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Effects of Sevoflurane and Isoflurane on Renal Function and on Possible Markers of Nephrotoxicity

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Background: **Low-flow sevoflurane anesthesia is associated with increasing circuit concentrations of compound A, which is nephrotoxic in rats, but the effect of compound A and low-flow sevoflurane anesthesia on renal function in humans is unclear. The authors compared the effects of high- and low-flow sevoflurane and isoflurane anesthesia on renal function and on several possible markers of nephrotoxicity in humans.**

Methods: **Forty-two patients without preexisting renal disease underwent either low-flow isoflurane (1 l/min, n = 14), low-flow sevoflurane (1 l/min, n = 14), or high-flow sevoflurane (6 l/min, n = 14) anesthesia for body-surface-area surgery scheduled to last at least 4 h. Twenty-four-hour urinary excretion of N-acetyl-β-glucosaminidase (NAG), β_2-microglobulin, protein, glucose, blood urea nitrogen (BUN), and serum creatinine concentrations were measured before and after anesthesia.**

Results: **There were no differences in blood urea nitrogen, creatinine, and creatinine clearance among the three groups after anesthesia. Increased urinary N-acetyl-β-glucosaminidase excretions were seen in the low-flow and high-flow sevoflurane groups, but not in the low-flow isoflurane group ($P < 0.01$). Ten patients in the low-flow sevoflurane group had 24-h urinary excretion of protein that exceeded the normal ranges after anesthesia, but only one patient in the isoflurane and none in the high-flow sevoflurane groups had this.**

Conclusions: **Low-flow sevoflurane anesthesia was associated with mild and transient proteinuria. However, the observed proteinuria was not associated with any changes in blood urea nitrogen, creatinine, and creatinine clearance in these patients with no preexisting renal disease. (Key words: Carbon dioxide absorbent; degradation product; inorganic fluoride.)**

SEVOFLURANE is biotransformed to inorganic fluoride ions[1,2] and degraded to compound A, fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether,[3,4] and it is nephrotoxic in rats.[4–9] However, whether it is toxic in humans has been the subject of several studies.[10–20] Some investigations in humans show increased renal excretion of markers such as α-glutathione-*S*-transferase (α-GST), protein (albumin), and glucose after low-flow sevoflurane anesthesia, suggesting possible nephrotoxicity,[10–12] whereas others show no change.[13–20]

The purpose of this investigation was to evaluate the renal effect of prolonged low-flow sevoflurane anesthesia in surgical patients by evaluating renal standards, such as blood urea nitrogen (BUN) and serum creatinine concentrations and creatinine clearance, and possible markers of nephrotoxicity, such as urinary excretion of N-acetyl-β-glucosaminidase (NAG), β_2-microglobulin, total protein, and glucose.

Methods

Forty-two patients classified as American Society of Anesthesiologists physical status 1 (40 men, 2 women) who were scheduled to undergo dental or orthopedic surgery that was expected to last at least 4 h were studied. Patients who showed evidence of abnormal hepatic or renal function, based on medical history, physical examination, or laboratory tests, were ex-

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cluded from the study. The hospital ethics committee approved the study, and patients gave written informed consent. Patients who were scheduled for surgery at each anatomic site (knee, shoulder, hand, and mandible; a tourniquet was inflated during the operation when the surgical site was in an extremity) were assigned consecutively to one of three groups (n = 14 in each group): the isoflurane group (anesthetized with isoflurane at a total flow of 1 l/min), the low-flow sevoflurane group (anesthetized with sevoflurane at 1 l/min), and the high-flow sevoflurane group (anesthetized with sevoflurane at 6 l/min). Isoflurane was selected as the control anesthetic because it undergoes less biotransformation and degradation by standard carbon dioxide adsorbents.[21,22] The high-flow sevoflurane group was included as a second control group because the use of higher fresh gas flow rates decreases the inspired concentration of compound A.

The anesthetic protocol was designed to result in prolonged high compound A concentrations. To increase the period of anesthesia, it was generally induced 60–90 min before the surgical procedure was expected to begin. 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) or vecuronium bromide (0.1 mg/kg) to facilitate tracheal intubation. After tracheal intubation, anesthesia was maintained with isoflurane or sevoflurane, air, and oxygen (FiO_2 = 0.4) at a total flow rate of 6 l/min. After 5 min, the fresh gas flow rate was reduced to 1 l/min in the low-flow groups. A semiclosed-circle system with a soda lime (Drägersorb 800, Dräger, Luebeck, Germany) was used to absorb carbon dioxide. The carbon dioxide absorbent was changed before the anesthetic was administered to each patient. The anesthesia machine was a North American Dräger Narcomed IIB (Telford, PA). Anesthetic was administered *via* a Penlon PPV Σ vaporizer (Penlon, Abingdon, United Kingdom) or a Muraco Forawic vaporizer (Muraco Medical, Tokyo, Japan). Two sevoflurane or isoflurane vaporizers were linked in series, permitting the administration of a high concentration of sevoflurane or isoflurane to patients in the low-flow system. The flow meters in the anesthesia machine were calibrated using Calibration Analyzer RT-200 (Allied Healthcare, St. Louis, MO) before each study. 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. The lungs were ventilated mechanically to a tidal volume of 8–10 ml/kg, with the ventilatory rate adjusted to maintain an end-tidal carbon dioxide partial pressure of 35–40 mmHg. We connected an "artificial nose" to the endotracheal tube for airway humidification. End-tidal concentrations of sevoflurane or isoflurane were analyzed using a Capnomac Ultima gas analyzer (Capnomac, Datex, Finland) that was calibrated immediately before each study using a cylinder that contained a mixture of gases of known concentrations. Minimum alveolar concentration-hours for sevoflurane and isoflurane exposures were calculated from the percentage anesthetic concentration and the duration of anesthetic exposure. Minimum alveolar concentration values were 2.4% for sevoflurane and 1.28% for isoflurane for the age group studied.[23,24] Anesthetic concentration was adjusted by the anesthesiologist to maintain the mean arterial blood pressure within ±20% of baseline. No adjunct anesthetics nor vasoactive drugs were used. A temperature probe (temperature probe model DT-300, Intermedical Co., Tokyo, Japan) was inserted into the center of the upper absorbent canister, and soda lime temperature was recorded at 5-min intervals. The room temperature was maintained at 25°C, and the humidity was maintained at 50%. Anesthesia was maintained for at least 240 min, even if surgery was completed earlier than anticipated. After completion of the surgical procedure, anesthetic administration was discontinued, and the fresh gas inflow rate was changed to 6 l/min of oxygen. After the patients opened their eyes and took a deep breath after verbal command, the endotracheal tube was removed. Lactated Ringer's solution was administered at 5–6 $ml \cdot kg^{-1} \cdot h^{-1}$ during anesthesia and at 2 $ml \cdot kg^{-1} \cdot h^{-1}$ for 16 h after cessation of anesthetic exposure.

All patients received cefotiam as an antibiotic perioperatively, which was given intravenously twice a day (2 mg per day) from immediately after the induction of anesthesia to day 2 after anesthesia. Thereafter, 600 mg cefotiam was administered orally for 5 days.

Clinical laboratory measures of BUN, creatinine, serum aspartate aminotransferase, alanine aminotransferase, and glucose concentrations were performed immediately before anesthesia and repeated 1, 2, 3, 5, and 7 days after initiation of anesthesia. Urine samples (24 h) were collected before anesthesia and were continued until at least 7 days after anesthesia. These samples were used to measure urinary excretion of NAG, β_2-microglobulin, protein, glucose, creatinine, and inorganic fluoride concentrations. Postanesthetic urine collection began at the end of anesthesia for each 24-h period

from 0–168 h. If urinalysis results were abnormal on day 7 after anesthesia (NAG, β_2-microglobulin, protein, and glucose), 24-h urine collection was continued until urinalysis results returned to normal ranges. The serum inorganic fluoride concentration was measured before anesthesia, 1 h after initiation of anesthesia, every 2 h during anesthesia, and again 0, 1, 2, 3, 16, 40, 64, 112, and 160 h after cessation of anesthesia.

Gas samples were obtained for compound A concentration analysis from the inspiratory limbs of the anesthetic circuit distal to the one-way valves *via* a capped stopcock port, using gas-tight glass syringes (Supelco, Bellefonte, PA). Samples were obtained from the inspiratory limb every 1 h after intubation and at the end of anesthesia. Inspiratory limb gas samples (100 ml) were injected into a sealed evacuated 155-ml sample bottle with stopper and aluminum crimp cap. By injecting 55 ml air, this sealed vacuous sample bottle returned to ambient pressure immediately before the concentrations of compound A in the circuit were measured. Thereafter, gas (200 μl) was extracted using a gas-tight syringe and injected into the gas chromatograph (GC-14A, Shimazu, Japan). A glass column with a length of 5 m and an interval diameter of 3 mm packed with 20% dioctyl phthalate on a Chromosorb WAW (GL Science Co., Tokyo, Japan) 80/100 mesh was maintained at 110°C in the gas chromatograph. The injection port was maintained at 130°C. A carrier stream of nitrogen flowing at 30 ml/min was delivered through the column to a hydrogen flame ionization detector. The gas chromatograph was calibrated by preparing standard calibration gases from stock solutions of compound A supplied by Maruishi Pharmaceutical (Osaka, Japan). Briefly, we prepared 1, 10, 40, and 100 ppm compound A by vaporizing stock solutions of compound A in a 155-ml bottle. We extracted 200 μl gas from the bottle and injected it into the gas chromatograph using a gas-tight syringe. Calibration curves were linear in the range of 1–100 ppm ($r^2 = 0.99$).

