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Prediction of Changes in the Clinical Pharmacokinetics of Basic Drugs on the Basis of Octanol–Water Partition Coefficients

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Abstract

A physiologically based pharmacokinetic model for basic drugs has been established on the basis of octanol–water partition coefficients of the non-ionized, unbound drugs (P_{oct}).

The parameters for the physiological model in man were estimated from a regression equation obtained for the relationships between the P_{oct} and the tissue-plasma partition coefficient, the hepatic intrinsic clearance ($CL_{int,h}$) and the blood-to-plasma concentration ratio in rabbits. The plasma concentrations observed after intravenous administration of ten basic drugs (3·2 mg kg^{-1}) to rabbits agreed with the levels predicted using the physiological model ($r = 0{\cdot}710$–$0{\cdot}980$). In man, the predicted plasma concentrations of basic drugs were in good agreement with reported values ($r = 0{\cdot}729$–$0{\cdot}973$), except for diazepam and pentazocine. Variations in plasma and brain-concentration profiles of clomipramine and nitrazepam in various disease states were simulated using the model. We assumed that the changes in unbound fraction of drug in serum (f_p), $CL_{int,h}$ and the hepatic blood flow rate were from 0·25- to 4-fold that of the control and that fat volume changed by 0·2- to 5-fold. With regard to changes in f_p, we predicted that the brain–plasma concentration ratio of clomipramine was 1·5- to 25-fold that of the control 24 h after intravenous administration, although the variations in the plasma concentration–time profiles were less marked.

Plasma concentrations predicted for several basic drugs were in good agreement with reported values and this physiological model could be useful for predicting drug-disposition kinetics in man.

Physiologically based pharmacokinetic models can be used clinically to predict changes in disposition kinetics in various disease states. Many reports have described variations in pharmacokinetic parameters such as the unbound fraction of drug in serum (f_p), hepatic flow (Q_{Liv}), total body clearance (CL_{tot}) and fat volume in various disease states (Stenson et al 1971; Sotaniemi et al 1977; Piafsky 1980; Barry et al 1990). There is a need for a physiological model which can be used to determine the pharmacokinetic parameters of drugs. However, much time-consuming effort is required to obtain the parameters needed to design a physiological model for each drug. It is extremely difficult to determine drug concentrations in tissues in man. Therefore, it is useful to predict the disposition kinetics in man by means of the animal scale-up method using values calculated using a physiological model (Ichimura et al 1984; Sawada et al 1985a; Nakashima et al 1987).

We reported a good correlation between the octanol–water partition coefficient (P_{oct}) and the tissue-to-plasma concentration ratio of an unbound drug (K_{pu}) (Yokogawa et al 1990), the red-blood-cell-to-plasma partition coefficient (D) and the hepatic intrinsic clearance ($CL_{int,h}$) (Ishizaki et al 1997) for ten basic drugs in rabbits, and regression equations were obtained.

The purpose of this study is to estimate pharmacokinetic parameters in man by substituting the P_{oct} values of the drugs into regression equations obtained from studies with rabbits and to predict changes in the disposition kinetics for basic drugs in various disease states using the physiological model.

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Materials and Methods

Materials

Biperiden, haloperidol (Dainippon, Osaka, Japan), chlorpromazine, clotiazepam (Yoshitomi, Osaka, Japan), clomipramine (Ciba Geigy, Japan), diazepam (Takeda, Osaka, Japan), nitrazepam, promethazine (Shionogi, Osaka, Japan), trihexyphenidyl (Nippon Lederle, Japan), and pentazocine (Sankyo, Tokyo, Japan) were used as supplied. Other chemicals were of reagent grade and used without purification.

Animal experiments

Experiments were performed on adult male albino rabbits, $2{\cdot}1 \pm 0{\cdot}2$ kg (mean ± s.d.), essentially as described elsewhere (Nakashima et al 1987). Briefly, the femoral artery was cannulated with polyethylene tubing, under light anaesthesia. Each drug (3·2 mg kg^{-1}) was dissolved in saline and injected over 1 min into the rabbits via the ear vein. To determine plasma concentrations, blood samples were withdrawn from the femoral artery through the cannula at designated time intervals after drug administration and collected in heparinized tubes. The plasma was separated by centrifugation and stored at −30°C until assay.

