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 model2-4 and clinical studies5-7 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, this concentration was considered to be the threshold of fluoride nephrotoxicity. In time, the corollary became that 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 biotransfor-

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0.068). Two of eight sevoflurane-high patients exhibited the lowest Uosm-max in the study; in one patient, Uosm-max was only 390 mOsm/kg H2O. Mean Uosm-max on postoperative days 2 and 3 ranged from 859 to 949 mOsm/kg H2O and was similar among groups and with preoperative values. Urinary NAG excretion increased fourfold in the sevoflurane-high group, doubled in the sevoflurane-cap 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 group, 20% in the sevoflurane-cap group, and 30% in the sevoflurane-high group), although not statistically significant, indicates that intravascular volume in the sevoflurane-high group was more expanded than in the other two groups; the attendant diuresis and diuresis may have compromised the maximum Uosm achievable in the sevoflurane-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-cap high group.

We believe these findings should be brought to the attention of readers of Anesthesiology. The use of sevoflurane, rather than an inhaled anesthetic such as isoflurane, is acceptable only if its safety is unquestioned. The findings in the sevoflurane-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.

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EDITORIAL VIEWS