Urinary NAG activity, β_2-microglobulin, and clinical laboratory tests, such as BUN, were measured in the clinical laboratories of the Self Defense Force Central Hospital. The clinical laboratories quantitatively assayed the urine for protein and glucose concentrations. These measurements were performed in a single-blinded manner. Serum and urinary inorganic fluoride ions were measured with an ion-selective fluoride electrode and Ionalyzed no. 920 (Orion Research, Boston, MA). Urinary NAG activity (24 h) was determined colorimetrically using a commercially available method (Shionogi, Osaka, Japan). Urinary β_2-microglobulin concentrations were measured by radioimmunoassay (β_2-Micro · RIA-BEARS, Dainabot, Tokyo, Japan). Urinary protein or glucose concentration (24 h) was determined by the pyrogallol red or glucose oxidase peroxidase method. The lowest determinable concentration of protein or glucose in our hospital was 5 mg/dl or 50 mg/dl, respectively. Electrophoresis was used to analyze the composition of total protein concentration in urine samples having concentrations >15 mg/dl by autoanalyzer CTE-150N (Jookou, Tokyo, Japan).

The total compound A exposure was calculated from the areas under the curve (AUC) of compound A concentration *versus* time by using the trapezoid rule (initial concentration was assumed to be zero).[25] Values are presented as mean ± standard deviation when they were distributed normally. Inter- and intragroup comparisons of laboratory data were performed using two-way repeated measures analysis of variance followed by the Student-Newman-Keuls *post hoc* test for multiple comparisons. Analyses of patient demographic data and the maximum data, such as serum fluoride concentrations, were performed with one-way analysis of variance followed by the Student-Newman-Keuls *post hoc* test. Concentrations of urinary excretion of protein and glucose were presented as medians because they were not distributed normally. Comparison of urinary excretion of protein and glucose among the three groups were performed with the Friedman test or Kruskall-Wallis test followed by Dunnett's or Scheffé's F *post hoc* test. The chi-squared analysis was used to determine whether the appearance rate of proteinuria or glucosuria differed among the three groups. Regression analysis was used to evaluate the correlation between inspired compound A AUC or peak serum fluoride concentration and mean values of several markers after anesthesia using Pearson's product-moment correlation coefficient or Spearman's rank test. Differences were considered significant when $P < 0.05$.

Results

Table 1 presents the characteristics of the patients in each of the three groups. There were no differences among groups in any measured variable. The individual peak and mean concentrations of compound A in the low-flow sevoflurane group was 41.2 ± 9.0 ppm and 29.1 ± 7.1 ppm, respectively. The corresponding value in the high-flow sevoflurane group was 7.2 ± 4.8 and

Table 1. Results for Individual Patients of Each Group

Group	Patient No.	Age (yr)	Sex	Height (cm)	Weight (kg)	Duration of Anesthesia (min)	MAC H	Duration of Surgical Procedure (min)	Surgical Site	Surgical Procedure	Duration of Tourniquet Inflation (min)	Blood loss (ml)	Mean Arterial Blood Pressure (mmHg)			Peak Fluoride Level (μM)	Compound A Concentration (ppm)		Compound A inspired AUC (ppm-h)
													Pre	Average	Lowest		Peak	Mean	
Low-flow isoflurane	1	41	M	158	54	250	3.5	195	Mandibula	Internal fixation		51	67	64	55	5.5			
	4	19	M	172	73	305	7.4	178	Shoulder	Arthroplasty		78	78	80	69	5.2			
	7	20	M	160	85	450	11.7	333	Knee	Ligament reconstruction	87	54	67	72	56	7.2			
	10	19	M	167	77	435	9.6	285	Shoulder	Arthroplasty		15	79	77	65	6.8			
	13	38	M	173	73	690	16.9	585	Knee	Ligament reconstruction	322	226	68	81	56	8.6			
	16	29	M	174	60	245	7.4	156	Knee	Ligament reconstruction	114	7	89	75	73	5.7			
	19	27	M	177	69	365	9.5	215	Shoulder	Arthroplasty		246	63	66	56	5.4			
	22	22	M	165	53	500	14.1	400	Knee	Ligament reconstruction	204	40	73	82	68	6.9			
	25	22	M	174	73	340	6.6	255	Shoulder	Arthroplasty		49	67	69	55	2.9			
	28	20	M	186	82	365	9.0	230	Shoulder	Arthroplasty		101	73	69	61	5.4			
	31	46	M	168	78	470	10.8	375	Knee	Ligament reconstruction	89	42	70	82	60	7.2			
	34	19	M	173	60	335	7.3	197	Hand	Internal fixation	74	6	67	70	65	4.5			
	37	19	M	171	67	410	11.9	320	Knee	Ligament reconstruction	255	52	70	80	66	3.4			
	40	20	M	179	65	440	11.2	290	Knee	Ligament reconstruction	149	19	75	84	64	4.0			
Mean ± SD		26 ± 9		171 ± 7	69 ± 10	400 ± 114	9.8 ± 3.4	287 ± 114			162 ± 32	70 ± 76	72 ± 7	75 ± 7	62 ± 6	5.6 ± 1.6			
Low-flow sevoflurane	2	30	M	173	67	480	8.6	325	Knee	Ligament reconstruction	147	4	67	72	55	45.1	38.6	28.5	227.7
	5	24	M	176	85	420	6.6	305	Knee	Ligament reconstruction	218	31	71	69	59	43.5	24.7	20.1	140.9
	8	29	M	170	67	375	11.2	315	Shoulder	Arthroplasty		260	73	73	60	78.8	56.9	46.3	289.6
	11	24	M	175	60	485	8.3	335	Knee	Ligament reconstruction	90	27	77	72	66	60.5	42.4	28.2	228.0

	14	24	M	173	73	300	6.2	214	Shoulder	Arthroplasty		233	76	75	62	55.7	36.6	31.7	158.7
	17	18	M	176	82	440	10.2	308	Knee	Ligament reconstruction	204	15	72	71	59	53.2	48.3	32.7	239.9
	20	26	M	176	79	385	16.4	274	Knee	Ligament reconstruction	168	2	83	85	73	74.4	45.9	36.3	233.1
	23	19	M	173	64	445	6.9	293	Hand	Internal fixation	157	4	76	72	62	36.0	34.0	24.4	180.9
	26	25	M	163	55	420	11.0	288	Knee	Ligament reconstruction	166	3	72	74	61	76.3	49.2	43.2	302.2
	29	21	M	176	78	380	8.7	293	Shoulder	Arthroplasty		72	83	81	69	62.1	40.0	32.0	202.5
	32	29	M	174	80	335	9.6	255	Shoulder	Arthroplasty		208	80	73	67	91.0	25.2	35.1	195.7
	35	26	M	165	63	370	8.3	265	Mandibula	Internal fixation		85	73	83	64	42.3	45.9	22.0	135.8
	38	21	M	178	65	340	8.0	285	Knee	Ligament reconstruction	112	39	74	73	62	63.4	42.5	38.8	220.0
	41	23	F	154	54	425	10.4	302	Shoulder	Arthroplasty		199	67	67	65	75.2	46.7	34.8	246.8
Mean ± SD		24 ± 4		172 ± 7	69 ± 10	400 ± 55	9.3 ± 2.6	290 ± 31			158 ± 15	84 ± 96	75 ± 5	74 ± 7	63 ± 5	61.3 ± 16.3*	41.2 ± 9.0†	29.1 ± 7.1†	192.1 ± 45.6†
High-flow	3	18	M	176	65	440	8.7	317	Shoulder	Arthroplasty		82	67	61	55	68.9	9.2	7.0	51.3
sevoflurane	6	31	M	172	55	305	4.0	215	Hand	Internal fixation	69	5	72	69	59	24.1	1.9	1.3	6.6
	9	25	M	172	75	465	11.4	310	Knee	Ligament reconstruction	245	158	78	85	67	66.3	4.8	4.1	32.1
	12	32	M	166	63	305	6.2	175	Shoulder	Arthroplasty		51	79	80	71	34.8	3.7	2.7	13.6
	15	20	M	173	75	465	11.8	321	Shoulder	Arthroplasty		87	85	90	75	82.3	13.6	6.3	48.5
	18	21	M	179	69	240	4.6	215	Knee	Ligament reconstruction	120	15	77	78	64	40.4	2.7	2.1	8.6
	21	22	M	183	69	345	6.7	280	Shoulder	Arthroplasty		189	69	67	56	32.1	12.2	5.1	29.2
	24	27	M	178	56	240	5.7	215	Mandibula	Internal fixation		23	69	74	60	32.1	2.4	2.0	8.2
	27	31	M	172	72	450	10.9	345	Knee	Ligament reconstruction	237	43	81	83	67	72.1	5.4	4.4	32.6
	30	21	M	174	71	475	8.9	329	Knee	Ligament reconstruction	200	23	76	73	63	61.2	15.1	9.6	76.1
	33	25	F	161	60	485	10.2	395	Knee	Ligament reconstruction	79	8	71	84	71	67.7	8.2	1.8	14.6
	36	24	M	179	74	480	14.1	331	Knee	Ligament reconstruction	145	7	77	77	63	67.4	4.7	6.5	51.8
	39	32	M	160	68	425	17.4	295	Knee	Ligament reconstruction	78	62	74	77	60	89.5	2.8	6.8	47.9
	42	29	M	171	72	460	10.9	308	Shoulder	Arthroplasty		10	67	66	55	58.3	13.7	4.1	31.1
Mean ± SD		26 ± 5		173 ± 7	67 ± 7	399 ± 91	9.4 ± 3.8	289 ± 62			147 ± 26	55 ± 58	75 ± 6	76 ± 8	63 ± 6	56.9 ± 20.5*	7.2 ± 4.8	3.9 ± 2.2	27.6 ± 18.3

Pre = preanesthesia; Average = average mean arterial blood pressure during anesthesia; Lowest = the lowest mean arterial blood pressure during anesthesia; AUC = area under the curve.

