TOXICITY FOLLOWING METHOXYFLURANE ANAESTHESIA

IV. The Role of Obesity and the Effect of Low Dose Anaesthesia On Fluoride Metabolism and Renal Function

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Since the publication of the initial reports from this institution,[1-3] the pathophysiology and aetiology of the nephrotoxicity following the administration of methoxyflurane have been explored rather completely. Various studies have established that the defect in the concentrating ability of the kidney is related to the effect of fluoride ion resulting from the biotransformation of methoxyflurane.[4-12] As expected, a correlation between methoxyflurane dose and serum fluoride ion has been demonstrated, but there have been rather large individual differences in every study.[5,6,10,11,13,14] Presumably these variations are related to differences in either uptake and distribution of the anaesthetic or the rates of biotransformation. Although a logical scheme for the metabolic pathways involved has been proposed,[4,15] the appropriate labelling studies have not been done to confirm these hypothetical pathways in man. In particular, the role of the organic fluorinated metabolites in providing a source of continuing fluoride ion has not been elucidated. In view of the very high lipid solubility of methoxyflurane, obese patients might be expected to take up more of the administered drug and hence have a larger store available for metabolism. In a previous publication we saw such an effect in one patient, but were unable to draw any meaningful conclusions.[16] The present study was designed to compare the effects of a standard exposure to methoxyflurane in normal and obese patients under as rigorous controls as possible in a clinical setting. A group of patients receiving another anaesthetic technique was also included as a control. In addition to the usual measures of renal function and fluoride ion concentration, the organic metabolite and renal clearances were also studied in an attempt to understand the puzzling differences in individual susceptibility to the nephrotoxicity of methoxyflurane.

Methods

Twenty patients scheduled for elective operations outside the body cavities were studied. (Table I) All patients were hospitalized for at least 24 hours before operation. None had a history of prior renal or hepatic disease, significant cardiopulmonary dysfunction, or long-term drug therapy. The design of the study and the procedures were described to the patients and informed consent was obtained

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TABLE I

	Male	Female	Surgical Procedure
N_2O (Control)	6	2	8 lumbar laminectomies
MOF Normal	5	1	3 lumbar laminectomies 1 fixation radius fracture 1 excision radial head and Keller Procedure
MOF Obese	6	1	6 lumbar laminectomies 1 removal plate from radius fracture

MOF = methoxyflurane.

TABLE II

Anaesthesia Time	MOF % (inspired) (concentration)	N_2O (litres/min)	O_2 (litres/min)	Meperidine	Curare
MOF patients					
0–5 min	0–1.5	0	8	0	4.0–4.5 mg
	(with I.V. thiopentone induction and succinylcholine for intubation)				
5–15	1.5	6	2	0	prn
15–35	0.5	6	2	0	prn
35–60	0.2 or less	3	2	0	prn
60 and over	0	prn	prn	prn	prn
N_2O patients					
0–5 min	0	0	8	2 mg/kg by 20 min.	4.0–4.5 mg
	(with I.V. thiopentone induction and succinylcholine for intubation)				
5–35	0	6	2	prn	prn
35–60	0	3	2	prn	prn
60 and over	0	prn	prn	prn	prn

MOF = methoxyflurane.
prn = as necessary.

after approval of the protocol by the University Medical Center Clinical Investigation Committee. The patients were then randomly assigned to receive either methoxyflurane or nitrous oxide-meperidine as their primary anaesthetic. The methoxyflurane group was further subdivided into "normal" and "obese" (defined as patients whose weight was more than 25 per cent over ideal weights from actuarial tables).[17] All patients were premedicated one hour before anaesthesia with pentobarbitone 2 mg/kg and atropine 0.01 mg/kg. The anaesthetic was given by one of the investigators according to a preset schedule (Table II). Induction was facilitated by intravenous thiopentone. A calibrated Pentec vaporizer and a semi-closed absorption system was used to deliver the methoxyflurane. All patients were intubated after intravenous administration of succinyl choline 1 mg/kg and ventilation was controlled to maintain arterial carbon dioxide tension between 30 and 40 torr. D-tubocurare was used as required. Parenteral fluid therapy during operation consisted of 10 ml/kg of 5 per cent dextrose and lactated Ringer's Solution during the first hour of anaesthesia and 5 ml/kg of the same solution each succeeding hour of anaesthesia and operation. Estimated blood loss was replaced with three times the volume of dextrose and lactated Ringer's Solution. No patient required blood transfusion. Post-operatively the patients received 20 ml/kg for 24 hours of 5 per cent

dextrose in 0.45 per cent sodium chloride with 20 mEq potassium per litre for the operative day and 40 ml/kg for 24 hours of the same solution on successive post-operative days. All patients were taking oral fluids by the second post-operative day. A conscious attempt was made by the investigators to maintain a positive fluid balance during the post-anaesthetic period by encouraging oral intake in the patients. Post-operative medication included meperidine, Percodan,® diazepam and Tylenol.®

All urine was saved in 24-hour aliquots starting at least one day before operation and continuing at least five days post-operatively. Venous blood samples were drawn every morning at 7 a.m. and additionally on the day of operation for determination of fluoride levels at the time the methoxyflurane was discontinued, one hour after discontinuance and between eight and twelve hours after discontinuance. Daily weights and 24-hour intake and output recordings were maintained on all patients.

