■ CLINICAL INVESTIGATIONS

Anesthesiology
83:449–458, 1995

Lippincott–Raven Publishers

Renal Function in Patients with High Serum Fluoride Concentrations after Prolonged Sevoflurane Anesthesia

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Background: **In studies of methoxyflurane-induced nephrotoxicity, renal-concentrating impairment has been observed only when serum inorganic fluoride concentrations exceed 50 μM. Prolonged sevoflurane anesthesia can result in serum inorganic fluoride concentrations in excess of 50 μM. The authors compared renal function after prolonged sevoflurane anesthesia with that after isoflurane anesthesia. In addition, they measured urinary excretion of N-acetyl-β-glucosaminidase (NAG), a sensitive index of renal tubular damage, during the 3-day period after anesthesia.**

Methods: **Thirty-four healthy patients who underwent either sevoflurane (23 patients) or isoflurane (11 patients) anesthesia at a total gas flow of 6 l/min for orthopedic surgery scheduled to last at least 5 h were studied. At 16.5 h after cessation of anesthesia, patients were administered 10 units of vasopressin and urine was collected frequently thereafter for evaluation of urinary osmolality. In addition, urinary excretion of NAG was measured before and on days 1–3 after anesthesia. Based on whether peak fluoride concentrations exceeded 50 μM, 23 patients anesthetized with sevoflurane were assigned to a sevoflurane$_{high}$ group (>50 μM) or a sevoflurane$_{low}$ (<50 μM) group.**

Results: **The eight patients in the sevoflurane$_{high}$ group had a mean peak fluoride concentration of 57.5 ± 4.3 μM. A significant, albeit weak, inverse correlation was found between peak fluoride concentration and maximal urinary osmolality after the injection of vasopressin ($r = -0.42$, $P < 0.05$). Mean maximum urinary osmolality tended to be lower in the sevoflurane$_{high}$ group (681 ± 60 mOsm/kg) than in the other two groups after administration of vasopressin, although the difference among the three groups did not quite reach a statistical significance ($P = 0.068$). One patient had a transient concentrating defect (maximum urinary osmolality = 390 mOsm/kg) on day 1 after anesthesia. Urinary excretion of NAG in both the sevoflurane$_{high}$ and sevoflurane$_{low}$ groups was greater on days 2 and 3 after anesthesia than before anesthesia. The increase in urinary NAG excretion was dose related with sevoflurane, but there was no difference in results of routine laboratory renal tests on days 2 and 3 after anesthesia among the three groups.**

Conclusions: **The authors concluded that sevoflurane anesthesia results in increased serum fluoride concentration, a tendency toward decreased maximal ability to concentrate urine, and increased excretion of NAG. However, the increase in urinary NAG excretion was not indicative of clinically significant renal damage in these patients with no preexisting renal disease. (Key words: Anesthetics, volatile: isoflurane; sevoflurane. Drugs: vasopressin. Ions: fluoride. Kidney: nephrotoxicity; urinary concentrating mechanism.)**

This article is accompanied by an editorial. Please see: Mazze RI, Jamison R: Renal effects of sevoflurane. ANESTHESIOLOGY 83:443–445, 1995.

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Received from the National Defense Medical College, Saitama, Japan, and the Central Hospital of Self Defense Force, Tokyo, Japan. Submitted for publication August 17, 1994. Accepted for publication June 5, 1995. Supported by grants from the Research Foundation of National Defense Medical College and Maruishi Pharmaceutical Company.

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THE nephrotoxicity associated with serum inorganic fluoride concentrations exceeding 50 μM after methoxyflurane anesthesia has been shown to result in impairment of renal-concentrating ability.[1] This threshold was determined by Cousins and Mazze[1] using a vasopressin test. Sevoflurane is biotransformed by hepatic microsomal enzyme P450 IIE1 with the release of inorganic fluoride,[2] and several studies have reported serum fluoride concentrations exceeding 50 μM during and after sevoflurane anesthesia.[3,4] In these studies, however, direct assessment of renal-concentrating ability, including vasopressin tests, was not performed. To our knowledge, there are only two studies in which vasopressin tests after sevoflurane anesthesia have been performed in humans.[5,6] Frink *et al.*[5] administered des-

mopressin intranasally to volunteers before and 1 and 5 days after sevoflurane anesthesia and found no difference between preoperative and postoperative maximal urinary osmolality in subjects administered sevoflurane (9.5 ± 0.1 MAC hours). However, their mean peak fluoride concentration was 47 ± 3 μM, and only three of seven volunteers studied had a peak plasma fluoride concentration in excess of 50 μM. Similarly, in our previous study, the mean peak fluoride concentration of patients undergoing sevoflurane anesthesia (10.6 ± 0.9 MAC hours) was 41.7 μM, although the responses to vasopressin of these patients were similar to those of patients with isoflurane anesthesia.[6] Only one patient exhibited a peak serum concentration greater than 50 μM in our study. Therefore, questions remain concerning the safety of sevoflurane, given that it can produce peak serum fluoride concentrations greater than 50 μM in surgical patients. The current study was designed to evaluate the renal-concentrating ability of patients undergoing sevoflurane anesthesia whose peak serum fluoride concentrations exceeded 50 μM. In addition, we measured urinary excretion of N-acetyl-β-glucosaminidase (NAG), a sensitive and noninvasive indicator of drug-induced renal tubular damage, to evaluate the nephrotoxicity of sevoflurane.