* $P < 0.01$ *versus* isoflurane group.

† $P < 0.01$ *versus* high-flow sevoflurane group.

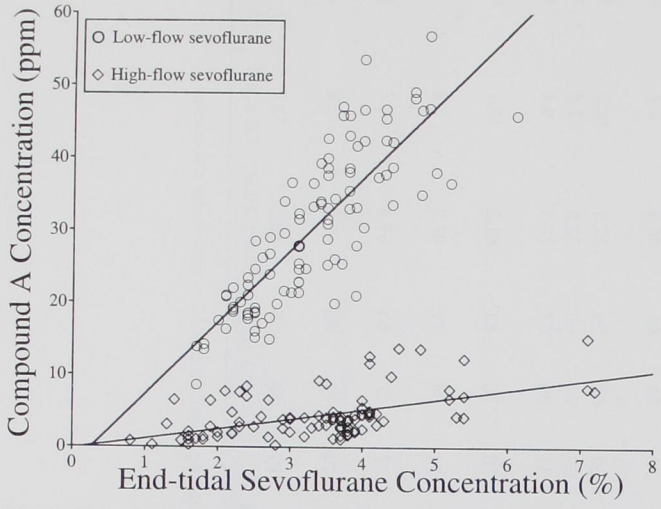

Fig. 1. The relation between compound A concentration and end-tidal sevoflurane concentration in the low-flow sevoflurane ($r^2 = 0.69$, $P < 0.001$) and high-flow sevoflurane groups ($r^2 = 0.30$, $P < 0.001$). The range of values obtained for compound A concentration was 8.6–56.9 ppm in the low-flow sevoflurane group and 0.3–15.1 ppm in the high-flow sevoflurane group.

3.9 ± 2.2 ppm, respectively (table 1). A strong relation was found between compound A concentration and end-tidal sevoflurane concentration in the low-flow sevoflurane group ($r^2 = 0.67$; $P < 0.001$; fig. 1). In contrast, the correlation between compound A concentration and end-tidal sevoflurane concentration in the high-flow sevoflurane group, although significant, was weaker ($r^2 = 0.30$; $P < 0.001$; fig. 1).

Serum fluoride concentrations and urinary excretion of fluoride in both the low-flow sevoflurane and high-flow sevoflurane groups were significantly greater than in the isoflurane group during or after anesthesia at both times (fig. 2). There were no significant differences between the low-flow sevoflurane and high-flow sevoflurane groups with respect to serum fluoride concentrations and urinary fluoride excretion (fig. 2).

Table 2 lists the normal ranges of several markers among patients in our hospital. Clinical laboratory baseline values did not differ in the three groups, and no abnormal changes in values of renal function studies were noted during the study period; neither elevated BUN and serum creatinine concentrations nor decreased creatinine clearances in any patients was seen (figs. 3–5).

Results of measurement of 24-h urinary excretion of NAG and β_2-microglobulin, protein, and glucose concentrations for the three groups before and 1–7 days after anesthesia are shown in figures 6–8 and table 3. Increased NAG excretions were seen in both the low-flow sevoflurane and high-flow sevoflurane groups (fig. 6). There were significant differences between the low-flow isoflurane group and the other two groups with respect to the maximum and mean values for urinary excretion of NAG. However, no significant difference existed in corresponding values between the low-flow sevoflurane and high-flow sevoflurane groups (table 3). Although urinary excretion of β_2-microglobulin (24 h) in the low-flow sevoflurane group was significantly greater on days 2–5 after anesthesia than before anesthesia, there was no significant difference among the three groups (fig. 7). There were also no significant differences in the maximum and mean values for urinary excretion of β_2-microglobulin among the three groups (table 3). Ten patients in the low-flow sevoflurane group showed 24-h urinary excretion of protein that exceeded the normal range of 150 mg/24 h after anesthesia. In contrast, one patient in the isoflurane group and none in the high-flow sevoflurane group exhibited a urinary excretion of protein >150 mg/24 h ($P < 0.01$; table 3). Urinary excretion of protein (24 h) was significantly higher than in both the isoflurane and high-flow sevoflurane group on days 1–4 after anesthesia (fig. 8). Furthermore, the maximum 24-h urinary protein excretion in the low-flow sevoflurane group was significantly greater than in the other two groups ($P < 0.01$; table 3). Electrophoresis revealed that the excreted protein consisted of approximately 80% albumin, 3% α_1-globulin, 4% α_2-globulin, 6% β-globulin, and 7% γ-globulin. There was no significant difference among the three groups in the number of patients who showed glucosuria or the maximum 24-h urinary excretion of glucose (table 3), although three patients in the low-flow sevoflurane group showed glucosuria after anesthesia (table 3; patients 26, 35, and 38); these three patients had the highest urinary excretion of protein in the low-flow sevoflurane group (table 3). However, the relation between proteinuria and glucosuria evident in the low-flow sevoflurane group was not found between proteinuria and increased eyzymuria or β_2-microglobulinuria; there was no correlation between urinary excretion of the amount of protein and of the amount of NAG or β_2-microglobulin (table 3).

No correlation was found between inspired compound A AUC and creatinine clearance (data not shown). There was also no correlation between peak fluoride concentration and the mean 24-h urinary excretion of β_2-microglobulin or protein in all patients and between inspired compound A AUC and the mean 24-h urinary excretion of NAG or β_2-microglobulin in patients who received sevoflurane (figs. 9B–E). The correlations between peak fluoride concentration and the mean 24-h urinary excretion of NAG in all patients and between inspired compound

