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Renal Effects and Metabolism of Isoflurane in Man

Richard I. Mazze, M.D., Michael J. Cousins, M.B., F.F.A.R.A.C.S.,† Gary A. Barr, M.D.‡*

The intra- and postanesthetic renal effects and metabolism of isoflurane were studied in nine surgical patients; six control patients received halothane. Isoflurane was metabolized to a slight extent, with a mean peak serum inorganic fluoride concentration of 4.4 ± 0.4 μM/l, measured six hours after anesthesia. Dose-related increases of inorganic and organic fluoride were found in the urine. At comparable anesthetic exposures five to ten times more organic fluoride metabolites of halothane were detected. Postanesthetic renal function, including the response to vasopressin, was normal in both groups. Intra-anesthetic depressions of renal blood flow (51 per cent of control), glomerular filtration rate (63 per cent of control) and urinary flow rate (34 per cent of control) during isoflurane anesthesia were similar to those seen with halothane. Metabolism of isoflurane to inorganic fluoride is of insufficient magnitude to cause renal dysfunction. (Key words: Anesthetics, volatile: isoflurane; Anesthetics, volatile: halothane; Kidney: nephrotoxicity; Biotransformation: isoflurane; Biotransformation: halothane; Ions: fluoride.)

ISOFLURANE (CHF_2-O-$CHClCF_3$; Forane§) is a pentafluorinated methylethyl ether. It is metabolized to inorganic fluoride in man[1] and animals,[1,2] but to a lesser extent than methoxyflurane. Previous animal studies with isoflurane have demonstrated an absence of nephrotoxicity associated with its administration.[2,3] The present study examines the intra- and postanesthetic renal effects and metabolism of isoflurane in surgical patients.

Methods and Materials

Fifteen male surgical patients, ASA physical status 1, from whom informed consent had been obtained, were randomly divided into isoflurane and halothane (control) groups. Patients with abnormalities in renal function or diseases with possible renal complications were excluded from the study; these criteria have been reported.[4] Preoperatively, measurements were made of serum and urinary osmolality, sodium, potassium, uric acid, creatinine, urea nitrogen, and inorganic fluoride concentrations. Twenty-four-hour urine volume and organic fluoride excretion were also determined. From the above data 24-hour urinary solute excretions and clearances were calculated. Overnight urine-concentrating ability was determined by restricting all intake beginning at 7 PM, obtaining a urine specimen at 7 AM the next morning and another one hour later. Osmolality of the 8 AM specimen was determined. Laboratory methods have been described.[5] Following premedication with morphine sulfate, 4–10 mg, and scopolamine hydrobromide, 0.4 mg, a urethral catheter was introduced to permit pre- and intra-anesthetic measurement of renal blood flow (RBF) and glomerular filtration rate (GFR), employing standard PAH (C_{PAH}) and inulin (C_{In}) clearance techniques. Seven patients anesthetized with isoflurane and five patients anesthetized with halothane were studied. There were three (20 to) 30-minute collection periods prior to induction and three additional collection periods during maintenance of anesthesia but before the start of the operative procedure.

Anesthesia was induced by inhalation of either isoflurane or halothane in concentra-

* Associate Professor of Anesthesiology.
† Assistant Professor of Anesthesiology.
‡ Research Fellow in Anesthesiology.
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TABLE 1. Isoflurane Patients—Preoperative and Operative Data

	Age (Years)	Preoperative Weight (kg)	MAC ×	Anesthesia Time (Hours)	= Dose (MAC Hours)	Arterial Isoflurane (mg/100 ml)	Operative Procedure
Patient 1	44	67.0	0.6	2.8	1.7	6.6	Rt. inguinal herniorrhaphy
Patient 2	75	81.0	0.6	2.0	1.2	7.0	Panendoscopy
Patient 3	50	92.0	1.0	4.5	4.5	11.5	Cholecystectomy
Patient 4	48	70.0	1.0	3.0	3.0	12.7	Excision of pilonidal sinus
Patient 5	56	82.0	0.5	4.0	2.0	8.7	Rt. dacrocystorhinostomy
Patient 6	46	89.0	1.0	3.8	3.8	11.2	Ventral herniorrhaphy
Patient 7	23	71.0	0.7	7.5	5.3	9.7	Lt. tympanomastoidectomy
Patient 8	27	56.0	0.6	5.3	3.2	8.6	Lt. tympanomastoidectomy
Patient 9	26	69.0	0.9	3.8	3.4	13.1	Fascia lata graft to lt. frontalis muscle
Mean	43.9	75.2		4.1			
± SE	±5.6	±3.9		±0.5			
P vs. halothane	>0.4	>0.2		>0.4			

