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Fluorometabolites of Methoxyflurane:

Serum Concentrations and Renal Clearances

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The concentrations of inorganic fluoride (F) and organic acid-labile fluoride (OALF) were studied in 15 patients at various times after receiving methoxyflurane. Sera contained 20.3 ± 7.2 (SD) μM F at the end of anesthesia and 35 ± 17 μM F the following day. OALF was present in concentrations of 212.1 ± 65 and 1,108 ± 247 μM at the end of anesthesia and the day after anesthesia, respectively. The concentrations decreased slowly after the second day. Three adolescent patients in the group showed little or no increase in serum F after anesthesia, but serum OALF showed the same levels and changes as in the other patients. The ratio of serum OALF/F remained constant after the first day. The renal clearances of F and OALF averaged 61 ± 43 and 12.7 ± 7.9 ml/min, respectively, and correlated with apparent urine flow rate (r = 0.6). The time course of the serum F concentration is consistent with the hypothesis that F is the causal agent for the polyuria that occasionally occurs after methoxyflurane anesthesia. (Key words: Fluorine; Fluoride; Methoxyflurane; Metabolites; Renal clearance.)

FLUORIDE ION (F), a metabolite of methoxyflurane, is considered a prime suspect in causing the renal dysfunction that occasionally occurs after methoxyflurane anesthesia.[1-4] The original basis for this suspicion arose from the case of a patient who developed polyuria and severe renal failure postoperatively. His serum F concentrations were ten times those of two patients who had also received methoxyflurane but showed no gross renal disturbance postoperatively.[3] The association of elevated serum F concentrations and clinical evidence of renal dysfunction has been confirmed in a well-controlled study by Mazze *et al.*, who used either halothane or methoxyflurane exclusively.[4, 5]

These studies, however, lack information on several points which would help our understanding of the metabolism of methoxyflurane and its relation to the nephrotoxicity. Mazze *et al.* reported no serum F concentrations immediately after the end of anesthesia, so that information about the time course of the serum F concentrations is incomplete. Such data might explain the typically delayed onset of polyuria.[2, 6, 7] The serum F concentrations that can be expected after the usual clinical use of methoxyflurane are not known because of too few patients and questionable methodology in one study[3] and because methoxyflurane was used exclusively in relatively long procedures in the other study.[5] Information about a metabolite containing organic acid-labile fluoride (OALF) is even more limited. Information about its relationship to F is of interest since the scanty data indicate that it is present in concentrations about 30 times higher, making it a potential reservoir for F. Renal clearance of these nonvolatile metabolites has received little attention, but could be very important in determining their serum concentrations.

All of the F and OALF data from patients who had received methoxyflurane anesthesia at the University of Rochester Anesthesia Department were reviewed to gain insight on these points and are the subject of this paper. The cases of 15 patients who received methoxyflurane anesthesia have been studied in

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TABLE 1. Patient Data, Exposure to Methoxyflurane, and Body Weight

	Age (Years)	Sex	Height (Feet, Inches)	Weight (Pounds)	Surgical Procedure	Methoxyflurane Anesthesia		
						Concentration Range (Per cent)	Duration (Hours)	Exposure (Per Cent-Min)
Patient 4	47	M	5-9	170	Gingivectomy	0.5	2.8	75
Patient 5	13	F	5-2	88	Spinal fusion	0.5-0.7	3.7	223
Patient 6	14	F	5-3	101	Spinal fusion	0.25-2.5	6	268
Patient 7	15	M	(5-5)*	108	Myringoplasty	0.6-1.0	2.2	58
Patient 8	24	M	5-9	143	Leg amputation	1.5-2.5	1.1	148
Patient 9	35	F	5-2	(138)*	Lumbar laminectomy	2.0-2.5	1.3	178
Patient 10	24	M	6-2	154	Hand scar repair	0.6-1.5	3.5	181
Patient 11	62	F	5-4	140	Facial fracture repair	0.5	2.2	161
Patient 12	32	M	5-7	150	Lumbar laminectomy	1.5	1.4	130
Patient 13	38	M	5-11	192	Lumbar laminectomy	2.0-2.5	1.1	124
Patient 14	19	M	5-8	154	Facial scar revision	0.25-2.0	2.0	143
Patient 15	59	F	5-5	151	Rhytidectomy	0.8-1.5	2.3	78
Patient 16	25	F	5-1	124	Hysterectomy	0.5-2.5	1.4	107
Patient 17	50	F	(5-4)*	272	Mastoidectomy	0.5-1.5	2	70
Patient 18	62	M	5-7	160	Femoral-popliteal bypass	0.5-2.5	3.2	172

