METHOXYFLURANE NEPHROTOXICITY

J.W. DESMOND, M.B., B.S., F.R.C.P.(C)

THE METABOLISM AND EXCRETION of methoxyflurane begins immediately after the onset of the anaesthesia and continues for 9 to 12 days[1,2,3] after which the storage depots of the intact drug approach depletion. Identified products of bio-transformation are carbon dioxide, fluoride ion, dichloroacetic acid and methoxyfluoroacetic acid. It is estimated that 29 per cent to 35 per cent of the methoxyflurane absorbed is metabolized (Figure 1), 7 per cent to 21 per cent undergoing cleavage of the ether linkage with production of carbon dioxide, fluoride ions and dichloroacetic acid. A large portion (40 per cent) is dechlorinated and oxidized to methoxydifluoroacetic acid, which is excreted promptly by the kidney. Significant quantities of nonvolatile fluoride ions are deposited in bone, i.e. 30 per cent to 55 per cent of the fluoride ion ingested in quantities above the average daily intake. Half of the remainder appears in the urine in 3 or 4 hours and the urinary excretion rate returns to control levels in approximately 24 hours. A part of that absorbed into the bone is released over several weeks and another portion is released much more slowly, about half of that remaining being lost in two years. In our studies, fluoride began to appear in the urine in 3 to 4½ hours after the initial exposure, reached a maximum excretion rate in 24 to 48 hours and then declined with a half life of approximately 36 to 48 hours. These facts support the conclusion that although blood levels of methoxyflurane constantly fall to 10 per cent to 12 per cent of peak concentration in 3 to 4 hours and to 1 per cent to 1.5 per cent in 24 hours, following cessation of the anaesthetic, there is continued transfer of methoxyflurane from storage depots to sites of enzymatic attack in quantities which permit maximum rates of hydrolysis for as long as 40 hours. One should remember that all biodegradation processes are slowed during the first twenty-four hours after surgery and that if for some reason the patient has been shocked by the surgery, this delay may be even further prolonged with excretion and metabolism of the drug in such cases continuing for an extended length of time. It must be noted that metabolism in the rat proceeds at four times the rate in the human and in the dog the comparative figure for metabolic rate is twice that of man.[4,5,6,8] In reviewing studies conducted on these animals one should keep these facts in mind.

If simultaneous or subsequent dechlorination at the ether cleavage occurs in the same molecule, oxalic acid could be a product and this has been demonstrated.[4,5,21,26] The time curve of the elimination of the various metabolites can shed some light on the dynamics of the enzymatic degradation processes. The release of fluoride ions in vivo is secondary to hydrolysis of the ether linkage. The fate of the inorganic fluoride is well known and its excretion by the kidney is prompt in human urine following exposure to methoxyflurane. Hudlicky[10] reports that spontaneous hydrolysis of C-F bonds proceeds easily in terminal – CF_2 –

Department of Anaesthesia, Toronto General Hospital and the University of Toronto.