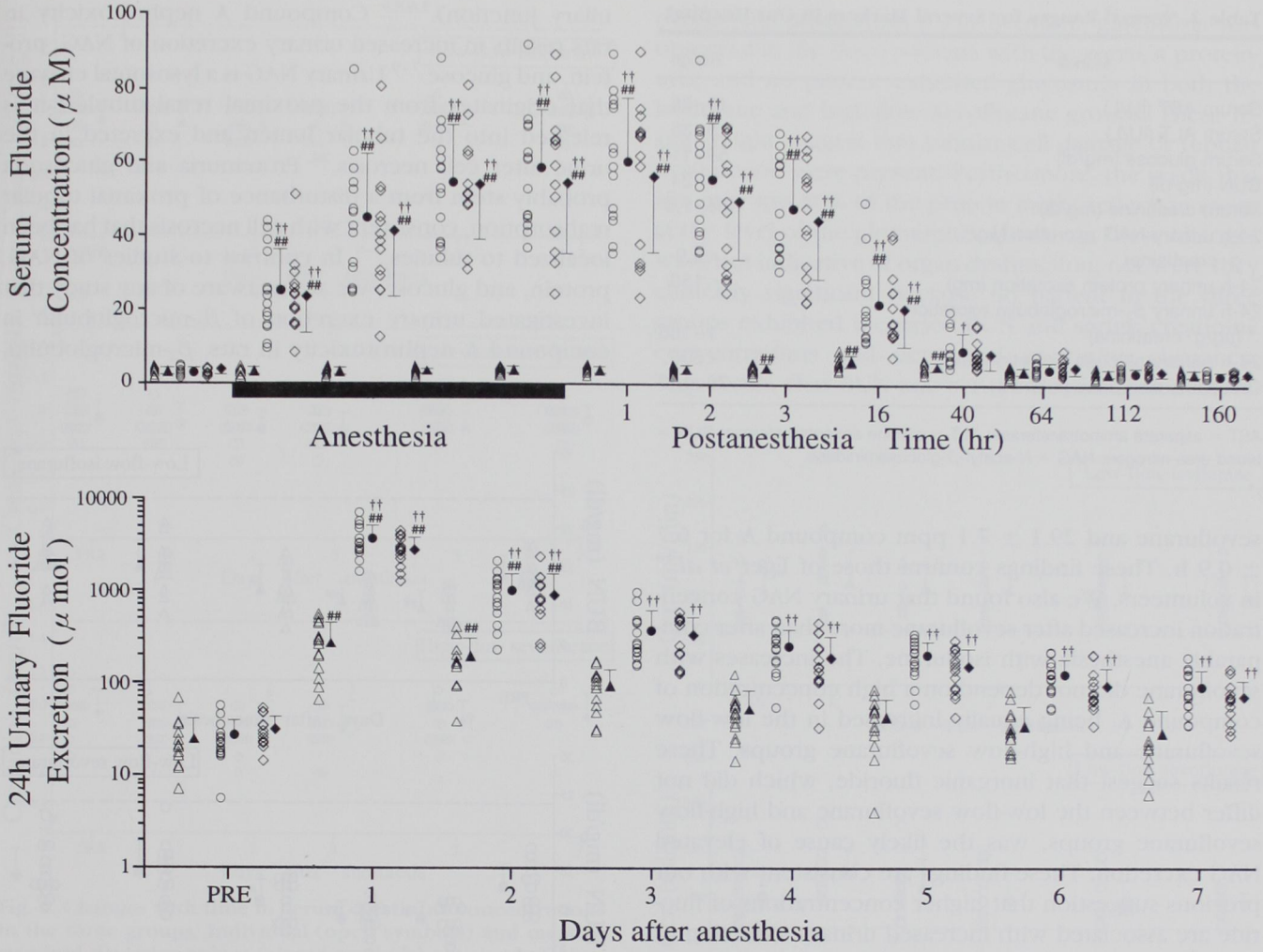

Fig. 2. Changes with time in serum inorganic fluoride concentrations (*top*) and 24-h urinary fluoride excretion (*bottom*) in the three groups. Individual (open symbols) and mean ± standard deviation values (closed symbols) are shown (triangle = low-flow isoflurane, circle = low flow sevoflurane, square = high-flow sevoflurane; n = 14). Note the logarithmic scale used in this graph. There was no significant difference in serum fluoride concentrations and urinary fluoride excretion between the low-flow sevoflurane and high-flow sevoflurane groups. ##$P < 0.01$ compared with each preoperative values. †$P < 0.05$, ††$P < 0.01$ compared with the isoflurane group.

A AUC and the mean 24-h urinary excretion of protein in patients who received sevoflurane were weak, although significant ($r^2 = 0.20$, $P = 0.003$ *versus* $r^2 = 0.17$, $P = 0.003$, respectively; figs. 9A, 9F). However, no correlation between peak fluoride concentration and the mean 24-h urinary excretion of NAG and between inspired compound A AUC and the mean 24-h urinary excretion of protein was found in the low-flow sevoflurane group ($P = 0.78$, $P = 0.89$).

Values for the serum aspartate aminotransferase and alanine aminotransferase increased slightly in the three groups compared with the preoperative values (table 4). There were no significant differences in aspartate aminotransferase and alanine aminotransferase values on the postanesthetic days (table 4) nor in the number of patients who exhibited abnormal value of aspartate aminotransferase or alanine aminotransferase among the three groups. No significant difference existed in the maximum or mean values for aspartate aminotransferase or alanine aminotransferase after anesthesia among the three groups (data not shown).

Discussion

Urinary excretion of protein increased in patients breathing 1.4 ± 0.4 minimum alveolar concentration

Table 2. Normal Ranges for Several Markers in Our Hospital

Marker	Range
Serum AST (IU/L)	10–35
Serum ALT (IU/L)	5–35
Serum glucose (mg/dl)	50–110
BUN (mg/dl)	8–24
Serum creatinine (mg/dl)	0.8–1.5
24-h urinary NAG excretion (μg/g · creatinine)	<2.9
24-h urinary protein excretion (mg)	<150
24-h urinary β_2-microglobulin excretion (μg/g · creatinine)	1–165
24-h urinary glucose excretion (mg)	<500
Creatinine clearance (ml/min)	70–140

AST = asparate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; NAG = *N*-acetyl-β-glucosaminidase.

sevoflurane and 29.1 ± 7.1 ppm compound A for 6.7 ± 0.9 h. These findings confirm those of Eger *et al.*[10] in volunteers. We also found that urinary NAG concentration increased after sevoflurane more than after comparable anesthesia with isoflurane. The increases with sevoflurane did not depend on a high concentration of compound A, being equally increased in the low-flow sevoflurane and high-flow sevoflurane groups. These results suggest that inorganic fluoride, which did not differ between the low-flow sevoflurane and high-flow sevoflurane groups, was the likely cause of elevated NAG excretion. These findings are consistent with our previous suggestion that higher concentrations of fluoride are associated with increased urinary excretion of NAG.[26]

The chemical structure of Compound A contains six fluoride atoms and undergoes cytochrome P-450-catalyzed defluorination at the fluoromethyl moiety,[9,27] which is similar to the P450-catalyzed defluorination of sevoflurane. Therefore, Eger *et al.*[10] speculated that defluorination of compound A may increase serum fluoride concentrations. Indeed, urinary excretion of fluoride increases in rats that receive compound A intraperitoneally.[9] However, in the current study no significant difference occurred between the low-flow sevoflurane and high-flow sevoflurane groups with respect to serum and urine fluoride concentrations. These results suggest that *in vivo* fluoride formation from compound A metabolism is not significant compared with that from sevoflurane.

The site of compound A nephrotoxicity in rats was the renal tubule, especially the tubulus in the region of the outer strip of the outer medullary layer (corticomedullary junction).[5,6,8,9] Compound A nephrotoxicity in rats results in increased urinary excretion of NAG, protein, and glucose.[7–9] Urinary NAG is a lysosomal enzyme that originates from the proximal renal tubules; it is released into the tubular lumen and excreted in the urine after cell necrosis.[28] Proteinuria and glucosuria probably stem from a disturbance of proximal tubular reabsorption, consistent with cell necrosis that has been localized to tubules.[7–9] In contrast to studies of NAG, protein, and glucose, we are unaware of any study that investigated urinary excretion of β_2-microglobulin in compound A nephrotoxicity in rats. β_2-microglobulin,

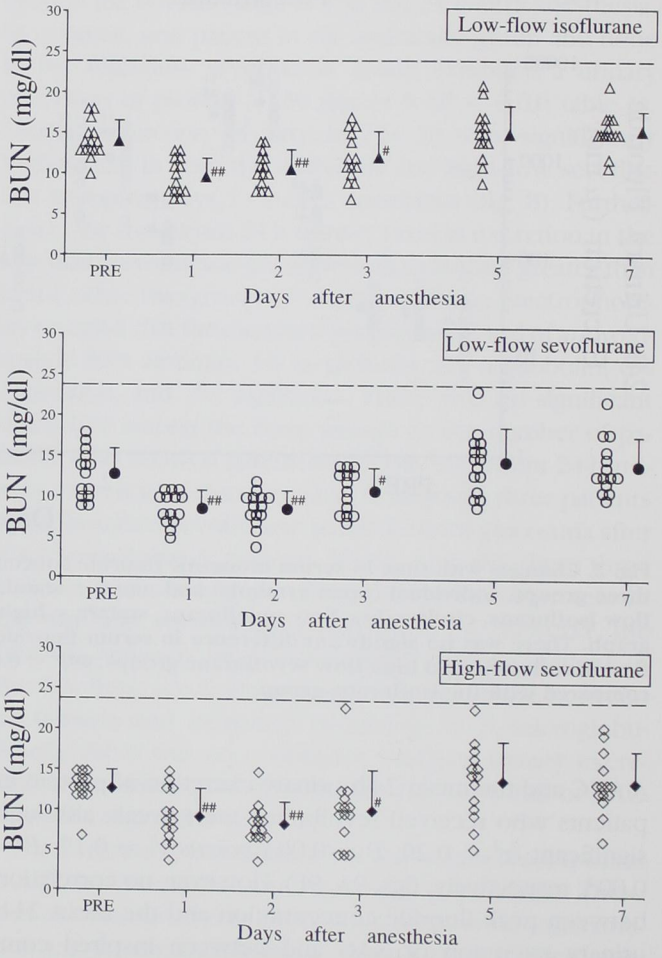

Fig. 3. Changes with time in blood urea nitrogen (BUN) concentrations in the three groups. Individual (open symbols) and mean + standard deviation values (closed symbols) are shown (triangle = low-flow isoflurane, circle = low flow sevoflurane, square = high-flow sevoflurane; n = 14). The dotted line represents the upper limit of the reference range. No abnormal changes in BUN were noted during the study period. #*P* <0.05, ##*P* <0.01 compared with each preoperative value.

