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Comparative Pharmacokinetic and Pharmacodynamic Properties of Oral and Intravenous (+)-Sotalol in Healthy Volunteers

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Abstract—The pharmacokinetic and pharmacodynamic properties of (+)-sotalol (BMY-5763) were studied to analyse the relationship between plasma concentration and QT_c prolongation in healthy male volunteers given single oral doses of 50, 100, 200 and 300 mg, repeated oral doses of 200 mg twice daily for 6·5 days, and single intravenous doses of 1·0 and 1·5 mg kg^{-1}. The plasma concentration of (+)-sotalol peaked about 3 h after oral administration and declined with a half-life of 7·9–9·7 h. The C_{max} and AUC showed dose-related increases, while the urinary recovery as the unchanged form remained constant (66–68% of the dose). During repeated oral administration the plasma concentration of (+)-sotalol reached almost a steady state on the 3rd day and there was no change in renal clearance of (+)-sotalol measured on the 1st, 4th and 7th days. After intravenous administration, (+)-sotalol in plasma decreased bi-exponentially with a terminal half-life of 7·6–8·3 h and the urinary recovery as unchanged drug amounted to 84–88% of the dose. The increase in QT interval was significant after a single oral administration except for the lowest dose, and regression analysis revealed a significant correlation between QT_c interval and concentration of (+)-sotalol in plasma. The same correlation was evident with repeated oral doses on the 1st, 4th and 7th days. In the case of single intravenous administrations of (+)-sotalol, a combined pharmacokinetic–pharmacodynamic model was attempted by assuming an effect compartment. This analysis was shown to be effective to adjust the lag of effect behind a rapid change in plasma concentration which occurred in the early distributive phase because there was no evidence that the metabolite made any significant contribution to the effect of (+)-sotalol.

Racemic sotalol is an anti-arrhythmic drug that possesses both β-adrenoceptor blocking and class III anti-arrhythmic activities. The dextro-rotary isomer, (+)-sotalol (BMY-5763), is one-twentieth to one-fiftieth as potent as (−)-sotalol in β-adrenoceptor blocking activity (Somani & Watson 1965), whereas the former is mainly responsible for class III anti-arrhythmic effects (Lynch et al 1984; Rowland 1985). Therefore, (+)-sotalol is expected to have advantages over racemic sotalol in treating a patient with arrhythmia and comorbid bronchospasm (Kuntz et al 1992).

Drugs that possess class III anti-arrhythmic activities, including (+)-sotalol, prolong the duration of ventricular repolarization and, therefore, increase the QT interval measured on surface electrocardiograms (Creamer et al 1986; Pollack et al 1989; Le Coz et al 1992). As regards racemic sotalol, the prolongation of the QT_c interval has been reported to relate to the plasma concentration and can be used to predict the effects at steady state (Le Coz et al 1992). Thus, the degree of QT-interval prolongation may act as a guide for adjusting the dosage in patients with cardiac arrhythmias. However, no study has been reported describing and comparing these relations after oral and intravenous administration of (+)-sotalol. Only the pharmacokinetic profile of intravenous (+)-sotalol has been reported (Poirier et al 1990).

In the present study, the prolongation of the QT interval was analysed in healthy male volunteers in conjunction with the comparative pharmacokinetic properties of (+)-sotalol after oral and intravenous administration.

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Materials and Methods

Subjects

A total of 39 healthy male Japanese volunteers, aged 22–43 (mean: 32·5) years and weighing 47·9–77·0 (61·7) kg, participated in this study after giving their informed consent. They were allocated to seven groups (1–7 in Table 1). First, (+)-sotalol was administered orally as single doses of 50, 100, 200 and 300 mg in a dose-increasing manner. At a dose of 200 mg, the effects of food-intake on the pharmacokinetics of (+)-sotalol were examined in a cross-over design at an interval of 10 days. Then, a multiple-dose study, in which 200 mg (+)-sotalol was given twice daily for 6·5 days (total 13 doses), was conducted. Six and three subjects received orally (+)-sotalol and placebo, respectively, after meals every 12 h in a double-blind design. Finally, (+)-sotalol was administered as an intravenous infusion over 10 min as single doses of 1·0 and 1·5 mg kg^{-1}. The study protocol was approved by the local Ethics Committee.

