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Resistance of Isoflurane to Biotransformation in Man

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Pulmonary and renal excretion of isoflurane and its metabolites was studied in nine surgical patients following administration of known quantities of isoflurane. Uptake and pulmonary washout were predictable by a mathematical model for inert vapors. The agreement between predicted and experimental data supports the view that isoflurane is subject to little or no biotransformation. The average recovery in exhaled air was 95 per cent, SE 7 per cent. The postoperative increase of urinary excretion of fluoride and organic fluorine accounted for less than 0.2 per cent of fluorine administered as isoflurane. This small extent of biotransformation is probably biologically insignificant, but only after extensive clinical experience can the hazard of delayed toxic response be conclusively evaluated. (Key words: Anesthetics, volatile, isoflurane; Biotransformation, isoflurane.)

ISOFLURANE (Forane¶) (1-chloro-2,2,2 trifluoroethyl difluoro-methyl ether) is a potent anesthetic agent synthesized in 1965.[1] It is an isomer of enflurane but does not produce the electroencephalographic abnormalities characteristic of enflurane.[2] Isoflurane has been found to have useful clinical properties.[3]

Animal studies suggest that isoflurane undergoes minimal or no metabolism. Miniature swine show no measurable hepatic uptake of isoflurane at various subanesthetic concentrations.[4] The concentration of fluoride in the bones of the animals[5] is not increased following exposure to isoflurane. The present study reports the extent of biotransformation of isoflurane in man.

Method

Patient Selection

Two groups of informed volunteer patients were studied. The experimental group consisted of nine patients who received isoflurane in oxygen for anesthesia for elective surgical operations (table 1). The second group of patients, a control group (table 1), received spinal anesthesia for comparable operations to determine whether surgery and hospital environment affect urinary excretion of fluorine. Patients were excluded when they had recently had anesthesia or when there was evidence of renal or hepatic impairment.

Anesthesia

Following denitrogenation with oxygen for 10 minutes, anesthesia was induced with thiopental (3–5 mg/kg, iv) and endotracheal intubation performed after muscle relaxation with succinylcholine (1 mg/kg). Anesthesia was then maintained with isoflurane in oxygen and intravenous administration of muscle relaxants, as previously described.[6,7] Before each study, the circuit was tested for tightness of seals in two ways: the endotracheal tube was replaced by a nylon bag and the system was filled with oxygen until the pressure inside the circuit was 10 torr above atmospheric pressure. The pressure had to stay unchanged for 15 minutes. Then the pressure was relieved and liquid isoflurane was injected into the circuit and vaporized with an oxygen flow (40 ml/min). The circuit included a mechanical ventilator that was functioning at the time the isoflurane was injected. The amount of isoflurane injected was chosen so that vapor

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TABLE 1. Patients Studied

	Age (Years)	Height (cm)	Weight (kg)	Body Fat Per Cent*	Minute Ventilation (l/min)		Surgical Operation		Duration of Anesthesia (Min)
					During	After	Type	ASA Status	
Experimental group, isoflurane anesthesia									
Patient 1	28	175	65	3.9	7.2	9.3	Left inguinal herniorraphy	I	100
Patient 2	52	175	95	16.5	7.7	11.4	Left inguinal herniorraphy	II	101
Patient 3	24	169	72	10.1	5.4	8.2	Left inguinal herniorraphy	I	92
Patient 4	24	175	64	3.4	6.7	11.8	Left inguinal herniorraphy	I	77
Patient 5	56	172	66	5.8	5.5	8.8	Lumbar laminectomy	I	156
Patient 6	39	187	99	12.5	5.9	8.5	Lumbar laminectomy	II	209
Patient 7	42	175	74	8.2	8.5	8.9	Osteotomy rt. fibula; realignment ankle mortise by open reduction, internal fixation; application long leg cast	I	165
Patient 8	46	161	79	17.1	7.5	7.5	Ventral incisional herniorrhaphy	I	103
Patient 9	56	183	86	9.6	7.3	9.6	Ventral hernia repair with Marlex graft	I	161
Mean	41	175	77.8	9.7	6.9	9.3			130
SD	13	7.5	13.0	5.0	1.1	1.4			44
SEM	4.3	2.5	4.3	1.7	0.35	0.5			15
Control group, spinal anesthesia									
Patient 1	57	172	77	10.9			Open reduction, internal fixation, left patellar fracture	I	135
Patient 2	59	168	73	11.0			Anal fistulectomy	I	50
Patient 3	56	168	66	7.6			Left inguinal herniorrhaphy and groin exploration	I	100
Patient 4	50	168	64	6.6			Arthrotomy rt. knee with joint debridement	II	150
Patient 5	51	193	81	3.4			Open reduction, internal fixation rt. hip fracture with placement endoprothesis head and neck of femur for metastatic squamous-cell carcinoma of lung	III	135
Mean	55	174	72.2	7.9					114
SD	3.9	11	7.2	3.2					40
SEM	1.7	5	2.2	1.4					18

