Renal Failure Following Enflurane Anesthesia

JOHN H. EICHHORN, M.D.,* JOHN HEDELY-WHITE, M.D., l THEODORE I. STEINMAN, M.D., 4
JOEL M. KAUFMANN, M.D., § L. HANS LAASBERG, C.H.E. 6

Enflurane (2-chloro-1,1,2-trifluoroethyl-
difluoromethyl ether; Ethesane, Ohio Medical
Products) has rapidly become very popular,
and is the inhalation agent most frequently
used at this hospital. Enflurane is bio-
transformed in part to inorganic fluoride ion.1
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. 2 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

* Clinical Fellow in Anesthesia.
| David S., Sheridan Professor of Anesthesia
| and Respiratory Therapy.
| Assistant Clinical Professor of Medicine.
| l Instructor in Surgery.
| 4 Principal Associate in Anesthesia (Chemical Engineering).

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Address reprint requests to Dr. Eichhorn: Department of Anesthesia, Beth Israel Hospital, Boston, Massachusetts 02215.
discharge from the hospital, on the twenty-second postanesthetic day. BCN 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. The peak value in this patient’s serum was 93 μmol/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, BCN 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 N.D. X. for and bilateral nephrectomy. Estimated blood loss was 4,000 ml. The lowest intraoperative blood pressure was 65/35 mm Hg, which was restored to 125/60 mm Hg in 5 minutes by rapid infusion of blood and crystalloid. Postoperative BCN never exceeded 25 mg/100 ml, and creatinine clearance was 55 ml/min. Serum fluoride levels were all normal, about 1.0 μmol/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. Peak serum fluoride levels following enflurane anesthesia rarely exceed 25 μmol/l. A mean peak level of 22.2 ± 2.8 μmol/l was recorded in a detailed study of ten patients. The threshold for fluoride-induced nephrotoxicity is believed to be 40–50 μmol/l. The inorganic fluoride concentration of 93 μmol/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 and three hours after anesthesia in another study.

Enflurane in high doses (2.5 per cent for six hours) can produce the characteristic lesion of vasospasm-resistant polycystic kidney in rats, with peak serum fluoride concentrations occurring four hours after anesthesia. On the other hand, Cousins et al. 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 μmol/l one hour after enflurane anesthesia. In this patient.

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**Table 1. Clinical Data in the Immediate Postanesthetic Period**

<table>
<thead>
<tr>
<th>Postoperative Day</th>
<th>Body Weight (kg)</th>
<th>Fluid Intake (ml)</th>
<th>Urinary Output (ml)</th>
<th>Blood Urea Nitrogen (mg/100 ml)</th>
<th>Serum Creatinine (mg/100 ml)</th>
<th>Serum Fluoride (μmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>61.0</td>
<td>3,000</td>
<td>2,200</td>
<td>29</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1</td>
<td>62.0</td>
<td>1,080</td>
<td>1,725</td>
<td>28</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>60.8</td>
<td>2,125</td>
<td>45</td>
<td>29</td>
<td>3.4</td>
<td>93.6</td>
</tr>
<tr>
<td>3</td>
<td>62.7</td>
<td>320</td>
<td>0</td>
<td>41</td>
<td>1.3</td>
<td>27.1</td>
</tr>
<tr>
<td>4</td>
<td>61.9</td>
<td>320</td>
<td>90</td>
<td>60</td>
<td>10.3</td>
<td>23.6</td>
</tr>
<tr>
<td>5</td>
<td>61.2</td>
<td>350</td>
<td>590</td>
<td>82</td>
<td>11.8</td>
<td>—</td>
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<tr>
<td>6</td>
<td>60.8</td>
<td>1,540</td>
<td>500</td>
<td>87</td>
<td>10.3</td>
<td>18.2</td>
</tr>
<tr>
<td>7</td>
<td>61.0</td>
<td>1,701</td>
<td>1,070</td>
<td>90</td>
<td>6.4</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>—</td>
<td>1,800</td>
<td>1,200</td>
<td>75</td>
<td>6.4</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>60.7</td>
<td>2,800</td>
<td>1,580</td>
<td>60</td>
<td>4.3</td>
<td>7.8</td>
</tr>
<tr>
<td>10</td>
<td>61.4</td>
<td>2,900</td>
<td>2,000</td>
<td>33</td>
<td>2.1</td>
<td>—</td>
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<tr>
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<tr>
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<td>—</td>
<td>2,650</td>
<td>2,250</td>
<td>20</td>
<td>2.4</td>
<td>2.8</td>
</tr>
</tbody>
</table>

* The normal fluoride level in serum of a person drinking fluoridated water is 0.5–1.0 μmol/l. Fluoride levels were determined in all serum samples that could be retrieved.
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. 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 \( \text{\mu mol/l} \). The third exposure to enflurane was for nephrectomy, and the subsequent peak fluoride level was 19 \( \text{\mu mol/l} \). 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.

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 \( \text{\mu mol/l} \) 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. However, as mentioned, another patient had very high post-enflurane fluoride levels while receiving enzyme-inducing drugs.

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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**REFERENCES**


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

PHILLIP O. BRIDENBAUGH, M.D.,* ROBERT I. BALFOUR, M.D.,† L. DONALD BRIDENBAUGH, M.D.,‡ DONALD F. LYSONS, M.D.,‖

Subsequent to the introduction of etidocaine by Adams in 1972,1 a number of well-controlled clinical studies were reported.2–4 Clinical comparisons were then made between etidocaine and other local anesthetic agents currently in use.5–7 Most recently, studies in animals8 and man9,10 have investigated the toxicity and physiologic side effects of these drugs. Some of those preliminary studies raised questions regarding the relative potencies of two concentrations of etidocaine, 1.0 and 1.5 per cent,2 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.7 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, intramuscular, 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 responsible during all measurements. When the quality of the epidural anesthesia was insufficient to accommodate intraoperative stimulation, supplemental anesthesia with methohexital drip or N2O–O2 (3:1:1.5:1) 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