Collection of plasma and urine samples

Blood (7 mL) was drawn from the antecubital vein immediately before and at 0·5, 1, 2, 3, 4, 5, 6, 8, 12, 24 and 30 h after single oral administration. Additional samples were taken at 36 and 48 h after the administration of 300 mg. In the multiple-dose study, blood was drawn before, and at 2, 3, 4, 6 and 8 h after the 1st, 7th and 13th (last) doses. Additionally, blood was drawn before and 4 h after the 3rd, 5th, 9th and

Table 1. Subjects and dosing regimens.

Group	n	Age (years)	Body weight (kg)	Dosing period (mg)						(mg kg^{-1})	
				I	II	III	IV	V	VI	VII	VIII
Oral administration											
Single dose											
1	6	32·3±5·0	64·0±8·7	50[f]	100[f]						
2	6	33·2±6·3	65·1±6·6			200[f]	200[n]				
3	6	33·0±2·8	64·7±8·2					300[f]			
Repeated doses (total 13 doses)											
4	6	31·0±6·9	62·1±7·0						200[n] b.i.d.		
5	3	33·0±5·0	57·4±5·0						0*[n] b.i.d.		
Intravenous administration											
Single dose											
6	6	32·7±6·9	60·9±6·8							1·0	
7	6	32·8±6·4	55·6±6·3								1·5

Values are expressed as means±s.d. [f]Fasting, [n]non-fasting, *placebo.

11th doses (morning doses), 1 h after the 1st dose and 1, 12, 24, 30, 36 and 48 h after the last dose. Blood samples were collected before, and at 0·167 (the end of infusion), 0·25, 0·333, 0·667, 1·167, 2, 4, 6, 8, 12, 24, 36 and 48 h after the commencement of drug infusion. Urine was collected 0–2, 2–4, 4–6, 6–8, 8–12, 12–24 h and 24–30 or 24–48 h after administration in the single-dose study. In the repeated-dose study, urine was collected 0–2, 2–4, 4–6 and 6–8 h after the morning dose on the 1st, 4th and 7th days and, additionally 8–12, 12–24 and 24–48 h after the last dose.

Analytical procedures

Concentrations of (+)-sotalol in plasma and urine were determined by an HPLC method which utilizes a derivatizing reagent to quantify the amounts of (+)- and (−)-sotalol, separately. Sotalol and the (−)-isomer in plasma and urine were extracted by using a Sep-Pak C_{18} column and derivatized with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate. The analytical column used was STR ODS II column (4·6 × 150 mm; particle size: 5 μm, Shimadzu Techno Research, Japan). The mobile phase consisted of 0·02 M $NH_4H_2PO_4$ and acetonitrile (60:40, v/v), and the flow rate was 1·0 mL min^{-1}. The effluent was monitored with a UV-detector (wavelength: 225 nm). *p*-Hydroxybenzoic acid isoamyl ester was used as an internal standard.

The maximum drug concentration in plasma (C_{max}) and the time required to reach maximum concentration (t_{max}) were calculated from the observed levels. The area under the plasma concentration–time curve (AUC) was calculated according to the trapezoidal rule. The time-profile of plasma concentration after oral administration was fitted to a one-compartment open model with first-order absorption and that after intravenous administration was fitted to a two-compartment open model using a nonlinear least-square method (Yamaoka et al 1981).

Assessment of safety

In the single-dose study, subjective and objective symptoms, and vital signs including blood pressure, pulse rate and body temperature were checked before administration and periodically until 30–48 h after administration. Routine laboratory tests including haematology, blood biochemistry and urinalysis were performed immediately before, 24 h and 7 days after administration. In the multiple-dose study the same items as shown above were checked before, during and 48 h after the administration period. Holter electrocardiogram (ECG) was monitored from 1 h before and until 12 h after the administration (SM-28, Fukuda Denshi Co. Ltd, Tokyo, Japan).