Inorganic fluoride (F) and acid-labile fluoride (ALF) were analyzed by direct electrode and diffusion methods previously described.[18] Organic acid-labile fluoride (OALF) is the difference of ALF and F. Serum and urine electrolytes, urea nitrogen, creatinine, uric acid and osmolality were done by auto-analyzer techniques in the nephrology laboratory. In addition, a complete blood count and SMA-12 was performed preoperatively and on the first and the third or fourth post-operative day. Clearance values were calculated using standard formulae.

Creatinine clearance was based on urine creatinine from the sample collected between 7 a.m. on day 1 to 7 a.m. on day 2, urine volume during the same period and serum creatinine from the sample taken at 7 a.m. on day 2.

Inorganic fluoride and organic acid-labile fluoride clearances were based on urine values from the sample collected between 7 a.m. day 1 and 7 a.m. day 2, urine volume collected during the same time-period and mean serum values from venous samples taken at 7 a.m. day 1 and 7 a.m. day 2.

The data were statistically analyzed by comparing the means of each sampling of one group with that of another group for the same sampling. Significant differences were those with a p value of less than 0.05 utilizing Student's non-paired t-test.[19] In addition, the values from each patient sampling were compared with the respective control base line determinations (pre-operative) and these mean changes from base line were tested for significance by analysis of variance.[20] For most determinations three comparisons were made: (1) methoxyflurane obese versus methoxyflurane normal, (2) methoxyflurane obese versus nitrous oxide control, and (3) methoxyflurane normal versus nitrous oxide control.

Results

The only significant differences among the controlled variables between the three groups were the obesity and drug dosage (Table III). In as much as the control group received no methoxyflurane, larger doses of meperidine and curare were necessary for surgical anaesthesia. There was no difference in body size between the control and normal methoxyflurane groups and no difference in arterial blood gases (and hence ventilation) between the three groups.

TABLE III

(n)	N_2O (8)	MOF (5)	MOF-obese (7)
Height (cm)	174.6 ±3.4	172.8 ±4.1	170.3 ±5.6
Weight (kg)	74.7 ±5.9	73.6 ±4.2	90.1 ±6.2*†
% ideal weigh	111.6 ±5.6	112.9 ±4.2	141.1 ±6.1*†
MOF (conc-min)	0	34.5 ±0.8	36.6 ±1.4
Thiopentone (mg/kg)	6.75±0.82	5.49±0.43	4.88±0.70
Succinylcholine (mg/kg)	1.08±0.07	1.04±0.12	0.95±0.05
Meperidine (mg/kg)	2.2 ±0.1	0.42±0.19	0.49±0.12
d-tubo-curare (mg/kg)	0.31±0.03	0.06±0.003	0.08±0.02
Pa_{CO_2} (torr)	28.5 ±1.1	30.7 ±1.3	28.8 ±1.2
Pa_{O_2} (torr)	117 ±7.7	125 ±19	114 ±32
pHa	7.50±0.07	7.47±0.002	7.44±0.02
Duration of operation (min)	93.4 ±5.6	104.2 ±8.0	107.6 ±8.6

MOF = methoxyflurane.
conc-min = % methoxyflurane vaporizer setting times number of minutes at that setting.
* = $p < 0.05$, MOF-Obese vs N_2O.
† = $p < 0.05$, MOF-Obese vs MOF.

In our patient population, the surgery-anesthesia experience produced relatively little change in renal function as judged by the control group. There was a slight decrease in serum osmolality on the first through the third day post-operatively, partially from increased urinary excretion resulting in decreased serum concentration of sodium and chloride and partially from hypoprotenaemia as a result of operative and sampling blood loss.* There were no other striking changes in serum and urine measurements. Creatinine clearance, uric acid clearance, and tubular reabsorption of phosphate were unchanged (Table IV). The major effect of methoxyflurane in both normal and obese patients was a decreased clearance of uric acid resulting in increased serum levels on the first post-operative day. This effect persisted through day 3 in the obese patients.

Of course, serum fluoride levels and excretion were markedly different in the patients given methoxyflurane (Table V). There was no significant difference in the mean levels and pattern of organic or inorganic fluoride in urine and serum between the obese and normal weight patients. However, there was a wide standard deviation of the serum organic acid labile fluoride in the obese patients which was significantly greater ($p < 0.05$) than the variation in the "normal" patients. If graphs of these levels in the obese and normal patients are compared, the difference becomes even more striking (Figure 1). Notice that patients number 6, 12, and 15 have the highest and most prolonged elevations of serum OALF. Patient 6 is particularly different in the slow rise and decline in both inorganic and organic fluoride (Figure 2). Another interesting feature of the serum fluoride patterns in both the normal and obese patients is the double peaks in serum inorganic fluoride (Figure 2). In all patients but number 6, there was an initial peak occurring at the time of discontinuing the methoxyflurane, a dip or plateau one hour after the end of anaesthesia and a second higher peak either 8 to 12 hours after anaesthesia or on the morning of the first post-operative day (16 to 22 hours after the end of methoxyflurane administration). In both groups, there was considerable variation in peak inorganic fluoride levels (Figure 2).

*Complete tabulation of the results is available from the authors.

