Population Pharmacokinetics of Fast Release Oral Diclofenac in Healthy Volunteers: Relation to Pharmacodynamics in an Experimental Pain Model

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Purpose. Population pharmacokinetics of a fast release diclofenac were assessed with special focus on pharmacodynamic implications.

Methods. In a double blind four-way crossover study, 20 healthy volunteers received orally 50 and 100 mg diclofenac-Na effervescent ("fast-release NSAID"), 50 mg diclofenac tablets ("control"), or placebo. Population pharmacokinetics of the fast release diclofenac were assessed using a nonlinear mixed effects modeling approach (NONMEM). Analgesic effects were investigated by means of an experimental pain model based on both pain-ratings and cortical evoked potentials after specific stimulation of nasal nociceptors with short pulses of gaseous CO_2.

Results. Pharmacokinetics of fast release diclofenac were best described by a two-compartment population model, with an estimated terminal half-life of 1.2 hours. Pharmacokinetics of diclofenac tablets were highly variable and a population pharmacokinetic model could not be obtained. As an indication of an early onset of analgesic effects, 100 mg fast release diclofenac but not the tablets significantly reduced the amplitudes of pain-related evoked potentials at 30 min after administration.

Conclusions. Earlier drug absorption and lower pharmacokinetic variability of the fast-release formulation are likely to be preserved in a population.

KEY WORDS: population pharmacokinetics; pharmacodynamics; drug absorption; double-blind four-way crossover study; diclofenac tablets; diclofenac-Na effervescent.

INTRODUCTION

The onset of analgesic action, its extent and duration are relevant for the treatment of acute mild to moderate pain, which is commonly treated by non-steroidal anti-inflammatory drugs (NSAIDs). Several fast-release oral formulations of NSAIDs have appeared on the market (1,2,3) expecting that the desired rapid onset of analgesic action can be better achieved with fast-release oral NSAIDs than with common tablet formulations. Fast and "normal" release formulations differ by their pharmacokinetics, namely by their time profile of substance liberation. The present study employed a population approach to the pharmacokinetics of a fast release oral NSAID to assess whether a true advantage in the population can be expected from a fast release formulation.

A new diclofenac-Na effervescent formulation as a fast release NSAID was compared to standard diclofenac tablets. To relate pharmacokinetics to pharmacodynamics, analgesic effects were assessed by means of an experimental human pain model. This pain model is based on evoked cortical potentials and pain ratings after specific stimulation (4) of nasal nociceptors with gaseous carbon dioxide (5). This model has been used to quantify the activity of several opioid and non-opioid analgesics (for example, (3,5–8)). To increase the predictive value, the pain model was extended at the occasion of the present investigation by methods of population pharmacokinetics and pharmacokinetic-pharmacodynamic modeling.

MATERIALS AND METHODS

Subjects and Protocol

This was a single-center, 4-way crossover, controlled, double blind, and double-dummy study. It was conducted according to the Declaration of Helsinki on biomedical research involving human subjects (Somerset West amendment). The local ethics committee approved the protocol. Twenty-one subjects were enrolled (11 men, 10 women, between the age of 18 and 45 years (median: 25 years), all within ±20% of their ideal body weight [men: median weight 75 kg, range 56–89 kg; women: median weight 58.5 kg, range 50–68 kg], 5 smokers, 15 non-smokers). At the beginning and at the end of the study the subjects' health was checked by general clinical examination and routine clinical laboratory tests.

After six hours fasting, the subjects received 50 mg or 100 mg Diclofenac-Na effervescent ("fast release"), 50 mg Diclofenac enteric coated tablet ("reference"), or placebo, together with 150 ml water, with an interval of at least six days. Food was not allowed during the observation period of five hours. However, the subjects were allowed to drink at will beverages free of alcohol or caffeine. Subjects remained seated until 70 min after drug intake. Later they were free to move except for periods of 80 to 100 min and 130 to 150 min after drug administration that were required for analgesimetric tests. Five men and five women started the measurements always in the morning, the others in the afternoon.

Reference Compounds, Analytical Procedures, and Plasma Concentrations

Fast-release diclofenac-Na effervescent was provided by Arzneimittelwerk Dresden GmbH, Dresden, Germany. Voltaren® 50, an enteric coated tablet containing 50 mg diclofenac-Na, served as a reference (Novartis Pharma GmbH, Nürnberg, Germany).

Venous blood samples (10 ml) were collected before and 5, 10, 20, 30, 40, 60, 80, 100 min and 2, 2.5, 3, 3.5, 4, and 5

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h after drug administration. After centrifugation at 3500 min^{-1}, plasma was separated and the samples were immediately frozen at −25°C. Diclofenac concentrations were analyzed by high performance liquid chromatography (HPLC) (9). The lower limits of detection and quantification were 4 ng/ml and 10 ng/ml, respectively. The accuracy over the calibration range of 10–2000 ng/ml was 99.5 ± 5%; the mean absolute deviation was 3.8 ± 3.3% (range 0.02–14.73%). If a sample contained a higher diclofenac concentration than the upper limit of the calibration range, it was diluted 1:2 and reanalyzed. Concentrations below the lower limit of quantification were regarded as zero.

