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Metabolism and Renal Effects of Enflurane in Man

Michael J. Cousins, M.B., B.S., F.F.A.R.A.C.S., L. Richard Greenstein, M.D.,† Ben A. Hitt, Ph.D.,‡ Richard I. Mazze, M.D.§*

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The metabolism and renal effects of enflurane were studied during and after anesthesia in ten surgical patients without renal disease; ten control patients received halothane. Enflurane was metabolized to inorganic fluoride with a mean peak serum level of 22.2 ± 2.8 μM four hours after anesthesia. Urinary inorganic and organic fluoride excretions were increased but oxalic acid excretion was not, suggesting that the latter is not an enflurane metabolite. Postanesthetic renal function, including the response to vasopressin, was normal in both groups. During enflurane anesthesia renal blood flow, glomerular filtration rate, and urinary flow rate were 77, 79, and 67 per cent of control values, respectively. In this study of patients without renal disease, metabolism of enflurane to inorganic fluoride was insufficient to cause clinically significant renal dysfunction. (Key words: Anesthetics, volatile, enflurane; Kidney, nephrotoxicity; Biotransformation, enflurane; Ions, fluoride; Toxicity, renal.)

ENFLURANE ($CHClF\text{-}CF_2\text{-}O\text{-}CHF_2$; Ethrane¶), a fluorinated methylethyl ether, is metabolized to inorganic fluoride in man[1] and animals.[2,3] Previous animal studies have demonstrated nephrotoxicity following six- and 10-hour exposures at 1 MAC. The present study examines the metabolism and renal effects of enflurane in man during and after anesthesia.

Methods and Materials

Twenty male general surgical patients, ASA physical status 1 or 2, from whom informed consent had been obtained, were randomly allocated to receive either enflurane or halothane. Patients with abnormalities in renal function or diseases with possible renal complications were excluded from the study. Preoperatively, serum and urinary osmolalities and serum sodium, potassium, uric acid, creatinine, urea nitrogen, and inorganic fluoride concentrations were measured. Twenty-four-hour urine volumes and urinary organic fluoride and oxalic acid concentrations also were determined. From the above, 24-hour urinary solute excretions and clearances were calculated. Prior to operation, overnight urine-concentrating ability was determined by restricting oral intake beginning at 7 PM and by 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.[3]

ANESTHETIC TECHNIQUE

Premedication consisted of intramuscular administration of morphine sulfate, 0.14 mg/kg, and scopolamine hydrobromide, 0.006 mg/kg. One hour later, anesthesia was induced by inhalation of either enflurane or halothane in concentrations as high as 3.5 per cent. For maintenance, the inspired concentration of the anesthetic agent was reduced to achieve an alveolar concentration of approximately 1 MAC, equal to 1.4 per cent for enflurane and 0.6 per cent for halothane.** A semiclosed

* Assistant Professor of Anesthesiology. Presently, Professor and Chairman, Unit of Anaesthetics and Intensive Care, Matthew Flinders University School of Medicine, South Australia 5042.

† Research Fellow in Anesthesiology.

‡ Research Associate in Anesthesiology.

§ Associate Professor of Anesthesiology.

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Address reprint requests to Dr. Mazze.

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** MAC was adjusted for ages of patients anesthetized with halothane[6]; proportionate adjustments were made for patients anesthetized with enflurane.

TABLE 1. Preoperative and Operative Data, Mean ± SE

	Patients' Ages (Years)	Patients' Preoperative Weights (kg)	MAC ×	Anesthesia Time (Hours)	Dose (MAC Hours)	Arterial Concentration (mg/100 ml)
Enflurane						
Mean	40.2	90.4*	0.6*	4.4	2.7*	13.3
SE	±3.7	±6.7	±0.03	±0.4	±0.3	±0.7
Halothane						
Mean	41.5	76.0	1.1	4.3	4.9	13.0
SE	±4.1	±2.5	±0.06	±0.5	±0.7	±0.7

* $P < 0.05$ *vs.* halothane.

circle system was employed with CO_2 absorption. 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. Gas samples were obtained for measurement of end-alveolar anesthetic concentration. Intra-anesthetic blood samples were obtained from a radial artery to measure *p*H, P_{O_2}, P_{CO_2}, and anesthetic concentration. Electrocardiogram, esophageal temperature, pulse rate and direct radial arterial blood pressure were continuously monitored. Serial blood samples were obtained at half-hourly intervals for serum inorganic fluoride determination. Measurements of renal blood flow (RBF) and glomerular filtration rate (GFR) were made in four patients anesthetized with enflurane, employing standard PAH and insulin clearance techniques. There were three 20–30-minute collection periods prior to induction of anesthesia and three collection periods before the start of the operative procedure during maintenance of anesthesia.

