Title: HALOTHANE INHIBITION OF DRUG METABOLISM IS STEREOSELECTIVE

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Introduction: The presence in a molecule of a center of asymmetry results in the formation of two stereoisomers (enantiomers). A 50:50 mixture of enantiomers is termed racemic. Many drugs used in anesthetic practice (eg. atropine, methohexital, ketamine) are administered as racemates. Drug enantiomers have identical physical properties but have different receptor affinities, may be metabolized differently and have different affinities for tissue and plasma protein binding sites.

Volatile anesthetics are inhibitors of drug metabolism, and halothane produces a 62% decrease in the intrinsic clearance of propranolol. Propranolol is used as a racemate, with the l-isomer being 100 times as potent a beta-blocker as the d-isomer. Thus, the aim of the study was to determine whether halothane-induced inhibition of drug metabolism is stereoselective.

Methods: We studied 8 dogs (27±2.4 kg) who had vascular catheters implanted 7 days previously. On Day 1 40mg propranolol (racemic) was infused into the portal vein of the awake dog, and blood samples were obtained over the next 4 hr for the measurement of d and l-propranolol concentrations by HPLC following derivitization with (-)-menthyl chloroformate. On Day 2, 24 hr later, the study was repeated during halothane anesthesia; thiopental (20 mg/kg iv) was followed by maintenance with 2.0 MAC halothane in oxygen. After 2 hr of halothane anesthesia, the propranolol infusion and blood sampling proceeded as on Day 1. The area under the plasma concentration/time curve, (AUC) and intrinsic clearance were calculated for l-propranolol, d-propranolol and total propranolol. The results were analyzed by Student's t-test for paired data or Wilcoxon rank sum test as appropriate, with $p<0.05$ as the minimum level of significance.

Results: Plasma concentrations of l-propranolol were lower than d-propranolol on both study days (Fig. 1). However, the concentrations of both enantiomers declined more slowly during halothane than on Day 1. Halothane reduced ($p<0.05$) the intrinsic clearance of total propranolol (Table). In addition, the clearance of the l-isomer fell from 11.0±2.7 to 2.6±0.7 L/min ($p<0.05$) while the clearance of the d-isomer fell from 4.3±0.8 to 1.5±0.3 L/min ($p<0.05$). The fall in clearance of l-propranolol (74±5%) was ($p<0.05$) greater than the fall in the clearance of d-propranolol (63±6%). Halothane anesthesia increased the AUC for total propranolol by 67.5±5.3% ($p<0.05$). However this was due to a proportionally greater increase in the concentrations of the pharmacologically active l-isomer than the d-isomer so that the AUC-d/AUC-l fell from 2.4±0.3 on Day 1 to 1.7±0.1 ($p<0.05$) during halothane (Table). Thus the AUC for d-propranolol was 142% higher than the AUC for l-propranolol when the animals were awake, compared to only 69% higher when the animals received halothane. The ratio of the plasma concentration of l to d-propranolol (L/D ratio) was (Fig. 2) higher at each time point during halothane than on the control day.

MEAN D AND L-PROPRANOLOL CONCENTRATIONS (FIG. 1)

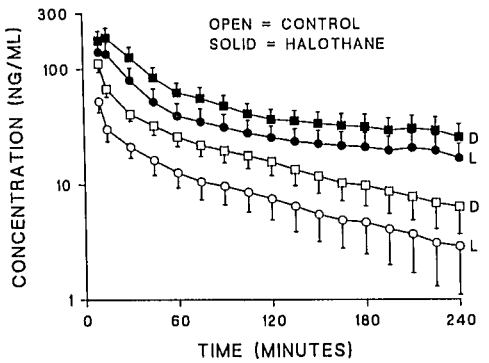

FIGURE 2. RATIO OF PLASMA CONCENTRATIONS OF L TO D PROPRANOLOL (L/D RATIO).

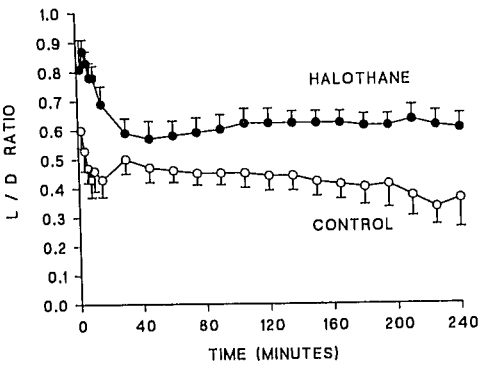

TABLE: PROPRANOLOL CLEARANCE (L/min) Ratio

	l	d	total	AUC-d/AUC-l
Awake	11.0 ±2.7	4.3+ ±0.8	6.1 ±1.1	2.4 0.3
Halothane	2.6* ±0.7	1.5*+ ±0.3	1.84* ±0.4	1.7 ±0.1

*$p<0.05$ vs. awake, +$p<0.05$ vs. l-propranolol.

Discussion: We have shown that halothane-induced inhibition of drug metabolism is stereoselective with a greater reduction of l than d-propranolol clearance. This will result in proportionally higher concentrations of l-propranolol during halothane than in awake dogs. As the l-isomer is 100 times more potent than the d-isomer, the pharmacodynamic effects will be substantially greater than would be predicted from the measurement of total propranolol concentrations alone. These findings suggest that the inhibition of metabolism of other racemic drugs used in anesthetic practice may also be stereoselective, with resultant toxicological implications for drug use in the perioperative period.

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