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Renal Responses to "Light" Methoxyflurane Anesthesia

W. D. Hetrick, M.D., B. Wolfson, M.B., F.F.A.R.C.S.,
D. A. Garcia, M.D., E. S. Siker, M.D.

Fifty-five patients scheduled for relatively short (1–2 hours) elective surgical procedures were divided into methoxyflurane and control groups. In both groups the potent inhalation agent used, methoxyflurane or halothane, was administered in the smallest amounts compatible with adequate anesthesia. Renal function was assessed by preoperative and postoperative measurements of serum urea, creatinine, sodium, and osmolality and urinary creatinine and osmolality and by calculation of creatinine, osmolar, and free-water clearances. In ten patients in each group serum and urinary fluoride levels were determined pre- and postoperatively. In addition, serum fluoride levels of 33 patients who had received methoxyflurane for vaginal deliveries were measured postpartum. No clinical or laboratory evidence of renal dysfunction was observed, and fluoride levels were markedly lower than those previously associated with renal toxicity. (Key words: Methoxyflurane; Nephrotoxicity; Fluoride.)

In 1966, Crandell *et al.*[1] described a syndrome of high-output renal failure following operation which they believed was associated with the administration of methoxyflurane (Penthrane). The syndrome was characterized by polyuria, dehydration, hypernatremia and elevated BUN. Additional findings included high serum osmolality coupled with low urinary osmolality and failure of exogenously administered pitressin to exert an antidiuretic effect. Since then, much evidence has accumulated to reinforce the etiologic association between methoxyflurane,[2–8] or more specifically the fluoride ion produced in its metabolism,[9, 10] and high-output renal failure. Perhaps the most conclusive proof of this association has been the work of Mazze and associates.[5, 10] However, a report by the National Research Council [11] has stressed the need for further investigation, especially under conditions closer to common clinical usage than those studied by Mazze *et al.*[5] The following is a report of such an investigation.

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Method

Healthy patients (ASA risk 1 or 2) with no known pre-existent renal problems, scheduled for elective operations which were expected to last between one and two hours, were considered eligible for this study. Random allocation to either methoxyflurane or control group was made by the toss of a coin prior to the preoperative visit. If the first patient scheduled for cholecystectomy was allocated to the methoxyflurane group, then the second such patient was placed in the control group. Patients having other operations were treated similarly, thus maintaining a balance between the two groups.

Every patient received a barbiturate, a narcotic, and atropine or scopolamine preoperatively. Thiopental (Pentothal) was used for induction, and anesthesia was maintained with nitrous oxide and oxygen, using at least 50 per cent nitrous oxide in a total flow of 4 l/min. Muscle relaxants, succinylcholine chloride (Anectine) to facilitate intubation and *d*-tubocurarine (Tubarine) during operation, were used as needed. Twenty-six patients received methoxyflurane and 29 patients, comprising the control group, received either halothane (Fluothane) or a narcotic. No specific course of fluid management was mandated by the protocol. Approximately 30 minutes after induction, light planes of anesthesia (characterized by such signs as lacrimation and increases in pulse rate and/or blood pressure) were deliberately achieved by reducing the inspired concentration of methoxyflurane or halothane or omitting intravenous increments of nar-

cotic. At this point the concentration of methoxyflurane or halothane was increased for approximately 15 minutes or a further increment of narcotic was administered. This sequence was repeated as often as necessary to assure administration of minimal quantities of anesthetic agent. Methoxyflurane was measured in arterial blood samples obtained just prior to the initial reduction in methoxyflurane concentration and at the end of the operation.

Delivered methoxyflurane concentrations in excess of 1 per cent were rarely used, and never after the initial 30-minute stabilization period. Because of this and because of constant efforts to reduce methoxyflurane concentrations, it is unlikely, although not impossible, that the levels of methoxyflurane ever exceeded those of the first arterial blood samples obtained. For this reason these initial levels are referred to as the "peak" levels in both Results and Discussion below.