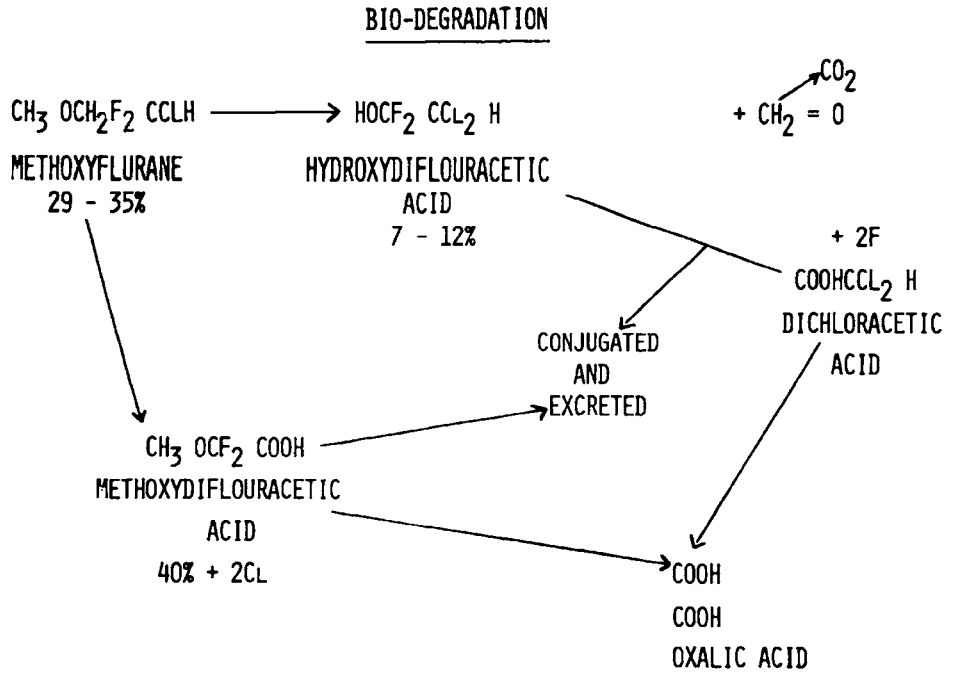

FIGURE 1. A condensed schematic of biodegration of methoxyflurane showing carbon dioxide, inorganic fluoride, oxalic acid and dichloroacetic acid as the main end products excreted by the urine. (From Mazze, R.I. and Cousins, M.J. Canad. Anaes. Soc. J. *20:* 64–80, January, 1973).

groups when oxygen is bonded to the same carbon. The identification of significant quantities of dichloracetic acid in the urine of patients exposed to methoxyflurane supports this mechanism. The inorganic fluoride found in the urine is identified as being mainly in the form of the salt of $CH_2 - O - CF_2 - COOH$, the source of which has been dechlorination of methoxyflurane. The foregoing data substantiates the route of biotransformation proposed by Van Dyke. The dechlorination proceeds at a greater rate than the cleavage of the ether linkage, as it does in the rat[3,11,12,13] (Figure 1).

A Review

Van Poznak and Artuzio[14] reported on the clinical use of methoxyflurane in man in 1960. It is estimated that since that time over 25 million patients have received the drug, which was advertized as a panacea because the surgeon could use epinephrine in association with this non-explosive agent. In spite of the problems of slow, difficult induction and prolonged recovery, methoxyflurane did eventually find a place in clinical practice. It was found to be useful in surgery of the eye, in obstetrics, in operations where a prolonged quiet period was required post-operatively. It supposedly did not sensitize the myocardium to catecholamines as did halothane and cyclopropane, and it produced very stable conditions once one was able to get over an often stormy induction period.

It was nearly five years after the introduction of the drug (1964) when Paddock reported 5 cases of high output renal failure.[15] Two of these patients died. In 1966 Crandell[1] reported toxic nephropathy in 17 per cent of 94 patients receiving the drug. Pezzi[16] also showed in 1966 that of 180 patients receiving methoxyflurane, 120 having abdominal operations, 20 patients showed evidence of nephrotoxicity and of these six subsequently died. In 1969 Lebowitz[17] reported two cases of high output renal failure; fortunately both his patients survived but in one case return to normal renal function took one year.

Kuzucu[18] reported on 115 cases, seven of whom received tetracycline. Three of his patients were elderly and obese and died of renal failure. Calcium oxalate crystals were found in the renal tubules of all three patients. Panner[19] reported two fatal cases who received methoxyflurane for more than four hours. Both had high levels of blood urea nitrogen and large volumes of urine within 24 hours of surgery. The second of his patients received tetracycline, but only after the onset of the polyuria. Both showed calcium oxalate crystals in the tubules at post mortem.

Taves[20] in 1970 following up the cases of Panner, showed a urinary fluoride level of 275 micromoles eight days after operation – ten times that of two uneventful patients. Serum and urinary fluorides were elevated 19 days after the operation in these cases. Inorganic fluoride clearance in the blood was 5.8 ml/min or 10 times normal, with a creatinine clearance of 6 ml/min. The organic fluoride after the anaesthetic was much higher than the inorganic fluoride except in the urine sample, implying that considerable metabolic degradation had occurred. Inorganic fluoride of more than 200 micromoles has been shown indirectly to be nephrotoxic and organic fluoride likely to be the source of the inorganic fluoride.[3,8]

Metabolites of methoxyflurane are chloride and fluoride ions, methyl difluoracetic acid, hydroxydifluoracetic acid and oxalic acid.[4,5,6] Fluoride and oxalic acid have both been shown to be nephrotoxic.[3,8] Mazze showed that patients on methoxyflurane had impaired ability to conserve body water, increasing sodium osmolality which failed to respond to vasopressin, leading to polyuria, hypernatraemia and dehydration.[1,3]

Frascino[22] exposed 11 patients to between 2.5 and 7.5 hours of methoxyflurane anaesthesia. These patients had normal creatinine clearance tests pre-operatively. He reported calcium oxalate crystals in the tubules of seven patients on whom he did biopsies and the urinary oxalates were raised to 96 – 400 mgm in 24 hours, the normal range being 45 mgm/24 hours.

