

## Methoxyflurane Revisited

### Tale of an Anesthetic from Cradle to Grave

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Methoxyflurane metabolism and renal dysfunction: Clinical correlation in man. By Richard I. Mazze, James R. Trudell, and Michael J. Cousins. ANESTHESIOLOGY 1971; 35:247-52. Reprinted with permission.

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 ( $190 \pm 21 \mu\text{M}$ ) significantly higher ( $P < 0.02$ ) than that of those with abnormalities in laboratory tests only ( $106 \pm 17$

$\mu\text{M}$ ). Similarly, patients with clinically evident renal dysfunction had a mean peak oxalic acid excretion ( $286 \pm 39 \text{ mg}/24 \text{ h}$ ) significantly greater ( $P < 0.05$ ) than that of those with laboratory abnormalities only ( $130 \pm 51 \text{ mg}/24 \text{ h}$ ). 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<sup>1</sup> that helped put to rest the second hottest topic in anesthesia of the previous decade, *i.e.*, the nephrotoxicity of methoxyflurane (Penthane<sup>®</sup>; Abbott Laborato-

ries, 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 ( $\text{F}^-$ ) and oxalic acid were metabolites of methoxyflurane and to extend the hypothesis put forward by Taves *et al.*<sup>2</sup> that  $\text{F}^-$  was responsible for methoxyflurane nephrotoxicity.

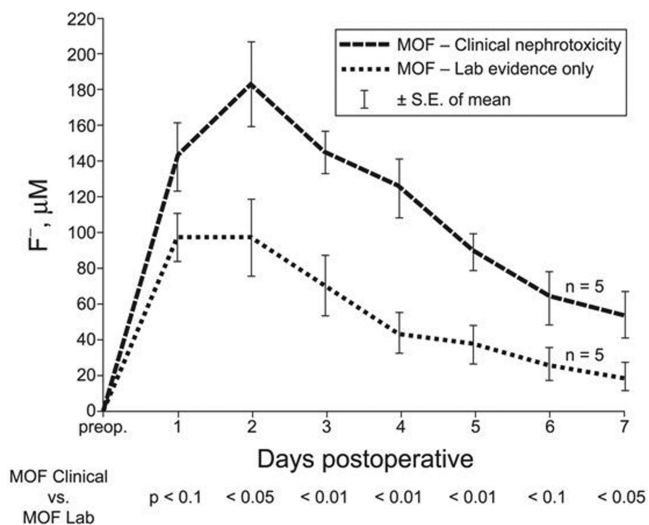
Introduced clinically by Abbott Laboratories in 1962, methoxyflurane was proposed by detail men (they were all men in those days) as the nontoxic replacement for halothane. However, in 1966, Crandell *et al.*<sup>3</sup> reported in this journal that 16 of 94 patients given methoxyflurane developed postoperative 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,<sup>4</sup> 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

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**Fig. 1.** Mean daily serum inorganic fluoride ( $F^-$ ) concentrations. Patients anesthetized with methoxyflurane (MOF) were divided into two subgroups, those with laboratory abnormalities in renal function (MOF Lab;  $n = 5$ ) and those with laboratory abnormalities as well as clinically evident renal dysfunction (MOF Clinical;  $n = 5$ ).<sup>1</sup> Preoperative inorganic fluoride concentration was approximately  $1 \mu M$  in all patients with no change after halothane anesthesia. Reprinted with permission from Mazze *et al.*<sup>1</sup>

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 have been administered with so few reports of nephrotoxicity?

To my surprise, 5 of the 12 patients who received methoxyflurane developed high-output renal insuffi-

ciency characterized by polyuria, lack of responsiveness to vasopressin, delayed return to preoperative urine-concentrating ability, marked weight loss, hypernatremia, serum hyperosmolality, and increased blood urea nitrogen and serum creatinine levels.<sup>5</sup> Similar laboratory abnormalities but of lesser magnitude were seen in most of the other 7 patients. The control group of patients anesthetized with halothane did not show these characteristics. Abbott Laboratories was also surprised by the results, and they sent consultants, Emanuel Papper, M.D. (former Professor and Chairman, Department of Anesthesia, Columbia University School of Medicine, New York, New York, and at the time, Dean, University of Miami, School of Medicine, Miami, Florida; 1915–2002), and Stanley Deutsch, Ph.D., M.D., (Professor and Chairman, Department of Anesthesia, University of Oklahoma, Health Sciences Center, Oklahoma City, Oklahoma), to my laboratory to examine the data. Their presence was somewhat intimidating, but they left convinced that the data were genuine.

