

## Comparison of Disposition Parameters of Quinidine and Quinine in the Rat

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The difference in disposition of quinidine (Qd) and its diastereomer quinine (Qn) after intravenous administration was examined in rats at doses ranging from 5 to 20 mg/kg. Dose-dependent kinetics in total clearance and in distribution volume of tissue based on a two-compartment model was observed for Qd; there was no evidence of nonlinearity for Qn. However, there was no significant difference between Qd and Qn for blood clearance at doses of 5 and 10 mg/kg, at which the blood clearances were almost equal to hepatic blood flow for both Qd and Qn since the excretion of Qd and Qn into the urine and bile was minimal. This indicates the elimination of these diastereomers to be non-restrictive in the liver. A concentration dependence in unbound volume of tissue distribution and in plasma protein binding was observed for Qd; there was no concentration dependence for Qn. Although affinity of the drug for components on or within the blood cells was not concentration-dependent for either Qd or Qn, a significantly higher binding capacity for Qn than for Qd was observed, attributable to blood cell binding. Based on these results, it is suggested that a larger number of binding sites exist for Qn than for Qd in the body. However, the dissociation binding constant for Qd is much lower than for Qn, resulting in a higher binding of Qd than Qn at low concentrations, with a reversal at high concentrations.

**Keywords** — quinidine; quinine; disposition; tissue distribution; non-restrictive elimination; blood cell affinity; nonlinear kinetics

### Introduction

Quinidine (Qd) and quinine (Qn) are diastereomers.<sup>1)</sup> Recent reports indicate that Qd is at least as potent, and possibly more potent than Qn as an antimalarial,<sup>2-4)</sup> and that this isomer is now gaining wider use.<sup>3)</sup> However, few comparative pharmacokinetic studies of Qd and Qn have been made.<sup>5-7)</sup> Therefore, the present study was undertaken to generate information on the difference in disposition of these two diastereomers in the body after intravenous administration of various doses in rats.

### Materials and Methods

**Materials** — Qd sulfate and Qn hydrochloride (Wako Pure Chemical Ind., Osaka, Japan) were used without further purification. Qd and Qn contained 5.0% and 3.1% respective dihydroderivatives<sup>8)</sup> by analysis utilizing a high performance liquid chromatographic (HPLC) method described below. All other reagents were commercially available and of analytical grade.

**Animal Experiments** — Male Wistar rats (240 — 280 g) were fasted overnight before the

experiment; cannulas (Atom disposable i.v. catheter 2F; Atom Co., Tokyo, Japan) were inserted into the femoral artery (for blood sampling) and vein (for drug administration) under light ether anesthesia. For bladder and bile duct cannulations, a midline abdominal incision was made under light ether anesthesia, and bladder and bile duct were cannulated with polyethylene tubing. The incision was then closed with a suture. All cannulated rats were kept in the supine position on restraining plates, and the experiment was performed in conscious animals after each animal had recovered from anesthesia. Fresh animals were used for each dose and experiment of Qd or Qn. The Qd sulfate and Qn hydrochloride were dissolved in normal saline. The total volume of drug solution administered ranged from 0.6 to 1.0 ml per animal.

A bolus of 5, 10, 15, or 20 mg/kg (as a base form) of Qd or Qn was injected into the femoral vein. Blood samples were collected at 1, 2, 3, 4, 6, 8, 10, 20, 30, 45, and 60 min, since Qd and Qn disposition could be described by a two-compartment model in the rat.<sup>4,9)</sup> The samples were heparinized, and the plasma separated by centrifugation for 1 min in a table-top microfuge.

The plasma was kept frozen until analysis. During the first 12 h after injection, urine and bile samples were collected through polyethylene tubes cannulated into the bladder and bile duct. Samples were assayed for Qd by HPLC equipped with fluorescence detector, as reported by Rakhit *et al.*<sup>10)</sup> Determination of Qn concentration was made by the same method used for Qd. This assay method permits measuring 0.1  $\mu\text{g/ml}$  Qd or Qn with no interference from the presence of their metabolites.

