Long-Duration Low-Flow Sevoflurane and Isoflurane Effects on Postoperative Renal and Hepatic Function

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Sevoflurane degradation by carbon dioxide absorbents during low-flow anesthesia forms the haloalkene Compound A, which causes nephrotoxicity in rats. Numerous studies have shown no effects of Compound A formation on postoperative renal function after moderate-duration (3–4 h) low-flow sevoflurane; however, effects of longer exposures remain unresolved. We compared renal function after long-duration low-flow (<1 L/min) sevoflurane and isoflurane anesthesia in consenting surgical patients with normal renal function. To maximize degradant exposure, Baralyme® was used, and anesthetic concentrations were maximized (no nitrous oxide and minimal opioids). Inspired and expired Compound A concentrations were quantified. Blood and urine were obtained for laboratory evaluation. Sevoflurane (n = 28) and isoflurane (n = 27) groups were similar with respect to age, sex, weight, ASA status, and anesthetic duration (9.1 ± 3.0 and 8.2 ± 3.0 h, mean ± SD) and exposure (9.2 ± 3.6 and 9.1 ± 3.7 minimum alveolar anesthetic concentration hours). Maximum inspired Compound A was 25 ± 9 ppm (range, 6–49 ppm), and exposure (area under the concentration-time curve) was 165 ± 95 (35–428) ppm · h. There was no significant difference between anesthetic groups in 24- or 72-h serum creatinine, blood urea nitrogen, creatinine clearance, or 0- to 24-h or 48- to 72-h urinary protein or glucose excretion. Proteinuria and glucosuria were common in both groups. There was no correlation between Compound A exposure and any renal function measure. There was no difference between anesthetic groups in 24- or 72-h aspartate aminotransferase or alanine aminotransferase. These results show that the renal and hepatic effects of long-duration low-flow sevoflurane and isoflurane were similar. No evidence for low-flow sevoflurane nephrotoxicity was observed, even at high Compound A exposures as long as 17 h. Proteinuria and glucosuria were common and nonspecific postoperative findings. Long-duration low-flow sevoflurane seems as safe as long-duration low-flow isoflurane anesthesia.

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All currently used volatile anesthetics are degraded to potentially toxic byproducts by carbon dioxide absorbents that contain strong bases. Carbon monoxide is formed from enflurane, isoflurane, and desflurane, with desflurane potentially causing carbon monoxide poisoning (1). The haloalkenes bromochlorodifluoroethylene and fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether (Compound A) are formed from halothane and sevoflurane, respectively.

Compound A causes nephrotoxicity in animals, specifically, corticomedullary proximal tubular necrosis, as evidenced by proteinuria, glucosuria, and enzymuria (2,3). Increased serum creatinine and blood urea nitrogen (BUN) occur at larger doses. The threshold (area under the curve of inhaled concentration versus time; AUC_{insp}) for Compound A renal tubular necrosis in animals is generally accepted to be 290–340 ppm · h in rats (3–5), 800 ppm · h in cynomolgus monkeys (6), and >612 ppm · h in swine (i.e., no toxicity up to this dose, and a threshold not established) (7).

Compound A formation is greater with lower fresh gas flow rates, larger sevoflurane concentrations, and use of barium hydroxide lime as compared with soda lime (8). Numerous clinical investigations have evaluated Compound A formation and postoperative renal function after low-flow and closed-circuit sevoflurane, in which maximum inspired Compound A concentrations typically averaged 8–24 ppm and

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20–32 ppm with soda lime and barium hydroxide lime, respectively (9–16). Compound A exposures (AUC_{insp}) in these investigations averaged 65 (12), 67 (9), 79 (15), 120 (10), 124 (14), 192 (16), 250 (11), and 260 (13) ppm · h. Most of these investigations evaluated standard clinical measures of renal function (creatinine clearance, serum creatinine, and BUN) and found no clinically significant effect of low-flow sevoflurane on renal function in surgical patients (9–16), as did others in which Compound A was not measured (17,18). Because proteinuria, glucosuria, and enzymuria are more sensitive than serum BUN and creatinine in detecting Compound A nephrotoxicity in rats (3,5,19), interest arose in applying these biomarkers in humans. Using these theoretically more sensitive, although clinically unvalidated, markers of perioperative renal tubular integrity (20,21), two initial investigations found no significant renal effect of low-flow (1 L/min) sevoflurane, assessed with both conventional and experimental markers of renal toxicity (14,15). Low-flow sevoflurane was considered as safe as low-flow isoflurane (14,15,21). The Food and Drug Administration subsequently permitted a change in the sevoflurane labeling, from a recommended lower limit of 2 to 1 L/min, but with a 2 minimum alveolar anesthetic concentration-hour (MAC-h) maximum exposure (because of a lack of data under the latter conditions).

