Renal Concentrating Function with Prolonged Sevoflurane or Enflurane Anesthesia in Volunteers

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Background: Sevoflurane, a new inhalational anesthetic, is biotransformed, producing peak plasma inorganic fluoride concentrations that may exceed 50 μM. We evaluated plasma inorganic fluoride concentrations with prolonged (> 9 MAC-h) sevoflurane or enflurane anesthesia in volunteers and compared renal concentrating function with desmopressin testing 1 and 5 days after anesthesia.

Methods: Fourteen healthy male volunteers received either enflurane or sevoflurane (1–1.2 MAC) for more than 9 MAC-h. Each volunteer was administered three tests of renal concentrating function, with intramuscular desmopressin and urine collections performed 1 week before anesthesia and 1 and 5 days after anesthesia. Venous blood samples were obtained for plasma fluoride concentrations during and after anesthesia. Creatinine clearance was determined by 24-h urine collections 7 days before and 4 days after anesthesia. Urine samples were obtained before and 1, 2, and 5 days after anesthesia for determination of n-acetyl-β-glucosaminidase and creatinine concentrations.

Results: Prolonged sevoflurane anesthesia (9.5 MAC-h) did not impair renal concentrating function on day 1 or 5 postanesthesia, as determined by desmopressin testing. Maximal urinary osmolality on day 1 postanesthesia was decreased (< 800 mosm/kg) in two of seven enflurane-anesthetized volunteers, however, mean results did not differ from the those of the control group. Mean peak plasma fluoride ion concentrations were 23 ± 1 μM 6 h postanesthesia for enflurane and 47 ± 3 μM at the end of anesthesia for sevoflurane (P < 0.01). There were no changes in creatinine clearance or urinary n-acetyl-β-glucosaminidase concentration in either anesthetic group.

Discussion: Prolonged sevoflurane anesthesia did not impair renal concentrating function, as evaluated with desmopressin testing 1 and 5 days postanesthesia in healthy volunteers. Although with prolonged enflurane anesthesia, mean maximal osmolality values on day 1 postanesthesia did not differ from sevoflurane values, there was evidence in two volunteers at this time point of impairment in renal concentrating function, which normalized 5 days postanesthesia. These results occurred despite a higher peak plasma fluoride ion concentration and greater total inorganic fluoride renal exposure with sevoflurane anesthesia. (Key words: Anesthesics, volatile; enflurane; sevoflurane. Biotransformation: enflurane; sevoflurane. Ions: fluoride. Kidney: nephrotoxicity.)

Biotransformation of methoxyflurane to produce increased plasma fluoride ion concentrations has been shown to cause polyuric nephropathy in rats1 and humans.2 Although enflurane does not appear to produce polyuric renal failure, prolonged enflurane anesthesia in volunteers has been shown to produce a transient impairment in renal concentrating ability evaluated by vasopressin testing.3

Sevoflurane is a new inhalation anesthetic which undergoes hepatic biotransformation in humans, producing peak plasma inorganic fluoride concentrations similar to those which result in renal impairment after methoxyflurane anesthesia.4,5 Although plasma concentrations of inorganic fluoride after sevoflurane anesthesia peak at greater than 50 μM, there is a much more rapid decline in plasma fluoride ion concentration than with methoxyflurane due to the rapid elimination of sevoflurane from the body preventing continued metabolism.6 Sevoflurane has not been shown to produce renal impairment despite administration to a large number of patients. However, an evaluation of renal concentrating ability using vasopressin testing after prolonged sevoflurane anesthesia has not been done. Therefore, we evaluated plasma inorganic fluoride concentrations and renal concentrating ability of healthy male volunteers with desmopressin testing after enflurane or sevoflurane anesthetics of prolonged (> 9 MAC-h) duration.
Materials and Methods

Fourteen healthy male volunteers were enrolled after approval had been obtained from the University of Arizona Human Subjects Committee. Volunteers were selected randomly to receive sevoflurane (n = 7) or enflurane (n = 7) anesthesia in a nonblinded manner for a duration of greater than 9 MAC-h.