* Estimated according to the equation[25]: per cent body fat = 100 (4.201/specific gravity − 4.312).

TABLE 2. Uptake and Excretion of Isoflurane

	Duration of Anesthesia (Min) (1)	Dose (g)			Maintenance Concentrations (mg/l)		Exhaled				Urinary Excretion (mg/72 Hours)		Per Cent of Uptake	
								Half Times						
		Predicted (2)*	Delivered by Syringe (3)	Measured (4)†	Inspired (5)	End-expired (6)	g (7)	VRG (Min) (8)	MG (Hours) (9)	FG (Hours) (10)	Fluoride (11)‡	Fluorine (12)‡	Metabolized (13)§	Recovered (14)¶
Patient 1	100	10.1	9.7	10.2	80	68	9.4	9	2.6	14	5.5	−3	0.08	92
Patient 2	101	23.7	18.7	24.5	129	104	19.2	15	2.8	23	3.6	−6	0.005	78
Patient 3	92	12.4	**	10.1	113	90	13.5	15	0.8	18	9.2	22	0.40	134
Patient 4	77	10.9	12.7	10.8	110	95	12.7	12	2.0	13	1.6	18	0.20	117
Patient 5	156	20.2	18.1	16.9	140	118	17.6	††	3.0	15	0.5	2	0.02	104
Patient 6	209	34.1	**	22.8	111	94	24.4	††	2.0	30	17.0	6	0.18	107
Patient 7	165	20.1	**	22.1	96	81	17.3	0.6		10	13.0	9	0.21	78
Patient 8	103	18.9	24.5	22.1	115	88	16.7	2	1.3	23	11.0	9	0.13	76
Patient 9	161	22.7	**	23.7	102	85	17.3	10	3.3	11	25.0	18	0.29	73
Mean	130	19.2		18.1	111	92	16.8	9.4	2.0	17.4	9.6	8.3	0.17	95
SD	44	7.5		6.2	18	14	5.1	5.2	1.0	6.6	7.9	9.7	0.13	21
SE	15	2.5		2.1	6	.6	1.7	2.0	0.3	2.2	2.6	3.2	0.04	7

* According to current theory governing inert gases.[11]

† Calculated according to Equation 2.

‡ Calculated as isoflurane $\left(\text{fluorine excretion/72 hr} \times \frac{184}{5 \times 19} \right)$.

§ Including fluoride deposited in skeleton: $\frac{2(11) + (12)}{1{,}000(4)} \times 100$. Numbers in parentheses represent values in the designated columns.

¶ Exhaled plus metabolized: $\frac{1{,}000(7) + 2(11) + (12)}{1{,}000(4)} \times 100$.