A two-hour urine sample and a clotted venous blood sample were collected before operation and daily for three days thereafter. Urea, creatinine, sodium, and osmolality were measured in serum, and creatinine and osmolality in urine samples. In addition, both serum and urinary fluoride levels were de-

TABLE 1. General Patient Data*

	Control 29 Patients	Methoxyflurane 26 Patients
Age (years)	45.6 ± 2.2	48.0 ± 2.0
Weight (pounds)	145.3 ± 5.0	154.5 ± 5.2
Height (inches)	65.0 ± 0.6	66.1 ± 0.8
Surface area (m^2)	1.73 ± 0.03	1.80 ± 0.03
Duration of anesthesia (min)	105.7 ± 7.8 (30–225)	94.4 ± 5.3 (65–145)
Blood methoxyflurane (peak) (mg/100 ml)	—	8.6 ± 0.8 (1.3–16.0)
Blood methoxyflurane (final) (mg/100 ml)	—	3.2 ± 0.3 (0.6–6.4)

* Values are means ± SE. Values in parentheses are ranges. No statistically significant differences between groups were observed.

TABLE 2. Preoperative and Postoperative Serum and Urinary Data, Control Values and Values after Methoxyflurane

	Control Day	Day 1	Day 2	Day 3
BUN (mg/100 ml)				
Control	13.3±0.8 (29)	10.2±0.9 (29)*	9.4±0.6 (24)*	11.3±1.0 (27)
Methoxyflurane	12.6±0.8 (26)	9.9±0.7 (24)*	9.8±0.8 (23)*	10.4±0.8 (26)*
Creatinine (mg/100 ml)				
Control	1.14±0.03 (29)	1.16±0.04 (29)	1.11±0.04 (29)	1.12±0.04 (27)
Methoxyflurane	1.13±0.03 (25)	1.15±0.03 (26)	1.14±0.04 (23)	1.16±0.05 (26)
Serum sodium (mEq/l)				
Control	136.8±0.9 (29)	135.1±0.7 (29)	133.2±0.9 (29)*†	134.4±0.9 (27)
Methoxyflurane	137.8±0.4 (26)	133.9±1.1 (26)*	136.1±0.8 (23)	136.2±0.8 (26)
Serum osmolality (mOsm/l)				
Control	293.8±2.6 (29)	285.2±2.3 (29)*	282.3±2.4 (29)*	284.1±2.0 (27)*
Methoxyflurane	288.8±2.3 (25)	282.2±2.1 (26)	286.4±2.3 (22)	286.9±2.2 (26)
Urinary osmolality (mOsm/l)				
Control	613.1±67.5 (28)	417.6±45.3 (29)*	466.4±45.6 (29)	467.5±64.5 (27)
Methoxyflurane	575.2±59.4 (25)	412.0±43.9 (26)*	385.5±48.8 (23)*	411.4±45.3 (26)*
Serum fluoride (μmol/l)				
Control	1.39±0.18 (10)	1.30±0.13 (10)	1.15±0.06 (10)	1.22±0.08 (10)
Methoxyflurane	2.00±0.51 (10)	32.9±4.3 (10)*†	17.9±2.6 (10)*†	12.2±2.4 (10)*†
Urinary fluoride (μmol/2 hr/1.73 m^2)				
Control	7.8±1.3 (9)	7.7±1.4 (10)	9.3±1.3 (10)	9.5±2.6 (10)
Methoxyflurane	8.2±1.8 (10)	161.2±27.2 (10)*†	138.2±10.5 (10)*†	79.8±9.4 (10)*†

Data are means±SE. Numbers in parentheses are numbers of observations.
* Significant difference ($P < 0.05$) between control day and observation day within each group.
† Significant difference ($P < 0.05$)) between control and methoxyflurane groups.

