Halothane Anesthesia Does Not Exacerbate Hepatic Dysfunction in Cirrhotic Rats


The authors have refined a model of cirrhosis in the rat and used it to determine whether the administration of halothane anesthe-
sia adversely affects preexisting liver disease. Male Wistar rats were placed on phenobarbital water and were assigned randomly to two groups. Group 1 rats were exposed by inhalation to carbon tetrachloride (CCl₄) at weekly intervals for 12 exposures while Group 2 rats received only air. All treatment including phenobar-
barbital then was withdrawn for 4 weeks. Rats then were bled for SGOT and SGPT determinations and 24 h later were exposed to 1.8% halothane in oxygen for 3 h (HAL); the remaining rats from each group were exposed to 100% oxygen for 3 h (O₂). Twenty-
four hours later, rats were killed and blood was obtained for SGOT and SGPT by cardiac puncture. Light microscopic histo-
logic examination was performed blind on liver sections for ci-
rrhosis and scored for superimposed acute focal necrosis. The weekly sublethal CCl₄ exposure resulted in histologically demon-
strable cirrhosis in all surviving Group 1 animals. The mean (±SD) SGOT (128 ± 32 IU/l) and SGPT (86 ± 24 IU/l) values for the Group 1 rats were significantly greater (P < 0.01) than those for Group 2 rats (98 ± 18 IU/l and 57 ± 12 IU/l, respectively). Cirrhotic animals showed neither deterioration in liver function nor acute liver cell necrosis after HAL compared with O₂. How-
ever, Group 2 rats showed a modest but significant increase in SGOT (P < 0.05) after HAL, while this change was not noted after O₂. Thus, 1.8% halothane anesthesia in oxygen did not result in superimposition of acute liver cell injury in already cirrhotic rats. (Key Words: Avisthetics, volatile: halothane. Liver: cirrhosis; he-
patotoxicity.)

THE INCIDENCE of chronic liver disease and the mortal-
ity rate from this condition progressively have in-
creased over the last three decades.¹ Two-thirds of all chronic liver disease in the United States is alcohol induced, and the per capita ingestion of potentially cirrhogenic quantities of alcohol continues to escalate.² Thus, more patients with chronic liver disease are expected to present to anesthesiologists for management of their liver-related and coexisting surgical problems.

Whether anesthesia per se exacerbates liver dysfunction in patients with preexisting chronic liver disease is unknown. In one report, patients with cirrhosis undergoing surgical treatment of portal hypertension and bleeding esophageal varices had greater deterioration in liver function than patients with normal liver function undergoing cholecystectomy.³ The lack of comparability between the study and control groups and the use of ether and cyclopropane for anesthesia lessen the validity of these results and their relevance to modern anesthetic practice.

There are many reasons why the assessment of appropriate anesthetic management of patients with liver disease has remained essentially uninvestigated. First, even in a relatively well-defined group such as alcoholic cirrhotics, the pattern and severity of the liver impairment are extremely variable. Thus, variance within experimental groups is large and statistical power low. Secondly, most of these patients already are being treated with a variety of drugs that may have their own effects on liver function. Thirdly, even if group sizes could be large enough to decrease variance, selecting appropriate variables to monitor deteriorating liver function can be difficult. Unfortunately, there is no single test, equivalent to glomerular filtration rate for renal function, that comprehensively will quantitate liver dysfunction; therefore, a combination of morpho-
logic, biochemical, and functional tests must be used.

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Lastly, it is difficult to separate the independent contributions of surgery and anesthesia on postoperative liver dysfunction. In the present study, we have used a model of cirrhosis in the rat, modified from an earlier description by McLean et al., to explore the hepatotoxic potential of halothane in established liver disease.

Methods

Forty male Wistar rats, 150 – 200 g, were fed a stock pellet diet and given drinking water containing sodium phenobarbital 0.05% (w/v) and dextrose 5% (w/v) (Group 1). After seven days they were exposed by inhalation to carbon tetrachloride (CCl₄) at weekly intervals by the method of McLean et al. In brief, a 160-1 Plexiglas® chamber was charged for 10 min by introducing 20 l/min of fully saturated CCl₄ vapor in air. This flow was maintained during exposure of rats, which at first was for 5 min but was increased step-wise to 15 min by the sixth week. Thereafter, the duration of exposure was maintained at 15 min for a further 6 weeks. Group 2 rats (N = 24) received no CCl₄ exposure during this 12-week period. Liver function tests then were performed on tail-blood samples by sequen-
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Results

Fourteen Group 1 animals died during the initial period of CCl₄ exposure from massive hepatic necrosis. Twenty-six rats survived the course of CCl₄ treatment, and all had histologically demonstrable hepatic cirrhosis (fig. 1). The presence of cirrhosis could be predicted readily from the abnormalities in the liver function tests (notably the albumin/globulin ratio) that were performed after 12 weeks of CCl₄ exposure (table 1). Four weeks after CCl₄ treatment, the mean values (±SD) of SGOT (128 ± 32 IU/l) and SGPT (86 ± 24 IU/l) for Group 1 rats were still significantly greater ($P < 0.01$) than those for Group 2 rats (92 ± 18 IU/l and 57 ± 13 IU/l, respectively).

There were no statistically significant differences between the two groups in mean arterial pressure (MAP), $P_{aco}$, $P_{ao}$, or blood glucose during the three hours of halothane anesthesia (table 2); both groups demonstrated significant hypercarbia, however.