** Leak in circuit or deviation from program.

†† Insufficient samples obtained for determination of half time.

concentration in the circuit was approximately 1 per cent. When this concentration was achieved the oxygen flow was stopped but the ventilator continued to operate. Gas samples of 0.2 ml from the circuit were then analyzed at 15-minute intervals. When the vapor concentration of isoflurane decreased not more than 10 per cent per hour, the circuit was considered to be tightly sealed.

Blood pressure and the electrocardiograph were monitored during anesthesia. The flow of oxygen into the system was adjusted to maintain a constant volume of gas in the rebreathing reservoir; the range of the mean flows was 235–360 ml/min. Ventilation was controlled with an Ohio Ventilator and was measured with a Wright respirometer in the inspiratory limb of the circuit. Liquid isoflurane from a 20-ml Hamilton gas-tight syringe was injected into the circuit via a stainless steel capillary by a syringe pump (Dose Regulated Anesthesia, Mark II, Quan, Inc.). The pump speed was controlled by a Data-Trak curve follower. The infusion was programmed to maintain a constant alveolar concentration of approximately 1.3 × MAC (MAC = 1.27 per cent[*]).

Three programs were utilized for slim, average, and obese patients, adjusted for 2, 10, and 19 per cent of the body weight as adipose tissue. The uptake (y_t) at time t of isoflurane in the average subject (70 kg body weight, 170 cm height) was determined by differentiation of the following equation:

$$Y_t = 995(1 - e^{-0.0003t}) + 183(1 - e^{-0.00\cdot2t}) + 22(1 - e^{0.3\cdot0t}) \quad (1)$$

in which the constants were derived from perfusion and volume of pharmacokinetic compartments[11] and partition coefficients of isoflurane.[**]

Samples of inspired and end-expired gas were drawn during the appropriate phase of respiration via a nylon cannula in the endotracheal tube at 4–10-minute intervals during anesthesia and during the early phase of recovery. Mixed expired gas was obtained at the same times at the outlet of a mixing chamber[9] interposed in the expiratory breathing tube. Gas samples were collected in 20-ml glass syringes.

Samples of arterial blood obtained periodically from a radial-artery cannula were analyzed to estimate fluoride concentrations and respiratory gases.

At the conclusion of anesthesia the effects of the muscle relaxant was reversed with atropine and neostigmine. When spontaneous ventilation was adequate, the breathing circuit was disconnected from the isoflurane source and the patient allowed to breathe oxygen-enriched room air. Ventilation was monitored during the desaturation period. The endotracheal tube was left in place until the patient reacted. Subsequently, ventilation was measured by maintaining a gas-tight fit with a face mask. A low-deadspace, unidirectional breathing valve ensured that the patient inspired room air and that the expired air was directed into the mixing chamber. A Wright respirometer in the inspiratory limb measured minute ventilation. Patients were instructed to breathe normally and not to hyperventilate while the mask was on the face.

Twenty-four-hourly samples of urine were collected preoperatively and for three to six days postoperatively in both experimental and control groups. Urines were stored on ice in polyethylene bottles during collection periods and refrigerated thereafter until analyzed.

Analytical Methods

Gas Analysis

During anesthesia isoflurane concentrations in inspired, mixed-expired and end-expired air samples were analyzed with a Beckman Infra-Red Medical Gas Analyzer (Model LB1). During the initial period of desaturation (approximately 10 minutes) mixed-expired samples were similarly analyzed until the concentrations approached 10 mg/l, the limit of reliable measurement of the Infra-Red apparatus. Subsequently, a Hewlett Packard gas chromatograph, (Model 402), fitted with a flame ionization detector, was used. Gas samples were injected with a l-ml gas-tight syringe (Glenco Scientific Inc.) into a 1.2-m (6 mm O.D.) glass column packed with Chromosorb P (30/60 mesh) coated with 10 per cent di-isodecylphthalate. The oven temperature was 100 C and the nitrogen carrier gas flow rate was 50 ml/min.