TABLE 2. Halothane Patients—Preoperative and Operative Data

	Age (Years)	Preoperative Weight (kg)	MAC ×	Anesthesia Time (Hours)	= Dose (MAC Hours)	Arterial Halothane (mg/100 ml)	Operative Procedure
Patient 1	50	78.0	1.0	2.5	2.5	10.8	Ventral herniorrhaphy
Patient 2	60	76.1	0.7	2.5	1.8	9.6	Skin graft lt. heel
Patient 3	24	82.5	1.0	3.0	3.0	10.1	Lt. inguinal herniorrhaphy
Patient 4	31	70.2	1.4	5.0	7.0	12.2	Thoracotomy and rt. upper lobectomy
Patient 5	58	85.0	1.0	7.3	7.3	11.7	Rt. radical neck dissection
Patient 6	58	90.9	1.0	8.0	8.0	10.1	Esophagogastrectomy and splenectomy
Mean	46.8	80.5		4.7			
± SE	±6.3	±3.0		±1.0			
P vs. isoflurane	>0.4	>0.2		>0.4			

tions of as much as 3.5 per cent. For maintenance, the inspired concentration of the anesthetic agent was reduced to achieve an alveolar concentration of approximately one MAC, equal to 1.2 per cent for isoflurane and 0.7 per cent for halothane. Succinylcholine, 1 mg/kg, was administered intravenously to facilitate endotracheal intubation, and *d*-tubocurarine, 0.2–0.6 mg/kg, was administered for surgical relaxation. Barbiturates and nitrous oxide were not administered. Intraanesthetic blood samples were obtained from a radial artery to measure *p*H, Po_2, Pco_2, and anesthetic concentration. Electrocardiogram, esophageal temperature, pulse rate, and direct radial arterial blood pressure were continuously monitored.

Postoperatively, serum and urinary biochemical measurements were made as during the preoperative period. Serum inorganic fluoride concentration was also measured at the termination of anesthesia and six hours after anesthesia. In addition, 24 to 48 hours following operation all patients received 2.5 units of vasopressin in oil, subcutaneously; urine was collected every four hours and osmolality determined in order to evaluate urine-concentrating ability.

No oral intake of food and fluids was permitted while testing overnight urine-concentrating ability or after midnight of the night preceding surgery. Upon arrival in the operating room, 15 ml/kg body weight of a solution consisting of ½ physiologic saline solution and ⅔ 5 per cent dextrose in water was administered, intravenously; this usually resulted in diuresis at a rate of 5–10 ml/min. During maintenance of anesthesia in the absence of surgical stimulation, while PAH and inulin clearances were being deter-

TABLE 3. Pre- and Postoperative Serum Values, Mean ± SE

	Na^+ (mEq/l)	K^+ (mEq/l)	Creatinine (mg/100 ml)	Urea Nitrogen (mg/100 ml)	Uric Acid (mg/100 ml)	Osmolality (mOsm/kg)	F^- (μmol/l)
Isoflurane							
Preoperative	139.3 ±0.8	4.26 ±0.08	1.01 ±0.06	14.9 ±1.3	5.81 ±0.37	287.1 ±2.4	2.9 ±0.1
Postoperative days 1–4	139.0 ±0.5	4.11 ±0.09	0.97 ±0.05	11.3 ±1.8	4.81 ±0.25	284.2 ±1.9	2.7 ±0.2
Halothane							
Preoperative	140.6 ±0.8	4.44 ±0.08	1.03 ±0.03	15.6 ±1.3	5.71 ±0.23	285.9 ±1.3	2.8 ±0.5
Postoperative days 1–4	138.1 ±1.1	4.38 ±0.15	0.98 ±0.03	12.0 ±0.5	6.45 ±0.52	283.7 ±2.4	2.3 ±0.3
P,* isoflurane *vs.* halothane	>0.1	>0.3	>0.5	>0.5	>0.4	>0.5	>0.1

* Preanesthetic–postanesthetic differences.

