

Inorganic Fluoride Nephrotoxicity:

Prolonged Enflurane and Halothane Anesthesia in Volunteers

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The effects of prolonged enflurane and halothane administration on urine-concentrating ability were determined in volunteers by examining their responses to vasopressin before anesthesia and on days 1 and 5 after anesthesia. A significant decrease in maximum urinary osmolality of 264 ± 34 mOsm/kg (26 per cent of the preanesthetic value) was present on day 1 after enflurane anesthesia, whereas subjects anesthetized with halothane had a significant increase in maximum urinary osmolality of 120 ± 44 mOsm/kg. Serum inorganic fluoride level peaked at $33.6 \mu\text{M}$ and remained above $20 \mu\text{M}$ for approximately 18 hours. Thus, the threshold level for inorganic fluoride nephrotoxicity is lower than previously suspected. (Key words: Anesthetics, volatile, enflurane; Anesthetics, volatile, halothane; Kidney, nephrotoxicity; Biotransformation, enflurane; Biotransformation, halothane; Ions, fluoride; Ions, bromide; Toxicity, renal.)

STUDIES of the renal effects of anesthetic agents have not usually included measurements of urine-concentrating ability. Rather, they have focused more on intra- and postanesthetic changes in renal blood flow, glomerular filtration rate, solute excretion, and urinary flow. Additionally, most studies have been carried out in surgical patients, so that it has been difficult to separate the renal effects of anesthesia from those of pre-existing disease and surgical trauma. Knowledge that the biotransformation of methoxyflurane to fluoride ion results in a polyuric nephropathy has focused attention on the effects of anesthetics on urine-concentrating ability.¹⁻³ Thus, when studies of the cardiovascular effects of prolonged enflurane anesthesia in healthy volunteers were proposed, it was considered an ideal opportunity to determine, also, whether enflurane administration resulted in a urine-concentrating defect. If a defect were ob-

served, it would be possible to measure at what inorganic fluoride level it had occurred. For control purposes, another group of volunteers was exposed to halothane, an agent not significantly biotransformed to inorganic fluoride.

Methods and Materials

Twelve healthy, male, unpremedicated volunteers were exposed to enflurane-oxygen anesthesia without operation.§ Mean enflurane exposure for the group was 9.6 ± 0.1 MAC hours (table 1); this value was determined by multiplying end-tidal enflurane concentration, as a fraction of MAC, times the duration of exposure (*i.e.*, MAC hours). A brief, 0.6-MAC hour, nitrous oxide exposure was also included in the experiment. After the enflurane study was completed, a control group of seven additional healthy, male, unpremedicated volunteers was exposed to 13.7 ± 0.8 MAC hours of halothane-oxygen anesthesia without operation. Methods of anesthetic administration and patient monitoring were the same for both groups, and have been reported.⁴ End-tidal halothane and enflurane concentrations were determined with a Beckman LB-2 infrared analyzer.

Each subject underwent three separate vasopressin urine-concentration tests: 2.5 units of vasopressin tannate in oil/70 kg of body weight were injected, subcutaneously, at approximately 12 noon, and all urine was collected at four-hour intervals for the next 24 hours. Maximum urine-concentrating ability may be determined by administering vasopressin in this manner.⁵ The first concentration test was performed a week prior to anesthesia; the next, one day after anesthesia; the last, five days after anesthesia. Subjects remained in the hospital for the duration of each test procedure. Serum samples were obtained prior to anesthesia, every hour during anesthesia, at two-hour intervals for the first eight hours after anesthesia, at four-hour intervals for the next eight hours, and at less frequent intervals for the next 30 hours. Sodium, potassium, chloride, creatinine and inorganic fluoride concentrations and osmolality were determined for all samples. Inorganic bromide concentration was measured in samples from sub-

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§ This study was approved by the Human Research Committee of the University of California, San Diego, and Veterans Administration Hospital, San Diego. Informed consent was obtained from all subjects.

