

OXALIC ACID EXCRETION AFTER METHOXYFLURANE AND HALOTHANE ANAESTHESIA*

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METHOXYFLURANE IS a general anaesthetic that has been implicated in the production of postoperative renal dysfunction.¹⁻⁶ The precise mechanism is unknown, but the finding of many oxalate crystals in the renal tubules,^{5,6} and large amounts of oxalic acid in the urine of patients who develop renal failure after methoxyflurane anaesthesia⁵ has suggested the possibility that oxalic acid may be partly responsible.

The present study was undertaken to measure the excretion of oxalic acid and alterations in renal function that occur after methoxyflurane and halothane anaesthesia.

PATIENTS AND METHODS

Fifteen patients, all of whom had normal renal function prior to their surgery were selected at random. Nine of these were anaesthetized with methoxyflurane and six with halothane. Details of the anaesthesia and surgery in the nine patients receiving methoxyflurane appear in Table I. Nitrous oxide and oxygen were passed through a vaporizer (Pentec), calibrated for methoxyflurane, into a semi-closed circle carbon dioxide absorption system, except in one instance (patient 7), when a non-rebreathing system was employed. The patients were all intubated and artificially ventilated mechanically. The total volume selected for each patient was approximately 50 per cent in excess of the value for the particular patient predicted on the Radford nomogram. Thus, it was unlikely that any patient was hypercarbic during the surgery. Signs suggesting inadequate tissue or organ perfusion did not occur at any time.

Fluids used postoperatively consisted of 5 per cent dextrose in water alternating with 5 per cent dextrose in saline. Total volume of fluids administered daily were between 1500 and 2500 mls.

Preoperatively and daily postoperatively the following laboratory measurements were performed: Urinalysis, BUN, serum creatinine, sodium, potassium, chloride, uric acid, bicarbonate, osmolality, calcium, and phosphate. Daily 24-hour urines were collected for determination of protein, creatinine, osmolality, calcium, phosphate, uric acid, and oxalic acid. Urine oxalic acid was measured by a modification of the method of Koch and Strong.^{7,8} The normal values were less than 55 mgm per day.

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TABLE I
CLINICAL DATA ON NINE PATIENTS RECEIVING METHOXYFLURANE ANAESTHESIA

Patient No.	1	2	3	4	5
Age (yrs)	43	38	74	61	40
Sex	F	M	M	M	F
Weight (kg)	51	71	71	77	73
Surface area (m ²)	1.51	1.88	1.74	1.96	1.71
Temperature °C	37	37	37	37	37
Pre-operative medication	Secobarbital	Secobarbital Amobarbital		Diazepam Vitamin K ₁	Secobarbital
Pre-operative sedation	Meperidine 100 mgm	Meperidine 10 mgm	Diazepam	Meperidine 100 mgm	Meperidine 100 mgm
Anaesthesia:	Thiopental 250 mgm Succinylcholine 50 mgm N ₂ O 4 L/min O ₂ 2L/min MOF 0.7% for 15 min	Thiopental 300 mgm Succinylcholine 40 mgm N ₂ O 4 L/min O ₂ 2L/min MOF 1.5% for 15 min	Thiopental 300 mgm Succinylcholine 40 mgm N ₂ O 3.5 l/min O ₂ 1.5L/min MOF 0.4% for 10 min	Thiopental 200 mgm Succinylcholine 60 mgm N ₂ O 3.5 l/min O ₂ 1.5L/min MOF 1% for 10 min	Thiopental 300 mgm Succinylcholine 40 mgm N ₂ O 3.5 l/min O ₂ 1.5L/min MOF 1% for 15 min
Induction	N ₂ O 1 L/min O ₂ 1L/min MOF 0.5% for 85 min MOF 0.25% for 25 min	N ₂ O 2 L/min O ₂ 1L/min MOF 0.75% for 25 min MOF 0.5% for 15 min	N ₂ O 3.5 l/min O ₂ 1.5L/min MOF 0.6% for 175 min Fentanyl 0.09 mgm D-tubocurarine 21 mgm	N ₂ O 1 L/min 1L/min MOF 0.5% for 85 min D-tubocurarine 15 mgm	N ₂ O 3.5 l/min O ₂ 1/5L/min MOF 0.5% for 65 min
Maintenance	Ligation and stripping of varicose veins	Lumbar discectomy	McMurrays osteotomy	cholecystoduodenostomy	Ligation and stripping of varicose veins
Surgical procedure	120 ml D/S 500 ml	50 ml D/S 500 ml	600 ml Lactated Ringer's Solution 3000 ml	800 ml Lactated Ringer's Solution 1000 ml	100 ml Lactated Ringer's Solution 1000 ml
Estimated blood loss Fluids given	Meperidine	Meperidine Diazepam	Meperidine	Meperidine Vitamin K ₁	Meperidine Secobarbital
Post-operative medication					

