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TITLE: HUMAN LIVER VOLATILE ANESTHETIC DEFLUORINATION: ROLE OF CYTOCHROME P450IIE1

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Oxidative biotransformation of the volatile anesthetics results in the liberation of inorganic fluoride ion, capable of producing dose-related nephrotoxicity. Fluoride production during methoxyflurane anesthesia causes frank renal failure, limits total MAC-hours of enflurane, and is of concern in the development of new volatile anesthetics. The cytochromes P450, a family of enzymes with multiple forms, catalyze volatile anesthetic biotransformation. Although evidence suggests that the cytochrome P450IIE1 is responsible for volatile anesthetic metabolism in animals, the identity of the human enzyme(s) that catalyze these reactions is presently unknown. The purpose of this investigation was to establish the role of P450IIE1 in human volatile fluorinated ether anesthetic metabolism *in vitro*, and to compare rates of human microsomal anesthetic defluorination.

Microsomes were prepared from livers of organ donors. Anesthetic metabolism (37°C, 30 min, closed vials) was measured at saturating substrate concentrations using a fluoride-specific electrode. Microsomal P450IIE1 content was determined by Western blot analysis using rabbit anti-rat P450IIE1 antibody.

Anesthetic defluorination rates for a typical donor are compared in Fig 1. In the 12 livers studies, there was considerable interindividual variability in defluorination rates (3-fold for METHOXYflurane, 5-fold for SEVOflurane, 15-fold for ENFlurane). Both ENF and SEVO defluorination rates were highly correlated with microsomal P450IIE1 content (r^2=0.87 for each, zero intercept) (Fig 2). In contrast, METHOXY metabolism was only partially related to P450IIE1 content (r^2=0.33, large non-zero intercept). Rates of ISoFlurane and DESflurane defluorination were too low to permit P450 isozyme identification using these techniques.

These results suggest that human microsomal ENF and SEVO defluorination are catalyzed exclusively by P450IIE1. METHOXY in contrast, is metabolzed by this, as well as other P450s. Microsomal defluorination rates were in the order METHOXY > SEVO > ENF > ISF > DES > 0. This rank order correlates well with plasma fluoride ion concentrations during anesthesia.

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FIGURE 1

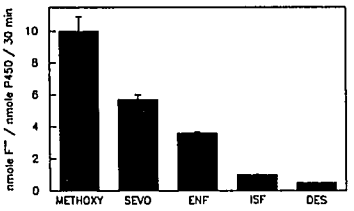
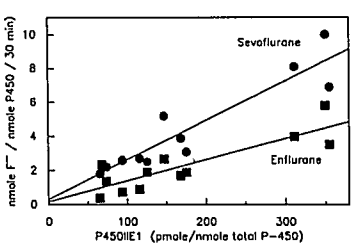


FIGURE 2



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Title PHARMACOKINETICS OF KETAMINE IN CHILDREN

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Ketamine (K) has been successfully administered by nasal route for preinduction of anesthesia in children.[1] The aim of this study was to determine pharmacokinetics of K, and its metabolite, norketamine (nK), following 5% K administered by venous (IV), nasal (IN) and rectal (IR) routes in children.

Thirty two healthly children undergoing minor urological surgery (age: 2-9 yr, weight: 10-30 kg) were included after informed consent of parents and Institutional approval. None of the children have rhinopharyngitis. After i.v. atropine, the children were randomly assigned to 4 groups: group IN_3 (n=8) received 3 mg. kg^{-1} IN K half dose into each nostril; group IN_9 (n=8) received 9 mg. kg^{-1} IN K half dose into each nostril; group IV_3 (n=7) received 3 mg. kg^{-1} IV K; group IR_9 (n=9) received 9 mg. kg^{-1} IN K throught a short rectal cannula. Thirtheen blood samples were collected before and during 360 min after K administration to measure K and nK plasma concentrations (gas liquid chromatography).and allow non compartimental (C_{max}, T_{max}, AUC, Cl/F and Vss/F) and compartimental ($T_{1/2abs}$ and $T_{1/2\beta}$) (SIPHAR PROGRAM), pharmacokinetic analysis. Statistic comparisons were carried out by ANOVA and Scheffe-F test when appropriate. $p < 0.05$ was considered as significant

Postoperatively, no nasal nor rectal lesions were observed. Pharmacokinetic parameters (mean ± SD) of K are listed in Table 1, and those of nk in Table 2. By nasal route, T_{max} and absorption time ($T_{1/2abs}$) were similar for the 2 doses, earlier than those obtained with intrarectal K. Lower plasma concentration led to lower AUC and bioavaibility was respectively 0.46 and 0.43 after larger and smaller nasal K, only 0.22 after rectal K. Concentrations of nK were lower than those of K in all groups, excepted in IR group. Absorption was earlier in nasal route contrasting with rectal route where first pass hepatic effect led to low concentrations of K associated with high concentrations of nK. These data confirm the good absorption of nasal route.

	C_{max} ng.ml^{-1}	T_{max} min	$T_{1/2abs}$ min	$T_{1/2\beta}$ min	V_{ss}/F l.kg^{-1}	Cl/F ml.min^{-1}.kg^{-1}	$AUC_{0-\infty}$ ng.ml^{-1}.min^{-1}
IV_3				125.25 ±45.73	1.06¶¶ ±0.57	21.96¶¶ ±9.84	148287 ±55311
IN_3	412 ±141	20.0 ±8.45	5.18 ¶ ±2.06	122.9 ±35.4	8.46¶¶ ±2.71	49.86¶ ±20.18	76425 ±28150
IN_9	1638 ±841	20.7 ±17.6	8.10 ±9.25	119.6 ±34.4	8.28¶¶ ±3.24	59.73 ±19.50	163642 ±64451
IR_9	1082 ±1307	48.9 ±51.5	16.54 ±9.88	114.8 ±37.7	19.16 ±8.77	118.10 ±69.94	109050 ±79432

Table 1: Pharmacokinetics of K. ¶ p<0.05 ; ¶¶ p<0.01 vs IR_9.

	C_{max} ng.ml^{-1}	T_{max} min
IV	341±66	50±32.4
IN_3	223±113	210.0±78.5¶¶
IN_9	497±290	132.7±94.6
IR_9	1510±1641	125.0±97.2

Table 2: Pharmacokinetics of nK. ¶¶ p<0.01 vs IV.

References
1- ANESTHESIOLOGY, 67:A514,1987.