Postoperatively, biochemical measurements of serum and urine were made daily, as during the preoperative period. Serum inorganic fluoride concentration also was measured at the termination of anesthesia and half-hourly for four hours after anesthesia. In addition, 24 to 48 hours following operation all patients received a subcutaneous injection of 2.5 units/70 kg body weight of vasopressin in oil; urine was collected every four hours thereafter and osmolality determined in order to evaluate urine concentrating ability.

FLUID THERAPY

Prior to anesthesia, food and fluids were allowed *ad libitum* except that no oral intake was permitted while testing overnight urine concentrating ability and after midnight of the night preceding operation. In the hour preceding induction of anesthesia 15 ml/kg body weight of a solution of ⅓ physiologic saline solution and ⅔ 5 per cent dextrose in water was administered, intravenously, to all patients; this usually resulted in diuresis at a rate of 5–10 ml/min. All measured intra- and post-operative 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 feeding. To each liter of fluid administered in the postoperative period 20 mEq KCl were added.

STATISTICAL METHODS

Means of each preoperative variable were determined for both groups and the values for patients anesthetized with enflurane compared with those obtained from patients anesthetized with halothane. Mean differences in pre- and postoperative values 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 oral fluids by the second postoperative day. Student's t test was used for statistical analysis. $P < 0.05$ was considered significant. Because this method of analysis may be relatively insensitive when changes

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occur in only a few patients at higher dosage, dose–response curves also were examined using regression analysis. Anesthetic dosage was determined by integrating end-alveolar anesthetic concentration, expressed as a fraction of MAC, over time of exposure (*i.e.*, MAC hours).[7]

Results

Preoperatively the groups did not differ significantly in any of the variables measured except as might be expected to occur due to chance (tables 1–3). The types and lengths of operations were also similar. During anesthesia all patients were adequately oxygenated

TABLE 2. 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^- (μM)
Enflurane							
Preoperative	141 ± 0.5	4.4 ± 0.1	1.0 ± 0.0	15 ± 1	6.7 ± 0.2	287 ± 1	1.8 ± 0.1
Postoperative days 1–4	140§ ± 0.5	4.4 ± 0.1	0.9 ± 0.0	9†‡ ± 1	6.3‡ ± 0.3	280† ± 1	8.3†‡ ± 1.3
Halothane							
Preoperative	140 ± 0.5	4.3 ± 0.1	1.0 ± 0.0	15 ± 1	6.4 ± 0.2	286 ± 1	1.9 ± 0.1
Postoperative days 1–4	137 ± 0.5	4.3 ± 0.1	1.0 ± 0.0	12* ± 1	7.2 ± 0.3	281* ± 1	1.6* ± 0.1

* $P < 0.05$ *vs.* preanesthesia.
† $P < 0.01$ *vs.* preanesthesia.
‡ $P < 0.05$ *vs.* halothane postanesthesia.
§ $P < 0.01$ *vs.* halothane postanesthesia.