Comparatively less information is available at higher Compound A exposures. Long-duration studies, at 11 (11), 7 (10), 13 (13), and 9 (16) MAC-h, using only BUN and creatinine, also showed no clinically significant renal effects of low-flow sevoflurane. In contrast, Higuchi et al. (16), who used urinary as well as serum indices, reported that low-flow sevoflurane with high Compound A exposures was associated with mild, transient, clinically insignificant postoperative proteinuria, said to be positively correlated with Compound A AUC_{insp}. Nevertheless, aspects of this investigation were quite unconventional (anesthetic concentrations were unusually large, two vaporizers in tandem were used to achieve larger sevoflurane and thus Compound A concentrations, and anesthesia was extensively prolonged both before and after surgery), and applicability of the results of this investigation to conventional anesthesia were therefore questioned. Thus, the renal effects of greater Compound A exposures remained incompletely resolved.

The purpose of this investigation, therefore, was to compare the effects of low-flow (≤1 L/min) sevoflurane and isoflurane anesthesia on renal function in humans undergoing long-duration (target 6- to 8-h) surgery and to use conventional serum as well as urinary markers of renal function. Effects on hepatic function were also evaluated.

Methods

Fifty-five ASA status I–III patients undergoing elective surgery with planned duration ≥8 h were studied at three hospitals (University of Washington, $n = 28$; Puget Sound VA Medical Center, $n = 15$; and University of Arizona, $n = 12$). The investigational protocol was approved by the IRB in all institutions. All patients provided written informed consent. Eligible patients were ≥18 yr old and without history of hepatic or renal disease (serum creatinine ≤1.5 mg/dL, on the basis of screening laboratory investigations performed at each hospital). Most patients were undergoing neck resection for tumor or spinal reconstruction surgery. Patients undergoing cardiopulmonary bypass, aortic cross-clamping, transplantation, or intraoperative arteriography were excluded, as were those having undergone general anesthesia within 1 wk or those treated with any experimental drug within 28 days of surgery. Women of childbearing potential were anesthetized only after a negative urine pregnancy test was obtained. Patients were randomized by blocks to receive sevoflurane or isoflurane by using separate randomization schemes at each hospital.

A minimum of 20 subjects per treatment group was planned. A two-group continuity-corrected χ^2 test was determined to have 84% power ($\alpha = 0.05$) to detect a difference between a sevoflurane proportion of 0.75 and an isoflurane proportion of 0.25 in the increased incidence of significant (defined as the maximal permissible increase) (22) postoperative creatinine concentrations with 20 subjects per group.

The anesthetic protocol was similar to that used previously (15); it was designed to result in large Compound A concentrations. Fresh Baralyme® (Allied Healthcare Products, St. Louis, MO) was used, the targeted flow rate was 0.8 L/min, and nitrous oxide was avoided and opioid use attenuated to maximize volatile anesthetic requirements. Anesthesia was induced with thiopental or propofol and fentanyl (50–100 μg) and was maintained with sevoflurane or isoflurane in oxygen (≥30%) and air at 5 L/min for 5 min. Nitrous oxide was not used in any patient. After 5 min, the total fresh gas flow was reduced to 0.8–1.0 L/min for the duration of the case. Hemodynamic stability was maintained by adjusting the inspired anesthetic concentration or, occasionally, by using small doses of fentanyl. No intraoperative neuraxial opioids or local anesthetics were used. End-tidal anesthetic concentrations were monitored, and inspiratory and expiratory gas samples in patients anesthetized with sevoflurane were obtained, as described previously (15).

Venous blood and spot urine samples were obtained for laboratory analysis on the morning of surgery, at 24 and 72 h after the end of surgery, and 2 h after anesthesia for fluoride measurement. Urine was

collected at 24-h intervals (0–24 and 48–72 h after anesthesia). The volume was measured, and an aliquot was frozen for later analysis.

Compound A concentrations were determined by gas chromatography, as described previously (15). All serum (creatinine, BUN, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and lactic dehydrogenase) and urine (glucose, protein, and creatinine) analyses were performed by a central commercial laboratory that used an autoanalyzer, except fluoride, which was determined by ion-selective electrode. Urine analyte concentrations were multiplied by the 24-h urine volume to obtain 24-h excretion. Creatinine clearance was calculated from the 0- to 24-h and 48- to 72-h urine creatinine excretion and the 24- and 72-h postoperative serum creatinine concentrations. Normal values were defined by the commercial laboratory. Results are expressed in conventional units. To convert from conventional (mg/dL) to SI units, multiply creatinine by 88.4 to obtain μmol/L and BUN by 0.357 to obtain mmol/L.

Anesthetic exposure was calculated as the product of end-tidal concentration and time, determined in 15-min intervals. Total exposure is expressed as MAC-h (corrected for age: sevoflurane MAC, 2.05%; isoflurane MAC, 1.15%). Compound A exposure was similarly calculated as the product of inspiratory (AUC_{insp}) or expiratory concentration and time, determined in 30-min intervals.

Results were analyzed on an intent-to-treat basis. Patients' demographic data were analyzed by one-way analysis of variance for continuous data, a 2×2 Fisher's exact test for sex and race, and the Cochran-Mantel-Haenszel test for ASA class. Serum and urine results were compared by two-way repeated-measures analysis of variance. Correlations with Compound A exposure were evaluated by linear regression analysis. Data were analyzed with SAS (SAS Institute, Cary, NC). Statistical significance was assigned at $P < 0.05$. Results are expressed as mean ± SD.