TABLE 4. Pre- and Postoperative Laboratory Data, Mean ± SE

	Solute Excretion/24 Hours							
	Na^+ (mEq)	K^+ (mEq)	Osmolality (mOsm)	F^- (μM)	Org F (mM)	Creatinine Clearance (ml/Min)	Weight (kg)	Urine Volume (l/Day)
Isoflurane								
Preoperative	148.7 ±13.8	73.0 ±13.1	697.1 ±84.6	43.5 ±7.3	0.7 ±0.2	103.3 ±7.1	75.4 ±3.9	1.40 ±0.19
Postoperative days 1–2	234.8 ±25.5	68.0 ±8.6	910.8 ±76.2	195.3 ±24.1	1.3 ±0.3	101.1 ±8.9	75.1 ±4.1	3.03 ±0.47
Halothane								
Preoperative	161.2 ±26.1	78.5 ±9.2	875.8 ±113.5	54.8 ±11.6	1.3 ±0.2	86.0 ±9.3	81.4 ±3.1	2.23 ±0.53
Postoperative days 1–2	140.8 ±29.2	82.2 ±11.3	773.3 ±72.2	37.2 ±6.2	13.8 ±4.2	91.3 ±9.4	81.1 ±4.0	2.20 ±0.40
P,* isoflurane *vs.* halothane	<0.05	>0.2	>0.2	<0.01	<0.01	>0.4	>0.2	<0.025

* Preanesthetic–postanesthetic differences.

mined, a decrease in mean blood pressure of 10–30 mm Hg usually occurred. The greatest changes were observed in patients anesthetized with isoflurane. These patients were treated by reducing the inspired anesthetic concentration and by infusing an additional one to two liters of intravenous fluids. All measured intra- and postoperative fluid losses, plus an additional 700 ml/day for insensible fluid losses, were replaced with the above or similar salt-containing intravenous solutions until patients were capable of oral alimentation. Twenty mEq of KCl were added to each liter of fluid administered in the postoperative period.

STATISTICAL METHODS

Means of each preoperative variable were determined for all patients anesthetized with isoflurane and values were compared with those obtained from all patients anesthetized with halothane. Mean preoperative–postoperative differences for each group were calculated and compared. Values from only the first two postoperative days were used for this calculation since almost all patients were taking fluids orally by the second postoperative day. Student's t test was used for statistical analysis. Because this method of analysis may be relatively

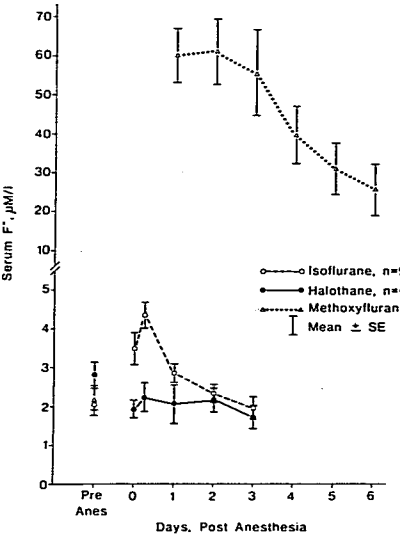

FIG. 1. Serum inorganic fluoride (F^-) concentrations prior to and following isoflurane and halothane anesthesia. There was a clinically insignificant increase in serum F^- concentration immediately following isoflurane anesthesia (0 time), reaching a mean peak value of 4.4 ± 0.4 μM/l six hours later. For comparison, data from a previous clinical study[10] in which patients received similar exposures to methoxyflurane are also presented. Mean peak serum inorganic fluoride concentration following methoxyflurane was higher, 61 ± 8 μM/l, and declined more slowly than with isoflurane. Note the change in scale of the vertical axis.

insensitive when changes occur in only a few patients at higher dosage, dose–response curves were also examined using regression analysis. Anesthetic dosage was considered to be the mean end-alveolar anesthetic concentration expressed as a fraction of MAC times the duration of exposure.

Results

Preoperatively, the groups did not differ significantly in any of the variables measured (tables 1–4). The types and lengths of operations were also similar. Postoperatively, significant differences between the groups were restricted almost entirely to those variables which measured metabolism of anesthetic. Among patients anesthetized with isoflurane there was an increase in serum inorganic fluoride level at the end of anesthesia, with a mean peak postanesthetic value of 4.4 ± 0.4 μM/l attained six hours after anesthesia (fig. 1). However, in no instance was a value greater than 5.5 μM/l measured. Twenty-four hours after anesthesia, differences between the isoflurane and halothane groups were no longer significant. There was also an increase in postoperative 24-hour urinary inorganic fluoride excretion ($U_{F^-}V$) among patients anesthetized with isoflurane (195.3 ± 24.1 μM/l) compared with those anesthetized with halothane (37.2 ± 6.2 μM/1) (table 4).¶ When examined by regression analysis, the increase in $U_{F^-}V$ was seen to be dose-related (fig. 2). Organic fluoride excretion was significantly greater in patients anesthetized with halothane (13.8 ± 4.2 mM/day) compared with isoflurane (1.3 ± 0.3 mM/day) and was dose-related for both agents (table 4, fig. 3).

