

Is Enflurane Defluorination Inducible in Man?

James R. Dooley, M.D.,* Richard I. Mazze, M.D.,† Susan A. Rice, Ph.D.,‡
James D. Borel, M.D.§

Serum inorganic fluoride (F^-) levels and anesthetic exposure were measured in 102 surgical patients to determine the effects of enzyme-inducing drugs on enflurane metabolism. Serum electrolytes, urea nitrogen and creatinine values were also determined. Patients were classified into four groups according to their current drug-intake histories: 1) control (no drug), 26 patients; 2) chronic ethanol, 31 patients; 3) chronic phenobarbital and/or phenytoin, 12 patients; 4) miscellaneous drugs, 33 patients. None of the regression lines of peak serum F^- on anesthetic exposure for the drug groups was significantly different from that of the control group. Five patients received enflurane anesthesia twice, with the regression line for the second exposure not significantly different from that for the first. Mean peak serum F^- level for all patients was $17.7 \pm 0.8 \mu M$, with the highest individual value in the study, $44.7 \mu M$, occurring in a control patient. Electrolyte, urea nitrogen, and creatinine values remained normal throughout the experiment. It is concluded that prior treatment with enzyme-inducing drugs does not increase enflurane defluorination in surgical patients, nor does it increase the risk of developing F^- nephropathy. (Key words: Alcohol. Anesthetics, volatile: enflurane. Biotransformation: enzyme induction; fluorometabolites. Ions: fluoride. Kidney: function; nephrotoxicity. Metabolism: enzyme induction.)

ENFLURANE is a pentafluorinated methylethyl ether and a substrate of the hepatic mixed-function oxidase system.¹ Its biotransformation results in the production of several metabolites, including inorganic fluoride (F^-), in man² and animals.³ In previous studies of surgical patients and volunteers, serum and urinary F^- levels following enflurane anesthesia were increased, but not to the extent implicated in the polyuric renal insufficiency associated with methoxyflurane metabolism.⁴⁻⁶ More than 200 commonly encountered chemicals induce enzymes of the hepatic mixed-function oxidase system, increasing their own metabolism and that of other agents. Induc-

tion of enflurane defluorination would lead to increased F^- formation and, possibly, to postanesthetic renal complications. The present study examines the effects of enflurane anesthesia on serum F^- levels of surgical patients receiving enzyme-inducing drugs up to the time of operation.

Methods and Materials

Informed consent was obtained from 102 surgical patients prior to operation.[†] Ninety-seven subjects were male; mean age for all subjects was 53 years. A detailed drug-intake history was obtained from each patient at a preoperative interview. Subjects then were divided into groups according to current preoperative drug-intake histories (table 1). Minimum group size was ten patients. The control group consisted of 26 individuals not exposed to any drug, including ethanol, within the two weeks preceding operation. The second group consisted of 31 patients who regularly consumed alcohol, but no other drug. The third group comprised 12 patients who had received phenobarbital and/or phenytoin, but no other drug, including alcohol. The last group consisted of the remaining 33 patients, who had been exposed to miscellaneous drugs. Preoperatively, serum electrolytes, urea nitrogen, and creatinine levels were measured. Any patient who had a serum urea nitrogen level above 20 mg/100 ml or a creatinine concentration of more than 1.5 mg/100 ml was excluded from the study.

Of the 102 patients, 73 were treated with a standardized anesthetic regimen. Diazepam, 10-15 mg, was administered the night before operation and again as premedication with atropine, 0.3-0.5 mg. Anesthesia was induced and maintained by inhalation of enflurane in oxygen. Succinylcholine, 1.0-1.5 mg/kg, was used to facilitate endotracheal intubation, and *d*-tubocurarine, 0.1-0.3 mg/kg, to provide surgical relaxation. A semiclosed circle system with soda lime canister was employed for CO_2 removal, and minute ventilation was controlled with an Air Shields ventilator at 100 ml/kg body weight. Electrocardiogram, pulse rate, and blood pressure were monitored throughout each procedure. The remaining 29 patients were treated as described above,

* Research Fellow.

† Professor of Anesthesia.

‡ Research Associate.

§ Research Assistant.

