



## Low-flow (1 l/min) Sevoflurane: Is It Safe?

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Key words: Anesthetic system: low-flow circuit. Anesthetics, volatile: sevoflurane; isoflurane. Kidney: nephrotoxicity; urinary excretion of enzymes. Toxicity: compound A. In June 1995, the Food and Drug Administration (FDA) approved the clinical use of sevoflurane, but with a warning that it not be used at fresh gas flows of less than 2 l/min because sufficient data had not been presented to establish its safety in that circumstance.\* The FDA was concerned that sevoflurane may cause adverse renal effects at low flows because it is degraded by the strong bases in CO<sub>2</sub> absorbents to fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether (compound A). [1] Compound A, a dose-dependent nephrotoxin in rats, [2,3] is not known to produce nephrotoxicity in humans, but it conceivably may do so at high concentrations. Its production is directly related to the temperature of the carbon dioxide absorbent, increasing as gas flow decreases. [4] The FDA informed Abbott Laboratories that if they wanted the warning removed, they would have to provide data showing that low-flow sevoflurane was safe. In April 1996, at a hearing of the Anesthetic and Life-Support Advisory Committee of the FDA, Abbott Laboratories requested that the low-flow warning be removed. [5] They presented data that showed that blood urea nitrogen (BUN) and serum creatinine concentrations in 503 patients administered sevoflurane at fresh gas flow rates of less or equal to 1 l/min (307 reported since the initial FDA hearing) were neither increased compared with preanesthetic values nor different from values measured in patients administered low-flow isoflurane. [5] They reported similar negative findings in an additional 211 patients administered sevoflurane at 1-2 l/min. [5]

The Abbott presentation did not go unchallenged. At the same hearing, Dr. E. I. Eger II presented a study in volunteers in which he and his coworkers administered 8 h of 1.25 MAC sevoflurane (N = 10) or desflurane (N = 9) at 2 l/min. [6] They reported abnormalities, greatest 2 or 3 days after anesthesia, in 24-h urinary excretion of albumin, glucose, and  $\alpha$ -glutathione-S-transferase ( $\alpha$ -GST), and  $\pi$ -glutathione-S-transferase ( $\pi$ -GST), enzymes restricted to the proximal and distal renal tubule, respectively, [7] in volunteers administered sevoflurane but not in those given desflurane. Albumin excretion transiently reached 4 g/24 h (normal less or equal to 30 mg/24 h) in one sevoflurane volunteer. They also measured BUN and serum creatinine concentrations in four sevoflurane volunteers and three desflurane volunteers but found no abnormalities. Mean peak inspired compound A concentration was 50 +/- 4 ppm for anesthetics averaging 10 MAC-h. They concluded that sevoflurane can produce renal injury as a consequence of exposure to compound A, even when administered in a manner consistent with FDA-approved labeling guidelines and that BUN and serum creatinine levels are not appropriate markers of compound A nephrotoxicity, particularly when measured on the day of anesthesia. Given these conflicting data, the FDA ruled that the low-flow warning should remain in the insert until further studies could be evaluated.

This issue of Anesthesiology contains two articles [8,9] that, no doubt, will become a part of the FDA's further assessment of the renal effects of low-flow (1 l/min) sevoflurane. In one, Kharasch et al. [8] used the same enzyme markers,  $\alpha$ -GST and  $\pi$ -GST, used by Eger et al., [6] as well as N-acetyl-beta-D-glucosaminidase (NAG), a more generally accepted indicator of renal tubule cytotoxicity. [10] They termed these finer indices of renal injury, as they are the markers shown to be sensitive for compound A nephrotoxicity in rats. Kharasch et al. [8] also measured postanesthetic days 1-3 urinary excretion of protein and the conventional indicators of renal function, BUN, and serum creatinine. In the other study, Bito et al. [9] used a similar strategy assessing renal function by measuring, on postanesthetic days 1-3, urinary excretion of NAG and alanine aminopeptidase (AAP), an indicator of injury to the proximal tubule brush border, [11] and BUN, serum creatinine, and creatinine clearance levels. Both studies compared the results of values obtained from patients treated with low-flow (1 l/min) sevoflurane with those from patients anesthetized with low-flow (1 l/min) isoflurane. Bito et al. [9] also compared low-flow sevoflurane data with results from patients treated with high-flow sevoflurane (6-10 l/min).