Just before the publication of this report, Taves *et al.*<sup>2</sup> had reported the case of a patient anesthetized with methoxyflurane who had increased serum  $F^-$  levels and clinical nephrotoxicity. They suggested that the nephrotoxic effects of methoxyflurane might be due to the release of  $F^-$  formed during methoxyflurane metabolism. This led Cousins, Trudell, and me<sup>1</sup> to measure  $F^-$  and oxalic acid in serum and urine from 10 of the patients in my previous study.<sup>5</sup> We found that the 5 patients with high-output renal insufficiency had a mean peak serum  $F^-$  level of  $190 \pm 21 \mu M$ , whereas the 5 other patients with only laboratory abnormalities had a mean peak serum  $F^-$  level of  $106 \pm 17 \mu M$  (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.*<sup>2</sup> 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<sup>†</sup> comprising the Committee on Anesthesia of the National Academy of Sciences–National Research Council. They authored a Special Report<sup>6</sup> 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

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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,<sup>5</sup> 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,<sup>7</sup> 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  $F^-$ ,  $< 50 \mu M$ ), subclinical toxicity (*i.e.*, lab abnormalities only) occurred with exposures of greater than 2.5–5.0 MAC-hours (peak  $F^-$ ,  $50-80 \mu M$ ), and clinical nephrotoxicity generally occurred at exposures of greater than 5 MAC-hours (peak  $F^-$ ,  $> 90 \mu M$ ). 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 vasopressin resistant, and developed renal histologic abnormalities.<sup>8</sup> 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.<sup>9</sup>

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.<sup>10</sup> In a confirmatory study, deuteration of methoxyflurane decreased defluorination and reduced nephrotoxicity.<sup>11</sup> Also with this model, we demonstrated toxic interaction between methoxyflurane and the potentially nephrotoxic antibiotic gentamicin<sup>12</sup> and showed that oxalic acid was not of primary importance in production of the methoxyflurane renal lesion.<sup>10</sup> 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.<sup>13</sup> (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, enflurane, isoflurane, and sevoflurane to produce  $F^-$  nephrotoxicity<sup>14-16</sup>—the rat model accurately predicted the nephrotoxic potential of these agents in humans.<sup>17,18</sup>

Mainly as a result of our two clinical studies<sup>1,5,7</sup> and the corroborating studies in Fischer 344 rats,<sup>8-16</sup> 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,<sup>5</sup> 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  $50 \mu M$ , 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).<sup>1,7</sup> Isoflurane and enflurane are more resistant to biodegradation and less soluble. They were examined in detail, and almost without exception, peak  $F^-$  levels were less than  $50 \mu M$  and were short-lived; laboratory or clinical abnormalities of renal function were not observed.<sup>17,18</sup> Sevoflurane is relatively insoluble in tissues but is more readily biodegraded than isoflurane. Seven to 15% of patients anes-

‡ Jon C. Kosek, M.D., Professor, VA Hospital, Palo Alto, and Stanford Pathology Department, provided invaluable collaboration in this and subsequent studies in rats.

§ Methoxyflurane continued to be used as a veterinary anesthetic for the next 20 years. In 1999, the manufacturer stopped distributing methoxyflurane in the United States and Canada. But it was only on September 6, 2005, that the Food and Drug Administration determined that it should be withdrawn from sales for reasons of safety and thus removed it from their list of available drugs. It is still available in Australia.

|| Oil/gas partition coefficients: methoxyflurane, 970; halothane, 224; isoflurane, 98; sevoflurane, 47; desflurane, 28; and nitrous oxide, 1.4.

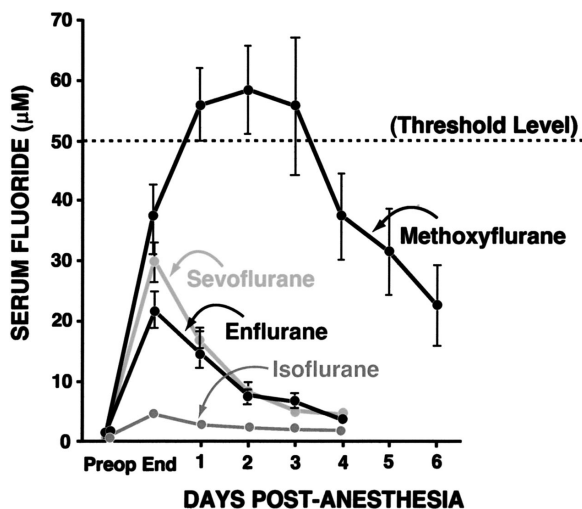


Fig. 2. Mean daily serum inorganic fluoride concentrations from patients anesthetized with methoxyflurane,<sup>7</sup> sevoflurane (data from the literature),<sup>18</sup> isoflurane,<sup>18</sup> and enflurane.<sup>17</sup> Patients anesthetized with methoxyflurane had higher serum inorganic fluoride concentrations that persisted longer than did those measured in the other subjects. Laboratory evidence of nephrotoxicity was seen at fluoride levels greater than 50  $\mu\text{M}$ .

thetized with sevoflurane, however, had peak  $\text{F}^-$  levels of greater than 50  $\mu\text{M}$  but for much shorter periods of time than after methoxyflurane and without adverse renal effects.<sup>#</sup> These findings support the concept that both the extent to which  $\text{F}^-$  levels increased and the duration they remained increased were major factors in the development of methoxyflurane nephrotoxicity. However, this issue is still not completely resolved, because it is possible that other metabolites unique to methoxyflurane, such as dichloroacetic acid, together with  $\text{F}^-$  might be the cause of methoxyflurane nephrotoxicity.<sup>19</sup>