**Plasma Protein Binding** — Pooled heparinized plasma from 4 to 5 rats was used for the determination of the unbound fraction of each concentration of Qd or Qn, since there is no effect of heparin or free fatty acids on Qd binding within human plasma.<sup>11)</sup> The plasma unbound fraction was determined by ultrafiltration (MPS-1, Amicon, Corp., Danvers, U.S.A.) after incubation at 37 °C for 7 min. The adsorption of the drugs for an MPS-1 apparatus was negligible (less 3.8% at 5  $\mu\text{g/ml}$ ). The Qd or Qn concentration in the chamber was in the same range as that *in vivo*.

The plasma binding parameters of Qd were calculated as<sup>12)</sup>

$$C_b = N_p C_u / (K_d + C_u) + \phi C_u \quad (1)$$

where  $C_b$  and  $C_u$  are the respective bound and unbound concentrations of Qd in plasma;  $N_p$ , the binding capacity of plasma protein;  $K_d$ , the dissociation constant corresponding to  $N_p$ ; and  $\phi$ , the linear coefficient for the binding.

**Blood-to-Plasma Concentration Ratio** — A conventional *in vitro* method was performed as follows: After administration of heparin at a dose of 0.1 ml per 100 g body weight (100 units), whole blood was collected *via* the femoral artery. Various amounts of Qd or Qn in 100  $\mu\text{l}$  of isotonic phosphate buffer solution (pH 7.4) was added to 2 ml of fresh whole blood of 4 or 5 rats. The samples were incubated with slow shaking for 30 min at 37 °C. After centrifugation, a portion of the plasma was removed and divided into two groups: one was used for the determination of plasma concentration of the drug; and the other for the determination of plasma unbound fraction. The Qd or Qn concen-

tration was adjusted to the same range as that *in vivo*. Hemolysis during the incubation was negligible. The blood-to-plasma ratio was calculated by dividing the spiked blood concentration ( $C_B$ ) by the determined plasma concentration ( $C$ ).

The ratio ( $\theta$ ) of drug concentration on or within blood cells ( $C_{RC}$ ) to plasma unbound concentration ( $C_u$ ) was also calculated as

$$\theta = C_{RC}/C_u = (C_B/C - 1 + H)/f_u H \quad (2)$$

where  $f_u$  is the unbound fraction in plasma and  $H$  is the hematocrit.

**Pharmacokinetic Analysis** — The Qd or Qn concentration data for individual animals were fitted to the equation  $C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t}$  for the plasma concentration  $C$  at time  $t$  by using the MULTI program,<sup>13)</sup> with equal weight on each datum.

The relationship between the unbound fraction in plasma ( $f_u$ ) and the volume of distribution at steady-state ( $V_{ss}$ ) was expressed as<sup>14)</sup>

$$V_{ss} = V_B C_B/C + f_u V_I + (1-f_u) R_{E/I} V_B (1-H) + V_T f_u / f_{u,T} \quad (3)$$

where  $V_B$ ,  $V_I$ , and  $V_T$  are the blood volume, the volume of extracellular fluid outside of plasma, and the tissue volume (except blood cells) into which the drug was distributed, respectively;  $f_{u,T}$ , the unbound fraction in the tissue; and  $R_{E/I}$ , the ratio of binding protein in extracellular fluids outside of plasma to that in the plasma. In the present study of the rat,  $V_B$  and  $V_I$  were taken as 54.0 and 297 ml/kg,<sup>15)</sup> respectively.  $R_{E/I}$  was taken as 1.4,<sup>16)</sup> assuming that the plasma proteins to which the drug binds are distributed like albumin, and that the distribution of albumin in the rat is the same as that in man. Measured  $H$  was 0.48. Therefore,  $V_T/f_{u,T}$  can be written as

$$V_T/f_{u,T} = (V_{ss} - 54.0(C_B/C) - 258f_u - 39.3)/f_u \quad (4)$$

In the case of nonlinear binding to plasma proteins, the *in vivo* mean plasma concentration for the plasma collecting time ( $\int_0^t C dt/t$ ) was used