The results of the two studies were the same. Kharasch et al. [8] reported either no change or decreases in postanesthetic BUN and serum creatinine values with no differences between the low-flow sevoflurane (N = 36) and isoflurane (N = 37) groups. There were no differences between the groups in 0-24 h, 24-48 h, and 48-72 h postanesthetic urinary excretion of any of the markers noted previously. Because patients studied by Kharasch et al. [8] were not admitted to the hospital on the morning of operation, they did not obtain preanesthetic collections for the 24-h urinary excretion variables. However, similar proportions of patients, up to 33% in each group, had postanesthetic values greater than the upper limit of normal. For example, one patient administered sevoflurane and two patients administered isoflurane had approximately 1 g/24 h of urinary protein excretion (normal less or equal to 150 mg/24 h). In the sevoflurane group, there was no correlation between high outlying values and high

compound A areas under the curve. Mean peak inspired compound A concentration was 27 +/- 13 ppm for anesthetics averaging 3.6 MAC-h.

Bito et al. [9] reported no differences in laboratory values among the groups exposed to low-flow (N = 16) or high-flow (N = 16) sevoflurane or to low-flow (N = 16) isoflurane. In general, BUN and creatinine values remained the same or decreased, and creatinine clearance increased after anesthesia, indicating that renal function was not adversely affected. Twenty-four-hour urinary NAG and AAP excretion increased significantly in all three groups but only to a small extent. Mean peak inspired compound A concentration was 28.8 +/- 11 ppm for low-flow sevoflurane anesthetics, averaging 7.1 MAC-h.

Kharasch et al. [8] and Bito et al. [9] concluded that the renal effects of low-flow (1 l/min) sevoflurane were no different from those of low-flow isoflurane, and therefore, sevoflurane was as safe as isoflurane during that circumstance. These conclusions, with which we agree, are reassuring in that regard. Nevertheless, we repeat the caution in our 1995 editorial, [12] "Until more experience is acquired in carefully designed clinical studies, we recommended that sevoflurane not be used in patients with impaired kidney function."

A question raised by the current studies is, how should postoperative renal function be assessed in surgical patients? Have the "gold standards" of clinical measurement of changes in renal function before and after anesthesia-BUN and serum creatinine-failed us? Should we turn to more difficult-to-perform tests of 24-h urinary excretion of protein, glucose, and experimental enzymatic markers of renal function to guide our clinical practice? We believe the answer is obvious. Measurements of BUN and serum creatinine are easily done, inexpensive, and, most importantly, prognostically significant in clinical medicine. It is neither practical nor cost effective to obtain 24-h urine collections from surgical patients to measure creatinine clearance, let alone to obtain 24-h urine collections to measure renal enzyme excretion. The latter tests also have not been adequately validated as reliable indicators of clinically significant renal injury to warrant their use for this purpose. [13] This question goes beyond anesthesia practice, for if BUN and serum creatinine are not adequate to assess the renal effects of anesthetics should they continue to be used elsewhere in clinical practice? Clearly, this is a situation where, "If it ain't broke, don't fix it!"

The unanticipated finding of elevated postanesthetic urinary protein excretion in 25% and 33% of patients anesthetized with low-flow sevoflurane and low-flow isoflurane, respectively, associated with normal BUN and serum creatinine values, in the study by Kharasch et al. [8] warrants further comment. In contrast to the unknown value of renal enzyme excretion as an indicator of renal injury, increased excretion of urinary protein is considered a reliable marker of renal impairment in nonsurgical patients. Is this amount of urinary protein excretion "normal" for surgical patients with the diagnoses and in the age group they studied? [8] Normal laboratory values are usually established in healthy young patients or in volunteers. In the absence of preanesthetic urine collections in the study by Kharasch et al., [8] it is difficult to interpret this result. Also, is it a finding that may occur during anesthesia at any fresh gas flow rate, or is it peculiar to low-flow anesthesia? These are only some of the questions that this finding raises.

Readers should be aware of the conflict of interest surrounding the issue of the renal toxicity of sevoflurane. Ohmeda, manufacturer of desflurane, a competing anesthetic, supported the research by Dr. Eger cited previously and other studies of sevoflurane and

compound A toxicity performed by him. He is a paid consultant to Ohmeda. Abbott Laboratories has supported the research performed by Dr. Kharasch. He is a paid consultant to Abbott Laboratories, as are we, having served on their Renal Advisory Panel for the past 3 yr. It is natural and appropriate that the pharmaceutical industry should consult with scientists with expertise in the relevant fields, but doing so may be problematic. This was recognized by the past editor of this journal, who wrote that the conflict of interest surrounding the issue of compound A toxicity could be ameliorated if independent sources conducted or funded the research rather than the competing pharmaceutical firm. [14] We agree with this viewpoint.

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\*Abbott Laboratories: Sevoflurane package insert. 06-9320-R2-Revised, June 1995.

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