The above account details the history of an anesthetic agent—from beginning to end. Like many other new drugs, methoxyflurane seemed safer than its predecessors. Astute clinical observation of unexpected adverse renal effects after its introduction<sup>3</sup> sparked scientific study to explain their etiology. Our cited classic article<sup>1</sup> established the basis for these studies and for studies of

# Compound A, an olefinic ether (fluoromethyl-1,1,3,3,3-pentafluoro-2-propenyl ether), degradation product of sevoflurane has been exhaustively investigated in patients as a potential cause of nephrotoxicity with no evidence to date that it causes clinically significant abnormalities.

the potential nephrotoxicity of other fluorinated anesthetic agents during the past three decades.

Amazingly, no lawsuits were filed citing methoxyflurane nephrotoxicity as a cause of injury. Rather, compelling scientific evidence led practitioners and the manufacturer to abandon methoxyflurane. All involved in these studies derived a great sense of satisfaction knowing that our research helped to shape clinical practice in a way that resulted in a decrease in anesthetic-related morbidity and mortality.

## References

- Mazze RI, Trudell JR, Cousins MJ: Methoxyflurane metabolism and renal dysfunction: Clinical correlation in man. *ANESTHESIOLOGY* 1971; 35:247-52
- Taves DR, Fry BW, Freeman RB: Toxicity following methoxyflurane anesthesia: II. Fluoride concentration in nephrotoxicity. *JAMA* 1970; 214:91-5
- Crandell WB, Pappas SG, Macdonald A: Nephrotoxicity associated with methoxyflurane anesthesia. *ANESTHESIOLOGY* 1966; 27:591-607
- Vandam LD: Report on methoxyflurane. *ANESTHESIOLOGY* 1966; 27:534-5
- Mazze RI, Shue GL, Jackson SE: Renal dysfunction associated with methoxyflurane anesthesia: A randomized, prospective clinical evaluation. *JAMA* 1971; 216:278-88
- Committee on Anesthesia, National Academy of Science-National Research Council: Statement regarding the role of methoxyflurane in the production of renal dysfunction. *ANESTHESIOLOGY* 1971; 34:505-9
- Cousins MJ, Mazze RI: Methoxyflurane nephrotoxicity: A study of dose-response in man. *JAMA* 1973; 225:1611-6
- Mazze RI, Cousins MJ, Kosek JC: Strain differences in metabolism and susceptibility to the nephrotoxic effects of methoxyflurane in rats. *J Pharmacol Exp Ther* 1973; 184:481-8
- Mazze RI, Cousins MJ, Kosek JC: Dose-related methoxyflurane nephrotoxicity in rats: A biochemical and pathologic correlation. *ANESTHESIOLOGY* 1972; 36:571-87
- Cousins MJ, Mazze RI, Kosek JC, Hitt BA, Love FV: The etiology of methoxyflurane nephrotoxicity. *J Pharmacol Exp Ther* 1974; 190:530-41
- Hitt BA, Mazze RI, Denson DD: Isotopic probe of the mechanism of methoxyflurane defluorination. *Drug Metab Dispos* 1979; 7:446-7
- Barr GA, Mazze RI, Cousins MJ, Kosek JC: An animal model for combined methoxyflurane and gentamicin nephrotoxicity. *Br J Anaesth* 1973; 45:306-12
- Bell LE, Hitt BA, Mazze RI: The influence of age on the distribution, metabolism and excretion of methoxyflurane in Fischer 344 rats: A possible relationship to nephrotoxicity. *J Pharmacol Exp Ther* 1975; 195:34-40
- Cousins MJ, Mazze RI, Barr GA, Kosek JC: A comparison of the renal effects of isoflurane and methoxyflurane in Fischer 344 rats. *ANESTHESIOLOGY* 1973; 38:557-63
- Barr GA, Cousins MJ, Mazze RI, Hitt BA, Kosek JC: A comparison of the renal effects and metabolism of enflurane and methoxyflurane in Fischer 344 rats. *J Pharmacol Exp Ther* 1974; 188:257-64
- Cook TL, Beppu WJ, Kosek JC, Mazze RI: Renal effects and metabolism of sevoflurane in Fischer 344 rats: An *in vivo* and *in vitro* comparison with methoxyflurane. *ANESTHESIOLOGY* 1975; 43:70-7
- Mazze RI, Cousins MJ, Barr GA: Renal effects and metabolism of isoflurane in man. *ANESTHESIOLOGY* 1974; 40:536-42
- Cousins MJ, Greenstein LR, Hitt BA, Mazze RI: Metabolism and renal effects of enflurane in man. *ANESTHESIOLOGY* 1976; 44:44-53
- Kharasch ED, Schroeder JL, Liggitt HD, Ensign D, Whittington D: New insights into the mechanism of methoxyflurane nephrotoxicity and implications for anesthetic development (part 2): Identification of nephrotoxic metabolites. *ANESTHESIOLOGY* 2006; 105:737-45