Title: CONFLICTING MECHANISMS OF HEPATIC INJURY WITH HALOTHANE AND ENFLURANE

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Introduction: Recent reports have promoted a unifying mechanism of anesthetic-induced hepatotoxicity involving hypoxia.[1,2] These are in conflict with the chemotoxic mechanism established for the original halothane animal model.[3] This study examines the role of biotransformation enzyme induction and body temperature in producing hepatotoxicity in the halothane-F_IO_2 = 0.14 model (HH) and the enflurane-F_IO_2 = 0.10-external heating (EHH) model. Differences in the chronology of the injury and the resulting liver pathology between the two models are also examined.

Methods: Male Sprague-Dawley rats (250-350 gm) were used in this study. For induction of biotransformation enzymes, rats received an IP injection of 100 mg/kg phenobarbital (PB) followed by 5 days of 1 mg/kg PB drinking water. Exposures were carried out on day 6 for 2 hr with the anesthetic and/or oxygen atmosphere. Maintenance of body temperature was accomplished by warming the animals via heaters attached to the underside of a metal plate which served as the floor of the chamber. Body temperatures were monitored using rectal probes. Exposure conditions were: HH: PB induction, 1% halothane, F_IO_2 = 0.14[3]; EHH: PB induction, 1.5-1.8% enflurane, F_IO_2 = 0.10, with heating of the animals to maintain normothermia[1]; Severe hypoxia: F_IO_2 = 0.05, with external heating. As a positive control for a chemotoxin, previously-untreated rats received 1 ml/kg CCl_4 in corn oil orally. To determine the important components to the HH and EHH models, a comparison of the requirements of PB induction and external heating to maintain normothermia for lesion development was made. Serum glutamate-pyruvate transaminase (SGPT) was measured as an indicator of hepatic damage at various time points after exposures. Liver tissue samples were fixed in buffered formalin and processed for histological assessment.

Results: Without external heating, the rats lost approximately 7°C in body temperature during anesthetic exposures. With the external heating, the body temperature was within 1°C of normothermia. Expression of the HH lesion required PB induction but not the maintenance of normothermia during anesthesia. HH induced hepatotoxicity followed a time course of development similar to that of CCl_4 with no alterations in SGPT or liver pathology until 6 hr post-exposure, progressing 4-fold to a maximum at 24 hr (SGPT=105±70 W-L units/ml, n=9). Liver pathology at 24 hr demonstrated the classic centrilobular damage with extensive vacuolization and some fat deposition.[3] EHH, on the other hand, did not require PB induction but did require maintenance of normothermia during anesthesia for expression of liver injury. The EHH model consistently produced elevated SGPT (205±273 W-L units/ml, n=14) and altered liver pathology (centrilobular watery vacuolization) immediately post-exposure which are indicative of anoxic liver injury[4] and were comparable to the results from exposures to severe hypoxia alone. Following the immediate increase, SGPT remained elevated throughout the EHH time course (SGPT: 6 hr=232±190; 24 hr=288±287) with a much greater expression of frank coagulative necrosis than that observed in the HH model.

Discussion: Both the requirements for expression of the HH-initiated hepatic injury as well as its time course of development proved quite dissimilar from that of the EHH model. The HH model required PB induction, EHH did not. HH did not require maintaining normothermia during anesthesia to produce a lesion, while EHH did. The temporal evolution of HH-induced necrosis was similar to that of CCl_4, while EHH was identical to that observed for a severe hypoxia exposure. Other agents such as fentanyl and thiopental have also been shown to be hepatotoxic under the conditions required to make enflurane hepatotoxic in the EHH model. Thus, the conditions of this model produce a severe hypoxia which allows any anesthetic that alters cardiac output or decreases hepatic blood flow to be "hepatotoxic". However, the requirement of hepatic enzyme induction and the chronology of lesion development would indicate that the hepatotoxicity observed in the HH model is via a chemotoxic mechanism and better relates to the unique hepatotoxicity observed with halothane clinically.

References:

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