EFFECTS OF CIMETIDINE ON QUINIDINE DISTRIBUTION IN RATS

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The effects of cimetidine on the time course of plasma concentration, plasma protein binding and tissue distribution of quinidine were studied in rats. The plasma disappearance of quinidine after a 25 mg/kg intravenous injection was fitted to a two compartment open model. In the cimetidine-treated rats (50 mg/kg), the pharmacokinetic parameters of quinidine, such as the plasma total body clearance (Cl_{tot}), the volume of distribution at steady state (V_{dss}) and the elimination rate constant of the central compartment (k_{el}) decreased to 62, 60 and 73%, respectively of those of the non-treated rats.

The plasma concentration of quinidine at steady state, after an intravenous injection (20 mg/kg body weight) followed by a constant rate infusion (0.2 mg/min/kg), increased from 3.02 to 5.11 $\mu\text{g/ml}$ after cimetidine treatment. The tissue-to-plasma concentration ratio (K_p) of heart, brain and muscle, determined in homogenates at steady state, decreased after cimetidine treatment. The effect of cimetidine lasted several hours after a cimetidine bolus intravenous injection. These decreases of K_p could satisfy quantitatively the decrease of V_{dss} . It may be concluded that the decrease of V_{dss} was due to the inhibition of tissue distribution (binding and/or partition to tissue components) of quinidine by cimetidine treatment.

Keywords — cimetidine; quinidine; drug interaction; tissue distribution; tissue-to-plasma concentration ratio; blood-to-plasma concentration ratio; protein binding

INTRODUCTION

Cimetidine, a histamine H_2 -receptor antagonist, is prescribed widely for the therapy of peptic ulcers and is well known to inhibit cytochrome P-450 mediated metabolism of a number of drugs such as theophylline,¹⁾ phenytoin²⁾ and warfarin.³⁾ Cimetidine not only inhibits the oxidative metabolism catalysed by cytochrome P-450, but also reduces the hepatic clearance of propranolol⁴⁾ and lidocaine,⁵⁾ which have high hepatic clearance, by decreasing hepatic blood flow. Recently, cimetidine was reported to decrease the distribution volume of lidocaine,^{6,7)} quinidine⁸⁾ and imipramine,⁹⁾ and is thought to affect plasma protein binding and/or tissue distribution of coexistent drugs. There has been little interest in studying drug interaction to decrease distribution volume, however. To study the mechanisms of this interaction, it is not enough to calculate the pharmacokinetic parameters of a compartment model using the time course of plasma concentration. In this report, the decrease of distribution volume was studied not only by pharmacokinetics but also using physiological parameters such as the plasma protein binding and the tissue-to-

plasma concentration ratio (K_p).¹⁰⁾ K_p is defined as the ratio of the drug concentration in tissue to that in emergent venous plasma, and the sum of products of K_p and volumes of all tissues yields the distribution volume. On the assumption that the free drug concentrations in plasma and/or tissue are the same, K_p becomes the ratio of free fractions of the drug in plasma to that in tissue. K_p is governed by reversible or non-reversible binding, and simple partition to protein and other components of plasma and tissues. K_p is an important parameter to analyze the change of distribution volume by drug interaction. Thus, in order to elucidate the mechanism(s) of the decrease of distribution volume by cimetidine, the effect of cimetidine on the pharmacokinetics, plasma protein binding and K_p of a cationic drug in rats was examined. Quinidine which is a popular antiarrhythmic agent was used as a test drug because it is metabolized by liver cytochrome P-450¹¹⁾ and there are only few reports showing the distribution volume of quinidine was decreased by cimetidine.⁸⁾

MATERIALS AND METHODS

Materials — Cimetidine was purchased from

Sigma Chemical Co., Ltd. (St. Louis MO, U.S.A.) and quinidine sulfate from Nakarai Chemicals (Kyoto, Japan). All the other reagents were commercial products and of analytical grade.