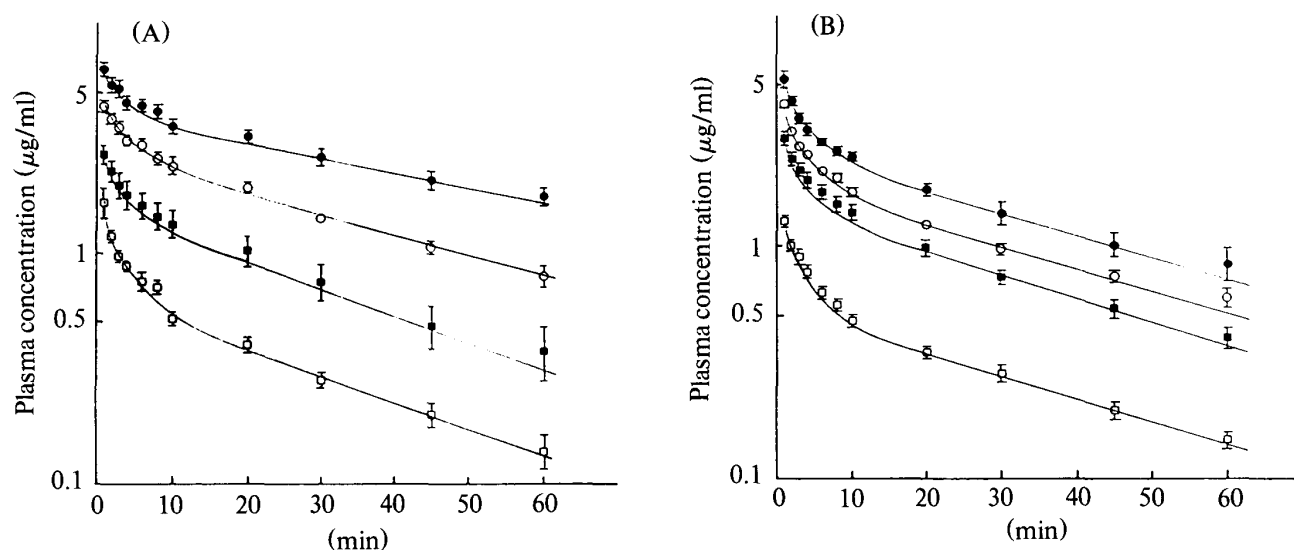


Fig. 1. Time Courses of Plasma Concentration of (A) Qd and (B) Qn in Rats after Intravenous Bolus Injections of 5 (□), 10 (■), 15 (○), and 20 (●) mg/kg

in the calculation, and the unbound concentration in the *in vivo* plasma was calculated by using Eq. 1.

All data represent the mean  $\pm$  S.E. The data were analyzed by ANOVA. When there was a

significant difference between the two populations, the Aspin-Welch method<sup>17)</sup> was adopted for data analysis, and Student's *t*-test was also used; a *p* value of 0.05 was considered significant.

TABLE I. Pharmacokinetic Parameters of Qd and Qn for a Two-Compartment Model Obtained by Curve-Fittings (Mean  $\pm$  S.E.)