Assay for drugs

Drug concentrations in plasma were determined by gas chromatography as described elsewhere (Nakashima et al 1987). Briefly, a gas chromatograph (GC-7A, Shimadzu, Kyoto, Japan) was equipped with a nitrogen-phosphorus detector (NPD; FTD-8, Shimadzu) and a 25 m × 0·24 mm i.d. ULBON R HR-52 (Sinwa Kako, Japan) flexible fused silica capillary column silanized and coated with a solution of SE-52.

Pharmacokinetic analysis

Prediction on the basis of physiological pharmacokinetics using differential equations was performed using a programme described elsewhere (Nakashima et al 1987). The concentration–time courses of each drug in plasma and tissues were analysed using a computer program (PPMODELS; Matsushita et al 1996) with NeXTSTEP 3·0 J based on the physiological model. The physiological parameters for rabbits and man were as reported elsewhere (Ichimura et al 1984).

Data analysis

The fit between the observed (C_{obs}) and the predicted (C_{pred}) concentrations of each drug was measured on the basis of the coefficient of determination, r^2, calculated from the equation:

$$r^2 = 1 - \sum dev^2/Sy^2$$

where $Sy^2 = \sum Y_{obs}^2 - \sum(Y_{obs})^2/n$, $dev^2 = (Y_{obs} - Y_{calc})^2$ and n is the number of determinations. In this calculation, the logarithmic values of C_{obs} and C_{pred} were used as Y_{obs} and Y_{calc} (Tsuji et al 1985).

Results

Predicting pharmacokinetic parameters for use in the physiological model in man

The parameters necessary for calculating plasma and tissue concentration–time courses using this physiological model are K_p, RBP (the blood-to-plasma concentration ratio) and $CL_{int,h}$. We have already reported the determination of these parameters in rabbits from the lipophilicity of basic drugs (Yokogawa et al 1990; Ishizaki et al 1997). These parameters were predicted for man on the basis of studies on the rabbit.

Calculation of drug K_p for various tissues

The pK_a and the P_{oct} of the basic drugs examined are shown in Table 1.

In our previous report (Yokogawa et al 1990), good correlation was obtained, in each tissue in rabbits, between P_{oct} and the tissue-to-plasma concentration-ratio (K_{pu}) for the unbound drug; the following regression equation was obtained.

$$K_{pu} - (1/f_{ui}) = \alpha P_{oct}^{\beta} \quad (1)$$

Table 1. Physicochemical properties of the ten basic drugs.

Drug	pK_a	Logarithm of the octanol–water partition coefficient of the non-ionized form of the drug*
Pentazocine	8·5	3·31
Nitrazepam	3·4	2·21
Haloperidol	7·8	3·23
Biperiden	8·8	4·25
Diazepam	3·5	2·99
Promethazine	9·1	4·81
Trihexyphenidyl	8·7	4·49
Chlorpromazine	9·3	5·19
Clotiazepam	3·6	3·49
Clomipramine	8·5	4·71

*Values were measured at pH 7·4 and 37°C.

where f_{ui} is the fraction of the non-ionized form of the free drug in the intracellular space (pH 7·0), β is the slope of the logarithmic plot and α is the value of $K_{pu} - (1/f_{ui})$ when P_{oct} is 1. The tissue K_{pu} values for ten basic drugs were estimated by substituting the α, β, and f_{ui} values listed in Table 2, into equation 1. The K_p values of each drug were obtained by multiplying the K_{pu} values by the f_p value for man (Table 3).

Table 2. Allometric parameters required to describe the tissue distribution of basic drugs on the basis of their octanol–water partition coefficients using equation 1.

Tissue	α	β	r
Lung	0·031	1·236	0·969
Brain	0·062	0·984	0·987
Heart	0·032	1·098	0·976
Kidney	0·075	1·037	0·965
Liver	0·064	0·884	0·971
Gut	0·058	1·020	0·985
Muscle	0·099	0·889	0·973
Fat	0·016	1·255	0·965
Skin	0·058	0·927	0·964
Bone	0·036	0·947	0·960

Values (except for kidney and liver, which were determined in this work) were obtained from Yokogawa et al (1990).