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

	Solute Excretion/24 Hours						Creatinine Clearance (ml/Min)	Weight (kg)	Urine (l/Day)
	Na^+ (mEq)	K^+ (mEq)	Osmolality (mOsm)	F^- (μmol)	Org F^- (mmol)	Oxalic Acid (mmol)			
Enflurane									
Preoperative	158.2 ± 13.3	62.1 ± 18.1	866 ± 44	46 ± 6	0.51 ±0.60	3.7 ± 0.3	109.5 ± 4.5	87.8 ±8.5	1.81 ± 0.21
Postoperative days 1–2	212.6* ± 24.8	73.6 ± 9.6	925 ± 73	1656†§ ± 276	2.22†§ ± 0.31	9.2 ± 2.4	139.9†‡ ± 5.7	88.0 ±8.5	2.74 ± 0.37
Halothane									
Preoperative	147.0 ± 12.7	60.7 ± 6.3	829 ± 63	46 ± 7	0.74 ± 0.14	3.9 ± 1.2	112.4 ± 7.1	74.2 ±1.8	1.64 ± 0.20
Postoperative days 1–2	203.4* ± 26.7	65.4 ± 7.5	1006* ± 73	77 ± 17	15.8† ± 2.15	5.3 ± 0.8	117.4 ± 5.1	75.1 ±2.0	2.61 ± 0.35

* $P < 0.05$ *vs.* preanesthesia.
† $P < 0.01$ *vs.* preanesthesia.
‡ $P < 0.05$ *vs.* halothane postanesthesia.
§ $P < 0.01$ *vs.* halothane postanesthesia.

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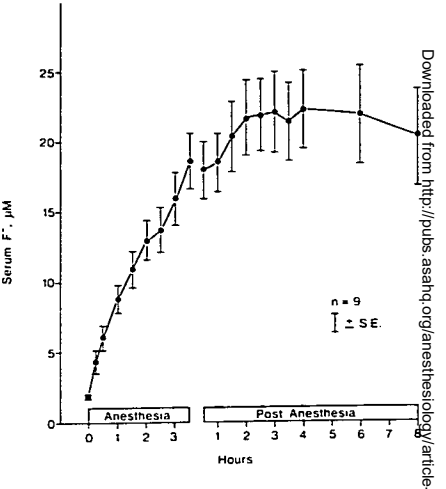

FIG. 1. Mean serum inorganic fluoride (F^-) concentrations during and after enflurane anesthesia. Data from Patient 10 are not included. The mean peak value, 22.2 ± 2.8 μM, occurred 4 hours after the end of anesthesia, but there was little difference among the values measured from samples obtained 1½ to 8 hours after anesthesia.

and ventilated and normal body temperature was maintained. Prior to surgical stimulation, decreases in mean arterial blood pressures of 10–30 torr occurred with both anesthetics. Rapid infusion of intravenous fluids, with anesthetic concentration maintained at MAC, was usually sufficient to restore blood pressures to preoperative values in patients anesthetized with halothane. However, to maintain mean pressures of 70–80 torr in patients anesthetized with enflurane, not only was fluid infusion necessary but anesthetic

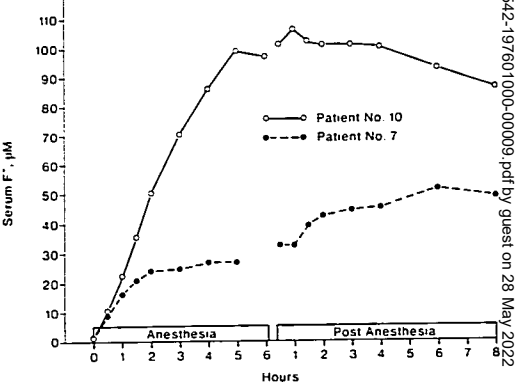

FIG. 2. Serum inorganic fluoride (F^-) concentrations during and after enflurane anesthesia in two atypical patients. Patient 10 was receiving several drugs thought to cause enzyme induction, and Patient 7 was markedly obese. In both of these patients inorganic fluoride concentrations were significantly higher than were the mean peak values measured in the remaining patients.

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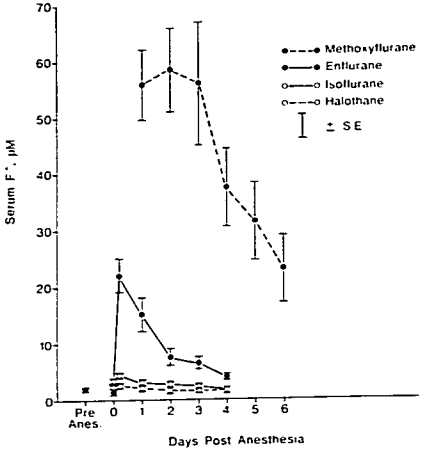

