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Anesthetic Biotransformation and Renal Function in Obese Patients during and after Methoxyflurane or Halothane Anesthesia

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Anesthetic biotransformation and renal function were studied in obese adult patients (148 ± 8 kg; mean ± SE) anesthetized for three hours with 60 per cent nitrous oxide plus either methoxyflurane or halothane for elective jejunoileal small-bowel-bypass operations. There was no evidence of persistent renal dysfunction in any patient postoperatively, but serum osmolality was elevated 72 hours after methoxyflurane anesthesia. Urine concentrating ability was not determined. Peak serum ionic fluoride concentration was 55.8 ± 5.8 μM/l two hours after discontinuation of methoxyflurane. Urinary ionic fluoride and oxalate excretions increased postoperatively. Compared with previously reported data from nonobese patients, serum ionic fluoride concentrations in obese patients increased more rapidly during methoxyflurane anesthesia and peaked higher and sooner after discontinuation of methoxyflurane.

The peak serum ionic fluoride concentration was 10.4 ± 1.5 μM/l at the conclusion of halothane anesthesia, significantly more than the corresponding value in nonobese patients.

Intraoperative liver biopsies from 23 of 27 patients showed moderate to severe fatty metamorphosis. Fatty liver infiltration may have increased hepatic anesthetic uptake and exposed more methoxyflurane or halothane to hepatic microsomal enzymes.

The more rapid elevation and higher peak levels of serum ionic fluoride following methoxyflurane, and to a lesser extent following halothane, may reflect increased anesthetic biotransformation in obese compared with nonobese patients. To avoid excessive serum ionic fluoride elevations the authors recommend limiting low-dose methoxyflurane anesthesia delivered to obese patients with potential fatty liver infiltration to no more than three hours. (Key words: Anesthetics, volatile, methoxyflurane; Anesthetics, volatile, halothane; Biotransformation, methoxyflurane; Complications, obesity.)

SINCE 1966, reports linking methoxyflurane anesthesia to postoperative renal tubular dysfunction have appeared.[1,2] It is now established that the specific renal effect is impaired urine-concentrating ability directly related to the total methoxyflurane dose administered and to the resulting serum levels of ionic fluoride following metabolism of methoxyflurane.[3,4]

Some investigators have questioned the relationship between obesity and methoxyflurane-induced renal dysfunction. Conceivably, the high lipid solubility of methoxyflurane and the increased amount of adipose tissue in obese patients could combine to maintain a source for continued methoxyflurane biotransformation and resulting prolonged elevations of serum ionic fluoride.[5,6] Indeed, there have been reports of renal dysfunction in obese adults following methoxyflurane anesthesia.[7–9]

The present study evaluated anesthetic biotransformation and renal function in obese patients anesthetized with methoxyflurane or halothane with the usual adjuvant drugs.

Methods

Thirty-one chronically obese adults (148 ± 8 kg, mean ± SE) without known renal or hepatic disease were randomly assigned to receive either methoxyflurane or halothane anesthesia for jejunoileal small-bowel-bypass operations (table 1). All patients received morphine (10–15 mg) and scopolamine (0.4–0.6 mg) intramuscularly for preanesthetic medication. Anesthesia was induced with

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TABLE 1. General Patient Data (Means ± SE)*

	Methoxyflurane	Halothane
Number of patients	19	12
Weight (kg)	153 ± 9.6	142.5 ± 7.6
Age (years)	30.9 ± 2.0	35.2 ± 1.6
Duration of anesthesia (min)	180	180

*There was no significant difference between groups.

thiamylal (2–4 mg/kg) followed by succinylcholine (1 mg/kg) for endotracheal intubation. Methoxyflurane from a Pentomatic vaporizer or halothane via a Copper Kettle was administered with 60 per cent nitrous oxide (3 liters nitrous oxide plus 2 liters of oxygen) for three hours. Delivered anesthetic concentration was adjusted to the least amount necessary to maintain systolic blood pressure (measured continuously via an indwelling radial artery catheter) near preoperative values. For example, Pentomatic concentration dial settings were usually 0.1 to 0.3 vol/100 ml and halothane concentrations as predicted from the Copper Kettle oxygen flow were about 0.5 vol/100 ml during maintenance of anesthesia. After three hours anesthesia was maintained with fentanyl and 60 per cent nitrous oxide.