TABLE IV

MEAN ± SEM (#N)

		Control	"Surg"	PO1	PO2	PO3	PO4	PO5
Urine volume collected (ml/24 h)	MOF Obese	1884±528 (7)	1519±243 (7)	2057±378 (7)	1926±254 (7)	2103±367 (7)	1746±275 (7)	1551±533 (5)
	MOF Normal	2699±668 (5)	1103±254 (5)	2394±406 (5)	2095±640 (5)	2337±581 (5)	1636±228 (5)	1745±295 (4)‡
	N_2O	1721±273 (8)	1314±199 (8)	2721±254 (8)	1982±280 (8)	1877±367 (8)	1805±271 (8)	2690±55 (3)
Serum creat. (mg%)	MOF Obese	1.13±0.05 (7)	—	1.09±0.04 (7)	1.09±0.04 (7)	0.97±0.04 (7)	0.94±0.04 (7)	0.98±0.04 (7)
	MOF Normal	0.96±0.05 (5)	—	0.96±0.07 (5)	0.98±0.07 (5)	0.92±0.07 (5)	0.86±0.07 (5)	0.96±0.09 (5)
	N_2O	1.06±0.06 (8)	—	0.96±0.07 (8)	1.02±0.06 (8)	0.94±0.07 (8)	0.98±0.05 (8)	0.98±0.04 (8)
Serum uric acid (mg %)	MOF Obese	6.58±0.59 (7)	—	7.84±0.55 (7)†	7.83±0.56 (7)†	6.74±0.69 (7)†	6.16±0.87 (7)	5.32±0.71 (6)
	MOF Normal	6.04±0.45 (5)	—	6.82±0.71 (5)‡	6.44±1.0 (5)	5.28±1.24 (5)	5.00±1.02 (5)	5.10±1.04 (5)
	N_2O	5.78±0.55 (8)	—	4.68±0.48 (7)	4.54±0.39 (8)	4.29±0.40 (8)	4.35±0.41 (8)	4.65±0.43 (8)
Urine uric acid (mg %)	MOF Obese	58.6±16.0 (7)	34.3±4.96 (7)†	34.3±6.34 (7)	48.6±7.74 (7)	59.7±12.5 (6)	51.8±12.6 (6)	49.4±10.8 (5)
	MOF Normal	33.0±9.1 (5)	43.2±6.84 (5)	28.4±4.74 (5)	53.0±12.6 (5)	45.0±4.56 (5)	44.2±3.27 (5)	46.8±6.66 (4)
	N_2O	44.6±2.83 (8)	61.8±9.47 (8)	44.1±11.7 (8)	51.2±8.71 (8)	55.5±9.82 (8)	44.1±7.96 (8)	30.7±7.86 (3)
Clearance creat. (ml/min)	MOF Obese	129±14.4 (7)	95±9.0 (7)	117±21.2 (7)	146±24.2 (7)	150±17.5 (7)	126±15.9 (7)	93±20.8 (5)
	MOF Normal	115±11.6 (5)	93±18.0 (5)	120±15.4 (5)	107±13.3 (5)	151±17.8 (5)	111±16.2 (5)	103±7.5 (4)
	N_2O	95±12.4 (8)	114±10.3 (8)	134±14.5 (8)	127±18.1 (8)	116±9.6 (8)	104±14.1 (8)	135±23 (3)
Clearance uric acid (ml/min)	MOF Obese	8.71±0.71 (7)	3.86±0.34 (7)†	6.14±1.60 (7)†	10.9±2.35 (7)	11.5±2.47 (6)	11.2±1.80 (6)	10.0±3.51 (5)
	MOF Normal	8.0±0.45 (5)	4.40±0.60 (5)‡	7.2±1.43 (5)‡	13.4±2.77 (5)	15.0±3.11 (5)	11.6±3.50 (5)	10.8±1.89 (4)
	N_2O	9.6±2.1 (8)	10.4±1.2 (8)	15.9±1.1 (8)	14.1±1.3 (8)	13.8±1.4 (8)	10.4±1.5 (8)	12.7±3.3 (3)
T.R.P. (%)	MOF Obese	82.3±1.73 (7)	80.1±4.18 (7)	82.6±1.57 (7)	89.0±0.87 (7)	90.5±0.72 (6)	88.7±1.46 (7)	86.2±4.12 (5)
	MOF Normal	86.8±2.40 (5)	82.8±3.81 (5)	85.4±3.17 (5)	87.8±1.83 (5)	89.6±0.93 (5)	86.0±1.84 (5)	86.0±1.41 (4)
	N_2O	83.9±2.0 (8)	87.8±1.66 (8)	83.5±2.23 (8)	86.0±3.04 (8)	88.2±2.76 (8)	87.2±1.67 (8)	78.7±9.94 (3)
Serum osmolarity (mOsm/kg)	MOF Obese	292±0.8 (7)	—	283±1.7 (7)	279±1.6 (7)	282±1.4 (7)	283±0.9 (7)	288±1.0 (7)
	MOF Normal	290±0.7 (5)	—	282±2.2 (5)	283±1.2 (5)	286±1.4 (5)	285±1.2 (5)	286±2.1 (5)
	N_2O	292±2.4 (8)	—	281±1.8 (8)	282±2.4 (8)	282±1.8 (8)	286±2.0 (8)	288±1.9 (8)
Urine osmolarity (mOsm/kg)	MOF Obese	614±128 (7)	596±80 (7)	459±97 (7)	428±57 (7)	472±82 (6)	520±92 (7)	529±111 (7)
	MOF Normal	403±111 (5)	665±63 (5)	433±68 (5)	452±92 (5)	428±56 (5)	454±64 (5)	458±49 (4)
	N_2O	466±57 (8)	554±71 (8)	378±76 (8)	422±71 (8)	425±64 (8)	388±50 (8)	345±54 (3)
Urine/Serum OSM	MOF Obese	2.11±0.43	2.09±0.27	1.65±0.35	1.51±0.20	1.66±0.29	1.81±0.32	1.84±0.3
	MOF Normal	1.39±0.38	2.35±0.21	1.53±0.24	1.58±0.32	1.50±0.20	1.59±0.22	1.60±0.1
	N_2O	1.59±0.19	1.96±0.25	1.28±0.27	1.50±0.25	1.47±0.22	1.34±0.17	