Quinidine Pharmacokinetic Study — Four male Sprague-Dawley rats, weighing 250–300 g, were used in the non-treated and in the cimetidine-treated studies. The rats were anesthetized with sodium pentobarbital (i.p., 44 mg/kg body weight) and fixed on a board. The left femoral artery and vein were cannulated with polyethylene tubings (PE-50, Clay-Adams, NJ, U.S.A.). The body temperature was kept at 37 °C using a heat lamp. Either cimetidine (25 mg/ml, 50 mg/kg body weight) or saline solution was injected (2.0 ml/kg) through the femoral vein cannula. Thirty minutes after a cimetidine injection, the rats were injected with quinidine (free base, 15.6 mg/ml, 25 mg/kg body weight). Blood samples (0.3 ml) were taken in heparinized polyethylene centrifuge tubes at 1, 3, 5, 7, 10, 15, 20, 30, 60, 90, 120, 180 and 240 min after a quinidine injection. Plasma was separated by centrifugation at $1000 \times g$ for 10 min. A 0.1 ml portion of plasma was used to determine the quinidine concentration.

Blood and Tissue Distribution of Quinidine

— Five male Sprague-Dawley rats were used in the non-treated and in each of four types of cimetidine-treated studies. The other conditions of rats were the same as described above. The femoral arteries and veins were cannulated with polyethylene tubings (PE-50). To obtain the quinidine plasma concentration at steady state (3 μ g/ml) in the non-treated study, a loading dose (20 mg/kg, bolus injection) was followed by an infusion (0.2 mg/min/kg) with a constant rate infusion pump (JP-WG, Furue Sci., Tokyo, Japan). The blood (0.1 ml) was taken from the cannula for quinidine determination 20 and 40 min after the initiation of an infusion. At the end of an infusion, 60 min, the whole blood was removed through two femoral artery cannulas. A 0.1 ml portion of blood was removed for quinidine determination and the remaining blood was centrifuged at $1000 \times g$ for 20 min, then 0.1 ml of plasma was sampled. After removal of the whole blood, the tissues were quickly excised and rinsed with an ice cold saline solution. The tissues were homogenized in three-fold volumes of 0.05 M Tris-HCl buffer (pH 7.4) using a high speed homogenizer (Physoctron Homogenizer,

Nichion Irica, Tokyo, Japan). In the interaction studies, cimetidine (25 mg/ml, 50 mg/kg) was injected intravenously 30, 90, 180 or 360 min before the whole blood removal. Quinidine administration (a bolus intravenous injection plus a constant rate infusion) was started 60 min before the whole blood removal. The quinidine concentrations in blood, plasma and tissue homogenates were determined.

Plasma Protein Binding of Quinidine — The plasma free fraction of quinidine (f_p) was determined by equilibrium dialysis of the remaining plasma for the tissue distribution study. Two chambers, one containing a mixture of 1.0 ml of rats plasma and 1.0 ml of 0.05 M Tris-HCl buffer (pH 7.4) and the other containing 2.0 ml of buffer solution, were separated by a molecular sieve membrane (Spectrapor II, Spectrum Med. Ind., CA, U.S.A.) and shaken at 37 °C for 5 h. The quinidine concentrations in both chambers were determined.

Analytical Method — The quinidine concentrations in plasma, blood, tissue homogenate and dialyzed solution were determined spectrofluorometrically by a method for quinine, which is a dextro-stereoisomer of quinidine, with a minor modification.¹²⁾ To 0.1 ml of plasma or blood, 1.5 ml of 0.1 N NaOH and 5.0 ml of ethylenedichloride were added. After shaking for 20 min and centrifugation at $1000 \times g$ for 10 min, 4.0 ml of the organic layer were taken and mixed with 4.0 ml of 0.1 N H₂SO₄. After shaking and centrifugation, the quinidine concentration in the aqueous layer was determined spectrofluorometrically at 350 nm for excitation and 445 nm for emission (Hitachi 650-10 spectrofluorometer, Hitachi Ltd., Tokyo, Japan). In a preliminary experiment, the final aqueous layer was spotted on a silica gel thin layer plate and the plate developed by a mixture of methanol-acetone (4:1, v/v).¹³⁾ Under irradiation of 350 nm light, only one spot corresponding to quinidine was detected. To 0.5 ml of homogenate or dialyzed solution, the same procedures were used. The minimum sensitivity of quinidine in blood, plasma, tissue homogenate and dialyzed solution were about 0.1, 0.1, 0.5 and 0.5 μ g/ml, respectively.