TABLE 1. Vital Statistics and Treatment Data (Mean \pm SE)

Anesthesia	Patient Data			Anesthetic Dose			Fluids		
	Age (Years)	Ht (cm)	Wt (kg)	Time (Hours)	Conc. (MAC)	MAC Hours	During Anesthesia	After Anesthesia	Total
Enflurane (n = 12)	22.5 \pm 0.5	180 \pm 1	74.0 \pm 2.9	7.9 \pm 0.3	1.2	9.6 \pm 0.1	1,558 \pm 50	1,333 \pm 36	2,892* \pm 65
Halothane (n = 7)	24.9 \pm 1.7	178 \pm 2	75.5 \pm 4.3	8.9 \pm 0.2	1.5	13.7 \pm 0.8	1,257 \pm 72	1,404 \pm 94	2,661† \pm 1.0

* All but two subjects received 0.45 per cent saline solution in 5 per cent dextrose solution; the two received lactated Ringer's solution in 5 per cent dextrose solution.

† All but one subject received lactated Ringer's solution in 5 per cent dextrose solution; the one received 0.45 per cent saline solution in 5 per cent dextrose solution.

TABLE 2. Serum and Urinary Values, Subjects Anesthetized with Enflurane (Mean \pm SE)

	Serum				Urinary Flow (ml/min)	24-hour Urinary Excretion				Creatinine Clearance (ml/min)
	Na ⁺ (mEq/l)	K ⁺ (mEq/l)	F ⁻ (μ M)	Creatinine (mg/100ml)		Na ⁺ (μ Eq/min)	K ⁺ (μ Eq/min)	Osmols (μ Osm/min)	F ⁻ (nmol/min)	
Preanesthesia	141 \pm 0.6	4.0 \pm 0.05	1.9 \pm 0.2	0.86 \pm 0.03	0.80 \pm 0.07	97 \pm 13	47 \pm 6	556 \pm 76	21 \pm 3	123 \pm 8
Intra-anesthesia*	141 \pm 0.3	4.6† \pm 0.16	17.0† \pm 2.3	1.26†¶ \pm 0.07	0.77 \pm 0.09	68 \pm 11	48 \pm 6	388 \pm 46	445†¶ \pm 78	80†§ \pm 10
Day 1 postanesthesia*	141 \pm 0.3	3.7† \pm 0.04	22.7† \pm 2.4	0.91 \pm 0.05	1.89† \pm 0.10	121§ \pm 6	42¶ \pm 5	577¶ \pm 55	1,743†¶ \pm 195	144 \pm 17
Day 2 postanesthesia*	141 \pm 0.3	4.2 \pm 0.11	10.0† \pm 1.1	0.81 \pm 0.04	1.12† \pm 0.12	116 \pm 12	25† \pm 3	474 \pm 52	565†¶ \pm 88	134 \pm 12
Day 5 postanesthesia	140 \pm 0.4	4.3† \pm 0.09	4.1† \pm 0.2	0.86 \pm 0.05	0.75 \pm 0.07	89 \pm 10	37§ \pm 5	478§ \pm 58	49†§ \pm 9	116 \pm 12

* Serum values are for midpoint of collection period.

† $P < 0.05$ vs. preanesthesia.

‡ $P < 0.01$ vs. preanesthesia.

§ $P < 0.05$ vs. same time period, halothane.

¶ $P < 0.01$ vs. same time period, halothane.

TABLE 3. Serum and Urinary Values, Subjects Anesthetized with Halothane (Mean \pm SE)

	Serum					Urinary Flow (ml/min)	Urinary Excretion					Creatinine Clearance (ml/min)
	Na ⁺ (mEq/l)	K ⁺ (mEq/l)	Br ⁻ (mEq/l)	F ⁻ (μ M)	Creatinine (mg/100 ml)		Na ⁺ (μ Eq/min)	K ⁺ (μ Eq/min)	Osmols (μ Osm/min)	Br ⁻ (μ Eq/min)	F ⁻ (nmol/min)	
Preanesthesia	141 \pm 0.6	4.0 \pm 0.09	0.09 \pm 0.02	1.3 \pm 0.1	0.94 \pm 0.09	0.70 \pm 0.08	84 \pm 12	48 \pm 6	526 \pm 42	0.04 \pm 0.01	18 \pm 2	101 \pm 9
Intra-anesthesia*	141 \pm 0.8	4.4† \pm 0.16	0.25† \pm 0.03	1.7 \pm 0.1	0.94¶ \pm 0.10	0.56† \pm 0.07	43† \pm 6	35† \pm 6	321† \pm 29	0.12† \pm 0.03	16¶ \pm 2	87† \pm 12
Day 1 postanesthesia*	142 \pm 1.0	4.1 \pm 0.07	1.13† \pm 0.08	1.7 \pm 0.1	0.99 \pm 0.10	1.45† \pm 0.17	168†§ \pm 26	66†¶ \pm 5	821¶ \pm 73	1.40† \pm 0.44	51†¶ \pm 5	133§ \pm 11
Day 2 postanesthesia*	140 \pm 0.5	4.1 \pm 0.10	2.80† \pm 0.17	1.7 \pm 0.1	0.96 \pm 0.08	0.83 \pm 0.20	106 \pm 21	32† \pm 5	610 \pm 82	1.22† \pm 0.30	25†¶ \pm 4	104 \pm 14
Day 5 postanesthesia	142 \pm 1.0	4.5† \pm 0.15	2.97† \pm 0.17	1.7 \pm 0.1	0.97 \pm 0.07	0.74 \pm 0.05	109 \pm 15	54§ \pm 5	622§ \pm 62	0.80† \pm 0.15	23§ \pm 3	112 \pm 9