TABLE I — *concluded*

	6	7	8	9
Patient No.				
Age (yrs)	60	57	40	40
Sex	F	F	F	F
Weight (kg)	96	82.5	45	60
Surface area (m ²)	2.07	1.85	1.4	1.6
Temperature °C	37	37	37	37
Pre-operative medication		Secobarbital		
Pre-operative sedation	Morphine 10 mgm	Meperidine 100 mgm	Morphine 8 mgm Scopolamine 0.4	Morphine 8 mgm Scopolamine 0.4
Anaesthesia:				
Induction	Thiopental 300 mgm Succinylcholine 40 mgm N ₂ O 3.5 L/min O ₂ 2L/min MOF 0.5% for min	Thiopental 380 mgm Gallamine 100 mgm N ₂ O 6.5 L/min O ₂ 2L/min MOF 1.6% into a NBR system for 10 min	Thiopental 300 mgm Succinylcholine 40 mgm N ₂ O 5 L/min O ₂ 2L/min MOF 1% for 10 min	Thiopental 250 mgm Succinylcholine 40 mgm N ₂ O 2.0 L/min O ₂ 2L/min MOF 0.5% for 10 min
Maintenance	N ₂ O 3.5 L/min O ₂ 2L/min MOF 0.5% for 65 min D-tubocurarine 30 mgm	N ₂ O 6.5 L/min O ₂ 2L/min MOF 1.6% for 115 min Gallamine 50 mgm	N ₂ O 3.0 L/min O ₂ 2L/min MOF 0.5% for 30 min N ₂ O 1 L/min O ₂ 1L/min MOF 0.5% for 45 min D-tubocurarine 18 mgm	N ₂ O 2.0 L/min O ₂ 2L/min MOF 0.5% for 35 min D-tubocurarine
Surgical procedure	Cholecystectomy	Exploration of common bile duct	Abdominal hysterectomy	Vaginal hysterectomy
Estimated blood loss Fluids given	85 ml D/s 500 ml Lactated Ringer's Solution 500 ml	100 ml D/s 1000 ml Lactated Ringer's Solution 500 ml	100 ml Lactated Ringer's Solution 2000 ml	300 ml D/s 500 ml Lactated Ringer's Solution 1000 ml
Post-operative medication	Morphine Propoxyphene	Meperidine	Meperidine Secobarbital	Meperidine Secobarbital Prochlorperazine

RESULTS

(1) *Oxalic acid excretion* (Table II and Figure 1)

(a) Methoxyflurane Anaesthesia.

Marked hyperoxaluria occurred after anaesthesia in all patients who received methoxyflurane. The highest values were present on the day after operation and decreased slowly thereafter. In five of the nine patients, values had not returned to normal by the seventh day. Preoperative oxalate excretion ranged from 23 to 42 with a mean of 35. Values on the first postoperative day ranged from 148 to 698 mgm with a mean of 404 mgm. By one week the values ranged from 28 to 184 mgm with a mean of 73 mgm. (Normal less than 55 mgm per day.) Insufficient data were available to calculate the total quantity of methoxyflurane administered to, and absorbed by any particular patient. However, the details in Table I indicate that patient 7 may have absorbed the greatest amount and it was in this patient that the highest oxalate values were obtained.

TABLE II
URINARY OXALATE EXCRETION AFTER METHOXYFLURANE ANAESTHESIA

Patient No.	Oxalate excretion before operation (mgm per day)	Oxalate excretion after operation days after operation (mgm per day)						
		1	2	3	4	5	6	7
1	35	380	217	141	134	84	70	62
2	23	368	159	80	78	85	80	72
3	35	400	196	186	170	162	111	101
4	52	540	390	297	193	190	185	184
5	36	473	412	138	120	102	104	90
6	27	243	227	166	99	71	45	40
7	31	648	550	320	196	126	88	39
8	30	148	105	84	70	52	32	28
9	42	389	229	108	60	58	55	44
Mean	35	404	276	169	113	103	86	73

(b) Halothane Anaesthesia (Table III and Figure 1).

No marked alterations in oxalic acid excretion occurred after halothane anaesthesia; the values remaining normal.