At the Toronto General Hospital we have had two patients who developed severe high output renal failure after long exposure to the drug. Five other patients with renal impairment required expert care by the nephrologists. Both the patients with severe renal failure survived. One of these patients has been previously reported.[23]

In 1971 Mazze[8] reported on two deaths and two other cases awaiting transplant following renal failure after methoxyflurane anaesthesia. Hollenberg reported from Boston on three cases of renal failure suggesting again that the fluorine ion is responsible for the tubular impairment.

Fung and Wade exposed dogs to one M.A.C. of methoxyflurane for 5 hours

using constant volume ventilation.[8] At autopsy at intervals from the first to 7th days they found marked destruction of tubular cells.

Inhibiting effects of inorganic fluorides on many enzyme systems are known, including those thought to be involved in the action of A.D.H. and the presence of polyuric renal insufficiency in rats as studied by Mazze[5] following the intravenous and intraperitoneal administration of sodium fluoride proved this. It is likely that other metabolites such as oxalic acid can also lead to the observed abnormalities in renal function. The case for inorganic fluoride as the prime nephrotoxin is, however, most compelling.

Mazze and Cousins[26] at Stanford University, using methoxyflurane in cardiopulmonary by-pass surgery, showed that with a mean peak arterial methoxyflurane concentration of 7.8 ∓ 1 mgm% (MAC 13.4 mgm%) there was no evidence of renal dysfunction in these patients.

We chose to study a group of patients who were having mastoidectomies and or tympanoplasties. These operations usually last for 2 to 3 hours and fortunately our series was uneventful as far as the operation itself was concerned. These cases therefore served as excellent controls for a study of this nature.

Material and Methods

Ten healthy patients picked at random were used in this study. One other patient was added to the study – a tonsillectomy whom we were able to follow for only one day but who proved to be an interesting case (No. 11).

Pre-Operative Assessment

Each patient was examined by the anaesthetist and found to be physically fit. In each case a pre-operative record was made of weight (Kg.), age, serum osmolality, blood urea nitrogen (BUN), electrolytes, urine specific gravity and pH, uric acid, haemoglobin, haematocrit, and electrocardiogram (Table I).

Procedure at Operation

All patients were premedicated with pantopon 10 to 20 mgm and hyoscine hydrochloride 0.4 or 0.6 mgm. Following the placement of the cardioscope electrodes the patient was given 250 to 300 mgm of sodium thiopentone, preoxygenated, intubated following succinylcholine chloride (75 mgm) and maintained on nitrous oxide and oxygen. From the moment the tracheal tube was inserted the patient was given methoxyflurane 1.6 per cent (inspired vapour concentrations were checked with a Mayo Vapour Analyzer) for exactly 3 minutes. Ventilation was controlled with an Air Shields Ventilator with a volume of 500 to 700 ml at a rate of 12 to 14 per minute. A non-rebreathing circuit was used with a Sierra valve and plastic corrugated tubing was also used as we tried to avoid problems arising out of the rubber solubility of this drug (Figure 2).

At exactly 3 minutes from commencement of methoxyflurane inhalation a blood sample was taken to measure the blood level and the vaporizer was adjusted to

TABLE I

Case No.	Age	WT/Kg	Na	K	Cl	CO_2	Hbg	H'crit	S. Osmolality	S. Creatinine	BUN	Urine pH	Urine S.G.
1	45	70.2	140	4.1	100	28	13.4	41	284	1.1	12	6.5	1017
2	46	57	137	4	103	25	11.9	35	289	.7	9	6.2	
3	31	98	139	4.8	97	29	15.4	46	290	.9	16	7	1022
4	62	67	140	4	104	27	15.8	47	285	1.1	15	6	1007
5	38	62	140	5	102	31	16	46	302	1.2	14	6	1025
6	32	51.6	138	4.1	101	28	13.6	40	286	.9	12	5.7	1017
7	29	76	139	4.5	102	28	14.1	42	296	1.2	19	6	1022
8	40	82.5	140	4.9	101	31	15.3	42	285	1.1	11	6.5	1027
9	34	54.5	141	3.6	101	28	12.8	38	288	.8	14	6.5	1014
10	20	66.9	136	4.3	94	29	14.1	44	290	1	13	6	1024
11		81	138	3.9	96	30	12	35	290	.7	16		