The only significant differences between groups insofar as renal function was concerned were in urinary volume and sodium excretion (table 4), which were greater after isoflurane approximately in proportion to the greater intra-anesthetic intake of fluid and sodium in the isoflurane group. There was no

¶ Fluoride excretion data from three patients included in this study have been reported.[1]

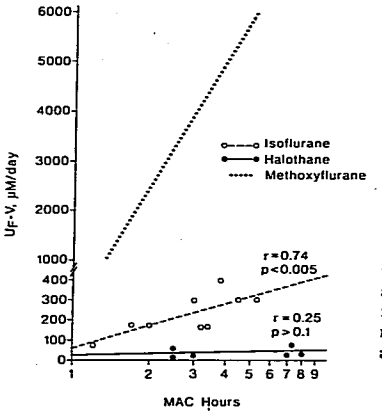

FIG. 2. Individual urinary inorganic fluoride excretion (U_F-V) values for the first two days following isoflurane and halothane anesthesia plotted against anesthetic dosage, expressed in MAC hours. There was a dose-related increase in U_F-V following isoflurane anesthesia only. For comparison, the regression line drawn from U_F-V data from a previous study[10] with methoxyflurane is also shown. U_F-V was approximately ten times greater following methoxyflurane than following isoflurane anesthesia at similar anesthetic dosages. Note the change in scale of the vertical axis.

significant pre- to postanesthesia difference in renal function variables within either group except the increased urinary volume following isoflurane. Regression analysis did not reveal a significant correlation of dosage with any renal function variable for either agent. The responses to vasopressin were appropriate in both groups (fig. 4). In every case maximum urinary osmolality equaled or exceeded the preoperative value and was greater than 600 mOsm/kg.

There was no difference between GFR's in the two groups prior to or during anesthesia (table 5). RBF and GFR during isoflurane anesthesia were 51 and 63 per cent of preanesthetic values, respectively. During halothane anesthesia GFR was 70 per cent of control. Technical problems with PAH analysis prevented this measurement in all patients anesthetized with halothane and in three patients treated with isoflurane. Urinary flow rate during isoflurane and halothane anesthesia were reduced to 34 and 51 per cent of preanesthetic values, respectively. However, mean intra-anesthetic urinary flow rate in each group was greater than 3 ml/min.

Discussion

The administration of methoxyflurane and its subsequent metabolism to inorganic fluoride results in dose-related, polyuric, vasopressin-resistant nephrotoxicity in man and animals.[4-10] In man, serum inorganic fluoride levels of approximately 50 μM/l result in subtle defects in urine-concentrating ability, with more overt changes occurring

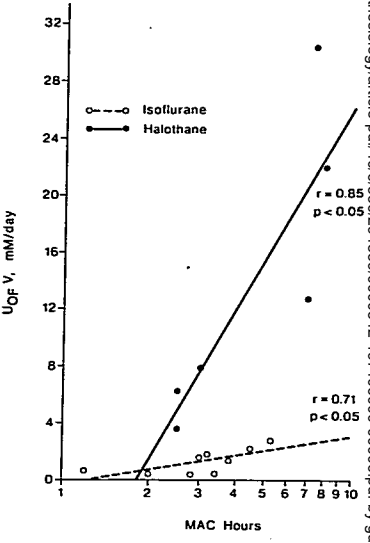

FIG. 3. Individual urinary organic fluoride excretion values following isoflurane and halothane anesthesia plotted against anesthetic dosage expressed in MAC hours. There were dose-related increases in organic fluoride excretion following both anesthetics. Five to ten times more organic fluoride was recovered in the urine following halothane than following isoflurane anesthesia.

when inorganic fluoride levels are in the range of 100 μM/l.[8,10] When inorganic fluoride levels exceed 150 μM/l, permanent renal damage may occur.[7,10]

The present study demonstrates biotransformation of isoflurane to inorganic fluoride, but to such a small extent that inorganic fluoride nephrotoxicity is unlikely. Peak serum inorganic fluoride levels were below 6 μM/l, even after isoflurane exposures of seven hours. This contrasts with peak serum inorganic fluoride levels of 30–175 μM/l (mean 61 ± 8 μM/l, fig. 1) in our previous study of surgical patients anesthetized with methoxyflurane.[10] Comparison of urinary excretion data from that study[10] and this indicates that at similar anesthetic exposures there was approximately ten times more metabolism of methoxyflurane than isoflurane to inorganic fluoride (fig. 2). Studies in Fischer 344 rats indicate that methoxyflurane is metabolized to inorganic fluoride approximately five times more than is isoflurane.[2] The data of Dobkin *et al.*[11] agree with the finding of minimal metabolism of isoflurane in surgical patients. In a series of 189 patients anesthetized with isoflurane for a mean duration of 178 minutes, they found a mean serum inorganic fluoride level at the end of anesthesia of 3.6 μM/l, with 12 μM/l the greatest individual value observed.

