Renal Effects of Enflurane and Halothane in Patients with Abnormal Renal Function

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Early studies of enflurane metabolism indicated that it was defluorinated approximately one-third as much as methoxyflurane.1-3 This raised the possibility that administration of enflurane might lead to nephrotoxicity in some patients, e.g., those with renal disease. Indeed, postoperative renal dysfunction has been reported in several patients with preexisting renal disease who then received enflurane.4-6 Thus, a controlled study was undertaken to evaluate the renal effects of enflurane in patients with mild to moderate preoperative renal dysfunction.

STUDY SUBJECTS AND METHODS

Fifty surgical patients with abnormal preoperative renal function were studied. Informed consent and institutional approval were obtained. The criterion for admission to the study was a preoperative serum creatinine (Cr) value between 1.5 and 3.0 mg · dl⁻¹ (table 1). The most common preoperative causes of renal insufficiency were hypertensive cardiovascular disease, arteriosclerotic heart disease, and diabetes. After entry into the study, patients were assigned randomly to receive either enflurane (n = 25) or halothane (n = 25) as the primary inhaled anesthetic. Premedication was also administered to them in addition to any other anesthetic adjuvant drugs deemed appropriate by the anesthesiologist. The scheduled surgical procedures were similar for both groups of patients. Approximately 75% were orthopedic, ENT, or general surgical, with the remainder being thoracic, peripheral vascular, or extrarenal genitourinary operations. Serum F⁻, Cr, urea nitrogen (BUN), and electrolyte measurements were made preoperatively, and 4, 24, 48, and 72 h after operation, methods have been described.7 Twenty-four-hour creatinine clearance (C₇₀) was measured in 10 randomly selected patients from each group, preoperatively, and day 1 postoperatively. Differences between groups were determined using unpaired t tests. Differences within groups were examined using repeated measure analysis of variance and multiple t tests with the Bonferroni correction to isolate different subgroups.8 P < 0.05 was considered significant.

RESULTS

Preoperatively, there were no significant differences between the groups in any of the variables (table 1). The mean duration of operation was 212 ± 26 min for patients anesthetized with enflurane and 171 ± 14 min for those anesthetized with halothane. After operation, there were small but statistically significant improvements in serum Cr and BUN values in both groups of patients (table 2). Creatinine clearance was improved postoperatively in both groups of patients, but the change was statistically significant only in patients anesthetized with enflurane. Postoperatively there were no differences between the two groups in any variable except serum F⁻. After enflurane, serum F⁻ peaked to 19.0 ± 3.0 μM 4 h after operation then fell to 16.8 ± 2.6, 11.0 ± 1.5, and 7.0 ± 0.8 μM, 24, 48, and 72 hours after anesthesia, respectively. Values in halothane-treated patients were essentially unchanged from control, reaching a peak of 3.2 ± 0.2 μM on the first day after operation.

DISCUSSION

In our study of surgical patients with mild to moderate renal insufficiency, both enflurane and halothane administration were associated with statistically significant (but clinically small) improvements in renal function. The fact that both creatinine and BUN levels were decreased suggests that the changes were not related to reduced protein intake. It is possible that this group of patients, most of whom had cardiovascular disease, had some improvement in cardiac function postoperatively and that improved...
creatinine and BUN levels were a reflection of this. Admittedly, urinary concentrating ability, the most sensitive indicator of F⁻ nephropathy, was not evaluated. However, the mean peak postoperative F⁻ level, 19.0 ± 3.0 µM, and its rate of decline were similar to values measured after enflurane anesthesia in patients with normal renal function in whom postoperative concentrating ability was not impaired. Subclinical concentrating defects are associated with postoperative F⁻ levels of 33–50 µM, while clinically evident renal impairment only occurs when F⁻ levels of 80–100 µM are sustained for several days.

The results of this study are in agreement with those of animal studies in which rats with surgically induced chronic renal insufficiency and those treated with gentamicin, a nephrotoxic antibiotic, did not suffer further impairment of renal function when exposed to enflurane or to halothane. Similarly, studies of anephric surgical patients and those with severe renal insufficiency administered enflurane have not demonstrated abnormalities in F⁻ kinetics or further postoperative deterioration of renal function.

At first glance, the results of the present study and those from the literature might be thought surprising, since approximately half of an injected dose of NaF, and presumably half of the F⁻ resulting from metabolism of the fluorinated anesthetics, is excreted by the kidneys. If renal F⁻ excretion were impaired, one might have expected higher serum F⁻ levels, which could have caused further renal damage. The fact that this did not occur was probably due to extrarenal F⁻ redistribution, primarily into bone. Indeed, F⁻ has a marked affinity for all calcified tissues, replacing ions and groups normally associated with hydroxyapatite crystals forming fluorapatites. Movement into bone occurs rapidly, autoradiographic studies having demonstrated 18F in the skeleton of rats within 2 min of iv injection. Removal of F⁻ is very slow, with the half-life for total body excretion estimated to be 9 years. Further support for the speculation that F⁻ is sequestered into bone comes from studies of anuric patients in whom 80% of an injected dose of 18F was taken up by bone in 1 h.