* Estimated.

various degrees of completeness to determine subsequent serum and urinary concentrations of two fluorometabolites, inorganic fluoride (F) and organic acid-labile fluoride (OALF), and renal clearances.

Methods

Inorganic fluoride (F) and acid-labile fluoride (ALF) were analyzed by direct electrode and diffusion methods, respectively.[5] Organic acid-labile fluoride (OALF) is the difference, ALF minus F. Almost all of the samples were analyzed for F on the day they were obtained, often within an hour or two. Clearance values were calculated for urine-collection periods (non-catheterized, generally continuous, 8-hour periods) during which blood samples were taken, and for collection periods when serum levels of F and OALF could be interpolated. Interpolations to midpoint of the urine-collection period were made from both straight-line and curved-line connection of serum data points. The straight-line data were used, but where they differed by more than 10 per cent from curved-line data the values were considered unreliable.

In 11 patients anesthesia was induced with thiopental sodium (Pentothal). Anesthesia was maintained with 50 per cent nitrous oxide and methoxyflurane with a vaporizer setting of 0.1 to 1.5 per cent. Neuromuscular blocking drugs were used as indicated. These patients received what will be referred to as "balanced anesthesia." The total methoxyflurane dose given to every patient was quantitated by the expression "per cent-minutes," which is the sum of the products of vaporizer settings and the respective minutes each setting was used.[9] This measure is given in table 1. Patients 8, 9, 12, and 13 received methoxyflurane only, with nitrous oxide being used initially to speed induction. Methoxyflurane vaporizer settings for these patients ranged from 1.5 to 2.5 per cent. End-tidal concentrations of methoxyflurane were measured at 0.25 to 0.44 vol per cent at various times during the anesthetic courses of Patients 8, 9, and 12, but were not measured for any other patients. Total gas flow rates were 4 l/min or more for all patients.

The ratio of OALF to F was calculated after subtracting from the inorganic fluoride concentration 1 μM, which would be expected to be present from the usual intake of fluoride in water and food.[10] Regression analyses of clearance data and t tests were done with programs published for the Olivetti Underwood Programma 101 computer.[11]

Detailed data for individual patients are contained in a thesis.[12]

Results

The serum inorganic and organic acid-labile fluoride (F and OALF) concentrations as a function of time after anesthesia are summarized in figure 1. Maximum concentrations of OALF appear to be reached later than those of F. The average F and OALF concentrations the day after anesthesia are 35.5 ± 17 and 1,108 ± 247 (SD) μM, respectively. The source of the very large standard deviation of the F concentrations, 49 per cent of the mean, arises from low values in three adolescent patients (5, 6, and 7) and a high value in Patient 13, who received methoxyflurane almost exclusively. The F concentrations for the adolescent patients and the adult patients who received the "balanced anesthesia" are given in table 2. There was no difference between the two groups at the end of anesthesia, but values for the adult patients were nearly doubled at 24 and 48 hours, whereas the concentrations in adolescent patients showed no change. In three patients, 16, 17, and 18, from whom blood was taken at intermediate times between 0 and 1 day, the serum F concentrations at 6–8 hours showed a doubling after anesthesia but showed little change for the next day. The highest serum F and OALF concentrations, 81.5 and 1,608 μM, respectively, were seen 24 hours after operation in Patient 13, who had received high concentrations of methoxyflurane for 84 minutes.