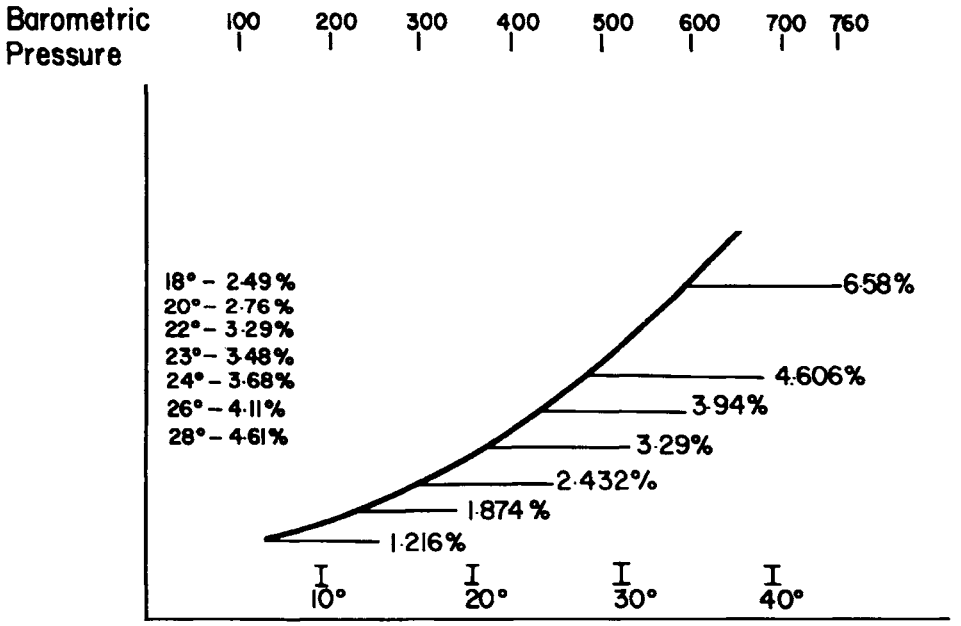

FIGURE 2. Method developed for use with the pentec vapourizer making compensations for barometric pressure and temperature to derive the inspired concentration of methoxyflurane in each case.

give a concentration of 0.16 per cent. This concentration was maintained for the rest of the operation.

Blood was taken again 13 minutes from the beginning of induction and at hourly intervals to demonstrate the level of methoxyflurane in the blood throughout the anaesthetic. During this early period the patient's blood pressure, pulse, E.K.G. and general condition were always under surveillance by another member of the Department. No relaxants were used except succinylcholine for tracheal intubation. The patients were then permitted to breath spontaneously following the initial 3 minutes of controlled ventilation to the end of the operation. Ventilatory volumes and rates were monitored with a Wright Spirometer in the circuit. Inspired and expired concentrations were easily measured because of the circuit being used. We were surprised that the average tidal volume in all cases was only 250 to 275 ml and that the rate of respiration was never more than 12 to 16 breaths a minute in any case. We determined the blood gases on all patients at the end of operation. Several patients had P_{CO_2} of 56 to 60 torr.

Lactated Ringer's solution was used routinely during operation, 500–800 ml being infused depending on the duration. No blood was used and no significant changes in blood pressure or pulse occurred. The electrocardiographic tracings were normal in all cases (Table II).

POST-OPERATIVE FOLLOW-UP

All patients were semiconscious at the end of the operation. In the recovery room the patient was given oxygen through a Puritan Nebulizer, at a flow of 10 litres per minute. In all cases the recovery period was uneventful.