In all volunteers, anesthesia was induced with propofol (2–2.5 mg/kg), and succinylcholine (1–2 mg/kg) was administered to facilitate tracheal intubation. Anesthesia was maintained with 1–1.2 MAC enflurane or sevoflurane in a 30–40% oxygen/air mixture (5 l total flow) for the desired duration. The lungs were ventilated with a tidal volume of 10–15 ml/kg with the ventilatory rate adjusted to maintain end-tidal carbon dioxide concentration between 30 and 35 mmHg. Anesthetic gases were delivered using a Draeger Narcomet 2B anesthesia machine (North American Dräger, Telford, PA) with a circle system using soda lime (Sodasorb, W. R. Grace, Lexington, MA). End-tidal anesthetic gas concentrations were monitored with a Datex Capnomac monitor (Datex Medical Instruments, Tewksbury, MA). Before anesthetic induction, a heparin lock catheter was placed in an arm vein and venous blood samples obtained for plasma fluoride concentration analysis before anesthesia, each hour for 4 h, and then every 2 h during anesthesia, at anesthetic end, and 2, 4, 6, 12, 18, 24, and 48 h after anesthesia.

A 24-h urine collection was performed before the preanesthetic desmopressin test (1 week preanesthesia) and 4 days postanesthesia for creatinine clearance evaluation. Urine samples were collected before and 1, 2, and 5 days after anesthesia for measurements of urinary n-acetyl-β-glucosaminidase (NAG) and creatinine concentrations to determine the urinary NAG/creatinine concentration ratio.

Lactated Ringer's solution was administered intravenously to all volunteers. Volunteers received 4 ml/kg before induction and then 2–5 ml · kg⁻¹ · h⁻¹ as required for hemodynamic stability (i.e., mean arterial pressure greater than 55–60 mmHg) during anesthetic administration. Intravenous fluid was continued at 2 ml · kg⁻¹ · h⁻¹ until oral intake resumed.

Renal Function Evaluation and Fluid Therapy

Blood samples were obtained from each volunteer between 5 and 7 days before and on days 1 and 5 after anesthesia for measurement of creatinine, blood urea nitrogen, and serum osmolality. Each volunteer underwent three tests for renal concentrating ability between 5 and 7 days before and 1 and 5 days after anesthesia. Volunteers received 20 μg intranasal desmopressin (desmopressin acetate, Ferring Pharmaceuticals, Malmo, Sweden), with urine samples collected after administration for determination of osmolality. Urine was collected at 2-h intervals for 14 h after intranasal desmopressin administration. During desmopressin testing, the volunteers' fluid intake was limited to 360 ml with meals. Volunteers remained within the medical facility (clinical research unit) during the desmopressin testing period.

We defined a renal concentrating defect as a maximal urinary osmolality of less than 800 mOsm/kg after administration of desmopressin. Tryding et al.⁶ have defined normal renal concentrating function in response to desamino-8-darginine vasopressin in healthy subjects according to age. The acceptable maximal urinary osmolality (mean ± 2 SD) was 850 mOsm/kg (age 20 yr) and 800 mOsm/kg (age 40 yr). Our oldest volunteer was 35 yr of age, and therefore we chose 800 mOsm/kg as a conservative low normal.

Analytical and Statistical Methods

Plasma fluoride concentration analysis was performed using an ion-selective electrode (Orion Research, Boston, MA) calibrated against a standard solution of sodium fluoride (1–100 μM).

Urinary NAG concentrations were determined using a fluorometric assay as described by Dance et al.⁷ Urinary creatinine concentrations were determined with Heinegard and Tiderstrom's modified Jaffé method.⁸ Urinary osmolalities were determined by the University of Arizona clinical laboratories using a freezing point depression method.

Group demographics were compared using Student's t tests. All other group comparisons were made using repeated-measures analysis of variance with Student's t tests where appropriate. Significance was defined as P < 0.05.

Results

Volunteer characteristics, anesthetic duration, and MAC-hour exposure for sevoflurane- and enflurane-anesthetized volunteers did not differ and are shown in table 1. The two volunteer groups did not differ in laboratory control values and showed no changes in laboratory values of renal and hepatic function per-
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Table 1. Volunteer Characteristics, Anesthesia Duration, and MAC Hour Exposure

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane</th>
<th>Enflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>25 ± 2</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>180 ± 2</td>
<td>183 ± 4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 ± 3</td>
<td>76 ± 4</td>
</tr>
<tr>
<td>Anesthetic duration (min)</td>
<td>513 ± 8</td>
<td>519 ± 5</td>
</tr>
<tr>
<td>MAC hour</td>
<td>9.5 ± 0.1</td>
<td>9.6 ± 0.1</td>
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</tbody>
</table>

formed before and 1 and 5 days after anesthesia (table 2).