Peak plasma concentrations, $C_{max,observed}$, and time to peak, $t_{max,observed}$, were read from the data. The lag-time, $t_{lag,observed}$, was defined as the time prior to the time corresponding to the first measurable (non-zero) concentration. The true lag time, is, however, a time between that time and the time of the first sample that contained diclofenac. To minimize the error produced by the above definition of $t_{lag,observed}$, the hypothesis that the fast release formulation had a shorter lag-time than the tablet was additionally verified by comparing the longest theoretically possible lag time of the fast release (i.e., the time of the first plasma sample with diclofenac > 0) with the shortest possible lag time of the tablets (i.e., the time of the last sample with diclofenac $= 0$). Equality between formulations of the amount absorbed of diclofenac was assessed by comparison of the areas under the plasma concentration versus time curves from drug intake to the time of the last plasma sample, AUC_{0-5h}, calculated using the linear trapezoidal rule for ascending concentrations, and the log-trapezoidal rule for descending concentrations (10). The parameters $t_{max,observed}$, $t_{lag,observed}$, dose normalized $C_{max,observed}$ and dose normalized AUC_{0-5h} were compared between medications by means of Friedman analyses of variance (ANOVA) on ranks, with Student-Newman-Keuls (S-N-K) tests as post-hoc analyses. Non-parametric 90% confidence intervals (11) of the ratios of dose normalized $C_{max,observed}$, and dose normalized AUC_{0-5h} were calculated after administration of 50 and 100 mg diclofenac effervescent ("test"), and 50 mg diclofenac tablets ("reference"). Effects of the hour of administration (morning versus afternoon), gender, or smoking habits on descriptive pharmacokinetic parameters were assessed using Mann-Whitney U-tests.

Population Pharmacokinetics of Fast Release Diclofenac

Population pharmacokinetics of fast release diclofenac were performed with NONMEM (version V, NONMEM Project Group, UCSF, San Francisco, CA, USA, (12)). The complete data set obtained after administration of 50 and 100 mg diclofenac was analyzed in a single step. One-compartment (not shown) and two-compartment models were tested, describing the plasma concentration versus time curves as a sum of exponentials with first order input:

$$C_p(t) = F \cdot Dose \cdot \lfloor \alpha_1 e^{-\lambda_1(t-t_{lag})} + \alpha_2 e^{-\lambda_2(t-t_{lag})} - (\alpha_1 + \alpha_2) e^{-k_a(t-t_{lag})} \rfloor \quad (1)$$

where λ_1 and λ_2 denote the slopes of the exponentially decreasing curve segments, k_a is the absorption rate constant, and α_1/F and α_2/F are the dose corrected intercepts with the ordinate of the back-extrapolated monoexponential decreasing slopes λ_1 and λ_2, and t_{lag} is the lag time between diclofenac ingestion and its appearance in plasma. The bioavailability F was arbitrarily set to 1, since an intravenous component of the study was not employed. Dose proportionality was accounted for by allowing the dose of 100 mg to be multiplied with an additional factor θ, i.e., dose was set to 50 mg when 50 mg were given, and set to $Dose = 100\ mg \cdot \theta$ when 100 mg had been administered.

Inter-individual error terms (η) were assigned in a stepwise fashion to each structural parameter of the pharmacokinetic model. The final model was selected on the basis of the NONMEM objective function, using the χ^2 approximation with the number of degrees of freedom equal to the difference in the number of parameters between two models (α-level 0.05). If by introducing a parameter the NONMEM objective function significantly decreased, this indicated that the fit was improved by the respective parameter, and it therefore remained part of the model. We also examined the quality of the prediction for the population by calculating the median absolute weighted residuals (MDAWR), calculated as (measured − predicted)/predicted, and the mean of the individual absolute weighted residuals (MAWR). The apparent terminal half-life, $t_{1/2,\lambda z}$, was calculated as $\ln(2)/\lambda_2$.

The inter-individual variability was assumed to be log-normally distributed:

$$P_i = \theta_{i,TV} e^{\eta_i}. \quad (2)$$

where P_i is the value of the parameter of the individual, $\theta_{i,TV}$ is the typical value (TV) of this parameter in the population, and η is a variable accounting for the inter-individual variability (IIV), with mean zero and variance ω^2. The residual error ε was also assumed to be log-normally distributed with mean zero and variance σ^2:

$$y = f(\Phi, x) \cdot e^{\varepsilon}, \quad (3)$$

where y is the dependent variable (i.e., plasma concentration), which is a function of known quantity x (i.e., time) and pharmacokinetic parameters ϕ (12). Practically, data were fitted in the log domain and the respective NONMEM statement was Y = LOG(F) + EPS(1). Estimates of variance components (ω^2 and σ^2) from NONMEM were converted into percent coefficients of variation (%CV) of the parameter in the population by taking their square root and multiplying it by 100. Calculations were performed using "first order conditional estimation" method and "η-ε interaction" to reduce the influence of model misspecification.

