**METABOLISM AND REGULATION I**

**Title:** CIMETIDINE PROTECTS AGAINST HALOTHANE-INDUCED HEPATOTOXICITY

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**Introduction.** It is well recognized that halothane-induced hepatic necrosis occurs when rats are pretreated with phenobarbital to produce enzyme induction and are then anesthetized with halothane under hypoxic conditions (14 percent oxygen) (1). It is thought that halothane is metabolized under these conditions to hepatotoxic intermediates by a reductive pathway, which also results in elevated plasma fluoride concentrations. However, it has recently been suggested that alterations in hepatic blood flow might also contribute to halothane hepatotoxicity (2).

Because cimetidine, a histamine (H2) receptor antagonist, is a potent inhibitor of hepatic drug metabolism, we postulated that cimetidine might protect against halothane-induced hepatotoxicity. This is a particularly important issue because of the large number of patients who present for anesthesia already receiving cimetidine. In addition, cimetidine is now widely used as part of a premedication regimen to reduce gastric acidity.

The purpose of the present study was, therefore, to determine the effect of cimetidine on halothane hepatotoxicity.

**Methods.** Groups of male Sprague-Dawley rats received phenobarbital 75 mg/kg intraperitoneally for 5 days and on the 6th day received either cimetidine (180 mg/kg, intraperitoneally) or saline, 60 minutes before anesthesia. The animals were then anesthetized in groups of six to eight in an anesthetic chamber with 1 percent halothane in 14 percent oxygen for 2 hours. Anesthetic concentrations within the chamber were verified by gas chromatography. The rats were sacrificed immediately or 24 hours after anesthesia and estimations were carried out of plasma inorganic fluoride, SGPT and histological grading of liver damage based on a scale of 0 to 4.

In order to determine the effect of cimetidine on drug metabolism in the hypoxic rat model, the aminopyrine "breath test" was studied in the post anesthetic recovery period. The aminopyrine breath test has been extensively used to assess drug metabolism in vivo (3). A tracer dose of [N-dimethyl 14C] aminopyrine was administered intravenously. Oxidation of the labelled methyl groups in the liver by cytochrome P-450 yields 14CO2. Thus measurement of rate of exhalation of 14CO2 provides a sensitive index of drug metabolism. The breath test was performed 2 hours after anesthesia in 8 phenobarbital-pretreated rats that had received cimetidine 180 mg/kg intraperitoneally 60 minutes prior to anesthesia with 1 percent halothane in 14 percent oxygen for 2 hours and in 6 rats that were similarly treated, but did not receive cimetidine.

**Results.** The effects of cimetidine on halothane hepatotoxicity are shown in the table.

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>n*</th>
<th>Histologic Score</th>
<th>SGPT U/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarb +</td>
<td>15</td>
<td>0.87 ± 0.15</td>
<td>35.67 ± 3.28</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>18</td>
<td>1.78** ± 0.10</td>
<td>60.94 ± 2.78</td>
</tr>
</tbody>
</table>

* n = number of rats  
** p < 0.001.

Values are expressed as mean ± SEM.

Cimetidine significantly decreased the histological severity of the lesion (p < 0.001) 24 hours after anesthesia without significantly altering SGPT levels.

Inorganic plasma fluoride levels measured immediately after anesthesia were elevated, 50% above baseline in the cimetidine-treated rats and 130% above baseline in the phenobarbital-pretreated rats. These differences were significant (p < 0.005) and were observed without cimetidine.

The aminopyrine half-life was significantly prolonged in phenobarbital-cimetidine-pretreated rats (75.89 ± 15.14 minutes) following halothane anesthesia under hypoxic conditions when compared with similarly treated rats that did not receive cimetidine (35.82 ± 1.09 minutes), indicating inhibition of drug metabolism produced by cimetidine.

**Conclusions.** We therefore conclude that cimetidine protects against halothane hepatotoxicity in the hypoxic-enzyme induced rat model, possibly due to inhibition of drug metabolism. However, there was no change in plasma fluoride concentrations suggesting that cimetidine does not inhibit the liberation of fluoride in vivo from halothane through the postulated reductive pathway. Further work is required to investigate the possible effects of concomitant administration of cimetidine and halothane on drug metabolism in man.

**References.**