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 Title : HEPATIC INJURY FOLLOWING HALOTHANE, ENFLURANE, AND ISOFLURANE ANESTHESIA IN RATS  
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**Introduction.** Halothane anesthesia administered to enzyme-induced animals in a hypoxic atmosphere consistently produces hepatic necrosis. The resulting reductive metabolism of halothane produces highly reactive intermediates that bind covalently to hepatic microsomal macromolecules. This injury does not occur frequently in practice, since hypoxia is a rare occurrence in clinical anesthesia. However, hypoxia is an occasional complication of the post-anesthetic recovery period, in which ventilation and inspired oxygen levels are less rigorously controlled. Our results suggest that during recovery, halothane is present in amounts sufficient to allow production of significant quantities of metabolites, and that the potential for hypoxia-induced liver injury exists during this period. This potential is less with enflurane or isoflurane.

**Methods.** Male Sprague-Dawley rats weighing approximately 350 g were given phenobarbital, 1 mg/ml water, to drink for four days. Plain water was administered for 24 hr prior to testing. The animals were divided into nine experimental and four control groups, each group consisting of 8-20 rats. The temperatures of all anesthetized animals were maintained from 37.0 to 38.5 C. Two groups received either 1% halothane or 2% enflurane in 12% oxygen. Five groups received 1% halothane in 100% oxygen followed by 8% oxygen-balance nitrogen, either immediately or after a 15-, 30-, 60-, or 120-min interval of 100% oxygen. Two groups received 2% enflurane or 1.4% isoflurane in 100% oxygen, followed immediately by hypoxia. Control groups received phenobarbital followed by hypoxia, phenobarbital only, or hypoxia without phenobarbital pretreatment. One group functioned as cage controls. Rats were killed 24 hr after the hypoxic insult and their livers examined using the criteria of McLain *et al.*<sup>1</sup> Significant differences between groups were tested using the Mann-Whitney U-test for ranking.

**Results.** As indicated by previous reports, liver injury occurred in the group receiving halothane in a hypoxic atmosphere. Histologic damage that occurred when hypoxia immediately followed halothane anesthesia was significantly greater ( $P < 0.05$ ) than that occurring in animals similarly treated with enflurane and isoflurane (fig. 1). When a 15-min

interval of oxygen was imposed between halothane anesthesia and hypoxia, a difference ( $P < 0.06$ ) in histologic score existed between animals anesthetized with halothane and control animals. Combined results from the 15- and 30-min delay groups were also different ( $P < 0.05$ ) from control. There was no difference between control and halothane groups when the oxygen interval was 60 or 120 min. The injury score of control animals receiving phenobarbital and hypoxia was comparable to that of the enflurane and isoflurane groups. No evidence of hepatic injury occurred in the remaining control animals.

**Discussion.** These results indicate that hepatic damage can result when hypoxia occurs following halothane but not following enflurane or isoflurane anesthesia. The vulnerable period in rats lasts for 15 to 30 min. In terms of washout of alveolar halothane, this may be equated to 30 to 120 min in humans.

#### Reference

1. McLain GE, Sipes IG, Brown BR: An animal model of halothane hepatotoxicity: Roles of enzyme induction and hypoxia. *Anesthesiology* 51:321-326, 1979

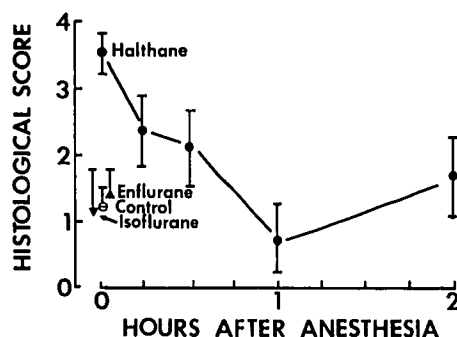


Fig. 1. Effects of enzyme induction and hypoxia (FIO<sub>2</sub> 0.08) on hepatic injury after halothane, enflurane, and isoflurane anesthesia.