	5 mg/kg		10 mg/kg		15 mg/kg		20 mg/kg	
	Qd	Qn	Qd	Qn	Qd	Qn	Qd	Qn
<i>n</i> <sup>a)</sup>	6	6	6	7	5	6	6	6
<i>k</i> <sub>12</sub>	0.227	0.212	0.252	0.197	0.131	0.252	0.172	0.308
(min <sup>-1</sup> )	$\pm 0.068$	$\pm 0.056$	$\pm 0.060$	$\pm 0.033$	$\pm 0.038$	$\pm 0.053$	$\pm 0.044$	$\pm 0.084$
<i>k</i> <sub>21</sub>	0.216	0.145	0.294	0.224	0.196	0.216	0.262	0.236
(min <sup>-1</sup> )	$\pm 0.064$	$\pm 0.028$	$\pm 0.080$	$\pm 0.019$	$\pm 0.032$	$\pm 0.039$	$\pm 0.064$	$\pm 0.045$
<i>k</i> <sub>10</sub>	0.0943	0.0610	0.0574	0.0540	0.0378	0.0565	0.0256	0.0552
(min <sup>-1</sup> )	$\pm 0.0260$	$\pm 0.0059$	$\pm 0.0104$	$\pm 0.0036$	$\pm 0.0044$	$\pm 0.0071$	$\pm 0.0033$	$\pm 0.0081$
<i>V</i> <sub>1</sub> (l/kg)	2.45	3.11	2.94	2.85	2.99	2.86	2.80	2.93
	$\pm 0.502$	$\pm 0.285$	$\pm 0.189$	$\pm 0.348$	$\pm 0.241$	$\pm 0.234$	$\pm 0.249$	$\pm 0.403$
<i>V</i> <sub>2</sub> (l/kg)	3.35	4.12	2.62	2.26	1.71	3.17	1.78	3.18
	$\pm 0.446$	$\pm 0.315$	$\pm 0.293$	$\pm 0.170$	$\pm 0.764$	$\pm 0.235$	$\pm 0.140$	$\pm 0.342$
<i>V</i> <sub>ss</sub> <sup>b)</sup>	5.80	7.22	5.56	5.11	4.70	6.03	4.58	6.11
(l/kg)	$\pm 0.668$	$\pm 0.494$	$\pm 0.434$	$\pm 0.411$	$\pm 0.378$	$\pm 0.282$	$\pm 0.798$	$\pm 0.338$
CL <sub>t</sub> <sup>c)</sup>	175	183	170	149	110	154	69.1	152
(ml/min/kg)	$\pm 13.6$	$\pm 11.2$	$\pm 33.2$	$\pm 17.0$	$\pm 8.0$	$\pm 10.2$	$\pm 16.4$	$\pm 18.1$
MRT <sup>d)</sup>	35.7	39.9	38.8	35.1	44.0	40.8	68.9	42.8
(min)	$\pm 7.20$	$\pm 3.01$	$\pm 7.31$	$\pm 1.36$	$\pm 5.42$	$\pm 4.67$	$\pm 6.72$	$\pm 4.70$

a) Numbers of animals used. b)  $V_{ss} = V_1(1 + k_{12}/k_{21})$  c)  $D/(C_1/\lambda_1 + C_2/\lambda_2)$ , where *D* is the dose. d)  $(C_1/\lambda_1^2 + C_2/\lambda_2^2)/(C_1/\lambda_1 + C_2/\lambda_2)$  See text details.

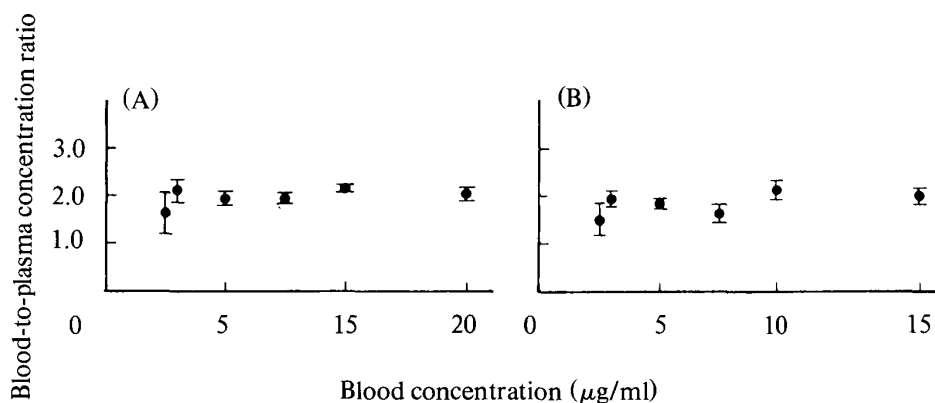


Fig. 2. Blood-to-Plasma Concentration Ratio of Qd and Qn as a Function of Total Blood Concentration