[**] Information received from J. F. Vitcha, Ohio Medical Products: $\lambda_{bl\,air} = 1.4$, $\lambda_{VRG\,air} = 3.5$, $\lambda_{MG\,air} = 5.6$, $\lambda_{fat\,air} = 98$.

Blood and Urinary Fluoride

Inorganic fluoride was measured by specific fluoride ion electrode.[6] The specific fluoride ion electrode was also employed for determination of total fluorine and total nonvolatile fluorine in urine following combustion of the sample in a hydrogen–oxygen flame[10] or in an Ogg-Schoninger flask, respectively.[6] The increase of fluoride concentration in blood above the preoperative level was measured with a specific fluoride ion electrode using the incremental addition of a standard fluoride solution, as described elsewhere.[10]

Clinical Assessment

The programmed infusion of isoflurane provided satisfactory operating conditions. In three patients hypotension occurred; it was treated by intravenous fluids and by decreasing the rate of isoflurane infusion into the circuit. Tachycardia developed in six patients and resolved spontaneously. Leaks were detected in the circuit in the cases of Patients 3, 6, and 7 by noting a sudden increase in the flow of oxygen required to maintain a constant volume in the rebreathing reservoir, and by detecting liquid isoflurane on the external surface of the system. The programming of the isoflurane infusion was faulty in the case of Patient 9, so approximately constant end-expired and arterial concentrations were not maintained. There was no problem in the cases of Patients 1, 2, 4, 5 and 8.

Results

Expired Isoflurane Concentrations

End-tidal isoflurane concentrations were analyzed to determine fluctuations in depth of anesthesia. The mean end-tidal isoflurane concentration during anesthesia was 92 mg/l (range 68–118 mg/l). The mean minute ventilation during anesthesia was 6.9 l/min (SD 1.1). The total uptake, "D," in each case was calculated as the sum of the differences between isoflurane concentrations in inhaled (C_{in}) and mixed exhaled (C_{ex}) air multiplied by minute ventilation ($\dot{V}$) and time intervals between sampling (t in minutes).

$$D = \dot{V} \times t \times (C_{in} - C_{ex}) \qquad (2)$$

In five cases (patients 1, 2, 4, 5, and 8) in which leaks in the circuit were not detected, the amounts of isoflurane delivered by syringe were similar to calculated uptakes (table 2, columns 3 and 4). During anesthesia, which lasted an average of 130 minutes (77–206 min), mean total uptake was 18.1 g (10.1–24.5 g).

To define the desaturation curves, the NONLIN digital computer program with a subroutine for the sum of three exponential functions was used to determine parameters of a curve that would optimally fit the experimental pulmonary excretion rate data. The data for each case were analyzed on a Univac 1106 computer, and exponents, k, were used to determine the desaturation half-times for three apparent pharmacokinetic compartments

$$\left(t_{\frac{1}{2}} = \frac{0.693}{k} \right).$$

The mean half-time in the nine patients for the first compartment (vessel-rich group, VRG) was 9.4 minutes (SE 2.0); for the second compartment (muscle group, MG) 2.0 hours (SE 0.3); and for the third compartment (fat group, FG) 17.4 hours (SE 2.2). The indices and exponents of the exponential functions representing three main pharmacokinetic compartments were also used to calculate the total amount exhaled

$$\left(A = \sum \frac{\text{index}}{\text{exponent}} \right).$$

To determine the typical pulmonary excretion curve all data from the nine patients were submitted to the same statistical analysis (Fig. 1). The following equation gave the best fit for the experimental data,

$$y_t = 231\, e^{-0.074t} + 60\, e^{-0.00721} + 4.0\, e^{-0.00068t} \text{ mg/min} \qquad (3)$$

where y_t is the rate of pulmonary desaturation in mg/min and t is time after the end of anesthesia in minutes.