Pharmacological evaluation

A standard 12-lead ECG was recorded before and 1, 2, 4, 8, 12 and 24 h after single oral administration, and before and periodically throughout the test period until 48 h after the last administration in the repeated-dose study (FCP4301, Fukuda Denshi) to calculate QT_c. The QT interval was measured from the onset of the Q wave to the end of the T wave according to the criterion of Lepeschkin & Surawicz (1952) and each recording was checked by the same investigator, who was unaware of the treatment received, to assure that the calculation had been correctly made according to the criterion.

In the intravenous infusion study, Holter ECG recorded on tape was processed and digitalized by a Holter ECG analysing system (DMC4100, Nihon Kohden, Tokyo, Japan) to calculate QT intervals at the same time-points as blood samplings for the measurement of drug concentrations.

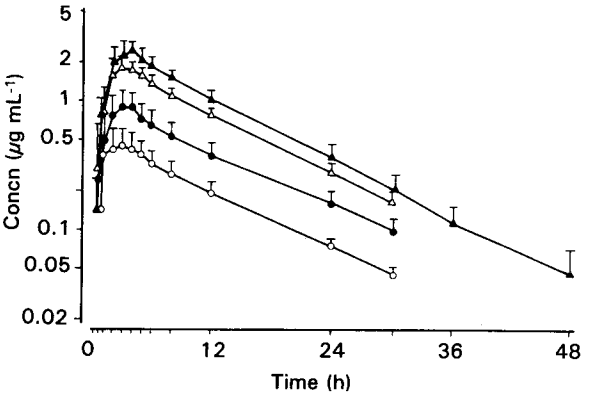

FIG. 1. Plasma concentration of (+)-sotalol following single oral administration of ○ 50, ● 100, △ 200 and ▲ 300 mg. Values are mean±s.d., n=6.

Table 2. Pharmacokinetic parameters of (+)-sotalol determined after single oral administrations of 50, 100, 200 and 300 mg to healthy male volunteers.

Dose (mg)	n	C_{max} ($\mu g\ mL^{-1}$)	t_{max} (h)	AUC ($\mu g\ h\ mL^{-1}$)	$t_{\frac{1}{2}}$ (h)	CL/F ($mL\ min^{-1}$)	UR (%)	CL_R ($mL\ min^{-1}$)
50	6	0·47±0·12	3·3±1·4	6·1±1·2	8·9±1·5	140±27	65·8±22·0	97±28
100	6	0·93±0·29	2·8±1·5	12·2±2·7	9·7±2·1	141±28	66·4±16·9	103±23
200	6	2·02±0·24	3·2±1·2	23·1±3·4	8·2±0·4	147±20	67·7±6·7	107±8
300	6	2·55±0·48	3·8±1·3	30·4±5·2	7·9±1·2	168±27	68·2±11·7	121±14

Values are expressed as means±s.d.; C_{max}, maximal plasma concentration; t_{max}, time required to reach C_{max}, AUC, area under the plasma concentration–time curve extrapolated to the infinity; $t_{\frac{1}{2}}$, biological half-life; CL/F, apparent total body clearance (F: absolute bioavailability); UR, urinary recovery within first 30 h; CL_R, renal clearance. Analysis of variance detected no significant difference among the four dosing groups.

Table 3. Pharmacokinetic parameters of (+)-sotalol determined after repeated oral administrations of 200 mg twice daily for 6·5 days to healthy male volunteers.

