Title: HALOTHANE ANESTHESIA HAS NO EFFECT ON THE M-3-GLUCURONIDATION OF MORPHINE

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INTRODUCTION. A large number of drugs are administered to surgical patients in the perioperative period. It is now well recognized that inhalational anesthetics alter the disposition of a number of drugs whose principal route of elimination is oxidation by the microsomal mixed function oxidase system in the liver. This reduction of drug metabolizing capacity results in higher drug concentrations during anesthesia with the potential for the development of drug toxicity. However, the effect of inhalational anesthetics on drug conjugation remains to be defined. The principal route of metabolism for morphine is by glucuronidation to morphine-3 glucuronide (M3G). The purpose of the present study, was to investigate the effect of halothane anesthesia on the glucuronidation pathway, by determining the effect of halothane on the production of the metabolite, M3G, and in addition the effect of halothane on the partial metabolic clearance of morphine by the specific pathway M-3-glucuronidation; partial metabolic clearance being defined as the fraction of drug excreted as the metabolite (M3G) times the total clearance of the parent drug, morphine.

METHODS. Six dogs, 22.2±0.8 kg (mean ± SEM) were anesthesized with pentobarbital 30 mg/kg i.v. followed by 1 mg/kg/hr for the duration of the study. Ventilation was controlled to maintain normocarbia (FIO_2=1.0). Following laparotomy, catheters were inserted into the portal vein, both femoral arteries and a femoral vein. Each dog received morphine 0.5 mg/kg into the portal vein. Arterial blood samples were obtained 8, 10, 12, 15, 20, 25, 30, 40, 50, 60, 70, 90, 105, 120, 135, 150, 165, 180, 195, 210, 240 and 270 min after drug administration during pentobarbital anesthesia. Halothane anesthesia (1.5 MAC) was then administered for the remainder of the study and the concentration monitored by the Engstrom Emma gas analyzer and gas chromatography. After 90 min halothane anesthesia, each dog again received morphine in an identical manner to that during pentobarbital anesthesia and the same blood sampling procedures were followed. Morphine and M3G concentrations in plasma were determined by HPLC. The area under the plasma concentration time curve (AUC) extrapolated to infinity was determined for morphine and its metabolite. Urine was collected throughout both study periods for the determination of unchanged morphine and M3G in urine. The partial metabolic clearance to M3G was then calculated. The significance of differences were determined by a paired t-test or Wilcoxon paired rank sum test as appropriate with $p<0.05$ being taken as minimal level of significance.

RESULTS. Halothane anesthesia had no effect on the partial metabolic clearance of morphine to M3G (Table 1) indicating that halothane anesthesia does not inhibit the specific pathway, M-3-glucuronidation. In addition the percent of drug excreted in the urine as unchanged drug (morphine) or as the metabolite (M3G) was not significantly different during pentobarbital or halothane anesthesia (Table 1).The production of M3G was assessed as the ratio of plasma M3G AUC to that of the AUC of unchanged morphine in plasma. The administration of halothane anesthesia had no significant effect on the plasma M3G AUC to plasma morphine AUC ratio (Fig 1).

FIG 1: EFFECT OF HALOTHANE ON PLASMA M-3-G AUC/PLASMA MORPHINE AUC.

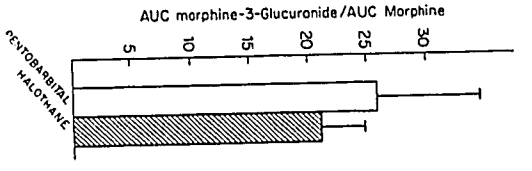

TABLE 1. EFFECT OF HALOTHANE ANESTHESIA ON MORPHINE GLUCURONIDATION

	Pentobarbital	Halothane	Significance
Morphine clearance (ml/min)	1880 ±631	1406 ±212	NS
Partial metabolic clearance as M3G (ml/min)	944 ±258	611 ±128	NS
% of Dose excreted as unchanged drug	9.5% ±3.1	8.6% ±2.4	NS
% of Dose excreted as M3G	56.9% ±11.1	41.6% ±7.9	NS

DISCUSSION. Halothane has previously been shown to inhibt the oxidation of a wide variety of drugs. However, we have been able to show that halothane has no effect on the generation of M3G from morphine by the glucuronidation pathway. In addition, halothane anesthesia did not inhibit the partial clearance of morphine by glucuronidation and had no effect on the percent of morphine excreted in the urine as unchanged drug or as the metabolite M3G.

We therefore conclude that the effects of halothane on drug metabolism may be relatively pathway specific, with glucuronidation being a more protected pathway than oxidation. Thus, it appears that halothane inhibits the metabolism of drugs undergoing oxidation but not those that are glucuronidated. If these findings are confirmed in humans, they will have important implications for rational drug use in the perioperative period.

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