A four-compartment model for uptake, distribution and excretion of inert gases was used to predict the desaturation curve.[11] The computation was done on the Univac 1106 digital computer, using a previously described mathematical procedure.[12] The predicted curve provided a good fit to the experimental data (fig. 1).

URINE

The urinary excretion of inorganic fluoride and that of organic fluorine in both groups are shown in figure 2. It can be seen that there were increases in excretion of both inorganic fluoride and organic fluorine during the three days after operation. Analyses of total fluorine by both methods (volatile and nonvolatile fluorine) were in agreement within the limits of experimental error. The increase of inorganic fluoride in the study group was significantly greater than that in the control group ($P < 0.01$). Due to large variation in excretion rates of organic fluorine, the difference in organic fluorine excretion between the two groups was not statistically significant ($P > 0.05$).

BLOOD FLUORIDE

Inorganic fluoride concentrations in blood increased above preoperative values in two cases only. The maximum increases were 0.02 and 0.1 μg/ml, respectively.

Discussion

The results of this study support the view that isoflurane is subject to little or no biotransformation in man. Ninety-five per cent of the dose administered was accounted for as unaltered drug excreted in exhaled air following exposure. Less than 0.2 per cent of the isoflurane administered appeared as urinary metabolites. This is less than has been observed in man with any other volatile halogenated anesthetic.

The model on which the program for closed-circuit administration was based is for a biochemically inert gas.[11] If a significant fraction of uptake had been subject to biotransformation, the program would not have produced the predicted concentration in arterial blood and the desired depth of anesthesia.[13] Since the concentration in end-expired air was as predicted and satisfactory surgical anesthesia was achieved in study subjects without modification of the program, it can be said that no significant metabolism or tissue binding

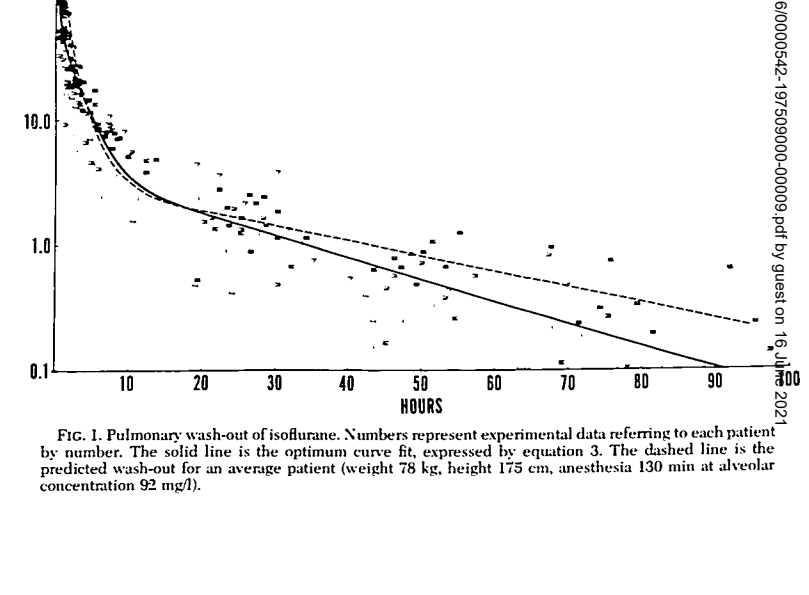

FIG. 1. Pulmonary wash-out of isoflurane. Numbers represent experimental data referring to each patient by number. The solid line is the optimum curve fit, expressed by equation 3. The dashed line is the predicted wash-out for an average patient (weight 78 kg, height 175 cm, anesthesia 130 min at alveolar concentration 92 mg/l).

took place. These observations corroborate the conclusions of Cromwell, Eger, and Stevens,[14] who obtained good agreement between predicted and measured uptake and washout of isoflurane.

Urinary inorganic fluoride and organic fluorine excretion rates rose more during the 72 hours following exposure in the group exposed to isoflurane than in the control group. The increase of fluoride ion achieved statistical significance, although its biological significance is questionable.