Table 3. Pharmacokinetic parameters of ten basic drugs.

Drug body clearance (min^{-1} kg^{-1})	Rabbit	Man		
	Unbound fraction of drug in serum[a]	Unbound fraction of drug in serum	Blood-to-plasma concentration ratio[b]	Total body clearance (mL min^{-1} kg^{-1})
Pentazocine	0·40	0·389[c]	0·776	13·0[l]
Nitrazepam	0·17	0·135[d]	0·641	1·41[m]
Haloperidol	0·23	0·125[e]	0·785	6·17[n]
Biperiden	0·39	0·097[f]	0·789	11·6[o]
Diazepam	0·091	0·032[g]	0·674	0·38[i]
Promethazine	0·22	0·23[h]	1·56	15·7[p]
Trihexyphenidyl	0·37	–	–	–
Chlorpromazine	0·095	0·035[i]	0·779	8·6[p]
Clotiazepam	0·03	0·01[j]	0·668	3·0[q]
Clomipramine	0·067	0·03[k]	0·947	10·8[r]

[a]Yokogawa et al (1990). [b]Calculated by equations 2, 3. [c]Sawada et al (1984). [d]Rieder & Wendt (1973). [e]Holley et al (1983). [f]Nakashima et al (1987). [g]Klotz & Reimann (1984). [h]DiGregorio & Ruch (1980). [i]Benet et al (1995). [j]Arendt et al (1982). [k]Arky (1996). [l]Ichimura et al (1984). [m]Ochs et al (1983). [n]Chang et al (1992). [o]Grimaldi et al (1986). [p]Taylor et al (1983). [q]Ochs et al (1984). [r]Evans et al (1980).

Calculation of the blood-to-plasma concentration ratio for drugs

In our previous report (Ishizaki et al 1997), log D_{fu} in rabbits correlated well with log P_{oct}, and the following regression equation was obtained:

$$D_{fu} = 0{\cdot}0108\, P_{oct}^{0{\cdot}970} \quad (2)$$

The D_{fu} of each drug was estimated by substituting P_{oct} into equation 2, and RBP was estimated by substituting the hematocrit (H_t, 0·45; Tsuji et al 1985), f_p for man and the value of f_u into equation 3. The results are shown in Table 3.

$$RBP = 1 + H_t\,(D_{fu} f_p f_u - 1) \quad (3)$$

Calculating $CL_{int,h}$ for the drug

In our previous report (Ishizaki et al 1997), log $CL_{int,h,fu}$ in rabbits correlated well with log P_{oct} and the following regression equation was obtained:

$$CL_{int,h,fu(rabbit)} = 0{\cdot}0875\, P_{oct}^{1{\cdot}338} \quad (4)$$

$CL_{int,h,fu}$ for each drug in man ($CL_{int,h,fu(man)}$) was estimated from Q_{Liv} and CL_{tot}. Q_{Liv} was 23·8 mL min^{-1} kg^{-1} (Ichimura et al 1984); the values of CL_{tot} used are listed in Table 3. The relationship between the $CL_{int,h,fu}$ values for rabbit and man is shown in Fig. 1. The correlation coefficient was high (r = 0·951) and the following regression equation was obtained:

$$CL_{int,h,fu(man)} = 0{\cdot}376\, CL_{int,h,fu(rabbit)}^{0{\cdot}785} \quad (5)$$

The regression equation (equation 6) between $CL_{int,h,fu}$ and P_{oct} for man was obtained by substituting equation 4 into equation 5.

$$CL_{int,h,fu(man)} = 0{\cdot}0555\, P_{oct}^{1{\cdot}05} \quad (6)$$

$CL_{int,h,fu(man)}$ was estimated from the P_{oct} of each drug by use of equation 6, and $CL_{int,h,f}$ for man was calculated by multiplying the value by f_u and f_p.

