Sevoflurane degradation by carbon dioxide absorbents may produce more than one nephrotoxic compound in rats

[La dégradation du sévoflurane par les absorbants de gaz carbonique peut produire plus d'un composé néphrotoxique chez les rats]

Caroline R. Stabernack MD,* Edmond I Eger II MD,† Uwe H. Warnken MD,‡ Harald Förster MD,‡ Douglas K. Hanks MD,§ Linda D. Ferrell MD§

Purpose: Degradation of sevoflurane by carbon dioxide absorbents produces compound A, a vinyl ether. In rats, compound A can produce renal corticomedullary necrosis. We tested whether other compounds produced by sevoflurane degradation also could produce corticomedullary necrosis.

Methods: Two groups of rats were exposed for four hours to sevoflurane 2.5% delivered through a container filled with fresh Sodasorb® and heated to 30°C or to 50°C, respectively. Compound A was added to produce an average concentration of 120 ppm in both groups. A third (control) group received 2.5% sevoflurane that did not pass through absorbent, and no compound A was added.

Results: As determined by gas chromatography, the higher temperature produced more volatile breakdown products, including compound A. Median necrosis of the corticomedullary junction in the 50°C group [10% (quartiles 1.0%–7.8%); $n = 20$] exceeded that in the 30°C group [5% (6.5%–15%); $n = 18$; $P < 0.02$], and both exceeded the median necrosis in the control group [0% (0.0%–0.2%); $n = 10$; $P < 0.02$]. The respective mean ± SD values for these three studies were: 12.8 ± 16.7%, 5.3 ± 4.4%, and 0.3 ± 0.5%.

Conclusion: Degradation products of sevoflurane other than compound A can cause or augment the renal injury in rats produced by compound A.

Objectif : *La dégradation du sévoflurane par les absorbants de gaz carbonique produit un éther vinylique, le composé A. Chez les rats, ce composé provoque une nécrose corticomédullaire rénale. Nous avons vérifié si d'autres composés issus de la dégradation du sévoflurane peuvent aussi provoquer cette nécrose.*

Méthode : *Deux groupes de rats ont été exposés pendant quatre heures à du sévoflurane à 2,5 % administré après avoir traversé un récipient rempli de Sodasorb® frais et chauffé respectivement à 30 °C ou à 50 °C. Du composé A a été ajouté pour produire une concentration moyenne de 120 ppm dans les deux groupes. Un troisième groupe (témoin) a reçu du sévoflurane à 2,5 %, qui ne traversait pas l'absorbant, et sans ajout de composé A.*

Résultats : *Les résultats de la chromatographie en phase gazeuse ont montré que sous la température la plus élevée, il y a eu plus de produits de dégradation volatils, y compris le composé A. Dans le groupe 50 °C, la nécrose moyenne de la jonction corticomédullaire dépassait [10 % (quartiles 1,0 %-7,8 %) ; n = 20] celle du groupe 30 °C [5 % (6,5 %-15 %) ; n = 18 ; P < 0,02] et les deux étaient plus élevée que celle du groupe témoin [0 % (0,0%-0,2 %) ; n = 10 ; P < 0,02]. Les valeurs respectives de la moyenne ± l'écart type ont été de 12,8 ± 16,7 %, 5,3 ± 4,4 % et de 0,3 ± 0,5 %.*

Conclusion : *Les produits de dégradation du sévoflurane, autres que le composé A, peuvent causer ou augmenter la lésion rénale produite par le composé A chez les rats.*

From the Department of Anesthesia and Perioperative Care,*† and the Department of Pathology,§ University of California, San Francisco, California, USA, and the Department of Experimental Anesthesiology,‡ University of Frankfurt, Germany.

Address correspondence to: Dr. Edmond I Eger, Department of Anesthesia and Perioperative Care, Box 0464, Science - 455, 513 Parnassus Avenue, University of California, San Francisco, California 94143-0464, USA. Phone: 415-476-6927; Fax: 415-476-9516; E-mail: egere@anesthesia.ucsf.edu

Reprints will not be available from the author.

