Title: Cimetidine Inhibits Lidocaine Plasma Clearance

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Introduction. Cimetidine, a highly effective suppressor of gastric acid secretion has been widely used for peptic ulcer disease and has been advocated for preoperative use to reduce the potential hazard for acid aspiration. In recent studies, however, cimetidine has been shown to reduce the biotransformation of warfarin, diazepam, chlorpromazine and propranolol.

This study in rats examines the effect of acute cimetidine administration on the plasma concentration of lidocaine after a lidocaine bolus or a lidocaine constant infusion. Since this frequently used local anesthetic requires hepatic extraction for plasma clearance, the possibility of an interaction with cimetidine and the magnitude of this interaction should be determined.

Methods. In the following three experiments, male Sprague-Dawley rats weighing 400-500 g were anesthetized with cyclopropane and the femoral artery and vein cannulated with PE 50 tubing. The animals were awakened and restrained.

In Group I (5 animals), a lidocaine dose of 5 mg/kg in 2 ml of saline was given IV over a 2-min period. A 0.5 ml arterial blood sample was drawn at 2, 5, 10, 30, and 90 min and analyzed by gas chromatography for lidocaine plasma content. In Group II (5 animals), a 4 mg/kg SC dose of cimetidine was given 1 hr prior to preparation as above and 2 mg/kg IV of cimetidine was administered 10 min prior to a 5 mg/kg IV lidocaine dose. Arterial samples for lidocaine content were drawn at 2, 5, 10, 15, 30, 60, 90, and 120 min. In Group III (9 animals) a constant infusion of 150 mg/min of lidocaine was started after a lidocaine IV bolus of 750 mg. Arterial content of lidocaine was determined in samples drawn at 45, 60, and 90 min. While the lidocaine constant infusion was continued, a cimetidine dose of 2 mg/kg was given IV. Arterial samples were drawn 15, 30, 60, and 90 min after the cimetidine dose.

Plasma half-life (T1/2) and total body clearance were calculated from the final slope of the lidocaine plasma content against time using regression analysis.

Results. The lidocaine T1/2 after a bolus dose of drug was observed to be 36 min in the awake rat, similar to the 30-min approximation of Keenan. After cimetidine administration the lidocaine T1/2 increased 36% to 50 min (Figure 1). On the basis of these plasma data, the total body clearance decreased 37% with cimetidine administration.

In the constant infusion of lidocaine experiment, a stable blood level of 2.26 μg/ml was achieved. When cimetidine was administered, the plasma lidocaine increased continuously reaching a level of 2.8 μg/ml at 90 min, representing a 26% increase in lidocaine plasma content (Table 1).

Discussion. Lidocaine plasma clearance is entirely related to hepatic biotransformation of the drug after the initial distribution phase. The 38% increase in the plasma T1/2 and the decrease in total body clearance of lidocaine in this study in animals treated with cimetidine could be the result of decreased hepatic blood flow or decreased oxidative biotransformation of lidocaine by hepatic microsomes. Data with other drugs suggest cimetidine may cause either or both effects. The similarity in rat and man of required hepatic oxidative biotransformation reactions for lidocaine plasma clearance would suggest that cimetidine can increase lidocaine toxicity when repeated boluses or continuous infusions of lidocaine are administered.

Table 1. Lidocaine Constant Infusion

<table>
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<th>Time (min)</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>90</th>
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<tbody>
<tr>
<td>Lidocaine conc (μg/ml)</td>
<td>2.20</td>
<td>2.26</td>
<td>2.29</td>
<td>2.46</td>
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<tr>
<td>SEM</td>
<td>0.12</td>
<td>0.14</td>
<td>0.12</td>
<td>0.16</td>
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<tr>
<td>N</td>
<td>9</td>
<td>9</td>
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References: