Effects of Cimetidine on Lidocaine Distribution in Rats

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The effects of cimetidine on the disappearance from plasma, plasma protein binding, tissue distribution, tissue binding in vivo and uptake by erythrocytes of lidocaine were studied in rats. The plasma disappearance of lidocaine after a 10 mg/kg bolus injection was analyzed by a two-compartment open model. In the cimetidine-treated rats (50 mg/kg bolus injection, plasma total body clearance (Cl_{p,IB}), the volume of distribution at the steady state (V_{ss}) and the elimination rate constant of the central compartment (k_{el}) of lidocaine decreased by 27, 28 and 32% of those in the non-treated rats, respectively.

The plasma concentration of lidocaine at the steady state, after a loading dose (7.62 mg/kg body weight) followed by an infusion (0.16 mg/min/kg), increased from 1.62 to 2.69 μg/ml after cimetidine treatment. The tissue-to-plasma concentration ratio (K_p) in spleen, stomach and skin decreased to 64, 62 and 62% of the values of the non-treated rats. In addition, the blood-to-plasma concentration ratio (R_p) decreased by 26% in cimetidine-treated rats. In vitro tissue-to-plasma concentration ratios (K_{p, in vitro}) of lidocaine in spleen, stomach and skin homogenate were decreased to 58, 45 and 68% by cimetidine treatment. In these tissues, the percentage decreases of K_p, in vitro agreed with those of K_p determined in vivo. The decrease of K_p by cimetidine treatment may be due to the inhibition of tissue binding of lidocaine.

The uptake of lidocaine by erythrocytes was decreased by cimetidine treatment. The pH profile of uptake was shifted to the higher pH side by the addition of cimetidine, indicating a decrease of the pH difference between intra- and extracellular spaces.

Keywords — cimetidine; lidocaine; drug interaction; tissue-to-plasma concentration ratio; blood-to-plasma concentration ratio; erythrocyte

Introduction

The treatment of duodenal ulcer has been dramatically changed from surgery to medication by the introduction of a number of pharmacologic approaches to antulcer therapy. The introduction of the potent H_2-receptor antagonist, cimetidine, was recognized as a major advance in antulcer therapy. However, it has become clear that cimetidine has an undesirable effect of binding to hepatic cytochrome P-450 and inhibiting the metabolism of a number of drugs metabolized by the hepatic microsomal oxidation system.1-3 Cimetidine also decreased the distribution volume of some cationic drugs, such as quinidine,4, 5 lidocaine6, 7 and imipramine.8 We have reported that the plasma total body clearance (Cl_{p,IB}) and the volume of distribution at the steady state (V_{ss}) of quinidine were decreased by cimetidine treatment by 38 and 40% from those in untreated rats, respectively. The tissue-to-plasma concentration ratio (K_p) of quinidine was decreased to an average of 65% in several tissues, but the plasma free fraction (f_p) of quinidine was not changed by cimetidine treatment. These results suggested that the cause of the decrease of K_p was mainly the decrease of the tissue distribution.4)

In the case of lidocaine, which is a popular antiarrhythmic agent and is metabolized by liver cytochrome P-450,9 V_{ss} was decreased by cimetidine treatment,6, 7 but little is known about the mechanism(s) of the decrease of V_{ss}. Then, in order to elucidate the mechanism(s) of the decrease of V_{ss} by cimetidine, the effect of cimetidine on the pharmacokinetics, plasma protein binding, K_p, in vitro tissue binding and the uptake by erythrocytes of lidocaine in rats were examined.

Materials and Methods

Material — Lidocaine, cimetidine and procaine hydrochloride were purchased from Sigma
Chemical Co., Ltd. (St. Louis, MO, U.S.A.). All the other reagents were commercial products of analytical grade.

**Lidocaine Pharmacokinetic Study** — Four male Sprague-Dawley rats, weighing 250—300 g, were used in the non-treated and in the cimetidine-treated groups. 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 lidocaine (10 mg/ml, 10 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, 45, 60, 75 and 90 min after lidocaine injection. Plasma was separated by centrifugation at 1000 × g for 10 min. A 0.15 ml portion of plasma was used to determine the lidocaine concentration.

