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## Renal Failure Following Enflurane Anesthesia

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Enflurane (2-chloro-1,1,2-trifluoroethyl-difluoromethyl ether; Ethrane, Ohio Medical Products) has rapidly become very popular, and is the inhalation agent most frequently used at this hospital. Enflurane is biotransformed in part to inorganic fluoride ion.<sup>1</sup> Fluoride ion-induced nephrotoxicity has been established as a cause of the vasopressin-resistant polyuric renal failure occasionally seen following exposure to significant doses of methoxyflurane.<sup>2</sup> Postanesthetic renal failure in a patient who received enflurane led to measurement of serum fluoride in a search for a possible etiologic factor.

### REPORT OF A CASE

A 66-year-old white man (65 inches tall, weight 61 kg) was admitted to the hospital for an elective ileal-loop urinary diversion as first-stage treatment for a carcinoma of the bladder, diagnosed six weeks previously by biopsy during cystoscopy using

enflurane anesthesia. A rectal carcinoma had been excised by anteroposterior resection three years prior to admission. The patient had angina pectoris and a documented previous myocardial infarction, and was subject to paroxysmal atrial fibrillation. Medications were nitroglycerin and digoxin. Preoperative blood urea nitrogen (BUN) was 23 mg/100 ml; serum creatinine was 1.4 mg/100 ml, urinalysis showed 1+ protein by dipstick, with a few leukocytes evident microscopically. Preoperative blood pressure was 140/80 torr.

The patient had a six-hour operation with an uneventful anesthetic course for the creation of the ileal loop. Anesthesia was induced with thiopental, 200 mg, and succinylcholine, 100mg, and was maintained with 66 per cent N<sub>2</sub>O, 33 per cent O<sub>2</sub>, and enflurane at an average concentration of 1 per cent for the six hours, and a total of 5 mg pancuronium. Intraoperatively, the lowest blood pressure was 110/65 torr and the lowest arterial blood P<sub>50</sub> was 123 torr. Immediately following the procedure urinary output was greater than 40 ml per hour.

As shown in table 1, urinary output exceeded fluid intake on the first postanesthetic day, and the patient lost 1.2 kg in body weight. The patient became virtually anuric on the second postanesthetic day. Urinary sodium was 106 mEq/l, potassium 6 mEq/l. Dipstick urinalysis showed pH 7, 3+ protein, and no glucose, and many erythrocytes were evident microscopically. Blood was drawn for determination of serum inorganic fluoride ion. An intravenous pyelogram showed no evidence of obstructive uropathy or extravasation. Furosemide in three doses totaling 130 mg had no effect. On the third postanesthetic day, the patient was anuric. A single dose of furosemide, 300 mg, had no effect. A contrast study of the ileal loop failed to show reflux from the loop into the ureters. Urinary output spontaneously returned the following day, then gradually increased. BUN and creatinine improved as shown in table 1. At the time of the patient's

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TABLE 1. Clinical Data in the Immediate Postanesthetic Period

Postoperative Day	Body Weight (kg)	Fluid Intake (ml)	Urinary Output (ml)	Blood Urea Nitrogen (mg/100 ml)	Serum Creatinine (mg/100 ml)	Serum Inorganic Fluoride ( $\mu\text{M/l}$ )
0	61.0	3,000	2,200	29	—	—
1	62.0	1,080	1,725	28	—	—
2	60.8	2,125	45	29	3.4	93.6
3	62.7	380	0	41	7.4	27.1
4	61.9	320	90	60	10.3	23.6
5	61.2	350	590	82	11.8	—
6	60.2	1,540	500	87	10.3	18.2
7	61.0	1,701	1,070	90	10.3	14.5
8	—	1,800	1,200	75	6.4	—
9	60.7	2,800	1,580	60	4.3	7.8
10	61.4	2,900	2,000	33	2.1	—
11	60.7	1,800	2,160	21	2.0	—
12	—	2,600	1,275	—	—	—
13	—	2,650	2,250	20	2.4	2.8

\* The normal fluoride level in serum of a person drinking fluoridated water is 0.5–1.0  $\mu\text{mol/l}$ . Fluoride levels were determined in all serum samples that could be retrieved.

discharge from the hospital, on the twenty-second postanesthetic day, BUN and creatinine were 37 and 1.7 mg/100 ml, respectively, and creatinine clearance was 39 ml/min.

