over the tablet formulation between 15 minutes and 3 hours post-dose may suggest the importance of earlier and sufficiently high drug exposure, as manifested by a shorter t_{max}, higher C_{max}, and higher cumulative AUC during the first hour post-dose reported in the current study. It also implies that a certain triggering point in the exposure to the drug may be required to halt the migraine pain cascade. Once such point is achieved, pain relief may be obtained and sustained thereafter for the remaining time of the 24 hours post-dose.[28]

The solution and the tablet formulations were both well tolerated in the current study. All AEs were mild or moderate, and were consistent with those known for diclofenac. Although the solution formulation had an overall lower incidence of treatment-emergent AEs, given the limited number of subjects exposed to each treatment, no definitive conclusions may be drawn based on this study.

In conclusion, this study demonstrates that compared with the tablet formulation of diclofenac potassium, the buffered solution formulation produces a more rapid absorption as reflected by a much faster time to a higher C_{max}, with a similar overall AUC. Although the presence of food affects the C_{max} of both formulations, t_{max} is less affected for the buffered solution formulation. The solution formulation renders an overall earlier higher exposure to diclofenac, which may be associated with an earlier onset of and sustained pain relief, as well as in the reduction of pain intensity arising from migraine headache.

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