Linear and nonlinear relations between structural parameters of the pharmacokinetic model and the volunteers' covariates (age, gender, weight, height, lean body mass, body surface area) were assessed using a generalized additive model (13) as described by Minto *et al.* (14). In addition, multiplicative relationships between covariates and pharmacokinetic parameters were tested directly with NONMEM.

Dose proportionality of diclofenac-Na effervescent provided, intraindividual interoccasion variability (IOV) between the two administrations of fast release diclofenac was subsequently modeled according to Karlsson and Sheiner (15). As proposed by these authors an estimate of an inter-individual variability smaller than the intra-individual interoccasion variability was taken as stopping criterion for the introduction of covariates. In this case, only covariates that change between

occasions would markedly contribute to further explanation of parameter variability (15).

Pharmacokinetic Pharmacodynamic Interrelations

Analgesic effects were assessed with an experimental human pain model based on both pain-ratings and cortical potentials after specific (4) stimulation of nasal nociceptors with short pulses of gaseous CO_2. The pain model has been described in detail elsewhere (3,5). In brief, CO_2-stimuli (30 stimuli, strength 65% v/v, duration 200 ms, stimulus rise-time below 20 ms, interstimulus interval approximately 20 s) were applied to the nasal mucosa by means of a device that allows for painful stimulation without concomitant alteration of mechanical or thermal conditions at the mucosa (16). The stimuli produced a sharp stinging pain. Tests of 10 min duration each were performed at baseline and 10, 30, 50, 85 and 135 min after administration of the medication. By means of a visual-analogue scale displayed on a computer monitor subjects estimated within 3–4 s after presentation of each CO_2-stimulus, its intensity relative to a standard stimulus (60% v/v CO_2, intensity defined as 100 Estimation Units (EU)) that was given at the beginning of the first session of each experiment (see insert of Figure 3). For statistical evaluation, the estimates of individual subjects were averaged separately for each session. Subjects were unaware that only one single stimulus concentration had been used, and ratings were made without interaction with the investigator. The EEG was recorded from five positions of the international 10/20 system (Cz, C3, C4, Fz and Pz) referenced to linked earlobes (Fp2 vs. A1 + A2). Stimulus linked EEG-segments of 2048 ms duration were sampled (250 Hz, band pass 0.2–30 Hz, pre-stimulus period 512 ms), and evoked potentials were obtained by averaging these records, separately for each recording position and session.

Based on differences of pain related parameters to baseline, pre-defined indicators of analgesia (5,17) were (i) a post-treatment decrease in pain-ratings, (ii) a post-treatment decrease of amplitudes of evoked potentials (i.e., base-to-peak amplitudes P1, N1, P2 (see insert of Figure 3), and peak-to-peak amplitude P1N1 and N1P2), and (iii) a post-treatment increase of latencies of evoked potentials (i.e., latencies of P1, N1, and P2). Since the study focused on a fast release NSAID, the primary target of data evaluation was the analgesic effect at 30 min after diclofenac intake, the other measurements serving to assess the effect's time profile. Statistics were done with SPSS 8.02 for Windows (SPSS Inc., Chicago, IL, USA; α-level 0.05). The pain-related parameter best suited for PK/PD assessment was identified discriminant analysis (18) and subsequently submitted to analysis of variance for repeated measures (within-subject factor "treatment"), with within-subjects contrasts to placebo as post-hoc analyses (18).

The concentration versus time profile of diclofenac at the effect site $C_{eff}(t)$ was described as a convolution ("*") of the diclofenac plasma concentration versus time profile, $C_p(t)$, and a transfer function $f_{eff}(t) = k_{e0}e^{-k_{e0}t}$:

$$C_{eff}(t) = C_p(t) * f_{,eff}(t), \quad (4)$$

where k_{e0} is the rate constant of the transfer process (19,20). Standard pharmacodynamic models were applied to relate effects to diclofenac effect site concentrations. The final model was selected based on the NONMEM objective function as described above.

RESULTS

Twenty subjects completed the study (10 men, 10 women). One subject was replaced for reasons unrelated to the study medication. The few side effects were two observations of a mild headache, one with 100 mg diclofenac effervescent, one with placebo.

Observed diclofenac plasma concentrations versus time are given in Fig. 1. $t_{lag,observed}$, $t_{max,observed}$, $C_{max,observed}$, AUC_{0-5h}, and the results of statistical comparison of the formulations are summarized in Table 1. Morning versus afternoon administration or the smoking habits produced no significant differences. However, after administration of diclofenac tablets but not of diclofenac-Na effervescent, the AUC_{0-5h} was greater in women than in men (median: 84881 and 73593 ng*min*ml^{-1}, respectively).