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Address reprint requests to Dr. Mazze: Anesthesiology Service (112A), Palo Alto Veterans Administration Hospital, Palo Alto, California 94304.

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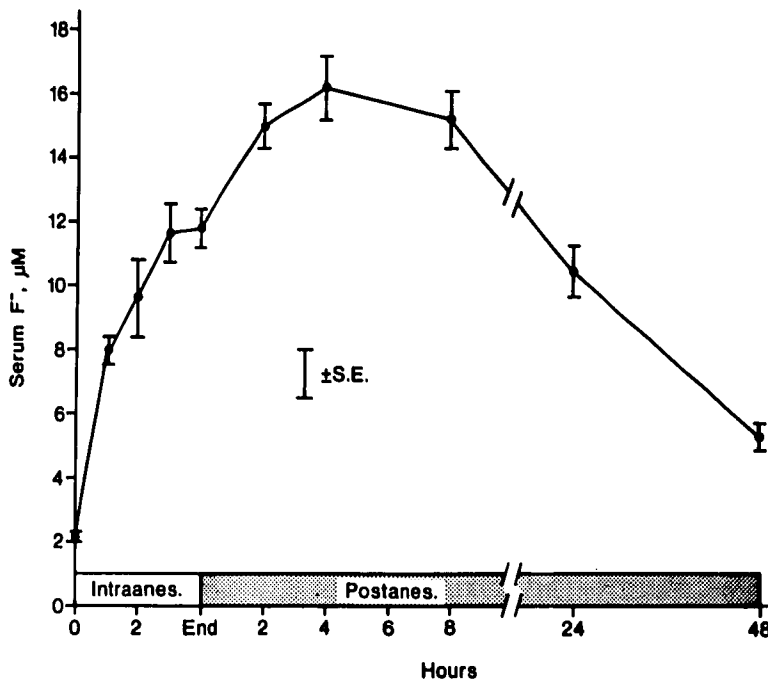


FIG. 1. Serum fluoride (F^-) levels for all patients at each sampling interval. Mean enflurane exposure was 2.16 ± 0.15 MAC hours. Serum F^- levels increased rapidly during anesthesia and in the early postoperative period. In most cases, the peak value occurred four hours after anesthesia was completed. The mean peak F^- value for all patients was $17.7 \pm 0.8 \mu M$.

TABLE 1. Composition of Treatment Groups

Group	Number	Approximate Daily Exposure at Time of Operation
Control	26	Not applicable
Ethanol	31	3.5 beers or 0.5 pint of whiskey; duration 0.5-30 years
Phenobarbital-phenytoin	12	3 phenobarbital, 90 mg; 3 phenytoin, 300 mg; 6 both. Duration of exposure, 5 years
Miscellaneous	33	1 acetaminophen, 40 gr; 2 acetylsalicylic acid, 30 gr; 2 amitriptyline, 10 mg; 2 chloral hydrate, 500 mg; 3 chlorthalidazine, 30 mg; 1 chlorpheniramine, 16 mg; 1 chlorpromazine, 300 mg; 3 codeine, .5 gr; 1 colchicine with probenecid, 1 mg and 1 g, respectively; 5 diazepam, 20 mg; 1 doxepin, 100 mg; 7 ethanol, occasional; 4 flurazepam, 30 mg; 1 hashish, occasional; 1 heroin, \$15; 8 hydrochlorothiazide, 100 mg; 1 imipramine, 200 mg; 2 indomethacin, 75 mg; 2 insulin-NPH, 15 units; 2 lithium, 900 mg; 1 marijuana, 1 joint; 1 methenamine mandelate, 4 gr; 3 methyl dopa, 750; 1 oxtriphylline, 400 mg; 1 pentazocine, 50 mg; 2 phenobarbital, 150 mg; 4 phenytoin, 300 mg; 1 promethazine with dextromethorphan, 40 ml; 3 propoxyphene, 400 mg; 1 propranolol, 40 mg; 1 reserpine, 25 mg; 2 thioridazine, 200 mg; 2 thyroid, 2 gr; 1 trimethadione, 1,200 mg
TOTAL	102	

except that anesthesia was induced intravenously with sodium thiopental and the choice of premedication and muscle relaxants was that of the anesthesiologist caring for the patient.