Day 1		Day 4		Day 7		
$AUC_{0\text{-}8\ h}$ ($\mu g\ h\ mL^{-1}$)	CL_R ($mL\ min^{-1}$)	$AUC_{0\text{-}8\ h}$ ($\mu g\ h\ mL^{-1}$)	CL_R ($mL\ min^{-1}$)	$AUC_{0\text{-}8\ h}$ ($\mu g\ h\ mL^{-1}$)	$AUC_{0\ 12\ h}$ ($\mu g\ h\ mL^{-1}$)	CL_R ($mL\ min^{-1}$)
9·0±2·0	112±19	17·3±1·4	108±13	17·0±1·9	23·3±2·1	109±12

Values are expressed as means±s.d. $AUC_{0\text{-}8\ h}$, $AUC_{0\ 12\ h}$: area under the plasma concentration–time curve during the time interval 0 to 8 h and 12 h after administration. The other abbreviations are as in Table 1.

Statistical analysis

When more than two means were compared, analysis of variance was used, followed by Student's *t*-test (two-tailed) or Dunnett's test with the level of statistical significance at $P<0·05$.

Results

Safety

No abnormality attributable to the test drug was observed in subjective and objective symptoms, vital signs, or laboratory tests. Therefore, oral and intravenous (+)-sotalol was concluded to be well tolerated in healthy subjects, at least within the range of doses tested in the present study.

Pharmacokinetics and pharmacodynamics

As shown in Fig. 1, the plasma concentrations of (+)-sotalol following oral administration of 50, 100, 200 or 300 mg on an empty stomach, fitted a one-compartment open model with first-order absorption. The mean value of t_{max} ranged from 2·8 to 3·8 h, and those of C_{max} and AUC increased in proportion to the given doses. The biological half-life ranged from 7·9 to 9·7 h and the urinary recovery was 66–68% of the dose as unchanged form irrespective of the dose (Table 2). There were no significant changes in these parameters between the administrations of 200 mg (+)-sotalol after over-night fasting and after a meal. In the repeated-dose study the plasma concentration of (+)-sotalol achieved almost a steady state on the 3rd day and fitted well to the simulated curve generated by using the parameters obtained in the subjects who took 200 mg after food. Throughout the study, the renal clearance remained constant (Table 3). After intravenous administration, the concentration of (+)-sotalol in plasma declined bi-exponentially with a terminal half-life of 7·6–8·3 h, and the C_{max} and AUC were proportional to the dose (Fig. 2, Table 4). When the values of total body clearance and urinary recovery were compared for single oral and intravenous administrations, the absolute oral bioavailability of (+)-sotalol was approximately 80–90%.

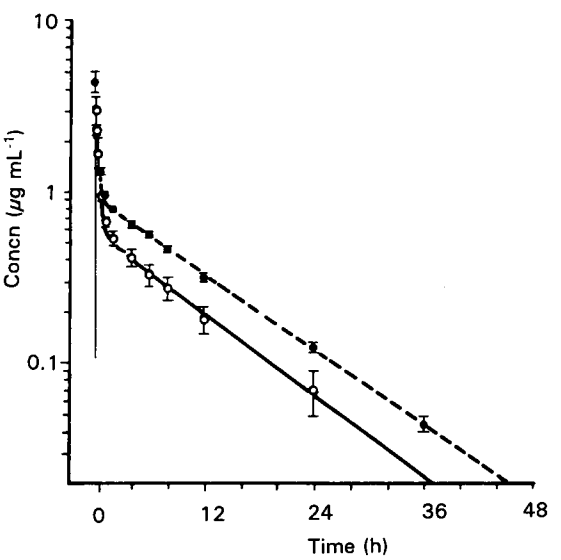

FIG. 2. Plasma concentration of (+)-sotalol following single intravenous administration of ○ 1·0 and ● 1·5 mg kg^{-1}. Values are mean±s.d., n=6.

Following a single oral administration of 100, 200 or 300 mg of (+)-sotalol, the QT interval corrected for heart rate, QT_c, was prolonged in a dose-dependent manner (Fig. 3). In addition, there was a linear correlation between the QT_c interval and (+)-sotalol concentration in plasma, and no distinct hysteresis was observed (Table 5). In the repeated-dose study significant prolongation of QT_c was observed from the 1st day of administration until the last day in the group treated with (+)-sotalol, whereas there was no significant change in this parameter in the group treated with placebo. When the correlation between the plasma concentration of (+)-sotalol was compared among the 1st, 4th and 7th days, the slope was almost the same on the 1st and 4th days, although it tended to be reduced on the 7th day (Table 6). On the other hand, a hysteresis was obvious in the

Table 4. Pharmacokinetic parameters of (+)-sotalol determined after single intravenous administrations of 1·0 and 1·5 mg kg^{-1} to healthy male volunteers.

