Cimetidine and Omeprazole Have Different Effects on Hepatic Extraction of Lidocaine in Rats

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The effect of two antisecretory drugs, omeprazole and cimetidine, on the hepatic extraction of indocyanine green and lidocaine was studied in the isolated perfused rat liver. Both indocyanine green and lidocaine are removed by the liver with high extraction efficiency in a flow-dependent manner. The elimination of lidocaine, but not indocyanine green, involves metabolism by the mixed-function oxidase in the liver. A selective effect on the hepatic extraction of lidocaine, but not indocyanine green, may therefore indicate an inhibition of hepatic mixed-function oxidase. To test this hypothesis, a nonrecycling system at a fixed perfusion flow rate was used to measure the extraction of lidocaine. Under control conditions, the extraction rate of lidocaine was 83% ± 8%. In the presence of omeprazole at concentrations of 0.9, 2.0, and 4.5 μg/mL, the extraction rates were 81% ± 9%, 82% ± 7%, and 75% ± 7%, respectively. These changes were not significantly different than control rates. In contrast, the increasing concentrations of cimetidine caused significant decreases in the hepatic extraction of lidocaine to values of 78% ± 8%, 63% ± 14%, and 48% ± 14% at concentrations of 0.25, 0.50, and 1.25 μg/mL, respectively. The hepatic extraction of indocyanine green, 39% ± 6%, was not affected by the administration of either omeprazole or cimetidine. Thus, in the rat, omeprazole seems to be a less potent inhibitor of cytochrome P-450 than cimetidine.

Cimetidine and omeprazole are two antisecretory drugs used to treat patients with peptic ulcer disease (1-4). Both are reported to inhibit the hepatic microsomal oxidative metabolism of other drugs such as antipyrine, phenytoin, and diazepam (5-7). Cimetidine has also been found to decrease the high-extraction, flow-dependent elimination of such drugs as propranolol (8) and lidocaine (9-10), probably by its potent effect on the hepatic mixed-function oxidase. The effect of omeprazole on the hepatic elimination of such high-extraction drugs has not yet been investigated. The present study investigates the effect of omeprazole on the first-pass extraction of lidocaine and indocyanine green (ICG) by the isolated, perfused rat liver. These two substances were chosen because both lidocaine and ICG are removed by the liver through high-extraction, flow-dependent mechanisms, but only lidocaine elimination involves metabolism by the mixed-function oxidase. A change in the extraction of lidocaine, but not ICG, would therefore indicate an inhibition of mixed-function oxidase by omeprazole. A similar set of experiments was also performed with cimetidine to verify the responsiveness of our model.

Materials and Methods
Liver Perfusion

Male Wistar rats weighing 250-350 g were anesthetized with chloral hydrate (400 mg/kg, IP). Liver perfusion was performed as previously described (11). In brief, rat livers were perfused in situ through the portal vein with oxygenated Krebs-Ringer bicarbonate buffer containing 20% washed human erythrocytes, 4 g/L glucose, and 20 g/L bovine serum albumin. A roller pump maintained perfusate flow through the liver in each experiment at a fixed rate, which varied from 10-12 mL/min in different experiments. Single-transit experiments were performed, and blood from the hepatic vein was not permitted to recirculate through the reservoir. The perfusate was oxygenated with a mixture of 95% O₂ and 5% CO₂, and the pH was maintained at 7.4. Perfusion was performed at 37°C in a thermostatically controlled cabinet.

Abbreviation used in this paper: ICG, indocyanine green.
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Liver viability was assessed by the usual criteria (12), i.e., a normal gross appearance, stable pH, bile flow >1 µL/min . g liver, and oxygen consumption >1 µmol/min . g liver, and was found to be >90% in the experiments using a similar experimental design. Actual values in our experiments varied from 1.1 to 1.3 µL/min . g liver and 1.2 to 1.5 µmol/min . g liver, respectively.

Experimental Design

Two groups of five rats each were used to study the effect of omeprazole on the hepatic extraction of lidocaine and ICG. In each group, an equilibration period of 10 minutes was followed by a nonrecycling perfusion for another 40 minutes with either lidocaine or ICG. During the final 30 minutes of this perfusion, omeprazole was added. The omeprazole was dissolved in 100% polyethylene glycol and diluted in bicarbonate buffer solution. Perfusates with omeprazole in increasing concentrations of 0.9, 2, and 4.5 µg/mL were added to the reservoir every 10 minutes. The 0.9 µg/mL concentration was chosen because this is the peak plasma level observed in humans after an intake of a single dose of 40 mg of omeprazole (5). The effect of cimetidine on lidocaine and ICG extraction was studied in another two groups of five rats each using a similar experimental design. The concentrations of cimetidine in the perfusate were 0, 0.25, 0.5, and 1.25 µg/mL, respectively; this also corresponds with the actual blood concentration during cimetidine therapy. The concentrations of lidocaine and ICG in the perfusate were 5 and 7 µg/mL, respectively, in all experiments. Samples for the measurement of lidocaine or ICG levels were obtained from the portal and hepatic veins at 2-minute intervals following 4 minutes of perfusion with each of the concentrations of either omeprazole or cimetidine. Extraction rates of lidocaine or ICG by the rat liver were expressed as a percentage and calculated as

\[
\text{Extraction rate (\%)} = \frac{C_p - C_H}{C_p} \times 100
\]

where \(C_p\) is the concentration in the portal vein and \(C_H\) is the concentration in the hepatic vein. The extraction rate for each of the 10-minute periods was considered the average of three consecutive measurements at 2-minute intervals.