"Surg" = day of operation. PO – post-operative day.
Creat. = creatinine.
T.R.P. = tubular reabsorption of phosphate.
* = $p < 0.05$, MOF obese vs MOF normal.
† = $p < 0.05$, MOF obese vs N_2O.
‡ = $p < 0.05$, MOF normal vs N_2O.

TABLE V

MEAN ± SEM (#N)

			"Surg"		
		Control	MOF D/C	1 h p̄ MOF D/C	8-12 h p̄ MOF D/C
Serum F (μM/1)	MOF Obese	1.57±0.10 (7)	29.6±3.58 (7)†	27.8±2.87 (7)†	39.2±2.08 (6)†
	MOF Normal	2.12±0.25 (5)	33.8±5.30 (5)‡	30.9±4.00 (5)‡	41.1±6.74 (5)‡
	N_2O	2.10±0.34 (8)	2.19±0.41 (6)	1.46±0.25 (8)	1.81±0.14 (8)
Serum OALF (μM/1)	MOF Obese	−0.05±0.14 (7)	192.6±20.9 (7)†	236.6±23.1 (7)†	825.9±112.1 (6)†
	MOF Normal	−1.0±0.30 (5)	189±7.16 (5)‡	254.6±4.7 (5)‡	735.7±55.6 (5)‡
	N_2O	−0.6±0.52 (8)	−0.05±0.52 (6)	−0.39±0.29 (7)	−0.1±0.28 (8)
Serum OALF/F	MOF Obese	—	6.8±0.86 (7)	9.1±1.23 (7)	21.6±3.41 (6)
	MOF Normal	—	6.1±0.88 (5)	8.7±0.95 (5)	19.4±2.43 (5)
	N_2O	—	—	—	—
Urine F (μM/1)	MOF Obese	52±8.5 (7)*	—	—	1582±162 (7)†
	MOF Normal	29±1.1 (3)‡	—	—	753±398 (2)
	N_2O	57.0±10.0 (7)	—	—	57.1±9.6 (7)
Urine OALF (μM/1)	MOF Obese	—	—	—	8020±2024 (7)
	MOF Normal	—	—	—	3939±2880 (3)
	N_2O	—	—	—	—
Clearance F (ml/min)	MOF Obese	38.0±5.7 (6)	—	—	39.5±3.5 (6)*
	MOF Normal	34.5±16.2 (3)	—	—	10.0±0.1 (2)‡
	N_2O	38.7±7.2 (7)	—	—	35.8±6.8 (7)
Clearance OALF (ml/min)	MOF Obese	—	—	—	9.6±1.8 (7)
	MOF Normal	—	—	—	7.1±5.3 (3)
	N_2O	—	—	—	—
Total urine F/24 h (μM/24 h)	MOF Obese	88±17 (7)	—	—	2248±245 (7)*†
	MOF Normal	102±62 (3)	—	—	667±184 (2)‡
	N_2O	94±15 (7)	—	—	95±13 (7)
Total urine OALF/24 h (μM/24 h)	MOF Obese	—	—	—	11299±2390 (7)
	MOF Normal	—	—	—	7336±5645 (2)
	N_2O	—	—	—	—

TABLE V (continued)

MEAN ± SEM (#N)

