Serum Inorganic Fluoride Concentrations during and after Halothane, Fluoxetine, and Methoxyflurane
Anesthesia in Man

CHARLES CREASER, M.D.,* AND ROBERT K. STOELTING, M.D.†

High-output renal failure occasionally follows methoxyflurane anesthesia.1,2 Recent evidence suggests that a metabolite of methoxyflurane, inorganic fluoride, is the nephrotoxin.3 The serum inorganic fluoride concentration and resulting renal dysfunction vary directly with the dose of methoxyflurane administered.3 Many patients who have developed renal dysfunction received unknown concentrations of methoxyflurane for prolonged periods, and some were obese. This study reports serum inorganic fluoride concentrations when low-dose methoxyflurane was administered for three or five hours to patients for whom narcotic premedication, thiamylal induction, and nitrous oxide–muscle relaxant supplementation during anesthetic maintenance were used. Serum inorganic fluoride changes were also measured in patients receiving nitrous oxide–halothane or nitrous oxide–fluoxetine anesthesia for three hours.

METHODS

Thirty-eight nonobese (weights 45–81 kg) adult patients (19–68 years old) with normal preoperative serum creatinine levels were studied during and after elective operations. All received morphine, 10–15 mg, and scopolamine, 0.4–0.6 mg, for premedication. Anesthesia was induced with thiamylal, 3–5 mg/kg, followed by succinylcholine, 1 mg/kg, to facilitate tracheal intubation. Ventilation was controlled with a volume ventilator. Halothane (five patients), fluoxetine (five patients), or methoxyflurane (17 patients) was administered for three hours with nitrous oxide, 60 per cent. Eleven additional patients received nitrous oxide–methoxyflurane for five hours. Nondepolarizing neuromuscular blockers were used as indicated. Systolic blood pressure was used as the main indicator of anesthetic depth. The delivered anesthetic concentrations were adjusted to the least amount necessary to maintain blood pressures near the preoperative values. Nitrous oxide–fentanyl was used to maintain anesthesia after the three- and five-hour observation times.

Venous blood samples for inorganic fluoride determinations were obtained immediately prior to induction, after one and three hours of anesthesia, and 2, 24, 48, and 72 hours after the conclusion of anesthesia. From patients who received methoxyflurane for five hours, an additional sample was obtained at the termination of anesthesia. Serum inorganic fluoride concentrations were measured with the fluoride ion-specific electrode.4 Serum creatinine was also measured for 24 to 72 hours postoperatively.

Arterial blood samples were obtained after one, three, and five hours of anesthesia for measurement of anesthetic concentration. Anesthetics were extracted into tetrachloroethylene and concentrations in mg/100 ml determined by gas chromatography.5 These values were converted to equivalent alveolar concentrations assuming a blood/gas partition coefficient of 13.6

Analysis of variance and linear regression were carried out for statistical analyses. P < 0.05 was considered significant.
RESULTS

Serum inorganic fluoride increased at rates of 6.0 and 6.8 μM/l/hour (not significantly different) during the first three hours of methoxyflurane anesthesia in the three- and five-hour exposure groups, respectively (fig. 1). The peak measured fluoride concentration (mean ± SE) occurred 24 hours postoperatively in both groups, and was greater in the patients receiving five hours of methoxyflurane (67.2 ± 8.8 cs. 43.9 ± 5.7 μM/l; P < 0.05). Fluoride decreased at similar rates in the two groups after the peak concentrations. Conversion of fluoride levels between 24 and 72 hours to log values and analysis by linear regression showed the fluoride half-life was 37.2 hours for the three-hour methoxyflurane exposure group and 38.5 hours for the five-hour methoxyflurane exposure group. Blood methoxyflurane concentrations converted to equivalent alveolar concentrations were 0.08 ± 0.02 vol per cent (range 0.04 to 0.12 vol per cent) for both groups.

Serum inorganic fluoride did not change significantly during or following nitrous oxide–halothane or nitrous oxide–fluoroexene anesthesia (table 1).

Serum creatinine did not change postoperatively (table 2).

DISCUSSION

Mazze et al. demonstrated that the severity of renal dysfunction following methoxyflurane anesthesia was proportional to the serum inorganic fluoride concentration. Hypematremia, serum hyperosmolality, and increased serum creatinine occurred in patients with peak mea-

<table>
<thead>
<tr>
<th>Table 1. Serum Inorganic Fluoride (μM/l) (Means ± SE)*</th>
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<td>Halothane (3 hours)</td>
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<td>Fluroxene (3 hours)</td>
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* Halothane and fluroxene were administered with nitrous oxide for three hours. Additional anesthesia after three hours was provided with nitrous oxide–fentanyl. Fluoride measurements were also made 5 and 24 hours after the start of anesthesia.
sured fluoride levels of 105.8 \( \mu \text{M} / \text{L} \). Patients with peak measured serum inorganic fluoride concentrations of 190.4 \( \mu \text{M} / \text{L} \) manifested these laboratory abnormalities plus polyuria, weight loss, and thirst. In their study, however, methoxyflurane was not administered in the usual clinical manner. Nitrous oxide supplementation was not used, and premedication was atropine alone. As a result, higher doses of methoxyflurane were necessary, often for several hours. More recently, Cousins et al. reported maximum serum inorganic fluoride concentrations of 45.7 \( \mu \text{M} / \text{L} \) 24 hours after low-dose (0.06–0.09 vol per cent), short-exposure (137 minutes) methoxyflurane anesthesia for cardiopulmonary bypass operations. However, cardiopulmonary bypass patients represent a very specialized group, exposed to decreased renal blood flow, hemodilution, hypothermia and nonpulsatile flow, and it is possible that fluoride changes would not be the same in the general surgical patient.