Population Pharmacokinetics of Fast Release Diclofenac

The final population pharmacokinetic model was a two-compartment model with interindividual variances assigned to α_2/F and k_a (Table 2, Fig. 2). The population central tendency of the apparent terminal half-life, $t_{1/2,\lambda 2}$, was 1.20 hours (95 CI: 0.96 to 1.60 hours). The subjects' weight was related to α_2/F by a multiplicative model. However, variabilities assigned to α_2/F and k_a were subsequently completely explained by the

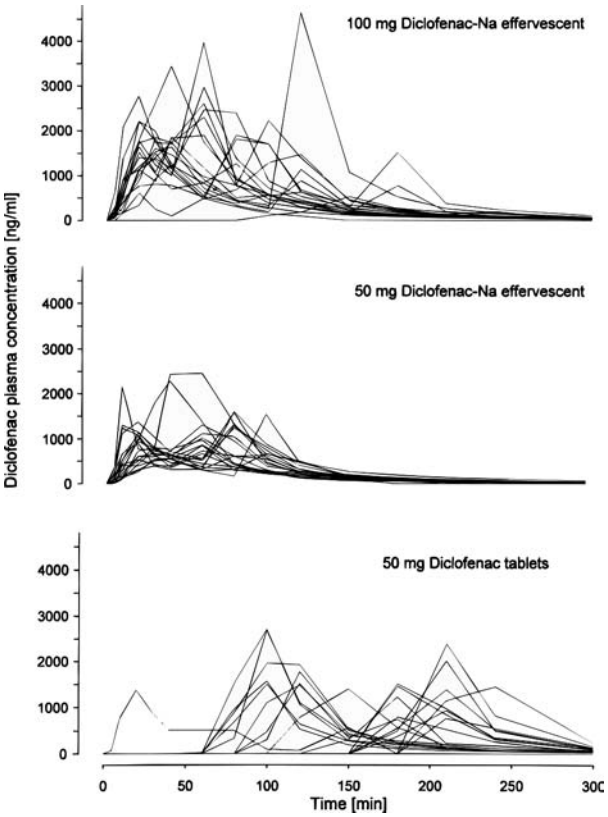

Fig. 1. Observed individual plasma concentrations after oral administration of 50 and 100 mg diclofenac-Na effervescent (fast release) and 50 mg diclofenac enteric coated tablets to 20 healthy volunteers.

Table 1. Descriptive Pharmacokinetic Parameters of Diclofenac After Oral Administration of 50 and 100 mg Diclofenac-Na Effervescent and 50 mg Diclofenac Conventional Tablets

	Diclofenac effervescent		Diclofenac conventional tablets 50 mg	Friedman ANOVA on ranks
	50 mg	100 mg		
$t_{lag,observed}$ [min]	0 (0–5) [5 (5–10)][c]	0 (0–80) [5 (5–100)][c]	110 (0–180) [110 (0–180)][c]	$\chi^2 = 31.7$, $p < 0.001$[a] [$\chi^2 = 28.5$, $p < 0.001$[a,c]]
$t_{max,observed}$ [min]	60 (10–102)	40 (20–150)	165 (20–242)	$\chi^2 = 27.9$, $p < 0.001$[a]
$c_{max,observed}$ [ng/ml]	1128 (628–2455)	2050 (526–4647)	1497 (761–2708)	$\chi^2 = 10.8$, $p = 0.005$[a,b]
Median ratio effervescent/ tablet (90% Cl)[b]; dose normalized	0.75 (0.6–0.86)[b]	0.7 (0.51–0.8)[b]	—	—
$AUC_{trapezoidal,0-5h}$ [ng*min/ml]	83770 (53371–188421)	163307 (31401–222759)	77859 (44417–126048)	not significant[b]
Median ratio effervescent/ tablet (90% Cl)[b]; dose normalized	1.01 (0.89–1.16)[b]	0.97 (0.83–1.04)[b]	—	—

Note: Median (n = 20) and range (or 90% non-parametric confidence intervals of the dose normalized values, where indicated).
[a] Post-hoc Student-Newman-Keuls test after Friedman analysis of variance on ranks (S-N-K test): $p < 0.05$ for each dose of the effervescent formulation versus tablet.
[b] Statistics were done for dose-normalized values.
[c] Lag-time differences were additionally tested by comparing the longest possible lag time of the fast release (i.e., the time of the first plasma sample with diclofenac concentration above the limit of quantification) with the shortest possible lag time of the tablets (i.e., the time of the last sample with diclofenac below the limit of quantification).