Results

Patients anesthetized with sevoflurane and isoflurane were similar with respect to age, weight, sex, ASA physical status, case mix, duration of anesthesia, and anesthetic exposure (MAC-h) (Table 1). Three patients in the Sevoflurane group, and no patient in the Isoflurane group, were taking nonsteroidal antiinflammatory drugs. Low-flow rates, most often 0.8 L/min, were maintained throughout the duration of anesthesia in both groups. One patient, with normal creatinine on screening laboratory results, had an increased preinduction creatinine (1.8 mg/dL) when analyzed at the central laboratory (this decreased to normal after surgery). Data from this patient were included in the analysis.

Inspired Compound A concentrations in individual sevoflurane patients are shown in Figure 1. The maximum concentration was 25 ± 9 ppm, and the average concentration throughout surgery was 16 ± 6 ppm. The largest inspired concentration was 50 ppm. Total Compound A exposure, calculated from AUC_{insp}, was 165 ± 95 ppm · h, and the largest exposure was 428 ppm · h (Table 1).

Renal effects of low-flow anesthesia were measured by serum creatinine and BUN concentrations (Fig. 2). There was no significant difference between groups at either 24 or 72 h. By using the maximal permissible increase in postoperative creatinine as a more sensitive measure (22), the number of sevoflurane and isoflurane patients with a serum creatinine ≥0.2 mg/dL more than the preanesthesia value was similar (two vs two respectively at 24 h, and two vs one at 72 h). Creatinine clearances in Sevoflurane and Isoflurane patients averaged 162 ± 65 and 142 ± 74 mL/min at 24 h and 167 ± 87 and 137 ± 64 mL/min at 72 h (not significantly different), and the distribution of values was similar between groups (Fig. 3A). A more sensitive analysis examined the relationship between creatinine clearance and Compound A exposure in Sevoflurane patients, to localize potential outliers exhibiting toxicity. There was no significant relationship between creatinine clearance and Compound A exposure (AUC_{insp}), either at 24 or 72 h after surgery (Fig. 3B). Patients with the largest Compound A exposures did not have the lowest creatinine clearance.

Renal effects of low-flow anesthesia were also measured by urinary protein and glucose excretion, which are more sensitive markers of Compound A nephrotoxicity than BUN and creatinine in rats (3,5,19). Proteinuria and glucosuria, defined using conventional laboratory normal limits, were extremely common. Proteinuria occurred in almost all patients. Neither urinary protein nor glucose excretion was different, however, after low-flow sevoflurane compared with isoflurane anesthesia, at either 0–24 or 48–72 h after surgery (Fig. 4). The Sevoflurane patient with the greatest postoperative proteinuria was also found to have preoperative 3+ proteinuria (but normal serum creatinine), suggesting a preexisting renal defect rather than an anesthetic-related etiology. There was no correlation between either 0- to 24-h or 48- to 72-h protein excretion and Compound A exposure (AUC_{insp}) (Fig. 5) or between glucose excretion and Compound A exposure (Fig. 6). Patients with the largest Compound A exposures did not have the highest protein excretion or glucose excretion. Similarly, there was no correlation between the postoperative change in protein or glucose excretion and Compound A exposure (not shown). No significant correlation was found between proteinuria

Table 1. Patient Demographics and Anesthetic Exposure

Variable	Sevoflurane (n = 28)	Isoflurane (n = 27)
Age (yr)	53 ± 13 (30–82)	60 ± 16 (27–89)
Sex (M:F)	14:14	18:9
Weight (kg)	82 ± 24 (48–157)	77 ± 10 (43–115)
ASA status (I/II/III)	1/18/9	3/14/10
Surgical procedure (n)		
Head/neck	13	12
Laminectomy or craniotomy	8	9
Esophagectomy or Whipple procedure	4	3
Other	3	3
Duration of anesthesia (h)	9.1 ± 3.0 (3.3–17.6)	8.2 ± 3.0 (4.0–13.0)
Duration of low-flow anesthesia (h)	8.9 ± 3.0 (3.1–17.5)	8.0 ± 3.0 (3.7–13.0)
Average anesthetic concentration (MAC)	1.0 ± 0.2 (0.7–1.5)	1.1 ± 0.2 (0.8–1.5)
Anesthetic exposure (MAC-h)	9.2 ± 3.6 (3.8–17.8)	9.1 ± 3.7 (4.2–18.5)
Compound A inspired mean (ppm)	16 ± 6 (4–34)	
Compound A inspired maximum (ppm)	25 ± 9 (6–49)	
Compound A inspired AUC (ppm · h)	165 ± 95 (35–428)	

Data are presented as mean ± SD (range) unless otherwise noted.
AUC = area under the curve.

and glucosuria in either the Sevoflurane or Isoflurane patients (not shown).

Renal effects of sevoflurane defluorination were also evaluated. Serum fluoride concentrations are typically maximal approximately 2 h after surgery. Serum fluoride concentrations were substantially larger after sevoflurane (48 ± 26 μM; range, 14–132 μM) compared with isoflurane (3 ± 7 μM; range, 0–33 μM) and exceeded 50 μM in six sevoflurane patients. There were no significant correlations between 24- or 72-h postoperative creatinine clearance or protein excretion and serum fluoride concentration 2 h after anesthesia (not shown).