The relatively great extent of halothane metabolism to organic fluoride[12] is confirmed by the present study. Halothane metabolism was dose-related, with approximately five to ten times more organic fluoride found in the urine after its administration than after isoflurane's (fig. 3). The principal organic fluoride metabolite of both drugs is trifluoroacetic acid.[1,12]

Also of interest was the rapidity with which serum inorganic fluoride levels returned to preanesthetic values after isoflurane anesthesia, compared with the slow return to baseline levels after methoxyflurane (fig. 1). This probably relates to methoxyflurane's greater solubility in all tissues and therefore its longer availability for postoperative metabolism. This would be a factor in isoflurane's toxicity were inorganic fluoride levels higher following its administration. As it is, the rapid removal of isoflurane from the blood is probably of little clinical significance.

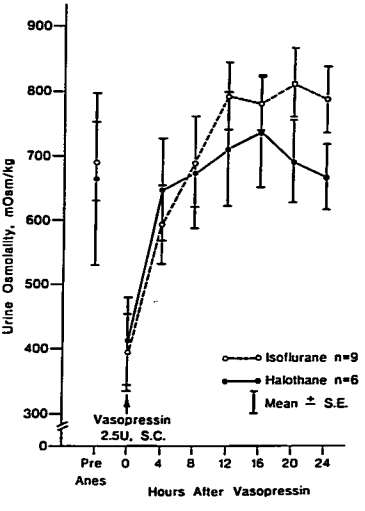

FIG. 4. Results of the postoperative vasopressin urine-concentration test. Vasopressin, 2.5 units, was administered 24–48 hours after anesthesia. There was no difference between the two groups in urine-concentrating ability. In all cases urinary osmolality was greater than 600 mOsm/kg and equaled or exceeded the preanesthetic value obtained from the overnight urine-concentration test.

Results of renal function studies support the conclusion that may be drawn from the metabolism data, that is, under the conditions of the present study, isoflurane administration does not result in inorganic fluoride nephrotoxicity. The absence of postoperative hypernatremia, serum hyperosmolality, increased serum creatinine and BUN, and excessive weight loss is strong evidence that postoperative renal function was normal. Definitive evidence that a urine-concentrating defect was not present is found in the normal response to vasopressin[13] (fig. 4). The finding of normal renal function is in agreement with the results of previous studies. There was no increase in BUN or serum creatinine in surgical patients in the

TABLE 5. Renal Blood Flow (C_{PAH}) and Glomerular Filtration Rate (C_{In}), Mean ± SE

	C_{PAH}* (ml/Min)	C_{In}* (ml/Min)	Filtration Fraction (Per Cent)	Urine Flow (ml/Min)
Isoflurane				
Pre-anesthesia	476.8 ±49.4 (4)	88.0 ±8.6 (7)	.21 ±.02 (4)	9.7 ±0.6 (7)
Intra-anesthesia	243.3 ±49.8 (4)	55.7 ±4.5 (7)	.25 ±.02 (4)	3.3 ±0.7 (7)
Halothane				
Pre-anesthesia	—	96.0 ±14.2 (5)	—	7.5 ±1.8 (5)
Intra-anesthesia	—	66.8 ±6.4 (5)	—	3.8 ±0.9 (5)

* Corrected to body surface area of 1.73 m².
† ( ) = number of observations.

report of Dobkin *et al.* noted above.[14] Also, Fischer 344 rats, an animal strain sensitive to the nephrotoxic effects of inorganic fluoride, showed no renal biochemical or morphologic evidence of toxicity following exposure to isoflurane at 1 MAC for as long as ten hours.[2]

Both isoflurane and halothane were associated with mild to moderate decreases in intra-anesthetic RBF, GFR, and urinary flow rate (table 5). These decreases in intra-anesthetic renal hemodynamics and function are similar in magnitude to decreases found with other agents when hydration was maintained.[15,16] Intraoperative changes in renal function are usually transient. In this study, GFR on postanesthesia day 1, as measured by creatinine clearance, was unchanged when compared with preanesthetic values (table 4).

In summary, isoflurane is minimally metabolized to inorganic fluoride in man. Postoperative renal dysfunction did not occur; intraoperative changes in renal function were similar to those seen with other agents.

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