

Clinical Reports

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Maternal and Neonatal Plasma Inorganic Fluoride Levels after Methoxyflurane Analgesia for Labor and Delivery

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Methoxyflurane is widely used^{1,2} to provide analgesia during labor and delivery. Prior studies in surgical patients have associated the metabolic degradation of methoxyflurane with elevation of plasma inorganic fluoride levels and the occurrence of dose-related renal dysfunction.^{3,4} It has been suggested that this complication can be avoided with a low-dose technique of methoxyflurane administration,⁵ which would avoid elevations of plasma fluoride to above the critical nephrotoxic level of 80–100 $\mu\text{M/l}$.

Limited data are available to assess the nephrotoxic potential of methoxyflurane in the mother.⁶ Even fewer data are available to describe plasma fluoride levels in the neonate following methoxyflurane analgesia during normal labor and delivery.^{7,8} We have extended these data by measuring, in a large number of mothers and infants over 48 hours, the effects of methoxyflurane analgesia on

levels of plasma inorganic fluoride, blood urea nitrogen (BUN) and serum creatinine.

METHODS AND MATERIALS

Fifty normal multiparous women with term infants in the vertex presentation were studied during labor and delivery. Informed consent was obtained, and a venous blood sample was drawn for inorganic fluoride analysis before administration of methoxyflurane. Patients who had renal disease, those who had received potentially nephrotoxic agents, including certain antibiotics, within the preceding six weeks, and patients who had received halogenated anesthetics within the previous month were excluded from the study.

During labor, intermittent analgesia was provided by self-administration of methoxyflurane, using a Cyprane inhaler. The inhaler dial setting was 5, corresponding to a delivered concentration of approximately 0.3 per cent.⁹ The inhaler was charged with 15 ml liquid methoxyflurane and given to the patient after labor was well established and pains had become severe. Intermittent self-administration was supervised by an anesthesiologist to insure proper use. The inhaler was weighed before and after use and the total volume of methoxyflurane calculated. Small doses of promethazine and meperidine were injected intravenously during labor when analgesia was not adequate.

During delivery, analgesia with 50 per cent nitrous oxide in oxygen plus methoxyflurane vaporized from a Pentec 2 vaporizer (not exceeding 0.35 per cent) was provided, using a standard anesthesia machine with circle absorption system. An effort was made

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to avoid loss of consciousness during delivery. Pudendal nerve block was performed for episiotomy. Apgar scores of neonates were assigned 1 and 5 minutes after delivery.

Venous blood for measurement of inorganic fluoride levels was drawn from mothers prior to administration of methoxyflurane, at the time of delivery, and 2, 12, 24 and 48 hours after delivery. Umbilical venous blood was obtained from neonates at delivery. In about half of the neonates femoral venous blood was also obtained 12, 24 and 48 hours after delivery. Concentrations of fluoride were also measured in random samples of neonatal urine. Plasma and urinary inorganic fluoride levels were measured with a fluoride-specific electrode¹⁰ from frozen samples shipped to Abbott Laboratories in plastic tubes.

Additional blood samples for BUN and creatinine determinations were obtained from some mothers and infants at the time of delivery and 24 and 48 hours later. Blood samples were similarly obtained for inorganic fluoride analyses from an additional 12 "control" mothers and their neonates who received spinal anesthesia, epidural anesthesia, or no anesthesia.

RESULTS

Mean maternal height and weight were 156 cm (range 150-180) and 71.5 kg (range 48.2-131.4), respectively, in the patients receiving methoxyflurane analgesia. Thirteen mothers were considered obese (weight more than 80 kg).

The mean volume of methoxyflurane used during labor (49 patients) was 6.7 ml (range 1.1-18.2). The mean duration of intermittent use (50 patients) was 139 minutes (range 13-375), while the durations of continuous use for delivery (45 patients) averaged 12.3 minutes (range 1-37).

