Influence of Sevoflurane on the Metabolism and Renal Effects of Compound A in Rats

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Background: The sevoflurane degradation product compound A is nephrotoxic in rats. In contrast, patient exposure to compound A during sevoflurane anesthesia has no clinically significant renal effects. The mechanism for this difference is incompletely understood. One possibility is that the metabolism and toxicity of compound A in humans is prevented by sevoflurane. However, the effect of sevoflurane on compound A metabolism and nephrotoxicity is unknown. Thus, the purpose of this investigation was to determine the effect of sevoflurane on the metabolism and renal toxicity of compound A in rats.

Methods: Male rats received 0.25 mmol/kg intraperitoneal compound A, alone and during sevoflurane anesthesia (3%, 1.3 minimum alveolar concentration, for 3 h). Compound A metabolites in urine were quantified, and renal function was evaluated by serum creatinine and urea nitrogen, urine volume, osmolality, protein excretion, and renal tubular histology.

Results: Sevoflurane coadministration with compound A inhibited compound A defluorination while increasing relative metabolism through pathways of sulfoxidation and β-lyase-catalyzed metabolism, which mediate toxicity. Sevoflurane coadministration with compound A increased some (serum creatinine and urea nitrogen, and necrosis) but not other (urine volume, osmolality, and protein excretion) indices of renal toxicity.

Conclusions: Sevoflurane does not suppress compound A nephrotoxicity in rats in vivo. These results do not suggest that lack of nephrotoxicity in surgical patients exposed to compound A during sevoflurane anesthesia results from an inhibitory effect of sevoflurane on compound A metabolism and toxicity. Rather, these results are consistent with differences between rats and humans in compound A exposure and inherent susceptibility to compound A nephrotoxicity.

FLUOROMETHYL-2,2-difluoro-1-(trifluoromethyl)vinyl ether (compound A) is the major product formed in normal clinical situations from degradation of sevoflurane by carbon dioxide absorbents which contain strong base.1,2 Compound A is nephrotoxic to rats when administered by inhalation or intraperitoneal injection, causing proximal tubular necrosis, increased serum creatinine, diuresis, and proteinuria.3,4 In rats, compound A undergoes a complex route of metabolism and bioactivation, which mediates the nephrotoxicity (fig. 1). Compound A reacts with glutathione to form glutathione conjugates (fig. 1, 2 and 3), which undergo cleavage to the corresponding cysteine S-conjugates (fig. 1, 4 and 5). N-acetylation of cysteine S-conjugates forms mercapturates (fig. 1, 6 and 7), which are excreted in urine. The cysteine S-conjugates are metabolized by rat renal β-lyase to reactive intermediates, which are reflected by the urine excretion of 3,3,3-trifluoro-2-(fluoromethoxy)propanoic acid.8 Like many other nephrotoxic haloalkenes, β-lyase-catalyzed metabolism of compound A cysteine S-conjugates is thought to mediate nephrotoxicity, because inhibition of renal S-conjugate uptake, β-lyase activity, or β-lyase-catalyzed metabolism diminished compound A nephrotoxicity, whereas glutathione and cysteine S-conjugates replicated compound A nephrotoxicity,8,9 and the sulfoxide conjugates were more toxic than other compound A conjugates to renal proximal tubular cells in culture.10 Compound A undergoes qualitatively similar biotransformation in humans.8,11–15

Compound A formation during sevoflurane anesthesia in surgical patients has been extensively evaluated and found to have no clinically significant effects.16–22 Investigations have typically compared low-flow sevoflurane with high-flow sevoflurane, low-flow isoflurane or desflurane, or intravenous anesthetics. In none of the published studies using low-flow or closed-circuit sevoflurane were there any differences between anesthetics in postoperative renal function as assessed by the standard markers of blood urea nitrogen, creatinine, and creatinine clearance, even in the patients with the highest compound A exposures. In patients undergoing very long procedures, greater proteinuria in patients receiving low-flow sevoflurane was seen in one investigation17 but not in any of the others. Proteinuria, however, is commonly seen after anesthesia with all halogenated and intravenous anesthetics.23 In a high-risk group of patients with preexisting renal insufficiency, a known risk factor for postoperative renal dysfunction, there was no difference between low-flow sevoflurane and low-flow isoflurane on renal function.20