* Serum values are for midpoint of collection period.

† $P < 0.05$ vs. preanesthesia.

‡ $P < 0.01$ vs. preanesthesia.

§ $P < 0.05$ vs. same time period, enflurane.

¶ $P < 0.01$ vs. same time period, enflurane.

jects anesthetized with halothane; duplicate determinations were accurate to within 10 per cent.⁶ Urine collections were made before and after administration of anesthesia and similar biochemical measurements were performed on these specimens. From the above, 24-hour urinary solute excretions and endogenous creatinine clearance, the latter a measure of glomerular filtration rate, were calculated.

FLUID THERAPY

Prior to the preanesthetic vasopressin test, food and fluids were allowed *ad libitum*. For the 24-hour duration of the vasopressin test, 8 ounces of liquid were allowed with each meal, but no additional fluids were permitted. Diet then was unrestricted until the night before anesthesia, when oral intake was not allowed after midnight. During anesthesia and until approximately 9 A.M. the next morning, subjects received 2,400 to 3,250 ml of fluid, intravenously (table 1). There was no further fluid restriction during the remainder of the experiment, except that fluids were limited during the postanesthetic vasopressin tests in the same manner as during the preanesthetic test.

STATISTICAL METHODS

Means of each variable were determined for each group of subjects for the five time periods studied, *i.e.*, preanesthesia, intra-anesthesia,[†] day 1 postanesthesia, day 2 postanesthesia, and day 5 postanesthesia. Means of changes from preanesthetic values to intra- and postanesthetic values for each drug were examined using paired *t* tests for statistical analyses. Additionally, the changes that occurred after enflurane anesthesia were compared with the changes that occurred after halothane, using unpaired *t* tests. Analysis of variance was used to determine dose-response relationships. *P* < 0.05 was considered significant.

Results

Prior to anesthesia, the groups did not differ in any of the variables measured except as might be expected to occur due to chance (tables 1-3). Enflurane dosage was lower than halothane dosage (table 1) because hypotension occurred with higher enflurane concentrations, necessitating early termination of several parts of the experiment.

The most significant finding of the study was the consistent decrease in maximum urinary osmolality in response to vasopressin administration on day 1 after enflurane anesthesia (fig. 1). Maximum urinary

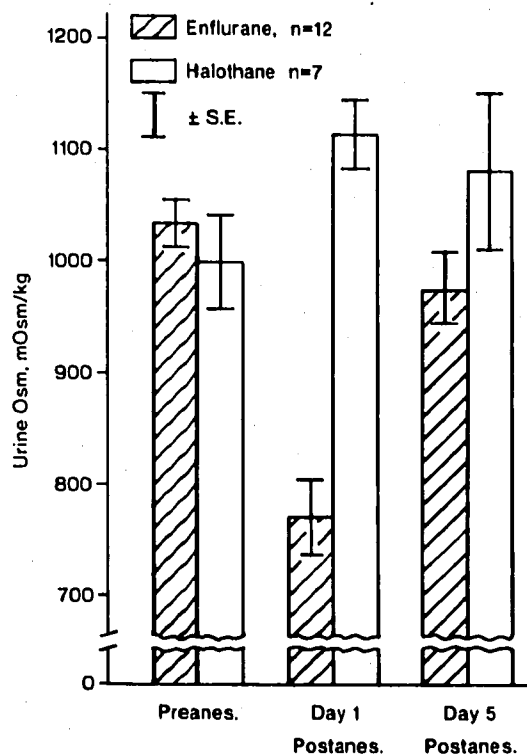


FIG. 1. Histogram showing maximum urinary osmolalities after vasopressin, mean \pm SE, for the two groups of patients. There was a decrease of 264 ± 34 mOsm/kg on day 1 after enflurane anesthesia, as opposed to an increase of 120 ± 44 mOsm/kg after halothane anesthesia. By day 5 after anesthesia, mean values had returned to preanesthetic levels.