The pattern of Patient 17, an adult, differed from that given in figure 1, or that seen in any other individual. Instead of the usual decreases from the second to the third day, this patient had increases in F, 45 to 63 μM, and OALF, 1,200 to 1,407 μM, associated with marked decreases in urinary output and renal clearance. The renal clearances for three 8-hour periods on the second day were 53 ± 6.7 (SD) ml/min F and 12.3 ± 1.9 ml/min OALF with a flow rate of 1.0 ± 0.25 ml/min. A 5-hour and an 8-hour collection period on the third day just before the blood was drawn showed clearances a third to a sixth as much, with flow rates of 0.54 and 0.31 ml/min.

The longest and most nearly complete urine collection was obtained from Patient 13. In the six days after anesthesia he excreted 16 liters of urine containing 16.3 and 87.3 mmol of F and OALF, respectively. This corresponds to about 6 ml of liquid methoxyflurane. Patient 18 excreted 10.8 and 66.2 mmol of F and OALF, equivalent to about 4.5 ml of methoxyflurane, in 4½ days.

An increase in the ratio of OALF to F in the serum following operation was observed in every patient. For the 13 patients for whom values were obtained immediately after operation and a day later, the ratios were 13.5 ± 7.3 and 36.9 ± 16.7 (SD), which is highly significant ($P < 0.001$). Table 3 shows the breakdown of OALF/F ratios by age of patient at various periods. The table shows that the adolescents had higher OALF to F ratios than the adults one to three days after anesthesia.

Table 4 shows the ratios of OALF/F for the one adolescent (Patient 6) and the five adults for whom such data are available for the period 3–8 days after anesthesia. The increase in the ratio of OALF to F noted between the end of operation and the following day was seen in each patient, but the ratios remained essentially constant thereafter for any given patient.

The renal clearances of F and OALF averaged 61 ± 43 (SD) and 12.7 ± 7.9 ml/min, respectively. The clearances for the first 24 hours were 70 ± 38 and 17 ± 9 ml/min. The large individual variations can be accounted for in part by differences in the apparent urine flow. Regression analysis of these clearance data reveals significant increases of both F and OALF clearances with increasing apparent urine flow rate (see table 5). The renal clearance of OALF correlated with that of F, $r = 0.76$ with $n = 51$. The ratio of the F clearance to the OALF clearance was not significantly different among patients as determined by the t test using the data from the seven patients with three or more clearance values.

Discussion

The time course of the inorganic fluoride (F) concentrations clearly shows that the highest concentrations are not reached in most individuals until some time after cessation of anesthesia and that they frequently do not decrease for two days. The adolescent patient may be an exception, since in the three ob-

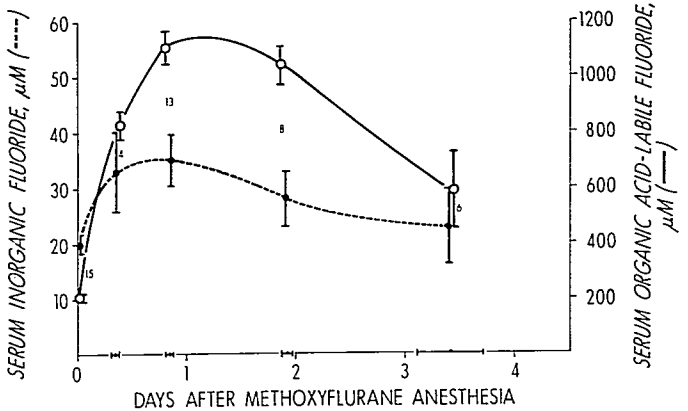

FIG. 1. Serum F (solid circles) and OALF (open circles) concentrations of all samples taken from 15 patients at various times after the end of anesthesia. The numbers are numbers of samples included in the means; bars are SE of the means.

served here, there was little or no increase in serum F after the end of anesthesia. The finding is contrary to Hook's expectation that the F concentration would be highest during the time of anesthesia,[2] but agrees with the observation of Holaday *et al.*[13] that the maximum excretion rate occurred, on the average, 17 hours after anesthesia. Also, the shapes of the curves are consistent with those published by Mazze *et al.*,[5] though the latter lacked data for concentrations at the end of anesthesia. The characteristic delay and prolonged elevation of serum F are consistent with the hypothesis that F is the cause of the polyuria which occasionally starts on the day of anesthesia[6] but more often appears the following day and persists for several days.[7]

The present data give some information about possible reasons for the delay in reaching the maximum serum F concentrations. Decreased renal clearance of F after operation is apparently not a cause, since the average renal clearance of F was slightly greater during the first 24 hours than the overall averages. Our data suggest that OALF becomes an important source of F after about 24 hours, inasmuch as the ratio of serum OALF to F was constant after that time; however, they do not prove that F is arising from OALF.