Indocyanine green concentration was determined with a spectrophotometer at a wavelength of 805 nm. Lidocaine levels were determined using a homogenous enzyme immunoassay (EMIT, Syva Laboratories, Palo Alto, CA). Standard curves for lidocaine and ICG levels were obtained using the perfusate as a zero reference.

Statistical Analysis

Differences between the various groups were compared using Student’s t test. \(P > 0.05\) was used as the level of significance.

Results

The effect of the various concentrations of omeprazole on the hepatic extraction of lidocaine and ICG is shown in Table 1. Lidocaine had a first-pass extraction rate of 83% that was not altered by increasing concentrations of omeprazole. The slight decrease in the rate of lidocaine extraction (75%) at an omeprazole concentration of 4.5 µg/mL was not statistically significant. As expected, omeprazole had no effect on the hepatic rate of extraction of ICG.

On the other hand, the presence of cimetidine in the perfusate was associated with a significant decrease in hepatic extraction of lidocaine (Table 2). This decrease was more evident at higher cimetidine concentrations. The rate of extraction was reduced to only 63% and 48% at cimetidine concentrations of 0.5 and 1.25 µg/mL, respectively. However, the hepatic extraction of ICG did not change even at the highest concentration of cimetidine.

Discussion

This study demonstrates that omeprazole had no effect on hepatic extraction of lidocaine. Cimetidine, probably because of its potent inhibitory effect on the cytochrome P-450 system, reduced the hepatic extraction of lidocaine. None of these drugs had any effect on ICG extraction because ICG is not metabolized by the cytochrome P-450 system. The current results are similar to those recently reported by Roberts et al. (13) who described a decrease in the rate of extraction of lidocaine by the isolated perfused rat liver when administered simultaneously with cimetidine. The current results demonstrate that omeprazole is a less potent inhibitor of the cytochrome P-450 system than cimetidine; therefore, the metabolism of lidocaine is not impaired by its simultaneous administration.

The effect of cimetidine on lidocaine extraction is not a result of a change in hepatic blood flow because the flow in each isolated perfused liver is fixed and the administration of cimetidine is not associated with a change in flow (14). The reduced hepatic rate of

<table>
<thead>
<tr>
<th>Omeprazole (µg/mL)</th>
<th>No. rats</th>
<th>Extraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lidocaine</td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td>83 ± 8</td>
</tr>
<tr>
<td>0.9</td>
<td>5</td>
<td>81 ± 9</td>
</tr>
<tr>
<td>2.0</td>
<td>5</td>
<td>80 ± 7</td>
</tr>
<tr>
<td>4.5</td>
<td>5</td>
<td>75 ± 7</td>
</tr>
</tbody>
</table>

NOTE. Values are given as mean ± SD.
Table 2. Effect of Cimetidine on Lidocaine and Indocyanine Green Extraction by the Perfused Rat Liver

<table>
<thead>
<tr>
<th>Cimetidine [µg/ml]</th>
<th>Nr. rats</th>
<th>Extraction (%)</th>
<th>Lidocaine</th>
<th>ICG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>86 ± 1</td>
<td>44 ± 6</td>
<td></td>
</tr>
<tr>
<td>0.25</td>
<td>6</td>
<td>78 ± 8</td>
<td>44 ± 5</td>
<td></td>
</tr>
<tr>
<td>0.50</td>
<td>5</td>
<td>63 ± 14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>43 ± 4</td>
<td></td>
</tr>
<tr>
<td>1.25</td>
<td>5</td>
<td>48 ± 14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>41 ± 4</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Values are given as mean ± SD.
<sup>a</sup>P = 0.007
<sup>b</sup>P = 0.0003.

Extraction of lidocaine is caused by either an inhibition of mixed-function oxidase or by an impaired hepatocellular uptake, which is less likely. The lack of effect of cimetidine on ICG extraction supports the hypothesis that the decrease in hepatic extraction of lidocaine in the presence of cimetidine is caused by an inhibition of mixed-function oxidase.

Omeprazole did not affect the hepatic extraction of lidocaine during 30 minutes of perfusion. It is unlikely that the onset of inhibition of the cytochrome P-450 system by omeprazole occurs later than 30 minutes because, in a recent study by Webster et al. [6], a decrease in the rate of extraction of antipyrine by the isolated perfused rat liver was observed almost immediately after the administration of omeprazole.

In conclusion, omeprazole seems to have no effect on the elimination of high-extraction drugs such as lidocaine by the rat liver. This study suggests that unlike cimetidine therapy [10,15], clinical use of omeprazole may not be complicated by alterations of the hepatic elimination of high-extraction drugs.

References

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