FIG. 3. Serum inorganic fluoride (F^-) concentrations prior to and following enflurane and halothane anesthesia. There was a significant increase in serum F^- concentration immediately following enflurane anesthesia, reaching a mean peak value of 22.2 ± 2.8 μM 4 hours after anesthesia was terminated. For comparison, data from previous clinical studies[7,15] in which patients received similar exposures to methoxyflurane and isoflurane are presented. Following methoxyflurane, mean peak serum F^- concentration was higher, 61 ± 8 μM, and declined more slowly than after enflurane.

concentration usually had to be reduced to approximately 0.6 MAC (table 1). For this reason, anesthetic dosages of patients anesthetized with enflurane were significantly lower than those of patients anesthetized with halothane.

Serum inorganic fluoride increased rapidly during enflurane anesthesia and early in the postanesthetic period, with a mean peak value of 22.2 ± 2.8 μM attained four hours after the conclusion of anesthesia (fig. 1). Although most values were less than 30 μM, there were two exceptions: one obese patient, Patient 7 (130 kg, 170 cm), had a peak serum inorganic fluoride of 52 μM following 4.0 MAC hours of enflurane, and Patient 10, had a peak serum inorganic fluoride of 106 μM following 3.8 MAC hours of enflurane anesthesia (fig. 2). The latter was a heavy cigarette smoker, had a history of heavy alcohol intake, and was taking several medications, including chlorpromazine, diazepam, and isoniazid. Chronic exposure to high doses of these substances is thought to cause enzyme induction, so his data are not included in the group means. Serum inorganic fluoride levels remained elevated for three to four days in all patients following enflurane anesthesia (fig. 3); however, by 48 hours after anesthesia values exceeded 10 μM in the obese patient only. Among patients anesthetized with enflurane, there also was an increase in 24-hour urinary inorganic fluoride excretion that persisted throughout the first four days following anesthesia (fig. 4). Organic fluoride excretion was significantly elevated in both groups and was considerably higher in patients anesthetized with halothane than with enflurane (table 3). However, no positive relationship between anesthetic dose and peak serum inorganic fluoride concentration (fig. 5), urinary inorganic fluoride excretion, or urinary organic fluoride excretion could be demonstrated with either agent. Oxalic acid excretion was not significantly increased following administration of either anesthetic.

Changes in renal function were minimal in both groups and did not reflect renal dysfunction (table 3). Postanesthetic urine flow and sodium excretion were increased in both groups; this probably was related to the increased intake of sodium-containing fluids during anesthesia and operation. Regression analysis did not reveal a significant correlation of anesthetic dosage with any renal function variable for either agent. The responses to vasopressin were normal in both groups (fig. 6). By the second day after anesthesia,

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maximum urinary osmolalities in all cases were within 10 per cent of the preanesthetic values and were greater than 600 mOsm/kg. It is of interest that 24 hours after anesthesia the patient whose serum inorganic fluoride concentration had peaked at 106 μM still had a level of 40 μM (fig. 2) and was able to concentrate urine to only 543 mOsm/kg following vasopressin administration. However, 48 hours after anesthesia his serum inorganic fluoride had decreased to 8.4 μM and maximum urinary osmolality in response to vasopressin administration was 911 mOsm/kg.

Renal blood flow and glomerular filtration rate during enflurane anesthesia were 77 and 79 per cent of the preanesthetic values, respectively; urine flow rate during enflurane anesthesia was 5.5 ml/min, or 67 per cent of the preanesthetic value (table 4).

Discussion

Studies of methoxyflurane nephrotoxicity in Fischer 344 rats have confirmed that inorganic fluoride is responsible for the acute polyuric lesion.[4] The nephrotoxic serum threshold concentration in Fischer 344 rats is 50 μM[5]; a similar value has been found in man.[2] In another study, exposure of Fischer 344 rats to enflurane for 6 to 10 hours resulted in vasopressin-resistant polyuria; as with methoxyflurane, this occurred when serum inorganic fluoride concentration was approximately 50 μM.[3] The latter findings suggest that there is a potential for enflurane nephrotoxicity in man. However, the results of the present study of surgical patients without renal disease do not support this. Following enflurane exposures averaging 2.7 ± 0.3 MAC hours, serum inorganic fluoride concentrations