**Blood and Tissue Distribution of Lidocaine** — Five male Sprague-Dawley rats were used in the non-treated and in each of the cimetidine-treated groups. The rats were treated as described above, and the femoral arteries and veins were cannulated with polyethylene tubing (PE-50). In the non-treated group, a loading dose (7.62 mg/kg bolus injection) was followed by an infusion (0.16 mg/kg/min) with a constant rate infusion pump (JW-WG, Furue Sci., Tokyo, Japan) to obtain the steady-state lidocaine concentration (about 2 µg/ml). The blood (0.3 ml) was taken from cannulas for lidocaine determination 20 and 40 min after the initiation of an infusion. At the end of an infusion for 60 min, the blood was removed through both femoral artery cannulas. A 0.15 ml portion of blood was removed for lidocaine determination and the remaining blood was centrifuged at 1000 × g for 20 min, then 0.15 ml plasma was taken as a sample. After removal of the whole blood, the tissues were quickly excised and rinsed with an ice-cold saline solution. The tissues were weighed and homogenized in three volumes of 0.01 M phosphate buffer containing 0.15 M KCl (pH = 7.0) using a high-speed homogenizer (Physcon Homogenizer, Nichion Irico Seisakusho, Tokyo, Japan). In the cimetidine-treated groups, cimetidine (25 mg/ml, 50 mg/kg) was injected intravenously 90 and 360 min before the whole blood removal. Lidocaine administration (a bolus injection plus a constant rate infusion) was started 60 min before the whole blood removal. The lidocaine concentrations in blood, plasma and tissue homogenate were determined.

**Plasma Protein Binding of Lidocaine** — The plasma free fraction of lidocaine (f<sub>P</sub>) was determined by equilibrium dialysis of the remaining plasma for the tissue distribution study. Two chambers, one containing 2.0 ml of rat plasma and the other containing 2.0 ml of 0.05 M Tris-HCl buffer (pH = 7.4) solution were separated by a molecular sieve membrane (Spectrapor II, Spectrum Med. Ind., CA, U.S.A.) and shaken at 37 °C for 14 h. The lidocaine concentrations on both sides of the membrane were determined.

**In Vitro Tissue Binding of Lidocaine** — Four male Sprague-Dawley rats, weighing 250—300 g, were used. The rats were decapitated and the spleen, stomach and skin were excised and rinsed with an ice-cold saline solution. The tissues were homogenized according to the same procedure described in the tissue distribution study. The tissue binding was determined by equilibrium dialysis at 37 °C for 14 h. The initial concentrations of lidocaine and cimetidine in each homogenate were 2.0 and 20 µg/ml, respectively. The initial concentration of cimetidine (20 µg/ml) was adjusted to the plasma concentration of lidocaine 90 min after the 50 mg/kg cimetidine intravenous injection (unpublished data). After equilibrium was attained, the lidocaine concentrations in homogenate and buffer were determined.

**In Vitro Uptake of Lidocaine by Rats Erythrocytes** — Male Sprague-Dawley rats were used. After injection of heparin at a dose of 100 U/100 g of body weight (0.1 ml), whole blood was collected through two femoral artery cannulas at 30 min. Erythrocyte suspension was prepared by the procedure of Horie et al. except for the buffer. We used 0.01 M phosphate buffer.
containing 0.15 mM KCl, pH 6.5, 7.0, 7.5 or 8.0. Rat blood was centrifuged at 1000 × g for 10 min at 4 °C. The pellet was washed with three volumes of the phosphate buffer and centrifuged at 750 × g for 10 min at 4 °C. This washing process for erythrocytes was repeated 3 times at 4 °C. Nine volumes of the same phosphate buffer was added to the pellet to make a 10 (v/v)% suspension. To determine the uptake of lidocaine by erythrocytes, 1.0 ml of erythrocyte suspension was preincubated for 3 min at 37 °C, then drug solution was added to the suspension via a microcyringe. The initial concentrations of lidocaine and cimetidine were 2 and 20 μg/ml, respectively. The mixture was incubated for 30 min at 37 °C and then centrifuged at 1000 × g for 10 min at 4 °C. The supernatant was separated and the concentration of lidocaine was determined.