Pharmacokinetic Parameters — The observed plasma concentrations (C_p) of an individual rat were fitted to Eq. 1 by the non-linear least squares regression. The area under plasma concentration curve from time zero to infinity

(AUC), the plasma total body clearance (Cl_{tot}) and the distribution volume at steady state (V_{dss}) are given by the following equations:¹⁴⁾

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

$$AUC = \int_0^\infty C_p dt = A/\alpha + B/\beta \quad (2)$$

$$Cl_{tot} = \text{Dose}/AUC \quad (3)$$

$$V_{dss} = \text{Dose} (A\beta^2 + B\alpha^2)/(B\alpha + A\beta)^2 \quad (4)$$

Tissue-to-Plasma Concentration Ratio (K_p)

— The apparent K_p at steady state is defined as

$$K_{p,app} = C_{tss}/C_{pss} \quad (5)$$

where C_{tss} and C_{pss} are tissue and plasma concentrations of quinidine at steady state, respectively. According to Chen and Gross,¹⁰⁾ K_p is calculated from $K_{p,app}$ as follows:

For the non-eliminating tissues,

$$K_p = K_{p,app} \quad (6)$$

For the eliminating tissue (liver),

$$K_p = K_{p,app}/F \quad (7)$$

where F is the availability of tissue and given by

$$F = 1 - Cl_{tot}/Q/R_b \quad (8)$$

where Q is the hepatic blood flow and R_b is the blood to plasma concentration ratio of quinidine.

Distribution Volume at Steady State Calculated by K_p ($V_{dss,Kp}$) — The $V_{dss,Kp}$ is given by the following equation:¹⁵⁾

$$V_{dss,Kp} = R_b \cdot V_b + \sum_i K_{p,i} \cdot V_{t,i} \quad (9)$$

where V_b and V_t are the volume of blood and tissue. Subscript i denotes the number of tissues. The V_b is given by the equations of Bischoff *et al.*¹⁶⁾

$$V_p = 44 \cdot (\text{body weight, kg})^{0.99} \quad (10)$$

$$V_b = V_p/(1 - H_t) \quad (11)$$

where V_p is the volume of plasma and H_t is the hematocrit value (0.45 in this study). The

TABLE I. *Tissue Volumes for Calculation of Tissue Distribution of Quinidine in Rats*^{a)}

Tissue	Volume ^{b)} (ml)
Lung	1.2
Liver	11.0
Kidney	2.0
Heart	1.0
Spleen	1.0
Stomach	1.2
Intestine	11.0
Brain	1.2
Muscle	125.0
Adipose	10.0
Skin	43.8

a) Cited from reference 15.

b) For a rat of 250 g body weight.

volumes of tissue (V_t) used in the calculation of $V_{dss,Kp}$ in this study are listed in Table I.¹⁵⁾

Statistical Analysis — All means are presented with their standard errors (means $\pm$ S.E.). The Student's t -test was utilized to estimate a significant difference between the non-treated group and the cimetidine-treated group, with $p = 0.05$ as the minimal level of significance.

FIG. 1. *Disappearance of Quinidine from Plasma after a Bolus Intravenous Injection with or without Cimetidine Treatment*

Each point and vertical bar represent the mean $\pm$ S.E. of four experiments. Lines are simulated using the parameters obtained from curve fitting. Key; ○, no treatment; ●, cimetidine treatment.

