Title: CONTRASTING EFFECTS OF INHALATIONAL ANESTHETICS ON IN VIVO DRUG METABOLISM

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Introduction. The effects of inhalational anesthetics on the elimination of drugs that are concomitantly present during the perioperative period have not been extensively investigated although exposure to inhalational anesthetics has been implicated as causing stimulation of drug metabolizing activity. In contrast, *in vitro* studies have suggested that the presence of inhalational anesthetics alters and in some cases inhibits *in vitro* drug metabolism in hepatic microsomal preparations. It is clear that defining the effects of individual anesthetic agents on the rate of drug elimination in the perioperative period is of great importance, since a wide spectrum of drugs are administered during the perioperative period. The purpose of the present study was to investigate the effects of the inhalational anesthetics on *in vivo* drug metabolism during the pre and post-anesthetic period using the aminopyrine "breath test" as a sensitive noninvasive index of drug metabolism.

Methods. The effects of the volatile anesthetics on drug metabolism *in vivo* were studied by measuring the rate of elimination of aminopyrine in rats. In order to avoid repeated blood sampling which would preclude meaningful serial studies in a small animal we have used the elimination of $^{14}CO_2$ in the exhaled breath following the administration of radiolabelled [N-dimethyl-^{14}C] aminopyrine as an *in vivo* index of drug metabolism. Oxidation of the labelled methyl groups on aminopyrine produces $^{14}CO_2$, which is exhaled in the breath. The rate of $^{14}CO_2$ exhalation can be used as an index of the rate of aminopyrine metabolism.

The rate of aminopyrine metabolism was measured following the injection of 1 μCi of ^{14}C-aminopyrine into the tail vein of each male Sprague Dawley rat. The rats were then placed in individual airtight restraining cages. The exhaled $^{14}CO_2$ was drawn by a vacuum through concentrated sulfuric acid to remove water vapor and then through a scintillation vial containing 10 ml of 2:1 (V/V) methanol-ethanol amine mixture to trap all of the exhaled $^{14}CO_2$. The scintillation vials containing the methanol-ethanolamine mixture were changed every 15 minutes and liquid scintillation fluid added. The trapped concentration of ^{14}C was then determined by liquid scintillation spectrometry. The logarithm of the concentration of $^{14}CO_2$ excreted in the breath was plotted against the midpoint of each time period and the slope of the line (Kel) calculated by least square regression analysis and the half-life (t-1/2) as 0.693/Kel.

The rate of aminopyrine metabolism was determined on three occasions in each rat; firstly on the day prior to anesthesia and then at 2 hours and 24 hours post anesthesia. The rats were anesthetized for 2 hours with either halothane, in concentrations of 0.125%, 0.25% or 1.0%, or enflurane (1.8%) or isoflurane (1.3%) in air.

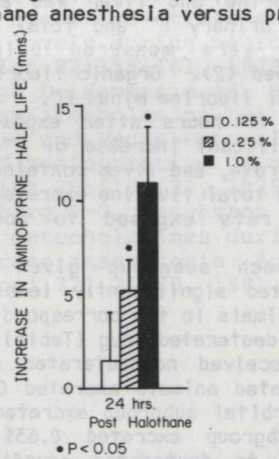
Results. The results are shown in the table. Halothane significantly prolonged the aminopyrine half-life both 2 and 24 hours after anesthesia. This was a dose dependent effect (Figure) with higher concentrations of halothane causing greater impairment of aminopyrine metabolism 24 hours after anesthesia. Although isoflurane caused a slight but significant prolongation of the aminopyrine half life 2 hours after anesthesia, this effect had disappeared by 24 hours. In contrast, enflurane exposure did not significantly affect the elimination of aminopyrine.

TABLE: Effect of volatile anesthetics on the in vivo demethylation of aminopyrine.

	Aminopyrine half-life (minutes ± SEM)		
	Before Anesthesia	2 hours Post Anesthesia	24 hour post Anesthesia
0.125% Halothane (n**=12)	40.7 ± 1.2	47.1* ± 3.3	42.2 ± 2.3
0.25% Halothane (n=12)	39.2 ± 1.0	44.5 ± 3.6	44.4* ± 1.7
1.0% Halothane (n=17)	41.3 ± 0.9	54.6* ± 3.5	54.0* ± 3.5
1.3% Isoflurane (n=11)	38.2 ± 1.6	44.1* ± 2.1	41.2* ± 3.0
1.8% Enflurane (n=11)	44.2 ± 2.0	43.6 ± 2.0	46.0 ± 1.7

*Significantly ($p<0.05$) different from preanesthesia half-life; **n = number of rats.

FIGURE: Change in aminopyrine half-life 24 hours after halothane anesthesia versus preanesthesia.



Conclusions. We have shown that halothane inhibits the rate of aminopyrine elimination in a dose dependent fashion for at least 24 hours. However, isoflurane has a much smaller effect which is short lasting. Enflurane, on the other hand, does not prolong aminopyrine elimination. These findings imply that volatile anesthetics may significantly reduce the elimination of drug administered in the perioperative period, with resultant increase in pharmacologic effect; and significant differences exist between the individual anesthetic agents.