### Results

Figure 1 shows the time courses of plasma concentration of Qd or Qn following i.v. bolus injection. The disposition of Qd and Qn in rats could be described by a two-compartment model, similar to the results in dog<sup>6)</sup> and in humans.<sup>4)</sup> The values of  $k_{10}$ ,  $V_2$ , and  $CL_t$  for Qd tended to decrease with increasing dose;  $V_2$  and  $CL_t$  decreased significantly at doses above 15 mg/kg (Table I: Differences between 5 and 15 mg/kg, between 5 and 20 mg/kg for  $V_2$ , and between 5 and 15 mg/kg, between 5 and 20 mg/kg, and between 15 and 20 mg/kg for  $CL_t$  were significant.). The value of MRT for Qd increased significantly at doses above 15 mg/kg (Differences between 5 and 20 mg/kg, between 10 and 20 mg/kg, and between 15 and 20 mg/kg were significant.). However, there were no significant differences between 5 and 10 mg/kg for these parameters. On the other hand, there was no indication of dose-dependency for Qn.

TABLE II. Total Blood Clearance after Intravenous Injection of Qd and Qn (Mean  $\pm$  S.E.)<sup>a)</sup>

Dose (mg/kg)	Qd (ml/min/kg)	Qn (ml/min/kg)
5	93.7 $\pm$ 7.30	95.0 $\pm$ 5.84
10	91.2 $\pm$ 17.8	77.5 $\pm$ 8.83
15	58.6 $\pm$ 4.27	79.5 $\pm$ 5.27
20	36.9 $\pm$ 3.59	78.6 $\pm$ 9.39

a) Numbers of animals are given in Table I. See text details.

There were significant differences between Qd and Qn for  $V_2$ ,  $V_{ss}$ , and  $CL_t$  at doses above 15 mg/kg and for  $k_{10}$  at 20 mg/kg, indicating concentration-dependencies in some of the variables for one or both drugs. This is simply due to the dose-dependency for Qd because of no dose-dependency for Qn.

The ratios of whole blood to plasma concentration were nearly constant at 2 (1.87 for Qd and 1.93 for Qn), as shown in Fig. 2. This value of Qd well accorded with the value of 1.84.<sup>18)</sup> Blood clearance is converted from plasma clearance *via* the ratio of drug concentration in whole blood to that in plasma (Table II). Significant differences in blood clearance between doses were the same as in  $CL_t$ , described above. Accordingly, significant differences between Qd and Qn for blood clearances were observed at both 15 and 20 mg/kg due to the dose-dependent kinetics of Qd elimination. At doses of 5 and 10 mg/kg, blood clearance for both Qd and Qn was almost equal to hepatic one, since the excretion of unchanged Qd or Qn into the urine and bile was negligible (Table III), in contrast to man.<sup>7,19,20)</sup>

TABLE III. Fraction Recovered from Urine and Bile during 12 h (Mean  $\pm$  S.E.)<sup>a)</sup>

	Dose (mg/kg)	Qd (%)	Qn (%)
Urine	5	0.325 $\pm$ 0.188	1.08 $\pm$ 0.234
	20	1.08 $\pm$ 0.197	0.895 $\pm$ 0.203
Bile	20	0.137 $\pm$ 0.040	0.290 $\pm$ 0.100

a) Fresh animals were used for each dose ( $n = 6$ ).