(2) *Other Laboratory Tests*

No alterations in BUN, serum creatinine, electrolytes, calcium, phosphate, uric acid, or osmolality were noted after either methoxyflurane (Table IV) or halothane anaesthesia. Twenty-four-hour urine excretions of protein, creatinine, calcium, phosphate, and uric acid were unchanged. The osmolar clearances were unchanged. The urinalysis in the postoperative period remained unchanged, except for the presence in the methoxyflurane group of large numbers of oxalate crystals.

DISCUSSION

In this study there was no alteration in renal function in the postoperative period with either methoxyflurane or halothane.

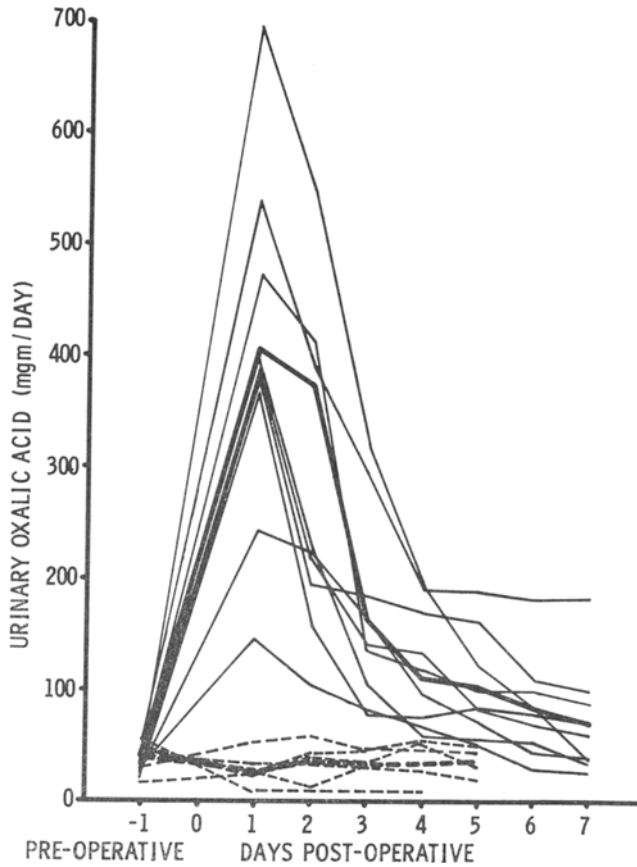


FIGURE 1. Urinary oxalate excretion after methoxyflurane and halothane anaesthesia. The continuous lines represent the daily urinary oxalic acid excretion after methoxyflurane anaesthesia in nine patients. The heavy continuous line represents the mean value. The interrupted lines represent the daily urinary oxalic acid excretion after halothane anaesthesia in six patients. The heavy interrupted line represents the mean value.

TABLE III
URINARY OXALATE EXCRETION AFTER HALOTHANE ANAESTHESIA

Patient No.	Oxalate excretion before operation (mgm per day)	Oxalate excretion after operation days after operation (mgm per day)					
		1	2	3	4	5	6
10	40	33	31	30	27		
11	44	22	41	37	53	33	
12	31	53	58	48	48	46	
13	17	27	42	45	54	52	
14	47	27	14	27	24	20	
15	55	10	9	10	10		
Mean	39	29	33	33	36	38	

TABLE IV
LABORATORY VALUES IN PATIENTS RECEIVING METHOXYFLURANE

Patient No.	Highest post-operative 24-hr urine volume	Highest BUN		Highest creatinine		Highest serum osmolality		Lowest urine osmolality		Highest serum sodium	
		pre-op	post-op	pre-op	post-op	pre-op	post-op	pre-op	post-op	pre-op	post-op
1	1980	12	10	0.8	1.0	307	297	280	197	140	137
2	2100	18	13	0.9	1.1	302	290	302	286	140	139
3	1200	16	16	1.1	1.1	291	292	340	345	140	138
4	1300	24	22	0.9	1.0	304	302	720	682	138	138
5	1600	15	13	0.8	0.7	287	293	408	392	138	139
6	1300	14	11	0.7	1.0	309	300	652	604	138	137
7	1900	15	11	0.9	0.8	297	283	409	437	142	134
8	700	19	17	0.8	1.1	294	298	480	475	136	140
9	2200	8	9	1.0	0.6	296	286	760	680	138	137

Of greater interest was the difference in oxalic acid excretion between the two groups. Oxalic acid excretion increased from 5 to 23 times in the methoxyflurane-treated group, whereas no change in oxalic acid excretion was seen in the halothane-treated group.