osmolality was decreased in every subject, with an average reduction of 264 ± 34 mOsm/kg, or 26 per cent of the preanesthetic value (*P* < 0.01 compared with preanesthetic control value). The greatest individual decrease was 470 mOsm/kg (39 per cent of the preanesthetic value) and the lowest maximum urinary osmolality was 590 mOsm/kg. By contrast, six of seven subjects treated with halothane, including the subject who received 0.45 per cent saline solution in 5 per cent dextrose solution, had increases in maximum urinary osmolality on day 1 after anesthesia. The decrease in maximum urinary osmolality after enflurane was not related to a decrease in glomerular filtration rate or solute excretion (table 2). Although both of these variables decreased during the intra-anesthetic period, they had returned to preanesthetic values by day 1 after anesthesia. By day 5, maximum urinary osmolality after enflurane had returned to preanesthetic values.

Serum inorganic fluoride level increased rapidly during enflurane anesthesia and for six hours after anesthesia. Mean peak inorganic fluoride concentrations were $18.7 \pm 2.2 \mu\text{M}$ at the end of anesthesia and $33.6 \pm 2.8 \mu\text{M}$ during the postanesthetic period (fig. 2). After reaching peak values, serum inorganic fluoride concentrations decreased quickly, declining by 50 per cent in

[†] Patients did not have urinary bladder catheters, so that this period began after subjects voided prior to induction of anesthesia and ended three to five hours after anesthesia was terminated, when subjects next voided.