**Analytical Method** — The lidocaine concentrations in samples were determined by using high-performance liquid chromatography (HPLC). To 0.15 ml of plasma or blood, 0.2 ml of 1 N NaOH, 0.1 ml of 17.6 μg/ml procaine hydrochloride (internal standard) and 3.0 ml of ethyl acetate were added. After shaking for 20 min and centrifugation at 1000 × g for 10 min, 2.5 ml of the organic layer was taken and mixed with 0.1 ml of 0.01 N H₂SO₄. After shaking and centrifugation, 0.01 ml of the aqueous layer was injected into the HPLC column (Hitachi 655, Hitachi Co., Ltd., Tokyo, Japan). The conditions of HPLC were as follows: The column was μBondapack alkyl phenyl (Waters Assoc., U.S.A.), the detector was an ultraviolet monitor (Hitachi 655-A 205 nm), the mobile phase was acetonitrile-0.006 (w/v)% phosphoric acid (30/70) and the flow rate was 2.0 ml/min. Under these conditions, the retention times of lidocaine and procaine were 9.0 min and 6.0 min, respectively. The same procedures were used with 0.5 ml of homogenate or dialyzed solution. The protein concentrations in rat erythrocytes were determined by Lowry’s method.

**Pharmacokinetic parameters** — The observed plasma concentrations (Cₚ) of an individual rat were fitted to a two-compartment open model (Eq (1)) by non-linear least-squares regression.

\[ C_p = A e^{-at} + B e^{-bt} \]  

(1)

The pharmacokinetic parameters of lidocaine such as the area under the plasma concentration curve from time zero to infinity (AUC), the plasma total body clearance (Clₜot), the volume of distribution at the steady state (Vₜss) and the elimination rate constant of the central compartment (kₑ) were calculated by means of the following equations.

\[ AUC = \int_0^\infty C_p \, dt = A/\alpha + B/\beta \]

(2)

\[ Cl_{tot} = \frac{Dose}{AUC} \]

(3)

\[ V_{tss} = \frac{Dose \cdot (A\beta^2 + Ba^2)/(B\alpha + A\beta)^2}{k_{e}} \]

(4)

\[ k_{e} = Cl_{tot} \cdot (A + B)/Dose \]

(5)

**Tissue-to-Plasma Concentration Ratio (Kₚ)** — Kₚ was calculated by the method described in the previous report. The apparent Kₚ (Kₚ,app) at the steady state is defined as

\[ K_{p,app} = \frac{C_{tss}}{C_{pss}} \]

(6)

where Cₜss and Cₚss are tissue and plasma concentrations of lidocaine at the steady state, respectively. According to Chen and Gross, Kₚ is calculated from Kₚ,app as follows:

For the non-eliminating tissues

\[ K_p = K_{p,app} \]

(7)

For the eliminating tissues (liver)

\[ K_p = K_{p,app}/F \]

(8)

where F is the availability of the tissue and is given by

\[ F = 1 - Cl_{tot}/Q/R_b \]

(9)

where Q is the hepatic blood flow (= 80 ml/min/kg) and R_b is the blood-to-plasma concentration ratio of lidocaine. The Clₜot was calculated from Cₚss and the infusion rate (= 0.16
Table I. Tissue Volumes used for Calculation of Tissue Distribution of Lidocaine in Rats \(^a,b\)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>1.2</td>
</tr>
<tr>
<td>Liver</td>
<td>11.7</td>
</tr>
<tr>
<td>Kidney</td>
<td>2.1</td>
</tr>
<tr>
<td>Heart</td>
<td>1.0</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.9</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.6</td>
</tr>
<tr>
<td>Intestine</td>
<td>13.5</td>
</tr>
<tr>
<td>Brain</td>
<td>1.4</td>
</tr>
<tr>
<td>Muscle</td>
<td>127.2 (^d)</td>
</tr>
<tr>
<td>Skin</td>
<td>50.5 (^d)</td>
</tr>
<tr>
<td>Blood</td>
<td>28.6 (^d)</td>
</tr>
</tbody>
</table>

\(^a\) Values are the means of ten rats.  \(^b\) Based on a 290 g body weight.  \(^c\) Tissue volumes except for muscle, skin and blood were determined in this experiment.  \(^d\) Calculated according to the equation of Bischoff et al. \(^17\)