Creatinine clearance values for both groups of volunteers are shown in table 2. Plasma inorganic fluoride concentrations are shown in figure 1. Mean peak plasma inorganic fluoride concentration for the enflurane group was 23 ± 1 μM at 6 h postanesthesia. The sevo-
flurane group had a higher mean peak plasma inorganic fluoride value, which was 47 ± 3 μM occurring at the end of anesthesia (P < 0.05). Three volunteers had a peak plasma fluoride concentration in excess of 50 μM, with one of the three volunteers having peak concentration greater than 60 μM.

Maximal urinary osmolalities for the sevoflurane group before and 1 and 5 days after anesthesia are shown by individual in table 3 and for the group in figure 2. The mean maximal osmolality value of 1,093 ± 34 mOsm/kg obtained before anesthesia did not differ from the values of 1,032 ± 31 and 1,144 ± 37 mOsm/kg obtained with desmopressin testing on days 1 and 5, respectively, after anesthesia. Only one volunteer who had received sevoflurane had a maximal urinary osmolality of less than 900 mOsm/kg on day 1 postanesthesia, which was 864 mOsm/kg. This volunteer also had the lowest preanesthesia maximal value (933 mOsm/kg) (table 3).

Table 2. Renal and Hepatic Function Studies with Prolonged Sevoflurane and Enflurane Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Preanesthesia (5–7 days preanesthesia)</th>
<th>Postanesthesia (day 1)</th>
<th>Postanesthesia (day 4)</th>
<th>Postanesthesia (day 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sevo</td>
<td>Enf</td>
<td>Sevo</td>
<td>Enf</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>120 ± 10</td>
<td>115 ± 10</td>
<td>119 ± 13</td>
<td>116 ± 14</td>
</tr>
<tr>
<td>Creatinine (mg/ml)</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>0.9 ± 0.0</td>
<td>0.9 ± 0.0</td>
</tr>
<tr>
<td>BUN (mg/ml)</td>
<td>14 ± 1</td>
<td>14 ± 1</td>
<td>13 ± 2</td>
<td>10 ± 0</td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>140 ± 1</td>
<td>141 ± 1</td>
<td>141 ± 1</td>
<td>143 ± 1</td>
</tr>
<tr>
<td>Serum osmolality (mOsm/kg)</td>
<td>292 ± 2</td>
<td>288 ± 2</td>
<td>293 ± 2</td>
<td>290 ± 1</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.6 ± 0.0</td>
<td>0.8 ± 0.1</td>
<td>0.5 ± 0.0</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>61 ± 5</td>
<td>64 ± 6</td>
<td>59 ± 4</td>
<td>63 ± 6</td>
</tr>
<tr>
<td>ALT (SGPT) (IU/L)</td>
<td>22 ± 3</td>
<td>21 ± 3</td>
<td>21 ± 3</td>
<td>21 ± 2</td>
</tr>
<tr>
<td>AST (SGOT) (IU/L)</td>
<td>22 ± 2</td>
<td>22 ± 2</td>
<td>31 ± 7</td>
<td>25 ± 5</td>
</tr>
</tbody>
</table>

AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); BUN = blood urea nitrogen; Sevo = sevoflurane group; Enf = enflurane group. Values shown are mean ± SEM; n = 7 for values.

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Fig. 1. Mean plasma inorganic fluoride ion concentrations during and after prolonged sevoflurane or enflurane anesthesia. The peak value for sevoflurane is 47 ± 3 μM (end of anesthesia) and for enflurane is 23 ± 1 μM (6 h postanesthesia). Data points are shown as mean ± SEM; n = 7 at each time point. *Differs from enflurane values at the same time point (P < 0.01).
The mean maximal urinary osmolalities for enflurane were 1,022 ± 24 mOsm/kg preanesthesia, 870 ± 51 mOsm/kg on day 1 postanesthesia, and 1,062 ± 58 mOsm/kg on day 5 postanesthesia (fig. 2). After enflurane anesthesia, two volunteers showed evidence of a renal concentrating deficit and were unable to produce urinary osmolalities greater than 800 mOsm/kg (631 and 798 mOsm/kg). There was no correlation between peak fluoride concentration or area under the fluoride concentration–time curve and maximal urinary osmolalities obtained for enflurane or sevoflurane volunteers. Urine output from the anesthetic period until the desmopressin test on day 1 after anesthesia did not differ between enflurane (2,371 ± 349 ml) and sevoflurane (2,649 ± 232 ml).