Prediction of the plasma concentration time-course by use of the physiological model in rabbits

The pharmacokinetic parameters required to establish the physiological model for the rabbit were estimated using equations 1–4. The values used for rabbit f_p were the observed values shown in Table 3. Fig. 2 shows the predicted and observed plasma concentration-profiles as a function of time after intravenous bolus injection of the ten basic drugs at a dose of 3·2 mg kg^{-1} into rabbits. There was good agreement between the predictions of the model and the observed concentrations of each drug in plasma.

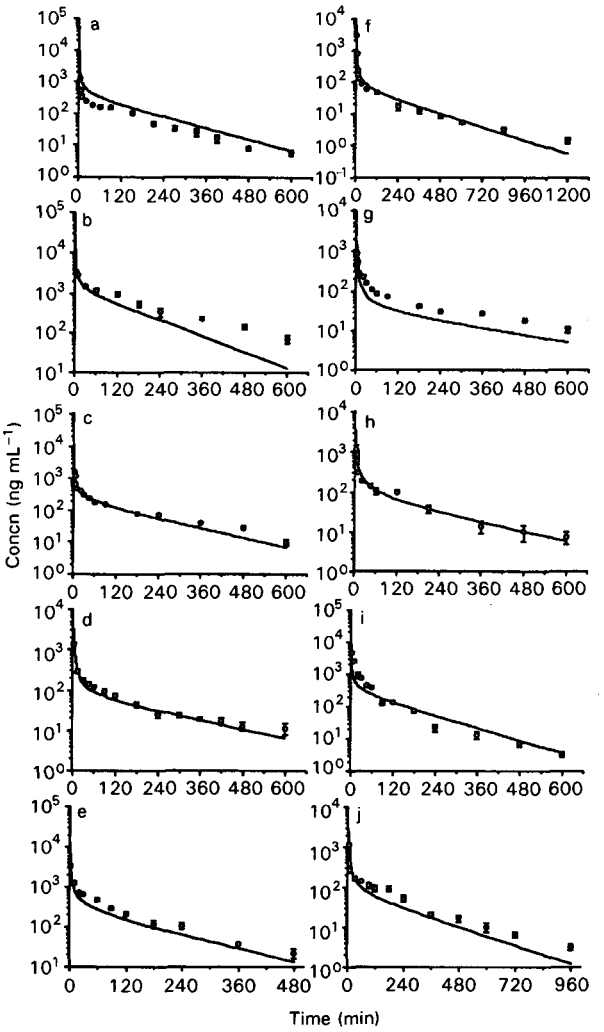

FIG. 2. Plasma concentrations predicted by the model (—) and those observed (○) after intravenous administration of drugs (3·2 mg kg^{-1}) to rabbits. a. Pentazocine, r = 0·886; b. nitrazepam, r = 0·710; c. haloperidol, r = 0·980; d. biperiden, r = 0·951; e. diazepam, r = 0·955; f. promethazine, r = 0·978; g. trihexyphenidyl, r = 0·878; h. chlorpromazine, r = 0·979; i. clotiazepam, r = 0·963; j. clomipramine, r = 0·923. Each data point represents the mean ± s.e.m. of results from three rabbits.

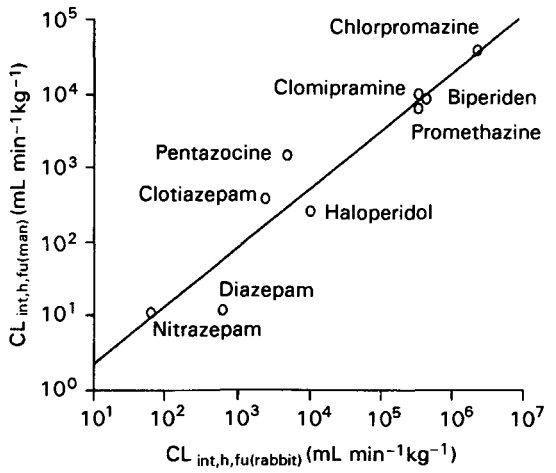

FIG. 1. Relationship between hepatic intrinsic clearance of the non-ionized unbound drugs ($CL_{int,h,fu}$) in rabbits and man; r = 0·951.