Dr. Eger is a paid consultant to Baxter Healthcare Corporation. This study was not funded by Baxter Healthcare Corporation (nor by any other external source), who did, however, supply compound A for these studies.

Accepted for publication August 20, 2002.

Revision accepted November 11, 2002.

CARBON dioxide absorbents can degrade sevoflurane [(CH_2F)-O-$CH(CF_3)_2$] to compound A [(CH_2F)-O-$C(CF_3)(=CF_2)$].[1] In rats, compound A can produce renal corticomedullary necrosis, proteinuria and enzymuria.[2–4] Sevoflurane degradation also produces compound B [CH_2F-O-$CH(CF_3)(CF_2$-O-$CH_3)$],[1,2] which, alone, is not toxic.[2] Compounds C[$(CF_2=C)(O$-$CH_2F)(CF_2OCH_3)$], D[$(CH_3$-O-$)CF=C(CF_3)(OCH_2F)$], and E (an isomer of D), but not free methanol, formaldehyde or formic acid, result from sevoflurane degradation by soda lime at 57°C.[1,5]

We hypothesized that some of these other degradation products might be nephrotoxic or augment the nephrotoxicity of compound A. To test this hypothesis, we exposed rats to identical concentrations of sevoflurane and compound A with the sevoflurane exposed to two absorbent temperatures, 30°C and 50°C, temperatures found in absorbents used during low-flow delivery of gases.[6] Since more degradation products result at higher temperatures, we predicted that greater renal injury should result in rats receiving sevoflurane exposed to hotter absorbent.

Methods

Sevoflurane was purchased from Abbott Laboratories (Abbott Park, Illinois, USA). Compound A was donated by Baxter Healthcare Corporation. Cylinders containing compound A were prepared by injecting liquid compound A and pressurizing each cylinder with nitrogen. One cylinder provided a calibration standard (512 ppm) and the other (2,767 ppm) was used to augment compound A delivery to the rats. Sevoflurane and compound A concentrations were analyzed by gas chromatography, referenced to standards prepared by injecting an aliquot of liquid into a flask of known volume.

Sevoflurane in oxygen was delivered via a humidifier (to ensure, as in low-flow clinical anesthesia, gas humidification) to an absorber placed in a waterbath to control temperature in the absorbent [2 kg fresh (i.e., not desiccated) Sodasorb® (Grace & Co., Atlanta, Georgia, USA) containing 15% water] at either 30°C or 50°C (measured in the centre of the absorbent REF 402/702A, YSI Inc., Yellow Springs, Ohio, USA; Figure). The sevoflurane vaporizer was adjusted to deliver 2.5% sevoflurane (measured every 5–15 min) to the rats despite sevoflurane degradation. Degradation produced more compound A at 50°C than at 30°C. Downstream from the absorbent we added compound A from the source cylinder to produce an overall concentration delivered to the rats of 120 ppm regardless of absorbent temperature

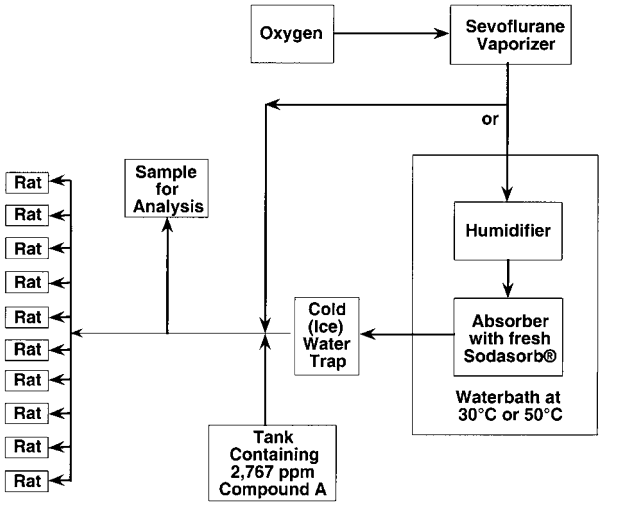

FIGURE This line drawing depicts the course of gas flow delivered to the rats. Sevoflurane is added to oxygen, and the combination is delivered to a humidifier placed in a waterbath at either 30°C or 50°C. After traversing the humidifier, the gases flow through Sodasorb® enclosed in a container in the waterbath. The gases leave the Sodasorb® and pass through a cold trap (a bottle surrounded by ice). Compound A may be added to the effluent from the cold trap in order to ensure (for the two test groups but not the control group) that the gases delivered to the rats contained 120 ppm compound A (as determined in a "sample for analysis"). In the case of the control studies, the humidifier-Sodasorb®-cold trap steps are bypassed and compound A is not added. For all study groups, the delivered sevoflurane concentration, as determined in "sample for analysis," is approximately 2.5%.