The maximum F concentrations in adult patients who received "balanced anesthesia" were below the levels thought to cause nephrotoxicity. The eight adult patients in this study had F concentrations of 36.7 ± 6.6 (SD) μM the day after anesthesia. Anesthetized rats (Sprague-Dawley) had increased urine flow and decreased medullary sodium which was just detectable with 50 μM F and increased threefold with about 300 μM F.[14, 15] The relationship between urine flow rate and serum F has been confirmed recently in the Fisher 344 strain of rats given either methoxyflurane or fluoride.[16] In the study of Mazze *et al.*, the patients who had clinical evidence of nephrotoxicity had concentrations of 190 ± 20.9 μM F and those with laboratory evidence only had values of 105 ± 17.8 μM F. Only one of the two patients in the present study who received primarily methoxyflurane and whose serum was sampled the day after anesthesia had a value (81 μM) within the range of those found by Mazze *et al.*[5] The average duration of operation for their patients was about 4 hours,[4] while our two patients received methoxyflurane for 1.5 and 1.1 hours.

TABLE 2. Serum F in Adolescents and Adults, Mixed Anesthesia

	Hours after Anesthesia					
	0		18–25		41–51	
	Number of Patients	Mean ± SD	Number of Patients	Mean ± SD	Number of Patients	Mean ± SD
Ages 13–15 years	3	18.2 ± 9.2 μM	3	17.4 ± 1.7 μM	3	16.5 ± 3.2 μM
Ages >18 years	8	18.9 ± 4.9 μM	8	35.5 ± 8.3 μM	3	35.9 ± 9.4 μM
P		0.9		<0.001		<0.05

TABLE 3. Serum OALF/F Ratios

	Hours after Anesthesia					
	0		6–25		25–80	
	Number of Observations	Mean ± SD	Number of Observations	Mean ± SD	Number of Observations	Mean ± SD
Ages 13–15 years	4	17.2 ± 11.5	4	65.0 ± 15.8	3	65.9 ± 22.4
Ages >18 years	13	10.3 ± 4.5	13	27.5 ± 7.1	8	31.5 ± 6.9
P		0.2		<0.001		<0.05

TABLE 4. Serum OALF/F Ratios

Days after Anesthesia	Patient 6	Patient 12	Patient 13	Patient 16	Patient 17	Patient 18
0	11.5	6.5	11.2	8.7	11.1	12.2
1	49.2	32.0	20.0	30.0	25.7	29.9
2	65.9	43.6	27.4	—	27.7	25.4
3–4	—	33.9	25.4	27.8	22.7	26.3
6–8	69.6	—	25.9	—	—	24.2

TABLE 5. Renal Clearance *vs.* Apparent Rate of Urine Flow

	Number	*r*	Slope	Intercept	*P*
All F	57	0.609	26.5	21.3	<0.001
Reliable F	45	0.560	24.3	25.7	0.001
All OALF	57	0.677	5.46	4.43	<0.001
Reliable OALF	45	0.598	3.96	6.25	0.001

Hence, the data from the two studies are not inconsistent and suggest that the high serum F concentrations associated with renal changes may not occur when methoxyflurane is used in "balanced anesthesia" for less than 3 hours.

The increases in serum F and OALF on the third day in Patient 17, in contrast to the patterns of the other patients, is of interest because of clues it might give to factors determining how well a patient handles methoxyflurane. It may be significant that this patient was very obese (table 1). From consideration of the high lipid solubility of methoxyflurane and from some preliminary data,[17] we believe that the obese patient maintains higher serum F and OALF levels longer than the lean patient. This possibility does not, however, explain why the serum fluoride concentrations 22 and 46 hours after operation were the same, 45 μM, and the 70-hour value was higher, 63 μM. The decrease in clearance values from the second to the third day would provide an explanation. There was also a decrease in urine flow rate; this might have been the cause of the decrease in the clearances.