Ventilation was controlled with a volume-limited ventilator and hourly blood–gas measurements confirmed arterial oxygen partial pressures greater than 80 torr and arterial carbon dioxide partial pressures 28–35 torr in all patients. Dimethyl tubocurarine was administered to produce skeletal muscle relaxation. Disposable anesthesia breathing circuits (not including soda lime) were employed to minimize exposure to trace amounts of inhalation anesthetics from previous anesthesia machine use. Furthermore, at least three days of routine use of anesthetic machines, during which time methoxyflurane was not administered, were interposed between studies.

Lactated Ringer's solution was administered at a rate of 3–5 ml/kg/hr up to a maximum of approximately 3 liters during operation. Blood transfusion was not done. Open-wedge biopsies were obtained from 27 patients during operation.

Venous blood samples were drawn immediately before induction of anesthesia, after one and three hours of anesthesia, and 2, 5, 24, 48, and 72 hours after discontinuation of methoxyflurane or halothane. Serum ionic fluoride was measured with an ion-specific fluoride electrode.[9] Additional preanesthetic and 24-, 48-, and 72-hour postanesthetic venous blood samples were analyzed for blood urea nitrogen, serum uric acid, creatinine, and osmolality.

Arterial blood samples were collected after one and three hours of methoxyflurane anesthesia. Methoxyflurane was extracted into tetrachlorethylene and gas chromatography was used to determine anesthetic concentration in mg/100 ml.[10]

Twenty-four-hour urine collections from the day before operation and for three days beginning at 6 AM the morning following operation were analyzed for ionic fluoride, oxalate, osmolality, creatinine clearance and total volume.

Preanesthetic control values were compared with the postoperative values within each group, and comparisons between groups were made utilizing a two-tailed Student's t test. Significance was defined as $P < 0.05$.

Results

Serum ionic fluoride concentrations increased ($P < 0.05$) during methoxyflurane administration, with the measured peak of 55.8 ± 5.8 μM/l (mean ± SE, range 19–105 μM/l) occurring two hours after discontinuation of methoxyflurane (table 2). Serum ionic fluoride concentrations five hours after discontinuation of methoxyflurane had decreased to 34.3 μM/l ($P < 0.05$). After one and three hours of anesthesia, arterial methoxyflurane concentrations were the same, 3.9 ± 0.5 mg/100 ml (equivalent alveolar concentration about 0.047 vol/100 ml). Extreme variability in extent of methoxyflurane biotransformation was evidenced by peak serum ionic fluoride concentrations in four patients of 90, 90, 92 and 105 μM/l two hours after discontinuation of methoxyflurane. Arterial methoxyflurane concentrations in these patients were similar to

TABLE 2. Mean Serum Ionic Fluoride Concentrations (μM/l) ± SE before, during and after Anesthesia

	Methoxyflurane–Nitrous Oxide Anesthesia	Halothane–Nitrous Oxide Anesthesia
Control	1.9 ± 0.3 (19)	2.0 ± 0.3 (12)
During anesthesia		
1 hour	21.4 ± 2.4 (18)*†	4.8 ± 0.8 (12)*
3 hours	41.8 ± 4.4 (19)*†	10.4 ± 1.5 (12)*
After methoxyflurane or halothane discontinued		
2 hours	55.8 ± 5.8 (19)*†	7.6 ± 1.3 (12)*
5 hours	34.3 ± 7.1 (7)*	
24 hours	30.7 ± 4.3 (19)*†	1.9 ± 0.4 (12)*
48 hours	19.3 ± 3.2 (17)*†	1.2 ± 0.1 (11)
72 hours	16.4 ± 3.4 (18)*†	1.3 ± 0.1 (11)

Numbers in parentheses are numbers of observations.
* $P < 0.05$ compared with control.
† $P < 0.05$, methoxyflurane vs. halothane.

those present in patients with lower serum ionic fluoride values. After three hours of halothane administration serum ionic fluoride concentration increased ($P < 0.05$) to 10.4 ± 1.5 μM/l (2.3 to 19 μM/l).