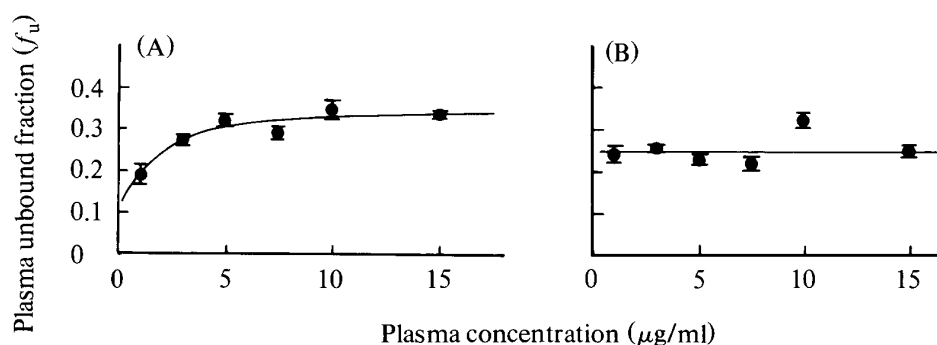


Fig. 3. Plasma Unbound Fraction of (A) Qd and (B) Qn as a Function of Total Plasma Concentration

Figure 3 shows the unbound fraction in plasma proteins. Nonlinear binding of Qd to plasma proteins was observed over the *in vivo* plasma concentration range, in accord with results of Fremstad *et al.*<sup>9)</sup> and Harashima *et al.*<sup>12)</sup> The fitted values of Qd for Eq. 1 were 0.850, 0.152  $\mu\text{g/ml}$ , and 1.80 for  $N_p$ ,  $K_d$ , and  $\phi$ , respectively. On the other hand, plasma protein binding of Qn was virtually constant over the concentration range examined. These indicate that Qn has more affinity than Qd in the plasma proteins.

The unbound volume of tissue distribution ( $V_T/f_{u,T}$ , *i.e.*, unbound volume of cellular distribution except for blood cells) for Qd decreased significantly at doses above 15 mg/kg (Table IV: Differences between 5 and 15 mg/kg, between 5 and 20 mg/kg, and between 10 and 20 mg/kg were significant). However, there was no tendency to dose-dependency for Qn. In addition, the calculated values of  $V_T/f_{u,T}$  based on the rat physical data for  $C_B$  and  $V_I$  were almost the same as those based on the interspecies physical data<sup>14)</sup> (*i.e.*,  $V_B = 80 \text{ ml/kg}$  and  $V_I = 260 \text{ ml/kg}$ ), as shown in Table IV.

The affinity of drug for components on or within the blood cells (erythrocytes) is shown in Fig. 4. The values of  $\theta$  were virtually constant over the present concentration range examined for these two drugs, and were 6.68 for Qd and 10.8 for Qn.

### Discussion

Dose-dependent kinetics of Qd elimination was clearly demonstrated in the present studies, as total plasma ( $CL_p$ ) and blood clearances decreased significantly with increasing dose (Tables I and II). On the other hand, no dose-dependent kinetics of Qn elimination was found over the present dose employed. Fremstad *et al.*<sup>9)</sup> reported a hepatic extraction ratio of Qd to be 0.81, calculated as hepatic clearance/liver blood flow, at a dose of 25 mg/kg which is within the range of nonlinear kinetics in the present study. A major contribution of the liver to elimination of Qn has also been reported in the rat,<sup>21)</sup> dog,<sup>21)</sup> and man.<sup>4)</sup> There is some question as to the hepatic blood flow in the rat in general, with estimates varying from 60 to 93 ml/min/

TABLE IV. Unbound Volume of Tissue Distribution ( $V_T/f_{u,T}$ )<sup>a)</sup> Estimated from Rat Physical Data and from the Interspecies Physical Data (in Parentheses)

Dose	5 mg/kg	10 mg/kg	15 mg/kg	20 mg/kg
Qd	38.6 $\pm$ 4.58 (38.2 $\pm$ 4.58)	30.4 $\pm$ 3.88 (30.0 $\pm$ 3.86)	19.7 $\pm$ 1.99 (19.5 $\pm$ 1.98)	16.3 $\pm$ 1.41 (16.1 $\pm$ 1.41)
Qn	27.9 $\pm$ 1.96 (27.6 $\pm$ 1.96)	19.6 $\pm$ 1.60 (19.3 $\pm$ 1.60)	23.1 $\pm$ 1.12 (22.9 $\pm$ 1.12)	23.4 $\pm$ 1.35 (23.2 $\pm$ 1.34)

a) Each value (l/kg) represents the mean  $\pm$  S.E.; numbers of animals are given in Table I.