Dose (mg kg^{-1})	n	C_{max} (μg mL^{-1})	AUC (μg h mL^{-1})	$t_{\frac{1}{2}\alpha}$ (h)	$t_{\frac{1}{2}\alpha}$ (h)	CL_T (mL min^{-1})	UR (%)	CL_R (mL min^{-1})
1·0	6	2·9±0·4	7·3±1·2	0·20±0·03	7·6±0·9	141±27	83·5±4·4	115±22
1·5	6	4·1±0·2	11·9±0·4	0·17±0·03	8·3±0·5	116±12	88·0±2·5	100±12

Values are expressed as means±s.d. $t_{\frac{1}{2}\alpha}$, $t_{\frac{1}{2}\beta}$: biological half-lives of distribution and elimination phases, respectively. The other abbreviations are as in Table 1.

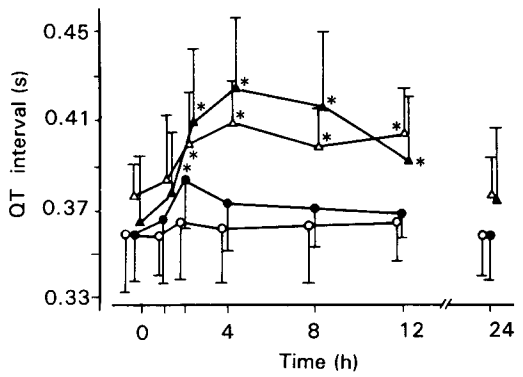

FIG. 3. Time-profiles of changes in QT interval following single oral administration of ○ 50, ● 100, △ 200 and ▲ 300 mg. *$P<0·05$ Dunnett's test, values are mean±s.d., n=6.

Table 5. Regression analysis of the relationship between plasma concentration of (+) sotalol (X: μg mL^{-1}) and QT_c interval (Y: ms) after single oral dose of (+)-sotalol.

Dose (mg)	n	Regression line	r^2
50	7	Y=0·358+0·00473 X	0·098
100	7	Y=0·357+0·0240 X	0·771
200	7	Y=0·375+0·0180 X	0·704
300	7	Y=0·363+0·0258 X	0·913

Mean QT_c values were plotted against mean plasma concentration (n=6) at each data-sampling point after administration. r, regression coefficient.

Table 6. Regression analysis of the relationship between plasma concentration of (+)-sotalol (X: μg mL^{-1}) and QT_c interval (Y: ms) on the 1st, 4th and 7th days in the repeated-dose study of (+)-sotalol.

Period	n	Regression line	r^2
1st day	6	Y=0·375+0·0256 X	0·902
4th day	4	Y=0·362+0·0269 X	1·000
7th day	8	Y=0·380+0·0114 X	0·672

Mean QT_c values were plotted against mean plasma concentration (n=6) at each data-sampling points after administration. r, regression coefficient.

correlation between plasma concentration of (+)-sotalol and QT prolongation after intravenous administration (Fig. 4A). To reduce the area of the hysteresis loop, pharmacokinetic–pharmacodynamic modelling was attempted by assuming an effect compartment as described by Gibaldi & Perrier (1982). By changing the value of k_{e0} depicted in the middle panel of Fig. 4 from 0 to 10 with a step of 0·1, the linear regression procedure was repeated to obtain the minimum AIC value (Akaike 1974). At the k_{e0} value of 1·1 h^{-1} the loop was maximally reduced and a correlation coefficient comparable with those achieved in association with oral administration was obtained (Fig. 4B).