TABLE 2

OPERATION

Case No.	Sodium Thiopentone Dose	$N_2O:O_2$	Circuit	Insp Conc 1st 3 mins after Ind	MOF in Blood at 3 mins.	Insp Conc C 3 mins to end of Operation	MOF in Blood at 13 mins. after Induct	MOF in Blood 1 hr. 13 mins after Induct	MOF in Blood 2 hrs. 13 mins after Induct	Ventilation during 1st 3 mins.	Ventilation During Rest of operation T.V. Rate
1	300	6:3	N.R.B.	1.6%	10 mg.%	.16%	1 mg.%	.9 mg.%	.8 mg.%	600 × 12	250 × 16
2	250	6:3	N.R.B.	1.6%	3 mg.%	.16%	.7 mg.%	.7 mg.%	.7 mg.%	500 × 14	200 × 16
3	300	6:3	N.R.B.	1.6%	4.8 mg.%	.16%	.5 mg.%	.7 mg.%	.7 mg.%	600 × 12	200 × 20
4	350	6:3	N.R.B.	1.6%	5 mg.%	.16%	.7 mg.%	.7 mg.%		600 × 12	300 × 12
5	200	6:3	N.R.B.	1.6%	6.3 mg.%	.16%	2.3 mg.%	.8 mg.%		700 × 12	275 × 11 300 × 12
6	275	6:3	N.R.B.	1.6%	5.6 mg.%	.16%	3.4 mg.%	.8 mg.%		500 × 12	250 × 12
7	300	6:3	N.R.B.	1.6%	6.8 mg.%	.16%	3 mg.%	1 mg.%		600 × 12	250 × 12 300 × 12
8	300	6:3	N.R.B.	1.6%	4.3 mg.%	.16%	.7 mg.%	.5 mg.%		600 × 12	300 × 14
9	200	6:3	N.R.B.	1.6%	3 mg.%	.16%	.9 mg.%	1 mg.%		500 × 12	250 × 14
10	250	6:3	N.R.B.	1.6%	3 mg.%	.16%	.7 mg.%	.8 mg.%		500 × 12	200 × 12
11	350	6:3	N.R.B.	1.6%	8 mg.%		.3 mg.%			700 × 14	300 × 16

TABLE 2 (*continued*)

Case No.	BP Pressure	Time of Operation Hrs.	Time of Operation Min.	Blood Gases at Termination of Operation	E.K.G.	Fluids During Operation	Fluids During 1st 24 hours Ringer Lactate	Puritan Setting
1	110–120 mmHg	2	10	pH 7.25 PaCO2 56 PO_2 118 CO_2 26		500 ml R/Lactate	800 ml./8 hr. shift	40% × 10 L
2	110–120 mmHg	2	0	pH 7.2 PaCO2 47 PO_2 185 CO_2 24		550 ml R/Lactate	800 ml./8 hr./24 hr. shift	40% × 10 L
3	130–150 mmHg	2	40	pH 7.31 PaCO2 47 CO_2 24, 5 PO_2 124		600 ml R/Lactate	800 ml/8 hr./24 hr. shift	40% × 10 L
4	120–140 mmHg	2	15	pH 7.19 PcCO2 65 PO_2 95 CO_2 26		700 ml R/Lactate	800 ml./8 hr./24 hr. shift	40% × 10 L
5	100–110 mmHg	2	15	pH 7.29 PaCO2 47 PO_2 122 CO_2 23.5		800 ml R/Lactate	800 ml./8 hr./24 hr. shift	40% × 10 L
6	100–110 mmHg	2	50	pH 7.31 PaCO2 48 PO_2 131 CO_2 25		450 ml R/Lactate	800 ml./8 hr./24 hr. shift	40% × 10 L
7	100–110 mmHg	3	30	pH 7.34 PaCO2 47 PO_2 156 CO_2 24.5		700 ml R/Lcatate	800 ml./8 hr./24 hr. shift	40% × 10 L
8	120–130 mmHg	1	55	pH 7.3 PaCO2 52 PO_2 149 CO_2 27		600 ml R/Lactate	800 ml./8 hr./24 hr. shift	40% × 10 L
9	100–120 mmHg	2	15	pH 7.36 PaCO2 47 PO_2 62 CO_2		500 ml R/Lactate	800 ml./8 hr./24 hr. shift	40% × 10 L
10	130–140 mmHg	1	10	Not Done		450 ml R/Lactate	800 ml./8 hr./24 hr. shift	40% × 10 L
11	120–140 mm Hg		50	Not Done		400 ml R/Lactate	Nil	40% × 10 L