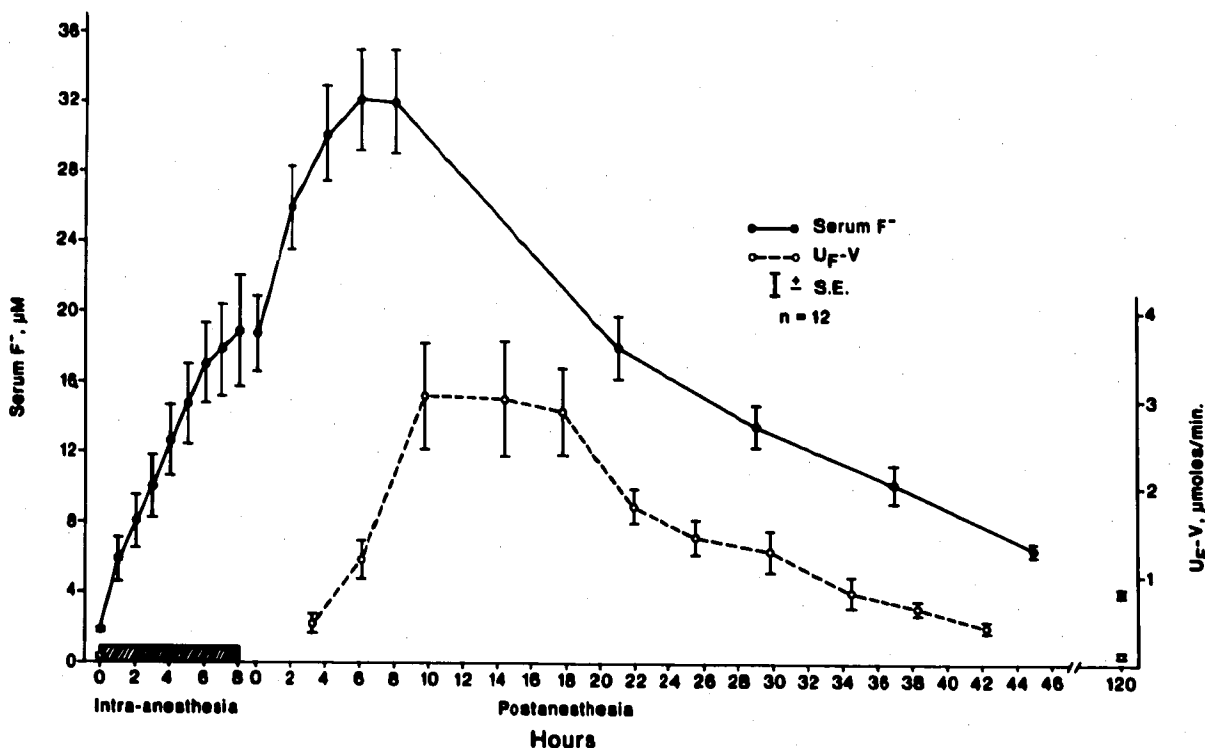


FIG. 2. Mean serum inorganic fluoride level (serum F^-) \pm SE and urinary inorganic fluoride excretion (U_{F-V}) \pm SE after enflurane anesthesia. Serum F^- increased rapidly during anesthesia and for the first six hours after anesthesia, then declined with a half-time of approximately 18 hours. U_{F-V} reached peak levels 10–18 hours after anesthesia, then declined at about the same rate as the decrease in serum F^- .

approximately 18 hours and by an additional 50 per cent in 18 more hours. Of interest, it is not possible to demonstrate an inverse correlation between individual peak serum inorganic fluoride levels and maximum urinary osmolality ($r = 0.09$) employing day 1 enflurane data alone (fig. 3). However, when data from patients anesthetized with halothane and from a previous study with methoxyflurane² are included in the analysis, expanding both the high and low ends of the serum inorganic fluoride–urinary osmolality dose–response curve, a strong inverse correlation is present ($r = 0.90$). Urinary inorganic fluoride excretion peaked ten hours after anesthesia, remained at high levels for the next eight hours, then declined at a rate roughly parallel to the rate of decrease in serum inorganic fluoride concentration (fig. 2).

Another finding of interest was the increase in serum creatinine concentration during enflurane anesthesia accompanied by a 35 per cent decrease in creatinine clearance (table 2). By contrast, serum creatinine concentration was unchanged during halothane anesthesia. The 13 per cent decrease in creatinine clearance during anesthesia with this agent was significantly less than the decrease that occurred with enflurane (table 3).

Serum inorganic bromide concentration increased

during halothane administration, reaching a value of 0.43 ± 0.11 mEq/l at the end of anesthesia (fig. 4). Bromide levels continued to increase after anesthesia, peaking approximately 35 hours after anesthesia and maintaining high levels until the conclusion of experimental measurements on the fifth day after anesthesia. Urinary inorganic bromide excretion peaked the morning after anesthesia, then peaked again on the morning of the second post-anesthetic day.

Discussion

It is well established that methoxyflurane administration in man and Fischer 344 rats results in a dose-related renal concentrating defect by virtue of anesthetic metabolism to inorganic fluoride.^{2,3} It is less clear whether enflurane metabolism to inorganic fluoride results in fluoride nephropathy. Also, the threshold level for inorganic fluoride nephrotoxicity is still debated.

With regard to the latter question, Cousins and Mazze² tested urine-concentrating ability in surgical patients anesthetized with methoxyflurane by comparing urinary osmolality, measured after overnight dehydration, before and after operation. Vasopressin concentration tests were administered only to patients who had abnormalities in the post-

operative dehydration test. Defects in concentrating ability were recorded only when serum inorganic fluoride levels exceeded $50 \mu\text{M}$. A similar threshold value has been determined in Fischer 344 rats.^{3,7,8} Other investigators have measured inorganic fluoride levels in surgical patients anesthetized with methoxyflurane, but have not measured urine-concentrating ability. Nevertheless, it has been stated that serum inorganic fluoride values as high as $100 \mu\text{M}$ are safe.^{9,10}

Data relating enflurane anesthesia and post-anesthetic urine-concentrating ability are scarce. Clinical polyuric renal failure has been reported to occur in only three surgical patients, all of whom have had pre-existing renal disease.¹¹⁻¹³ Cousins *et al.*¹⁴ reported a controlled, randomized, prospective study of surgical patients without renal disease, anesthetized with a mean enflurane dose of 2.7 ± 0.3 MAC hours. Preoperatively, urine-concentrating ability was measured after overnight dehydration. Postoperatively, vasopressin was administered to determine urine-concentrating ability, in most cases 48 hours after the end of operation. Mean peak serum inorganic fluoride level in this study was $22.2 \pm 2.8 \mu\text{M}$. Their results showed no significant difference between pre- and postanesthetic urine-concentrating abilities, nor was there a difference between groups of patients anesthetized with enflurane as compared with halothane. Interpretation of the results of this study would have been simplified had vasopressin been used to measure preanesthetic as well as post-anesthetic urine-concentrating ability.