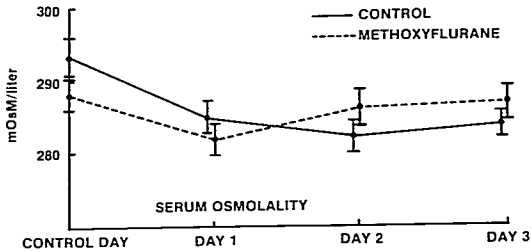

FIG. 1. Preoperative and postoperative serum osmolalities (mean ±SE) in control and methoxyflurane groups.

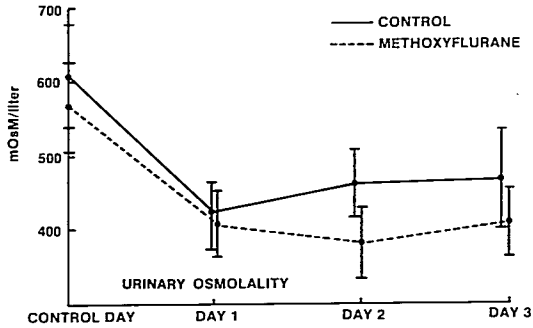

FIG. 2. Preoperative and postoperative urinary osmolalities (mean ±SE) in control and methoxyflurane groups.

termined using a fluoride-specific electrode ¶ in the last ten patients in each group. Creatinine, osmolar, and free-water clearances were calculated from these measurements.

Statistical comparisons between the values obtained on control and postoperative days were carried out using a two-tailed Student's t test. Comparisons between groups were also made for each day.

From an additional 33 patients who had received nitrous oxide, oxygen, and methoxyflurane for analgesia during vaginal delivery, blood samples were obtained within 12 to 36 hours of delivery and analyzed for fluoride content.

¶ Orion Research Incorporated, Cambridge, Massachusetts 02139.

Results

Table 1 shows the two groups to be comparable with respect to age, height, weight, surface area, and duration of anesthesia. It also shows the peak blood levels of methoxyflurane and levels at the end of the procedure. Table 2 shows the findings in blood and urine for the two groups before and after operation, and figures 1 through 4 are graphic representations of the serum and urinary changes in osmolality and fluoride.

In the control group, BUN was significantly decreased on the first and second postoperative days, serum sodium on the second postoperative day, serum osmolality on each postoperative day, and urinary osmolality on the first postoperative day. In the methoxyflurane group BUN was significantly decreased on each postoperative day, serum sodium and

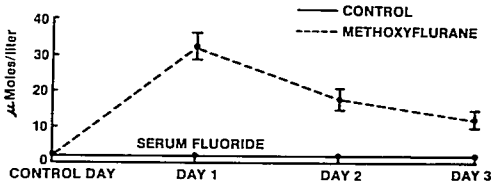

FIG. 3. Preoperative and postoperative serum fluoride levels (mean ±SE) in control and methoxyflurane groups.

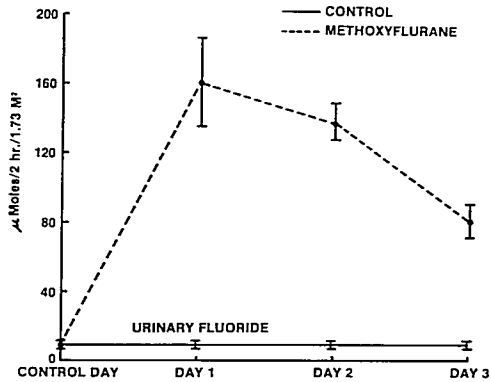

FIG. 4. Preoperative and postoperative urinary fluoride levels (mean ±SE) in control and methoxyflurane groups.

osmolality on the first postoperative day, and urinary osmolality on each postoperative day. Significant increases in urinary and serum fluoride were seen on each postoperative day in all patients receiving methoxyflurane. There were significant intergroup differences in sodium levels on the second postoperative day and fluoride levels in serum and urine on each postoperative day.