TABLE 3A

FOLLOW UP FOR 3 TO 4 DAYS

Pt. No.	Day No.	Na^+	K^+	Cl^-	CO_2	Uric Acid	S.C. Creatinine	Serum Osmolality	Urine Osmolality	BUN	Urine Vol./24 hrs.	Creatinine Clearance ml/min	Creatinine Urine Mg./%
1	1	137	4.6	100	26	6.7	1.1	286	480	13	2500	115	73
	2	138	4.7	95	28	6.1	.9	286	523	11	1200	153	165
	3	135	4.7	98	28	5.2	1.0	285	419	13	1200	98	118
	4	136	4.6	97	27	5.0	1.0	287	491	13	1400		114
2	1	137	4.2	102	27	4.5	.7	285	328	9	2400	117	49
	2	139	3.9	103	24	4.4	.8	285	307	9	2100	84	45
	3	139	4.1	103	26	4.4	.8	287	299	10	1200	101	97
3	1	138	5.0	100	28		.9	295	648	23	1900	199	136
	2	142	4.8	100	29		1.6	294	632	24	2000	189	136
	3	139	4.8	101	30		1.0	291	618	20	1300	97	108
4	1	137	4.0	99	28		1.1	285	346	11	2300	90	62
	2	139	4.0	100	27		.9	285	378	10	1300	80	80
	3	138	4.4	100	30		.9	287	592	10	900	108	156
	4	140	4.8	100	31		.6	284	590	10	1200	121	87
5	1	138	3.8	101	26		1.3	281	766	15	3950	72	34
	2	143	4.1	108	24		1.3	282	303	15	2650	95	67
	3	142	5.3	101	29		1.2	284	351	13	2400	90	65
6	1	135	4.3	97	27		.9	277	249	6	3900	75	25
	2	139	3.9	103	24		.8	283	202	9	2150	84	45
	3	137	4.3	100	30		.6	283	451	12	1000	108	124
	4	139	4.6	101	30		.7	292	532	10	1100	106	97
7	1	145	4.1	101	29		1.4	308	279	16	1400	35	54
	2	145	4.4	100	28		1.2	696	254	20	900	31	60
	3	143	4.8	101	29		1.1	291	284	21	900	32	65
	4	140	4.2	97	30		1.1	293	308	20	900	32	56
8	1	142	3.9	101	30	8.4	1.1	294	728	15	3000	390	206
	2	142	4.0	100	33	8.4	1.1	293	456	13	2300	90	62
	3	143	4.1	98	33	8.3	1.2	290	434	13	1920	123	111
9	1	140	4.1	100	30	4.8	.6	293	308	15	1500	146	84
	2	139	4.1	99	32	5.7	.8	286	480	14	1000	108	124
	3	137	4.5	100	25	5.6	.6	289	578	14	1230	117	82
10	1	139	4.5	99	30		1.2	299	486	13	3100	149	83
	2	140	4.5	98	30		1.1	289	500	13	1000	147	84
11	1	141	4.4	95	31		1.0	294	314	13	3000	117	56

TABLE 3B

INORGANIC FLUORIDE IN URINE
(Methoxyflurane Anaesthesia)

Pt. No.	Day No.	Total Fluoride exc/24 hrs.	24 hour Fluoride parts/million	Inorganic Fluoride Ion Concentration mg/ml	Inorganic Fluoride Ion Concentration mM/l	24 hour Urine Vol./(ml)	24 hour Fluoride mg	24 hour Fluoride mM	Inorganic Fluoride Ion Excretion Rate mM/hour
1	1	76.25	4.85 M	30.5	1604	2500	76.3	4.02	16
	2	34.8	4.35 M	29.0	1525	1200	34.8	1.83	76
	3	26.4	3.6 M	24.0	1262	1100	26.4	1.39	58
	4	12.2	1.31 M	8.7	458	1400	12.2	0.64	27
2	1	33.6	2.1 M	14.1	742	2400	33.8	1.78	74
	2	33.6	2.4 M	17.1	899	2100	35.9	1.89	79
	3	30.0							
3	1	125.4	9.9 M	66.0	3472	1800	125.4	6.60	275
	2	150.0	11.25 M	75.0	3945	2000	150.0	7.89	229
	3	48.1	5.55 M	37.0	1946	1300	48.1	2.53	105
4	1	41.4	27 M	18.0	946	2300	41.4	2.18	90.8
	2	20.4	25.5 M	17.0	894	1200	20.4	1.07	44.6
	3	24.3	40.5 M	27.0	1420	900	24.3	1.28	53.3
	4	15.6	19.5 M	13.0	683	1200	15.6	0.82	34.2
5	1	18.17	6.9 M	4.6	242	3950	18.2	0.96	40
	2	16.43	9.3 M	6.2	326	2650	16.4	0.86	35.8
	3	9.12	5.7 M	3.8	200	2400	9.1	0.48	20.0
6	1	39.0	1.5 M	10.0	526	3900	39.0	2.05	85.4
	2	9.25	6.45 M	4.3	226	2150	9.31	0.49	20.4
	3	9.0	1.35 M	9.0	473	1000	9.0	0.47	19.6
	4	5.52	6.9 M	4.6	242	1200	5.5	0.29	52.1
7	1	68.6	7.25 M	49.0	2577	1400	68.6	3.61	150
	2	21.6	3.6 M	24.0	1262	900	21.6	1.14	48
	3	45.0	7.5 M	50.0	2630	900	45.0	2.37	99
	4	31.5	5.25 M	35.0	1841	900	31.5	1.66	69
8	1	174.0	8.7 M	58.0	3051	3000	174.0	9.16	382
	2	73.5	5.25 M	35.0	1841	2100	73.5	3.87	161
	3	70.0							
9	1	37.5	3.75 M	25.0	1315	1500	37.5	1.97	82
	2	16.65	2.78 M	18.5	973	900	16.7	0.88	37
	3	11.1	2.78 M	18.5	973	600	11.1	0.58	24
10	1	49.6	2.4 M	16.0	842	3100	49.6	2.61	109
	2	31.0	4.65 M	31.0	1631	1000	31.0	1.63	68
11	1	36.0	1.8 M	12.0	631	3000	36.0	1.89	79