Hepatic effects of anesthesia were measured by serum AST and ALT concentrations (Fig. 7). There were no significant differences between anesthetic groups at either 24 or 72 h after anesthesia. Abnormal postoperative values were observed in both anesthetic groups, as observed previously (13,15,23), but the proportion of abnormal values was not different between anesthetic groups. There was no significant correlation between Compound A exposure and the increase in serum AST or ALT concentrations 24 or 72 h after anesthesia (results not shown).

Discussion

The results of this investigation demonstrate that the effects of low-flow sevoflurane and isoflurane on renal function were not significantly different. Postoperative renal function in both groups was similar, as assessed with serum creatinine and BUN, creatinine clearance, and urine excretion of protein and glucose. In Sevoflurane patients, there was no correlation between any measure of renal function and Compound A exposure. Low-flow sevoflurane anesthesia as long as 17 hours (and 428 ppm · h Compound A) was not associated with renal function abnormalities. There was no evidence for any "nephrotoxic threshold" of Compound A exposure. Increases in serum fluoride concentration were not associated with changes in renal function. Low-flow sevoflurane and isoflurane anesthesia had comparable effects on postoperative hepatocellular integrity, as measured by AST and ALT. Thus, low-flow sevoflurane in surgical patients, in a paradigm designed to maximize Compound A concentrations, and with Compound A exposures as large as 428 ppm · h, had no demonstrable adverse renal or hepatic effects in comparison with low-flow isoflurane.

As with many clinical investigations, there were limitations with the protocol design. A relatively small number of patients were studied. Most patients were admitted to the hospital the morning of surgery; therefore, preoperative 24-hour urine collections could not be reliably obtained. Comparisons were made between anesthetic groups, and pre- and postanesthesia analysis was not possible.

Renal function assessments were confined to serum creatinine and BUN, creatinine clearance, and urine protein and glucose excretion. Serum creatinine, BUN, and creatinine clearance are the standard, and prognostically significant, tests of renal function (21). Urine protein and glucose were measured because they were sensitive markers of Compound A effect in rats (24) and have been widely used in sevoflurane clinical studies, although they are of questionable use (see below). Urinary excretion of proximal tubular enzymes (*N*-acetyl-β-D-glucosaminidase and α-glutathione-*S*-transferase), although sensitive biomarkers of nephrotoxicity in rats, have not been validated in humans (20,25).

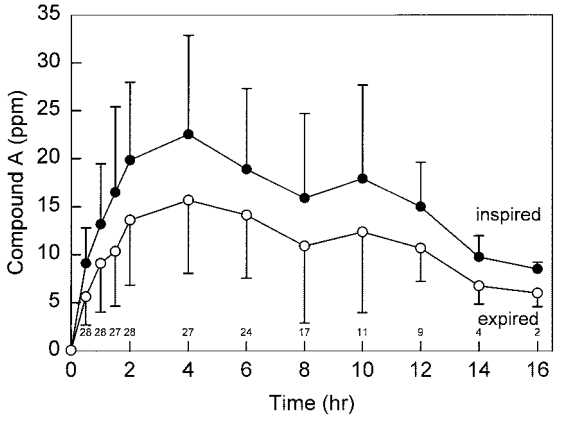

Figure 1. Inspired and expired Compound A concentrations in patients anesthetized with sevoflurane. The number of patients comprising each data point is shown above the *x* axis.

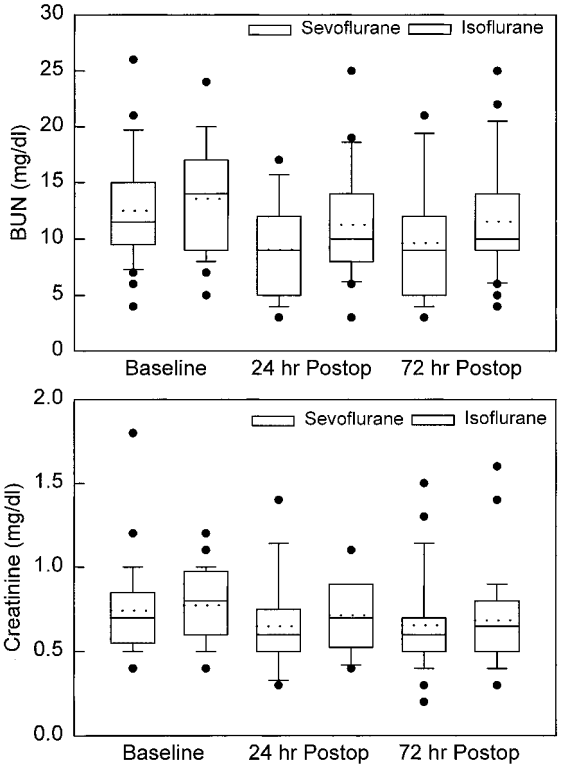

Figure 2. Serum creatinine and blood urea nitrogen (BUN) concentrations before and after low-flow anesthesia. Data are depicted with box plots. Shown are the mean (dotted line), median, 25th–75th percentiles (box boundaries), and 10th–90th percentiles (whiskers). Outliers beyond 10%–90% are shown as individual data points. There were no significant differences between anesthetic groups.