Discussion

Throughout the entire test period, no abnormality attributable to the test drug was found in subjective and objective symptoms, vital signs, and routine laboratory tests, indicating that (+)-sotalol (BMY-5763) was well tolerated in healthy subjects.

The disposition pharmacokinetics of (+)-sotalol we have found in the present study are similar to those previously reported after oral administration of racemic sotalol (Le Coz et al 1992) and intravenous injection of (+)-sotalol (Poirier et al 1990). Terminal half-life was approximately 8–9 h and a linear pharmacokinetic profile was found.

In the case of quinidine, which also prolongs the QT_c interval, its active metabolites contribute to the effect, and the degree of their contribution is different after oral and intravenous administration (Vozeh et al 1985; Ha et al 1987; Uematsu et al 1987). However, there was no evidence that metabolites make any significant contribution to the drug's effects for (+)-sotalol.

QT_c increased and then decreased in association with the rise and fall of plasma concentration after single oral administrations of more than 100 mg, repeated oral administrations of 200 mg twice daily and single intravenous administrations of 1·0 and 1·5 mg kg^{-1}. It was clear from the hysteresis plots that the prolongation of the QT_c interval was related directly to plasma concentrations of (+)-sotalol in plasma after single oral administration. This implies that a state of equilibrium could be obtained between plasma and relevant receptor-site concentrations at all times, probably because the absorption and elimination of (+)-sotalol are slow as judged from the t_{max} and $t_{\frac{1}{2}}$ values. This concept is not inconsistent with the one-compartmental characteristics of the drug after oral administration (Whiting et al 1980; Holford & Sheiner 1981). In association with repeated oral administration, the slope of the correlation between plasma concentration and QT_c interval was similar on the 1st and 4th day, while it was slightly reduced on the 7th day. Le Coz et al (1992) concluded that the maximal increase in QT_c duration at steady state after treatment with racemic sotalol could be

