CORRESPONDENCE

While awaiting arrival of the emergency team, the nurse administered 100% \text{O}_2 by a self-inflating device. On arrival, the emergency team noted no spontaneous respirations, pinpoint pupils, pulse 78 beats/min, and blood pressure 118/60 mmHg. She was unresponsive to verbal commands and vigorous shaking. Fetal heart rate (FHR) was 60 beats/min from a baseline of 150. Naloxone (0.4 mg) was given as an intravenous bolus to which the patient responded immediately with prompt awakening. Seven minutes after naloxone, FHR increased to 150-160 beats/min. The rest of her labor course was unremarkable.

At 4:20 pm, the patient underwent a normal spontaneous vaginal delivery of an 8.8 lb, 1-oz female infant with Apgar scores of 9 and 10 at 1 and 5 min, respectively.

Sufentanil is a highly lipophilic opioid with a strong affinity for the opioid receptors. Its lipophilicity is advantageous in limiting its mean residence time in CSF, thereby minimizing potential side effects, such as delayed respiratory depression. However, early respiratory depression is of concern. Recently, a case report appeared that described respiratory depression after a single dose of intrathecal sufentanil in a laboring parturient.

The exact mechanism by which the respiratory arrest occurred in our patient is not clear. According to the study by Hansdorff et al., intrathecal sufentanil has a mean residence time of 0.9 h in CSF but almost 7 h in plasma. They pointed out that, after repeated doses of intrathecal sufentanil, there was a theoretical risk of accumulation of this drug in plasma but not in CSF. This may explain the respiratory arrest seen in our patient. The second dose of sufentanil was given approximately 3.40 min after the first dose, at a time when the plasma concentration of the first dose, insufficient by itself, may have been augmented by the second dose to that above the threshold for respiratory arrest. However, cephalad migration of sufentanil in the CSF leading to central respiratory depression, cannot be ruled out. D’Angelo et al., from our observation of the cephalad extent of sensory changes resulting from intrathecal sufentanil administered at the lumbar spinal level, cautioned about the potential for respiratory depression.

There are few data regarding the optimal dose of intrathecal sufentanil for labor analgesia, for either the initial bolus or repeat doses.


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Sevoflurane, Fluoride Ion, and Renal Toxicity

To the Editor—In a recent editorial regarding a study by Kharasch et al., Brown claims that sevoflurane is “biotransformed in a quantitative fashion similar to enflurane.” How “similar” are they? In patients with renal impairment, sevoflurane administration resulted in average serum fluoride concentrations 85% greater than those given enflurane. It has been reported that 8.1% of adult patients given sevoflurane had a serum fluoride concentration greater than 50 μg/l. What is the corresponding percentage for enflurane? Brown’s conclusion is not supported by the data.

Anesthesiology, V 83, No 1, Jul 1995

Sevoflurane, Fluoride Ion, and Renal Toxicity

Anesthesiology, V 85, No 1, Jul 1996

Sevoflurane ion is not biotransformed to a significant extent in the liver. The renal clearance of fluoride may be greater than that observed with enflurane. The renal clearance of fluoride in the patient with renal failure is increased. However, the renal clearance of fluoride is greater than the renal clearance of fluoride in the patient with normal renal function.

Anesthesiology, V 85, No 1, Jul 1996

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Anesthesiology, V 85, No 1, Jul 1996
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I mention that sevoflurane is not biotransformed to a greater extent than enfurane simply is not reliable.

Also, nothing was mentioned in the editorial about other products of the biotransformation by cytochrome P450 of sevoflurane in vivo, namely hexafluoroisopropanol (HFIP) and the single carbon product that eventually results from the broken-off fluoromethoxy group of sevoflurane. Sevoflurane is unique compared to enfurane, isoflurane, and desflurane in that it contains a monofluorinated methoxy group rather than a difluoromethoxy group. The former by necessity undergoes a different mechanism of biotransformation after initial P450 metabolic attack.

The frenetic push toward convincing us that all this fluoride (and stoichiometric amounts of HFIP plus single carbon fragments) is not clinically important, is an attempt to obfuscate the fact that sevoflurane is an old anesthetic that moves us back in the direction of the heavily biotransformed agents of the past. How long did it take to report methoxyfluorane nephrotoxicity after its introduction to clinical practice in 1959? Seven years. How many millions of anesthetics had been given with it by then before that particular toxicity became apparent? How long did it take before (most of us) recognized the existence of halothane-related hepatotoxicity? Are these toxicities related to biotransformation? Of course. Can we remotely predict these toxicities? No. Our recent strategy has been to develop volatile agents that undergo the lowest possible biotransformation, a strategy that makes sense.

The notion that somehow sevoflurane is no longer important in nephrotoxicity, to which Brown and Kharasch et al. have attached so much importance, obscures a more basic and important fact about this drug, which soon may be given to millions of Americans. Sevoflurane is heavily biotransformed. The editorialist’s aversion to “shibboleths and jigsaw puzzles” nowistanding, the “fluoride issue” is not resolved.

Kharasch et al. point out that inorganic fluoride is a nephrotoxicant and cite the example that deuterium of methoxyfluorane, which decreases methoxyfluorane P450-dependent metabolism and fluoride release, diminishes renal toxicity. Despite their own citation, these authors attempted to dissociate serum fluoride concentrations from renal toxicity, by concluding that “neither peak systemic fluoride concentrations nor duration of fluoride increase alone can be applied nonselectively to all anesthetics to explain or predict nephrotoxicity.

They imply that there may be some other metabolite or unknown metabolic consequence of methoxyfluorane biotransformation that causes renal toxicity. After many years of methoxyfluorane study, none has been found. Further, they suggest, without proposing any mechanism, that the small amount of fluoride produced in the kidney is relevant to nephrotoxicity, whereas the large amount of serum fluoride that passes through the kidney for excretion is irrelevant.

We moved steadily, after the first fluorocarbon anesthetics were introduced, toward agents with less biotransformation, for sound toxicologic reasons. Sevoflurane, which was rejected by Baxter-Travenol and Anaquest (Ohmeda) for clinical development, is a step backward, despite the likelihood that it will have desirable clinical characteristics.

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In Reply.—My editorial1 was focused only on my thoughts concerning the article by Kharasch et al.2 in the same issue. The toxicity of compound A, hexafluoroisopropanol, toxicity, and other aspects of sevoflurane, both political and scientific, were not discussed. The editorial was strictly confined to commentaries of the novel concept that local renal production and hence high renal concentrations of fluoride ion may be of greater importance in renal toxicity from fluorinated inhalation anesthetics than is hepatic fluoride production as measured by the plasma fluoride concentration. Contrary to Tinker and Baker’s contention, neither my editorial (nor Kharasch et al.’s original paper5) discounted the nephrotoxic potential of fluoride ions. The issue was whether renal or hepatic production of fluoride was the more important vector of nephrotoxicity with inhalation anesthetics. The fact remains that several publications have documented plasma fluoride concentrations well in excess of 50 µmol/l, whether from sevoflurane, enfurane, isoflurane, or fluoride ion intoxication,5 without evidence of renal toxicity.

Tinker and Baker refer repeatedly to “heavy biotransformation.” Let me supply the facts. Eight percent of the enfurane dose and 3–5% of the sevoflurane dose1,4 are metabolized. Tinker and Baker are