
Serum inorganic fluoride concentration and urinary inorganic fluoride excretion were found to be markedly elevated in ten patients previously shown to have methoxyflurane induced renal dysfunction. Five patients with clinically evident renal dysfunction had a mean peak serum inorganic fluoride level (190 ± 21 μM) significantly higher (P < 0.02) than that of those with abnormalities in laboratory tests only (106 ± 17 μM). Similarly, patients with clinically evident renal dysfunction had a mean peak oxalic acid excretion (286 ± 39 mg/24 h) significantly greater (P < 0.05) than that of those with laboratory abnormalities only (130 ± 51 mg/24 h). That patients anesthetized with halothane had insignificant changes in serum inorganic fluoride concentration and oxalic acid excretion indicates that these substances are products of methoxyflurane metabolism. A proposed metabolic pathway to support this hypothesis is presented, as well as evidence to suggest that inorganic fluoride is the substance responsible for methoxyflurane renal dysfunction.

IN September 1971, Michael Cousins, M.B., F.F.A.R.A.C.S. (then Assistant Professor, Stanford Department of Anesthesia, Stanford, California, now Professor and Head of Anesthesia and Pain Management, The University of Sydney, Sydney, Australia), Jim Trudell, Ph.D. (then Research Associate, Stanford Department of Anesthesia, now Professor of Chemistry of Anesthesia, Stanford Department of Anesthesia), and I published an article in this journal that helped put to rest the second hottest topic of the 1960s—i.e., the nephrotoxicity of methoxyflurane (Penthrane®, Abbott Laboratories, Abbott Park, IL). (The hottest topic of the 1960s was the putative hepatotoxicity of the inhaled halogenated anesthetic, halothane.) Data from our clinical study led us to propose a metabolic pathway to support the premise that inorganic fluoride (F⁻) and oxalic acid were metabolites of methoxyflurane and to extend the hypothesis put forward by Taves et al.² that F⁻ was responsible for methoxyflurane nephrotoxicity.

Introduced clinically by Abbott Laboratories in 1962, methoxyflurane was proposed by detail men (they were all men in those days) as the nontoxic replacement for halothane. However, in 1966, Crandell et al.³ reported in this journal that 16 of 94 patients given methoxyflurane developed postoperative nephropathy characterized by diuresis, dehydration, increased blood urea nitrogen, and failure to concentrate urine in response to vasopressin administration. The article was accompanied by an editorial by Vandam,⁴ who stated that Crandell’s results were open to question because of faulty experimental design and clustering of so many cases in a single institution with almost no substantiating reports from other centers. He called for a randomized, prospective clinical study to answer the questions raised by Crandell’s report. But the 1960s ended with no further light shed on the matter. There were no additional major clinical or laboratory reports of nephrotoxicity (or lack thereof), and use of methoxyflurane increased during the next 5 yr to a rate of approximately 2
million anesthetics per year. By 1970, methoxyflurane had been administered to more than 10 million patients.

In 1969, as a recently appointed faculty member at Stanford with a research interest in renal function during anesthesia, I was engaged in micropuncture studies of the effects of anesthetics on ion transport in isolated segments of proximal tubule nephrons. Micropuncture studies are technically difficult to accomplish and, to be perfectly honest, often tedious. Therefore, to make life more interesting during my days in the operating room at the Palo Alto Veterans Administration Hospital (Palo Alto, California), I embarked on a randomized, prospective clinical evaluation of renal function during methoxyflurane anesthesia that was intended to overcome the flaws in Crandell’s work. My supposition was that its results would prove Crandell wrong, because how could 10–12 million anesthetics per year be clinically useful, as indicated by its 12–15 million patients? Before publication, we presented the results of our study to an august group of leaders in the field comprising the Committee on Anesthesia of the National Academy of Sciences-National Research Council. They authored a Special Report stating that although methoxyflurane nephrotoxicity seemed to occur under some circumstances, the agent was clinically useful, as indicated by its 12–15 million cases. The previous report suggested that the nephrotoxic effects of methoxyflurane might be due to the release of F\(^{-}\) formed during methoxyflurane metabolism. This led Cousins, Trudell, and co-workers\(^{1}\) to measure F\(^{-}\) and oxalic acid in serum and urine from 10 of the patients in my previous study.\(^{5}\) We found that the 5 patients with high-output renal insufficiency had a mean peak serum F\(^{-}\) level of 190 ± 21 μM, whereas the 5 other patients with only laboratory abnormalities had a mean peak serum F\(^{-}\) level of 106 ± 17 μM (fig. 1). Oxalic acid excretion paralleled serum F\(^{-}\) levels. In view of these data, we were able to extend the hypothesis of Taves et al.\(^{2}\) and concluded that F\(^{-}\) was the primary nephrotoxin because (1) there was a correlation between the degree of nephrotoxicity and the extent of methoxyflurane biotransformation, (2) F\(^{-}\) is a potent inhibitor of enzymes thought to be involved in the action of vasopressin (antidiuretic hormone), (3) postoperative polyuria was resistant to vasopressin administration, and (4) high levels of oxalic acid usually result in chronic renal disease with kidney stone formation. We also were able to postulate two complementary metabolic pathways for the metabolism of methoxyflurane to F\(^{-}\) and oxalic acid.