The reason why compound A formation during sevoflurane anesthesia in surgical patients does not alter renal function is incompletely understood. One potential...
explanation is simply that rats in the experimental toxicology studies received comparatively greater compound A doses than the doses to which humans are exposed during surgery.\textsuperscript{15} A second potential explanation is the numerous quantitative differences between humans and rats in the bioactivation and toxicity of compound A.\textsuperscript{8,10–12,15,24} A third potential explanation is that rats in experimental studies have been exposed exclusively to compound A, whereas patients are exposed to sevoflurane as well as compound A, and sevoflurane may diminish the toxicity of compound A. It is well known that the toxicokinetics (disposition) and/or the toxicodynamics (tissue injury and compensatory protective mechanism) of haloalkyl toxins can be modified by the coadministration of other haloalkyl compounds.\textsuperscript{25,26} Thus, the intrinsic toxicity of compound A may be similar between rats and humans, but actual toxicity may be diminished by coadministration of sevoflurane. Nevertheless, this hypothesis has never been tested. Therefore, the purpose of this investigation was to determine the effect of sevoflurane on the metabolism and toxicity of compound A in rats.

Materials and Methods

Chemicals and Reagents
Fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether (FDVE, 99.92% purity) and sevoflurane were provided by Abbott Laboratories (Abbott Park, IL). Dichloroacetic acid, magtrieve, and benzophenone hydrazine were purchased from Aldrich (Milwaukee, WI); methylene chloride and hydrochloric acid were purchased from Fisher Scientific (Pittsburgh, PA); ethyl acetate (GC grade) was purchased from Burdick and Jackson (Muskegon, MI); and anhydrous ether was purchased from J.T. Baker (Phillipsburg, NJ). All stock drug solutions and buffers were prepared using Milli-Q grade water (Millipore, Bedford, MA).

N-acetyl-S-[1,1-difluoro-2-fluoromethoxy-2-(trifluoromethyl)ethyl]-L-cysteine (N-Ac-DFEC, 6), (E, Z)-N-acetyl-S-[1-fluoro-2-fluoromethoxy-2-(trifluoromethyl) vinyl]-L-cysteine ((E, Z)-N-Ac-FFVC, 7), N-acetyl-S-[1,1-difluoro-2-fluoromethoxy-2-(trifluoromethyl)ethyl]-L-cysteine sulfoxide (N-Ac-DFEC-SO, 12), and (E, Z)-N-acetyl-S-[1-fluoro-2-fluoromethoxy-2-(trifluoromethyl) vinyl]-L-cysteine sulfoxide ((E, Z)-N-Ac-FFVC-SO, 13) were synthesized as described previously,\textsuperscript{8} as was 3,3,3-trifluoro-2-(fluoromethoxy)propanoic acid (F-propionic acid, 8).\textsuperscript{27}

Animal Treatments
All animal experiments were approved by the University of Washington Animal Use Committee (Seattle, Washington) and conducted in accordance with American Association for Accreditation of Laboratory Animal Care guidelines. Male Fisher 344 rats (250–300 g; Harlan, San Diego, CA) were housed in individual metabolic cages, provided food and water ad libitum, and maintained on a 12-h light–dark cycle. Twelve rats were randomized to one of two treatment groups after baseline blood (saphenous vein) and 24-h urine samples were obtained. Six rats received FDVE (0.25 mmol/kg in corn oil, 0.125 mmol/ml) via intraperitoneal injection. Six rats were anesthetized with sevoflurane for 1 h, injected...
intrapertitoneally with compound A (0.25 mmol/kg), and then exposed to 2 more hours of sevoflurane. Animals were exposed in a 20-l inhalation chamber to 3% sevoflurane (1.3 minimum alveolar concentration) in oxygen at 6 l/min, administered via a calibrated vaporizer, without the use of any carbon dioxide absorbent, with constant monitoring of chamber gas concentration to maintain sevoflurane concentration at 3% and minimize any carbon dioxide rebreathing (Capnomac Ultima; Datex, Madison, WI). Animals rested on a warming pad, with constant monitoring to maintain rectal temperature at 37°C. Rats were returned to the metabolic cages after recovery from anesthesia, and urine was collected on ice for 24 h. Rats were anesthetized with pentobarbital and killed by cardiac exsanguination. Kidneys were immediately excised, trimmed, and cut in a midtransverse plane through cortex and medullary pyramid, and a section was fixed in 10% neutral buffered formalin. The remainder was flash frozen in liquid nitrogen and stored at −80°C.