The present study overcomes many of the deficiencies of previous investigations.^{1,2,10,14-17} Highly reliable, identical methods of measuring urine-concentrating ability were employed before and

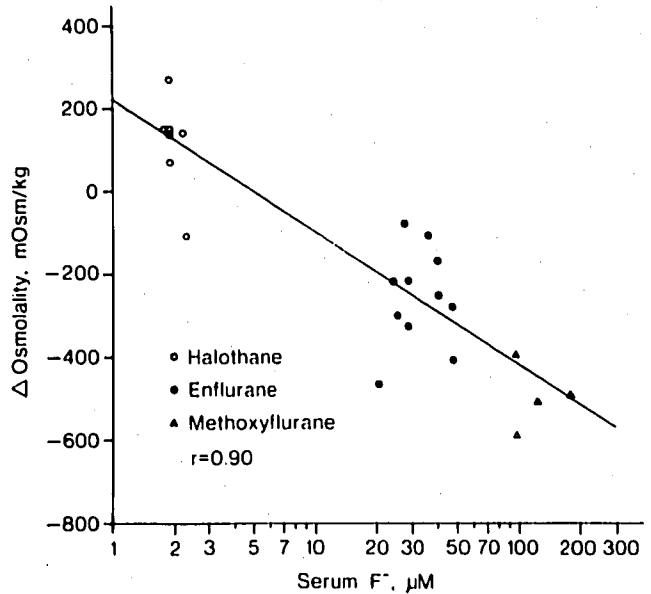


FIG. 3. Individual changes in urinary osmolality following enflurane, halothane and methoxyflurane anesthesia plotted against peak serum inorganic fluoride levels; methoxyflurane data are from a previous study.² As peak serum inorganic fluoride level increased, the ability to concentrate urine decreased ($r = 0.90$).

after anesthesia. Subjects were free of systemic disease and were not operated upon. Inadvertently, subjects anesthetized with halothane received lactated Ringer's solution in 5 per cent dextrose, whereas subjects treated with enflurane generally received 0.45 per cent saline solution in 5 per cent dextrose. Because intravenous fluids were administered for only one day, it is unlikely that the differences in solute content of these solutions

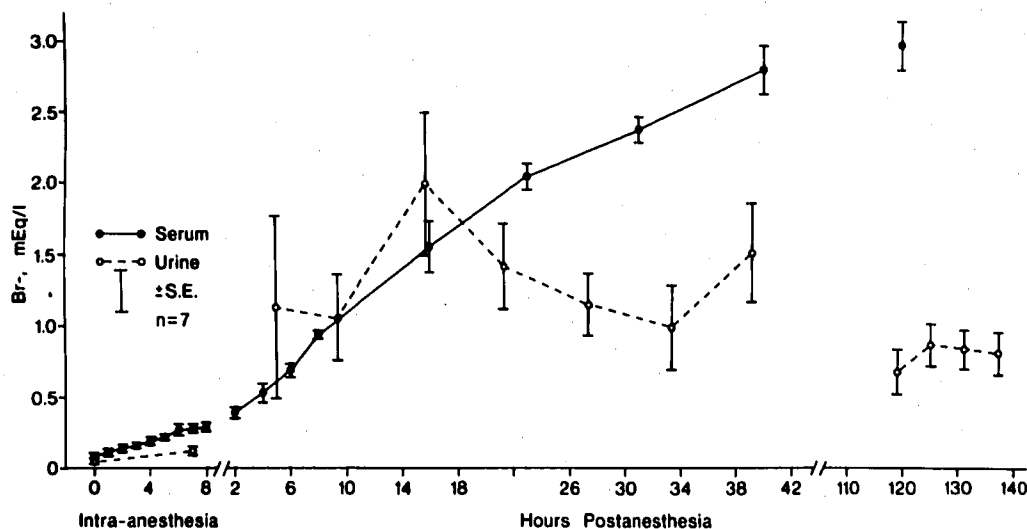


FIG. 4. Mean serum inorganic bromide level (—) \pm SE and urinary inorganic bromide excretion (---) \pm SE following halothane anesthesia. Serum Br^- level peaked on day 2 after anesthesia and remained at maximum levels throughout the remainder of the experimental measurements. $U_{\text{Br}-V}$ peaked on the first day after anesthesia and by the fifth day was returning towards control values.