The mechanism or site of production of the hyperoxaluria after methoxyflurane anaesthesia is unknown. A recent study in man⁹ showed that between 29 and 35 per cent of absorbed methoxyflurane is exhaled unchanged, 40 per cent is dechlorinated and oxidized to methoxydifluoroacetic acid, and 7 to 21 per cent undergoes cleavage of the ether linkage producing CO₂, fluoride ions, and dichloroacetic acid. If dechlorination of dichloroacetic acid occurs, oxalic acid would be produced. It is also possible that methoxyflurane could interfere with the metabolism of the various precursors of oxalic acid in the liver or intestinal tract, resulting in excessive oxalate production, but these possibilities must await further investigation.

The relationship of oxalic acid excretion and calcium oxalate crystals in the kidney tubules to renal failure is controversial. On the one hand it is known that hyperoxaluria, such as can occur in ethylene glycol intoxication¹⁰ or congenital hyperoxaluria¹¹ can result in failure. Infusion of oxalic acid into animals causes a polyuric renal failure.¹² However, even in acute and chronic renal failure where no hyperoxaluria has occurred, calcium oxalate crystals are frequently seen within the tubules.^{13,14} Their significance is uncertain. In one study, the finding of crystals did not correlate in any way with the severity of renal disease either histologically or clinically.¹³ In another study a direct correlation was found between the quantity of oxalate crystals in the kidney and the duration of oliguria.¹⁴ In patients receiving methoxyflurane, oxalate crystals are present in a greater frequency than in those not receiving methoxyflurane,^{5,6} and the more severe the azotaemia, the higher is the proportion of tubules containing oxalate crystals.⁶

The mechanism by which oxalic acid damages the kidneys is uncertain. Galle,¹⁵ injected large amounts of oxalic acid into rats and studied their deposition in the kidney by light and electron microscopy, and x-ray spectrography. The crystalline deposits first appeared in the cytoplasm of the renal tubular cells. As the crystals grew larger they destroyed the cells and were discharged into the tubular lumen. The crystals may then act to obstruct the lumen directly.

The absence of alteration in renal function during or following the hyperoxaluric state of the patients reported here could indicate that hyperoxaluria plays no part in the etiology of methoxyflurane induced nephrotoxicity. Alternatively greater quantities of oxalic acid may be required in the kidney if demonstrable toxicity is to develop, or additional factors may need to be present. These may include inadequate renal perfusion with blood, inadequate tubular luminal perfusate, and the presence of other drugs. Tetracycline is suspected of having a deleterious effect on renal function when used in patients who have received methoxyflurane anaesthesia.¹⁶

Methoxyflurane nephrotoxicity has also been attributed to the fluoride ion which is a metabolite of methoxyflurane.¹⁷ In 1963, Ditzler¹⁸ questioned the advisability of including the fluorine atom in the structure of anaesthetic drugs. Levels of fluoride in the blood and urine may be very high during and after methoxyflurane

anaesthesia¹⁷ and abnormally high fluoride levels can produce a polyuric state in man.¹⁹

In conclusion, it appears likely that methoxyflurane nephrotoxicity is multifactorial in etiology. The precise role of increased oxalate levels in this syndrome has not yet been elucidated. However, serious consideration should be given to the wisdom of using this agent in those rare patients with congenital hyperoxaluria.

SUMMARY

Oxalic acid excretion was measured in nine patients receiving methoxyflurane and six patients receiving halothane. Oxalic acid excretion increased from 5 to 23 times in the immediate postoperative period in patients receiving methoxyflurane, whereas no increase was noted in those receiving halothane. Despite the striking increase in oxalic acid excretion, no alteration in renal function and no polyuric state developed. The renal failure that occasionally develops after methoxyflurane anaesthesia appears to be multifactorial in origin and a hyperoxaluric state may play a role in some instances.

RÉSUMÉ

On a mesuré l'excrétion d'acide oxalique chez neuf malades anesthésiés au méthoxyflurane et six malades anesthésiés au fluothane. L'excrétion d'acide oxalique a autmenté de 5 à 23 fois durant la période post-opératoire chez les malades anesthésiés au méthoxyflurane alors que chez les autres on n'a noté aucune augmentation. Malgré cette augmentation frappante de l'excrétion d'acide oxalique, il ne se produisit pas de changement dans la fonction rénale ni de polyurie. Bien que l'insuffisance rénale qui se produit quelquefois après l'anesthésie au méthoxyflurane semble être due à plusieurs facteurs, il semble évident que la dose d'anesthésique administrée peut être un facteur crucial.

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