Urinary NAG/creatinine ratios for enflurane and sevoflurane groups are shown in figure 3. We used the urinary NAG/creatinine ratio, rather than absolute NAG value, in an attempt to compensate for variation in urinary flow. NAG/creatinine values before anesthesia were higher in the sevoflurane group (71.6 ± 26.5) than in the enflurane group (24.5 ± 7.9). Values did not change within either group at days 1, 2, and 5 after anesthesia compared to preanesthetic values, and values did not differ between the sevoflurane- and enflurane- anesthetized groups, instead remaining within the reported normal range for healthy subjects of 20–100 nmol NAG·h⁻¹·mg⁻¹ creatinine.

**Discussion**

Renal concentrating function after 9.5 MAC-h sevoflurane anesthesia showed no impairment at 1 and 5 days postanesthesia compared to preanesthesia values. In contrast, prolonged enflurane anesthesia impaired renal concentrating function in response to desmopressin administration in two of seven volunteers on
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day 1 but not on day 5 after anesthesia. However, the mean peak osmolality values for enflurane and sevoflurane 1 day after anesthesia did not differ statistically.

Prolonged enflurane anesthesia has been shown to produce a decrease in maximum urinary osmolality after vasopressin administration. Mazze et al. administered enflurane or halothane to healthy volunteers for 9.6 and 13.7 MAC-h, respectively. They demonstrated decreased urinary osmolality on day 1 after anesthesia compared to control values with enflurane anesthesia. These were normal by day 5 after anesthesia. No change was seen in the halothane group. 3

Our goal, similarly, was to compare the effect of prolonged sevoflurane administration on renal concentrating function to that of enflurane. Enflurane did produce a decrement in renal concentrating function in some of our volunteers, yet our results for this anesthetic were not as significant as were those observed by Mazze et al. They found that maximal urinary osmolality was decreased in every subject (lowest osmolality 590 mOsm/kg). Our results showed a wider variation in urinary concentrating function 1 day after anesthesia, with five volunteers maintaining normal function and two volunteers having apparent abnormal renal concentrating function in response to desmopressin (maximal osmolality < 800 mOsm/kg).

Several differences do exist between the study by Mazze's group 3 and our investigation. First, Mazze et al. used subcutaneous vasopressin tannate in oil to increase urinary concentration, but we used intranasal desmopressin. Intranasal desmopressin was used because the vasopressin tannate formulation is no longer commercially available. Intranasal desmopressin is a reliable test of urinary concentrating function and produces only minimal subject discomfort. Our dose of 20 µg intranasally produces a consistent response in volunteers (with doses as small as 10 µg being effective) and produces no cardiovascular side effects. In all of our volunteers, urinary osmolality increased to greater than 900 mOsm/kg with this dose during preanesthesia testing. Second, we used propofol for induction rather than thiopental.

Third, plasma inorganic fluoride concentrations in our enflurane-anesthetized volunteers were less than those obtained by Mazze et al. Mean maximal serum fluoride concentration obtained in their volunteers was 33.6 ± 2.8 µM at 6 h postanesthesia, whereas our results showed a value at 6 h of 23 ± 1 µM. Reasons for the difference in fluoride values for a comparable duration of anesthesia are not entirely clear; however, one factor could be liver enzyme function. We were very careful to screen for possible exposure to hepatocellular enzyme-inducing agents in our volunteers and requested no over-the-counter drug use or alcohol intake during the 2-week study period. The report by Mazze et al. does not state whether volunteers were screened for drug or alcohol intake. In addition, Mazze et al. do not mention their method of serum inorganic fluoride determination; however, in all likelihood a fluoride ion electrode similar to ours was used. For whatever reason, the higher serum fluoride value in the study by Mazze et al. may have been responsible for their greater number of volunteers' exhibiting impairment of renal concentrating function.