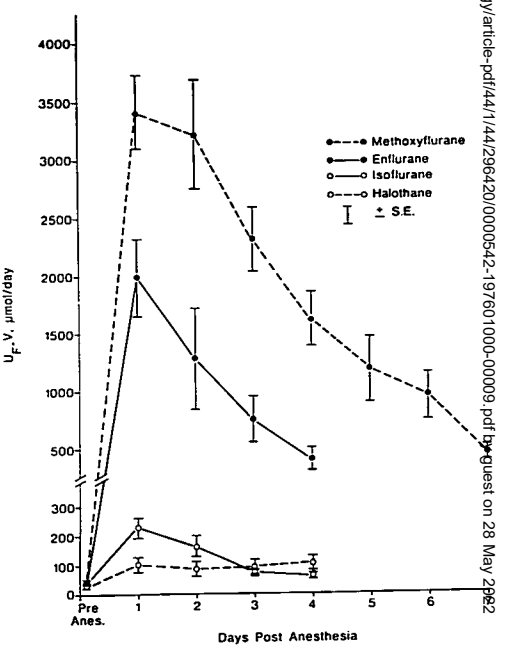

FIG. 4. Urinary inorganic fluoride excretion (U_F-V) prior to and following enflurane and halothane anesthesia. Following enflurane administration there was a significant increase in U_F-V that persisted for the duration of the experiment. For comparison, data from previous clinical studies[7,15] in which patients received similar exposures to methoxyflurane and isoflurane are presented. Following methoxyflurane anesthesia urinary inorganic fluoride was greater and declined more slowly than after enflurane. Note the change in scale of the vertical axis.

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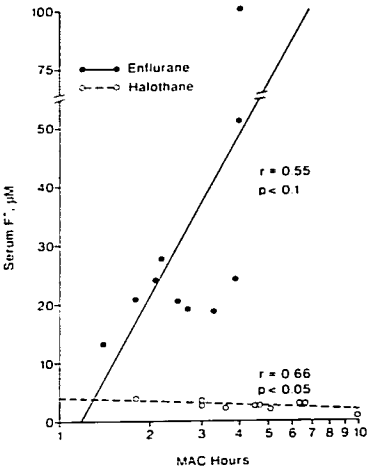

FIG. 5. Individual peak serum inorganic fluoride (F^-) concentrations following enflurane and halothane anesthesia plotted against anesthetic dosage expressed in MAC hours. A positive correlation between anesthestic dosage and peak serum F^- could not be demonstrated with either drug.

in the nephrotoxic range generally were not present. Exceptions occurred in the obese patient who had a peak serum inorganic fluoride level of 50 μM following a dose of 4.0 MAC hours of enflurane and in the patient exposed to substances that may have caused enzyme induction. The latter patient had a peak serum inorganic fluoride concentration of 106 μM following an enflurane exposure of 3.8 MAC hours. However, in all patients anesthetized with enflurane, including the two mentioned above, serum inorganic fluoride peaked earlier, at a lower level, and fell much more rapidly than it did in a comparable group of patients anesthetized with methoxyflurane (fig. 3).[7] Serum inorganic fluoride level peaked at 22.2 ± 2.8 μM approximately four hours after enflurane anesthesia, and decreased by 50 per cent in 31 hours. After methoxyflurane anesthesia the peak serum inorganic fluoride level was 61 ± 8 μM. This value occurred 48 hours following anesthesia, with an additional 78 hours required for a 50 per cent decrease in concentration. Since the peak serum inorganic fluoride level and the duration that high levels are maintained determine whether renal lesions will occur, there is a greater risk of developing inorganic fluoride nephrotoxicity after methoxyflurane than after enflurane anesthesia.