(Figure). The dose selected (120 ppm) was estimated from previous studies to produce some renal injury but not injury so severe as to obscure an increase in injury should it occur.[4] We condensed water in the absorbent effluent with an ice trap to prevent condensation in the cylinders containing the rats and to preclude exposing the rats to increased temperatures.

After approval by the University of California Committee on Animal Research, we purchased 48 male Wistar rats (Charles River Lab., Wilmington, Massachusetts, USA) weighing 150–200 g. Each rat ate standard rat chow and water ad libitum in housing that provided a 12-hr light/dark cycle. Food was withdrawn 18 hr before study to mimic the fasting status of patients preoperatively.

Each rat was placed in a clear cylinder sealed at each end (except for holes for gas flow) with rubber stoppers, and anesthetized with sevoflurane. Rectal temperature was sustained at 36.6°C to 38.2°C. Gas flow

TABLE Effect of sevoflurane with and without compound A with and without other degradation products on injury to the renal corticomedullary junction

		Group		
		Control	*30°C*	*50°C*
Sevoflurane concentration		2.5%	2.5%	2.5%
Gases passed through Sodasorb®		No	Yes	Yes
Compound A added		No	Yes	Yes
Number of rats		10	18	20
% corticomedullary junction injury	Mean	0.3	5.3	12.8
	SD	0.5	4.4	16.7
	Median	0.0	5.0	10.0
	0.25 quartile	0.0	1.0	6.5
	0.75 quartile	0.25	7.8	15
Mann-Whitney U test		$P < 0.005$		
				$P < 0.02$
		$P < 0.005$		

Sevoflurane was delivered at approximately 2.5% inspired to all rats for four hours. The 30°C and 50°C groups of rats also received compound A at a concentration of 120 ppm. Part of the compound A came from the degradation of the sevoflurane and part from added compound A (i.e., added to produce a total inspired compound A concentration of 120 ppm). Percent injury in the corticomedullary junction of the kidney after exposing rats to sevoflurane 2.5% that passed through the absorbent Sodasorb® was greater when the absorbent was heated to 50°C than when it was heated to 30°C. The control group (no compound A) had no injury. The results differed significantly among all groups.

through each cylinder maintained a carbon dioxide concentration of < 7 mmHg.

The study began by diverting the sevoflurane delivered from the vaporizer to the Sodasorb® (except for control rats where sevoflurane without compound A was administered without passage through Sodasorb®). Compound A was added from the source as indicated. The concentrations of sevoflurane and compound A were adjusted so that the target concentrations, on average, were achieved.

Exposure to 2.5% sevoflurane with/without compound A was discontinued after four hours. The oxygen flow of 4–8 $L \cdot min^{-1}$ continued for several minutes during recovery. The rats were returned to their cages and given water and rat chow ad libitum Two days later, the rats were killed by administration of 100% carbon dioxide. The right kidney was removed, bivalved and immediately placed in 10% buffered formalin. Tissue slices were stained with hematoxylin and eosin, randomly arrayed, and examined by a pathologist blinded to the condition of exposure (D.K.H.) who estimated the percentage of necrotic cells plus dying (apoptotic) cells (cells with acidophilic nuclear changes) at the corticomedullary junction.

Data for the percentage of necrotic/apoptotic cells were skewed. Thus, we applied the Mann-Whitney U test and present the results as median values and quartiles, as well as means and standard deviations. We accepted that $P < 0.05$ indicated statistical significance.