Table 2. Parameters of the Population Pharmacokinetic Models for Diclofenac-Na Effervescent as Estimated by NONMEM, with Modeling of Intrasubject Interoccasion Variability (*IOV*)

	Fixed effects: Population central values (and % SEE)	Random effects [%CV]	
		IIV	IOV
α_1/F [ml^{-1}]	48.7 (36%)	—	—
α_2/F [ml^{-1}]	8.22 (36%)	—	45.8
λ_1 [min^{-1}]	0.0266 (11%)	—	—
λ_2 [min^{-1}]	0.00965 (13%)	—	—
k_a [min^{-1}]	0.0482 (11%)	—	28
t_{lag} [min]	3.79 (4%)	—	—
σ^2		Residual Error 46.2	
Objective function		−148.107	
MDAWR		0.349	
MAWR		0.544	

Note: Plasma concentrations were best described by a two-compartment model (Eq. 1). Data were fitted in the log domain. Each model parameter was a candidate for (IOV) and interindividual variability (*IIV*). Whether or not variability remained part of the final model was judged on the basis of goodness-of-fit criteria. The dashes indicate that the respective parameters were tested during model building, but rejected from the final model. The parameters α_1 and α_2 are normalized to a dose of 1 mg. *IIV*: interindividual variability. *%CV*: percent coefficient of variation, calculated as 100 times the square root of the variance of η. This is approximately the %CV of the parameter in the population. The residual error is also given as %CV, calculated as 100 times the square root of σ^2. % *SEE*: percent coefficient of variation of the population parameter estimate, calculated as 100 times the ratio of the standard error of estimate (*SEE*) to the estimated parameter. *MDAWR*: Median absolute weighted residuals. *MAWR*: Mean individual absolute weighted residuals.

intra-individual interoccasion variability (IOV). The inter-individual variability (IIV) was consequently eliminated from the model. Since IOV of α_2/F was greater than IIV, weight was finally eliminated as a covariate since the stopping criterion for covariates proposed by Karlsson and Sheiner (15) was met.

A plot of the measured individual values divided b the predicted typical values for the population (without IOV; Fig. 2, bottom) showed no consistent pattern in terms of overestimation of the plasma concentrations after one diclofenac dose or underestimation after the other dose. This suggests dose-proportionality of the diclofenac-Na effervescent formulation, which was verified by the fact that allowing the dose of 100 mg to be multiplied by a factor did not significantly improve the fit, and the 95% confidence interval of that factor included 1.

Multiple attempts failed to obtain a population fit of the diclofenac plasma concentrations after administration of the diclofenac tablets.

Pharmacokinetic Pharmacodynamic Interrelations

Discriminant analysis identified the amplitude P1 at the frontal recording position Fz to distinguish best between medications (Wilks Lambda 0.899). At 30 min after diclofenac administration, there was a significant effect of the factor "medication" on this parameter in the repeated measures analysis of variance ($F = 3.249$, $p = 0.028$). However, only the highest dose of diclofenac-Na effervescent produced analgesic effects significantly different from placebo (within-subject contrasts: $p = 0.041$; Fig. 3). While a more pronounced reduction of this amplitude after 50 mg diclofenac-Na effervescent as compared to placebo was seen ($p = 0.195$; Fig. 3), the 50 mg tablets had no effect at all ($p = 0.785$). A significant effect of the medication was also found for pain ratings 30 min after drug intake. The highest dose of diclofenac reduced pain ratings most but this was not statistically significant in the post-hoc analysis; however, the

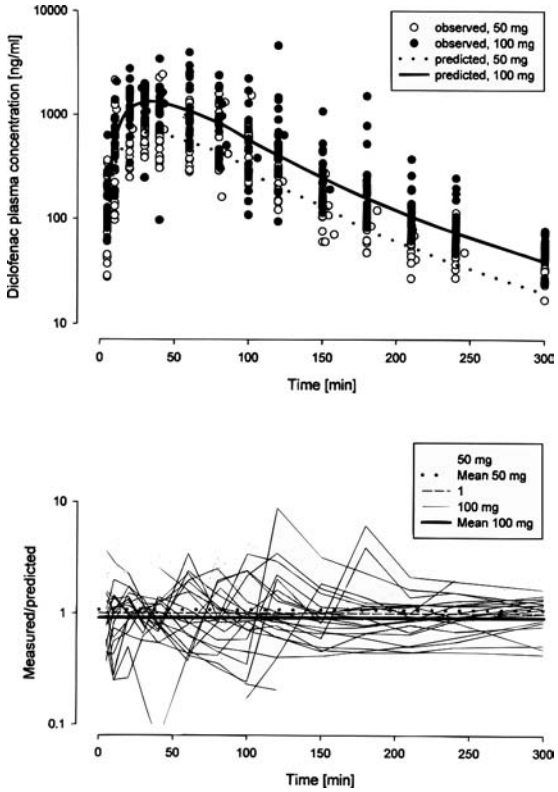

Fig. 2. Population fits of the diclofenac plasma concentrations after oral administration of fast release diclofenac (without intra-individual interoccasion variability). Top: Plasma concentrations of diclofenac after oral administration of 50 (open circles) and 100 mg (closed circles) diclofenac-Na effervescent to 20 healthy volunteers. The thick line shows the plasma concentrations over time of the population central tendency ("typical subject": dotted line: dose = 50 mg, line: dose = 100 mg) as calculated by a two-compartment population pharmacokinetic model. Bottom: Plot of individual measured plasma concentrations divided by the plasma concentration predicted as population central tendency. No consistent pattern arises between the two doses, indicating dose proportionality.