TABLE II. *Pharmacokinetic Parameters of Quinidine with or without Cimetidine Treatment*^{a)}

	No treatment	Cimetidine treatment ^{b)}
<i>A</i> (μg/ml)	13.9 ± 6.3	13.7 ± 4.0
<i>α</i> (min ⁻¹)	0.608 ± 0.143	0.528 ± 0.158
<i>B</i> (μg/ml)	5.31 ± 0.20	9.02 ± 0.18 ^{c)}
<i>β</i> (10 ⁻³ min ⁻¹)	6.41 ± 0.27	6.67 ± 0.80
<i>AUC</i> (μg min/ml)	853 ± 27	1446 ± 185 ^{c)}
<i>Cl</i> _{tot} (ml/min/kg)	29.5 ± 0.9	18.2 ± 2.4 ^{c)}
<i>V</i> _{dss} (l/kg)	4.47 ± 0.07	2.67 ± 0.05 ^{c)}
<i>k</i> _{el} (10 ⁻³ min ⁻¹)	22.6 ± 4.7	16.5 ± 3.6 ^{c)}

a) Values are the means ± S.E. of four experiments.
min before an intravenous injection of quinidine (25 mg/kg).

b) Cimetidine was injected (50 mg/kg) 30

c) Significantly different from the non-

RESULTS

Effects of Cimetidine Treatment on Quinidine Elimination from Plasma

The disappearance of quinidine in plasma after an intravenous injection with or without cimetidine treatment is shown in Fig. 1. The disappearance of quinidine followed a biexponential curve in both the non-treated and the cimetidine treated rats. The plasma concentrations of quinidine at the terminal phase in the cimetidine treated rats were significantly higher than those in the non-treated rats. Typical pharmacokinetic parameters are listed in Table II. The *Cl*_{tot}, *V*_{dss} and *k*_{el} decreased by 38, 40 and 27%, respectively, and *AUC* increased by 70% by cimetidine treatment (*p* < 0.05). However, the rate constant at the terminal phase (*β*) was not altered by cimetidine.

Effects of Cimetidine Treatment on C_{ps}, Blood Distribution and Plasma Protein Binding of Quinidine

The plasma concentration (*C_p*) of quinidine during an infusion for 60 min with or without cimetidine treatment are shown in Fig. 2. Within 30 min after a loading dose (20 mg/kg, bolus injection) and an infusion (0.2 mg/min/kg), *C_p* reached a steady state (*C_{ps}*). Sixty minutes after quinidine administration, *C_{ps}*, *R_b* and *f_p* of quinidine with or without cimetidine treatment were determined and are listed in Table III. The values *C_{ps}* for the four types of cimetidine treatments were increased from 3.02 μg/ml to an average of 5.11 μg/ml (the ranged being 4.26 to 6.17 μg/ml). The *R_b* values were not altered with cimetidine treatment. The data for *f_p*, only at 180 and 360 min after cimetidine

treatment decreased significantly. In a preliminary experiment, the effect of dilution of plasma was studied. The *f_p* values of quinidine with or without dilution were 0.368 ± 0.027 (*n* = 3) and 0.336 ± 0.045 (*n* = 3), respectively at 3 μg/ml of quinidine level. It was shown that the dilution of plasma had no effects on *f_p*.

Effects of Cimetidine Treatment on Tissue Distribution of Quinidine

FIG. 2. *Plasma Concentration Profiles of Quinidine after a Bolus Intravenous Injection Followed by a Constant Rate Infusion with or without Cimetidine Treatment*

Each point and vertical bar represent the mean ± S.E. of five experiments. a) Cimetidine was intravenously injected (50 mg/kg) 30, 90, 180 and 360 min before the whole blood removal. b) A loading dose (20 mg/kg) was followed by an infusion (0.2 mg/min/kg) of quinidine. Key: (○) no treatment, and (●) 30 min, (△) 90 min, (▲) 180 min and (□) 360 min after cimetidine treatment.