Following halothane anesthesia, cirrhotic animals (Group 1) showed no further deterioration in liver function, as assessed by transaminase levels and liver necrosis indices (Figs. 2 to 4). Group 2 rats, however, showed a modest but statistically significant ($P < 0.05$) increase in SGOT (fig. 2). The mean liver necrosis index was not altered significantly in either group after halothane compared with oxygen treatment (fig. 4).

| Table 1. Liver Function Tests* for Cirrhotic (Group 1) and Control (Group 2) Rats |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Group [n]       | SGOT± (IU/l)    | SGPT± (IU/l)    | Total Bilirubin† (mg/dl) | Albumin:Globulin‡ |
| 1 (26)          | 393 ± 496       | 238 ± 38§       | 0.5 ± 0.15           | 0.94 ± 0.04‡    |
| 2 (24)          | 103 ± 8        | 48 ± 11         | 0.1 ± 0.03           | 1.2 ± 0.02      |

* Tested at conclusion of CCl₄ exposures; see "Methods" in the text.
† Number of rats.
‡ Mean ± SD values.
§ $P < 0.01$.
¶ $P < 0.05$.

SGPT levels in cirrhotic rats were lower after oxygen treatment than before, indicating some improvement in liver function (fig. 3).

Discussion

Subhuman primates are the only animals in which chronic administration of alcohol reliably results in the typical postnecrotic cirrhosis found in humans. In rodents, progression beyond the fatty liver stage is rare, even after continuous high-dose administration of alcohol.

The rat model of cirrhosis was modified from a previously reported model. Refinements were incorporated to increase the yield of cirrhosis and to decrease the mortality in the early stages. We added dextrose to the drinking water to prevent death from hypoglycemia, which often is seen during the first few weeks of CCl₄ treatment. Furthermore, we exposed rats to CCl₄ weekly rather than twice weekly to minimize the development of resistance to CCl₄ hepatotoxicity. Because the genesis of cirrhosis is dependent on provoking repeated bouts of acute hepatic necrosis, we fasted the animals before exposure to enhance acute hepatotoxicity of CCl₄. The overall yield of viable cirrhotic animals by this modified technique was 65%.

Many similarities exist between CCl₄-induced liver disease in the rat and cirrhosis in the human. Hepatomegaly, splenomegaly, portosystemic shunts, varices, ascites, pleural effusions, poor synthetic function of the

| Table 2. Cardiorespiratory Data for Cirrhotic (Group 1) and Control (Group 2) Rats during Halothane Anesthesia |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Group [n]*      | $\text{pH}^{\dagger}$ | $P_{aco}$± (mmHg) | $P_{ao}$± (mmHg) | MAP± (mmHg)    |
| 1 (9)           | 7.33 ± 0.04     | 153 ± 55        | 189 ± 90        | 75 ± 22        |
| 2 (11)          | 7.32 ± 0.06     | 153 ± 55        | 189 ± 90        | 71 ± 13        |

* Number of rats.
† Mean ± SD values.
‡ Lowest mean arterial pressure.
liver, coagulation problems, and testicular atrophy are common features. Thus, although we have the usual reservations for extrapolating animal data to humans, we believe that the rat model of CCl$_4$-induced cirrhosis is a valid one for examining the effects of anesthetics on liver function in the setting of preexisting liver disease.

Anesthesia with halothane 1.8% v/v (or about 1.5 MAC for the rat) in oxygen for 5 h did not result in superimposition of acute liver injury in cirrhotic rats, although it did result in slight liver dysfunction in the normal rats. This suggests that the cirrhotic state confers some measure of resistance to halothane-induced hepatic dysfunction. A possible explanation is that biotransformation of halothane to hepatotoxic intermediates is reduced in cirrhotic rats. The extent of halothane metabolism, however, was not assessed in this study. Another reason for their relative resistance to hepatotoxicity from halothane may be attributed to the cirrhotic rats being "selected out" as survivors of the CCl$_4$-induced lesion. However, more recent unpublished studies in our laboratory refutes this explanation, since we were able to produce further hepatic dysfunction by manipulation of the experimental conditions.

It is also possible that the modest hypercarbia present during anesthesia conferred "luxury" hepatic perfusion by its direct vasodilating effect on the splanchnic circulation. While this effect may be necessary to maximize protection, it still does not explain the different effect that halothane had on liver function in normal and cirrhotic animals, since both groups were equally hypercarbic (table 2).

The high inspired oxygen concentration used in our study also must be considered when interpreting the results. Diminished hepatic oxygen delivery, secondary to halothane-induced cardiorespiratory depression, may be a critical factor in the anesthetic management of patients with liver disease, especially when hepatic perfusion already is compromised. Apparently, the high FIO$_2$, breathed during anesthesia did exert an ameliorative effect, since the SGPT significantly improved in the cirrhotic rats exposed to oxygen alone.

Volatile agents have distinct advantages over intravenous anesthetic agents in patients with liver disease.
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First, they can be used with a high inspired oxygen concentration, which may be important in some cirrhotic patients with severe intrapulmonary shunting. Secondly, alterations in pharmacokinetics from liver disease may occur through changes in hepatic blood flow, drug binding, volume of distribution, and drug biotransformation. Although these factors are often important for the intravenous anesthetics, they are not important for the volatile anesthetics, which do not depend to any extent on the liver for their elimination. While this study does not purport to show that halothane is the most appropriate agent for use in patients with chronic liver disease, this study supports the contention that halothane anesthesia is not contraindicated in those patients.

References