Materials and Methods

Written informed consent for participation was obtained from each patient before study after approval from our hospital ethics committee had been obtained. A total of 34 ASA physical status 1 male patients scheduled to undergo orthopedic surgery expected to last at least 5 h were studied. We selected patients scheduled for peripheral orthopedic surgery without major blood loss, such as knee ligament reconstruction (tables 1 and 2). A tourniquet was inflated during the operation when the surgical site was in an extremity. Patients with abnormal renal function were excluded; normal renal function was confirmed by routine laboratory renal tests, overnight urine-concentrating test, and determination of urinary NAG excretion. Patients were assigned to receive either sevoflurane (23 patients) or isoflurane (11 patients) anesthesia. Thirty minutes after receiving an intramuscular injection of atropine (0.5 mg) and midazolam (0.08 mg/kg), each patient received an intravenous injection of thiopental (3–5 mg/kg) and succinylcholine (1 mg/kg) to facilitate tracheal intubation. A radial arterial catheter was inserted to monitor arterial blood pressure and to obtain blood samples for analysis of arterial blood gases and serum inorganic fluoride concentrations. An intraurethral catheter was inserted to facilitate measurement of urinary output. Anesthesia was maintained with sevoflurane or isoflurane, air, and oxygen ($F_{I_{O_2}} = 0.3$) at a total gas flow of 6 l/min. A semiclosed-circle system with a soda lime canister (Wakolime; Wako Pure Chemical, Osaka, Japan) was used to absorb carbon dioxide. The volatile anesthetic was administered *via* a Penlon vaporizer (PPV Σ; Penlon, Abingdon, United Kingdom) or a Muraco vaporizer (Forawic; Muraco Medical, Tokyo, Japan). Anesthesia was maintained for at least 300 min, even if surgery was completed earlier than anticipated. Ventilation was assisted or controlled to maintain carbon dioxide tension at 40 mmHg and arterial oxygen tension greater than 100 mmHg. End-tidal concentrations of sevoflurane or isoflurane were analyzed with a Capnomac Ultima gas analyzer (Capnomac; Datex, Helsinki, Finland), which was calibrated immediately before each study using a cylinder that contained a mixture of gases of known concentrations. The MAC hours for sevoflurane and isoflurane exposures were each calculated from the percent anesthetic concentration and the duration of anesthetic exposure. The MAC values were 2.05% for sevoflurane[7] and 1.15% for isoflurane.[8] Anesthetic concentration was adjusted by the anesthesiologist to maintain systemic arterial blood pressure within ±20% of baseline.

Serum inorganic fluoride concentration was measured before anesthesia, at 1 h after initiation of anesthesia and then every 2 h during anesthesia, and at 0, 1, 2, 3, 6, 14, 16, 20, 40, and 64 h after cessation of anesthesia. Lactated Ringer's solution was administered 5–6 $ml \cdot kg^{-1} \cdot h^{-1}$ during anesthesia and 2 $ml \cdot kg^{-1} \cdot h^{-1}$ for 16 h after cessation of anesthetic exposure. Thirty minutes after administration of intravenous fluids had been completed—that is, 16.5 h after the end of anesthetic exposure—each patient received a subcutaneous injection of 10 units of aqueous vasopressin, urine was collected every 30 min for 4 h, and urinary osmolality was determined to evaluate renal-concentrating ability. During vasopressin testing, each patient's oral intake was restricted.

Urine collection began 24 h before anesthesia and continued until 72 h after cessation of anesthesia. Before operation and on days 2 and 3 after anesthesia, overnight urine-concentrating ability was determined by restricting oral intake beginning at 8 PM and obtaining one urine specimen at 6 AM the next morning and another 1 h later. The osmolality of the 7 AM specimen

Table 1. Clinical Characteristics of Patients Studied

	Isoflurane	$Sevoflurane_{high}$	$Sevoflurane_{low}$
n	11	8	15
Age (yr)	28 ± 3	24 ± 1	29 ± 2
Height (cm)	168 ± 3	170 ± 2	170 ± 2
Weight (kg)	68 ± 4	75 ± 4	69 ± 3
Anesthetic time (min)	402 ± 18	458 ± 8	435 ± 19
MAC hours	9.2 ± 1.3	14.0 ± 0.7*	9.9 ± 0.7
Mean end-tidal anesthetic concentration (MAC)	1.3 ± 0.5	1.8 ± 0.3*	1.4 ± 0.2
Blood loss (ml)	120 ± 29	67 ± 25	156 ± 69
Amounts of fluid administered during and after anesthesia ($ml \cdot kg^{-1}$)	68.0 ± 1.2	66.6 ± 1.7	68.7 ± 1.9
Surgical site and procedure			
Knee (ligament reconstruction)†	6	8	9
Leg (lengthening of lower legs)†	1	0	1
Hand/arm (nerve transfer)†	1	0	1
Spine (enlargement of spinal canal)	1	0	2
Hip (osteotomy)	0	0	1
Shoulder (arthroplasty)	2	0	1

Values are mean ± SE.

* $P < 0.01$, $sevoflurane_{high}$ *versus* isoflurane.; $P < 0.05$, $sevoflurane_{high}$ *versus* $sevoflurane_{low}$.

† Tourniquet application.

was determined. Clinical laboratory studies were performed immediately before anesthesia and repeated 24, 48, and 72 h after initiation of anesthesia.

All patients received antibiotics perioperatively. The specific antibiotic was determined by the patient's surgeon, who was not involved in the study. No patient received aminoglycosides (33 patients received cephalosporins and one patient aspoxicillin; table 2). Antibiotics were administered intravenously twice a day from immediately after the induction of anesthesia to day 2 or 3 after anesthesia, and thereafter 600 mg cefotiam was administered orally for 3–5 days. Only two patients (patients 17 and 22; table 2) received cefotitam prophylactically (600 mg) for 4 or 5 days before operation because of a puncture wound of the knee.

Serum inorganic fluoride ion was measured with an ion-selective fluoride electrode and Ionalyzer No. 901 (Orion Research, Boston, MA). Serum and urinary osmolality were measured with a Model 3D3 osmometer (Advanced Instruments, Norwood, MA) using a freezing point depression test. Urinary NAG activity was determined by spectrophotometric assay using sodio *m*-cresolsulfonphthaleinyl *N*-acetyl-β-D-glucosaminide as described by Noto *et al.*[9] Urine enzyme activity was expressed relative to creatinine concentration as units of NAG activity/g · creatinine. In our hospital, the normal range of this parameter is 0.04–2.85 U/g · creatinine.