The highest individual blood urea nitrogen levels were 22 and 30 mg/100 ml in the methoxyflurane and control groups, respectively; these were associated with creatinine concentrations of 0.8 and 1.7 mg/100 ml. The highest individual creatinine levels were 2.1 mg/100 ml in both groups, associated with BUN's of 11.3 and 5 mg/100 ml in the methoxyflurane and control groups, respectively.

The upper limit of normal for serum osmolality in our laboratory is 305 mOsm/l. This was exceeded postoperatively in five patients in the methoxyflurane group and three patients in the control group. One patient in the methoxyflurane group had a serum sodium concentration of 147 mEq/l on the third postoperative day. This was the only patient in either group with serum sodium above the accepted upper limits of normal of 146 mEq/l.

Table 3 shows clearances calculated from the above values, and figure 5 is a graphic representation of osmolar and free-water clearance data. Free-water clearance, represented by the shaded areas, is obtained by subtracting osmolar clearance (area under the solid line) from urinary output (area under dotted line), and represents the number of milliliters of water which would need to be added to, or

subtracted from, urinary output to produce urine which is iso-osmotic with plasma. Thus, a negative free-water clearance represents a concentrated or hyperosmotic urine and a positive free-water clearance represents a dilute or hypo-osmotic urine.

In the control group a significant decrease in osmolar clearance and increase in free-water clearance were seen on the third postoperative day. In the methoxyflurane group a significant increase in creatinine clearance was seen on the first postoperative day and a significant increase in free-water clearance was seen on the second postoperative day. Intergroup comparisons revealed a significantly lower osmolar clearance in the control group than in the methoxyflurane group on the third postoperative day.

Postpartum serum fluoride levels in the obstetric patients are shown in table 4.

Discussion

Isolated blood levels of an anesthetic agent provide only an approximate indication of depth of anesthesia and an even less reliable index of total dose. However, the mean peak methoxyflurane concentration of 8.6 mg/100 ml, roughly equivalent to 0.66 MAC in the presence of 50 per cent nitrous oxide, representing an additional 0.5 MAC, suggests moderate planes of anesthesia even at peak depth. The final mean level of 3.2 mg/100 ml, equivalent to approximately 0.25 MAC, is less than the "MAC awake" value described by Stoelting *et al.*[12] for methoxyflurane, indicating that the concentration of methoxyflurane had been reduced adequately at the appropriate time. It should be noted, however, that peak values obtained ranged as high as 16.0 mg/100 ml, suggesting that some patients were more deeply anesthetized than necessary.

Although some estimate of total methoxyflurane dosage made available to the patient would be of theoretical value, the technique employed, involving a semiclosed circuit, rubber tubing, and constant attempts to reduce input concentration, made this impossible. However, it is of clinical interest that vaporizer settings during the maintenance phase were commonly in the 0 to 0.4 per cent range, and that methoxyflurane administration was needed only rarely after peritoneal closure.

Since total urinary outputs were not available in this study, free-water clearances were calculated from two-hour samples. It is realized that two-hour sampling is a far-from-optimum technique, due to variations in urinary output and also in urinary and serum

TABLE 3. Preoperative and Postoperative Renal Clearance Data, Control Values and Values after Methoxyflurane

	Control Day	Day 1	Day 2	Day 3
Creatinine clearance (ml/min/1.73 m²)				
Control	95.3 ± 7.2 (28)	130.8 ± 29.0 (29)	103.4 ± 17.8 (29)	78.1 ± 7.2 (27)
Methoxyflurane	81.2 ± 6.8 (26)	118.6 ± 10.2 (26)*	91.3 ± 7.0 (23)	88.4 ± 6.8 (26)
Osmolar clearance (ml/min/1.73 m²)				
Control	1.86 ± 0.15 (28)	2.09 ± 0.26 (29)	1.45 ± 0.19 (29)	1.18 ± 0.12 (27)
Methoxyflurane	1.77 ± 0.14 (25)	2.12 ± 0.26 (26)	1.56 ± 0.12 (23)	1.60 ± 0.17 (26)
Free-water clearance (ml/min/1.73 m²)				
Control	−0.62 ± 0.17 (28)	−0.17 ± 0.24 (29)	−0.26 ± 0.18 (29)	0.04 ± 0.18 (27)*
Methoxyflurane	−0.60 ± 0.17 (25)	−0.16 ± 0.20 (26)	0.02 ± 0.21 (23)*	−0.21 ± 0.19 (26)

Data are means ± SE. Numbers in parentheses are numbers of observations.
* Significant difference ($P < 0.05$) between control day and observation day within each group.
† Significant difference ($P < 0.05$) between control and methoxyflurane groups.