TABLE III. C_{pss} , R_b and f_p of Quinidine with or without Cimetidine Treatment^{a),b)}

Period after cimetidine treatment ^{c)} (min)	Parameters of Quinidine		
	C_{pss} ($\mu\text{g/ml}$)	R_b	f_p
No treatment	3.02 ± 0.38	1.62 ± 0.107	0.35 ± 0.02
30	$6.17 \pm 0.50^d)$	1.52 ± 0.289	0.36 ± 0.04
90	$4.77 \pm 0.28^d)$	1.49 ± 0.248	0.35 ± 0.03
180	$4.26 \pm 0.60^d)$	1.61 ± 0.333	$0.22 \pm 0.04^d)$
360	$5.22 \pm 0.65^d)$	1.83 ± 0.158	$0.29 \pm 0.03^d)$

a) Values are the means $\pm$ S.E. of five experiments. b) A loading dose (20 mg/kg) was followed by an infusion of quinidine (0.2 mg/min/kg). c) Cimetidine was intravenously injected (50 mg/kg). d) Significantly different from the non-treated group ($p < 0.05$).

TABLE IV. K_p of Quinidine with or without Cimetidine Treatment^{a),b)}

Tissue	Period after cimetidine treatment ^{c)} (min)				
	No treatment	30	90	180	360
Lung	48.0 ± 5.89	$28.9 \pm 4.49^d)$	57.3 ± 13.3	$29.4 \pm 1.76^d)$	$30.8 \pm 3.63^d)$
Liver	24.9 ± 3.89	21.8 ± 1.20	$19.4 \pm 1.67^d)$	21.1 ± 1.39	$18.4 \pm 1.86^d)$
Kidney	36.6 ± 3.97	$26.1 \pm 4.28^d)$	30.3 ± 5.06	$31.3 \pm 2.49^d)$	$24.4 \pm 2.05^d)$
Heart	9.93 ± 0.58	$6.46 \pm 1.07^d)$	$6.90 \pm 1.18^d)$	$7.43 \pm 0.48^d)$	$7.20 \pm 0.75^d)$
Spleen	28.9 ± 6.01	$13.5 \pm 2.86^d)$	$16.5 \pm 3.92^d)$	$19.3 \pm 0.94^d)$	17.9 ± 1.69
Stomach	9.10 ± 1.53	7.69 ± 1.48	7.66 ± 0.62	$6.34 \pm 1.39^d)$	4.10 ± 0.26
Intestine	11.1 ± 0.90	$8.79 \pm 1.42^d)$	9.45 ± 1.70	9.63 ± 1.33	9.75 ± 0.94
Brain	1.26 ± 0.11	$0.61 \pm 0.01^d)$	$0.90 \pm 0.09^d)$	$0.95 \pm 0.02^d)$	$0.72 \pm 0.23^d)$
Muscle	3.55 ± 0.31	$3.02 \pm 0.32^d)$	$2.60 \pm 0.29^d)$	$2.84 \pm 0.26^d)$	$2.34 \pm 0.32^d)$
Adipose	1.42 ± 0.10	1.32 ± 0.32	1.42 ± 0.21	1.37 ± 0.28	1.95 ± 0.43
Skin	3.77 ± 0.78	$1.99 \pm 0.38^d)$	$1.66 \pm 0.34^d)$	$2.26 \pm 0.42^d)$	3.03 ± 0.14

a) Values are the means $\pm$ S.E. of five experiments. b) A loading dose (20 mg/kg) was followed by an infusion of quinidine (0.2 mg/min/kg). c) Cimetidine was intravenously injected (50 mg/kg). d) Significantly different from the non-treated group ($p < 0.05$).

TABLE V. $V_{dss, Kp}$ of Quinidine with or without Cimetidine Treatment^{a)}

Period after cimetidine treatment ^{b)} (min)	$V_{dss, Kp}$ ^{c)} (l/kg)
No treatment	5.23 ± 0.44
30	$3.95 \pm 0.20^d)$
90	$4.04 \pm 0.59^d)$
180	$3.87 \pm 0.28^d)$
360	$3.75 \pm 0.40^d)$

a) Values are the means $\pm$ S.E. of five experiments. b) Cimetidine was intravenously injected (50 mg/kg). c) Calculated from K_p using Eq. 9. d) Significantly different from the non-treated group ($p < 0.05$).