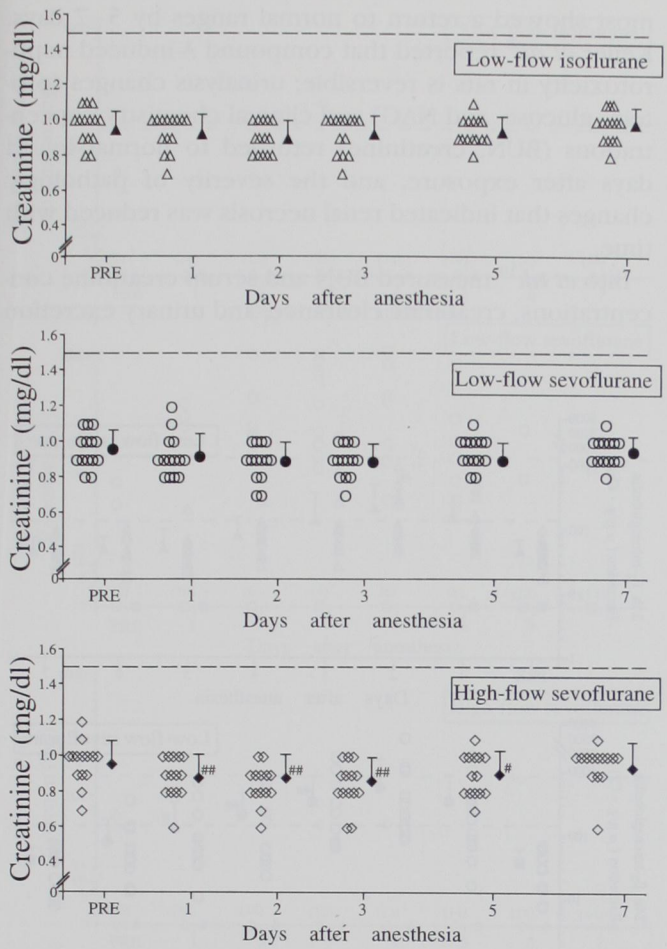

Fig. 4. Changes with time in serum creatinine concentrations in the three groups. Individual (open symbols) and mean + standard deviation values (closed symbols) are shown (triangle = low-flow isoflurane, circle = low flow sevoflurane, square = high-flow sevoflurane; n = 14). The dotted line represents the upper limit of the reference range. No abnormal changes in serum creatinine concentration were noted during the study period. *#P* <0.05, *##P* <0.01 compared with each preoperative value.

a low-molecular-weight protein, is freely filtered through the glomerulus; >99% is reabsorbed by the proximal convoluted tubules, therefore, urinary excretion of β_2-microglobulin is used as a measure of abnormal tubular function.[28]

In the current study, increased urinary NAG:creatinine ratios were seen in both the low-flow sevoflurane and high-flow sevoflurane groups. The significant excretion of NAG in the high-flow sevoflurane group corresponds with findings from our previous studies.[26] Twenty-four-hour urinary excretion of protein in the low-flow sevoflurane group was significantly greater than in the other groups. Furthermore, glucosuria was observed in the three patients with the greatest proteinuria, and no patient exhibited glucosuria in both the isoflurane and high-flow sevoflurane groups. These results might suggest that tubular cell damage or tubular dysfunction were present. Furthermore, the result that albumin was 80% of the protein might reflect an event at the level of the glomerulus. However, these changes were not indicative of organ dysfunction, nor were they clinically significant because no patient in the three groups exhibited increased BUN and serum creatinine concentrations and decreased creatinine clearance. This result, that BUN and serum creatinine concentra-

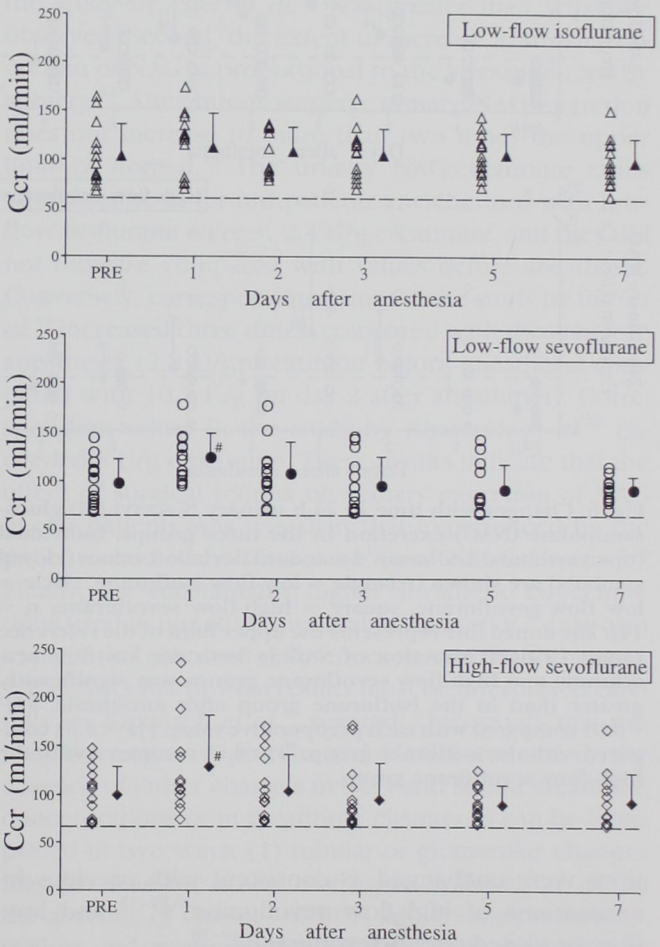

Fig. 5. Changes with time in creatinine clearance in the three groups. Individual (open symbols) and mean + standard deviation values (closed symbols) are shown (triangle = low-flow isoflurane, circle = low flow sevoflurane, square = high-flow sevoflurane; n = 14). The dotted line represents the lower limit of the reference range. No abnormal changes in creatinine clearance were noted during the study period. *#P* < 0.05 compared with each preoperative value.

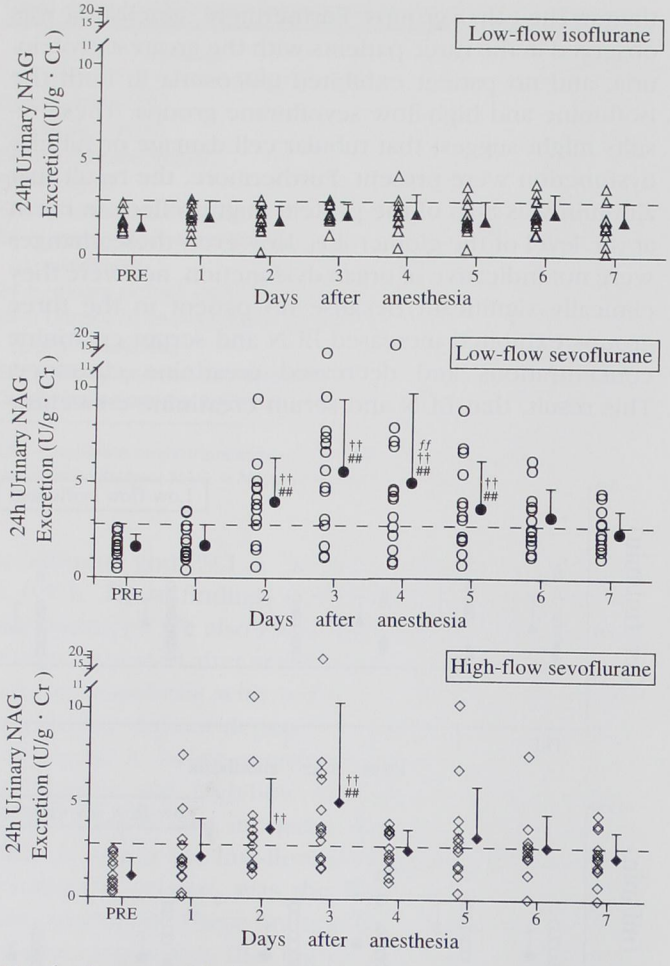

Fig. 6. Changes with time in 24-h urinary N-acetyl-β-D-glucosaminidase (NAG) excretion in the three groups. Individual (open symbols) and mean + standard deviation values (closed symbols) are shown (triangle = low-flow isoflurane, circle = low flow sevoflurane, square = high-flow sevoflurane; n = 14). The dotted line represents the upper limit of the reference range. Urinary excretion of NAG in both the low-flow sevoflurane and high-flow sevoflurane groups was significantly greater than in the isoflurane group after anesthesia. ##P <0.01 compared with each preoperative value. ††P <0.01 compared with the isoflurane group. ff$P$ <0.01 compared with the high-flow sevoflurane group.

tions were unchanged, is consistent with previous investigations of high-flow sevoflurane[26,29-33] and low-flow or closed-circuit sevoflurane.[10-20]

The urinary abnormalities in this study were transient, consistent with previous investigations in volunteers[10] and rats.[8] Eger *et al.*[10] reported that the urinary abnormalities (protein, glucose, and α-glutathione-*S*-transferase) were greatest 2 or 3 days after anesthesia in volunteers who received low-flow sevoflurane, but most showed a return to normal ranges by 5–7 days. Keller *et al.*[8] reported that compound A-induced nephrotoxicity in rats is reversible; urinalysis changes (protein, glucose, and NAG) and clinical chemistry concentrations (BUN, creatinine) returned to normal by 14 days after exposure, and the severity of pathologic changes that indicated renal necrosis was reduced with time.