Urinary ionic fluoride excretion was 107.2 ± 10.9 μM/l before methoxyflurane and 3,840 ± 939 μM/l ($P < 0.05$) the first postoperative day (table 3). In the same group urinary oxalate increased from 31.9 ± 3.1 mg/24 hours to 481.2 ± 170 mg/24 hours ($P < 0.05$) on the first postoperative day. Urinary fluoride and oxalate excretion decreased 48 and 72 hours postoperatively but remained significantly above controls. These values did not change significantly after halothane anesthesia. Conceivably, greater urinary ionic fluoride excretion could have occurred on the day of halothane anesthesia and operation, but this cannot be documented since urine collection was not started until 6 AM on the morning following anesthesia and operation.

Prolonged alterations in renal function tests were not detected in any patient during the first 72 hours postoperatively (table 3). However, serum osmolality was significantly increased 72 hours following methoxyflurane administration. In addition, serum uric acid was somewhat elevated above normal values (4–7 mg/100 ml) in both anesthetized groups preoperatively and postoperatively. Serum uric acid increased the first day after methoxyflurane anesthesia but the change was not statistically significant. However, the serum uric acid level was significantly higher than in the halothane group on the first postoperative day. Intraoperative liver biopsies from 23 of 27 patients biopsied showed moderate to severe fatty metamorphosis.

Discussion

Serum ionic fluoride increased more rapidly during methoxyflurane anesthesia in obese adult patients than in previously reported nonobese patients (table 4).[11] In addition, peak serum ionic fluoride concentrations were greater and occurred sooner after discontinuation of methoxyflurane in obese patients. For example, peak serum ionic fluoride in obese patients was 55.8 μM/l two hours after discontinuation of methoxyflurane, and levels were decreasing five hours after discontinuation of methoxyflurane. In contrast, the peak serum ionic fluoride concentration of 43.9 μM/l occurred 24 hours after discontinuation of methoxyflurane administration in nonobese adults.[11] However, since serum ionic fluoride values in nonobese patients two to 24 hours after discontinuation of methoxyflurane were not obtained, it is possible that the 24-hour serum ionic fluoride concentration may not reflect the extent or time of maximum change. Finally, small but

TABLE 3. Blood and Urine Values (Mean ± SE)

	Preoperative	Postoperative		
		24 hours	48 hours	72 hours
Blood urea nitrogen (mg/100 ml)				
Methoxyflurane	10.8 ± 1.4 (12)	6.8 ± 1.1 (12)	6.1 ± 0.7 (12)	6.8 ± 0.9 (11)
Halothane	9.9 ± 0.7 (11)	6.8 ± 0.6 (12)	6.6 ± 0.8 (10)	7.2 ± 1.0 (11)
Serum uric acid (mg/100 ml)				
Methoxyflurane	7.7 ± 0.7 (12)	8.7 ± 0.71 (12)	7.7 ± 0.7 (12)	8.2 ± 1.1 (12)
Halothane	7.3 ± 0.4 (12)	6.8 ± 0.4 (12)	6.6 ± 0.6 (10)	7.1 ± 0.4 (11)
Serum creatinine (mg/100 ml)				
Methoxyflurane	0.8 ± 0.1 (18)	0.6 ± 0.1 (18)	0.6 ± 0.1 (18)	0.7 ± 0.1 (18)
Halothane	1.0 ± 0.1 (11)	0.9 ± 0.1 (12)	0.8 ± 0.1 (11)	0.8 ± 0.1 (11)
Serum osmolality (mOsm/kg)				
Methoxyflurane	282.3 ± 2.1 (12)	284.0 ± 1.5 (12)	279.4 ± 2.6 (12)	289.9 ± 3.1*† (12)
Halothane	280.4 ± 4.5 (12)	278.3 ± 1.7 (12)	280.1 ± 1.2 (12)	279.8 ± 1.6 (11)
Creatinine clearance (ml/min)				
Methoxyflurane	125.5 ± 14.5 (9)	155.9 ± 21.2 (8)	149.9 ± 25.9 (9)	129.6 ± 26.5 (5)
Halothane	106.6 ± 12.5 (9)	189.7 ± 34.0 (9)	103.7 ± 19.3 (8)	114.1 ± 27.2 (6)
Urinary ionic fluoride (μM/l)				
Methoxyflurane	107.2 ± 10.91 (11)	3,840 ± 939*† (10)	2,366 ± 406*† (10)	1,618 ± 358*† (9)
Halothane	64.3 ± 12.9 (11)	95.6 ± 28.2 (9)	56.1 ± 10.4 (9)	72.1 ± 6.8 (8)
Urinary oxalate (mg/24 hr)				
Methoxyflurane	31.9 ± 8.1 (10)	181.2 ± 170.0*† (10)	231.4 ± 59.5*† (10)	131.6 ± 32.3*† (9)
Halothane	20.4 ± 6.6 (9)	26.3 ± 8.7 (7)	30.6 ± 12.1 (9)	21.9 ± 9.4 (7)
Urinary osmolality (mOsm/kg)				
Methoxyflurane	702.4 ± 63.2 (10)	692.7 ± 77.4 (10)	662.7 ± 90.4 (10)	618.0 ± 79.7 (12)
Halothane	572.1 ± 72.6 (12)	506.7 ± 58.1 (12)	479.7 ± 71.1 (10)	535.6 ± 84.0 (10)
Urine volume (ml/24 hr)				
Methoxyflurane	1,687 ± 362 (11)	1,571 ± 167 (12)	1,477 ± 206 (12)	1,473 ± 232 (12)
Halothane	1,901 ± 336 (12)	1,774 ± 323 (12)	1,755 ± 340 (12)	1,551 ± 177 (12)