	PO1	PO2	PO3	PO4	PO5
Serum F (μM/l)	35.1±2.81 (7)† 35.5±5.14 (5)‡ 1.55±0.15 (8)	25.1±5.50 (7)† 20.9±2.40 (5)‡ 1.54±0.11 (8)	17.3±5.26 (7)† 12.3±1.54 (5)‡ 1.59±0.11 (8)	12.6±5.32 (7) 8.38±1.27 (4)‡ 1.60±0.14 (8)	9.7±4.57 (7) 5.5±0.72 (5)* 1.71±0.18 (8)
Serum OALF (μM/l)	863.1±104.9 (7)† 690.6±37.1 (5)‡ −0.05±0.29 (8)	603.9±98.4 (7)† 387±21.9 (5)‡ −0.15±0.27 (8)	353.0±85.6 (7)† 207.4±9.3 (5)‡ −0.27±0.24 (8)	248.9±79.9 (7)† 138.2±7.1 (4)‡ −0.3±0.17 (8)	172.8±78.7 (7)* 86±12.6 (5)* −0.3±0.18 (8)
Serum OALF/F	24.9±2.66 (7) 20.9±2.90 (5) —	25.8±3.06 (7) 19.5±2.43 (5) —	21.5±2.81 (7) 17.9±1.89 (5) —	21.6±2.06 (7) 17.8±2.75 (4) —	17.8±1.40 (7) 15.8±1.42 (5) —
Urine F (μM/l)	1322±328 (7)† 784±509 (3) 50.1±5.8 (7)	904±160 (7)† 341±215 (4) 61.4±11.0 (7)	517±64 (7)† 357±144 (4) 67.1±13.4 (7)	389±72 (7)† 234±91 (4) 58.0±8.7 (7)	225±40 (5)* 174±56 (4) 40.0±5.6 (3)
Urine OALF (μM/l)	6518±2440 (6) 5239±1484 (3) —	4350±1090 (7) 2292±1008 (4) —	2330±398 (7) 1857±342 (4) —	1497±307 (7) 951±111 (4) —	614±65 (5) 660±83 (4) —
Clearance F (ml/min)	64.8±15.9 (6) 30.4±7.2 (3)‡ 61.9±5.2 (7)	74.4±19.7 (6)* 23.8±8.9 (4) 45.6±6.0 (7)	63.4±13.4 (6) 40.4±7.5 (4) 49.7±4.1 (7)	55.1±9.0 (6) 37.3±11.7 (4) 45.3±7.8 (7)	37.4±9.2 (4) 30.1±6.2 (4) 54.5±15.7 (3)
Clearance OALF (ml/min)	14.1±2.4 (6) 14.4±3.7 (3) —	15.8±4.7 (7) 10.6±4.1 (4) —	17.1±6.7 (7) 16.4±3.5 (4) —	13.0±3.6 (7) 10.8±1.3 (4) —	8.1±2.8 (5) 11.4±2.9 (4) —
Total urine F/24 H (μM/24 h)	2370±370 (7)*† 1198±339 (3)‡ 128±7 (7)	1648±318 (7)*† 590±246 (4) 99±12 (7)	1027±159 (7)† 658±148 (4)‡ 114±13 (7)	626±132 (7)† 428±162 (4) 100±15 (7)	314±81 (5) 255±64 (4) 107±13 (3)
Total urine OALF/24 H (μM/24 h)	12036±2938 (6) 11285±3794 (3) —	8072±1956 (7) 4612±1858 (4) —	4514±777 (7) 3957±638 (4) —	2315±368 (7) 1710±121 (4) —	826±154 (5) 1090±93 (4) —

"Surg" = day of operation, PO – post-operative day.
MOF = methoxyflurane.
MOF D/C = at the time methoxyflurane vaporizer was turned off.
F = inorganic fluoride.
OALF = organic acid-labile fluoride.
* = $p < 0.05$, MOF obese vs MOF normal.
† = $p < 0.05$, MOF obese vs N_2O.
‡ = $p < 0.05$, MOF normal vs N_2O.

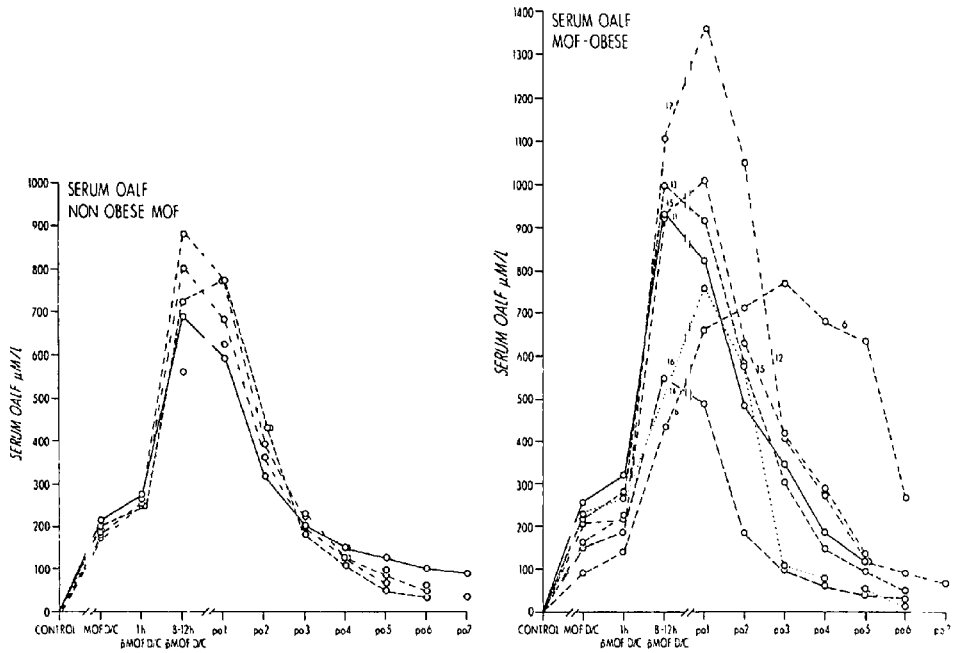

FIGURE 1. Changes in serum organic acid labile fluoride (OALF) before and after methoxyflurane anaesthesia (MOF). MOF D/C = methoxyflurane vaporizer turned off.

DISCUSSION

Further documentation of the increased serum inorganic fluoride concentrations after methoxyflurane anaesthesia is hardy necessary.[6,10,11,13,14,16,21–25] However, we believe that the demonstration of the equally marked elevation of an organic fluoride compound may cast some light on the pathways and variability of the biotransformation of the drug. Although the early peaks in serum inorganic fluoride were not related to the OALF concentrations, the more prolonged elevations occurred in the patients with the highest OALF levels. This suggests that the organic fluoride can serve as a pool for further inorganic fluoride production. That the relationship was more apparent in the obese patient supports the argument that the very lipid soluble methoxyflurane is stored in fat to a greater extent in these patients. The inorganic fluoride ion levels may remain elevated longer in the obese patients as a result of this deposition.