Bito *et al.*[19] measured BUN and serum creatinine concentrations, creatinine clearance, and urinary excretion

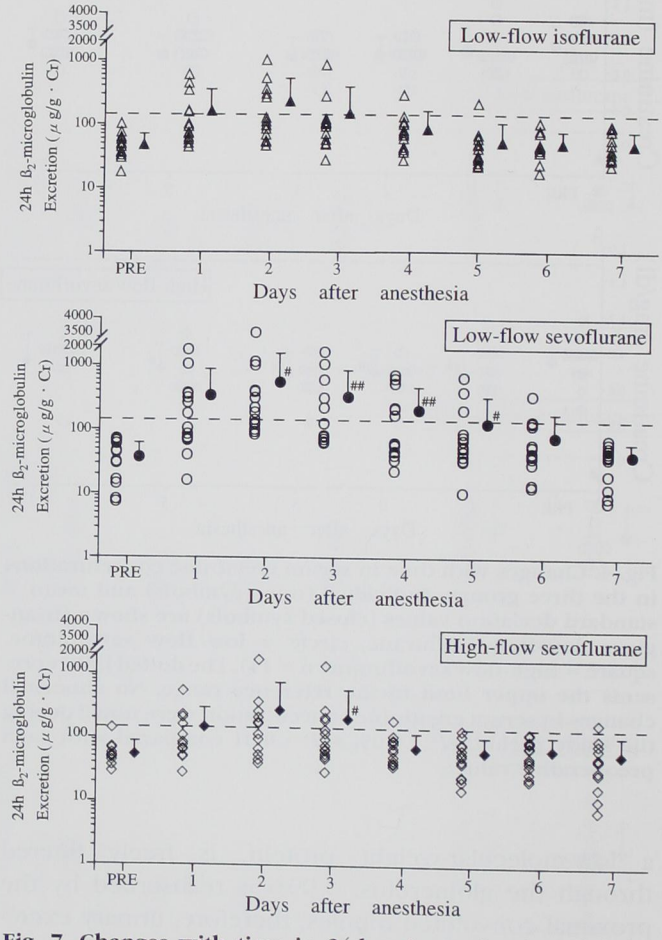

Fig. 7. Changes with time in 24-h urinary β_2-microglobulin excretion in the three groups. Individual (open symbols) and mean + standard deviation values (closed symbols) are shown (triangle = low-flow isoflurane, circle = low flow sevoflurane, square = high-flow sevoflurane; n = 14). Note the logarithmic scale used in this graph. The dotted line represents the upper limit of the reference range. Urinary excretion of β_2-microglobulin in both the low-flow sevoflurane and high-flow sevoflurane groups was significantly greater after anesthesia than before anesthesia. There was no significant difference among the three groups. #P <0.05, ##P <0.01 compared with each preoperative value.

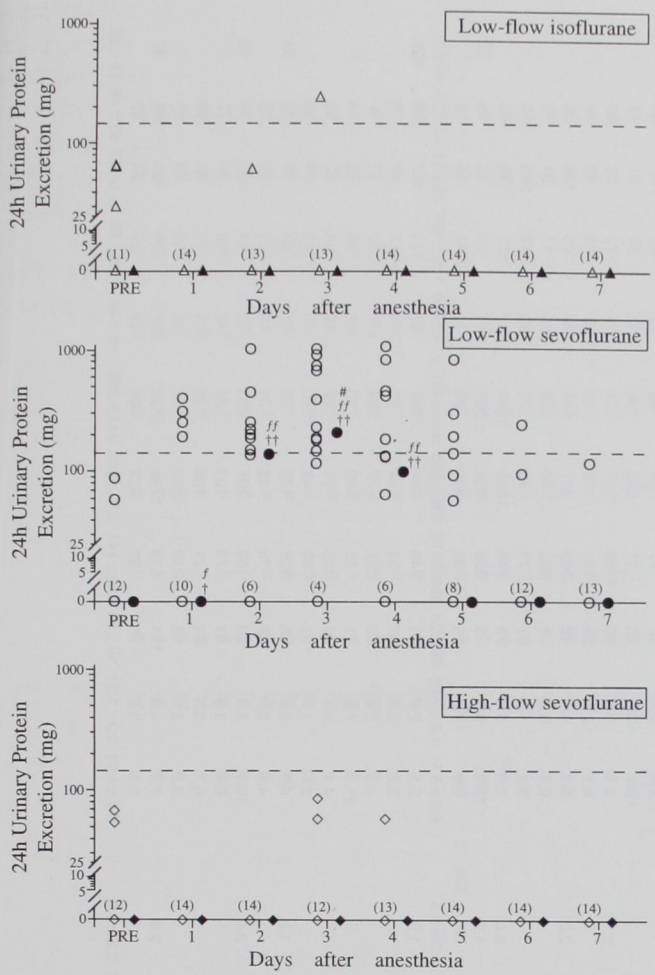

Fig. 8. Changes with time in 24-h urinary protein excretion in the three groups. Individual (open symbols) and median values (closed symbols) are shown (triangle = low-flow isoflurane, circle = low flow sevoflurane, square = high-flow sevoflurane; n = 14). When the urinary concentration of protein was below the lowest determinable level, the urinary excretion of protein was zero. The number of urine samples below the lowest determinable level is shown. Note the logarithmic scale used in this graph. The dotted line represents the upper limit of the reference range. Urinary excretion of protein in the low-flow sevoflurane group was significantly greater than in the isoflurane and high-flow sevoflurane groups after anesthesia. †P <0.05, ††P <0.01 compared with the isoflurane group. ^{f}P <0.05, ^{ff}P < 0.01 compared with the high-flow sevoflurane group. #P <0.05 compared with each preoperative value.

of NAG on postanesthetic days 1–3 in patients with gastric cancer who underwent gastrectomy. Kharasch *et al.*[20] measured BUN and serum creatinine concentrations and urinary excretion of NAG, protein, and glucose in patients who underwent primarily lower abdominal surgery. The results of the two studies were the same: there were no differences in values by anesthetic or flow rate. The discrepancy regarding urinalysis changes noted among the results we obtained and those by Eger II *et al.*,[10] Bito *et al.*,[19] and Kharasch *et al.*,[20] might arise from the concentration and exposure time of compound A and the extent of surgical trauma. First, compound A nephrotoxicity in rats is dose dependent,[5,6,18,9] and the dose-dependent effect may be applicable to humans.[11] The inspired compound A AUC in the studies by Bito *et al.*[19] and Kharasch *et al.*[20] were 122 ppm/h and 79 ppm/h, respectively, whereas the corresponding values in our study and that of Eger *et al.*[10] were 192 ppm/h and 328 ppm/h, respectively. Furthermore, the 24-h urinary excretion of protein in the study by Eger *et al.*[10] was greater than what we observed. Second, the extent of increase in urinary excretion of NAG is proportional to the stress induced by surgery.[34] After minor surgery, urinary NAG excretion does not increase to more than two times the upper limit of normal.[34] The urinary NAG:creatinine ratios after anesthesia for our patients anesthetized with low-flow isoflurane were < 2.3 U/g creatinine, and they did not increase compared with values before anesthesia. Conversely, corresponding values in the study by Bito *et al.*[19] increased three times, compared with those before anesthesia (2.8 U/g creatinine before anesthesia compared with 10.5 U/g on day 2 after anesthesia). Corresponding values in the study by Kharasch *et al.*[20] exceeded 5 U/g creatinine. These results indicate that the effect of surgical trauma on urinary excretion of NAG in our patients was less than that experienced by the patients studied by Bito *et al.*[19] and Kharasch *et al.*[20] Finally, the substantially higher anesthetic concentrations used in our study and that of Eger *et al.*[10] may also explain the observed differences in urinalysis changes.

The NAG and protein results must be interpreted carefully, as Kharasch *et al.*[20] warned. Our results that urinary excretion of protein and NAG increased in the absence of either changes in BUN and serum creatinine concentrations or in creatinine clearances can be interpreted in two ways: (1) tubular or glomerular changes may occur in the absence of organ dysfunction, or (2) the absence of changes of BUN and creatinine concentrations and creatinine clearance may indicate that there was no relevant damage and that the other changes were unimportant. Mazze and Jamison,[35] in an editorial accompanying the articles by Bito *et al.*[19] and Kharasch *et al.*,[20] also discussed how postoperative renal function should be assessed in patients undergoing surgery. Measurement of BUN and creatinine concentrations are es-

Table 3. Time Course of Urinary Excretion of NAG, β_2-Microglobulin, Protein, and Glucose in Individual Patients