See text details.

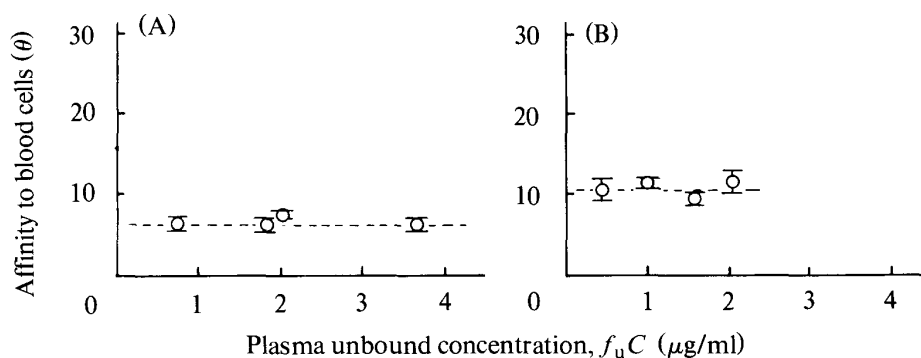


Fig. 4. Blood Cells-to-Unbound Plasma Concentration Ratio ( $\theta$ ) of (A) Qd and (B) Qn

kg.<sup>22-26)</sup> The elimination of Qd and Qn into the urine and bile was minimal in rats, in accord with the results of Anderson *et al.*<sup>21)</sup> and Fremstad *et al.*<sup>9)</sup> Therefore, calculated blood clearances of Qd and Qn at doses of 5 and 10 mg/kg (at which kinetics are linear) were almost equal to hepatic ones, which are within the high range of hepatic blood flows irrespective of highly bound drugs in the plasma (Fig. 3). Furthermore, blood clearance of Qn after injection of 5 mg/kg into the left carotid artery was  $77.8 \pm 6.05$  ml/min/kg (mean  $\pm$  S.E.,  $n=4$ ) in other experiments. This value is comparable to those after i.v. injection of 5 and 10 mg/kg of Qn (Table II), indicating no contribution of the lungs to blood clearance. Based on these results, it appears that the elimination of these two diastereomers is non-restrictive in the liver.<sup>27)</sup>

At higher doses of 15 and 20 mg/kg of Qd blood clearance decreased significantly, and blood clearance after 20 mg/kg decreased almost two-fifths after 5 mg/kg. This is due to liver metabolism, since Yu *et al.*<sup>28)</sup> reported dose-dependent kinetics of Qd in a rat liver perfusion study. Furthermore, it has been reported that the liver is the major elimination organ for Qd in the rat.<sup>9)</sup> Although metabolism differs among species, the present findings of dose-dependency has been reported to occur in man.<sup>29,30)</sup>

Although the volume of central compartment ( $V_1$ ) for Qd remained constant irrespective of the dose (Table I), the volume of tissue compartment ( $V_2$ ) and the unbound volume of tissue distribution ( $V_T/f_{u,T}$ ) significantly de-