Values are presented as mean ± SE. Subjects receiving sevoflurane were divided into two groups based on whether peak inorganic fluoride concentration exceeded 50 μM ($sevoflurane_{high}$ group) or was less than 50 μM ($sevoflurane_{low}$ group). Differences between the three study groups were analyzed with ANOVA using Scheffé's F procedure. *P* values less than 0.05 were considered to indicate statistical significance. A power analysis was performed to determine the possibility of type II error with the JMP statistical software package (SAS Institute, Inc., Cary, NC) for Macintosh computers.

Results

Eight patients receiving sevoflurane had a peak fluoride concentration greater then 50 μM. Therefore, there were 8 patients in the $sevoflurane_{high}$ group and 15 in the $sevoflurane_{low}$ group. Tables 1 and 2 list the clinical characteristics of the patients studied. There were no hypotensive episodes in any of the patients. The three groups of patients were similar in clinical characteristics, with the exception of MAC hours. Mean MAC hours in the $sevoflurane_{high}$ group were significantly greater than in each of the other two groups ($P < 0.01$, $sevoflurane_{high}$ *vs.* isoflurane; $P < 0.05$, $sevoflurane_{high}$ *vs.* $sevoflurane_{low}$).

Urinary NAG excretion can increase in a variety of circumstances, including after the administration of

Table 2. Results for Individual Patients of Each Group

Group	Patient No.	Age (yr)	Duration of Anesthesia (min)	MAC hour	Peak Fluoride Level (μM)	Duration Greater than 50 μM (h)	Surgical Site	Surgical Procedure	Duration of Tourniquet Inflation (min)	Amounts of Fluid Administered during and After Anesthesia (ml)	Urinary Osmolality after Injection of Vasopressin (mOsm/kg) PRE	Urinary Osmolality after Injection of Vasopressin (mOsm/kg) MAX	Urinary NAG Creatinine Ratio (U/g · creatinine per 24 h) PRE	Urinary NAG Creatinine Ratio (U/g · creatinine per 24 h) MAX	Urinary Osmolality after Overnight Dehydration (mOsm/kg) PRE	Urinary Osmolality after Overnight Dehydration (mOsm/kg) POD2	Urinary Osmolality after Overnight Dehydration (mOsm/kg) POD3	Antibiotic Administered
Isoflurane	1	26	455	11.2	4.7		Knee	Ligament reconstruction	164	5,240	260	790	2.15	1.03	805	850	1,000	Cefotiam
	2	20	475	11.6	3.2		Knee	Ligament reconstruction	156	3,790	295	650	1.09	1.50	845	855	830	Cefotiam
	3	32	395	12.1	6.3		Knee	Ligament reconstruction	226	5,350	452	728	0.56	3.97	807	808	900	Cefotiam
	4	31	440	12.6	7.4		Leg	Lengthening of leg	186	4,050	242	760	1.54	1.85	820	840	825	Cefotiam
	5	21	350	4.1	6.3		Shoulder	Arthroplasty		3,800	530	1,125	2.24	3.64	830	850	800	Cefotiam
	6	28	355	8.1	6.8		Knee	Ligament reconstruction	198	5,020	385	850	1.29	2.05	900	810	850	Cefotiam
	7	33	300	1.6	4.7		Spine	Enlargement of spinal canal		3,790	795	890	1.4	2.68	830	914	820	Cefotiam
	8	21	395	7.9	7.4		Knee	Ligament reconstruction	157	5,430	650	860	0.05	2.13	1,125	930	1,100	Cefotiam
	9	51	415	9.2	4.2		Arm	Nerve transfer		3,750	306	749	1.39	3.91	803	810	861	Cefotiam
	10	21	490	16.2	5.3		Knee	Ligament reconstruction	229	4,060	480	780	1.18	1.80	1,180	948	1,200	Cefotiam
	11	22	350	6.5	4.0		Shoulder	Arthroplasty		6,070	450	790	0.04	2.23	880	865	811	Cefotiam
Mean ± SE		28 ± 3	402 ± 18	9.2 ± 1.3	5.5 ± 0.4				188 ± 12	4,577 ± 257	441 ± 52	816 ± 37	1.17 ± 0.02	2.24 ± 0.30	893 ± 40	865 ± 15	909 ± 40	
Sevoflurane$_{high}$	12	22	425	13.0	51.9	1.1	Knee	Ligament reconstruction	161	5,350	275	567	1.10	2.47	1,079	827	880	Cefotiam
	13	29	465	14.2	86.8	14.3	Knee	Ligament reconstruction	267	4,870	261	708	2.19	20.08	940	872	970	Cefotiam
	14	23	480	15.2	52.6	3.7	Knee	Ligament reconstruction	188	4,460	291	740	1.29	6.89	804	832	826	Cefotiam
	15	22	465	15.7	50.9	3.5	Knee	Ligament reconstruction	173	5,700	490	765	2.35	6.22	1,018	894	1,050	Aspoxicillin
	16	26	470	11.8	56.3	5.9	Knee	Ligament reconstruction	197	5,480	830	980	2.03	5.20	880	926	1,050	Cefmetazole
	17	23	425	16.2	56.8	5.8	Knee	Ligament reconstruction	192	4,610	130	390	2.09	6.30	815	846	963	Cefotiam
	18	20	480	10.9	50.9	0.4	Knee	Ligament reconstruction	288	3,690	550	630	1.25	6.18	852	845	900	Cefotiam
	19	27	450	15.1	53.7	2.1	Knee	Ligament reconstruction	175	5,550	474	670	0.34	2.37	1,120	827	925	Cefotiam
Mean ± SE		24 ± 1	458 ± 8	14.0 ± 0.7	57.5 ± 4.3	4.6 ± 1.6			210 ± 18	4,964 ± 243	413 ± 78	681 ± 60	1.58 ± 0.25	7.06 ± 2.07	939 ± 43	859 ± 13	946 ± 28	
Sevoflurane$_{low}$	20	19	310	5.2	30.6		Knee	Ligament reconstruction	172	3,220	635	770	1.55	2.94	930	950	1,000	Cefotiam
	21	24	440	8.6	31.6		Knee	Ligament reconstruction	155	4,480	225	735	1.98	7.62	820	865	925	Cefotiam
	22	30	440	11.9	41.1		Knee	Ligament reconstruction	82	5,640	430	780	1.63	5.69	1,050	1,000	950	Cefotiam
	23	50	380	8.3	45.0		Spine	Enlargement of spinal canal		4,950	420	940	0.40	5.40	800	853	760	Cefotiam
	24	24	480	13.9	46.8		Knee	Ligament reconstruction	149	4,790	370	735	1.70	2.42	857	861	893	Cefmetazole
	25	22	530	14.3	44.7		Knee	Ligament reconstruction	160	5,400	321	804	1.13	2.55	983	947	868	Cefotiam
	26	38	460	11.3	40.5		Knee	Ligament reconstruction	150	4,410	320	840	1.34	2.30	802	816	860	Cefotiam
	27	33	470	10.3	29.5		Knee	Ligament reconstruction	145	3,690	369	845	0.76	2.21	811	908	889	Cefotiam
	28	31	365	8.4	36.8		Spine	Enlargement of spinal canal		4,610	611	894	1.00	3.34	1,292	863	825	Cefotiam
	29	20	320	6.3	19.5		Knee	Ligament reconstruction	205	4,650	722	1,158	2.15	1.84	1,188	856	1,010	Cefmetazole
	30	27	485	9.5	41.1		Knee	Ligament reconstruction	205	5,000	430	783	1.39	1.98	972	867	909	Cefotiam
	31	44	420	10.2	33.2		Hip	Osteotomy		5,750	620	650	1.08	2.31	900	920	816	Cefotiam
	32	19	425	6.6	33.5		Shoulder	Aryhroplasty		4,060	370	810	0.94	1.91	1,220	1,000	1,250	Cefotiam
	33	27	580	13.7	39.5		Hand	Nerve transfer	405	4,900	470	710	1.70	5.50	812	850	1,016	Cefotiam
	34	25	425	10.5	37.9		Leg	Lengthening of leg	270	5,240	305	705	1.93	718	860	820	896	Cefotiam
Mean ± SE		29 ± 2	435 ± 19	9.9 ± 0.7	36.8 ± 1.9				191 ± 26	4,719 ± 179	441 ± 37	811 ± 32	1.38 ± 0.13	3.68 ± 0.52	953 ± 42	892 ± 15	926 ± 30	