In our previous evaluation of moderate-duration (average three to four hours) low-flow sevoflurane (79 ± 54 ppm · h Compound A), showing no difference compared with isoflurane, we cautioned that additional studies were required to assess longer duration low-flow sevoflurane anesthesia and larger Compound A exposures (15). This evaluation of long-duration (average nine hours) low-flow sevoflurane

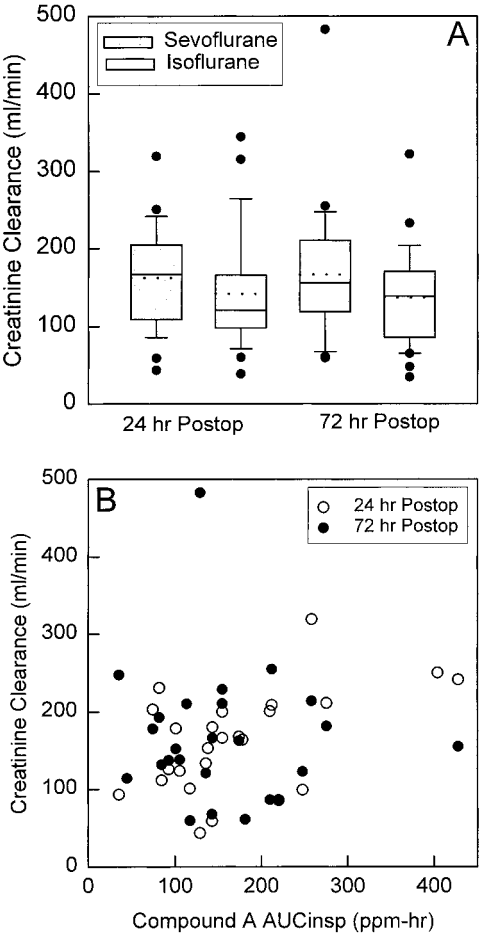

Figure 3. Creatinine clearance after low-flow anesthesia. (A) Data are depicted with box plots. Shown are the mean (dotted line), median, 25th–75th percentiles (box boundaries), and 10th–90th percentiles (whiskers). Outliers beyond 10%–90% are shown as individual data points. There were no significant differences between anesthetic groups. (B) Relationship between creatinine clearance and Compound A exposure in sevoflurane patients 24 and 72 h after anesthesia. AUC_{insp} = area under the curve of inhaled concentration versus time.

(165 ± 95 ppm · h Compound A) addresses that limitation. This investigation, which evaluated serum BUN and creatinine, as well as urine protein and glucose excretion, adds to and extends the results of our and others' previous intermediate-duration low-flow studies with serum and urine biomarkers, long-duration low-flow studies with only BUN and creatinine, and more recent long-duration low-flow studies with both serum and urine biomarkers. The Compound A exposure in this investigation was larger than the 50 ppm · h for three hours of sevoflurane (26), 65 ppm · h for four hours (12), 67 ppm · h for five hours (9), 79 ppm · h for four hours (15), 120 ppm · h for seven hours (7 MAC-h) (10), and 124 ppm · h for 7 MAC-h (14,27) in previous studies. Larger Compound A exposures have been studied [250 ppm · h for 16 hours (11 MAC-h) (11), 260 ppm · h for 13 hours (13

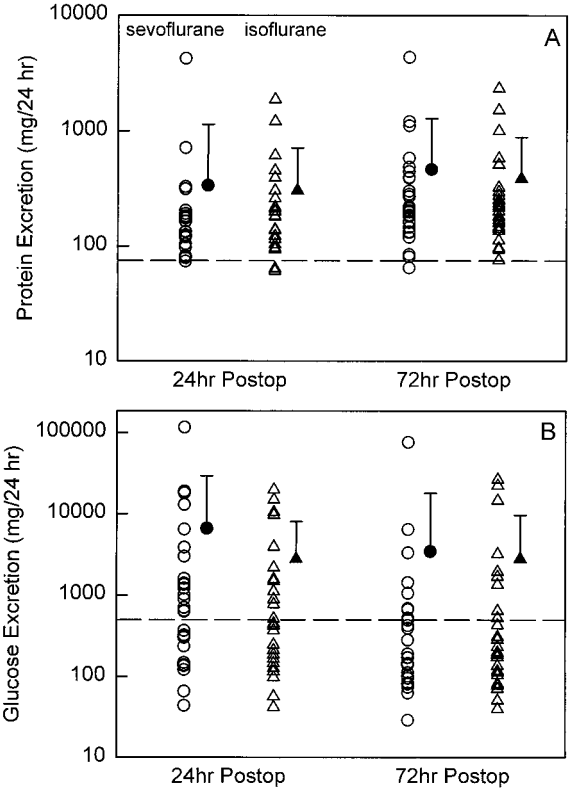

Figure 4. Excretion of protein (A) and glucose (B) in urine collected 0–24 and 48–72 h after anesthesia. Individual and mean values are shown. The dotted line represents the upper limit of the reference range. There were no significant differences between Sevoflurane (●) and Isoflurane (▲) patients.