End-tidal enflurane concentrations ranged from 1 per cent (0.6 MAC) to 3 per cent (1.8 MAC); these were continuously measured with a Beckman LB-2 Medical Gas Analyzer and plotted with a strip-chart recorder. MAC hours of enflurane exposure were determined by planimetric measurement of the area under the tracing. Blood samples for serum F^- analysis were obtained prior to operation and 2, 4, 8, 24, and 48 hours after operation. Fluoride levels were measured with an Orion Model 801 Ionalyzer and a fluoride-specific electrode.⁷ Samples obtained at 24 and 48 hours were also assayed for serum electrolytes, urea nitrogen, and creatinine values.

Regression lines to estimate the dependence of peak serum F^- on enflurane exposure were calculated for each group. The F statistic was used to test the null hypothesis that the slope and intercept of the regression line for each treatment group equalled the slope and intercept of the regression line for the control group.⁸ Also, the slopes of the regression lines for the two methods of anesthetic induction and for the two enflurane exposures were compared by t tests. Mean pre- and postoperative serum electrolyte, urea nitrogen, and creatinine levels were calculated for each drug-treatment group and compared with those of the control group by the Student t test. $P < 0.05$ was considered significant.

Results

Serum F^- increased rapidly during enflurane anesthesia and early in the postoperative period, with a mean peak value of $17.7 \pm 0.8 \mu M$. In most patients the peak value occurred four hours after the conclusion of anesthesia (fig. 1). Although F^- levels in most patients did not exceed $30 \mu M$, there were occasional exceptions. Interestingly, the highest peak serum F^- level, $44.7 \mu M$, occurred in a control patient exposed to 4.7 MAC hours of enflurane. Twenty-four hours after operation this patient's F^- level had decreased to $38.1 \mu M$, and by 48 hours it was $16.3 \mu M$. There was no significant difference between the regression lines for the standardized (inhalational) and thiopental (intravenous) anesthetic induction methods (fig. 2), nor was there a significant difference between the regression lines for the control group and the ethanol ($F = 2.009$), phenobarbital-phenytoin ($F = 1.275$), and miscellaneous ($F = 3.040$) groups (fig. 3). Serum electrolyte, urea nitrogen and creatinine levels did not change significantly after anesthesia; values for all patients remained within normal limits. Serum creatinine data are presented in table 2.

Five patients had anesthesia with enflurane twice with the intervals between the first and second ex-

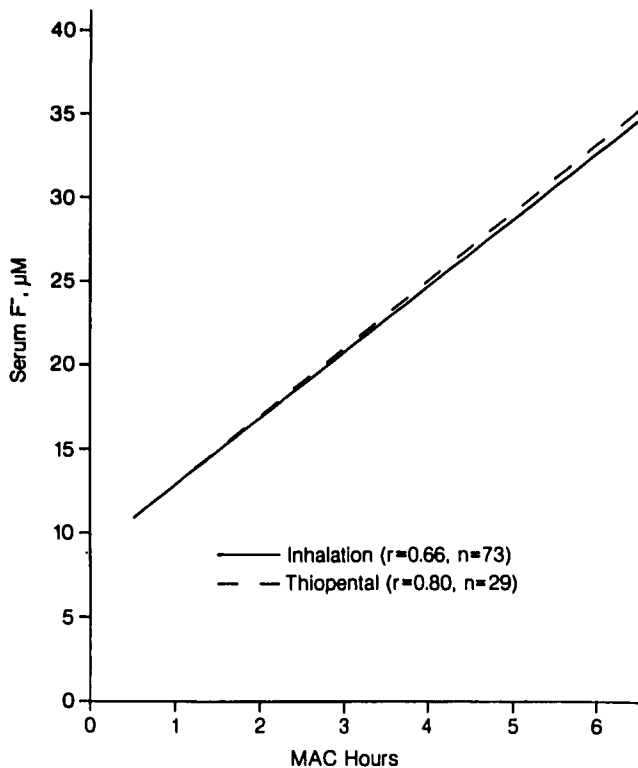


FIG. 2. Regression lines for patients, grouped by methods of anesthetic induction. The slopes of the two regression lines are not statistically different by t test.