PRE = preadministration or preanesthesia; MAX = maximum urinary osmolality after injection of vasopressin or maximum value in urinary NAG excretion during the 3-day period after anesthesia; POD2 = 2 days postanesthesia; POD3 = 3 days postanesthesia.

various types of antibiotics[10] and surgery.[11] Therefore, we analyzed the data separately for 25 patients who received cephalosporins and underwent tourniquet inflation (7 for isoflurane, 7 for sevoflurane$_{high}$, and 11 for sevoflurane$_{low}$) to reduce the variety of circumstances that might influence urinary NAG excretion. Neither the duration of tourniquet inflation nor the daily dose of cephalosporins administered differed significantly among the three groups. Among these 25 patients, there was no significant difference in mean MAC hours among the three groups (table 3). The mean peak serum fluoride concentration in the sevoflurane$_{high}$ group was 55.8 ± 3.4 μmol/l, observed 1 h after cessation of anesthesia (fig. 1). The mean time that peak fluoride concentrations exceeded 50 μmol/l in this group was 4.6 ± 1.6 h. The mean peak serum fluoride concentration in the sevoflurane$_{low}$ group was 36.8 ± 1.9 μmol/l, observed at cessation of anesthesia (fig. 1). The corresponding value in the isoflurane group (n = 11) was 4.8 ± 0.5 μmol/l, observed 16 h after cessation of anesthesia (fig. 1).

The results of clinical laboratory studies for the three groups are shown in table 4. The three groups did not differ in laboratory baseline values, and no abnormal changes in values of renal function studies were noted during the study period.

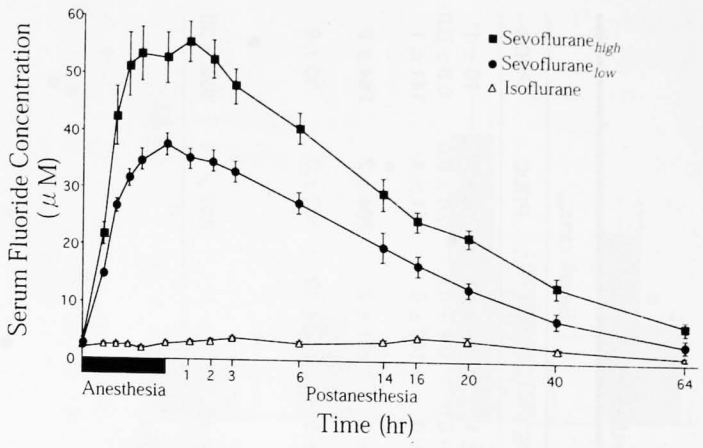


Fig. 1. Mean serum inorganic fluoride ion concentrations during and after sevoflurane or isoflurane anesthesia. The sevoflurane$_{high}$ group (n = 8) consisted of patients with a peak serum fluoride concentration in excess of 50 μmol/l after sevoflurane anesthesia, and the sevoflurane$_{low}$ group (n = 15) consisted of patients whose peak fluoride concentrations were below 50 μmol/l after sevoflurane anesthesia. The mean peak value in the sevoflurane$_{high}$ group was 55.8 ± 3.4 μmol/l (1 h postanesthesia), in the sevoflurane$_{low}$ group 36.8 ± 1.9 μmol/l (at cessation of anesthesia), and in the isoflurane group (n = 11) 4.8 ± 0.5 μmol/l (16 h postanesthesia). Data points represent mean ± SE.