**Distribution Volume at the Steady State**

**Calculated from** \(K_p (V_{dss, K_p})\) — The \(V_{dss, K_p}\) is calculated by using the following equation \(^16\):  

\[
V_{dss, K_p} = R_b \times V_b + \sum K_{p,i} \times V_{i,i}
\]  

(10)

where \(V_b\) and \(V_t\) are the volumes of blood and tissue. Subscript \(i\) denotes the number of tissues. The \(V_b\) is given by the equations of Bischoff et al. \(^17\):

\[
V_b = 44 \times \text{(body weight, kg)}^{0.99}
\]  

(11)

**Fig. 1. Disappearance of Lidocaine from Plasma after Bolus Intravenous Injection with or without Cimetidine Treatment**

Each point and vertical bar represent the mean ± S.E. of four experiments. Lines are simulated using the parameters obtained from curve fitting.

- ○ - , no treatment; - ● - , cimetidine treatment.

\[
v_b = \frac{V_p}{(1 - H_t)}
\]  

(12)

where \(V_p\) is the volume of plasma and \(H_t\) is the hematocrit value (0.45 in this study). The volume of tissues \((V_t)\) used in the calculation of \(V_{dss, K_p}\) in this study are listed in Table I.

**In Vitro Tissue-to-Plasma Concentration Ratio** \((K_{p, \text{vitr}})\) — The \(K_{p, \text{vitr}}\) was defined by the following equation \(^18\):

\[
K_{p, \text{vitr}} = \frac{C_t}{C_f} = \frac{(C_b + C_i)}{C_f} = 1 + d \times \frac{C_{b, \text{wtd}}}{C_f}
\]  

(13)

Table II. Pharmacokinetic Parameters of Lidocaine with or without Cimetidine Treatment \(^a\)

<table>
<thead>
<tr>
<th></th>
<th>No treatment</th>
<th>Cimetidine treatment (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) ((\mu g/ml))</td>
<td>10.3 ± 2.3</td>
<td>7.50 ± 1.8</td>
</tr>
<tr>
<td>(\alpha) (min(^{-1}))</td>
<td>0.552 ± 0.05</td>
<td>0.360 ± 0.03 (^c)</td>
</tr>
<tr>
<td>(B) ((\mu g/ml))</td>
<td>2.48 ± 0.14</td>
<td>3.55 ± 0.33 (^c)</td>
</tr>
<tr>
<td>(\beta) (min(^{-1}))</td>
<td>0.021 ± 0.001</td>
<td>0.022 ± 0.002</td>
</tr>
<tr>
<td>(AU/C) ((\mu g\cdot min/ml))</td>
<td>133.6 ± 9.8</td>
<td>180.7 ± 4.26 (^c)</td>
</tr>
<tr>
<td>(Cl_{tot}) (ml/min/kg)</td>
<td>76.2 ± 6.0</td>
<td>55.5 ± 1.3 (^c)</td>
</tr>
<tr>
<td>(V_{dss}) (l/kg)</td>
<td>3.11 ± 0.29</td>
<td>2.25 ± 0.21 (^c)</td>
</tr>
<tr>
<td>(k_d) (min(^{-1}))</td>
<td>0.105 ± 0.007</td>
<td>0.070 ± 0.010 (^c)</td>
</tr>
</tbody>
</table>

\(^a\) Values are the means ± S.E. of four experiments.  \(^b\) Cimetidine was injected (50 mg/kg) 30 min before an intravenous injection of lidocaine (10 mg/kg).  \(^c\) Significantly different from the non-treated group \((p < 0.05)\).
where \( C_t \), \( C_b \), and \( C_f \) are the tissue concentration, the tissue bound concentration and the tissue free concentration of lidocaine, respectively. \( d \) is the dilution factor (\( d = 4 \) in this study) and \( C_{b,\text{dil}} \) is the bound concentration of lidocaine in the diluted tissue homogenate.

**Statistical Analysis** — All means are presented with their standard errors (mean ± S.E.). Student’s \( t \)-test was utilized to estimate the significance of differences between the non-treated group and the cimetidine-treated group, with \( p = 0.05 \) as the minimal level of significance.