Table IV demonstrates the change in K_p of quinidine with or without cimetidine treatment.

The K_p of heart, brain and muscle at all times after cimetidine treatment decreased significant-

ly by an average of 30, 37 and 24%, respectively. The K_p of lung, liver and kidney showed significant decrease occasionally after cimetidine treatment. Table V demonstrates V_{dss, K_p} calculated using Eq. 9. The V_{dss, K_p} decreased significantly by an average of 25% in all cases after cimetidine treatment.

DISCUSSION

The pharmacokinetic study showed that cimetidine reduced the plasma total body clearance (Cl_{tot}) of quinidine by 38%, the distribution volume at steady state (V_{dss}) by 40% and the elimination rate constant (k_{el}) by 27%. However, the rate constant of the terminal phase (β) was not changed by cimetidine. The elimination of quinidine in rats occurs only by the metabolism *via* cytochrome P-450 dependent pathways in the liver.¹⁷⁾ Since cimetidine has been reported to inhibit these pathways,¹⁻³⁾ the decrease of k_{el} by cimetidine treatment was due to the decrease of the metabolizing ability in the liver.

Cimetidine was reported to decrease the clearance of propranolol⁴⁾ and lidocaine⁵⁾ which have high hepatic clearance. This effect was partially attributed to a 30% reduction of blood flow by cimetidine.⁴⁾ Although quinidine was not a drug of high hepatic clearance, the decrease of hepatic blood flow contributed to the decrease of Cl_{tot} to some extent.

The decrease of Cl_{tot} was caused by not only the metabolic inhibition and the decrease of hepatic blood flow but also by the decrease of distribution volume. There is a report of by Furancillo *et al.*⁸⁾ which showed a single dose of cimetidine to rats significantly reduced Cl_{tot} of quinidine by 35% and the distribution volume by 20%, but did not affect k_{el} . The variety of changes of k_{el} may depend on the cimetidine dose used in the experiments and the size of data variances to distinguish significant difference.

The reason for the decrease of V_{dss} was suspected at first to be due to the decrease of the plasma free fraction (f_p) so that the tissue-to-plasma concentration ratio (K_p) was decreased. But f_p of quinidine did not change at 30 and 90 min after cimetidine treatment. It is similarly reported that the plasma protein binding of quinidine was unaffected by cimetidine treatment in normal volunteers.¹⁸⁾ These results indicate that cimetidine cannot displace quinidine from the binding site of plasma protein while the f_p of

quinidine decreased significantly at 180 and 360 min after cimetidine treatment. These results show that cimetidine increased the binding of quinidine to plasma protein for over 180 min after cimetidine treatment, thus in part causing a decrease of V_{dss} . The reasons for the decreased f_p by cimetidine over 180 min is more difficult to understand because the plasma levels of both drugs were less than those at earlier periods. In addition, the phenomenon was contrary to what the inhibition of plasma protein binding causes. It may be that (1) cimetidine increased the plasma levels of binders to quinidine and/or (2) cimetidine increased the affinity of binders in plasma to quinidine. Quinidine is a basic drug and binds not only albumin but also α_1 -acid glycoprotein or lipoprotein.¹⁹⁾ Bolton *et al.* reported that cimetidine increased the serum lipoprotein level in normal volunteers²⁰⁾ whereas it was reported that the level of α_1 -acid glycoprotein was not altered significantly with and without cimetidine treatment.^{6,18)} The understanding of the precise mechanism remains for further investigations.

