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Mechanism of Liver Necrosis in Hyperthyroid Rats

To the Editor:—I read with great interest the recent article by Berman *et al.*[1] on the hepatotoxicity of halothane, enflurane, and isoflurane in rats pretreated with triiodothyronine (T3). These authors felt that their data suggest a mechanism of liver damage different from that previously proposed of toxic intermediate production via a reductive pathway.[2] On the contrary, their data are consistent with this theory.

Previous studies by Israel and co-workers[3] have demonstrated the presence of a hypermetabolic state in the liver of rats pretreated with T3. Their work suggests that diminished amounts of oxygen would reach the areas of the terminal hepatic vein (central vein), resulting in a relative hypoxia in this zone III of the liver.

As a result, a relative shift to a reductive pathway of biotransformation would be expected, increasing the production of reactive intermediates and the hepatotoxicity of volatile anaesthetic agents. In light of this, Berman's data would support the relationship between reductive metabolism and hepatic toxicity.

It would be of interest to see if a free radical scavanger such as N-acetylcysteine or cystamine could play a protective role in this setting, further supporting the hypoxia–reductive metabolism link to the hepatotoxicity of halothane.

Also, the authors did not state whether the histologic findings in the enflurane- and isoflurane-treated rats were significantly different compared with the phenobarbital and air control.

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3. Israel Y, Videla L, Bernstein J: Liver hypermetabolic state after chronic ethanol consumption: Hormonal interrelations and pathogenic implications. Fed Proc 34:2052–2059, 1975

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In reply:—Dr. Carmichael suggests that the mechanism of liver necrosis induced by isoflurane, enflurane, and halothane in hyperthyroid rats[1] is consistent with the production of toxic intermediates via a reductive pathway. We do not agree for the following reasons: 1) Liver cytochrome P-450 is decreased in triiodothyronine (T_3) pretreated rats (reference 5 in our article[1]), an effect opposite to that of phenobarbital. Therefore, the metabolism of volatile anesthetics would be inhibited, and for halothane this appears to be confirmed by the observation of Smith* who observed that, in T_3 pretreated rats compared with euthyroid rats anesthetized with halothane in 21% oxygen, the tissue levels of the reductive metabolites of halothane, chlorotrifluoroethane, and chlorodifluroethylene are reduced markedly. Furthermore, plasma levels of inorganic fluoride, another reductive metabolite of halothane, are not elevated in hyperthyroid rats anesthetized with halothane in 21% oxygen but are elevated markedly in phenobarbital pretreated rats anesthetized with halothane under hypoxic conditions.[2] 2) Isoflurane and enflurane undergo limited oxidative metabolism but are not metabolized in the presence of low oxygen tensions (reference 13 in our article[1]). 3) Under aerobic or anerobic incubation conditions, no *in vitro* covalent binding of ^{14}C from halothane could be detected in liver microsomal proteins prepared from hyperthyroid rats* and the amount of ^{14}C from halothane covalently bound to hepatic microsomal lipids prepared from hyperthyroid rats was significantly less than the amount bound to microsomal lipids prepared from euthyroid and phenobarbital pretreated rats.* Because euthyroid rats did not have hepatotoxicity develop *in vivo, in vitro* covalent binding to microsomal lipids does not correlate with halothane-induced liver damage. Thus the available data indicate that the mechanism of hepatotoxicity induced by the volatile anesthetics in hyperthyroid rats may not be via a reductive pathway.

* Smith AC: Halothane hepatoxicity in hyperthyroid rats. Ph.D. Thesis Vanderbilt University, 1982.

We speculated[1] that anesthesia-induced hepatotoxicity observed in hyperthyroid rats may be hypoxic damage to hypermetabolic centrilobular cells resulting from anesthetic-induced depression of splanchnic blood flow. This speculation is consistent with the report[3] cited by Dr. Carmichael indicating the presence of a hypermetabolic state of the liver induced by thyroxine, not T_3 as stated by Dr. Carmichael.

Smith *et al.*† have observed that the administration of cysteamine and N-acetylcysteine potentiate, whereas diethylmaleate, which depletes glutathione, reduces halothane-induced liver damage in hyperthyroid rats. Others[4] have shown that N-acetylcysteine reduces halothane hepatotoxicity in T_3 pretreated rats. Thus, the role of free radical scavangers in this setting is uncertain.

Table 4 in our article[1] shows that 36 hyperthyroid rats anesthetized with pentobarbital (not phenobarbital) and 36 nonanesthetized hyperthyroid rats (air control) did not have hepatic lesions develop. We think this is significantly different from isoflurane-, enflurane-, and halothane-anesthetized hyperthyroid rats that did not have hepatotoxicity develop.

† Smith AC, James RC, Berman ML, Harbison RD: Paradoxical effects of pertubation of intracellular glutathione on halothane-induced hepatotoxicity in hyperthyroid rats. Fundamental and Applied Toxicology: In press.

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Preoperative Management of Atrial Fibrillation

To the Editor:—Our goal as anesthesiologists is to determine if adequate rate control in atrial fibrillation has been achieved preoperatively and to maintain that control throughout the operative and postoperative period. This may require therapeutic intervention with drugs that slow atrioventricular conduction or avoidance of agents that facilitate atrioventricular conduction. The clinical report by Kopman[1] of two cases presenting for cardiac surgery with atrial fibrillation and inadequate rate control stresses these points.

Both patients presented by the author were receiving digoxin and had apparently normal digoxin levels; however, frequently a high to subtoxic level is required for adequate rate control.[2] Indeed, in past years digitalization of patients in atrial fibrillation consisted of digitalis administration until nausea and vomiting occurred, then the dosage was reduced slightly. Present day success is evaluated clinically by a ventricular response consistently less than 100 beats/min, by the absence of a significant pulse deficit, and by the lack of a rapid ventricular rate during stress testing.

Preoperative anxiety with the release of catecholamines may increase atrioventricular conduction and the ventricular response in inadequately digitalized patients. Traditionally, additional digitalis or combination therapy with propanolol is administered to these patients. More recently, the calcium channel blocker, verapamil, has been shown to be effective in controlling the rate in patients with atrial fibrillation.[3] Furthermore, a reassuring preoperative visit with an adequate preoperative sedative to allay anxiety along with the administration of digitalis the morning of surgery should facilitate rate control.