**Results and Discussion**

**Effects of Cimetidine Treatment on Lidocaine Elimination from Plasma**

The disappearance of lidocaine from plasma after a 10 mg/kg intravenous injection with or without cimetidine treatment (50 mg/kg, intravenous injection) is shown in Fig. 1. The plasma disappearance of lidocaine followed a biexponential curve in both the non-treated and the cimetidine-treated rats. The plasma concentrations of lidocaine at the terminal phase were significantly increased by cimetidine treatment. The pharmacokinetic parameters are listed in Table II. The \( AUC \) increased by 35% and \( \text{Cl}_{\text{tot}} \), \( V_{\text{dss}} \) and \( k_{\text{c1}} \) decreased by 27, 28 and 32%, respectively, with cimetidine treatment (\( p < 0.05 \)). The rate constant at the distribution phase (\( \alpha \)) decreased by 35% but the rate constant at the terminal phase (\( \beta \)) did not change with cimetidine treatment.

The effects of cimetidine treatment on the plasma elimination of lidocaine explain the decreases of \( \text{Cl}_{\text{tot}} \) and \( V_{\text{dss}} \). At first, the 27% decrease of \( \text{Cl}_{\text{tot}} \) was considered to be due to the inhibition of oxidative metabolism by cimetidine treatment. Because lidocaine is eliminated only from the liver by metabolism mediated by cytochrome P-450 and cimetidine has been reported to inhibit this pathway, \(^{1-3} \) the metabolism of lidocaine is thought to be impaired by cimetidine treatment. Further, lidocaine is a drug of high hepatic clearance, \(^{19} \) so the \( \text{Cl}_{\text{tot}} \) may be considered to be affected by the change of hepatic blood flow. Reduced \( \text{Cl}_{\text{tot}} \) of lidocaine caused by congestive heart failure \(^{19} \) and by the concomitant administration of propranolol, \(^{20} \) which is known to decrease the hepatic blood flow, has been reported, and ranitidine, an \( H_2 \)-receptor blocker, decreased the \( \text{Cl}_{\text{tot}} \) of lidocaine by 15%. Ranitidine does not inhibit the oxidative metabolism catalyzed by cytochrome P-450, \(^{1,22} \) so the decrease of \( \text{Cl}_{\text{tot}} \) of lidocaine by ranitidine treatment is presumably explained by the decrease of hepatic blood flow as above. Considering these reports and the fact that the hepatic clearance of lidocaine is blood-flow-limited, it may be concluded that the decrease of \( \text{Cl}_{\text{tot}} \) of lidocaine by cimetidine treatment was mainly due to the decrease of the hepatic blood flow rather than the inhibition of hepatic metabolism, though cimetidine may inhibit the metabolism of lidocaine.

The reasons for the decrease of \( V_{\text{dss}} \) by cimetidine treatment were suspected to be the changes of the plasma protein binding and the tissue binding of lidocaine. To confirm this, the plasma free fraction (\( f_p \)), the blood-to-plasma concentration ratio (\( R_b \)) and the tissue-to-plasma concentration ratio (\( K_p \)) of lidocaine

![Fig. 2. Plasma Concentration Profiles of Lidocaine after a Bolus Intravenous Injection Followed by a Constant Rate Infusion with or without Cimetidine Treatment](image-url)

Each point and vertical bar represent the mean ± S.E. of five experiments.

- **a)** Cimetidine was intravenously injected (50 mg/kg) 90 and 360 min before the whole blood removal.
- **b)** A loading dose (7.62 mg/kg) was followed by an infusion (0.16 mg/kg/min) of lidocaine.
- ○, no treatment; ●, 90 min after cimetidine treatment; △, 360 min after cimetidine treatment.
were determined with and without cimetidine treatment.