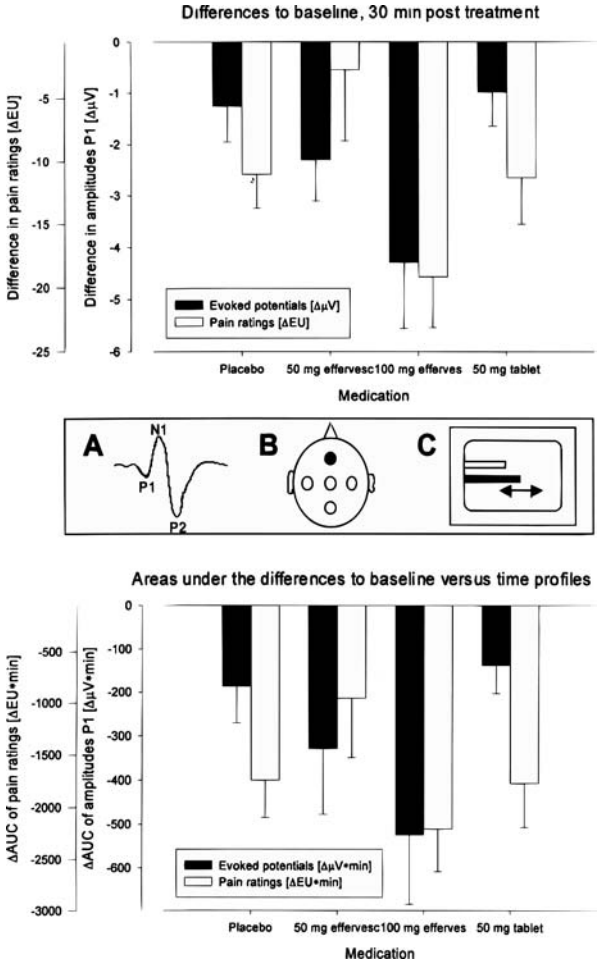

Fig. 3. Effects of the study medication on pain related parameters (means and standard errors): Top: At 30 min after diclofenac intake the amplitude P1 at recording position Fz was significantly reduced by 100 mg diclofenac-Na effervescent. The dose of 50 mg diclofenac effervescent reduced this amplitude not significantly ($p = 0.195$) while 50 mg diclofenac tablets had no effect at all ($p = 0.785$). The dose of 100 mg diclofenac effervescent tendentially reduced the pain ratings at 30 min. However, the lower doses had no statistically significant effect on pain ratings. Bottom: The area under the effect (differences to baseline) versus time curve for the amplitude and for the pain ratings were tendentially, but not statistically significant, reduced by diclofenac effervescent, while the diclofenac tablets had no effect on these pain-related parameters. EU: Estimation units, i.e., arbitrary units measuring the actual length of the computerized visual analog scale used for estimation of pain intensity. Insert: (A) Components of the pain-related evoked potential, (B) recording positions, Fz is marked by a black spot, (C) Intensity estimates on the computer screen.

effect of the lower doses was inconsistent, and the placebo effect was considerable (Fig. 3, top). A tendency toward a dose related reduction of the area under the curve of amplitude P1 versus time curve was seen after administration of diclofenac-Na effervescent (Fig. 3, bottom) but did not reach statistical significance ($F = 2.378$, $p = 0.079$; differences to placebo: 50 mg effervescent: $F = 1.747$, $p = 0.202$, 100 mg effervescent: $F = 9.59$, $p = 0.061$, 50 mg tablet: $F = 0.21$, $p = 0.652$). Similar to the observations at 30 min after drug intake, the AUC under the differences in pain ratings was most reduced by 100 mg diclofenac effervescent (Fig. 3, bottom). However, this effect missed statistical significance ($F = 2.364$, $p = 0.081$).