**Sample Analyses**

Plasma urea nitrogen was measured spectrophotometrically using the Infinity urea nitrogen reagent (Thermo DMA, Louisville, CO) according to the manufacturer’s directions. Plasma creatinine was measured using Vitros Crea slides on a Vitros 250 chemistry system (Ortho-Clinical Diagnostics, Rochester, NY). Urine osmolality was determined using an Advanced Instrument (Norwood, MA) model 3D3 freezing point osmometer. Urine protein concentrations were measured spectrophotometrically using a microprotein kit (Sigma 611-A; Sigma-Aldrich, St. Louis, MO). Urine fluoride concentrations were measured using a fluoride-specific electrode (Thermo Electron Corp., Waltham, MA). Thawed urine (80 μl) was added to 20 μl low-level total ionic strength adjustment buffer (1 m NaCl in 1 m acetic acid, adjusted to pH 5.0–5.5 with 5 m NaOH). An aliquot (40 μl) was then placed on the inverted electrode, and a microscope cover slip was placed on top. Fluoride concentrations in unknowns were calculated from electrode voltage using a standard curve prepared by analyzing calibration standards of fluoride in water (0.1–5 mM). Urine concentra-

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<thead>
<tr>
<th>Table 1. Influence of Sevoflurane on Compound A Nephrotoxicity</th>
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<tr>
<td><strong>Compound A</strong></td>
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<tr>
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<tr>
<td>BUN, mg/dl</td>
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<tr>
<td>Serum creatinine, mg/dl</td>
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<tr>
<td>Urine volume, ml</td>
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<tr>
<td>Urine protein, mg/24 h</td>
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<tr>
<td>Urine osmolality, mOsm/kg</td>
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<tr>
<td>Necrosis (1 = low, 4 = high) [median]</td>
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</table>

Results are mean ± SD. * Significantly different from predose value (P < 0.05). † Significantly different from compound A only (P < 0.05). BUN = blood urea nitrogen.

several compounds of compound A-mercapturic acid conjugates, their corresponding sulfoxides, and 3,3,3-trifluoro-2-(fluoromethoxy)propanoic acid in urine were determined by high-pressure liquid chromatography–mass spectrometry as described previously.

Formalin-treated kidney sections were embedded in paraffin, and sections were stained with hematoxylin and eosin. They were examined by a veterinary pathologist who was unaware of the animal treatments. Histopathologic changes were recorded in regard to location, character, and severity. The semiquantitative severity score consisted of a range from 0 to 4 (respectively normal, minimal, slight, moderate, and marked), which reflects the degree and distribution of the tubular necrosis.

**Statistical Analysis**

Data were analyzed using repeated-measures analysis of variance with Student-Newman-Keuls comparisons, or unpaired t test as appropriate using SigmaStat (SPSS Science, Chicago, IL). All results are reported as the mean ± SD. Statistical significance was assigned at P < 0.05.

**Results**

The dose of compound A used in these experiments (0.25 mmol/kg) was based on the threshold dose for nephrotoxicity observed in previous experiments. Renal effects (urine volume, protein excretion and osmolality, serum creatinine and urea nitrogen, and necrosis; table 1) were similar to those seen previously at this intraperitoneal dose and at approximately 350–400 ppm-h inhaled compound A. Coadministration of compound A with 3 h of sevoflurane increased some but not all measures of renal toxicity (table 1). The increase in serum creatinine and urea nitrogen concentrations, and histologic evidence of proximal tubular necrosis caused by compound A, were greater in rats that also received 3 h of sevoflurane anesthesia. In contrast, changes in urine volume, osmo-

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sulfoxide.

Fluoride, F-propionic acid, N-Ac-DFEC-SO (12) 0.078 ± 0.020 0.073 ± 0.024 0.08 3.3

oromethyl) vinyl]-L-cysteine; F-propionic acid (8)

(E, Z)-N-Ac-FFVC (7) (E, Z)-N-Ac-FFVC

urine volume and protein excretion.4,5,9 The lack of further change in urine volume and protein excretion, but not other (urine volume, osmolality, and protein excretion) indices of renal toxicity were increased by coadministration of trichloroethylene with chloroform, which is also metabolized predominantly by CYP2E1, decreased CYP2E1-catalyzed trichloroethylene metabolism.25,26