Effects of Cimetidine Treatment on $C_{\text{ps}}$, $Cl_{\text{tot}}$, $R_b$ and $f_p$ of Lidocaine

The plasma concentration ($C_p$) of lidocaine during a constant rate infusion for 60 min with or without cimetidine treatment (50 mg/kg, bolus injection) are shown in Fig. 2. Within 30 min after a loading dose (7.62 mg/kg, bolus injection) and an infusion (0.16 mg/kg/min), $C_p$ reached a steady state ($C_{\text{ps}}$). At the end of an infusion of lidocaine for 60 min, $C_{\text{ps}}$, $Cl_{\text{tot}}$, $R_b$ and $f_p$ of lidocaine with or without cimetidine treatment were determined and the results are listed in Table III. The $C_{\text{ps}}$ for the two types of cimetidine treatments were increased from 1.62 $\mu$g/ml to 2.67–2.71 $\mu$g/ml. The $Cl_{\text{tot}}$ of lidocaine was decreased by 32–35% by cimetidine treatment ($p < 0.05$). There was no significant difference between the $Cl_{\text{tot}}$ in Table II and Table III. The $R_b$ values were decreased to 75% of those of the non-treated rats by cimetidine treatment. The $f_p$ values in both cases after cimetidine treatment were not altered. These results agreed well with those of Jackson et al., and suggested that cimetidine can not displace lidocaine from the binding sites of plasma protein (albumin, $\alpha_1$-acid glycoprotein or $\beta$-lipoprotein). It is interesting that the $R_b$ of lidocaine was decreased by 26% by cimetidine treatment, although that of quinidine was not decreased by cimetidine treatment. The mechanism(s) of this decrease will be discussed later.

Effects of Cimetidine Treatment on Tissue Distribution of Lidocaine

Table IV demonstrates the change in $K_p$ of

### Table III. $C_{\text{ps}}$, $Cl_{\text{tot}}$, $R_b$ and $f_p$ of Lidocaine at the Steady State with or without Cimetidine Treatment $a$, $b$

<table>
<thead>
<tr>
<th></th>
<th>Period after cimetidine treatment $c$</th>
<th>90</th>
<th>360</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{ps}}$ (mg/ml)</td>
<td>1.62±0.32</td>
<td>2.67±0.48</td>
<td>2.71±0.53</td>
</tr>
<tr>
<td>$Cl_{\text{tot}}$ (ml/min/kg) $d$</td>
<td>91.2±7.70</td>
<td>61.3±6.05</td>
<td>59.0±6.16</td>
</tr>
<tr>
<td>$R_b$</td>
<td>1.27±0.16</td>
<td>0.98±0.10</td>
<td>0.90±0.09</td>
</tr>
<tr>
<td>$f_p$</td>
<td>0.38±0.04</td>
<td>0.36±0.09</td>
<td>0.38±0.07</td>
</tr>
</tbody>
</table>

$a$ Values are the means ± S.E. of five experiments. $b$ A loading dose (7.62 mg/kg) was followed by an infusion of lidocaine (0.16 mg/kg/min). $c$ Cimetidine was intravenously injected (50 mg/kg). $d$ Calculated from $C_{\text{ps}}$ and infusion rate (0.16 mg/kg/min). $e$ Significantly different from the non-treated group ($p < 0.05$).

### Table IV. $K_p$ of Lidocaine with or without Cimetidine Treatment $a$, $b$

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Period after cimetidine treatment $c$</th>
<th>90</th>
<th>360</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>3.80±0.68</td>
<td>3.80±1.01</td>
<td>7.56±1.87</td>
</tr>
<tr>
<td>Liver</td>
<td>11.5±2.99</td>
<td>16.7±5.14</td>
<td>8.42±2.25</td>
</tr>
<tr>
<td>Kidney</td>
<td>17.2±2.74</td>
<td>21.0±0.35</td>
<td>21.1±1.80</td>
</tr>
<tr>
<td>Heart</td>
<td>2.73±0.10</td>
<td>1.82±0.49</td>
<td>4.24±0.42</td>
</tr>
<tr>
<td>Spleen</td>
<td>4.78±0.44</td>
<td>3.06±0.46</td>
<td>5.26±0.77</td>
</tr>
<tr>
<td>Stomach</td>
<td>4.01±0.96</td>
<td>2.50±0.47</td>
<td>2.64±0.71</td>
</tr>
<tr>
<td>Intestine</td>
<td>2.22±0.15</td>
<td>1.92±0.33</td>
<td>2.57±0.49</td>
</tr>
<tr>
<td>Brain</td>
<td>3.24±0.76</td>
<td>2.86±0.47</td>
<td>2.97±0.55</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.68±0.39</td>
<td>0.78±0.12</td>
<td>1.36±0.17</td>
</tr>
<tr>
<td>Skin</td>
<td>2.58±0.49</td>
<td>1.61±0.36</td>
<td>1.70±0.41</td>
</tr>
</tbody>
</table>