Analgesia with methoxyflurane during labor was considered satisfactory in 45 of the 50 mothers. Although the protocol limited the intermittent use of methoxyflurane to 15 ml per mother, two patients received 17.2 and 18.6 ml, respectively. This was the result of adding 15 ml of liquid methoxyflurane to the vaporizer when the wick was still moist from the previous day's use. Fluoride

TABLE 1. Plasma Inorganic Fluoride Concentrations ($\mu\text{M/l}$)

Samples taken	Methoxyflurane	
	Mothers	Neonates
Admission (pre-delivery)		
Mean \pm SEM	2.9 \pm 0.2	—
Range	0.7 to 10.5	—
Number	49	—
At delivery		
Mean \pm SEM	23.1 \pm 1.6	16.3 \pm 1.4
Range	7.0 to 53.8	3.7 to 49.2
Number	50	47
Postpartum, 2 hours		
Mean \pm SEM	22.7 \pm 1.8	—
Range	4.8 to 64.1	—
Number	48	—
Postpartum, 12 hours		
Mean \pm SEM	16.0 \pm 2.9	10.8 \pm 1.6
Range	4.4 to 74.5	2.5 to 30.2
Number	26	26
Postpartum, 24 hours		
Mean \pm SEM	13.0 \pm 1.6	12.5 \pm 2.1
Range	2.4 to 70.3	2.1 to 66.2
Number	48	32
Postpartum, 48 hours		
Mean \pm SEM	10.9 \pm 1.6	11.1 \pm 1.5
Range	2.3 to 43.9	2.7 to 34.1
Number	29	25

values in these two patients were, nevertheless, near the mean values for the other patients in the study group. Two mothers delivered in bed and three delivered on the table before nitrous-oxide-methoxyflurane analgesia could be given; hence, values for duration of continuous use of methoxyflurane in these five patients were zero and have been excluded from the calculated mean time.

Apgar scores of 7 or more were recorded for 47 neonates at 1 minute and for 48 neonates at 5 minutes. Apgar scores of only 1 at 1 minute in two neonates were attributed to unanticipated complications during delivery, unrelated to methoxyflurane administration. At 5 minutes, these two neonates had Apgar scores of 6 and 8, respectively.

Table 1 indicates the means and ranges of plasma inorganic fluoride concentrations in mothers and neonates who received methoxyflurane. In maternal plasma, mean peak level of inorganic fluoride of 23.1 $\mu\text{M/l}$ occurred at delivery, and the level was only slightly less two hours later (22.7 $\mu\text{M/l}$). Fluoride levels gradually declined thereafter,

however, to 16.0 $\mu\text{M/l}$ 12 hours postpartum and to 13.0 and 10.9 $\mu\text{M/l}$ 24 and 48 hours postpartum, respectively. Plasma inorganic fluoride increased to more than 50 $\mu\text{M/l}$ in two mothers, but no clinical or laboratory evidence of renal dysfunction was observed in either of these mothers or in their neonates. A slight elevation of serum creatinine to 1.7 mg/100 ml (normal 0.4–1.5) was found 24 hours after delivery in one mother. This was not considered significant. Eight weeks later, this patient's serum creatinine was 0.9 mg/100 ml. These changes in serum creatinine were associated with BUN levels of 7.0 and 9.0 mg/100 ml, respectively, both values being slightly below the normal range (10–20 mg/100 ml). BUN and creatinine determinations were not performed in the other patient who had a plasma inorganic fluoride elevation to more than 50 $\mu\text{M/l}$.

Plasma inorganic fluoride levels in nine "control" mothers at delivery averaged 1.3 \pm $\mu\text{M/l}$ (range 0.91–2.06). These did not differ significantly from maternal venous fluoride levels in the study group before administration of methoxyflurane (2.9 $\mu\text{M/l}$) ($P \geq 0.05$, Student's *t* test).

The mean concentration of inorganic fluoride in venous cord blood at the time of delivery in infants whose mothers received methoxyflurane analgesia was 16.3 $\mu\text{M/l}$. Twelve hours later the concentration of fluoride in peripheral venous blood had decreased to 10.8 $\mu\text{M/l}$, and it remained at about that level for the next 36 hours. Mean plasma inorganic fluoride values at delivery and early during the postpartum period were approximately 25 per cent lower in the neonates than in the mothers. Twenty-four hours after delivery fluoride levels in the mothers and neonates were essentially the same. The mean plasma fluoride concentration at the time of delivery in control infants whose mothers did not receive methoxyflurane was 1.2 \pm 0.19 $\mu\text{M/l}$ (range 0.95–1.39 $\mu\text{M/l}$). In the methoxyflurane and control groups, mean maternal plasma fluoride levels at the time of delivery were 23.1 and 1.2 $\mu\text{M/l}$, respectively, a significant difference ($P < .05$).