Group	Patient Number	24-h Urinary NAG Excretion (U/g · creatinine)													24-h Urinary β^2-Microglobulin Excretion (μg/g · creatinine)											
		Pre	Days after Anesthesia										Max	Mean	Pre	Days after Anesthesia										Max	Mean
			1	2	3	4	5	6	7	8	9	10				1	2	3	4	5	6	7	8	9	10		
Low-flow isoflurane	1	1.9	2.8	2.8	2.8	2.7	2.0	2.2	1.9				2.8	2.4	19	47	73	62	73	50	52	64				73	60
	4	1.3	2.3	1.4	2.1	0.5	1.4	2.9	0.2				2.9	1.5	37	74	55	51	39	35	85	30				85	52
	7	1.3	2.2	2.9	2.0	1.6	2.2	3.4	3.4	2.2			3.4	2.5	61	97	272	114	43	23	25	42	41			272	88
	10	2.8	2.1	1.9	2.0	2.2	2.2	2.3	2.0				2.3	2.1	78	53	59	53	46	52	51	38				59	50
	13	1.4	3.0	1.8	2.7	3.0	3.7	3.8	3.6	2.4			3.8	3.1	53	621	383	111	71	30	19	54	60			621	184
	16	1.7	2.3	1.9	1.9	2.4	0.5	0.6	2.1				2.4	1.7	105	354	1061	907	303	45	39	102				1061	401
	19	1.8	2.0	0.1	1.1	2.4	2.8	3.4	1.5				3.4	1.9	31	62	116	77	109	33	46	32				116	68
	22	1.8	2.0	2.4	3.0	4.3	0.4	1.7	0.6				4.3	2.1	40	469	550	285	138	27	50	32				550	222
	25	1.2	1.9	1.8	2.0	1.8	1.8	2.1	1.7				2.1	1.9	52	174	311	107	64	63	50	33				311	115
	28	1.3	2.4	1.9	2.2	1.4	1.7	1.2	1.6				2.4	1.8	52	162	104	126	114	54	78	100				162	105
	31	2.5	2.2	2.3	1.9	2.7	3.1	3.0	3.0	2.7			3.1	2.6	65	79	91	117	86	224	111	86	30			224	114
	34	1.5	1.2	1.6	3.0	1.9	1.4	1.1	1.2				3.0	1.6	35	67	49	29	29	24	43	24				67	38
	37	1.3	1.6	2.0	2.1	1.8	1.6	1.8	1.7				2.1	1.8	28	69	182	58	37	33	46	27				182	65
	40	1.3	0.8	1.3	1.9	1.9	1.9	2.0	1.7				2.0	1.6	47	109	134	99	78	72	49	37				134	82
Mean ± SD		1.6±0.5	2.1±0.6	1.9±0.7	2.2±0.5	2.3±0.9	1.9±0.9	2.3±0.9	1.9±0.9	2.5±0.3			2.9±0.7	2.9±0.5	50±22	174±178	245±277	157±224	88±70	55±51	53±24	50±27	43±15			280±284	118±97
Low-flow sevoflurane	2	2.0	1.5	3.7	4.9	4.7	4.1	4.2	4.4	3.1	3.0	2.4	4.9	3.9	63	1852	3671	1682	657	410	142	77	60	70	64	3671	1213
	5	1.8	0.5	0.7	1.3	1.0	1.4	1.3	1.6				1.6	1.1	74	89	131	67	36	36	57	49				131	67
	8	1.6	1.9	4.3	6.7	4.3	3.4	2.7	2.3				6.7	3.7	17	42	109	84	60	214	39	57				214	87
	11	2.1	2.1	6.1	7.8	7.3	2.2	3.8	1.2				7.8	4.3	17	111	129	232	223	57	14	21				232	113
	14	1.6	1.1	4.8	1.8	1.6	2.1	1.9	2.0				4.8	2.2	46	77	89	76	65	56	42	53				89	65
	17	2.1	1.3	5.2	5.8	3.3	3.9	3.9	2.5				5.8	3.7	48	17	232	135	48	34	31	10				232	72
	20	1.8	2.8	4.0	1.2	4.4	0.8	3.2	3.0	2.1			4.4	2.8	70	1108	1217	74	559	73	63	66				1217	451
	23	0.6	1.2	4.3	4.7	2.8	3.2	2.4	1.8				4.7	2.9	33	191	193	86	63	48	46	39				193	95
	26	2.7	3.5	1.6	7.2	8.0	5.6	4.2	3.7	2.2			8.0	4.8	49	386	337	646	176	93	125	53				646	260
	29	1.3	1.1	3.2	9.6	4.7	2.2	2.6	2.0				9.6	3.6	8	282	148	229	24	11	31	8				282	104
	32	0.8	1.2	1.8	3.2	2.4	2.3	1.4	1.2				3.2	1.9	31	71	98	70	60	57	359	49				359	109
	35	1.7	2.6	4.9	7.5	7.0	6.7	5.8	3.1	2.0			7.5	5.4	73	376	1065	1094	738	677	140	43				1094	591
	38	2.5	3.6	9.5	14.7	18.9	8.9	6.3	4.6	1.9			18.9	9.5	9	329	404	325	234	84	45	45	22			404	209
	41	1.5	1.4	2.9	2.9	0.9	6.9	2.7	2.3				6.9	2.8	15	80	433	83	43	41	15	13				433	101
Mean ± SD		1.7±0.6	1.8±1.0	4.1±2.2	5.7±3.7	5.1±4.6	3.8±2.4	3.3±1.5	2.5±1.1	2.3±0.5			6.8±4.1*	3.8±2.0†	39±24	358±513	590±955	349±481	213±250	135±187	82±91	42±21	42±15			657±932	253±318
High-flow sevoflurane	3	0.4	2.0	1.9	1.8	1.7	1.8	2.3	2.5	1.9			2.5	2.0	53	248	391	294	91	124	127	106	108			391	197
	6	0.7	2.2	3.4	3.6	3.7	3.8	3.9	2.4				3.9	3.3	47	53	59	61	44	17	47	19				61	43
	9	1.3	0.1	7.3	4.8	3.8	4.3	0.2	0.1				7.3	2.9	60	221	177	204	117	27	27	8				221	112
	12	2.3	7.6	10.7	21.8	1.7	1.9	3.0	2.4				21.8	7.0	71	55	180	70	97	86	99	55				180	92
	15	1.8	1.2	4.1	3.9	3.6	3.4	3.0	2.3				4.1	3.1	32	115	71	82	42	48	50	53				115	66
	18	1.0	1.3	1.4	1.7	2.5	1.9	1.5	1.9				2.5	1.7	61	30	48	55	40	45	41	35				55	42
	21	2.0	2.1	2.5	3.8	1.3	1.4	2.7	4.6	1.8			4.6	2.6	56	226	122	73	75	63	78	53	55			226	98
	24	2.5	4.8	3.4	2.3	2.2	2.9	2.5	2.6				4.8	3.0	32	70	43	31	49	23	32	32				70	40
	27	0.9	1.7	1.8	2.2	2.3	10.3	7.7	4.1	2.6			10.3	4.3	39	169	397	223	70	146	135	74	59			397	173
	30	0.5	0.4	4.5	6.4	4.1	0.5	2.7	0.9				6.4	2.8	51	73	103	52	42	89	84	77				103	74
	33	0.7	1.8	2.9	6.7	3.5	3.2	2.9	1.8				6.7	3.3	54	91	186	129	101	71	93	89				186	108
	36	1.0	3.2	1.7	3.6	1.0	2.7	2.4	1.7				3.6	2.3	46	219	282	144	55	58	56	51				282	123
	39	2.6	1.2	3.7	7.3	2.8	6.9	3.2	4.0	2.6			7.3	4.2	151	573	1799	1454	201	89	103	184	87			1799	629
	42	0.9	2.9	3.3	3.2	3.6	3.2	3.0	2.9				3.6	3.2	75	82	222	104	39	28	24	12				222	73
Mean ± SD		1.3±0.8	2.3±1.9	3.8±2.5	5.2±5.1	2.7±1.0	3.4±2.5	2.9±1.6	2.4±1.2	2.2±0.5			6.4±4.9†	3.3±1.3†	59±29	159±141	291±365	213±365	76±44	65±38	71±37	61±46	77±25			308±443	134±150

Low-flow	1	68	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
isoflurane	4	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	7	0	0	0	0	0	0	0	0	0			0	[0]	0	0	0	0	0	0	0	0	0		0	[0]
	10	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	13	0	0	0	250	0	0	0	0	0			250	[0]	0	0	0	0	0	0	0	0	0		0	[0]
	16	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	19	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	22	0	0	64	0	0	0	0	0				64	[0]	0	0	0	0	0	0	0	0			0	[0]
	25	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	28	67	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	31	0	0	0	0	0	0	0	0	0			0	[0]	0	0	0	0	0	0	0	0	0		0	[0]
	34	31	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	37	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	40	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
[Median]		[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]			[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]		[0]	[0]
Low-Flow	2	92	200	208	240	139	144	98	119	168	220	0	240	[144]	0	0	0	0	0	0	0	0	0	0 0	0	[0]
sevoflurane	5	0	0	0	702	0	0	0	0				702	[0]	0	0	0	0	0	0	0	0			0	[0]
	8	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	11	0	0	196	400	475	96	0	0				475	[96]	0	0	0	0	0	0	0	0			0	[0]
	14	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	17	0	0	225	192	190	0	0	0				225	[0]	0	0	0	0	0	0	0	0			0	[0]
	20	60	0	0	756	0	0	0	0	0			756	[0]	0	0	0	0	0	0	0	0	0		0	[0]
	23	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	26	0	260	259	1040	432	59	0	0	0			1040	[259]	0	2.0	1.9	4.6	0.9	0	0	0	0		5	[0.5]
	29	0	0	140	195	133	198	0	0				198	[133]	0	0	0	0	0	0	0	0		0	[0]	
	32	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	35	0	408	1022	942	858	862	249	0	0			1022	[858]	0	2.4	8.4	7.0	5.5	3.4	0	0	0		8	[2.9]
	38	0	319	464	972	976	304	0	0	0			976	[319]	0	5.8	1.6	2.4	3.2	0	0	0	0		6	[0.8]
	41	0	0	154	120	66	0	0	0				154	[0]	0	0	0	0	0	0	0	0			0	[0]
[Median]		[0]	[0]	[147]	[217]	[100]	[0]	[0]	[0]	[0]			[233]‡	[202]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]		[0]	[0]
High-flow	3	71	0	0	0	0	0	0	0	0			0	[0]	0	0	0	0	0	0	0	0	0		0	[0]
sevoflurane	6	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	9	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	12	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	15	56	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	18	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	21	0	0	0	0	0	0	0	0	0			0	[0]	0	0	0	0	0	0	0	0	0		0	[0]
	24	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	27	0	0	0	0	0	0	0	0	0			0	[0]	0	0	0	0	0	0	0	0	0		0	[0]
	30	0	0	0	60	0	0	0	0				60	[0]	0	0	0	0	0	0	0	0			0	[0]
	33	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	36	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
	39	0	0	0	90	60	0	0	0	0			90	[0]	0	0	0	0	0	0	0	0	0		0	[0]
	42	0	0	0	0	0	0	0	0				0	[0]	0	0	0	0	0	0	0	0			0	[0]
[Median]		[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]			[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]		[0]	[0]

Pre = preanesthesia; Max = maximum value after anesthesia; Mean = mean value after anesthesia; Med = median value of urinary excretion of protein or glucose after anesthesia.

