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Pharmacokinetic Analysis of the Absorption Characteristics of Diclofenac Sodium in Man by use of a Multi-segment Absorption Model

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Abstract

The pharmacokinetic analysis of an oral sustained-release preparation of diclofenac sodium has been investigated using multi-segment absorption models in which it has been assumed that the gastrointestinal tract can be divided into several segments in each of which the drug has its own lag-time and absorption rate constants.

Plasma concentration-time data for sustained release diclofenac sodium in man were fitted both by a conventional pharmacokinetic method assuming first-order absorption and by a multi-segment absorption model. The plasma concentration of diclofenac sodium calculated on the basis of the multi-segment absorption model was found to correlate with the observed plasma concentration.

It was concluded that diclofenac sodium data can be better described by a multi-segment absorption model than by a conventional pharmacokinetic model. The results also show that multi-segment absorption models are suitable for pharmacokinetic analysis of plasma drug-concentration data with irregular or multiple peaks in the absorption profiles, and also for the pharmacokinetic analysis of sustained-release preparations.

The kinetics of absorption of drugs are complex and might be affected by rate of disintegration, solubility, excipients and coatings of oral dosage forms. Physicochemical properties, such as variations in drug solubility as a result of changes in pH along different segments of the gastrointestinal tract, might lead to precipitation and redissolution of a drug. Because of these complexities, profiles of plasma concentration against time sometimes exhibit multiple peaks or shoulders. In general, data showing the dependence of plasma-drug concentration on time after oral administration are analysed by compartmental analysis assuming first-order absorption and elimination. It is, however, not appropriate to describe multiple-peak data by conventional compartmental analysis. In recent years discontinuous absorption models have been proposed (Suverkrup 1979; Zimmerman 1983; Kaniwa et al 1986) to characterize plasma concentration data for which absorption processes are irregular. Discontinuous absorption models are, however, not always satisfactory, because sustained-release drugs have both slow and fast release characteristics. Because of this different release pattern several different rates of absorption, lag-time, and fractions might be observed in the gastrointestinal tract. Multifraction absorption models have recently been reported for drugs which give irregular or discontinuous absorption profiles (Murata et al 1987, 1989). The multifraction approach provides a suitable alternative to the analysis of plasma concentrations of drugs which are, after oral administration, absorbed from different segments of gastrointestinal tract with several different rates and lag-times. This study describes the use of a multifraction absorption model of diclofenac sodium given as sustained-release forms to healthy volunteers.

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Materials and Methods

Study design

This study was an open-label, randomized, single dose trial (performed by Ciba-Geigy investigators at Summit, NJ, USA). Twenty healthy adult volunteers participated in the study. The subjects received one 100-mg diclofenac sodium sustained-release tablet after fasting, one 100-mg voltaren sustained-release tablet after a standardized breakfast and one 100-mg diclofenac sodium buffered aqueous solution after fasting. Blood samples (8 mL) were taken at 0, 0·25, 0·5, 0·75, 1, 1·5, 2, 2·5, 3, 3·5, 4, 5, 6, 7, 8, 12, 16 and 24 h after dosing. After the administration of aqueous solution, blood samples were taken at 0, 0·083, 0·166, 0·25, 0·33, 0·5, 0·66, 0·83, 1, 1·25, 1·5, 2, 2·5, 3, 4, 5, 6 and 8 h. The plasma samples for diclofenac sodium were analysed by HPLC (Chan et al 1982). Because multiple peaks were not observed with diclofenac sodium solution and sustained release voltaren given with food, this paper describes and compares solely the pharmacokinetic parameters of a single 100-mg dose of voltaren sustained-release tablets given after fasting.