creased with increasing dose, in contrast to Qn. These indicate a nonlinear tissue distribution of Qd. In general, the physiological distribution of most drugs is governed by two factors:<sup>31)</sup> (a) their reversible binding equilibrium with proteins and/or other constituents in blood and tissues and (b) the concentration difference of unbound drug, which depends on membrane permeability. In the present study, the plasma protein binding was studied in spiked plasma, and nonlinear plasma protein binding for Qd was observed in contrast to Qn. Fremstad *et al.*<sup>9)</sup> showed the unbound fraction of Qd in plasma *in vivo* during the elimination phase to be from 0.25 to 0.30 in the concentrations below 3  $\mu\text{g/ml}$ . These values are comparable to the present ones (Fig. 3), indicating minimal interaction between Qd and its metabolites. This would be interpreted by the fact that metabolism is the conversion of one chemical species to a more hydrophilic one. Although nonlinearity in  $V_T/f_{u,T}$  for Qd was observed, the unbound fraction of Qd in the *in vivo* mean plasma concentration for the plasma collecting time ( $\int_0^t C dt/t$ ) was used in the present calculation of  $V_T/f_{u,T}$ . Therefore, a calculated value of  $V_T/f_{u,T}$  would be a mean value.

Nishiura *et al.*<sup>32)</sup> reported that the *in vivo* tissue-to-plasma concentration ratios were almost constant at three steady-state levels (0.2, 0.4, and 1.0  $\mu\text{g/ml}$ ) of Qd in rats. However, Harashima *et al.*<sup>12)</sup> reported a nonlinear tissue distribution of Qd in rats after i.v. injection of 30 mg/kg. This discrepancy is simply due to the difference in the plasma levels, which in the

former case, were within the linear concentration range obtained at doses of 5 and 10 mg/kg of Qd in the present study (Fig. 1). Based on these considerations, there is likely a nonlinear tissue binding in Qd. However, there was no concentration-dependency for blood cell affinity, as mentioned below. On the other hand, the unbound volume of tissue distribution of Qn remained constant irrespective of dose, indicating a higher binding capacity and a larger dissociation constant to the tissues for Qn than for Qd in rats. Consequently, this results in a higher binding of Qd than Qn at low concentrations, with a reversal at high concentrations in the tissues.

There was no significant difference between Qd and Qn for  $V_2$ ,  $V_{ss}$ , and  $V_T/f_{u,T}$  at a dose of 5 mg/kg. This may be explained as follows: Since the two  $pK_a$ 's of Qd (4.00 and 8.57<sup>33)</sup>) are very close to the  $pK_a$ 's of Qn (4.13 and 8.30<sup>19)</sup>), it seems reasonable that the difference in pH-dependent distribution of unbound drug between intra- and extracellular space,<sup>31,34)</sup> and in lipid solubility is minimal between these diastereomers.

The almost equal distribution of Qd and Qn between plasma and whole blood was observed over the present concentration range examined (Fig. 2). Harashima *et al.*<sup>12)</sup> reported that at blood concentrations below 2  $\mu\text{g/ml}$ , the ratio of Qd decreased with decreasing blood concentration. In the present study, the ratios at blood concentrations below 2  $\mu\text{g/ml}$  could not be determined because of the limit of detection; however, the nonlinearity in this ratio was almost explained by that in the serum binding of Qd.<sup>12)</sup> Since several processes are occurring simultaneously within the blood in terms of drug distribution, one needs to consider not only binding within plasma but also the affinity of drug components on or within the erythrocytes.<sup>35)</sup> Therefore, the parameters  $\theta$  estimated from Eq. 2 would be a more principal one in the estimation of drug affinity for blood cell components. Indeed, as shown in Fig. 4, Qn had a significantly higher binding capacity than Qd for blood cell components.

A binding linear coefficient ( $\xi$ ) for the blood cells, calculated as

$$\xi = C_{RC,b}/C_u = \theta - 1 \text{ (hence, } C_{RC} =$$

$C_{RC,b} + C_u$  where  $C_{RC,b}$  is the total bound concentration in blood cell components), was 5.68 for Qd, in accord with the value of 5.6.<sup>12)</sup> This value of Qn was 9.80. The linearity in blood cell binding for Qd presented here is consistent with results for humans,<sup>36)</sup> whose red cell uptake of Qd was a passive partition of free drug between plasma and cells. Furthermore, Qd taken up by the red cells was largely associated with the red cell contents (94.4%) rather than the cell membranes. Therefore, it is presumed that blood cell binding in these diastereomers in rats is also due to cell contents.

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