Results

Average sevoflurane concentrations for the four hour exposures were 2.39 ± 0.05% (control rats; $n = 10$), 2.53 ± 0.09% (Sodasorb® at 30°C; $n = 18$; in one run only eight rats were available), and 2.51 ± 0.14% (Sodasorb® at 50°C; $n = 20$). Average compound A concentrations were 121.0 ± 23.4 and 120.4 ± 14.7 ppm, respectively, for the last two groups. Average absorbent temperatures were 31.6 ± 0.9°C and 50.4 ± 1.9°C, close to the waterbath temperatures.

Kidneys from control rats (no compound A added) displayed no significant corticomedullary junction necrosis (Table). Both groups of rats exposed to compound A had necrosis ($P < 0.005$). Necrosis was significantly greater in rats exposed to sevoflurane passed through absorbent at 50°C than absorbent at 30°C ($P < 0.02$).

Discussion

Our results suggest that degradation products other than compound A may cause renal injury or augment the injury. But are studies in rats relevant to humans? Rats[2–4] show a dose-related nephrotoxicity from compound A evidenced by proteinuria, enzymuria, and necrosis of the corticomedullary junction. Humans[6–9] show proteinuria and enzymuria at approximately the same compound A doses that produce these effects in rats. Unless one assumes that the correlation of these markers with necrosis applies in rats but not humans, humans also have necrosis. However, in humans the finding of injury may be rare because it takes prolonged sevoflurane anesthesia at high concentrations and at low inflow rates and with fresh soda lime to produce injury, and even then the injury is transient.[6–9] The clinical relevance of renal injury from compound A (and now, other compounds) continues to be debated.

Our results may have implications concerning the differences in results of studies of the renal effects of compound A in humans. Some studies find proteinuria and enzymuria after prolonged sevoflurane anesthesia,[6–9] while others do not.[10] The studies that find proteinuria and enzymuria were conducted in warmer rooms. Perhaps a warmer environment increases the remote risk of renal injury from sevoflurane anesthesia.

References

1 *Wallin RF, Regan BM, Napoli MD, Stern IJ.* Sevoflurane: a new inhalational anesthetic agent. Anesth Analg 1975; 54: 758–65.

2 *Morio M, Fujii K, Satoh N, et al.* Reaction of sevoflurane and its degradation products with soda lime. Toxicity of the byproducts. Anesthesiology 1992; 77: 1155–64.
3 *Keller KA, Callan C, Prokocimer P, et al.* Inhalation toxicity study of a haloalkene degradant of sevoflurane, compound A (PIFE), in Sprague-Dawley rats. Anesthesiology 1995; 83: 1220–32.
4 *Gonsowski CT, Laster MJ, Eger EI II, Ferrell LD, Kerschmann RL.* Toxicity of compound A in rats. Effect of increasing duration of administration. Anesthesiology 1994; 80: 566–73.
5 *Förster H, Warnken UH, Asskali F.* Various reactions of sevoflurane with the individual components of soda lime (German). Anaesthesist 1997; 46: 1071–5.
6 *Eger EI II, Koblin DD, Bowland T, et al.* Nephrotoxicity of sevoflurane versus desflurane anesthesia in volunteers. Anesth Analg 1997; 84: 160–8.
7 *Eger EI II, Gong D, Koblin DD, et al.* Dose-related biochemical markers of renal injury after sevoflurane versus desflurane anesthesia in volunteers. Anesth Analg 1997; 85: 1154–63.
8 *Higuchi H, Sumita S, Wada H, et al.* Effects of sevoflurane and isoflurane on renal function and on possible markers of nephrotoxicity. Anesthesiology 1998; 89: 307–22.
9 *Goldberg ME, Cantillo J, Gratz I, et al.* Dose of compound A, not sevoflurane, determines changes in the biochemical markers of renal injury in healthy volunteers. Anesth Analg 1999; 88: 437–45.
10 *Ebert TJ, Frink EJ Jr, Kharasch ED.* Absence of biochemical evidence for renal and hepatic dysfunction after 8 hours of 1.25 minimum alveolar concentration sevoflurane anesthesia in volunteers. Anesthesiology 1998; 88: 601–10.