Based on the statistics, the amplitude P1 at position Fz was chosen as effect measure for PK/PD analysis. Since after administration of placebo no statistically significant difference between the six pain assessments was found, individual placebo values were not further considered in the analysis. For convenience, calculations were done with the amplitude reductions multiplied with -1. Plotting diclofenac plasma concentrations versus the effects observed at the same time, and connecting these points in time order, counterclockwise hysteresis resulted (Fig. 4A). This indicates a time delay between the plasma concentrations of diclofenac and the effect versus time profiles. Due to a large intra- and intersubject variability in the effect data, it was not possible to obtain reliable individual fits. A naive pooled data approach was therefore chosen. Based on the statistics, and to avoid further increase of data noise in the analysis, only the dose of 100 mg diclofenac effervescent was assessed for PK/PD relationship. Individual pharmacokinetic parameters from the population fit with IOV were introduced into the calculations. A log-linear model with slope *m* best

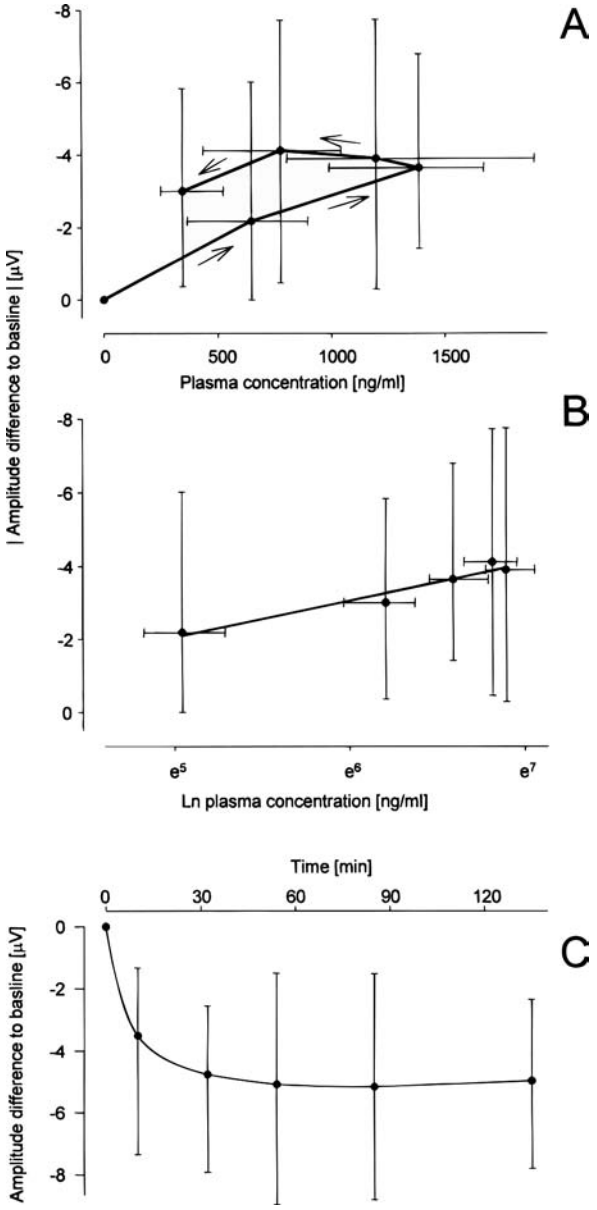

Fig. 4. (A) Counterclockwise hysteresis of the median observed decrease from baseline of amplitude P1 at recording position Fz observed after oral administration of 100 mg diclofenac-Na effervescent versus the median observed diclofenac plasma concentrations. The error bars give the interquartile ranges. (B) Plotting the same effect measure versus the median calculated natural logarithm of diclofenac effect-site concentrations, the hysteresis collapsed. (C) Median and interquartile ranges of observed decreases from baseline of amplitude P1 at recording position after oral administration of 100 mg diclofenac-Na effervescent (dots and error bars) and effects predicted by the pharmacokinetic-pharmacodynamic population model (line). The fit was obtained using a naive-pooled data approach.

described the diclofenac effect site concentration versus effect relationship (see also Eq. 4):

$$Effect(t) = m \cdot \ln(C_p(t) * k_{e0}e^{-k_{e0}(t-t_{lag})}). \quad (5)$$

Estimated parameters were $k_{e0} = 0.079$ min^{-1} (corresponding to a $t_{1/2,ke0}$ of 8.8 min), and $m = 0.74$. The standard errors of estimate were large with 86% and 22% for k_{e0} and m, respectively. When plotting diclofenac concentrations at effect site versus the effects on the amplitude P1 in temporal succession of effect-concentration data pairs, the hysteresis collapsed (Fig. 4B). The effects predicted by the model are given in Fig. 4C.