$a$ Values are the means ± S.E. of five experiments. $b$ A loading dose (7.62 mg/kg) was followed by an infusion of lidocaine (0.16 mg/kg/min). $c$ Cimetidine was intravenously injected (50 mg/kg). $d$ Significantly different from the non-treated group ($p < 0.05$).
Tissue Distribution of Lidocaine

TABLE V.  $V_{\text{dss}}, K_p$ of Lidocaine with or without Cimetidine Treatment $^a$  

<table>
<thead>
<tr>
<th>Period after cimetidine treatment $^b$ (min)</th>
<th>$V_{\text{dss}}, K_p$ $^c$ (l/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>2.13±0.20</td>
</tr>
<tr>
<td>90</td>
<td>1.57±0.08 $^d$</td>
</tr>
<tr>
<td>360</td>
<td>1.63±0.18 $^d$</td>
</tr>
</tbody>
</table>

$a$) Values are the means ± S.E. of five experiments.  
$b$) Cimetidine was intravenously injected (50 mg/kg).  
$c$) Calculated by using Eq. (10).  
$d$) Significantly different from the non-treated group ($p < 0.05$).

lidocaine with and without cimetidine treatment. The $K_p$ of spleen, stomach and skin after cimetidine treatment decreased significantly to 64, 62 and 62% of those the non-treated rats, respectively. In spleen, the effect of cimetidine disappeared 360 min after cimetidine treatment. The reason(s) for this is not clear, but it may result from the fact that the concentration of cimetidine in the spleen was much lower than in the other two tissues 360 min after cimetidine treatment (spleen = 0.5 µg/g, stomach = 7 µg/g and skin = 6 µg/g, unpublished data). The $K_p$ of liver of the non-treated and the two types of cimetidine-treated rats were calculated by dividing $K_p, \text{app}$ by the availability ($F$) of liver. The $K_p$ values of liver in all cases were about 10—12 times larger than the corresponding $K_p, \text{app}$, because lidocaine shows a high hepatic clearance and $F$ is very small ($F < 0.1$). Table V lists $V_{\text{dss}}, K_p$ calculated by using Eq (10). The $V_{\text{dss}}, K_p$ was decreased by an average of 25% in the two types of cimetidine treatment. Good agreement was observed in the percentage decrease between $V_{\text{dss}}$ (Table II, 28%) and $V_{\text{dss}}, K_p$ (Table V, 25%). The role of the decrease of the hepatic blood flow ($Q$) in the decrease of $\text{Cl}_{\text{tot}}$ of lidocaine by cimetidine treatment should also be considered. For a high hepatic clearance drug, the decrease of $Q$ affects the $K_p$ of the liver calculated by using Eq (8). The percentage decrease of $Q$ was not determined in this experiment, so the reported value of 15% was taken. The $K_p$ values of the liver for the two kinds of cimetidine treatments were calculated to be 36.9±11.4 (90 min) and 21.7±5.80 (360 min) (mean ± S.E. of five experiments) without significant difference from the non-treated rats. The $V_{\text{dss}}, K_p$ with cimetidine treatments were 1.80±0.09 (90 min) and 1.79±0.20 (l/kg) (360 min) and were significantly different from the non-treated rats. The percentage decreases were 15%. Thus, whether the decrease of $Q$ is considered or not, it was thought that the decrease of $V_{\text{dss}}$ was due to the decrease of $K_p$ in several tissues.

Because the $f_p$ of lidocaine was not changed by cimetidine treatment, the reason for the decrease of $K_p$ in spleen, stomach and skin was suspected to be the increase of the lidocaine free fraction in a tissue ($f_i$). The reason for the increase of $f_i$ was thought to be the inhibition of the binding of lidocaine to tissue components by cimetidine. Then, the effects of cimetidine on the tissue binding of lidocaine to spleen, stomach and skin homogenate were examined by equilibrium dialysis.

**Effects of Cimetidine Treatment on in Vitro Tissue Binding of Lidocaine**

$K_p, \text{vitro}$ values of lidocaine in several tissue homogenates are listed in Table VI; those in spleen, stomach and skin were significantly decreased to 58, 45 and 68%, respectively, by cimetidine treatment ($p < 0.05$).