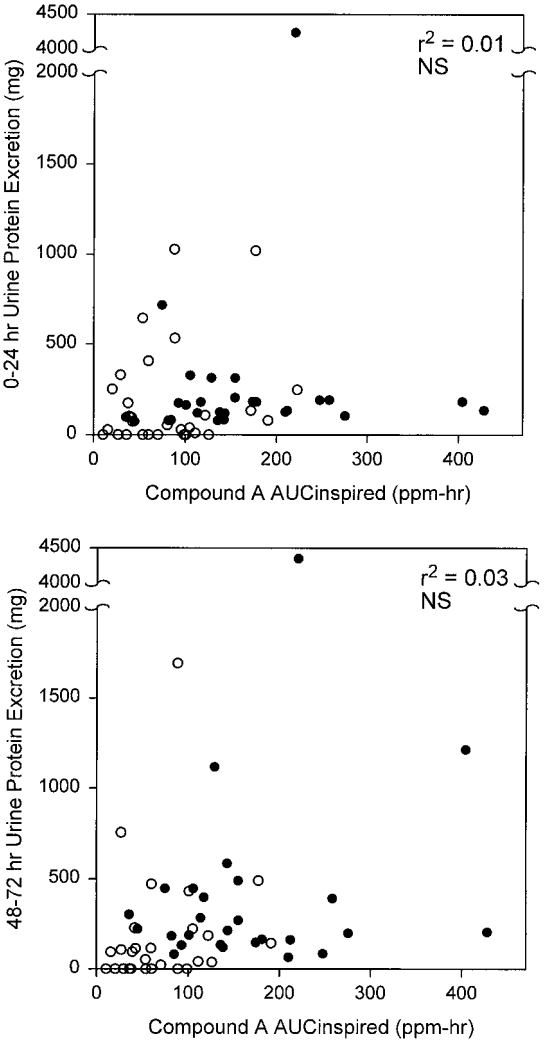

Figure 5. Relationship between urine protein excretion and Compound A exposure in patients anesthetized with low-flow sevoflurane in this (●) and our prior (○) investigation (15). The latter data, obtained by using an identical protocol, are added to increase the total *n*. $AUC_{inspired}$ = area under the curve of inhaled concentration versus time; NS = not significant.

MAC-h) (13), and 260 ppm · h for 16 hours (11 MAC-h) (28)], although these evaluated only BUN and creatinine. Until recently, only one study with larger Compound A exposure (192 ppm · h for seven hours; 9 MAC-h) examined urinary protein and glucose excretion as well as BUN and creatinine (16). Coinciding with the conduct of this investigation, and reported recently, Obata et al. (29) evaluated long-duration (16 MAC-h) sevoflurane (277 ppm · h Compound A for 16 hours) by using both serum and urinary evaluations. The maximum Compound A exposure (428 ppm · h) in the present investigation was much larger than that (302 ppm · h) in the study claiming changes in renal function (16).

There is nearly uniform congruence that low-flow sevoflurane anesthesia and Compound A formation have no significant renal effects in surgical patients, as compared with low-flow isoflurane and/or high-flow sevoflurane (with minimal Compound A exposure). By using standard clinical measures of renal function (creatinine clearance, serum creatinine, and BUN), neither this nor any other investigation has found any specific effect of low-flow sevoflurane on renal function (9–18,29,30). Of particular importance is that long-duration sevoflurane was devoid of renal effects, presently and previously (10,11,13,29). Because serum BUN and creatinine were less sensitive than proteinuria, glucosuria, and enzymuria in detecting Compound A nephrotoxicity in rats (3,5,19), interest arose in evaluating these biomarkers in humans. Although clinically unvalidated, with the meaning of a positive result yet undefined, these sensitive tests nonetheless possess predictive negative value (15,20,21). The present evaluation and previous evaluations (14,15,29,30) of low-flow sevoflurane, measuring urinary excretion of protein, glucose, albumin, *N*-acetyl-β-D-glucosaminidase, alanine aminopeptidase, α- and π-glutathione-*S*-transferases, or a combination of these also showed no effect on postoperative renal function compared with other anesthetics. Most notably, the most recent investigation, which evaluated