Pharmacokinetic analysis

Pharmacokinetic parameters were obtained by compartmental analysis. The TOPFIT 2·0 (Heinzel et al 1993) program was used to model plasma concentration-time data assuming first-

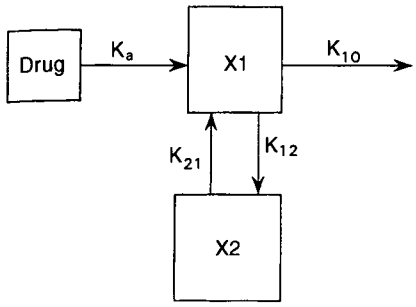

FIG. 1. Standard two-compartment first-order absorption model.

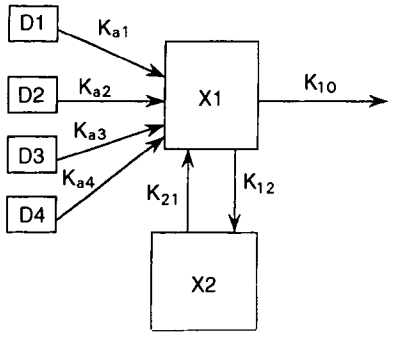

FIG. 2. A four-segment two-compartment first-order absorption model.

order absorption. In the first, conventional pharmacokinetic, approach (Model 1, Fig. 1) a two- or three-compartment model was fitted to plasma concentration-time data. In some subjects data were also weighted by $1/c^2$, where c is the plasma concentration. Decision on the appropriateness of the compartment model was based upon the sum of the residual squares and the Akaike criterion (Yamaokao et al 1978). In the second approach, the same data sets with three or four segments of absorption model and two- or three-compartment model (Model 2, Fig. 2) were fitted. The number of compartments used in both models was identical for a given individual.

Pharmacokinetic parameters were calculated using the equations:

Model 1: conventional pharmacokinetics (two-compartment model)

$$MRT_{abs} = t_{lag} + 1/k_a \quad (1)$$

$$MRT_{disp} = 1/\alpha + 1/\beta - 1/K_{21} \quad (2)$$

$$MRT_{total} = MRT_{disp} + MRT_{abs} \quad (3)$$

where t_{lag} is the lag-time, k_a is the absorption rate constant, α and β are the rate constants for the distribution phase and elimination phase, respectively and K_{21} is the apparent first-order rate constant for the movement of drug from compartment 2 to compartment 1. MRT_{abs}, MRT_{disp} and MRT_{total} are the mean absorption, disposition and total residence times.

Model 2: multi-segment pharmacokinetic model (2-compartment, 4-segment, TOPFIT 2·0; Heinzel et al 1993)

$$MRT_{tabs} = X_1\,(1/K_{00} + t_{lag1}) + X_2\,(1/K_{60} + t_{lag2}) + X_3\,(1/K_{70} + t_{lag3}) + X_4\,(1/K_{80} + t_{lag4}) + 1/K_{01} \quad (4)$$

Where X_1, X_2, X_3 and X_4 are the amounts of drug in different segments of the gastrointestinal tract, K_{00}, K_{60}, K_{70}, K_{80} and K_{01} are rates of absorption in those different segments, and t_{lag1}, t_{lag2}, t_{lag3} and t_{lag4} are the lag-times in the different compartments.

$$MRT_{disp} = 1/\alpha + 1/\beta - 1/K_{21} \quad (5)$$

$$MRT_{total} = MRT_{disp} + MRT_{abs} \quad (6)$$

The pharmacokinetic parameters for both models (two-compartment model) were calculated using the equations:

$$\text{Half-life} = 0{\cdot}693/\beta \quad (7)$$

$$AUC_{model} = \text{Dose}/(K_{10} \times V_C) \quad (8)$$

where AUC_{model} is the area under the plot of plasma concentration against time, K_{10} is the apparent first-order elimination rate constant from the central compartment and V_C is the volume of the central compartment,

$$\text{Oral clearance } CL/F = \text{Dose}/AUC_{model} \quad (9)$$

$$V_C/(F) = \text{Dose}/C_0 \quad (10)$$

$$V_t/F = V_c/F \times K_{12}/K_{21} \quad (11)$$

where CL is clearance, F is bioavailability, C_0 is initial concentration, V_t is the volume of the tissue compartment, K_{12} is the apparent first-order rate constant for the movement of drug from compartment 1 to compartment 2, and K_{21} is defined under equation 3.