This study, however, was not the last word on the subject. Before publication, we presented the results of our study to an august group of leaders in the field comprising the Committee on Anesthesia of the National Academy of Sciences-National Research Council. They authored a Special Report\(^{6}\) in this journal stating that although methoxyflurane nephrotoxicity seemed to occur under some circumstances, the agent was clinically useful, as indicated by its 12–15 million cases.
administrations, and that the evidence at the moment was “clearly inadequate either to condemn its continued use or to remove it from suspicion.” They recommended that additional studies be performed to determine whether there was a simple dose–response relation between methoxyflurane administration and nephrotoxicity, and to investigate what other factors in addition to the anesthetic might be operant in the causation of nephrotoxicity.

Cousins and I were already moving in that direction. In my initial study, premedication and anesthetic adjuvants such as thiobarbiturates and nitrous oxide were omitted to avoid the confounding effects of other drugs. In fact, some critics had suggested that methoxyflurane dosage might have been unusually high because of this. Therefore, we embarked on a randomized, controlled, dose–response clinical study of methoxyflurane as it was used in clinical practice with other agents. This study, published in 1973, demonstrated dose-related abnormalities in 10 of 18 patients anesthetized with methoxyflurane. No toxicity was seen at exposures of less than 2.5 MAC-hours (minimum alveolar concentration of the anesthetic times hours of administration) (peak $F_{\text{MAC}}$, < 50 μM), subclinical toxicity (i.e., lab abnormalities only) occurred with exposures of greater than 2.5–5.0 MAC-hours (peak $F_{\text{MAC}}$, 50–80 μM), and clinical nephrotoxicity generally occurred at exposures of greater than 5 MAC-hours (peak $F_{\text{MAC}}$, > 90 μM). Control patients anesthetized with halothane had no abnormalities. It seemed clear that methoxyflurane could produce dose-related polyuric renal insufficiency.

Ethical considerations limit what can be studied safely in patients, so Cousins and I set a goal of developing an animal model of methoxyflurane nephrotoxicity. Before its introduction, renal studies had been conducted in dogs and in Sprague-Dawley rats with no evidence of nephrotoxicity. Aware that there are species and strain differences in the metabolism and effects of drugs, we examined the defluorination and renal effects of methoxyflurane in five different rat strains. We found that two strains, Fischer 344 and Buffalo, were avid metabolizers of methoxyflurane but that only the Fischer 344 rat strain became polyuric, was vaspressin resistant, and developed renal histologic abnormalities. Similarly, injection of identical doses of $F^-$ (NaF) produced a much greater degree of renal insufficiency in Fischer 344 rats than in Buffalo rats. Later with this animal model, we were able to demonstrate dose-related, biochemical and renal morphologic lesions after methoxyflurane anesthesia similar to those seen in humans.

In subsequent studies with Fischer 344 rats, we established the key role of anesthetic metabolism in the nephrotoxicity of methoxyflurane: Induction of hepatic microsomal enzymes with phenobarbital increased the extent of the methoxyflurane renal lesion, and enzyme inhibition with SKF-525A produced the opposite effects. In a confirmatory study, deuterium of methoxyflurane decreased defluorination and reduced nephrotoxicity. Also with this model, we demonstrated toxic interaction between methoxyflurane and the potentially nephrotoxic antibiotic gentamicin and showed that oxalic acid was not of primary importance in production of the methoxyflurane renal lesion. Later, we examined the effect of age on methoxyflurane toxicity and found that young rats were less susceptible to $F^-$ nephrotoxicity than older ones, perhaps because of greater deposition of $F^-$ in developing bone. (It was of interest that there were no case reports of methoxyflurane nephrotoxicity in children, despite use of the agent in this population.) In addition, we examined the potential for halothane, enfurane, isoflurane, and sevoflurane to produce $F^-$ nephrotoxicity—the rat model accurately predicted the nephrotoxic potential of these agents in humans.

Mainly as a result of our two clinical studies and the corroborating studies in Fischer 344 rats, methoxyflurane disappeared from anesthesia practice in the late 1970s. Approximately 100 cases of clinical nephrotoxicity were reported during its clinical lifetime, most in the early years after its introduction into practice before our studies were published. There were perhaps 20 methoxyflurane renal-related deaths.

In the 10 yr that followed the original study, my laboratory published a total of 14 clinical and 24 animal studies that examined the issue of halogenated anesthetic nephrotoxicity. In addition to a peak $F^-$ level of greater than 50 μM, we postulated that patients and rats anesthetized with methoxyflurane were particularly vulnerable to $F^-$ nephrotoxicity because it was readily metabolized to $F^-$ and because of its high solubility in fat and other tissues. High tissue solubility permitted prolonged postoperative defluorination resulting in near peak $F^-$ levels for 2–3 days after administration of the anesthetic had terminated (fig. 2). Isoflurane and enfurane are more resistant to biodegradation and less soluble. They were examined in detail, and almost without exception, peak $F^-$ levels were less than 50 μM and were short-lived; laboratory or clinical abnormalities of renal function were not observed.

Sevoflurane is relatively insoluble in tissues but is more readily biodegraded than isoflurane. Seven to 15% of patients anes-
methoxyflurane, such as dichloroacetic acid, together cause it is possible that other metabolites unique to however, this issue is still not completely resolved, be-

sors. Astute clinical observation of unexpected adverse


References