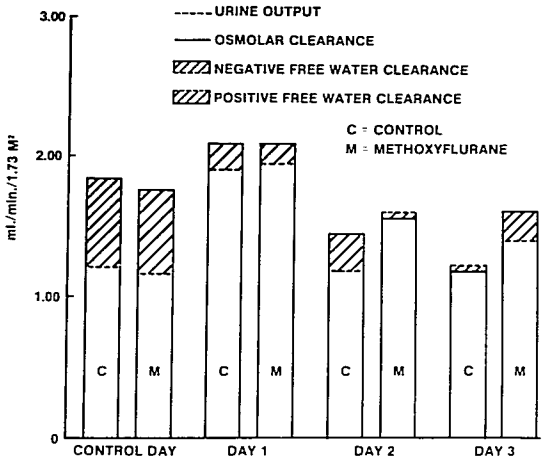

FIG. 5. Mean preoperative and postoperative osmolar and free-water clearances in control and methoxyflurane groups.

osmolality from one such period to another within the day. However, it was known that the values obtained from these samples were accurate, being minimally dependent on patient or nursing-staff cooperation. The same could not be said had an attempt to obtain 24-hour urine collections been made. Further, it was hoped that the constancy of hospital routine with regard to the time and amount of food and fluid intake would minimize variations and enhance reliable comparisons between the two groups. We feel that the results have justified this hope.

Free-water clearance is accepted as an indication of the ability of the kidney to concentrate or dilute urine, although it does not indicate the appropriateness of either response. Inappropriate diuresis, however, would be associated with a positive free-water clearance. Although positive free-water clearances were observed on one observation day in each group, consistently positive free-water clearances throughout the observation period were not seen in either group. Thus, neither group showed the characteristic continued inappropriate polyuria of methoxyflurane nephrotoxicity. Further, no significant difference between free-water clearances in the two groups was observed at any time.

The significant reductions in urinary osmolality seen on each postoperative day in the present methoxyflurane group are similar to the results cited by Merkle *et al.*[12] as a possible methoxyflurane effect. In the latter series, however, the urinary osmolalities in the control group remained steady throughout the observation period and were significantly different on each day from those in the methoxyflurane group. In the present study, a reduction in urinary osmolality was also observed postoperatively in the control group. While the magnitude of this decrease was not statistically significant after the first day, it was nevertheless sufficient to negate any statistical difference between control and methoxyflurane groups. Merkle[12] did not report serum osmolalities. In the present study the significant serum hypo-osmolality seen in the methoxyflurane group on the first day returned towards but not beyond normal on the successive two days, while hypo-osmolality persisted in the control group throughout the observation period. Viewed as isolated findings, therefore, the changes in serum and urinary

TABLE 4. Serum Fluoride Levels in 33 Postpartum Patients

	Mean ± SE	Range
Duration of anesthesia (min)	28.8 ± 2.3	10–75
Serum fluoride (μmol/l)	11.6 ± 1.4	3.4–44.9

osmolalities in the methoxyflurane group could represent a normal renal response to a reduction in serum osmolality. Mazze *et al.*[8] reported slight hyponatremia and hypo-osmolality in their control group, a response similar to that described as a normal reaction to operation and anesthesia by Hayes and Goldenberg.[14] The latter authors also described an increase in urinary osmolality which may occur even in the face of marked serum hypo-osmolality, and they suggest that this results from "forced" ADH secretion during operation. In the present series, serum hypo-osmolality occurred in the control group throughout the observation period, but was seen in the methoxyflurane group on the first postoperative day only. Hyponatremia was a significant finding in the control group on the second postoperative day only and in the methoxyflurane group on the first postoperative day only. Although urinary osmolalities were greater in the control than in the methoxyflurane group, these differences were not statistically significant. Thus, neither the data from the methoxyflurane group nor the data from the control group in this study conformed to this previously-described "normal" pattern.[14]