Considering that the $K_p, \text{vitro}$ was determined

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TABLE VI.  $K_{p, \text{vitro}}$ of Lidocaine with or without Cimetidine Treatment $^a$, $^b$

<table>
<thead>
<tr>
<th>Tissue</th>
<th>No treatment $^c$</th>
<th>Cimetidine treatment $^c$, $^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen</td>
<td>9.85±1.98</td>
<td>5.75±1.25 $^e$</td>
</tr>
<tr>
<td>Stomach</td>
<td>7.48±1.06</td>
<td>3.37±0.61 $^e$</td>
</tr>
<tr>
<td>Skin</td>
<td>19.5±0.51</td>
<td>13.2±1.71 $^e$</td>
</tr>
</tbody>
</table>

$a$) Values are the means ± S.E. of four experiments.  
$b$) Calculated by using Eq. (13).  
$c$) Initial concentration of lidocaine in the suspension was 2 µg/ml.  
$d$) Initial concentration of cimetidine in the suspension was 20 µg/ml.  
$e$) Significantly different from the non-treated group ($p < 0.05$).
after dilution and homogenization and by equi-
librium dialysis for a long time, the percentage
decreases of the two types of tissue-to-plasma
concentration ratio, $K_p$ (Table IV) and $K_p$, \textit{vivo}
(Table V) in spleen, stomach and skin agreed
well. These results suggested that cimetidine in-
hibited the tissue binding of lidocaine. Post \textit{et al.}
reported that nortriptyline, a cationic drug, dis-
placed lidocaine from tissue binding sites.\textsuperscript{23}
They explained this displacement in term of an
inhibition of lidocaine binding to phospholipid
by nortriptyline, since both drugs have been
shown to interact with phospholipid. It was also
reported that the binding of cimetidine to isolat-
ed liver cytochrome P-450 was enhanced by the
reconstitution of cytochrome P-450 with phos-
pholipid.\textsuperscript{24} Thus, it is possible that cimi-
didine has a similar effect on lidocaine tissue bind-
ing to nortriptyline (competitive inhibition)
considering that the inhibitory effect of cimeti-
dine in the spleen depended on the cimetidine
concentration. However, the precise inhibition
mechanism remains to be established.

Effects of pH and Cimetidine Treatment on
Uptake of Lidocaine by Rat Erythrocytes

The pH profile of uptake of lidocaine by rat
erthrocytes with and without cimetidine treat-
ment is shown in Fig. 3. The uptake of lidocaine
by rat erythrocytes depended on the pH of the
incubation buffer and was decreased by cimet-
dine treatment. The pH profile of the uptake
was shifted to the higher pH side by cimetidine
treatment.

The uptake of lidocaine by rat lung slices
depended on the pH of incubation buffer and the
uptake percentage increased three times with
an increase of the pH of the incubation buffer from 7.0 to 8.0. These results and high
$K_p$ of lidocaine suggest that the distribution
of lidocaine to erythrocytes and tissues obeyed
the pH-partition theory. The shift of the pH profile
of uptake to the higher pH side may reflect a de-
crease of the pH difference between the intra-
and extracellular spaces. It was reported that
amiloride which is an imidazole compound in-
creased the microclimate pH of the intestinal
lumen by inhibiting the Na$^+$ -H$^+$ exchanger.\textsuperscript{25}
Similarly, cimetidine may affect on the pH-
maintaining system, resulting in a decrease of
the partition coefficient of lidocaine.

In conclusion, cimetidine treatment increased
the lidocaine plasma concentration in rats. The
pharmacokinetic parameters such as $C_l$, $V_{dss}$
and $k_{el}$ of lidocaine were decreased by cimetidi-
tine treatment. The $K_p$ values of spleen, stom-
ach and skin were decreased by cimetidine treat-
ments both \textit{in vivo} and \textit{in vitro}. The uptake of
lidocaine by erythrocytes depended on the pH of
the incubation buffer and was decreased by
cimetidine treatment. The mechanism of the de-
crease of $V_{dss}$ by cimetidine treatment may be
the inhibition of tissue binding.

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