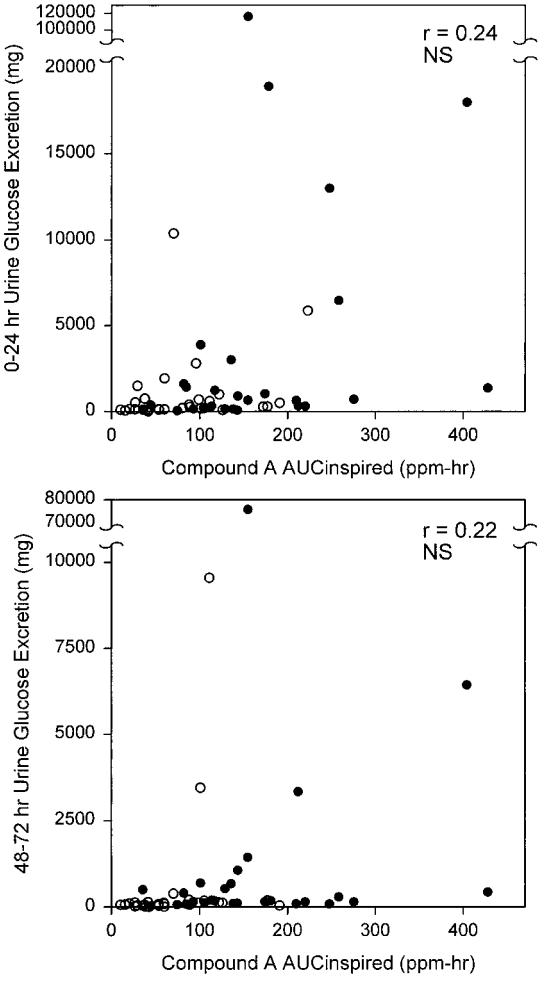

Figure 6. Relationship between urine glucose excretion and Compound A exposure in patients anesthetized with low-flow sevoflurane in this (●) and our prior (○) investigation (15). The latter data, obtained by using an identical protocol, are added to increase the total *n*. $AUC_{inspired}$ = area under the curve of inhaled concentration versus time; NS = not significant.

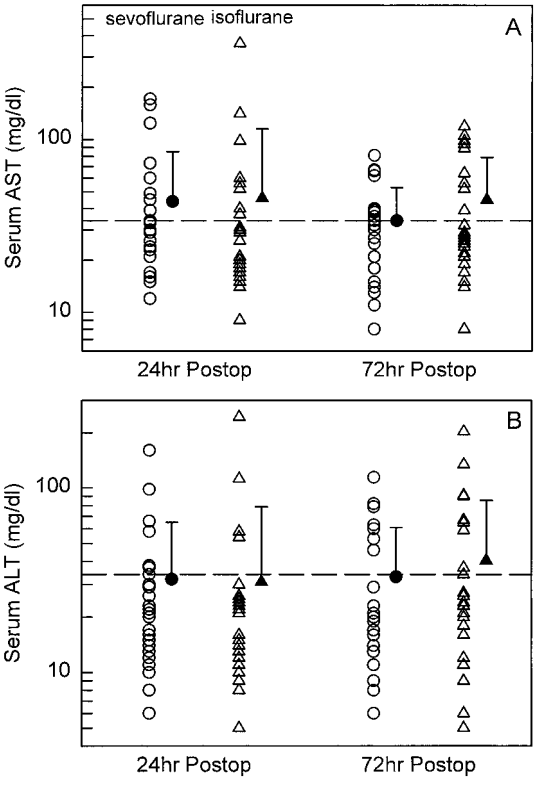

Figure 7. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations 24 and 72 h after anesthesia. Shown are individual and mean values (±SD). The dotted line represents the upper limit of the reference range. There were no significant differences between Sevoflurane (●) and Isoflurane (▲) patients.

ultra-long-duration (17 MAC-h) low-flow sevoflurane by using serum and urinary markers, found no renal effects of Compound A formation (29).

The exception to these multiple investigations is the one that reported that long-duration low-flow sevoflurane was associated with mild, transient postoperative proteinuria, albeit clinically insignificant (16). Although there was no change in serum creatinine and BUN, creatinine clearance, urine β_2-microglobulin, or *N*-acetyl-β-D-glucosaminidase, in agreement with all other investigations, the isolated mild proteinuria was at variance. Protein excretion was said to be significantly correlated with Compound A exposure (up to 302 ppm · h). Higuchi et al. (16) suggested that the difference between their results and those of previous investigations might arise because their Compound A exposures [136–302 vs 38–243 ppm · h (14) or 10–223 ppm · h (15)] were greater. However, this investigation (35–428 ppm · h) and recent (135–478 ppm · h) (29) investigations, with larger Compound A exposures, and showing no increased proteinuria (versus other anesthetics) and no correlation between protein excretion and Compound A exposure, do not support this supposition. Other aspects of the Higuchi et al. study were also atypical. Inspired anesthetic concentrations were unusually large, two vaporizers in tandem were used, and anesthesia was extensively prolonged both before and after surgery. In addition, the albuminuria was considered to indicate changes in glomerular permeability rather than tubular toxicity. Nevertheless, even at the largest doses in rats, Compound A caused proximal tubular necrosis but no structural glomerular changes (19). An explanation for the results of Higuchi et al. is not apparent, and they remain divergent from all other investigations in surgical patients.

Another notable aspect of our results is the high frequency of proteinuria and glycosuria. With laboratory normal limits, "abnormal" proteinuria occurred in nearly all patients and glucosuria in approximately one third. Others also found proteinuria in nearly all patients and glucosuria in approximately half (with

both sevoflurane and isoflurane) (29). This is even more than the one third of patients showing proteinuria after shorter anesthetics (15). Proteinuria also occurred with desflurane and even after propofol (31,32). Thus, proteinuria (defined with normal laboratory values) after anesthesia and surgery is a common finding and does not *per se* (and in the absence of a comparison or control group) (33) indicate renal toxicity. Application of normal laboratory values, usually derived from awake healthy young subjects or volunteers, to surgical patients or perhaps even anesthetized nonsurgical volunteers does not seem justified (34).

