Renal Effects of Sevoflurane

Anesthesiologists have been concerned about the potential renal toxicity of inhaled anesthetic agents since 1966, when Crandell et al. 1 described nephrotoxicity associated with methoxyflurane anesthesia. Development of an animal model 2,4 and clinical studies 4,7 established that the condition was dose related and secondary to biotransformation of methoxyflurane to inorganic fluoride. Generally, laboratory—but not clinical—evidence of renal dysfunction, i.e., slight hypernatremia and serum hyperosmolality, was associated with peak serum fluoride concentrations of approximately 50–80 μM (normal range 1–3 μM); patients with minor clinical symptoms and moderate laboratory abnormalities had peak fluoride concentrations of 80–120 μM; and major clinical signs and symptoms of high output renal failure, such as severe polyuria, dehydration, thirst, and weight loss, accompanied by marked hypernatremia, serum hyperosmolality, and increased BUN and serum creatinine, were associated with peak fluoride concentrations greater than 120 μM. In some patients, particularly when the initial abnormalities went unrecognized and the systemic effects of dehydration progressed, the condition evolved from polyuric to oliguric renal failure. Not all patients recovered; the death rate from methoxyflurane-induced nephrotoxicity in approximately 100 cases reported in the literature in the early 1970s was about 25%.

Because evidence of methoxyflurane renal dysfunction was not observed when peak fluoride concentrations were less than 50 μM, 7 this concentration was considered to be the threshold of fluoride nephrotoxicity. In time, the corollary became that peak fluoride concentrations greater than 50 μM presaged a bad renal outcome, which was an unwarranted extrapolation of the original observations. Acceptance of the 50-μM peak fluoride concentration theory of methoxyflurane nephrotoxicity led to the question posed as each new fluorinated anesthetic was introduced, “Will biotransformation of this agent result in peak fluoride concentrations greater than 50 μM and, therefore, in renal insufficiency?”

The introduction of sevoflurane has again raised this issue. In this case, the nephrotoxicity may be mediated by another mechanism in addition to fluoride toxicity. Degradation of sevoflurane in soda lime leads to the formation of fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether (commonly known as Compound A), an olefin shown to be nephrotoxic in rats. 8 The applicability of this finding in humans is unknown.

In a study reported in this issue of Anesthesiology, Higuchi et al. 9 compared the effects of sevoflurane and isoflurane anesthesia on renal function in 34 healthy patients who underwent orthopedic surgery. Two patients received sevoflurane for each one who received isoflurane, because the authors correctly anticipated that the sevoflurane patients would distribute themselves in two groups according to their postoperative serum fluoride concentration—those with peak serum concentrations greater or less than 50 μM (sevoflurane high and sevoflurane low, respectively). As it turned out, there were 8 in the sevoflurane high group and 14 in the sevoflurane low group, in addition to 11 control patients who received isoflurane. Furthermore, most gas flows were 6 l/min, which should have minimized exposure to Compound A. Several aspects of renal function were assessed: creatinine clearance (CCr), a measure of glomerular filtration rate; urinary excretion of N-acetyl-b-glucosaminidase (NAG), an indicator thought to mark acute injury to the proximal renal tubule; 10 and maximal urinary osmolality (Uosm max), a reflection of the integrated function of the loops of Henle, collecting tubules, and medullary circulation. Uosm max was measured in response to two different stimuli: after 8 h of overnight water deprivation preoperatively and on postoperative days 2 and 3, and after subcutaneous vasopressin administration on postoperative day 1.

On the first postoperative day, Uosm max of the sevoflurane high group was less than that of the other groups, although the difference did not quite attain statistical significance. Uosm max (in mOsm/kg H2O) averaged 816 in the isoflurane group, 811 in the sevoflurane low group, and 681 in the sevoflurane high group (P <
0.068). Two of eight sevoflurane$\text{\textsubscript{high}}$ patients exhibited the lowest Uosm-max in the study; in one patient, Uosm-max was only 390 mOsm/kg H$_2$O. Mean Uosm-max on postoperative days 2 and 3 ranged from 859 to 949 mOsm/kg H$_2$O and was similar among groups and with preoperative values. Urinary NAG excretion increased fourfold in the sevoflurane$\text{\textsubscript{high}}$ group, doubled in the sevoflurane$\text{\textsubscript{normal}}$ group, and did not change in the isoflurane group. This finding indicates a mild, temporary injury to the renal tubule in those receiving sevoflurane, but does not imply a long lasting or clinically significant effect.

This study is open to criticism. The patients were not distributed according to a random design. The division into two sevoflurane groups was retrospective, and, given the results, there were too few patients to provide sufficient power to demonstrate a statistically significant difference. The method used to measure urinary concentrating ability on the first postoperative day was not the same as that used on the other days; therefore, Uosm-max on the first postoperative day is not comparable with the other values. Although the three groups of patients received similar volumes of intravenous fluid postoperatively, the average increase in Ccr (10% in the isoflurane, 20% in the sevoflurane$\text{\textsubscript{normal}}$, and 30% in the sevoflurane$\text{\textsubscript{high}}$ groups), although not statistically significant, indicates that intravascular volume in the sevoflurane$\text{\textsubscript{high}}$ group was more expanded than in the other two groups; the attendant natriuresis and diuresis may have compromised the maximum Uosm achievable in the sevoflurane$\text{\textsubscript{high}}$ group, despite normal urinary concentrating ability. The authors acknowledge these limitations. Overall, there was no indication of any serious or long-lasting injury to the kidney in the sevoflurane$\text{\textsubscript{high}}$ group.

We believe these findings should be brought to the attention of Anesthesiology. The use of sevoflurane, rather than an inhaled anesthetic such as isoflurane, is acceptable only if its safety is unquestioned. Our findings in the sevoflurane$\text{\textsubscript{high}}$ group, in our opinion, raise the possibility that sevoflurane could worsen renal function, albeit temporarily, in patients with preexisting renal disease. There are other data that bear on this issue. In studies presented to the FDA in January, 1995, Abbott Laboratories, makers of sevoflurane, summarized data from almost 2,000 adult patients anesthetized with sevoflurane, including both those with normal renal function and those with preoperatively increased concentrations of BUN and serum creatinine. In both populations, there was no difference in the effect of sevoflurane compared with that of a control anesthetic on postoperative renal function. However, the reports of patients with renal impairment have only been published in abstract form and the total number of patients studied is less than 100. More importantly, the duration of anesthesia was relatively brief (1-2 MAC hours), and NAG excretion was not measured. In our opinion, this sample size is not large enough, nor are the study conditions sufficiently rigorous, to draw definitive conclusions regarding the safety of sevoflurane in that population. Until more experience is acquired in carefully designed clinical studies, we recommend that sevoflurane not be used in patients with impaired kidney function.

Richard I. Mazze, M.D.
Chief of Staff
Veterans Affairs Palo Alto Health Care System
Professor of Anesthesia
Stanford University School of Medicine

Rex Jamison, M.D.
Director of Dialysis
Veterans Affairs Palo Alto Health Care System
Professor of Medicine (Nephrology)
Stanford University School of Medicine
3801 Miranda Avenue
Palo Alto, California 94304

References


Anesthesiology. V 83, No 3, Sep 1995
EDITORIAL VIEWS