The double peaks in serum inorganic fluoride concentration may result from the depression of hepatic microsomal enzyme systems during clincial anaesthesia.[26] Thus, although the amount of substrate (methoxyflurane) delivered to the liver is much lower during the post-anaesthetic period, the increasing activity of the enzymes responsible for biotransformation may result in more inorganic fluoride production. Another reason for this phenomenon may relate to the finite capacity of the microsomal enzyme systems. Thus, only a small proportion of the large load of substrate (methoxyflurane) presented to the liver during clinical anaesthesia may be biotransformed even if enzyme activity is normal. This facet of anaesthesia biotransformation has recently been confirmed in rats.[27] The same total enflurane

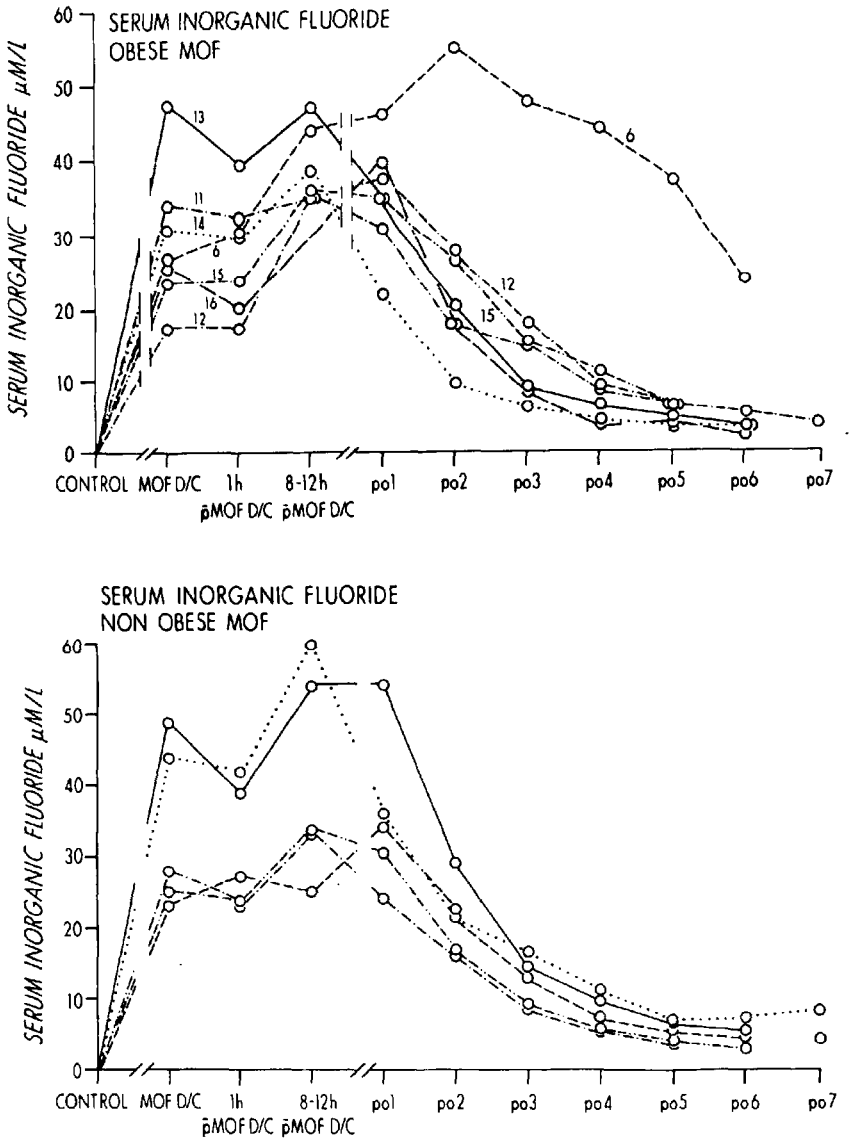

FIGURE 2. Changes in serum inorganic fluoride before and after methoxyflurane anaesthesia (MOF). MOF D/C-methoxyflurane vaporizer turned off.

or methoxyflurane dose produced a two-fold increase in urinary fluoride excretion when given at a sub-anaesthetic concentration over 48 hours compared with an anaesthetizing concentration for 2½ hours. It is also possible that decreased hepatic blood flow during anaesthesia[28] resulted in delivery of less anaesthetic to the hepatic cells. As mentioned, some of the inorganic fluoride may be coming from the organic metabolite which did not rise to peak levels until eight to twelve hours after discontinuing the anaesthetic. Despite the fact that serum OALF values peaked rapidly and were 10 to 20 times greater than inorganic fluoride, there was virtually no change in OALF clearance over the course of the experiment. In con-

trast, inorganic fluoride clearance almost doubled and followed the serum changes (Table V). OALF is undoubtedly an organic acid which would be excreted predominantly by renal tubular secretion[29] in contrast to inorganic fluoride which would be primarily filtered. It is possible that the OALF is protein bound, which would account for this effect; but there has been no study of this to our knowledge.