Prediction of the plasma concentration time-course by use of the physiological model in man

The pharmacokinetic parameters required to establish the physiological model for man were estimated using equations 1–3 and 6. The f_p values for man were the observed values shown in Table 3. Fig. 3 shows the predicted and reported plasma concentration profiles as a function of time after intravenous bolus injection of eight basic drugs in man. Except for diazepam and pentazocine there was good agreement

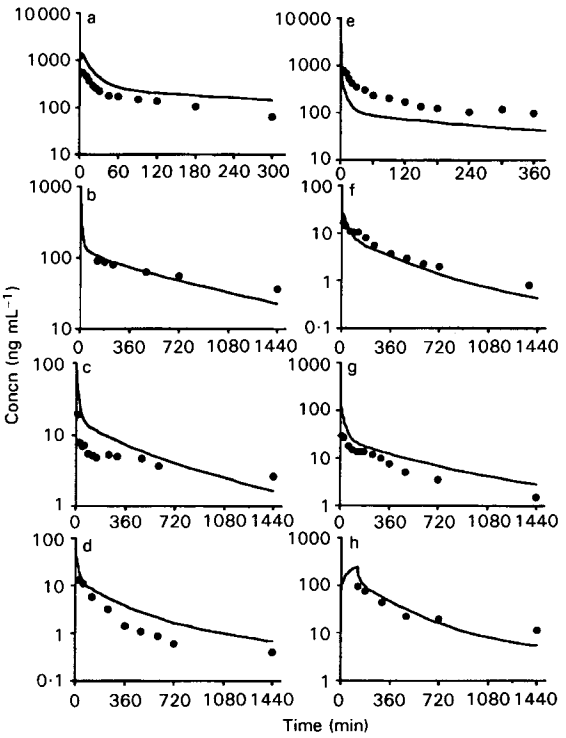

FIG. 3. Plasma concentrations predicted by the model (—) and those observed (●) after intravenous administration of basic drugs to man. a. Pentazocine (1 mg kg^{-1}; Yamamoto et al (1978)); b. nitrazepam (0·159 mg kg^{-1}, r = 0·831; Rieder & Wendt (1973)); c. haloperidol (0·0522 mg kg^{-1}, r = 0·705; Cheng et al (1987)); d. biperiden (0·043 mg kg^{-1}, r = 0·809; Grimaldi et al (1986)); e. diazepam (0·15 mg kg^{-1}; Greenblatt et al (1989)); f. promethazine (0·173 mg kg^{-1}, r = 0·973; Taylor et al (1983)); g. chlorpromazine (0·156 mg kg^{-1}, r = 0·729; Midha et al (1981)); h. clomipramine (0·746 mg kg^{-1}, 2 h infusion, r = 0·798; Evans et al (1980)).

(r > 0·705) between the predictions of the model and the observed concentrations of each drug in plasma.

Prediction of changes in clinical disposition kinetics in disease states using the physiological model

The above models were used to estimate changes in clinical pharmacokinetics by using parameters of different sizes. When f_p was changed, $CL_{int,h}$ or Q_{Liv}, or both, changed from 0·25- to 4-fold the control value and the fat volume changed from 0·25- to 5-fold. Fig. 4 simulates the plasma and brain concentration time-courses for 24 h after intravenous bolus injection of clomipramine or nitrazepam at a dose of 0·02 mg kg^{-1} in man. When the f_p of clomipramine was changed, the plasma concentrations after 24 h were slightly different (0·102–0·173 ng mL^{-1}). However in the brain, which is the target organ, the concentrations changed by approximately 30-fold (0·154–4·26 ng mL^{-1}). On the other hand, nitrazepam concentrations in the plasma and brain changed by 40-fold (0·067–2·65 ng mL^{-1}) and 600-fold (0·024–14·5 ng mL^{-1}), respectively. The brain–plasma concentration ratios ($K_{p,app}$) of clomipramine and nitrazepam changed by 1·5- to 25-fold and by 0·36- to 5·5-fold, respectively. When $CL_{int,h}$ was changed, the plasma concentrations of clomipramine and nitrazepam after 24 h changed by 10- and 100-fold, respectively. When Q_{Liv} was changed, the plasma concentrations of clomipramine and nitrazepam after 24 h changed by 10- and 1·7-fold, respectively. When fat tissue volume was changed, the plasma concentrations of both drugs changed by 1·5-fold. When $CL_{int,h}$, Q_{Liv} or the fat tissue volume was changed, the $K_{p,app}$ of these drugs remained approximately constant.