When urinary concentration of protein or glucose were below the lowest determinable level, they were zero.

* $P < 0.05$, † $P < 0.01$ *versus* isoflurane group.

‡ $P < 0.05$ *versus* high-flow sevoflurane group.

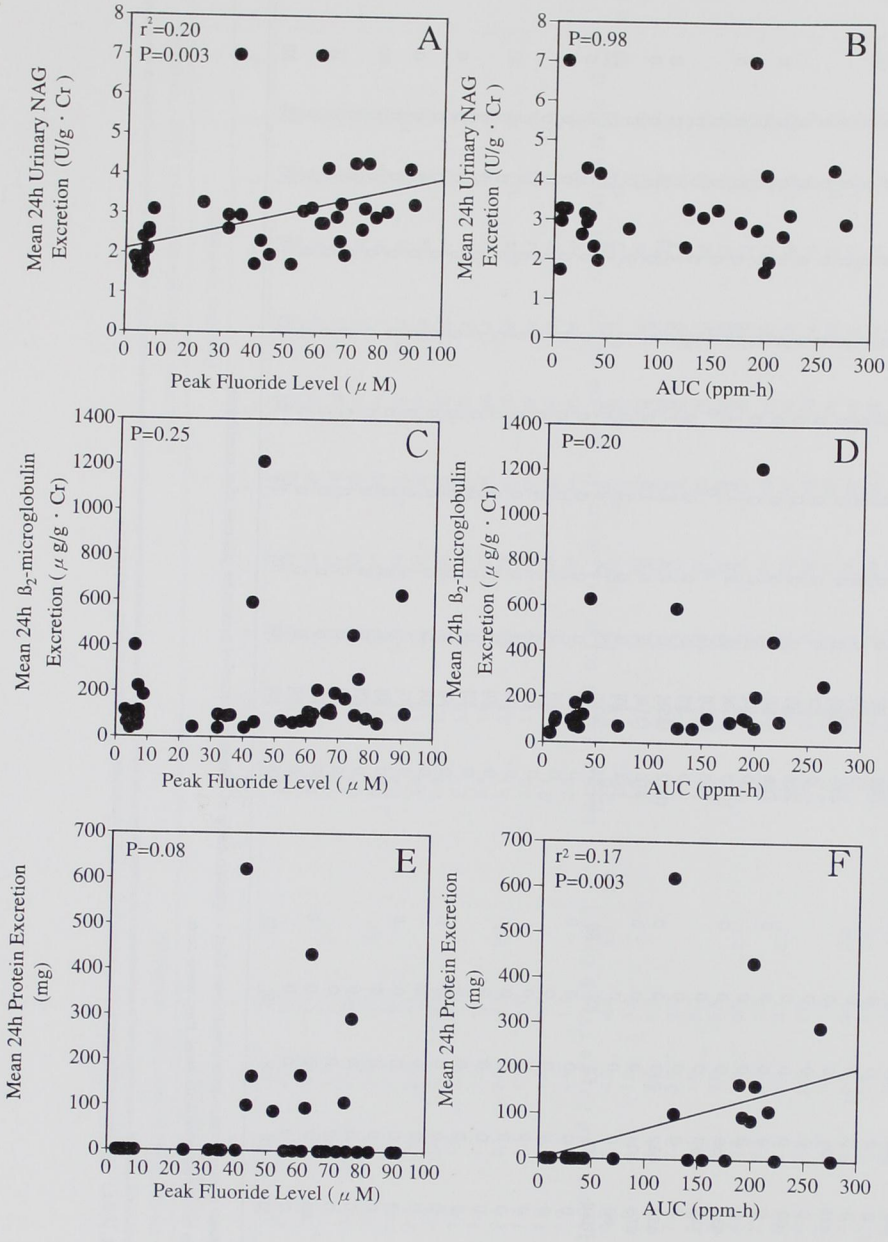

Fig. 9. The relation between mean values after anesthesia for urinary N-acetyl-β-D-glucosaminidase (NAG) excretion and peak fluoride concentrations in patients in the three groups (*A*, n = 42) or areas under the inspired compound A concentration *versus* time curves (inspired compound A AUC) in patients who received sevoflurane (*B*, n = 28). The relation between mean values after anesthesia for urinary excretion of β_2-microglobulin and peak fluoride concentrations in patients in the three groups (*C*, n = 42) or inspired compound A AUC in patients who received sevoflurane (*D*, n = 28). The relation between mean values after anesthesia for urinary excretion of protein and peak fluoride concentrations in patients in the three groups (*E*, n = 42) or inspired compound A AUC in patients who received sevoflurane (*F*, n = 28).

tablished indices of renal function, reflecting function in the preceding 12–24 h, and they are prognostically significant in clinical medicine.[35] In contrast, measurement of urinary enzyme excretion has not been validated adequately as a reliable indicator of clinically significant renal injury in humans.[36] There is also the criticism that urinary enzymes are too sensitive, in that elevations are sometimes present in the absence of other measurable abnormalities.[28] That increased enzymuria denotes tubular cell necrosis is not proved in humans.[36] An increase in NAG concentrations was not seen in combination with an increase in protein concentrations in this study. In contrast to our previous study,[26] in the current study we did not find that patients in whom serum inorganic fluoride concentrations were >50 μM had greater urinary excretion of NAG compared with patients in whom serum inorganic fluoride concentrations were <50 μM. Consequently, results can be interpreted to support the suggestion that the changes of NAG concentrations were inconsequential.

Table 4. Preoperative and Postoperative Serum Values, 24-Hour Urine Volume

	Group	Preanesthesia	Day 1	Day 2	Day 3	Day 5	Day 7
Serum AST (IU/L)	Low-flow isoflurane	17 ± 4	27 ± 6*	27 ± 8*	23 ± 9†	20 ± 5	19 ± 5
	Low-flow sevoflurane	18 ± 6	29 ± 20	34 ± 24*	35 ± 27*	27 ± 10	21 ± 7
	High-flow sevoflurane	17 ± 4	32 ± 24†	35 ± 28*	32 ± 27†	25 ± 11	21 ± 6
Serum ALT (IU/L)	Low-flow isoflurane	13 ± 5	15 ± 6	16 ± 6	19 ± 10	22 ± 12*	22 ± 10*
	Low-flow sevoflurane	16 ± 7	18 ± 10	22 ± 14	29 ± 23*	36 ± 19*	31 ± 15*
	High-flow sevoflurane	15 ± 7	18 ± 10	21 ± 16†	24 ± 14*	27 ± 17*	25 ± 14*
Serum glucose (mg/dl)	Low-flow isoflurane	88 ± 6	92 ± 14	93 ± 10	94 ± 9	94 ± 9	96 ± 9
	Low-flow sevoflurane	92 ± 8	96 ± 11	97 ± 9	99 ± 12	95 ± 8	90 ± 11
	High-flow sevoflurane	87 ± 10	95 ± 13	98 ± 10	95 ± 9	95 ± 9	93 ± 13
Urine volume (ml/24 h)	Low-flow isoflurane	1,005 ± 380	2,321 ± 847*	1,305 ± 469	1,168 ± 299	1,091 ± 351	1,131 ± 392
	Low-flow sevoflurane	1,033 ± 240	2,064 ± 724*	1,511 ± 449†	1,214 ± 249	1,179 ± 449	1,169 ± 248
	High-flow sevoflurane	1,158 ± 460	1,988 ± 580*	1,588 ± 481	1,379 ± 657	1,213 ± 242	1,289 ± 382

AST = asparate aminotransferase; ALT = alanine aminotransferase.

Values are mean ± SD; n = 14 in each group

* $P < 0.01$ *versus* preanesthetic value.

† $P < 0.05$ *versus* preanesthetic value.

Compared with urinary enzymes, increased urinary excretion of protein is a reliable marker of renal impairment.[35,37] However, proteinuria obviously can occur in completely benign situations and need not be predictive of subsequent renal malady.[37] Albuminuria in the absence of low-molecular-weight proteinuria is considered a specific and sensitive indicator of changes in the determinants of glomerular permeability.[37,38] Indeed, there were no significant differences among the three groups with respect to urinary excretion of β_2-microglobulin, which is a highly sensitive indicator of proximal tubular function. However, we do not know whether the benign forms of proteinuria apply to the results we found in this investigation.

In conclusion, our study shows that low-flow sevoflurane anesthesia for 6.7 h was associated with increases in urinary protein. In these young, healthy patients without renal disease, this proteinuria was transient and was not associated with changes of BUN concentration, creatinine concentration, or creatinine clearance. However, further studies will be needed to resolve the renal effect of low-flow sevoflurane anesthesia in patients with preexisting renal disease, in those who received potential nephrotoxic drugs, such as aminoglycosides, or in elderly patients.

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