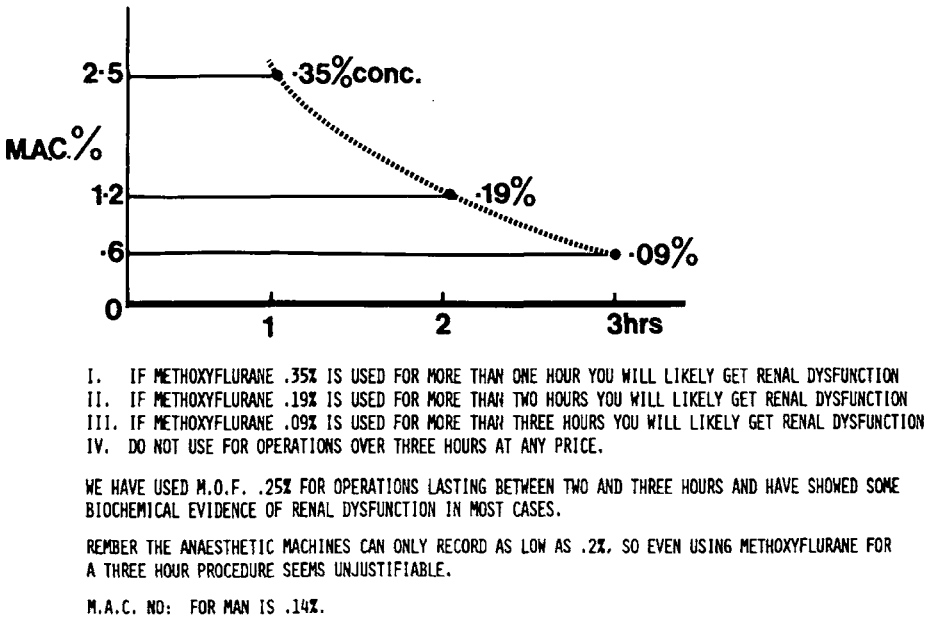

FIGURE 3. Recommendations for the use of methoxyflurane to prevent nephrotoxicity.

The post-operative hospitalization for these patients was four or five days. During this period renal function was assessed by daily determination of serum creatinine, blood urea nitrogen, uric acid, electrolytes and osmolality, urine osmolality, creatinine clearance, urine creatinine, urine volume, and inorganic fluoride excretion over each 24 hour period. The results of the study are tabulated (Table III).

DISCUSSION

A number of recent studies have been carried out using semiclosed circuits.[9,27] With all respect due to the investigators, such studies are of no value and unacceptable for the obvious reason that true values for inspired and expired concentrations of gases breathed by the patients can be measured only in non-rebreathing circuits.

The most striking finding in our study was the large volume of low osmolality urine produced by the patients during the first few post-operative days. Even though we used ridiculously low doses of methoxyflurane this still occurred in most of the patients. Another important and impressive finding was the large amount of inorganic fluoride found in the 24 hour urine specimens. Although all these patients received the same amount of methoxyflurane during their anaesthesia there was a marked difference in the effect it had on urine volume and in the fluoride excreted. This raises the question of whether or not individuals metabolize the drug at different rates. The effect on each patient's tubular mechanism may also vary.