$$\text{Volume of distribution at steady state } Vd_{ss} = V_t + V_c \quad (12)$$

Results

Plots of plasma concentration against time for diclofenac after oral administration were analysed both by a conventional pharmacokinetic method assuming a single first-order absorption rate with a lag-time and by a multi-segment method where absorption takes place from different segments of the gastrointestinal tract and with multiple lag-times. Figs 3 and 4 show the fits obtained by the two methods and Table 1 lists the different pharmacokinetic parameters calculated by use of the

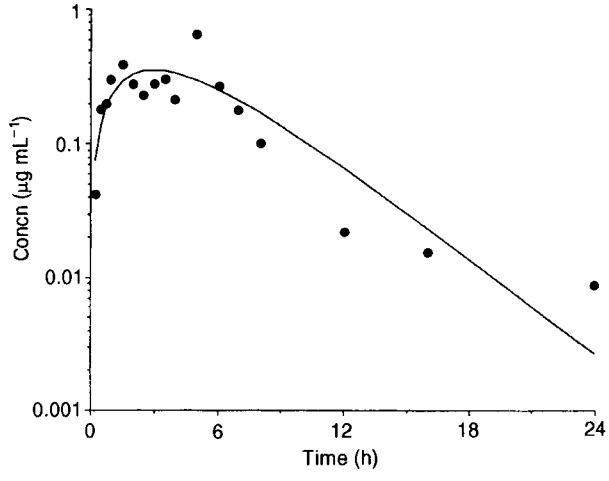

FIG. 3. Plasma concentration–time profile of diclofenac sodium for a typical subject fitted to a conventional pharmacokinetic model.

Table 1. Pharmacokinetic parameters (mean ± s.d.) of diclofenac sodium using conventional pharmacokinetics and a multi-segment absorption model.

Parameter	Conventional pharmacokinetics	Multi-segment model*
Absorption rate constant (h^{-1})	0·192 ± 0·127	0·370 ± 0·292
Half-life (h)	6·69 ± 6·47	4·13 ± 4·46
CL/F (mL min^{-1})	593·45 ± 178·44	627·25 ± 134·98
Area under the plasma concentration-time curve (μg h mL^{-1})	3·05 ± 0·92	2·77 ± 0·59
K_a (h^{-1})	2·70 ± 4·10	-
Rate of absorption from segment 00 (h^{-1})	-	44·7 ± 166·6 (2·24 ± 4·8)
Rate of absorption from segment 60 (h^{-1})	-	67·1 ± 151·9 (6·3 ± 10·7)
Rate of absorption from segment 70 (h^{-1})	-	75·4 ± 216·7 (7·0 ± 11·1)
Rate of absorption from segment 80 (h^{-1})	-	4·81 ± 8·72
Mean disposition residence time (h)	8·02 ± 8·23	2·28 ± 2·23
Mean absorption residence time (h)	2·85 ± 1·83	6·84 ± 6·45
(Volume of the central compartment)/F (L)	96·1 ± 85·5	11·58 ± 11·36
(Volume of distribution at steady state)/F (L)	221·8 ± 217·0	84·34 ± 92·35
Lag-time (h)	0·65 ± 0·74	-
Lag-time 1 (h)	-	0·28 ± 0·39
Lag-time 2 (h)	-	1·4 ± 0·90
Lag-time 3 (h)	-	3·72 ± 1·75
Lag-time 4 (h)	-	4·85 ± 2·37
Akaike criterion	−19·0 ± 17·2	−63·92 ± 22·59
Sum of the residual squares	0·32 ± 0·80	0·012 ± 0·04
Correlation coefficient (r)	0·85 ± 0·085	0·996 ± 0·004

*Numbers in parentheses are after deleting outliers (three values for rate of absorption from segment 00, four values for rate of absorption from segment 60 and two values for rate of absorption from segment 70).