Table 3. Clinical Characteristics of Patients Who Received Cephalosporins and Underwent Tourniquet Inflation

	Isoflurane	Sevoflurane$_{high}$	Sevoflurane$_{low}$
N	7	7	11
Anesthetic time (min)	429 ± 19	456 ± 9	449 ± 24
MAC hours	11.4 ± 1.1	13.8 ± 0.7	10.5 ± 0.9
Mean end-tidal anesthetic concentration (MAC)	1.6 ± 0.3	1.8 ± 0.3	1.4 ± 0.3
Duration of tourniquet inflation (min)	188 ± 12	210 ± 18	191 ± 26
Daily dose administered from after induction of anesthesia to 3 days postanesthesia (g)	2.4 ± 0.3	1.9 ± 0.2	2.2 ± 0.3
Cephalosporins			
Cefotiam	6	6	9
Cefoxitin	1	0	1
Cefmetazole	0	1	1

Values are mean ± SE.

Neither urinary osmolality before vasopressin administration nor the total amounts of fluids administered during and after anesthesia differed among the three groups (tables 1 and 2). The mean maximum urinary osmolalities after injection of vasopressin in the isoflurane, sevoflurane$_{high}$, and sevoflurane$_{low}$ group were 816 ± 37, 681 ± 60, and 811 ± 32 mOsm/kg, respectively (table 2, fig. 2). Although mean maximum urinary osmolality in the sevoflurane$_{high}$ group tended to be lower than that in each of the other two groups, the overall difference marginally failed on one-way ANOVA to reach statistical significance ($P = 0.068$, statistical power = 53%). Power analysis indicated that at least four additional patients were required to obtain a significant difference with the same standard errors and structural results as the current sample. The two patients who exhibited the lowest and second-lowest maximum urinary osmolality belonged to the sevoflurane$_{high}$ group (patients 12 and 17; table 2, fig. 2). The lowest maximal osmolality in the group of all patients was 390 mOsm/kg, in a patient given sevoflurane whose peak serum fluoride concentration was 56.8 μmol/l and whose fluoride concentration remained greater than 50 μmol/l for 6 h (patient 17). There was a significant, albeit weak, inverse correlation between

Table 4. Results of Laboratory Tests of Renal Function for Patients with Prolonged Isoflurane or Sevoflurane Anesthesia

	Isoflurane				Sevoflurane$_{high}$				Sevoflurane$_{low}$			
	PRE	POD1	POD2	POD3	PRE	POD1	POD2	POD3	PRE	POD1	POD2	POD3
BUN (mg/ml)	14 ± 1	9 ± 0*	9 ± 1*	9 ± 1†	13 ± 1	9 ± 1†	10 ± 1*	10 ± 1*	13 ± 1	8 ± 1†	10 ± 1*	10 ± 1*
Creatinin (mg/ml)	0.9 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.0	0.8 ± 0.0	0.8 ± 0.0	0.8 ± 0.0	1.0 ± 0.0	0.8 ± 0.0	0.8 ± 0.0	0.8 ± 0.0
Sodium (mM)	142 ± 1	140 ± 1	140 ± 1	142 ± 1	141 ± 0	140 ± 0	141 ± 1	141 ± 1	142 ± 1	140 ± 1	141 ± 1	141 ± 1
Serum osmolality (mOsm/kg)	281 ± 5	279 ± 3	282 ± 4	285 ± 3	286 ± 2	281 ± 2	284 ± 2	284 ± 2	286 ± 3	282 ± 5	281 ± 4	278 ± 2
Creatinine clearance (ml/min)	95 ± 3	105 ± 5	99 ± 8	90 ± 8	93 ± 2	112 ± 10	103 ± 3	96 ± 9	89 ± 2	116 ± 8	114 ± 13	92 ± 10
Urinary osmolality after overnight dehydration (mOsm/kg)	893 ± 40		865 ± 15	909 ± 40	953 ± 42		892 ± 15	926 ± 30	939 ± 43		859 ± 13	946 ± 28

PRE = preanesthesia; POD1 = 1 day postanesthesia; POD2 = 2 days postanesthesia; POD3 = 3 days postanesthesia; BUN = blood urea nitrogen.
Values are mean ± SE; n = 11 for the isoflurane group, 8 for the sevoflurane$_{high}$ group, and 15 for the sevoflurane$_{low}$ group.
* $P < 0.05$ compared to preanesthetic value.
† $P < 0.01$ compared to preanesthetic value.

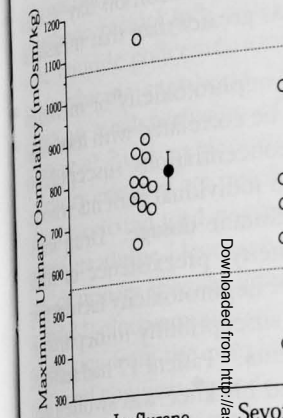
peak fluoride concentration and maximal urinary osmolality after the injection of vasopressin in patients who received sevoflurane ($r = -0.42$, $P < 0.05$).

All patients were able to concentrate urine effectively after overnight dehydration (table 2). In the three groups, urinary osmolality did not differ on day 2 or 3 after anesthesia from the value obtained before anesthesia. In addition, there were no significant differences in overnight urine-concentrating ability among the three groups. Urinary osmolalities after overnight dehydration of the one patient who exhibited impairment of renal-concentrating ability (patient 17) was 815 mOsm/kg before anesthesia, 846 mOsm/kg on day 2 after anesthesia, and 963 mOsm/kg on day 3 after anesthesia (table 2).

