Methoxyflurane Anesthesia in Pediatric Patients:
Evaluation of Anesthetic Metabolism and Renal Function

Robert K. Stoelting, M.D.,* and Christine Peterson, R.N.†

Serum ionic fluoride concentrations during and following low-dose (6.0 mg/100 ml, 3 hours) methoxyflurane anesthesia and elective operation were measured in 13 pediatric patients (mean age 10.2 years; mean weight 34.5 kg). Peak measured serum ionic fluoride concentration was $21.6 \pm 3.3 \mu mol/1$ 24 hours after anesthesia. In a previously reported study of adult patients (47.5 years; 71.9 kg), the peak measured serum ionic fluoride concentration was $43.9 \pm 5.7 \mu mol/1$ 24 hours after low-dose (6.8 mg/100 ml, 3 hours) methoxyflurane anesthesia. Possible explanations for lower serum ionic fluoride concentrations in pediatric patients compared with adults include 1) slower metabolism of methoxyflurane; 2) increased renal clearance of ionic fluoride from the blood; 3) greater storage of ionic fluoride in bone; 4) more rapid methoxyflurane elimination in the postoperative period. Serum uric acid increased (4.4 to 6.4 mg/100 ml, not significant) 24 hours after anesthesia and operation, while blood urea nitrogen and serum creatinine and osmolality were unchanged postoperatively. (Key words: Anesthesiology, volatile: methoxyflurane; Biotransformation: methoxyflurane; Ions, fluoride; Anesthesia, pediatric.)

DOSE-RELATED polyuric renal dysfunction may follow methoxyflurane anesthesia. The nephrotoxin is a metabolite of methoxyflurane—ionic fluoride. The amount of ionic fluoride produced depends on the amount of methoxyflurane metabolized and the levels of serum ionic fluoride determine the extent of renal impairment.

A knowledge of the changes in serum ionic fluoride levels after methoxyflurane anes-

* Associate Professor of Anesthesia and Pharmacology.
† Anesthesia Research Nurse.

Received from Indiana University School of Medicine, Indianapolis, Indiana 46202. Accepted for publication May 7, 1974. Supported by a grant from Abbott Laboratories, North Chicago, Illinois 60064.

† Ionic fluoride is more precise than inorganic fluoride since fluoride which might not be detected with the ion-specific electrode could be present in inorganic complexes.2

Methods

Thirteen patients (age $10.2 \pm 0.7$ years (mean $\pm$ SE), range 6–12 years; weight $34.5 \pm 3.9$ kg, range 21–42 kg) undergoing elective noncardiac operations were studied. Premedication was with morphine (0.1–0.2 mg/kg) and atropine (0.1–0.3 mg) intramuscularly 60 minutes preoperatively. Anesthetic induction was with thiamylal (3–4 mg/kg), followed by succinylcholine (1 mg/kg) and tracheal intubation. Anesthetic maintenance was with nitrous oxide (60 per cent) and methoxyflurane in oxygen. Total flows were 5 l/min in all patients. Methoxyflurane was vaporized from a Copper Kettle and the delivered concentrations adjusted to the least amount necessary to maintain systolic blood pressure near the awake preoperative level. After 3 hours methoxyflurane was discontinued and any additional necessary anesthesia provided with nitrous oxide and
fentanyl. Ventilation was controlled with a volume ventilator. Competitive neuromuscular blockers were administered when necessary for skeletal muscle paralysis.

Peripheral venous blood samples were drawn before, during, and 2, 24, and 48 hours after methoxyflurane anesthesia. Serum ionic fluoride in these samples was measured with an ion-specific electrode.\textsuperscript{5} Arterial blood samples were drawn after 1 and 3 hours of methoxyflurane anesthesia. The methoxyflurane in the arterial samples was extracted into tetrachloroethylene\textsuperscript{6} and the anesthetic concentration measured by gas chromatography.

Data were analyzed with Student's t test; \( P < 0.05 \) was considered significant.

### Results

Serum ionic fluoride concentrations increased significantly from 2.0 ± 0.3 \( \mu \text{mol/l} \) (mean ± SE) to 11.0 ± 1.3 \( \mu \text{mol/l} \) after 3 hours of methoxyflurane–nitrous oxide anesthesia (Table 1). Arterial methoxyflurane concentrations were 5.6 and 6.0 mg/100 ml (2.8 to 8.0 mg/100 ml) after 1 and 3 hours of anesthesia, respectively. This corresponds to an alveolar concentration of about 0.07 vol per cent, assuming a blood-gas partition coefficient of 13.\textsuperscript{7} Peak measured serum ionic fluoride levels were 21.6 ± 3.3 \( \mu \text{mol/l} \) 24 hours after discontinuing methoxyflurane.

Serum uric acid increased from 4.4 ± 0.4 mg/100 ml preoperatively to 6.4 ± 0.8 mg/100 ml (not significant) on the first day after operation and was 5.1 ± 0.8 mg/100 ml at 48 hours. Blood urea nitrogen, serum creatinine, and osmolality did not change from control levels during the first 48 postoperative hours.