Discussion

This study has demonstrated that a physiologically founded pharmacokinetic model based on octanol–water partition coefficients is useful for estimating the clinical pharmacokinetics of lipophilic basic drugs. The essential pharmacokinetic parameters K_p, RBP, and $CL_{int,h}$ in man were predicted using the P_{oct} of the drugs and values obtained from experiments with rabbits.

Taking f_p into consideration, Sawada et al (1985b) reported that there was good correlation between the distribution of various acidic and basic drugs in rats and man, and that the K_{pu} of various tissues in man can be predicted from the values measured for rats. We also confirmed that there was good correlation between biperiden K_{pu} values measured in various tissues of rats and rabbits (Nakashima et al 1987). Therefore, we assumed that the K_p for man can be estimated by multiplying the value of K_{pu} calculated by use of equation 1 by the value of f_p for man. Assuming that f_p is corrected for the species difference in the D_f, as for the K_p, we estimated the RBP for man by use of equation 2.

Sawada et al (1985b) reported good correlation between the $CL_{int,h}$ values of various acidic and basic drugs for rats and man. Boxenbaum (1982) reported that for dogs and man the correlation between $CL_{int,h}$ values for a variety of benzodiazepine drugs was better than that between CL_h values. In this study, we found poor correlation between CL_{tot} values of basic drugs for rabbits and man (r = 0·733) but for $CL_{int,h,fu}$ the correlation was good (r = 0·951; Fig. 1).

Because it was recognized that the plasma concentrations predicted by the model for the ten basic drugs in rabbits were in good agreement with the observed values (r = 0·710–0·980), we assumed this physiological model could be widely applied to the disposition kinetics of basic drugs. We also recognized that the plasma concentrations predicted for the basic drugs in man were in good agreement with reported values. However, despite good agreement for diazepam and pentazocine in rabbits, there was no agreement in man. The plasma concentrations predicted for diazepam were lower than those measured whereas those predicted for pentazocine exceeded the reported values. The reason for the lack of agreement is probably because of differences between $CL_{int,h,fu}$ in rabbits and man, as shown in Fig. 1. Thus for diazepam the predicted value of $CL_{int,h,fu}$ is higher than the reported value whereas the value predicted for pentazocine is lower. However, good agreement was obtained between predicted and reported values of the plasma concentration when the reported value of $CL_{int,h,fu}$ for man was applied.

However, except for diazepam and pentazocine, the plasma concentrations predicted for basic drugs in man were in good agreement with the reported values (r = 0·729–0·973), and so we suggest that the physiological model using this method is useful for predicting disposition kinetics in man.

We attempted simulations of plasma and brain concentration time-profiles for nitrazepam and clomipramine under various