The results of measurement of urinary excretion of NAG for the three groups before and 1, 2, and 3 days after anesthesia are shown in fig 3. In the isoflurane group, there was no difference between urinary excretion of NAG during the 3-day period after anesthesia and that before anesthesia. Urinary excretion of NAG in the sevoflurane$_{high}$ and sevoflurane$_{low}$ groups was significantly greater on days 2 and 3 after anesthesia than before anesthesia, and was also significantly greater than that of the isoflurane group on day 2 after anesthesia. The maximum urinary excretion of NAG during the 3-day postoperative period for sevoflurane$_{high}$ was significantly greater than that of the isoflurane group ($P < 0.05$; fig. 4). This significant difference was recognized even in patients limited to those who were administered cephalosporins and underwent tourniquet inflation ($P < 0.05$; fig. 4). The patient whose serum fluoride concentration was highest (86.8 μmol/l) had the highest maximum urinary excretion of NAG (20.08 U/g · creatinine) of all patients studied (patient 13; table 1). No correlation was found between maximum urinary osmolality after injection of vasopressin and maximal urinary excretion of NAG. Urinary NAG excretion by four patients (patients 16, 23, 25, and 33; table 2) was measured until day 7 after anesthesia. In these cases, urinary NAG excretion after anesthesia peaked by postanesthesia day 3, and urinary NAG subsequently returned to normal levels by day 6 after anesthesia (values for these four patients returned to normal levels by days 4, 6, 4, and 3 after anesthesia, respectively).

Discussion

The renal effect of anesthetics would be best studied in volunteers not subjected to surgery.[12] However, we



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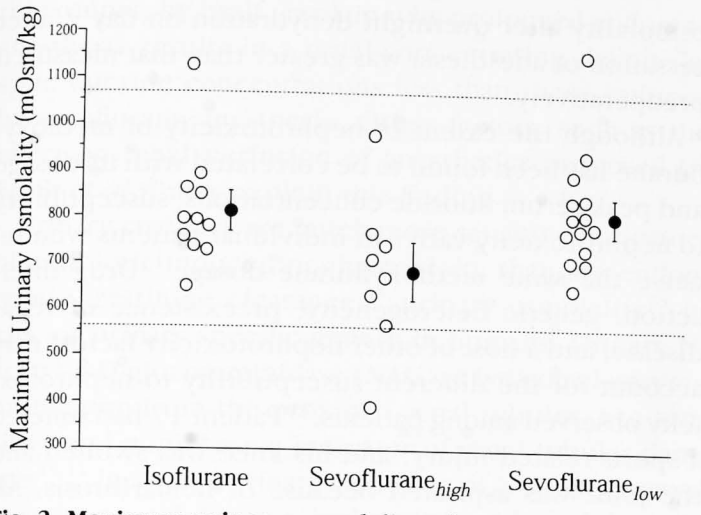

Fig. 2. Maximum urinary osmolality after injection of vasopressin in each patient (open circles). Ten units of aqueous vasopressin was administered 16.5 h after cessation of anesthesia. Closed circles and error bars represent mean ± SE. Mean maximal urinary osmolalities in the isoflurane, sevoflurane$_{high}$, and sevoflurane$_{low}$ groups were 816 ± 37 (650–1125), 681 ± 60 (390–980), and 811 ± 32 (630–1158) mOsm/kg, respectively. The dotted line represents the range of the twice standard deviation from the mean of the isoflurane group. No significant differences were found among the three groups ($P = 0.068$).

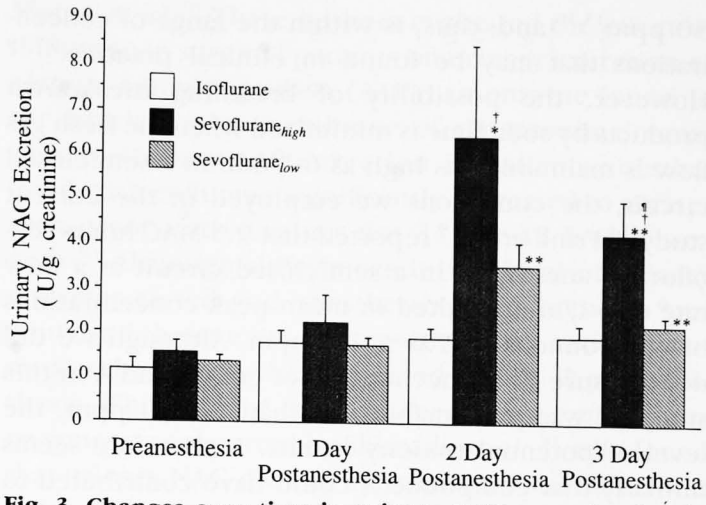

Fig. 3. Changes over time in urinary NAG excretion in the three groups. Urinary excretion of NAG in both the sevoflurane$_{high}$ and the sevoflurane$_{low}$ groups was significantly higher after than before anesthesia. Data points represent mean ± SE. *$P < 0.05$; **$P < 0.01$ compared with each preoperative value. †$P < 0.05$ compared with the isoflurane group. ¶$P < 0.05$ compared with the sevoflurane$_{low}$ group.

believe the effects of surgical trauma and hemorrhage on renal function in the current study were minimal and were probably the same in the three groups, because the sites of surgery in our healthy patients were almost always in the extremities, and blood loss was negligible. In addition, we made an effort to maintain stable hemodynamics. Because we used a Penlon vaporizer, which permits a maximum anesthetic concentration of 7%, we were able to administer higher concentrations of sevoflurane in the current study than in our previous study. We were, therefore, able to obtain patients whose peak inorganic fluoride concentration exceeded 50 μmol/l.

The total dosage of anesthetic in the sevoflurane$_{high}$ group was significantly greater than that in the other two groups (table 1). However, when only those patients who underwent tourniquet inflation were considered, no significant difference was found among the three groups in total anesthetic dosage (table 3). Although MAC hours in the sevoflurane$_{high}$ group tended to be greater than in the other two groups, it is unlikely that poor renal perfusion caused by greater concentration of anesthetics occurred in the sevoflurane$_{high}$ group, because we adjusted individual anesthetic concentrations to maintain stable hemodynamics.