The metabolism data above are supported by the results of renal function studies. They demonstrate that, under the conditions of the present study, enflurane 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 renal concentrating defect was not present is found in the normal response to vasopressin (fig. 6). These data are in agreement with the results of previous studies of surgical patients without renal disease. There was no increase in BUN or serum creatinine following enflurane anesthesia in surgical patients studied by Dobkin *et al.*,[8] and Graves and Downs[9] have made a similar observation. However, nephrotoxicity has been reported to occur after enflurane in surgical patients with decreased preoperative renal function; this may be related to enflurane metabolism to inorganic fluoride.[10,11] Inorganic fluoride is excreted in the urine at a rate approximately half the glomerular filtration rate[12]; its concentration in serum is related to the balance between production, on the one hand, and redistribution to bone and excre-

TABLE 4. 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)
Enflurane				
Pre-anesthesia	597 ± 14	108 ± 4	18 ± 1	8.2 ± 1.1
Intra-anesthesia	458 ± 29	85 ± 6	20 ± 1	5.5 ± 1.4

* Corrected to body surface area of 1.73 m^2.
n = 4, all observations.

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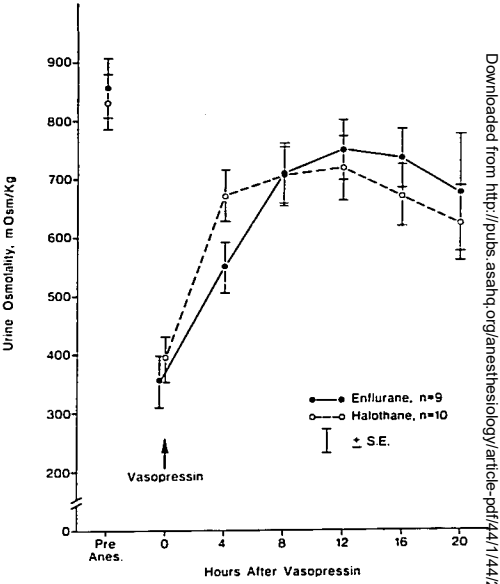

FIG. 6. Results of the postoperative vasopressin urine concentration test. Vasopressin in oil, 2.5 units/70 kg body weight, was administered at time 0 and urine collected every 4 hours thereafter. There was no difference between the two groups in urine-concentrating ability. In all cases urinary osmolality was greater than 600 mOsm/kg and was within 10 per cent of the preanesthetic value obtained from the overnight urine concentration test.

tion in the urine on the other.[13] It is possible that in a patient with a marked reduction in glomerular filtration rate, serum inorganic fluoride could remain in the nephrotoxic range for enough time to produce a renal concentrating defect. It seems reasonable to avoid enflurane in the management of patients who have significantly reduced glomerular filtration rates before anesthesia. In clinical practice the most readily available indicators of decreased glomerular filtration rate are increased BUN and serum creatinine concentrations.

It should be noted that enflurane administration was associated with slight decreases in renal blood flow, glomerular filtration rate, and urine flow rate during anesthesia (table 4). These decreases in intra-anesthetic renal hemodynamics and function are similar in magnitude to decreases reported to occur with halothane,[14,15] isoflurane,[15] and thiopental–N_2O[16] when hydration was maintained. As in previous studies, intraoperative changes in renal function were transient. In the present study, glomerular filtration rates, as measured by 24-hour endogenous creatinine clearance, had returned to or exceeded preanesthetic values by the first day after anesthesia.

The present study demonstrates considerable variation among individuals in enflurane defluorination at the same dosage; this is similar to variations in methoxyflurane defluorination found in man[7] and animals[5,9] and is characteristic of the metabolism of most drugs. The amount of defluorination that occurs as a result of enflurane administration is controlled by a number of factors. These include the maximal rate of metabolism and the length of time that the concentration of drug remains at a level sufficient to permit metabolism to occur at this rate. For a relatively less soluble drug, such as enflurane (oil–gas partition coefficient 98) the maximum rate of metabolism would be maintained for

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only a short period, compared with a much more soluble drug such as methoxyflurane (oil–gas partition coefficient 970). The unexpectedly high peak serum inorganic fluoride level (51 μM) in the obese patient (130 kg, 170 cm) may have resulted from individual variation in metabolism, or it may have reflected an unusually large amount of enflurane storage in fat and, therefore, prolonged postoperative availability of substrate. Increased metabolism secondary to enzyme induction may be the explanation for the serum inorganic fluoride level of 106 μM observed in Patient 10. Enzyme induction increases the amount and may also qualitatively change the enzyme(s) of the mixed-function oxidase system.[17] In view of the patient's history of exposure to enzyme-inducing agents, it would be logical to suspect that enzyme induction had occurred. *In-vivo* studies with Fischer 344 rats[2] and *in-vitro* studies with rat hepatic microsomes[18] have shown that enzyme induction does not significantly increase the defluorination of enflurane. Whether enzyme induction increases enflurane defluorination in man is unknown. However, it is important to answer this question, as increased metabolism in a patient with impaired renal function could result in prolonged persistence of nephrotoxic inorganic fluoride levels.