The quantities of methoxyflurane used in this study were far less than those suggested by Lowe[28] as being safe. Exceedingly small maintenance doses were used in this study and Figure 3 shows our recommendations for those who feel they would like to continue using the agent.

In 1971 a similar study involving 22 laryngectomies was carried out. Sixteen patients received methoxyflurane and a control group of six patients received halothane. The results of this study were presented in 1972 at the Canadian Anaesthetists' Society meeting in Halifax. Renal function in this group was followed for 18 to 21 days. Urinary oxalates were increased by six to ten fold of normal and an increase in oxalate was observed for 8 to 10 days in some cases. Patient uptake of methoxyflurane was from 8 to 14 ml during the 4 to 5 hours, averaging from 2 to 3 ml per hour.

Fluoride and oxalic acid have both been shown by Mazze and Cousins[4,26] to cause disruption of the renal tubular cells. Fung[8] in Winnipeg has shown the same thing in the dog. Mazze stated in 1971 that methoxyflurane should be put back into Phase 11 of a research project and this was suggested to the American Food and Drug Administration. The experience reported here suggests that he was right in his assessment and we recommend that the drug should be abandoned.

Summary

Methoxyflurane used as an anaesthetic even in low doses can cause renal dysfunction. We suggest that the drug be abandoned.

Discussion

Un certain nombre de travaux récents ont été effectués à l'aide de circuits semi-fermés.[9,27] Malgré tout le respect que méritent les chercheurs concernés, de tels travaux sont sans valeur et inacceptables pour la raison évidente que les grandeurs réelles des concentrations de gaz inspirées et expirées par les malades ne peuvent être mesurées qu'au moyen de dispositifs sans rebreathing.

La constatation la plus remarquable au cours de notre étude a été le volume considérable d'urine à basse osmolalité excrétée par les malades durant les quelques premiers jours post-opératoires. Bien que nous n'ayons utilisé que des doses ridiculement basses de méthoxyflurane, ce phénomène survint néanmoins chez la plupart des malades. Une autre constatation importante et impressionnante fut la quantité considérable de fluore inorganique trouvée dans les échantillons d'urines des 24 heures. Bien que ces malades aient reçu la même quantité de méthoxyflurane au cours de leur anesthésie, il y eut une différence marquée dans l'effet que produisit cet agent sur le volume urinaire et sur le fluore excrété. Ceci soulève la question à savoir si oui ou non les individus métabolisent le méthoxyflurane à des rythmes différents. L'effet sur le mécanisme tubulaire pourrait aussi varier avec chaque malade.

Les quantités de méthoxyflurane utilisées dans cette étude furent beaucoup moindres que celles que suggérait Lowe[28] comme étant sans danger. Des doses d'entretien excessivement petites furent employées dans cette étude et la Figure 3 traduit nos recommandations à l'intention de ceux qui se sentiraient enclins à persister dans l'emploi de cet agent.

En 1971, une étude semblable impliquant 22 laryngectomies fut poursuivie. Seize malades reçurent du méthoxyflurane alors qu'un groupe de contrôle de six malades reçurent de l'halothane. Les résultats de cette étude furent rapportés, en 1972, au congrès de la Société Canadienne des Anesthésistes à Halifax. La fonction rénale chez les malades de ce groupe fut observée durant 18 à 21 jours. Les oxalates urinaires furent augmentés de six à dix fois la normale, cette augmentation en oxalate se prolongeant dans certains cas de 8 à dix jours. L'adsorption de méthoxyflurane chez ces malades variait de 8 à 14 ml au cours des 4 à 5 heures d'anesthésie, avec une moyenne de 2 à 3 ml par heure.

Mazze et Cousins[4,26] ont démontré que le fluore et l'acide oxalique causaient tous deux un éclatement des cellules tubulaires rénales. Fung,[8] à Winnipeg, a constaté le même effet chez le chien. Mazze, en 1971, affirmait que le méthoxyflurane devrait être reculé à la Phase II d'un projet de recherche, suggestion qu'endossait l'Administration Américaine des Aliments et des Drogues. L'expérience rapportée ici incite à croire qu'il avait raison et nous recommandons que le méthoxyflurane soit abandonné.

Résumé

Le méthoxyflurane utilisé même à de faibles doses comme anesthésique peut entraîner des troubles de la fonction rénale. Nous suggérons que l'emploi de cet anesthésique soit abandonné.

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