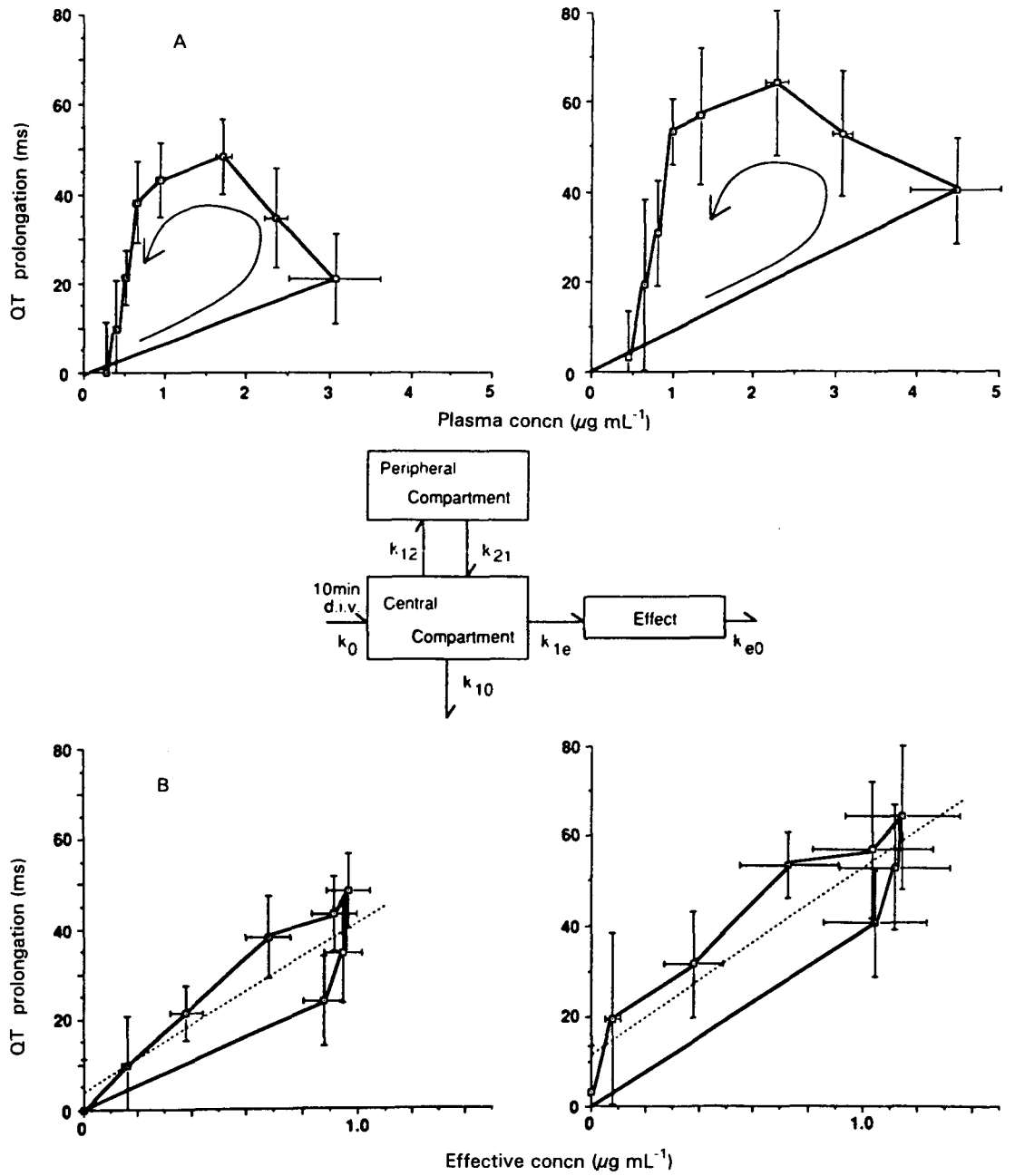

FIG. 4. Relationship between the plasma concentration of (+)-sotalol and QT interval after single intravenous administration. A. The prolongation of QT interval was plotted against plasma concentration of (+)-sotalol and connected in time order. Doses of (+)-sotalol were 1 mg kg^{-1} (left panel) and 1·5 mg kg^{-1} (right panel). B. By assuming an effect compartment according to the model described in the scheme of middle panel, the prolongation of QT was plotted against the concentration of (+)-sotalol in the effect compartment, as the effective concentration. Each symbol and bar represent mean ± s.d. (n = 6).

predicted from single-dose administration. However, those authors treated healthy subjects with racemic sotalol only for four days and found that prediction errors were significant in 20% of measurements and predictions, most of which were due to overestimation. Considering our results together with those of Le Coz et al (1992), it may be speculated that a decrease in the prolongation of repolarization by (+)-sotalol, which may be attributable to an up-regulation of potassium channels, should occur later than the 4th day of repeated administration.

On the other hand, intravenous administration presents an initial non-equilibrated period where plasma concentration and effect may be out of phase. A hysteresis was evident between the plasma concentration and QT prolongation after intravenous administration of the drug. As shown in Fig. 4, the non-equilibrated period between plasma concentration and effect can be described by a first-order rate constant which allows pharmacodynamics to be modelled as a function of plasma concentration. As a result, the area of the hysteresis loop could be reduced to yield a correlation coefficient comparable with that obtained after oral administration.

All of the presently available anti-arrhythmic agents have a narrow therapeutic index. Depending on the routes of drug elimination, hepatic or renal dysfunction may affect the serum concentration achieved. High concentrations of racemic sotalol, such as those that may be observed in patients with renal insufficiency, have been reported to increase the risk of drug-induced pro-arrhythmia (Kontopoulos et al 1981). Excessive increase in the QT interval is commonly observed in patients with torsades de pointes arrhythmia. The present study suggests that anti-arrhythmic therapy with (+)-sotalol should be guided by the degree of QT prolongation, because it can predict the effective concentration of drug at the relevant receptor site. However, it should be further clarified whether the anti-arrhythmic effect is reduced during long-term therapy in accordance with the reduction of QT prolongation.

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