Title: SEVOFLURANE ANESTHESIA AND BIOTRANSFORMATION IN MAN

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Introduction. Sevoflurane (fluoromethyl hexafluoroisopropyl ether), a new volatile inhalation anesthetic, with a blood-gas partition coefficient of 0.6[1], was evaluated in man to determine its clinical safety, pharmacologic properties and extent of biotransformation.

Method. With institutional approval, six health, informed, adult male volunteers were anesthetized for one hour after a thorough medical work up. Blood pressure, EKG and EEG were continuously recorded. Respiratory frequency and minute volumes were recorded every 3-5 minutes. Inspiratory and expiratory air samples were analyzed by gas chromatography (GC) for sevoflurane concentration every 1-5 minutes. Arterial blood samples were analyzed every 15 minutes for respiratory gases, sevoflurane concentration, inorganic fluoride[2] and total nonvolatile fluorine levels[2]. Sevoflurane was given by mask in oxygen from a Vernitrol (R) vaporizer in a partial rebreathing, CO_2 absorbing circle system. Anesthesia was induced by rapidly increasing the concentration of sevoflurane to 10%. Three per cent was used for maintenance. No other drugs were used before or during anesthesia. Following exposure, exhaled air samples were analyzed by GC over the next four days. Consecutive twelve hour urine collections, beginning with the morning of exposure through the fourth post exposure day, were analyzed for inorganic fluoride and total nonvolatile fluorine. Venous blood was analyzed for inorganic fluoride and total nonvolatile fluorine on post exposure days 1-4.

Results. Induction of anesthesia was achieved within one minute and without excitement. Respiratory frequency was elevated 23% over preanesthetic values throughout anesthesia. Minute volume remained constant. $PaCO_2$ averaged 51 (SD 4.3) torr, pHa 7.33 (SD-0.02) and the PaO_2 405 (SD 84) torr during anesthesia. The blood pressure fell 23.5 (SD 8.5)% during induction but returned to pre-induction values during maintenance. The pulse rate remained constant. The EKG revealed no arrhythmias. The predominate EEG rhythm was 10 cycles/sec with no silent periods. Emergence time averaged 11 (SD 3) min. Two subjects exhibited transient excitement during emergence. A thorough post-anesthetic medical follow-up revealed no significant unexplained change from the pre-anesthetic evaluation. Mean arterial blood concentrations of sevoflurane were 83.8 mg/L at 15 minutes and by 30 minutes were stable at approximately 67 mg/L (Table 2). Arterial blood levels of inorganic fluoride rose to 22.1 (SD 6.1) uM/L by the end of the exposure. (Table 2). Nonvolatile urinary metabolites were identified as fluoride ion and an organofluorine compound (Table 3). A total of 0.90mM of fluoride and 1.43mM of an organic fluorine compound were excreted. The half times for excretion of metabolites were, respectively, 16.3 hr and 13.8 hr. The fraction of sevoflurane excreted as urinary metabolites was 1.9%.

Discussion. Sevoflurane induced anesthesia as rapidly as cyclopropane and was readily accepted by the volunteers. It stimulated respiratory frequency while PCO_2 was increased moderately and blood pressure was depressed. It caused no cardiac arrhythmias and had no effect on renal functions or serum enzymes. Plasma fluoride concentrations rose moderately during anesthesia but fell promptly toward normal in 24 hours. Sevoflurane is a promising anesthetic and deserves further clinical evaluation.

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References. 1. Wallin, RF, Regan, BM, Napoli, MD, Stern, IJ: Sevoflurane: A new inhalational anesthetic agent. Anesth. Analg. 54:758-766, 1975.
2. Chase, RE, Holaday, DA, Fiserova-Bergerova, V, Saidman, LJ, Mack, FE: Biotransformation of Ethrane in Man. Anesth. 35:262-267, 1971.

Table 1. Pulmonary Excretion of Sevoflurane:

Compartment	Grams	Half-time (Hours)	%Pulmonary Excretion
VRG	3.42(0.55)*	0.18(.036)	48.9(11.2)
MG	2.80(1.50)	1.83(.20)	36.0(9.3)
FG	1.16(0.74)	20.0(6.1)	15.1(5.7)
Total	7.38(2.32)		100.

Table 2. Arterial Blood Concentrations from Start of Exposure:

Time	Sevoflurane (mg/L)	Fluoride (uM/L)	Org. Fluorine (uM/L)**
Pre	0	N/A	5.7(0.5)
15 min	83.8(18.3)	10.5(2.8)	66.0(44.8)
30 min	66.9(13.1)	17.0(5.0)	74.3(26.5)
45 min	65.1 (9.8)	19.5(6.6)	80.5(22.3)
60 min	68.2(12.3)	22.1(6.1)	83.4(41.4)
24 hrs		4.4(1.3)	26.0(18.0)
48 hrs		3.4(1.2)	9.6(5.3)

Table 3. Urinary Metabolites:

	Total Excreted (uM)	Half-time (hours)
Fluoride ion	0.90(0.18)	16.3(1.9)
Organic F	1.43(0.26)**	13.8(4.6)

*All figures are the mean and in parentheses, the standard deviation
**Assumes six atoms of fluorine per molecule.