When the report of an abnormal serum fluoride was received (Bio-Science Laboratories, Van Nuys, California), all available serum samples were retrieved from the hospital clinical laboratory freezer for fluoride analysis in the Department of Anesthesia laboratories. All fluoride measurements were made with an Orion Model 96-06 ion-specific electrode.<sup>3</sup> The peak value in this patient's serum was 93  $\mu\text{mol/l}$ , found on the second postanesthetic day; values on subsequent days decreased in an exponential-decay pattern over the time of the gradual return of improved renal function (table 1).

Six weeks following this operation, BUN was 10 mg/100 ml and creatinine 1.2 mg/100 ml; urinalysis showed only bacteria, leukocytes, and amorphous crystals. The patient underwent radical cystectomy with  $\text{N}_2\text{O}$ ,  $\text{O}_2$ , and halothane anesthesia. Estimated blood loss was 4,000 ml. The lowest intraoperative blood pressure was 65/35 torr, which was restored to 125/60 torr in 5 minutes by rapid infusion of blood and crystalloid. Postoperative BUN never exceeded 25 mg/100 ml, and creatinine clearance was 55 ml/min. Serum fluoride levels were all normal, about 1.0  $\mu\text{mol/l}$  or less, postoperatively. The patient recovered and was discharged from the hospital.

## DISCUSSION

Enflurane is more resistant to biotransformation and yields less inorganic fluoride ion than equianesthetic doses of methoxyflurane. The fluoride ion excreted following enflurane

disappears more rapidly than that excreted following methoxyflurane.<sup>4</sup> Peak serum fluoride levels following enflurane anesthesia rarely exceed 25  $\mu\text{mol/l}$ .<sup>5</sup> A mean peak level of  $22.2 \pm 2.8$   $\mu\text{mol/l}$  was recorded in a detailed study of ten patients.<sup>6</sup> The threshold for fluoride-induced nephrotoxicity is believed to be 40–50  $\mu\text{mol/l}$ .<sup>2,4,5</sup> The inorganic fluoride concentration of 93  $\mu\text{mol/l}$  recorded in this case is definitely within the potentially nephrotoxic range. Further, it is very likely that the true peak serum fluoride concentration was even higher, because the first measurement was 48 hours after the end of anesthesia. Peak fluoride concentrations occurred four hours after anesthesia in a detailed prospective investigation<sup>6</sup> and three hours after anesthesia in another study.<sup>5</sup>

Enflurane in high doses (2.5 per cent for six hours) can produce the characteristic lesion of vasopressin-resistant polyuria in rats, with peak serum fluoride concentrations occurring four hours after anesthesia. On the other hand, Cousins *et al.*<sup>6</sup> conclude from their study of patients without renal disease that in man metabolism of enflurane to inorganic fluoride is insufficient to cause clinically significant renal dysfunction. One patient who was receiving several drugs thought to cause enzyme induction had a peak fluoride concentration of 106  $\mu\text{mol/l}$  one hour after enflurane anesthesia. In this patient,

vasopressin induction of urine concentration was suppressed on the first postanesthetic day but was normal thereafter, with no other renal abnormality.

Polyuria and deterioration of renal function following enflurane anesthesia have been reported to occur in a patient with a failing transplanted kidney.<sup>9</sup> A renal biopsy showed the expected chronic changes, but also acute damage of proximal tubules. A second exposure to enflurane was followed by mild polyuria, no change in renal function, and a peak serum fluoride ion concentration of 16  $\mu\text{mol/l}$ . The third exposure to enflurane was for nephrectomy, and the subsequent peak fluoride level was 19  $\mu\text{mol/l}$ . The clinical picture and the acute histologic changes were interpreted as suggestive of fluoride-induced nephrotoxicity. The authors postulated that the threshold for fluoride-induced nephrotoxicity may be lower in diseased kidneys, so that comparatively normal peak fluoride concentrations might be toxic. Another case of transient polyuria and abnormal renal function following enflurane has also been reported, but fluoride ion concentrations were not determined.<sup>10</sup>

The patient reported here had an uneventful comparatively long exposure to enflurane. No obvious cause of ischemic renal failure existed, and the patient was not exposed to any other known nephrotoxin. He may have had mild polyuria on the first postoperative day. Then followed transient renal shutdown, with gradual return of normal urinary output. Even though reflux from the ileal loop to the ureters was not seen, the intravenous pyelogram strongly suggested that obstructive uropathy was not the precipitating factor. Other causes of acute renal failure, including congestive heart failure, hypovolemia, and hypercalcemia, were not observed. The patient had a remarkably elevated serum fluoride level (probably even higher than the 93  $\mu\text{mol/l}$  measured on the second postanesthetic day) and abnormally slow clearance of the residual fluoride ion. The overall picture suggests severe fluoride-induced nephrotoxicity.