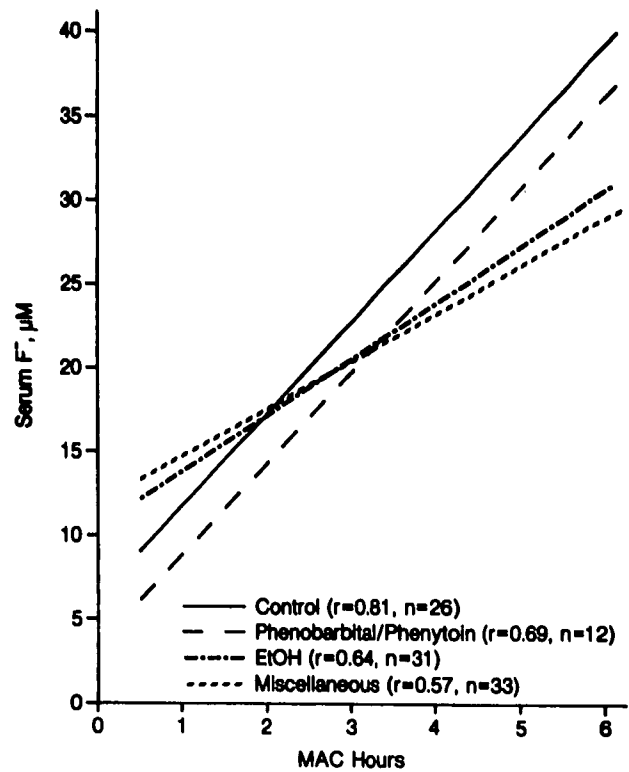


FIG. 3. Regression lines for patients, grouped by preoperative drug-intake history. There is no significant difference between the regression lines for any drug group and the control group.

posures ranging from five to 23 weeks. The second exposures did not result in increases of serum F^- to levels higher than those predicted from the initial exposure (fig. 4).

Discussion

Enflurane and methoxyflurane are substrates of the hepatic mixed-function oxidase system, so their metabolism could be expected to be similar.¹ Enhanced biotransformation of methoxyflurane has been demonstrated both *in vivo* and *in vitro*. However, the results of previous studies of the induction of enflurane metabolism are inconsistent. Hitt *et al.*⁹ demonstrated that chronic subanesthetic exposure to enflurane increased its own metabolism and also resulted in increased hepatic cytochrome P-450 levels in rats. Berman *et al.*¹⁰ demonstrated that a single anesthetizing exposure of enflurane in man enhanced steroid metabolism, suggesting enzyme induction. Additional support for the concept that enflurane defluorination is inducible comes from several clinical reports of patients with serum F^- levels close to $100 \mu M$ following enflurane anesthesia.^{4,11,12} It was suggested that enzyme induction may have contributed to these unusual F^- values. To the contrary,

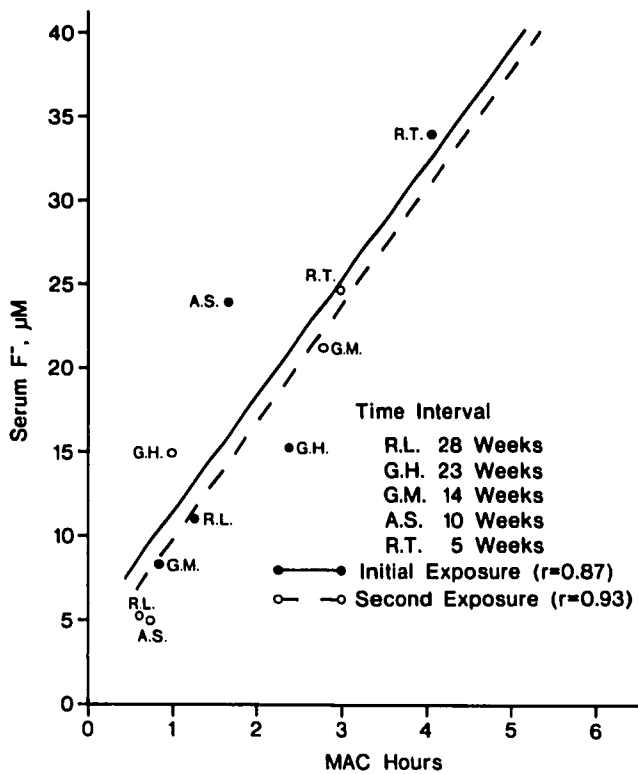


FIG. 4. Regression lines for patients having two exposures to enflurane. There is no significant difference between the serum fluoride levels following initial exposure and repeated exposure to enflurane.