The above discussion shows that the decrease of V_{dss} calculated from the time course of plasma quinidine concentration, was mainly due to the decreases of binding and/or distribution of quinidine to tissues after cimetidine treatment, even though the decrease of f_p contributed to the decrease of V_{dss} to a certain extent after 180 min. To obtain direct evidence of decreasing V_{dss, K_p} was determined by the measurement of quinidine concentration in tissues isolated at steady state. Cimetidine decreased K_p of quinidine in the heart, brain and muscle significantly at all sampling times and also decreased K_p of lung, liver and kidney significantly in many cases (Table IV). The mechanism(s) of the decrease of K_p in tissues may be that (1) cimetidine inhibited the distribution to tissue components, (2) non-linear tissue binding of quinidine or (3) cimetidine increased the intracellular pH of tissues. Kato *et al.* reported that the quinidine binding to muscle homogenate did not depend on the drug concentration and that this binding decreased to 40% after extraction of lipid from muscle.²¹⁾ It was reported that the binding of quinidine to *n*-butanol treated liver homogenate decreased to less than a half of that of non-treated homogenate, whereas the binding to heat-treated homogenate decreased only slightly

compared to that of non-treated homogenate.²²⁾ Furthermore, it was reported that the binding of cimetidine to isolated liver cytochrome P-450 was enhanced by the reconstitution of this fraction with phospholipid.²³⁾ These reports suggest that lipid is the main distribution site of quinidine in tissues. Thus it is possible that cimetidine has some interactions with lipid and phospholipid and inhibits the distribution (partition and/or binding) of quinidine to lipids resulting in the decreases of K_p of these tissues.

Harashima *et al.* reported that quinidine showed non-linear tissue binding that was explained by saturable binding to tissue phospholipid.¹³⁾ In the case where plasma concentration of quinidine was increased by cimetidine treatment, as was observed in this report, quinidine K_p of certain tissues may decrease.

Chlorpromazine, which is a cationic drug, was reported to decrease the pH difference between mucosal and serosal sides of the rat intestinal wall by inhibiting the serosal alkalization, indicating an effect on proton transport systems of cells.²⁴⁾ It may be said that the pH change of tissues by cimetidine affects the K_p of quinidine because the pK_a of quinidine is 8.6 and the high K_p value can be explained by the pH partition theory.

The effect of cimetidine was observed as soon as 10 min after an injection and lasted at least 360 min. The plasma cimetidine level rapidly decreased after an injection. The elimination half life of cimetidine in rats was 50 min (unpublished data), so the plasma concentration of cimetidine was below 1% of the initial concentration at 360 min. This lasting effect indicates that cimetidine irreversibly decreased the tissue distribution of quinidine.

The two types of volume of distributions at steady state, V_{dss} (Table II) and V_{dss,K_p} (Table V) in the cimetidine-treated rats, decreased by 25 and 40%, respectively, compared to the non treated rats ($p < 0.05$). Considering that V_{dss,K_p} was calculated from K_p *in vitro* in several isolated tissues after homogenization and that the removal of blood from tissues was incomplete, good agreement was observed in the values of both distribution volumes and in their decreased percentages by cimetidine. Since quinidine has a narrow therapeutic range in clinical use, if the drug action correlates with plasma levels, the increase of plasma quinidine levels may cause

severe adverse effects such as cinchonism, arrhythmias and syncope. On the other hand, if the drug action relates to tissue levels, the results of drug interactions may be complicated. Therefore, when cimetidine and quinidine are prescribed concurrently, it is necessary to carefully monitor not only the plasma quinidine concentrations but also the pharmacological responses.

In conclusion, cimetidine treatment of rats increased the quinidine plasma concentration. The pharmacokinetic analysis shows decreases of Cl_{tot} , V_{dss} and k_{el} of quinidine by cimetidine treatment. The K_p values of several tissues at steady state of quinidine were determined to be decreased after cimetidine treatment. The decrease in K_p can account for the greater part of the decrease of V_{dss} *in vivo*, and the rest may be due to the other causes discussed above. Although interest in drug interaction of the decrease of V_{dss} has not been high, it may necessary to being more concentrated attention to this area in the field of clinical medication. The precise mechanisms of the decrease of V_{dss} should be further studied to enable a prediction of adverse effects of drug interaction.

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