The results of this experiment show that sevoflurane did not diminish compound A nephrotoxicity. Rather, some (serum creatinine and urea nitrogen, and necrosis) but not other (urine volume, osmolality, and protein excretion) indices of renal toxicity were increased by coadministration. This response pattern was unusual, because urine volume, osmolality, and protein excretion are typically much more sensitive markers of compound A nephrotoxicity, whereas serum creatinine and urea nitrogen are often unaffected.4-6,9 The lack of further change in urine volume and protein excretion with sevoflurane plus compound A was not because a maximal response had been reached with 0.25 mmol/kg compound A alone, because higher compound A doses did produce greater urine volume and protein excretion.4,5,9 Nevertheless, further mechanistic elucidation would require additional experiments and was not the aim of the current investigation. It is also possible that any other anesthetic may have also increased the renal toxicity of

did not significantly decrease.

Table 2. Influence of Sevoflurane on Compound A Metabolism

<table>
<thead>
<tr>
<th>Urinary Excretion</th>
<th>Compound A</th>
<th>Compound A and Sevoflurane</th>
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<tbody>
<tr>
<td>N-Ac-DFEC, µmol/24 h</td>
<td>7.4 ± 1.3</td>
<td>3.3 ± 1.4*</td>
</tr>
<tr>
<td>(E, Z)-N-Ac-FFVC, µmol/24 h</td>
<td>4.3 ± 0.7</td>
<td>2.3 ± 1.4*</td>
</tr>
<tr>
<td>N-Ac-DFEC-SO, µmol/24 h</td>
<td>0.078 ± 0.020</td>
<td>0.073 ± 0.024</td>
</tr>
<tr>
<td>F-propionic acid, µmol/24 h</td>
<td>1.04 ± 0.21</td>
<td>0.74 ± 0.22*</td>
</tr>
<tr>
<td>Fluoride, µmol/24 h</td>
<td>49.7 ± 9.9</td>
<td>39.5 ± 11.6*</td>
</tr>
<tr>
<td>Sulfoxidation index, %†</td>
<td>1.1 ± 0.3</td>
<td>2.3 ± 0.6*</td>
</tr>
<tr>
<td>β-Lyase index, %‡</td>
<td>8.1 ± 0.8</td>
<td>12.5 ± 2.5*</td>
</tr>
</tbody>
</table>

Results are mean ± SD. Predose urine fluoride excretion was 0.8 ± 0.0 and 0.9 ± 0.0 µmol/24 h in compound A and compound A-sevoflurane animals. * Significantly different from control (P < 0.05). † N-Ac-DFEC-SO/(N-Ac-DFEC-SO + N-Ac-DFEC) × 100%. ‡ F-propionic acid/(F-propionic acid + N-Ac-DFEC-SO + N-Ac-DFEC + [E, Z]-N-Ac-FFVC) × 100%.

Discussion

The results of this experiment show that sevoflurane altered compound A metabolism. The decrease in urine fluoride excretion when compound A was coadministered with sevoflurane is all the more remarkable because sevoflurane itself is metabolized to inorganic fluoride. Fluoride excretion after sevoflurane anesthesia in rats has been reported to be approximately 15-40 µmol/24 h.29,30 The expected result, therefore, was that urine fluoride would have increased, due to defluorination of both compound A and sevoflurane. Decreased rather than increased fluoride excretion suggests sevoflurane inhibition of compound A defluorination in vivo. In addition to conjugation with glutathione and subsequent defluorination of these conjugates, compound A also undergoes oxidative defluorination.51 Both compound A and sevoflurane oxidation are catalyzed by the same enzyme, cytochrome P4502E1 (CYP2E1), and sevoflurane inhibits compound A defluorination in vitro.51 Compared with compound A concentrations, the much higher sevoflurane concentrations in vivo likely inhibited P450-mediated compound A oxidative defluorination, resulting in less fluoride excretion. Reasons for the decreased excretion of compound A mercapturates, yet increased β-lyase and sulfoxidation indices, reflecting relative flux through these pathways, are not apparent.