Failure to excrete fluoride because of the oliguria on the second postanesthetic day conceivably could have contributed to the

very high initial serum fluoride level. No data or reported studies support this idea. Even if this were to be the case, the levels demonstrated still would reflect an abnormally large amount of total circulating fluoride ion.

It appears that enflurane has the potential to generate nephrotoxic serum levels of inorganic fluoride ion. Why it happened in this patient is unclear. However, this patient had been briefly exposed to enflurane six weeks earlier. Although enflurane has not been proven to be an enzyme inducer, it can be speculated that the first exposure caused enzyme induction so that the subsequent longer exposure caused generation of abnormally large amounts of inorganic fluoride ion. Enzyme induction with phenobarbital does not influence post-enflurane fluoride excretion in rats.<sup>1</sup> However, as mentioned, another patient had very high post-enflurane fluoride levels while receiving enzyme-inducing drugs.<sup>6</sup>

Until further experience allows more data, the benefits versus the risks of enflurane as an anesthetic agent for patients who have abnormal renal function preoperatively should be carefully considered. Also, if a patient receiving enflurane should be exposed intraoperatively to a potential cause of renal failure, consideration should be given to the immediate discontinuation of enflurane. Finally, any patient who receives enflurane and then develops polyuria or abnormal renal function should have serial serum inorganic fluoride ion analysis.

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## Bupivacaine and Etidocaine for Lumbar Epidural Anesthesia for Intra-abdominal Pelvic Surgery, A Double-blind Study

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Subsequent to the introduction of etidocaine by Adams in 1972,<sup>1</sup> a number of well-controlled clinical studies were reported.<sup>2-4</sup> Clinical comparisons were then made between etidocaine and other local anesthetic agents currently in use.<sup>5-7</sup> Most recently, studies in animals<sup>8</sup> and man<sup>9,10</sup> have investigated the toxicity and physiologic side effects of these drugs. Some of these preliminary studies raised questions regarding the relative potencies of two concentrations of etidocaine, 1.0 and 1.5 per cent,<sup>5</sup> and also the relative efficacies of bupivacaine, 0.75 per cent, and etidocaine, 1.0 per cent, in providing satisfactory "visceral" anesthesia for lumbar epidural anesthesia.<sup>7</sup>

This study represents a controlled, prospective double-blind study of etidocaine, 1.0 and 1.5 per cent, and bupivacaine, 0.75 per cent, comparing the clinical variables of sensory, motor, and "visceral" anesthesia for lumbar epidural anesthesia for pelvic surgery.

### METHODS

Sixty female patients were randomly assigned to three drug groups according to a

predetermined code. All patients were classified ASA 1 or 2 and were scheduled for elective abdominal hysterectomy. They ranged in age from 20 to 68 years. They were informed of the nature of the study and oral consent was obtained. A standardized premedication regimen included chloral hydrate, 500 mg, for sleep the night before operation and meperidine, 50-100 mg, plus atropine, 0.4 mg, im, 60 minutes prior to administration of the anesthetic.

A standard lumbar epidural puncture was performed at the L2 interspace and 20 ml of local anesthetic drug were administered. (A nurse in the Anesthesia Department who had no other contact with the study prepared a coded syringe filled with appropriate local anesthetic and delivered it to the anesthesiologist.) All three local anesthetic solutions (etidocaine, 1.0 and 1.5 per cent, and bupivacaine, 0.75 per cent) contained epinephrine, 1:200,000. Patients were awake and responsive during all measurements. When the quality of the epidural anesthesia was insufficient to accommodate intraoperative stimulation, supplemental anesthesia with methohexital drip or N<sub>2</sub>O-O<sub>2</sub> (3 l:1.5 l) was administered.

Following administration of the unknown local anesthetic agent, measurements of times to onset and to complete sensory and motor blockade were made. Initial onset was defined as the time between the start of the injection and the first detectable loss of sensation in

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