Numbers in parentheses are numbers of observations.
* $P < 0.05$ compared with control.
† $P < 0.05$, methoxyflurane vs. halothane.

TABLE 4. Mean Serum Ionic Fluoride Concentrations (μM/l) ± SE in Obese *vs.* Nonobese Patients

	Obese (153 ± 9.6 kg)	Nonobese[11] (71.9 ± 4.9 kg)
Control	1.9 ± 0.3 (19)	1.2 ± 0.1 (17)
During methoxyflurane–nitrous oxide anesthesia		
1 hour	21.4 ± 2.4 (18)*	12.0 ± 1.4 (17)
3 hours	41.8 ± 4.4 (19)*	20.1 ± 2.7 (17)
After methoxyflurane discontinued		
2 hours	55.8 ± 5.8 (19)*	24.3 ± 2.4 (16)
5 hours	34.3 ± 7.1 (7)	
24 hours	30.7 ± 4.3 (19)	43.9 ± 5.7 (17)
48 hours	19.3 ± 3.2 (17)	25.4 ± 2.4 (9)
72 hours	16.4 ± 3.4 (18)	17.2 ± 3.1 (9)

* $P < 0.05$, obese *vs.* nonobese.

statistically significant increases in serum ionic fluoride occurred during and following halothane anesthesia in obese but not in nonobese patients. These serum ionic fluoride data suggest increased methoxyflurane and halothane biotransformation by obese patients. Possible explanations included a greater fraction of administered anesthetic dose exposed to hepatic microsomal enzymes and/or increased hepatic microsomal enzyme activity in obese compared with nonobese patients.

Fatty liver infiltration may occur in 75 per cent of obese patients.[12] In the present study, 23 of 27 obese patients studied had moderate to severe fatty liver infiltration. Considering the increased hepatic lipid content of the obese patients and the high lipid solubility of methoxyflurane and halothane, we speculate that fatty liver infiltration may increase hepatic anesthetic uptake and expose more methoxyflurane or halothane to the hepatic microsomal enzymes for biotransformation.

A greater fraction of the administered methoxyflurane or halothane might undergo biotransformation if large amounts of anesthetic were stored in fat, since adipose tissue would serve as a reservoir to provide drug for continued delivery to the liver. Although fat has a large capacity for storing methoxyflurane and halothane, the small blood flow to fat (about 5 per cent of the cardiac output)[13] would limit anesthetic delivered to adipose tissue. Furthermore, increasing obesity may be associated with less than a commensurate increase in blood flow to fat, so that blood flow to this tissue (ml/100 g/min) may be less in obese than nonobese patients.[14] Poor blood flow to fat plus the low dose (concentration times duration of administration) of methoxyflurane or halothane administered to obese patients makes it unlikely that enough additional anesthetic was stored in the enlarged fat compartment to maintain a source for prolonged hepatic biotransformation. Indeed, previously predicted prolonged elevations of serum ionic fluoride concentrations in obese patients following methoxyflurane anesthesia did not occur. However, longer administration of methoxyflurane or measurements beyond 72 hours postoperatively might have demonstrated sustained elevations of serum ionic fluoride in obese compared with nonobese patients.