Another important aspect of these results is the lack of correlation between renal function and serum fluoride concentration, as observed before (15,35). Until recently, the 50 μM serum fluoride threshold for methoxyflurane nephrotoxicity (36) was considered applicable to all defluoridated anesthetics. However, subsequent experience with enflurane, isoflurane, and, most recently, sevoflurane, with fluoride routinely >50 μM without renal consequence, altered this concept (34,35,37). Indeed, serum fluoride averaging 110 μM (38) after sevoflurane had no effect on renal concentrating ability (39), the metabolic defect traditionally associated with methoxyflurane. Rather than the former concept that hepatic defluoridation and systemic fluoride >50 μM portend nephrotoxicity, a more recent hypothesis (37) and supporting data (40) posit that intrarenal metabolism (which occurs with methoxyflurane but not sevoflurane) is more relevant with respect to renal toxicity. Continued concerns over systemic fluoride concentrations >50 μM with contemporary volatile anesthetics seem unwarranted.

Why then does low-flow sevoflurane not alter renal function in surgical patients, whereas Compound A can clearly cause nephrotoxicity in animals? The explanation probably involves species differences in dose, disposition, and susceptibility. First, Compound A exposures in patients undergoing 4–8 MAC-h of low-flow sevoflurane (5–10 μmol/kg) (41) are substantially less than the dose necessary to elicit (threshold) toxicity in rats (200 μmol/kg) (19). Second, there are species differences in Compound A disposition. Compound A nephrotoxicity, like that of numerous other haloalkenes, is generally accepted to occur by a well characterized mechanism involving glutathione conjugate formation, cleavage to cysteine conjugates, renal uptake of cysteine and glutathione conjugates, and intrarenal metabolism by cysteine conjugate β-lyase to toxic reactive intermediates (24,42). *In vitro*, renal β-lyase activity and β-lyase metabolism of Compound A-cysteine conjugates are approximately 8–30 times greater in rat versus human kidneys (43). *In vivo*, the relative metabolic flux of Compound A through toxification versus detoxification pathways was sixfold greater in rats than humans (41). Greater susceptibility in rats versus humans, because of similar metabolic differences, has also been observed with other nephrotoxic haloalkenes (44). The threshold for Compound A renal tubular necrosis in animals is generally accepted to be 290–340 ppm · h in rats (3–5), 800 ppm · h in cynomolgus (3-kg) monkeys (6), and >612 ppm · h (i.e., no toxicity up to this dose) in 78-kg swine (7), equivalent to 900–1200, 350, and >23 ppm $\cdot$ h^{-1} $\cdot$ kg$^{-3/4}$ respectively, by using allometric scaling (45). Assuming that the primate value (350 ppm $\cdot$ h^{-1} $\cdot$ kg$^{-3/4}$) applies to humans, an equivalent threshold for Compound A nephrotoxicity in a 75-kg person would be 9000 ppm · h (approximately 20 times the largest reported human exposure). Although allometric scaling normalizes physiologic differences across species (45), it does not account for metabolic differences (46), and renal β-lyase activity is greater in rats than in nonhuman primates (43); hence, scaled values may not be constant across species.

How should these latest low-flow sevoflurane results guide clinical practice? Although it was revised after initial drug approval, the sevoflurane labeling contains the following warning per the Food and Drug Administration: "Although data from controlled clinical studies at low flow rates are limited, findings taken from patient and animal studies suggest that there is a potential for renal injury which is presumed due to Compound A. Animal and human studies demonstrate that sevoflurane administered for more than 2 MAC-hr and at fresh gas flow rates of <2 L/min may be associated with proteinuria and glycosuria. To minimize exposure to Compound A, sevoflurane exposure should not exceed 2 MAC-hours at flow rates of 1 to <2 L/min. Fresh gas flow rates <1 L/min are not recommended." Nevertheless, it is now clear that postoperative proteinuria and glycosuria are ubiquitous and not limited to sevoflurane, and the studies on which the above warning were based did not use comparison groups. There are now substantially more data, and from well controlled clinical studies with exposures up to 16 MAC-h and at flow rates far less than 1–2 L/min. They show no clinically significant renal effects associated with low-flow sevoflurane. A recent editorial asked whether the flow rate restriction on sevoflurane is prudent or excessively conservative (47). On the basis of accumulated evidence, we suggest the latter. Continued proscription against low-flow sevoflurane does not seem justified.

In summary, the results of this investigation showed no significant differences, by using serum creatinine, BUN, creatinine clearance, or urinary protein or glucose excretion, between the renal effects of sevoflurane and isoflurane in surgical patients undergoing long-duration low-flow anesthesia for up to

17 hours. There was no correlation between Compound A exposure and any renal function variable. No evidence for low-flow sevoflurane nephrotoxicity was observed, even at large Compound A exposure. Proteinuria and glucosuria were common and nonspecific postoperative findings. There were no significant differences in liver enzymes between patients anesthetized with low-flow sevoflurane and isoflurane. Long-duration low-flow sevoflurane seems as safe as long-duration low-flow isoflurane and moderate-duration low-flow sevoflurane.

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