influenced the results of the study. Thus, the urine-concentrating defect observed in enflurane-treated subjects was probably due to anesthetic biodegradation to inorganic fluoride.

The present study helps to define the threshold of inorganic fluoride nephrotoxicity. Serum inorganic fluoride level peaked six hours after enflurane anesthesia at a concentration of approximately 33 μM (fig. 2). Twelve hours later, by which time serum inorganic fluoride level had decreased to 21 μM , vasopressin was administered. By the end of the vasopressin test, serum inorganic fluoride level had decreased to approximately 8 μM . Thus, during the 24-hour test period, average serum inorganic fluoride level was only 15 μM , yet subjects had a 25 per cent reduction in maximum urine-concentrating ability compared with preanesthetic values. What, then, is the threshold of inorganic fluoride nephrotoxicity? Since a no-effect level was not achieved, a precise threshold cannot be defined. Also, organ toxicity is related not only to the peak level of the toxic substance, but to the length of time the organ is exposed to high levels, *i.e.*, the area under the curve. In the present study, the kidneys were exposed to a mean peak serum inorganic fluoride level of 33.6 μM , with values above 20 μM for 18 hours; this combination proved to be nephrotoxic. Whether peak serum inorganic fluoride level is a more significant determinant of nephrotoxicity than is duration of elevation cannot be established from these data.

What are the clinical implications of a concentrating defect of the magnitude demonstrated in the present study? They are probably inconsequential in patients without renal disease. All subjects evidenced considerable renal reserve, in that they were able to concentrate urine to an osmolality at least twice that of plasma. Also, the rapid decrease of serum inorganic fluoride level after enflurane anesthesia suggests that maximum urine-concentrating ability may have returned to preanesthetic values even sooner than the fifth postanesthetic day, the day on which the second vasopressin test was carried out. Since surgical patients generally are exposed to lower enflurane doses than were the volunteers in the present study, and, therefore, have lower serum inorganic fluoride levels,¹⁴ it is likely that enflurane anesthesia will not adversely affect their renal function and fluid homeostasis. On the other hand, surgical patients with pre-existing renal disease could be harmed by superimposing an inorganic fluoride load on already-damaged kidneys. In these individuals, a urine-concentrating defect might be of longer duration than in the volunteers examined in the present study, since excretion of inorganic fluoride would be impaired.

The more-than-twofold differences in peak serum inorganic fluoride levels among subjects anes-

thetized with essentially the same dose of enflurane are not unexpected (fig. 3). Since subjects were not known to have been exposed to enzyme-inducing drugs or chemicals, this difference probably represents normal biologic variation. Differences in drug metabolism of this magnitude are common and are thought to be under genetic control; they have been found with anesthetic^{2,10,14-18} as well as nonanesthetic compounds.¹⁹ The genetic aspect of control of metabolism in the present study is illustrated by identical twin subjects, both anesthetized with enflurane. Their peak inorganic fluoride levels were the lowest measured in the study and were virtually the same, 21.6 and 24.3 μM .

Finally, this study confirms the findings of Johnstone *et al.*²⁰ and Tinker *et al.*²¹ regarding serum inorganic bromide levels in subjects anesthetized with halothane. Values approaching 3 mEq/l were measured, with peak levels persisting until five days after anesthesia, when the experiment was concluded. Psychoactive levels of inorganic bromide are thought to be in the range of 6-10 mEq/l, with levels of 25-75 mEq/l encountered in cases of deep coma.²² At present, it is not known whether the levels noted in our subjects were psychoactive. Since the half-life of bromide in human blood is approximately 11.5 days,²³ it is possible that psychoactive bromide levels could be achieved if halothane anesthetics were repeated frequently, as in patients having burn-dressing changes.

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