Differences between obese and nonobese patients with respect to the distribution of cardiac output might alter the extent of anesthetic biotransformation. For example, if splanchnic blood flow were increased in chronically obese patients, a larger portion of the cardiac output would pass through the liver before reaching the pulmonary circulation, thereby exposing a greater fraction of the administered methoxyflurane or halothane to hepatic microsomal enzymes. However, without measurements of hepatic blood flow during anesthesia this remains speculative.

Increased hepatic microsomal enzyme activity in obese patients could increase anes-

thetic biotransformation. For example, drugs, cigarette smoking, patient age and sex, and dietary habits may influence hepatic microsomal enzyme activity.[15,16] None of our obese patients was receiving medications known to produce enzyme induction preoperatively. Cigarette smoking habits, patient age, and numbers of men and women were similar for obese and nonobese patients. Dietary habits were probably different and may have influenced microsomal enzyme function, though this cannot be quantitated.

Arterial methoxyflurane concentrations were less in obese than nonobese patients (3.9 *vs.* 6.9 mg/100 ml) despite the similar methoxyflurane concentrations delivered in the two groups. The reason for lower arterial methoxyflurane concentrations in obese patients is not clear. However, greater methoxyflurane biotransformation in obese patients could result in lower arterial methoxyflurane concentrations than in nonobese patients.

Renal clearance of anesthetic metabolites could also influence serum ionic fluoride concentrations. That obese patients were able to clear methoxyflurane metabolites from the serum to an extent similar to clearance in nonobese patients was suggested by urinary ionic fluoride and oxalate excretions postoperatively. For example, the maximum urinary ionic fluoride excretion after methoxyflurane anesthesia in obese patients (3,840 μM/l) was similar to that found by Cousins *et al.*[17] (3,122 μM/l) in nonobese patients. In the same obese patients urinary oxalate excretion was 481 mg/24 hours, compared with 421 mg/24 hours found by Silverberg *et al.*[18] in nonobese patients. Conceivably, urinary ionic fluoride and oxalate excretion would have been greater in obese than in nonobese patients during and in the first few hours after anesthesia and operation, corresponding to the time when serum ionic fluoride concentrations suggested greater biotransformation in the obese group. However, urine collections were not initiated until 6 AM on the morning after operation, when differences in serum ionic fluoride concentrations were less. Therefore, similar urinary ionic fluoride and oxalate excretions in obese and nonobese patients were not unexpected.

The question whether obese patients are more vulnerable to methoxyflurane-induced renal dysfunction remains unanswered. Results of gross measurements of renal function were not altered after either methoxyflurane or halothane anesthesia, with the exception of significantly increased serum osmolality 72 hours postoperatively in the methoxyflurane group. Serum uric acid was significantly greater the first day postoperatively in obese patients anesthetized with methoxyflurane compared with the corresponding value in obese patients anesthetized with halothane. However, this difference did not represent a statistically significant increase from the control serum uric acid value before methoxyflurane anesthesia. Nevertheless, the primary lesion in methoxyflurane nephrotoxicity consists of impaired urine-concentrating ability; the renal function tests used in the present investigation would be relatively insensitive to such a derangement. Recently Cousins and Mazze[4] reported that the extent of renal dysfunction following methoxyflurane anesthesia was directly related to the peak measured serum ionic fluoride concentration. Subclinical toxicity (increased serum uric acid and impaired urine-concentration ability) was present when serum ionic fluoride exceeded 50 μM/l. When serum ionic fluoride was 90–120 μM/l, slight clinical toxicity (serum hyperosmolality and hypernatremia, low urinary osmolality, polyuria) was present. Therefore, serum ionic fluoride concentrations may have prognostic value as to the potential occurrence of methoxyflurane-induced renal dysfunction. Indeed, the peak serum ionic fluoride concentration (55.8 μM/l) in obese patients after three hours of methoxyflurane anesthesia was in the range associated with subclinical renal toxicity; four of our obese patients had peak serum ionic fluoride levels of 90 μM/l or more. In contrast, serum ionic fluoride concentrations greater than 50 μM/l were rarely present in nonobese patients until low-dose methoxyflurane had been administered for 5 hours.[11] Therefore, we recommend limiting low-dose methoxyflurane anesthesia delivered to obese patients with potential fatty liver infiltration to no more than three hours.

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