Possible explanations for differences between the two groups include: 1) In the absence of significant intergroup differences, the results occurred by chance. 2) Differences in water and electrolyte intake during and after operation, which were not controlled in this study, resulted in apparent differences in response. 3) The fluoride produced by metabolism of methoxyflurane, albeit in modest amounts, produced a short-lived antagonistic effect on the action of the "forced" ADH secretion described previously, allowing the kidney to resume normal function at an earlier time. This explanation would support the suggestion that fluoride ion produced by methoxyflurane metabolism inhibits the effect of ADH as a dose-related phenomenon. Excessive inhibition of ADH in the patients receiving methoxyflurane was not observed in this study, since a positive free-water clearance was seen on the second postoperative day only. No evidence of dehydration was seen in any patient, and serum sodium changes revealed no significant hypernatremia. Six of 12 patients in Mazze's[8] series had sodium levels in excess of 146 mEq/l, and two had levels in excess of 157 mEq/l.

Serum and urinary fluorides were significantly elevated in all patients receiving methoxyflurane in this study. However, the levels attained were lower than those associated with nephrotoxicity in previous reports.[9, 10] Thus, the maximum serum level in the present series was 60.5 μmol/l. This was considerably less than the 275 μmol/l observed in one patient by Taves.[9] It was also less than the mean peaks of 190.4 and 105.8 μmol/l, respectively, in patients with overt renal dysfunction and laboratory evidence of dysfunction reported by Mazze *et al.*[10] Cousins *et al.*[15] observed no renal problems in a series of patients undergoing open-heart surgery under light methoxyflurane anesthesia. The mean postoperative fluoride levels were slightly higher than those reported here. It has been suggested by Gillies[16] that a serum fluoride level below 50 μmol/l is unlikely to be associated with renal dysfunction. In the present study, the one patient with a level of 60.5 μmol/l developed no renal problems.

Crandell *et al.*[1] reported elevations of BUN in some of their patients, and both Mazze *et al.*[8] and Merkle *et al.*[13] cited significant increases in serum creatinine in their patients who received methoxyflurane. However, the highest mean postoperative concentrations of creatinine were 1.22 and 1.19 mg/100 ml in Mazze's and Merkle's series, respectively. As Dobkin[17] has pointed out, increases in serum creatinine which remain within the accepted normal range, even if statistically significant, can hardly be considered conclusive evidence of glomerular dysfunction. The question of interpretation does not arise in the present study, however, since no significant increase in either BUN or serum creatinine occurred at any time in the postoperative period.

It is difficult to compare serum osmolality figures obtained in the present study with those of Mazze *et al.*[8] because of preoperative differences. However, the marked difference between the methoxyflurane and control groups in Mazze's study was not seen in the present one.

Although the results of this study do not preclude a renal effect of methoxyflurane, even when used as described, for operations of the duration described, they do not suggest the production of renal dysfunction. The absence of such dysfunction combined with the low serum fluoride levels obtained lends further support to the etiologic link between the two. The results also suggest that measurement of postoperative fluoride levels provides a method of assessing the safety of any technique involving the use of methoxyflurane. For example, low fluoride levels were obtained in obstetric patients, and no renal complications were observed. The one relatively high level (44.9 μmol/l) followed an hour of anesthesia in a patient who had an obstetric complication. Although no postpartum problem was seen in this patient, the fluoride level does reinforce the fact that, when using methoxyflurane, as time wears on caution must not be allowed to wear off.

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