There appeared to be an increase of organic fluorine in the urine, although it lacked significance because of a large standard deviation and the small number of cases. The total amount of fluoride and organic fluorine excreted during the first three postoperative days by the experimental group was higher than that of the control group ($P < 0.01$). Hitt *et al.*[15] reported similar studies involving three patients. Their values of inorganic fluorine are in agreement with our data. Their preoperative and postoperative values of organic fluorine (non-ionic fluoride) were higher than ours, perhaps due to environmental influences or to differences in the analytical procedures. However, they also observed increases of both forms of fluorine in urine on the day of operation and on the first postoperative day. They suggested that a small amount of isoflurane is metabolized to trifluoroacetic acid, fluoride, chloride, CO_2 and H_2O. No change in renal function, including response to vasopressin, was found following isoflurane anesthesia.[16]

We have excluded environment as a factor causing increased fluorine excretion, since no increase occurred in the control group. It is possible that contaminants of the isoflurane were responsible. The purity of the isoflurane is reported to be 99.98 per cent or better, and some of the impurity is trifluoroethanol (TFE).†† Small quantities of substances like TFE with high water solubility and high susceptibility to biotransformation would tend to be extracted continuously from vapor in the lung during the maintenance phase of anesthesia and could be converted to urinary metabolites equivalent in fluorine content to 0.2 per cent of the amount of isoflurane absorbed.

Whether isoflurane is subject to biotransformation to a small extent, or not at all,

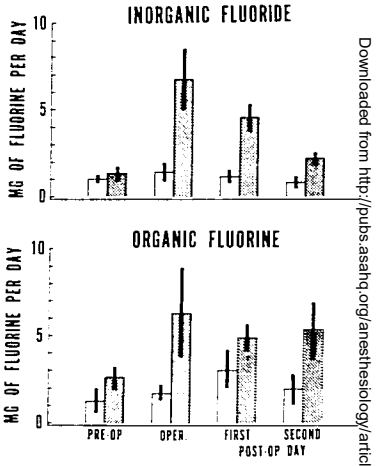

FIG. 2. Twenty-four-hour urinary excretion of fluoride and organic fluorine (± SE) in control (open column) and isoflurane groups (striped column).

may be of consequence. Delayed toxic reactions following general anesthesia have been ascribed to three mechanisms, all dependent on biotransformation of the anesthetic. A toxic metabolite may be formed in sufficient quantity to injure susceptible tissues. This appears to be the case with the fluoride ion or oxalic acid derived from methoxyflurane, which interferes with renal function[17,18] and with the trifluoroethanol derived from fluroxene in experimental animals, which causes systemic toxicity and death.[19,20] A second mechanism depends on irreversible oxidation or alkylation of fixed cellular elements by highly reactive intermediate products of biotransformation. This has been demonstrated to result in hepatic necrosis in mice exposed to labeled bromobenzene.[21] Toxicity is dose-dependent in both of the above mechanisms. It is unlikely that isoflurane metabolism could result in either type of toxicity because of its resistance to biotransformation.

The third mechanism involves formation of an antigen by the condensation of a fragment of the parent drug with a cellular protein to which the body responds by formation of cell-mediated antibodies. The occurrence of hepatic necrosis following exposure to halothane

†† J.F. Vitcha, Ohio Medical Products, Personal communication.

has been ascribed to this mechanism.[22] Specific hypersensitivity to halothane has been reported in at least two persons who had been exposed repeatedly to halothane,[23] and animal studies have demonstrated the capacity of a metabolite of halothane to form active antigenic material.[24] Such hypersensitivity is rare and, presumably, is not dose-related. Hence, even though isoflurance is less subject to biotransformation than halothane and the other halogenated anesthetic hydrocarbons that have been studied, it may be necessary to wait for more extensive clinical experience before this hazard can be evaluated.

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