Soda lime, which was used in this study, converts sevoflurane to an olefin referred to as compound A,[13,14] which is nephrotoxic in rats.[15,16] The threshold of compound A for renal tubular necrosis in rats is 25–

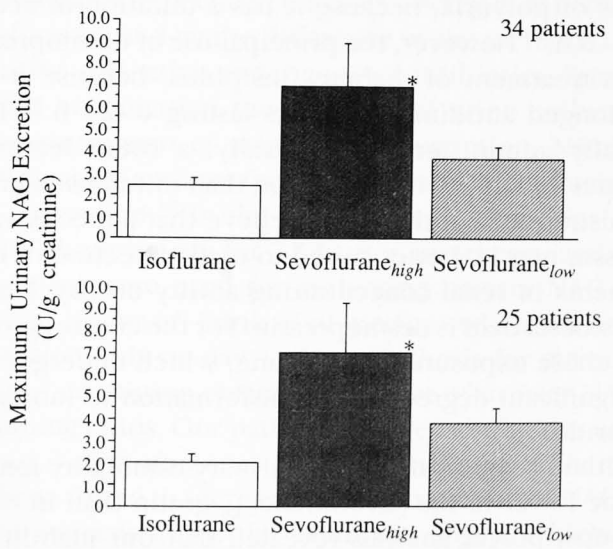

Fig. 4. Maximum urinary NAG excretion after anesthesia. (*Top*) With all patients included (34 patients), maximum urinary NAG excretion after anesthesia in the sevoflurane$_{high}$ group significantly differed from the isoflurane group ($P < 0.05$). (*Bottom*) With patients limited to those who were administered cephalosporins and underwent tourniquet inflation (25 patients), a significant difference was also found in maximum urinary NAG excretion after anesthesia between the sevoflurane$_{high}$ and the isoflurane group ($P < 0.05$).

50 ppm[15,16] and, thus, is within the range of concentrations that may be found in clinical practice.[17,18] However, the possibility of breathing breakdown products by soda lime is minimized when the fresh gas flow is maintained as high as 6 l/min in a semiclosed circuit, the conditions we employed in the current study.[14] Frink *et al.*[19] reported that 9.5 MAC hours sevoflurane anesthesia in a semiclosed circuit at a flow rate of 5 l/min resulted in mean peak concentrations of compound A of 7.6 ± 1.0 ppm. Although we did not measure the concentration of compound A in this study, it was presumably less than 25–50 ppm, the level of potential toxicity in rats. It therefore seems unlikely that compound A could have contributed to production of the transient abnormalities in urinary concentrating ability and NAG excretion detected in this study.

Mazze *et al.*[12] and Frink *et al.*[5] compared responses to vasopressin or desmopressin before and after prolonged anesthesia in volunteers. We were unable to perform vasopressin tests before anesthesia because of limitations created by the length of the preoperative period of study. Overnight preoperative and postoperative urine-concentrating ability testing was, therefore, substituted for comparison of preoperative with postoperative urine-concentrating ability. Aqueous vasopressin is now widely used in the differential diagnosis of polyuria, because it has a duration of action of 2–6 h.[20] However, the principal use of desmopressin is in treatment of diabetes insipidus, because it has prolonged antidiuretic effects lasting 6–24 h.[20] It is usually administered intranasally, a route featuring greater variability in absorption than intramuscular administration. We therefore believe that aqueous vasopressin may be better suited to early detection of decrements in renal-concentrating ability on day 1 after anesthesia than is desmopressin. For the control group, we chose exposure to isoflurane, which undergoes an insignificant degree of biotransformation to inorganic fluoride.

Although mean maximum urinary osmolality tended to be lower in the sevoflurane$_{high}$ group than in other groups, power analysis revealed that our inability to detect a difference among the three groups probably resulted from a type II error. Patient 17, who had the lowest maximum urinary osmolality, appeared to have abnormal renal-concentrating ability, because his value was more than 3 SD less than the mean of the control isoflurane group. This patient's renal function returned to normal by 2 days after anesthesia, because urinary osmolality after overnight dehydration on day 2 after cessation of anesthesia was greater than that measured preoperatively.

Although the extent of nephrotoxicity of methoxyflurane has been found to be correlated with its dosage and peak serum fluoride concentrations, susceptibility to nephrotoxicity varies in individual patients who receive the same methoxyflurane dosage.[1] Drug interaction, genetic heterogeneity, preexistence of renal disease, and a host of other nephrotoxicity factors may account for the different susceptibility to nephrotoxicity observed among patients.[21] Patient 17 had suffered a sports-related injury, and his knee was swollen and the joint was aspirated because of hemarthrosis. Although he had no signs of infection, he prophylactically received 600 mg cefotitam orally each day for 4 days before anesthesia. The results of preoperative renal function testing of patient 17 were normal, as confirmed by laboratory renal tests, an overnight urine-concentrating test, and determination of urinary excretion of NAG (table 1). Preoperative administration of antibiotics may have contributed to the difference in concentrating ability between patient 17 and the two other patients who had similar or greater peak fluoride concentrations (patients 13 and 16). Cephalosporins do not commonly have nephrotoxic effects at therapeutic doses, although they are potentially nephrotoxic.[10,22,23] Furthermore, patient 17 received only a low dose of cefotitam. Consequently, we believe it unlikely that preoperative administration of cefotitam contributed to the concentrating defect in patient 17, although we cannot exclude this possibility entirely.

In neither the study by Frink *et al.*[5] nor our own previous study[6] did any patient anesthetized with sevoflurane exhibit an abnormality in renal-concentrating ability. This may have been the case because of the difference in antidiuretic activity between desmopressin and aqueous vasopressin, and also because only one patient in our study and three patients in the study by Frink *et al.*[5] had a peak serum inorganic fluoride concentration greater than 50 μmol/l. Mazze *et al.*[12] found that a decrease in maximum urinary osmolality occurred after injection of vasopressin tannate in every subject who had undergone prolonged anesthesia with enflurane, although the mean peak fluoride concentration was 33.6 μmol/l. In the study by Frink *et al.*, prolonged enflurane anesthesia (9.5 MAC hours) produced a renal-concentrating deficit in two of seven subjects with mean fluoride concentrations of 26 μmol/l. The shape of the time-concentration curve for serum fluo-

ride cannot, by itself, explain why prolonged enflurane anesthesia results in a renal-concentrating deficit despite fluoride concentrations less than those induced by sevoflurane anesthesia. Other factors, such as the effect on renal perfusion of anesthetics proposed by Frink *et al.*,[5] may explain this finding.