DISCUSSION

Pharmacokinetic parameters of diclofenac tablets varied much more than that of fast-release diclofenac. Formulations differed most in lag-time and time to peak plasma concentration, while the AUC_{0-5h} were within the accepted limits of bioequivalence (95% CI: 0.8–1.25). A gender difference in AUC_{0-5h} observed with tablets but not with the fast release diclofenac further supported the much higher pharmacokinetic variability of conventional tablets. A lower volume of distribution related to the lower body weight, an augmented bioavailability of the tablets in women, or a different disposition are possible explanations for the larger AUC_{0-5h} in women than in men. Weight had some effects on the pharmacokinetics of diclofenac effervescent as demonstrated in the initial population pharmacokinetics model. However, this was not seen in the trapezoidal AUC_{0-5h} of the effervescent formulation but only with the tablets. In contrast to others (21) we did not observe pharmacokinetic differences related to the time of administration, possibly because of smaller differences in the administration times (6 hours in our study, 12 hours in the study of Mustofa *et al.* (21)).

The inability to obtain a population model for the tablets may indicate that the pharmacokinetic variability with the tablets was so high that it made a population central tendency impossible to find. This was probably owing to the long and highly variable lag time. We did not provide NONMEM with the observed lag times because this would have violated the population approach for the most important parameter. The population central values of other pharmacokinetic parameters appeared to be of minor importance when for the main difference between formulations, i.e., the lag time, no population estimate could be obtained. Since the study's focus was on the fast release diclofenac, more in-depth analysis of the tablet's pharmacokinetics was not performed, for example the application of more sophisticated error models to deal with the lag time problem. The main difference between formulations, i.e., highly variable pharmacokinetics with the tablets, and comparatively predictable pharmacokinetics with the fast release diclofenac, appeared to be sufficiently justified with the present analysis.

The population central tendency of the terminal half-life of 1.2 h agrees with the literature (22). The population model had variances assigned to parameters related to drug input (k_a, α_2/F, the latter likely due to bioavailability). In contrast, variances of parameters related to drug distribution were too small to significantly improve the goodness of fit. Similarly, when introducing IOV, the contribution of the subjects' weight to the explanation of pharmacokinetic variability became unimportant. In other words, IOV after oral administration of diclofenac in an individual subject was higher than the IIV explained by the subjects' weight. The short lag time with the fast release formulation is unlikely to be of clinical relevance. However, by applying goodness-of-fit criteria, it had to remain part of the model.

The effects of diclofenac on evoked potentials were seen in amplitudes P1. This differs from a previous study with the same pain model and a comparable design where the effects of ibuprofen were seen mainly on amplitudes P1N1 (3). However, both amplitudes P1 and P1N1 may be considered as early components of the pain-related evoked potentials. For evoked-potentials after painful stimulation of the tooth-pulp, it had been demonstrated that earlier components of evoked potentials correlated with the physical stimulus intensity, while later components were related to the estimates of pain-intensity (23). In addition, after CO_2-laser stimulation the later amplitude P2 was reported to be most likely associated with pain-related cognitive function (24). The fact that diclofenac influenced an early component of the pain-related evoked potentials thus agrees with the results obtained with ibuprofen (3). So far, amplitudes P1 and P1N1 cannot be functionally distinguished. Studies in progress employing functional imaging and magneto-encephalography may allow for a more specific understanding of the different components of pain-related evoked potentials.

The results support the therapeutic relevance of the pharmacokinetic differences between fast release and conventional oral diclofenac formulations. The results at 30 min after drug administration point toward a faster onset of analgesia with diclofenac-Na effervescent. However, the pharmacodynamic data were noisy, and the error of PK/PD parameter estimate was large. Therefore, the $t_{1/2,ke0}$ value of 8.8 min (k_{e0} = 0.079 min^{-1}) should be understood as an indication of a short delay between pharmacokinetics and pharmacodynamics, without putting too much emphasis on the specific numeric value. This short delay contrasts with other reports of relatively low k_{e0} values for NSAIDs. In a pain model that employs injection of uric acid into the knee joint of rats, the k_{e0} was 0.0008 min^{-1} (25). Species differences or the different natures of the pain models, with a strong inflammatory component of the uric acid model, might have caused these differences. In a human pain model employing evoked potentials and pain ratings after painful dental stimulation (26), k_{e0} values were 0.0045 to 0.018 min^{-1} for ibuprofen, and 0.009 to 0.015 min^{-1} for flurbiprofen. This is already closer to the value reported here. When considering that Suri *et al.* faced a large intrasubject variability in their data and their estimates had been made with the average pharmacokinetic and effect data (26), the estimates from both studies may include a comparable degree of imprecision. A short delay between NSAID pharmacokinetics and pharmacodynamics appears not unrealistic in the light of reports of comparable therapeutic effects of morphine and ketorolac for acute pain treatment (27). In addition, a significant correlation between ibuprofen plasma concentrations and its analgesic effects suggests that differences between plasma and effect site concentrations of an NSAID can be small (28).

The present study showed that a fast release NSAID has advantages over a common tablet formulation. These pharmacokinetic advantages are likely to be preserved in the population. When additionally considering the short delay between pharmacokinetics and pharmacodynamics, it is reasonable to assume that the pharmcokinetic advantages will result in faster onset and better predictability of therapeutic effects.

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