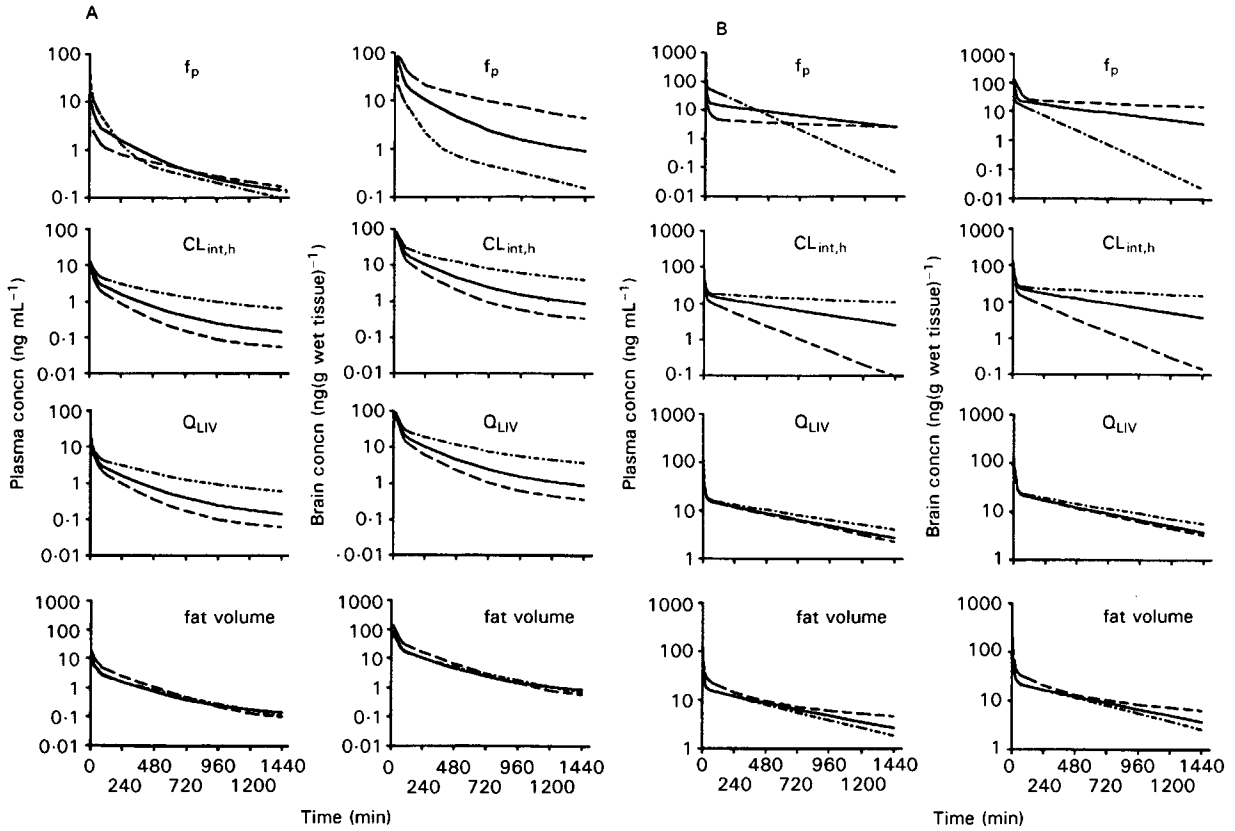

FIG. 4. Plasma and brain concentration profiles simulated by the model after intravenous administration of A. clomipramine or B. nitrazepam (0·02 mg kg^{-1}) to man, when the parameters f_p, $CL_{int,h}$, Q_{Liv} or fat volume were changed. The change in the ratio of f_p, $CL_{int,h}$ or Q_{Liv} to the control value is 0·25 (– · – · –) or 4 (– – – –). The change in the ratio of fat volume to the control value is 0·2 (– · – · –) or 5 (– – – –). Control (—).

conditions, namely changes of f_p, $CL_{int,h}$, Q_{Liv}, and the volume of fat tissue. When Q_{Liv} was changed, the variation in plasma concentration 24 h after intravenous injection of clomipramine was 10-fold higher than that of nitrazepam. When $CL_{int,h}$ was changed, the variation in plasma concentration 24 h after intravenous injection of nitrazepam was 6-fold more than that for clomipramine. Because CL_{tot} for clomipramine and nitrazepam is 10·8 and 1·41 mL min^{-1} kg^{-1}, respectively, and Q_{Liv} for man under normal conditions is 21·4 mL min kg^{-1} (Ichimura et al 1984), these results reflect the pharmacokinetics of liver blood flow- or clearance-limiting processes. Although the brain/plasma ratio ($K_{p,app}$) was almost always constant, when f_p was changed, the time-profiles of the brain concentration were more varied than those of the plasma concentration. Therefore, the changed f_p in disease states influences the concentration in the brain, which is the target organ, rather than the plasma concentration, so conclusions should not be drawn from the plasma concentration alone when evaluating drugs and side-effects.

In conclusion, application of drug pK_a, P_{oct} and f_p values enables prediction of disposition kinetics in man. These results suggest that it is dangerous to change the plasma and tissue concentration time-courses of basic drugs in various disease states. Thus, it would be expected that this new method could be helpful for predicting changes in the effectiveness and side-effects of basic drugs in various disease states, and the disposition kinetics of unknown drugs in man from drug information or in-vitro studies.

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