Urinary enzymes are much more sensitive indicators of antibiotic-induced nephrotoxicity than are endogenous creatinine clearance,[24] urinary osmolality[25] in rats, or urinary specific gravity in humans. Urinary N-acetyl-β-D-glucosaminidase (NAG), a lysosomal enzyme originating from the proximal renal tubules, is a sensitive and noninvasive indicator of renal tubular damage.[10,11] Increased urinary excretion of NAG is observed in various renal diseases, in drug-induced renal damage, after surgery, and during episodes of rejection after renal transplantation.[10,11] Urinary excretion of NAG correlated most closely among urinary enzymes with the dose of antibiotic used.[10] Correlations were found between the degree of excretion of NAG and impairment of concentrating ability in dogs[26] and rats[27] with papillary necrosis induced by ethyleneimine. Thus, urinary excretion of NAG is a sensitive indicator of drug-induced renal abnormalities.[10] The extent of increase in urinary excretion of NAG is proportional to the stress induced by surgery.[11] After minor surgery, urinary NAG activity does not increase to more than twice the upper limit of normal.[11] Indeed, the urinary NAG/creatinine ratios for our patients anesthetized with isoflurane did not exceed twice the upper limit of normal. All of our patients received antibiotics. Cephalosporins, as well as aminoglycosides, have been reported to increase urinary NAG excretion.[28,29] In addition, we do not know whether limb ischemia was a factor responsible for the increase in urinary excretion of NAG. Therefore, we compared the urinary excretion of NAG only in those patients who received cephalosporins and underwent tourniquet inflation. Because the maximum urinary NAG/creatinine ratio in the $\text{sevoflurane}_{\text{high}}$ group was significantly greater than that in the isoflurane group, even for this limited set of patients, it is unlikely that limb ischemia, type of surgery, or antibiotic administration accounted for the increase in maximum urinary excretion of NAG in the $\text{sevoflurane}_{\text{high}}$ group in this study.

It is of note that it was not on day 1, but rather on days 2 and 3 postanesthesia, at which time the serum fluoride ion concentrations had returned to normal, that significant elevation of urinary NAG excretion occurred. This finding agrees with those obtained by Motuz *et al.*[30] These authors evaluated the effect of enflurane in surgical patients on urinary excretion of alanine aminopeptidase (AAP), an enzyme found in the brush border membrane of the proximal renal tubule. Urinary AAP excretion in patients anesthetized with enflurane significantly increased to greater than preoperative values not 24 but 48 h after surgery.[30] Although differences in the kind of urinary enzymes tested and anesthetics used between our study and theirs exist, increased urinary excretion of renal tubular enzymes occurred on day 2 postanesthesia. This type of delay in the increase of urinary enzymes was reported by Shimada *et al.*,[31] who found that urinary NAG did not increase until 12 h, but was increased in 12–24-h urine specimens and reached a maximum value within 48 h after injection of inorganic mercury in rats. They suggested that the release of NAG into urine or significant lysosomal degradation occurred at a later time period than mercury damaged proximal tubules. These findings indicate that urinary enzymes in renal tubules do not increase immediately after the serum concentration of the toxin responsible for renal damage reaches a peak value, and that there is a delay in the increase of excretion of urinary enzymes in renal tubules.

In the study by Frink *et al.*,[5] the urinary NAG/creatinine ratio did not increase after prolonged sevoflurane anesthesia. We speculate that this discrepancy between results is caused by the difference in the methods used for urine collection and the use of antibiotics. Frink *et al.* did not mention the duration of urine collection for measurement of urinary NAG excretion. Notably, 24-h samples are best for precise evaluation of urinary NAG excretion.[10] In the current study, urine was collected continuously for 72 h after anesthesia, and 24-h samples were used for evaluating urinary NAG excretion. However, Frink *et al.* performed a 24-h urine collection only on day 4 after anesthesia for measurement of creatinine clearance and not of urinary NAG/creatinine ratios. Our patients received antibiotics until at least 3 days after anesthesia. Cephalosporin therapy has been found to increase urinary excretion of NAG.[28] In the current study, the isoflurane group, which received cephalosporins to an extent similar to the sevoflurane group, had no increase in NAG excretion during the 3-day postanesthesia period, indicating that that increases in urinary NAG excretion were caused by sevoflurane anesthesia. It is possible, however, that cephalosporins potentiated fluoride-induced renal damage, and that, as a result, urinary NAG excretion in both the

$sevoflurane_{high}$ and $sevoflurane_{low}$ groups significantly increased after anesthesia.

Our study demonstrates that sevoflurane administration was associated with a dose-related increase of urinary NAG excretion and a transient, significant defect in concentrating ability in one patient and the tendency toward a transient concentrating defect in a group of patients exposed to a high dose of sevoflurane. In these young, healthy patients without renal disease, the results were inconsequential. However, further studies will be required to establish the safety of sevoflurane anesthesia in patients with preexisting renal disease.

The authors thank the surgeons and nurses in the operating room and orthopedic wards of their hospitals, for their cooperation; Professor Kono, Department of Public Health, National Defense Medical College, for his assistance with statistical analysis; and R. Endo, for his assistance in measuring urinary N-acetyl-β-glucosaminidase excretion.

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Biopharmaceu
Fentanyl Devi

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Steven L. Shafer, M.D.‖

Background: **Compared with**
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Received from the Department
Montréal, Québec, Canada; the De
Alto Department of Veterans Affair
fornia; the Department of Anesthe
Medicine, Stanford, California; an
University of Oregon, Eugene, Or
August 8, 1994. Accepted for publi
in part by the Merit Review Progra
Affairs, a Paul Janssen Fellowshi
Anesthetists, the Anesthesia/Pharm
Palo Alto Institute for Research a
Ohmeda Pharmaceuticals (formerl

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