Our results indicated that serum inorganic fluoride values after three hours of nitrous oxide—methoxyflurane anesthesia for elective operations in nonobese patients without known renal disease were far below the levels reported to produce laboratory evidence of renal dysfunction. The maximum mean elevation of 43.9 \( \mu \text{M} / \text{L} \) 24 hours after three hours of methoxyflurane exposure approximates the peak concentration reported by Cousins et al. in cardiopulmonary bypass patients. As expected from a dose-related response, patients exposed to five hours of methoxyflurane anesthesia had greater and more prolonged elevations in serum inorganic fluoride (fig. 1). However, the rates of methoxyflurane biotransformation appeared to be the same in the two groups. This was suggested by similar rates of serum inorganic fluoride accumulation during the first three hours of anesthesia and nearly identical rates of decline 24 hours after anesthesia.

The low dose of methoxyflurane was possible because of narcotic premedication, barbiturate induction, and nitrous oxide supplementation, which decreased the amount of methoxyflurane necessary for operation. Anesthetic concentrations were kept low by using systolic blood pressure as a guide and by not attempting to produce surgical muscle relaxation with methoxyflurane.

Our results indicate that low-dose, short-duration methoxyflurane anesthesia results in a mean fluoride elevation below values reported to produce renal dysfunction. Serum creatinine did not increase during the first 24 hours postoperatively. However, individual variations in metabolism, the presence of drug-inducing enzymes, or inability to administer low doses of methoxyflurane despite adjuvant drugs could produce a greater response and hazard of renal impairment. Three patients in this study had peak serum inorganic fluoride concentrations greater than 100 \( \mu \text{M} / \text{L} \) at 24 hours. One patient received methoxyflurane (0.08–0.12 per cent) for three hours and had a peak measured serum fluoride concentration of 120 \( \mu \text{M} / \text{L} \). Peak fluoride concentrations were 112 and 110 \( \mu \text{M} / \text{L} \) in two patients exposed to five hours of methoxyflurane anesthesia despite maintenance of alveolar concentrations between 0.06 and 0.10 per cent.

Mrs. Susan Baldwin performed the fluoride determinations. Dr. Bruce E. Rodda performed the statistical analyses.

### References


### Table 2. Serum Creatinine (mg/100 ml) before and after Anesthesia and Operation (Means ± SE)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>24 Hours</th>
<th>48 Hours</th>
<th>72 Hours</th>
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<tbody>
<tr>
<td>Halothane</td>
<td>0.50</td>
<td>±0.16</td>
<td>±0.10</td>
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<td>(3 hours)</td>
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<tr>
<td>Fluoxetine</td>
<td>0.56</td>
<td>±0.25</td>
<td>±0.21</td>
<td>±0.33</td>
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<tr>
<td>(3 hours)</td>
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<td></td>
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<tr>
<td>Methoxyflurane</td>
<td>0.64</td>
<td>±0.21</td>
<td>±0.14</td>
<td>±0.30</td>
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<tr>
<td>(3 hours)</td>
<td></td>
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<tr>
<td>Methoxyflurane</td>
<td>0.50</td>
<td>±0.24</td>
<td>±0.20</td>
<td>±0.13</td>
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<td>(5 hours)</td>
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* Twenty-four-, 48- and 72-hour values are postoperative samples.

A Source of Errors in Assessing Neuromuscular Blockade

FELIX G. FREUND, M.D.,* AND JAYAD K. MERADI, M.D.†

The actions of muscle relaxants and their antagonists are commonly assessed by measuring the force of adduction of the thumb in response to stimulation of the ulnar nerve. The tetanic response is considered a more sensitive index of the degree of muscle paralysis than the single twitch because repetitive stimulation often uncovers appreciable muscle fatigue when single-twitch strength is relatively unaffected.1-5

During both tetanic electrical stimulation of the ulnar nerve and voluntary effort, the force of adduction of the thumb of the normal adult is 6–9 kg.6-10 In many reported studies an inadequate instrument has been used, namely, the Grass FT-03 transducer, which according to manufacturer’s specifications is capable of measuring a maximum of only 2 kg when fitted with the stiffest of four available springs.11-23 A second transducer, the FT-10, will measure up to 10 kg.

We calibrated one FT-03 and one FT-10 transducer using a set of accurate weights, a Grass polygraph, and an amplification system with the gain adjusted to give identical pen deflections when the transducers were each loaded with 2 kg. Figure 1 illustrates the results, which agree with the manufacturer’s specifications and clearly show that the response of the FT-03 was limited to 2.2 kg, while that of the FT-10 was linear to 10 kg. Although neither transducer had perfect linearity, deviations were small enough to be of no clinical significance. The Grass FT-03 transducer, intended for use in small-animal studies, is patently inadequate for measuring the force of adduction of the thumb of the adult, because this force is three to five times greater than the measuring capability of the transducer.

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