Random urine samples from neonates exposed to methoxyflurane showed a mean concentration of urinary fluoride of 72.5

$\mu\text{M/l}$. This indicates that the neonate is able to excrete the fluoride ion. Although the normal urinary fluoride level in neonates has not been established, the normal level in adults is 25–50 $\mu\text{M/l}$.^{**}

The limited data obtained in mothers (15 cases) and neonates (10 cases) exposed to methoxyflurane indicate that BUN and serum creatinine values remained within the normal range. All BUN levels were within normal limits, although levels in neonates exposed to methoxyflurane were slightly higher than those in the unexposed controls.

The peak maternal plasma inorganic fluoride levels were significantly related ($P \leq 0.05$) to the volume of methoxyflurane used ($r = 0.58$) and to the duration of methoxyflurane administration ($r = 0.45$).

DISCUSSION

We have shown that inhalation of methoxyflurane to produce analgesia during labor and delivery is associated with elevation of inorganic fluoride ion in the plasma not only of the mother, but also of the neonate. In neither mother nor infant, however, did the elevations fall into the dangerous range (80–100 $\mu\text{M/l}$)^{3,4,5} associated with nephrotoxicity. Inorganic fluoride remained elevated for several days after delivery, but gradually decreased, more rapidly in the mother than in the neonate.

Our data also show that the plasma levels of fluoride ion in mother and neonate can be predicted to some extent from the volume of methoxyflurane utilized.

After methoxyflurane analgesia, renal function, as measured by BUN and creatinine, remained essentially within normal limits during the first 48 hours after delivery. Similar results have been reported by Rosen *et al.*,⁶ and Creasser *et al.*⁸

Our studies included a greater number of patients, especially neonates, systematically followed for a longer period than in previous studies. We also determined inorganic fluoride levels in mothers and infants not exposed to methoxyflurane. We conclude that methoxyflurane can be safely administered by intermittent inhalation during labor

^{**} Abbott Laboratories: Personal communication.

as a means of providing analgesia, followed by continuous nitrous oxide-methoxyflurane analgesia during delivery, if low doses are utilized.

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Superior Vena Caval and Bronchial Obstruction during Anesthesia

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Superior vena caval syndrome may result from anaplastic carcinoma of the lung or other malignant disease.¹ It is rarely found in association with Hodgkin's disease,² although lymphomas may produce the syndrome.^{3,4} Lymphadenopathies can cause extrinsic compression of the mainstem bronchi.² The onset of such obstructive syndromes is usually insidious. The acute development of both problems during anesthesia for a staging laparotomy for Hodgkin's disease and subsequent management form the subject of this report.

REPORT OF A CASE

A 16-year-old girl who had Hodgkin's disease, mixed-cellular type, complained only of a non-productive cough, worst on recumbency, anorexia, and a 5-pound weight loss. The preoperative chest x-ray showed massive bilateral hilar adenopathy, and overpenetrated views revealed severe compression of the right lower lobe bronchus and

bronchus intermedius by subcarinal and perihilar nodes.

Meperidine, 50 mg, hydroxyzine, 50 mg, and atropine, 0.5 mg, were administered preoperatively. Anesthesia was induced with thiopental and endotracheal intubation was facilitated with succinylcholine. Nitrous oxide: oxygen (70:30) was supplemented with meperidine, 50 mg, and *d*-tubocurarine, 12 mg, iv. The patient remained supine. The systolic blood pressure quickly fell from 100 to 65 torr, and the pulse rate increased from 80 to 120 beats/min. These values returned to control levels only after administration of 1,000 ml of Ringer's lactate solution and calcium chloride, 200 mg, iv, but blood pressure remained labile.

Immediately after intubation, bilateral ronchi were noticed. Endotracheal suctioning was performed, and arterial blood gases determined. P_{iO_2} was 100 torr, P_{aO_2} 35 torr, pH 7.40. The oxygen concentration was increased to 50 per cent.

The laparotomy with splenectomy and node biopsies lasted three hours. Three liters of dextrose, 5 per cent in Ringer's lactate solution were administered. At the end, facial cyanosis and swelling at the site of the cervical node biopsies were evident. With F_{iO_2} 1.0, P_{aO_2} was 85 torr, P_{aCO_2} 35 torr, pH 7.20. The patient was taken to the recovery room with the endotracheal tube *in situ*. Chest-wall movement and spontaneous breath sounds were diminished on the right and were present only during the mid-portion of each respiratory cycle, compared with the left. The abdominal muscles were active during exhalation.

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