The striking increase in variability of organic fluoride concentrations in the serum in the obese patients is puzzling, given the relative constancy of conditions and similarity of inorganic fluoride concentrations and variation. Although gross liver function testing was estimated (serum values for bilirubin, SGOT, LDH, etc, did not change), it is possible that there is more marked variation in liver microsomal enzyme function in the fatty-infiltrated liver of obese patients.[24] The studies of Stoelting, *et al.* suggest that lower methoxyflurane blood levels result in higher serum inorganic fluoride levels in obese patients than in normal weight patients, but both their studies lack standardization of fluid regimen, associated drugs, and blood sampling, so no firm conclusions can be reached.[21,24] In regard to the nephrotoxicity of the drug, neither Stoelting nor ourselves have applied the most discriminative test, that of measuring urinary concentrating ability.[5] However, none of our patients had a peak serum inorganic fluoride level of more than 60 μmol/l, so that a defect in concentrating ability is unlikely.[11]

The only renal function affected in this study was the clearance of uric acid (Table IV). The initial study of Mazze, *et al.* reported significant increases in serum uric acid after methoxyflurane.[5] Although Robertson and Hamilton have suggested that this is the most sensitive index of the renal lesion produced by methoxyflurane,[30–32] other work has not substantiated this observation.[10,14,22,33] One of these studies in particular reported serum inorganic fluoride concentrations similar to the present study.[10] However, the patients were on cardiopulmonary bypass with forced diuresis. In addition, only the average urate serum and clearance values were reported in the post-operative period. Elevated blood uric acid may be on the basis of increased production or decreased tubular clearance. In this study, the marked decrease in uric acid clearance in the methoxyflurane group leaves little doubt as to the mechanism involved. In addition, the obese group was affected for longer than the patients of normal weight. In the first study of Mazze, *et al.* uric acid clearances also decreased significantly.[5] However, their second study is confusing. Although they state that there were dose-related increases in serum uric acid concentrations, no data are given and mean uric acid clearance actually increased in the methoxyflurane patients.[11] Other organic acids can interfere with the excretion of uric acid[28,34] and the serum levels of OALF are high enough to produce this effect (Table V). It is surprising that this relationship has not been noted universally (see above), but the fact that the whole surgical-anaesthetic experience may produce changes in urate production and excretion clouds the issue. For instance, in the control patients in Mazze's studies (halothane,[5,11] morphine-nitrous oxide[10]) and in ours (meperidine-nitrous oxide), uric acid clearance increased after anaesthesia and operation. However, an interaction of the organic acd metabolite of methoxyflurane (OALF) and uric acid would provide a logical explanation for the observations of Robertson and Hamilton.[30–32]

We recognize two major defects in this study. We have already discussed the

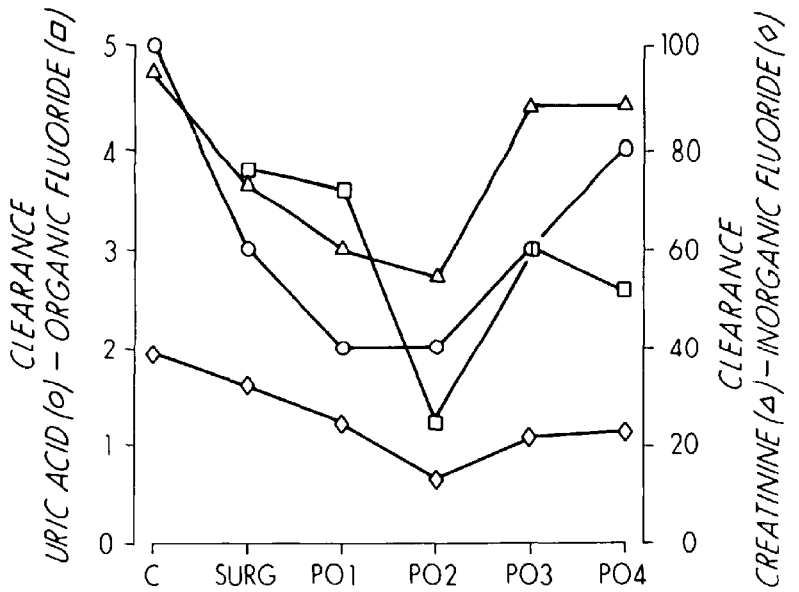

FIGURE 3. Renal clearances in patient number 6.

lack of documentation of urinary concentrating ability. Secondly, in using a semi-closed circle system with rubber tubing for delivering the methoxyflurane, we realize that we cannot measure the "dose" of methoxyflurane given. However, in as much as ventilation was standard and relatively constant (as judged from arterial carbon dioxide tension) and the same vaporizer (calibrated by gas chromatography) was used for all patients with strict attention to time at each vaporizer setting, a reasonably uniform methoxyflurane exposure was given to each patient. In setting up the study, we were primarily interested in duplicating clinical conditions. In addition, administration of other drugs was carefully controlled and recorded as was fluid intake and output. In this setting, the variability in serum inorganic fluoride levels was striking, particularly considering the relatively small number of patients. It is of interest that the only patient in the study who received antibiotics was the one with the most deviant serum fluoride pattern (number 6, Figure 1). She was started on methicillin during operation for removal of an infected plate which had been stabilizing a forearm fracture. On the second post-operative day, the antibiotic was changed to cephalexin as a result of the cultures taken at operation. Although other antibiotics (tetracycline and gentamycin) have been implicated in the nephrotoxicity of methoxyflurane,[35–37] the main aberration in this case was the prolonged elevation of the serum levels of fluoride. Both methicillin and cephalexin are predominately excreted by renal tubular secretion through the organic acid pathway[38] and theoretically could interfere with the secretion of both uric acid and OALF. However, renal clearances of both creatinine and inorganic fluoride were also dereased transiently in this patient (Figure 3). Consequently, decreased filtration could account for the elevated fluorides. Serum inorganic fluorides were not at nephrotoxic levels,[11] and we could find no other cause for the decreased clearances in this patient.