In addition to renal concentrating ability, we evaluated other indices of renal function. Serum osmolality postanesthesia remained unchanged from preanesthetic values with either sevoflurane or enflurane. Creatinine clearance was not changed with either group when values obtained before and 4 days after anesthesia were compared. The excretion of NAG was evaluated using the urinary NAG/creatinine ratio before anesthesia and for 5 days after anesthesia. This enzyme, present in the renal tubules, has been used as a measure of nephrotoxicity of certain drugs as well as a monitor of renal transplant rejection and becomes elevated with tubular injury. No increase in this enzyme occurred in either sevoflurane- or enflurane-anesthetized volunteers. The NAG/creatinine ratio remained within normal range and would be expected to increase to 400–800 with renal injury. We are unaware of any evidence that this test is a good monitor for potential fluoride-induced nephrotoxicity.

Other studies evaluating renal function after prolonged sevoflurane anesthesia in surgical patients have not evaluated renal concentrating function. Kazama and Ikeda 15 did not find evidence of renal insufficiency after up to 15 MAC-h sevoflurane anesthesia using routine renal function tests. Kobayashi et al. 5 studied plasma electrolyte, blood urea nitrogen, and creatinine values as well as urine output after prolonged (13.5 MAC-h) sevoflurane anesthesia in surgical patients and found no evidence of nephrotoxicity.

Mean peak plasma fluoride ion concentrations after sevoflurane anesthesia in our study were 47 ± 3 µM. Three sevoflurane-anesthetized volunteers achieved peak fluoride concentrations in excess of 50 µM (highest 63 µM) and did not demonstrate a defect in renal concentrating function on day 1 postanesthesia. A previous study with methoxyflurane demonstrated defects

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in concentrating function when 50 μm was exceeded. After methoxyflurane anesthesia, plasma fluoride ion concentrations remained near peak (i.e., > 50 μm) for 72 h. In contrast, after sevoflurane anesthesia, plasma fluoride concentrations decrease rapidly to 50% of peak by 12 h after anesthetic discontinuation. This rapid decrease in plasma inorganic fluoride concentration appears to be due to the rapid elimination of sevoflurane, preventing further hepatic biotransformation. A peak plasma fluoride ion concentration of 50 μm in healthy volunteers may be insufficient to produce renal impairment if it is not sustained for several hours. However, renal concentrating function was evaluated the morning after sevoflurane and enfurane anesthesia, which does not correspond with the time of peak inorganic fluoride ion concentration. This is particularly true with the sevoflurane group. It is possible that if testing of renal concentrating function coincided with the time of peak plasma fluoride ion concentration, different results from those obtained in this study might be obtained.

Our investigation evaluated plasma fluoride concentration and renal concentrating function only in healthy volunteers presumed free of hepatocellular enzyme induction. There is evidence from animal studies that sevoflurane metabolism is increased with cytochrome P450 enzyme induction from ethanol, isoniazid, and phenobarbital, producing higher plasma fluoride ion concentrations. It is still unknown if prolonged sevoflurane anesthesia in an individual with enzyme induction might cause renal concentrating function impairment.

Evaluation of plasma fluoride concentration curves from sevoflurane and enfurane volunteers leads to an interesting question. Why did some volunteers in the enfurane group have a defect in renal concentrating function, while the total fluoride ion exposure was greater with sevoflurane anesthesia? Interpretation of the results leads us to consider the possibility that renal fluoride ion exposure as a result of biotransformation may not be the entire explanation for renal concentrating impairment after enfurane. Although the high and prolonged plasma fluoride concentrations after methoxyflurane are undoubtedly sufficient to be the cause of renal injury, it may be possible that the more minor changes in renal concentrating ability as demonstrated with vasopressin testing after enfurane in this and the study by Mazze et al. may not be solely the result of plasma fluoride concentrations. Other possible causative factors may exist. Renal perfusion with enfurane in humans decreases during surgical anesthesia. In chronically instrumented animals, renal perfusion is maintained at 1 MAC but reduced to a greater extent at 1.7–1.8 MAC with enfurane than with halothane or isoflurane. In rats, sevoflurane preserves renal perfusion, similar to isoflurane in the same model.

Results of this study indicate that prolonged administration of sevoflurane to our group of seven young, healthy volunteers did not produce a renal concentrating defect when evaluated 24 h and 5 days after anesthesia.

References


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