That oxalic acid excretion was not increased is in agreement with results of studies of enflurane metabolism in Fischer 344 rats.[2] This suggests that defluorination of enflurane is not complete and that urinary organic fluorinated metabolites also are formed. This was found to be the case. The pathway for enflurane metabolism has not been established, but it is suspected that biodegradation proceeds via hydroxylation of the beta carbon; spontaneous defluorination then results. The end products of metabolism, therefore, should be inorganic chloride, inorganic fluoride, and difluoromethoxydifluoroacetate. Preliminary studies with methyl ^{14}C enflurane indicate that one mole of inorganic fluoride is produced for every mole of enflurane metabolized. This is the appropriate stoichiometry for the proposed pathway.††

†† Hitt and Mazze, unpublished data.

A somewhat surprising finding was the inability to demonstrate a positive correlation between enflurane dosage and metabolism. In a previous study,[7] a dose–response relationship between methoxyflurane dosage and metabolism had been observed. The inability to correlate anesthetic dosage and metabolism in this study is probably accounted for by: 1) individual differences in rates of metabolism, particularly when the number of patients studied is small; 2) the lesser solubility of enflurane in fat, making that tissue less important as a reservoir of anesthetic agent for postoperative metabolism; 3) the absence of patients at the high end of the enflurane dosage curve (no dose greater than 4.0 MAC hours).

In summary, enflurane was significantly metabolized to inorganic and organic fluoride in man. Postoperative renal dysfunction did not occur; intraoperative changes in renal function were similar to those reported with other agents.

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Obstetric Anesthesia

LIDOCAINE TRANSFER Placental transfer of lidocaine administered to pregnant sheep and removal of the drug from the fetal circulation were determined. Responses of the hemodynamic and acid–base state in the mother and fetus were also studied. Lidocaine readily crossed the placenta and appeared in the fetal blood as early as one minute following injection. Disappearance of lidocaine in the asphyxiated fetus tended to be slower than in the normal one. Lidocaine produced a transient decrease in fetal heart rate accompanied by decreases in blood *p*H and oxygenation. Lidocaine also reduced umbilical blood flow and, in some instances, uterine blood flow. The decrease in umbilical blood flow was more pronounced in the initially asphyxiated fetus. *(Morishima HO, and others: Transfer of Lidocaine across the Sheep Placenta to the Fetus. Am J Obstet Gynecol 122: 581–588, 1975.)*

MECONIUM Continuous fetal heart rate (FHR) monitoring and routine fetal scalp blood sampling were utilized in the evaluation of 366 fetuses during labor. One hundred and six patients had meconium in the amniotic fluid at some time during labor. During the 366 labors, 26,110 uterine contractions were monitored. The incidences of FHR patterns as percentage of uterine contractions were calculated for the meconium and non-meconium groups. Although there was a 3½-fold increase in the incidence of low 5-minute Apgar scores (less than 7) in the meconium group, signs of fetal distress were, with rare exception, not significantly different from those in the non-meconium group. The presence of meconium in the amniotic fluid without signs of fetal asphyxia (late decelerations and acidosis) is not a sign of fetal distress and need not be an indication for active intervention. The combination of fetal asphyxia and meconium staining of the amniotic fluid, however, does enhance the potential for meconium aspiration and a poor neonatal outcome. Universal fetal heart rate monitoring and appropriate fetal acid–base evaluation are recommended for following patients with meconium in the amniotic fluid during labor. *(Miller FC, and others: Significance of Meconium during Labor. Am J Obstet Gynecol 122: 573–580, 1975.)*