In conclusion, our findings suggest: (1) Even with rigid control of patient selection, surgical operation, adjuvant drugs and methoxyflurane administration, there is marked variability in the resulting biotransformation of the drug. (2) The only consistent biochemical abnormality, other than biotransformation, was a decrease in uric acid clearance and an increased serum uric acid which was more prolonged in the obese patients. (3) There was more variability in organic fluoride metabolism in obese than in patients of normal weight, suggesting that this group handles the biotransformation in a different fashion. (4) Even with only one hour of relatively low concentrations of methoxyflurane, three of twelve patients had peak serum inorganic fluoride levels approaching those associated with mild nephrotoxicity (greater than 50 micromoles per litre).[11]

In view of the demonstrated interaction of various drugs with the potential nephrotoxicity of methoxyflurane, and since it may be difficult to predict when a patient may need drug therapy in the post-operative period, we suggest that methoxyflurane be used only where exposure time can be limited to 60 to 90 minutes at low doses. In addition, the anaesthetist should be in a position to follow the patient closely to monitor and control the type of drugs given during the post-operative period while there is still possible danger of nephrotoxicity from the biotransformation of the anaesthetic.

Summary

Seven obese and five normal weight patients were studied before, during and after one hour of methoxyflurane-nitrous oxide anaesthesia during peripheral surgical operations and compared with eight patients of normal weight anaesthetized with nitrous oxide-meperidine and d-tubocurare. Estimates were made of renal function, including serum and urinary electrolytes, osmolarity, uric acid, urea and creatinine. Renal clearances for the latter three substances were also calculated. Serum and urinary inorganic and organic fluoride concentrations were measured, as were renal clearances. This low dose methoxyflurane anaesthesia resulted only in a decrease in uric acid clearance among all the measures, when compared to the meperidine-nitrous oxide controls. The clearance of uric acid remained depressed for longer in the obese patients, but otherwise they did not differ from the normal weight patients. It is possible but not proven that depressed uric acid clearance may be related to the organic fluoride metabolite and an early indicator of methoxyflurane renal toxicity. The previously documented biotransformation of methoxyflurane was seen in this study. A double peak in serum inorganic fluoride was shown in all patients but one. Rather large differences in peak levels of serum inorganic fluoride occurred. The only significant difference between the obese and normal weight patients as far as fluoride metabolism was concerned was a greater variability in the serum inorganic fluoride levels in the obese patients. It would appear that the obese patient metabolizes methoxyflurane in a quantitatively if not qualitatively different fashion than the normal weight patient, perhaps because of fatty infiltration of the liver. Caution is advised in the use of methoxyflurane for more than 90 minutes of low concentration administration in view of the unpredictability of the biotransformation.

RÉSUMÉ

Douze patients dont sept obèses et cinq normaux, soumis à une chirurgie extra-abdominale, ont été étudiés avant, durant et après une heure et demi d'anesthésie à faible concentration de méthoxyflurane et protoxyde d'azote. Une comparaison a été faite avec huit sujets normaux anesthésiés au N_2O, mépéridine et d-tubocurare. Les fonctions rénales ont été estimées y compris les électrolytes sériques et urinaires, l'osmolarité, l'acide urique, l'urée et la créatinine. Les clearances des trois dernières substances ont été mesurées ainsi que les concentrations sériques et urinaires du fluor inorganique et organique et leur clearance.

Parmi toutes les mesures faites, seule la clearance de l'acide urique a diminué avec cette petite concentration de méthoxyflurane par comparaison à celle observée après anesthésie à la mépéridine avec protoxyde d'azote. La clearance de l'acide urique demeure basse plus longtemps chez les obèses. Par ailleurs, ceux-ci ne différent pas des patients normaux. Il est possible, bien que non prouvé, que cette dépression de la clearance d'acide urique soit due à la formation de métabolite du fluor et qu'elle puisse servir comme indice précoce de toxicité rénale du méthoxyflurane.

La biotransformation du méthoxyflurane qui a déjà été documentée, a été retrouvée dans cette étude. Le graphique des modifications du fluor inorganique a montré chez tous les patients, sauf un, une courbe à double crête.

On a constaté des différences relativement prononcées dans les concentrations de pointe du fluor inorganique. En ce qui concerne le métabolisme du fluor, une grande variabilité dans le taux de fluor inorganique sérique chez les obèses était la seule différence observée entre ceux-ci et les patients normaux.

Il semble que le patient obèse métabolise le méthoxyflurane d'une façon quantitativement sinon qualitativement différente du patient normal, peut-être à cause d'une infiltration graisseuse du foie.

On recommande la prudence, même lors de l'usage d'une faible concentration de méthoxyflurane pour une anesthésie de durée supérieure ou égale à 90 minutes, en raison d'un taux de biotransformation dont l'importance est difficile à prévoir.

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