The renal clearances of F and OALF as a whole appear to be highly variable and related to apparent urine flow rate. The means $\pm$SD found in this study were 61 ± 43 and 12.7 ± 7.9 ml/min, respectively, with a positive correlation with apparent urine flow rate ($r = 0.6$). Inaccurate timing because of the interval collection of the noncatheterized urine samples would lead to such a correlation and probably explains some of the variation and correlation found here. However, the finding compares favorably with recent data from subjects who received radioactive fluoride.[18] Calculations of those data show a renal clearance of 43.6 ± 23 ml/min with a correlation coefficient of 0.8 with the urine flow rate. The clearance of F divided by the clearance of creatinine showed the same relative variability, 0.35 ± 0.18; hence, errors in urine collection were not the cause of variability. Variation is more closely related to chloride clearance than to urine flow rate *per se*, although in experiments with dogs, when chloride clearance was very low, fluoride clearance followed urine flow rate more closely.[19]

Assuming fluoride clearance is affected by urine flow rate or chloride clearance, then it might be possible to prevent excessive serum concentrations and nephrotoxicity by management of fluids and electrolytes. This hypothesis is supported by a recent study in dogs[20] in which a concentrating defect was produced by fluoride during hydropenia, but the same rate of infusion of fluoride was without effect during hypotonic NaCl diuresis. It should be noted that an increased urine flow rate will decrease the concentration of fluoride in the urine, and it may be this, rather than any effect on clearance rates and serum levels, which is responsible for the protective effect noted. In any event, variations in fluid and electrolyte management might provide an explanation for the extreme variation in the reported incidence of nephrotoxicity following methoxyflurane that has been so puzzling.[7]

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Drugs and Their Actions

INTRAOCULAR PRESSURE Changes in intraocular pressure (IOP) in man were compared following topical application of propranolol, lidocaine, and two beta-adrenergic blocking agents devoid of local anesthetic activity. Propranolol and lidocaine had equal local anesthetic effects, and both decreased IOP in normal patients and in patients with simple chronic glaucoma. Neither of the two non-anesthetic beta blockers affected IOP. The authors concluded that the ability of topical propranolol to decrease IOP is related to its anesthetic activity, not to its beta-blocking effect. None of the compounds lowered IOP in acute glaucoma. (*Musini, A., and others: Comparison of the Effect of Propanolol, Lidocaine, and Other Drugs on Normal and Raised Intraocular Pressure in Man, Am. J. Ophthalmol. 72: 773–781, 1971.*)

DRUG-INDUCED PULMONARY EDEMA An episode of acute pulmonary edema in a heroin addict is attributed to alleged intravenous injection of the contents of three capsules (10 mg each) of Librium (chlordiazepoxide). Diffuse rales and rhonchi, frothy pink sputum, and severe arterial hypoxemia ($pH = 7.10$, $P_{O_2} = 28$ torr, $P_{CO_2} = 44$ torr) were present. On the patient's admission to the hospital, the chest x-ray showed diffuse, poorly defined infiltrates throughout both lungs, and a normal heart. The edema cleared after 72 hours following treatment with mechanical ventilation, antibiotics, steroids and alkalinization. No measurements of serum drug levels are reported. (*Richman, S., and Harris, R. D.: Acute Pulmonary Edema Associated with Librium Abuse, Radiology 103: 57–58, 1972.*) EDITOR'S COMMENT: The incidence of pulmonary edema secondary to intravenous self-administration of drugs is likely to increase. We hope that some of these cases will be studied in detail regarding their hemodynamic state (cardiac output, pulmonary artery and capillary wedge pressures, etc.) in order to clarify the cause of the edema. Although the direct "toxic" effect of heroin and other drugs on the pulmonary capillaries has been suggested as a cause, there is little sound evidence to support it. The effect of the drug on ventilation and the ensuing hypoxia are more likely to be responsible. The affected individuals provide an ideal model for studying hemodynamic responses following and during recovery from severe, acute hypoxemia.