Sevoflurane effects on compound A metabolism are analogous to the altered metabolism of haloalkyl toxins by the coadministration of other halogenated compounds. For example, trichloroethylene undergoes both CYP2E1-catalyzed oxidation and conjugation with glutathione and subsequent S-conjugates bioactivation, resulting in toxicity. Coadministration of trichloroethylene with chloroform, which is also metabolized predominantly by CYP2E1, decreased CYP2E1-catalyzed trichloroethylene metabolism.25,26

The results of this experiment show that sevoflurane did not diminish compound A nephrotoxicity. Rather, some (serum creatinine and urea nitrogen, and necrosis) but not other (urine volume, osmolality, and protein excretion) indices of renal toxicity were increased by coadministration. This response pattern was unusual, because urine volume, osmolality, and protein excretion are typically much more sensitive markers of compound A nephrotoxicity, whereas serum creatinine and urea nitrogen are often unaffected.4-6,9 The lack of further change in urine volume and protein excretion with sevoflurane plus compound A was not because a maximal response had been reached with 0.25 mmol/kg compound A alone, because higher compound A doses did produce greater urine volume and protein excretion.4,5,9 Nevertheless, further mechanistic elucidation would require additional experiments and was not the aim of the current investigation. It is also possible that any other anesthetic may have also increased the renal toxicity of...
compound A. In the current experiment, a nonsevoflu-
ran anesthetic was not used as the control, because the
hypothesis was that sevoflurane specifically, not anesthe-
sia in general, might prevent compound A toxicity.

If sevoflurane effects on compound A are similar in
humans and rats, then the lack of suppression of com-
 pound A nephrotoxicity by sevoflurane in rats in vivo
does not support the notion that compound A exposure
in humans is prevented by sevoflurane coadministration.

Were the intrinsic toxicity of compound A similar in rats
and humans but actual toxicity diminished by coadmin-
istration of sevoflurane in humans, sevoflurane would
have been expected to reduce compound A toxicity in
these rat experiments. Rather, these experiments sup-
port the notion that rats and humans differ in their
susceptibility to compound A nephrotoxicity.

There are at least two potential explanations for the
difference between humans and rats in compound A
renal effects. One is simply the compound A dose to
which patients are exposed. Whereas the nephrotoxic
threshold in rats is 0.2–0.25 mmol/kg, patients are ex-
posed to much lower (at least 40-fold) doses of com-
 pound A (typically 0.005 mmol/kg for a 3- to 4-h anes-
thetic). A second potential explanation is the well-
known interspecies differences in the metabolism of
compound A, which is thought to mediate toxicity. For
example, in rats compared with humans, there are (1)
greater rates of compound A-glutathione conjugate for-
mation in hepatic microsomes and cytosol, (2) greater
β-lyase-catalyzed metabolism of compound A-cysteine
conjugates in vitro in rat kidneys, (3) greater excretion
of N-Ac-DFEC relative to (E, Z)-N-Ac-FVFC in rats, (4)
greater excretion of 3,3,3-trifluoro-2-fluoromethoxy-
propanoic acid (reflecting β-lyase-catalyzed FDVE cysteine
conjugates metabolism) in vivo in rats, (5) greater
ratio of 3,3,3-trifluoro-2-fluoromethoxypropanoic acid
(toxicification) to mercapturates (detoxication) in urine in
rats, (6) relative resistance of human proximal tubu-
lar cells to the cytotoxic effects of FDVE-cysteine-S-con-
gjugates, and (7) greater sulfonation of compound A
mercapturates.

There are some differences between the rat model
used in these experiments and clinical scenarios. Rats
received compound A by intraperitoneal injection,
rather than by inhalation, to better control the dose.
However, compound A nephrotoxicity is similar
whether it is administered by inhalation or intraperito-
neal injection. In humans, the amount of sevoflurane
to which patients are exposed is several orders of mag-
itude greater than that of compound A. In these
experiments, the compound A dose had to be high
enough to elicit a reproducible effect (0.25 mmol/kg),
which resulted in a dose much higher than equivalent
exposures in humans (approximately 0.005 mmol/kg).

In summary, in rats, coadministration of compound A
together with sevoflurane, compared with compound A
alone, increased compound A metabolism via pathways
that mediate toxicity, and increased some but not all
indices of nephrotoxicity. These results do not suggest
that lack of nephrotoxicity in surgical patients exposed
to compound A during sevoflurane anesthesia results
from an inhibitory effect of sevoflurane on compound A
metabolism and toxicity. Rather, these results are con-
sistent with differences between rats and humans in
compound A exposure and inherent susceptibility to
compound A nephrotoxicity.

The authors thank Dale Whittington, B.S. (Research Scientist, Department of
Anesthesiology, University of Washington, Seattle, Washington), for technical
assistance in the urine analysis.

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