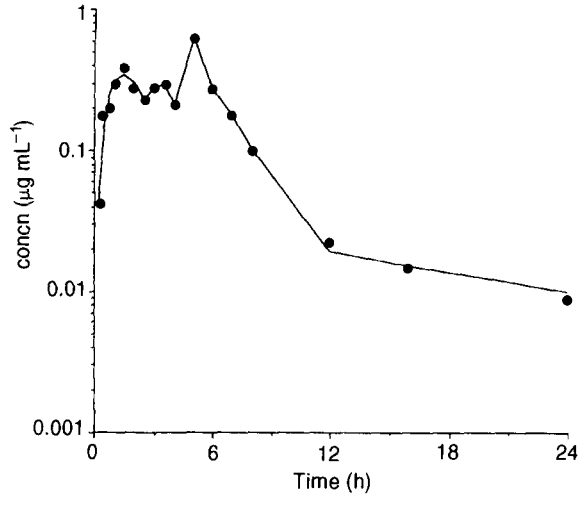

FIG. 4. Plasma concentration–time profile of diclofenac sodium for the same subject fitted to a multi-segment pharmacokinetic model.

two approaches. There were marked differences in the plasma concentration-time profiles for the different subjects and the time to reach maximum plasma concentrations varied from 2 to 5 h in the majority of the subjects. The number of peaks varied, furthermore, from subject to subject. Three peaks were observed for eleven subjects and four peaks for nine subjects. Drug was absorbed with different rate constants and different lag-times from the gastrointestinal tract. The absorption rate constants from different segments of gastrointestinal tract were extremely variable. In some of the subjects absorption from a particular segment seemed to take hundreds of hours. Attempts to minimize some of these rate constants by the addition or deletion of one segment did not improve the fit as judged by the sum of the residual squares and the Akaike criterion. When the absorption rate constant values in some subjects (considered as outliers) were excluded for the calculation of mean value, however, reasonable absorption rate constants were observed from different segments of the gastrointestinal tract (Table 1). There were significant differences among values obtained for mean absorption and disposition residence times (MRT_{abs} and MRT_{disp}), volume of distribution of the central compartment (V_C) and the volume of distribution at steady state (Vd_{SS}), the correlation-coefficient (r^2), the Akaike criterion and the sum of the residual squares, but no statistical difference was found for elimination half-life, oral clearance and the area under the curve (AUC) for the two methods of fitting. The fitting criteria sum of the residual squares, r^2, and the Aikaike criterion were significantly lower for the multi-segment absorption model than for conventional pharmacokinetic modelling.

Discussion

The atypical plasma concentration-time patterns seen in this study occur frequently. Multiple peaks have been observed with cimetidine (Funaki et al 1988), penicillamine (Bergstrom et al 1981), diltiazem (Murata & Noda 1993) and sulphisoxazole and allopurinol (Murata et al 1987). There are many reasons for a drug to exhibit multiple peaks after oral administration. One explanation might be enterohepatic recirculation, but in this circumstance the appearance of the peak might be independent of route of administration. Because the curves representing intravenous administration of diclofenac (Willis et al 1979) and oral administration with food did not exhibit multiple peaks, it can be assumed that the occurrence of multiple peaks is not a consequence of enterohepatic recirculation but a result of the absorption of diclofenac sodium from different segments of the gastrointestinal tract.

It is, therefore, concluded that multi-segment absorption models are suitable for pharmacokinetic analysis of plasma-drug concentration data with irregular or multiple-peak

absorption profiles, and also for the analysis of sustained-release preparations. This approach is useful for comparing the absorption profiles of different sustained-release formulations. Such a model is also useful for prediction of plasma concentrations after multiple oral administration and for the design of suitable dosage regimens for drugs which give multiple peaks.

Acknowledgement

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