Barr *et al.*³ were not able to demonstrate increased enflurane defluorination in Fischer 344 rats treated with phenobarbital prior to enflurane anesthesia in spite of hepatic morphologic evidence of enzyme induction. In a clinical study, peak F^- levels in six surgical patients chronically treated with barbiturates were not significantly different from those in control subjects.¹² *In-vitro* studies employing hepatic microsomes prepared from phenobarbital-treated rats, also, did not show significant stimulation of enflurane defluorination.^{13,14} Although methoxyflurane defluorination was increased 7.3–9.5 times, enflurane defluorination was not increased in one experiment¹³ and was increased by 1.6 times above control level in the other.¹⁴

The present study was designed to resolve the conflict of whether enflurane defluorination could be induced in surgical patients. The answer to the question appears to be, no. Treatment with relatively large doses of the potent enzyme-inducing agents, phenobarbital and phenytoin, did not significantly increase enflurane defluorination above control levels. Similarly, treatment with less potent inducing agents, ethanol and enflurane, had little effect. Exposure to agents in the miscellaneous group, often three or

more at a time, also did not enhance defluorination. Ideally, it would have been desirable to collect 24-hour urine specimens, in addition to blood samples, from all patients, in order to quantitate metabolite production more precisely. However, this aspect of experimental design had to be balanced against the practical problems encountered in obtaining complete urine collections from large numbers of patients. It was decided that clinically reliable information regarding enflurane defluorination could be obtained from blood samples alone.

Data from the present study also support previous investigations regarding the renal effects of enflurane. Postoperative polyuria was not observed, and serum electrolyte, urea nitrogen and creatinine concentrations remained normal. Following an average exposure of all patients to 2.2 ± 0.2 MAC hours of enflurane, the mean peak serum F^- level in the present study was only $17.7 \pm 0.8 \mu M$. This had declined to $10.5 \pm 0.8 \mu M$ 24 hours after anesthesia and was $5.4 \pm 0.4 \mu M$ at 48 hours. This peak serum F^- level was approximately half that associated with a minimal (26 per cent) concentrating defect in a previous study of volunteers anesthetized with enflurane for 9.6 ± 0.1 MAC hours⁵; it was slightly less than the peak F^- level ($22.2 \pm 2.8 \mu M$) reported in another study of surgical patients anesthetized for 2.7 ± 0.3 MAC hours, who did not develop a concentrating defect.⁴ Thus, it appears that enflurane anesthesia in patients without pre-existing renal disease does not result in F^- nephropathy. However, we wish to repeat the precaution against the use of enflurane in patients with abnormal renal function.^{4,5} Polyuric renal dysfunction following enflurane anesthesia has been reported to occur in only three patients, all of whom had renal impairment prior to operation.^{11,15,16} Although Carter *et al.*¹⁷ have reported that peak serum F^- levels after enflurane anesthesia were similar in

TABLE 2. Serum Creatinine

Group	mg Creatinine/100 ml Serum (Mean \pm SE)		
	Preoperative	Postoperative	
		Day 1	Day 2
Control (n = 26)	1.05 \pm 0.04	1.00 \pm 0.04 (23)	0.98 \pm 0.04 (20)
Ethanol (n = 31)	1.03 \pm 0.03	0.99 \pm 0.03 (31)	0.97 \pm 0.03 (19)
Phenobarbital-phenytoin (n = 12)	0.88 \pm 0.08	0.81 \pm 0.05 (12)	0.91 \pm 0.06 (9)
Miscellaneous (n = 33)	0.98 \pm 0.04	0.92 \pm 0.04 (26)	0.99 \pm 0.05 (21)

healthy patients, anephric patients, and patients with poor renal function, it seems prudent to avoid administration of any drug that is biotransformed to a nephrotoxic product to patients who have renal impairment.

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