The above data notwithstanding, there have been three case reports of deterioration of renal function after enflurane administration in surgical patients with preexisting renal insufficiency. In one case, F⁻ levels exceeded 90 µM, and the authors suggested that enzyme induction as a consequence of a previous enflurane anesthesia 6 weeks earlier might have caused the high F⁻ levels that led to the renal damage. However, induction of enflurane metabolism is rare, and enflurane itself does not induce its own metabolism. In the other two cases, the connection between enflurane administration and the postoperative exacerbation of renal damage was even more tenuous. Considering that more than 45 million enflurane anesthetics have been administered in the United States alone, this low incidence of adverse renal effects could be explained by chance.

In summary, both enflurane and halothane anesthesia were associated with slight improvements in postoperative renal function in surgical patients with preexisting chronic renal insufficiency. There were no differences in the renal effects of either anesthetic. Both are equally suitable if general anesthesia is indicated for operation in surgical patients with mild to moderate renal insufficiency.

### References


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Table 2. Preoperative and Postoperative Data (Mean ± SE)

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<thead>
<tr>
<th></th>
<th>Halothane</th>
<th>Enflurane</th>
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<tbody>
<tr>
<td></td>
<td>Cr (mg·dL⁻¹)</td>
<td>BUN (mg·dL⁻¹)</td>
</tr>
<tr>
<td>Preoperative</td>
<td>1.90 ± 0.06</td>
<td>32.6 ± 2.4</td>
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<tr>
<td>Postoperative Day 1</td>
<td>1.68 ± 0.06*</td>
<td>29.4 ± 2.4*</td>
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<tr>
<td>Postoperative Day 2</td>
<td>1.77 ± 0.09†</td>
<td>25.3 ± 2.5†</td>
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<tr>
<td>Postoperative Day 3</td>
<td>1.78 ± 0.10†</td>
<td>29.1 ± 2.6</td>
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* P < 0.005 versus preoperative.
† P < 0.05 versus preoperative.

Noncardiogenic Pulmonary Edema Following Laryngeal Obstruction

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Pulmonary edema is a recognized complication of acute upper airway obstruction, especially in the pediatric population.1,2 Interestingly, when pulmonary edema occurs, it usually follows relief of the obstruction. We present a case of noncardiogenic pulmonary edema that occurred in an adult patient after the treatment of upper airway obstruction following extubation of the trachea caused by a combination of laryngospasm and laryngeal edema.

REPORT OF A CASE

A 46-year-old man was admitted for an elective total hip arthroplasty. He had been in good health except for degenerative arthritis of both hips. Preoperatively, he had a hematocrit of 46%, total protein of 7.2

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mg/dl, serum albumin of 4.1 mg/dl and a pH of 7.43, Pco2 35 mmHg, and PaO2 87 mmHg, with a FiO2 of 0.2. Anesthesia was induced with diazepam 5 mg, thiopental 275 mg, and succinylcholine 120 mg, iv. The trachea was intubated easily with an 8-mm cuffed portex tube. Anesthesia was maintained with 70% nitrous oxide and 1.0% isoflurane along with 16 mcg metocurine iv. Cephalolin 1.0 g was administered iv at the beginning of the 4-hour surgery. Blood loss was estimated at 600 ml; the patient received 4 l lactated Ringer’s solution iv. At the end of the procedure, the paralysis was reversed with 2.5 mg of neostigmine and 0.5 mg glycopyrrolate iv. The trachea was extubated uneventfully with an end-tidal Pco2 of 38 mmHg. On admission to the recovery room, stridor, marked abdominal excursions, and intercostal retractions were evident with little movement of air. Ventilatory assistance was initiated with mask and Ambu-bag. Physical examination revealed no evidence of neuromuscular blockade and nerve stimulation revealed no posttetanic facilitation or fade in response to a tetanic stimulus. Because ventilation remained difficult to achieve with the mask and Ambu-bag, 40 mg of succinylcholine was administered iv with a partial resolution of the apparent upper airway obstruction, pH was 7.15, PaCO2 61 mmHg, and PaO2 160 mmHg. After the return of muscle function, audible grunting and stridor again were noted, along with a rocking respiratory motion, pH was then 7.17, PaCO2 57 mmHg, and PaO2 114 mmHg (with a FiO2 of 0.50-0.80). We decided to reintubate the trachea. During direct laryngoscopy following the administration of a second dose (40 mg) of succinylcholine iv, the vocal cords were closed, reddened, and edematous. Attempts to insert