### Discussion

Peak measured serum ionic fluoride concentrations occurred 24 hours after discontinuing methoxyflurane in both adult\textsuperscript{8} and pediatric patients. In contrast, serum ionic fluoride levels were significantly less in pediatric patients during and after anesthesia (Table 1), the measured peak being about half that in adults (21.6 \( \mu \text{mol/l} \) vs. 43.9 \( \mu \text{mol/l} \)) who received methoxyflurane for 3 hours, at a mean arterial concentration of 6.8 mg/100 ml. Since serum ionic fluoride parallels renal dysfunction after methoxyflurane anesthesia,\textsuperscript{1} the low measured peak serum ionic fluoride in children may imply greater safety for methoxyflurane in pediatric patients. No evidence of renal dysfunction was detected in adults until serum ionic fluoride was 50 \( \mu \text{mol/l} \), and these changes may not be clinically significant.\textsuperscript{1} Serum hyperosmolality and polyuria occurred in adults when serum ionic fluoride was 90–120 \( \mu \text{mol/l} \). Indeed, no report of polyuric renal dysfunction in pediatric patients has appeared in the literature.

Possible reasons for lower serum ionic fluoride concentrations in children compared with adults include: 1) slower rates of methoxyflurane metabolism; 2) increased renal clearance of ionic fluoride from the blood; 3) greater storage of ionic fluoride in bone; 4) more rapid methoxyflurane elimination in the postoperative period.

Hepatic microsomal enzyme function may influence the extent of methoxyflurane metabolism. Indeed, phenobarbital enhances methoxyflurane metabolism, as evidenced by greater fluoride concentrations in bones.\textsuperscript{8} However, enzyme induction was not known to be present in any of the adult or pediatric patients. Nevertheless, enzyme induction from diet or inhaled pollutants may have been more likely in the adult patients. On this basis methoxyflurane metabolism would be
increased in adults and resulting serum ionic fluoride concentrations greater. In contrast, microsomal enzymes may be underdeveloped in the neonate. Furthermore, sex hormones may stimulate drug-metabolizing enzymes, and these substances would have been present in lesser amounts in the pediatric patients. If enzyme function remained underdeveloped in our 6–12-year-old patients, the extent of methoxyflurane metabolism would be less and the resulting serum ionic fluoride concentrations lower than corresponding modalities in adults. Since enzymatic activity for methoxyflurane metabolism was not known, one cannot further speculate as to the role this mechanism may have had in the different serum ionic fluoride concentrations observed in adults and children. Large doses of secobarbital (100 mg/kg) administered to phenobarbital-treated rats resulted in cytochrome P-450 destruction. The thioanalog of secobarbital, thiamylal (2–4 mg/kg), which was used for anesthetic induction in the present pediatric patients, was also used for induction in the adults with whom they are compared. Therefore, it would seem likely the impacts of thiamylal on cytochrome P-450 and subsequent methoxyflurane metabolism and resulting serum ionic fluoride concentrations, if any, would have been similar in the two groups.

As with adults, there was marked variability in the extents of methoxyflurane metabolism in the children as reflected by serum ionic fluoride concentrations. The greatest fluoride increase (48 μmol/l) occurred in a 6-year-old boy who weighed 21 kg. Serum ionic fluoride decreased to 23 μmol/l at 48 hours.

Renal clearance of fluoride would influence serum ionic fluoride concentrations. Evidence in man suggests that the kidney efficiently and rapidly eliminates fluoride by glomerular filtration. There is a variable amount of fluoride tubular reabsorption which is inversely related to urine flow. Indeed, the urine-concentration defect from excessive serum ionic fluoride concentrations may be prevented by maintaining diuresis. A comparison of ionic fluoride renal clearance abilities of pediatric and adult patients was not possible. However, glomerular filtration as reflected by serum creatinine was not changed following methoxyflurane anesthesia in either adult or pediatric patients. Postoperative urinary output, although not measured, was not recorded as inadequate or excessive in pediatric or adult patients.

Serum uric acid increased transiently after methoxyflurane but never exceeded normal levels. No evidence of renal dysfunction was suggested by blood urea nitrogen or serum creatinine or osmolality measurements. However, more sensitive indices, such as urine-concentrating ability or response to vasopressin, might have shown dysfunction when these measurements were unchanged.

Greater skeletal deposition of fluoride could account for lower serum ionic fluoride levels in pediatric patients compared with adults. About half the ionic fluoride resulting from methoxyflurane metabolism may be incorporated into the hydroxyapatite crystals of the mineral matrix of bone, from which it is slowly released. Metabolically more active bone in younger patients may have taken up more ionic fluoride and prevented serum ionic fluoride elevations as large as those in adults. Indeed, young rats deposit and retain greater amounts of dietary fluoride in bone than do adult rats. Furthermore, children (4–6 years) excrete less inorganic fluoride in the urine than adults. Perhaps children have more skeletal sites available for fluoride deposition and consequently more fluoride is deposited in bone and less is available for urinary excretion. Although increased skeletal storage of fluoride is an attractive explanation for the lower serum ionic fluoride concentrations in young vs. adult patients, it cannot be confirmed by our data.

Although the methoxyflurane doses were similar for adults and pediatric patients, it is possible that greater ventilation and cardiac output in children postoperatively could accelerate methoxyflurane elimination, leaving less anesthetic to be metabolized. Furthermore, smaller fat compartments in children could result in less anesthetic storage to maintain a metabolic pool for subsequent methoxyflurane metabolism. These differences would be reflected as lower serum ionic fluoride concentrations following methoxyflurane ad-
ministration in pediatric patients compared with adults. However, lower serum ionic fluoride concentrations in children were present during methoxyflurane anesthesia (i.e., 1 and 3 hours, table 1) before the above factors would have been important considerations. Therefore, postoperative serum ionic fluoride differences between children and adults due primarily to the above speculations seem unlikely.

The authors acknowledge the advice of Drs. Kenneth A. Haselby and Edmond E. Eger, II, in the preparation of this manuscript.

References