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The Safety of Sevoflurane in Humans

This month's issue contains two articles[1,2] that address the potential toxicity of a degradation product of sevoflurane, fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether [compound A]. This is not a new issue; the reaction of sevoflurane with soda lime to form compound A was first reported by Wallin *et al.*[3] in 1975. The potential toxicity of this reaction product as well as the propensity of sevoflurane to be biotransformed to inorganic fluoride were major considerations in the original decision not to pursue development of the anesthetic as a substitute for halothane. Perhaps an equally compelling reason was that enflurane and isoflurane were also introduced as alternatives to halothane at about the same time.

Why then has sevoflurane (or for that matter, desflurane) reappeared at this time? One possible explanation is that the development of intravenous agents that produce rapid induction and emergence from anesthesia has caused anesthesiologists to seek inhalational agents with similar properties. Another explanation may be related to the fact that the patent for isoflurane will soon expire and its price is likely to decrease. Thus, the pharmaceutical industry may have a business interest in developing new inhalational anesthetics. Regardless of the reason, before we add any new drug to our armamentarium, we should be sure that its potential for toxicity has been thoroughly investigated and that it has a favorable risk:benefit ratio.

Morio *et al.*[1] and Frink *et al.*,[2] therefore, should be commended for attempting to determine the risk of organ toxicity associated with the use of sevoflurane. Unfortunately, their studies do not resolve the issue. Morio *et al.*[1] exposed male and female Wistar rats for 3 h to compound A concentrations ranging from 110–490 ppm. Ten of 12 rats died during exposure to 460–490 ppm and 3 of 12 died at 340–350 ppm, one during exposure and two after surviving for 4 days. All 12 rats exposed to 250–290 ppm of compound A survived for 2 weeks, at which time they were killed. Non-lethal signs of toxicity, which occurred at all doses, included ear and tail flush, decreased locomotion, decreased respiratory rate, cyanosis, tremor, ptosis, and piloerection. Similar effects followed a 1-h exposure to concentrations of compound A up to 1,190 ppm. Morio *et al.*[1] calculated that the mean LC_{50} (lethal concentration in 50% of rats) was 420 ppm in male rats and 400 ppm in female rats exposed for 3 h. Histopathologic examination of the lung tissue of rats that died during exposure revealed congestion, hyperemia, and hemorrhage. The kidneys of animals that died after an interval of 4 days showed degeneration and necrosis of renal tubules. No other histopathologic abnormalities were noted.

Frink *et al.*[2] administered sevoflurane in a 50:50 mixture of O_2:N_2O, using a low flow (<1 l/min) circle circuit, to 16 patients having surgical procedures lasting in excess of 3 h. Soda lime was employed as the CO_2 absorbent in eight cases and baralyme was used in the remainder. The mean sevoflurane exposure was approximately 2.0 MAC-hours. Of the five known degradation products, only compound A was detectable. Generally, its concentration increased with time and it tended to be higher with baralyme than with soda lime. Inhaled concentrations of compound A were approximately two times higher than exhaled concentrations, indicating that patient uptake had occurred. The highest individual compound A concentration was 61 ppm in a case in which baralyme was used; the highest level when soda lime was employed was 15 ppm. Results of postoperative studies of hepatic and renal function did not differ from those of preoperative examinations.

Thus, in rats, compound A was lethal at 340–350 ppm and significant signs of toxicity were present at levels as low as 110 ppm. In humans, 61 ppm of compound A were detected in the anesthesia circuit of one patient for whom baralyme was the CO_2 absorbent, and 10–25 ppm was found in five other circuits, including three for whom soda lime was the CO_2 absorbent. The dilemma then is relatively straightforward. What is a safe level of compound A in humans?

There are no clear answers regarding the determination of permissible levels of exposure to toxic chemicals in humans, particularly, those that are inhaled only once or twice in a lifetime. Most commonly used is the so-called safety factor approach (later termed uncertainty factor), which was introduced in the mid-1950s in response to a demand for legislative guidelines to regulate potentially carcinogenic food additives.[4] The allowable human daily intake was determined by dividing the *no observed effect level* (NOEL) in laboratory animals by an uncertainty factor, usually 100. The latter figure is the product of two separate uncertainty factors of 10 each, one intended to account for the presumed increased sensitivity of humans relative to laboratory animals, and the other to account for the wide range of toxicologic sensitivity in the heterogeneous human population. In the 1970s, the concept was broadened to better reflect the underlying data base: if reliable data based on *chronic* human exposure were available, the uncertainty factor could be reduced to 10; however, if data were available only from *acute* human exposure, the factor of 100 should remain. If there were no long-term or acute human data and animal data were scanty, a greater uncertainty factor, *i.e.*, 1,000, should be

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used.[5] There are other more mathematically based models for estimating permissible exposure to potential toxic substances, but they are no better than the uncertainty factor approach.[4]

Using the data from the studies of Morio *et al.*[1] and Frink *et al.*[2] to calculate the uncertainty factor for sevoflurane exposure, a value of <2 is derived when baralyme was the CO_2 absorbent and <8 when soda lime was used (NOEL in rats, 110 ppm; peak compound A level, 61 ppm with baralyme and 15 ppm with soda lime). These uncertainty factors are far below those considered acceptable. Even more striking, the LC_{50} in rats (400–420 ppm) was only seven times greater than the peak compound A level observed in human studies when baralyme was the CO_2 absorbent. The question is whether the uncertainty factor principle, which is considered arbitrary even when it is used in the circumstance for which it is intended, *i.e.*, chronic exposure to food additives, should be applied to a single exposure to an inhalational anesthetic agent? While the circumstances of exposure are vastly different, factors of 2–8 are very low and, in my opinion, should not be ignored.

A few additional comments about the two studies are in order. The study by Morio *et al.*[1] leaves several questions unanswered: the two rats that were autopsied after surviving 4 days had renal necrosis, but no biochemical data are provided and the description of the histologic findings is minimal. Similarly, the pulmonary lesion that killed the majority of animals during acute exposure to 460–490 ppm is only minimally described. Thus, the nature of the toxic response to compound A requires further biochemical and morphologic definition. Regarding the work by Frink *et al.*,[2] the relatively low sevoflurane exposures studied is cause for concern. Although the exposures are representative of those that usually occur in the investigators' practice, considerably greater exposures are bound to occur occasionally with the likelihood of higher levels of compound A.[6]

That brings us to the issue of risk *versus* benefit. If sevoflurane filled a vast gap in the formulary of anesthetic drugs, then it would seem worthwhile to use it at this time. However, its major benefit compared with current agents is the ability to rapidly change depth of anesthesia. Thus, sevoflurane could be used in pediatric practice instead of halothane and in general anesthesia practice instead of isoflurane. However, halothane is virtually free of toxicity in children, particularly when only used for induction, and isoflurane is uniquely devoid of delayed organ toxicity. Meanwhile, the risk of administering sevoflurane is still unknown. Double-bonded breakdown products such as compound A can irreversibly bind to tissue macromolecules resulting in major organ toxicity, as apparently occurred in the study by Morio *et al.*[1] Also, the risk of developing fluoride nephropathy remains a possibility. Fluoride levels were not reported in the rats studied by Morio *et al.*,[1] although it could have been a factor in their demise. The biodegradation of compound A to inorganic fluoride has not been studied, and fluoride levels in excess of 50 μM have been reported in several clinical sevoflurane studies.[7,8] The fact that sevoflurane has been administered without apparent organ toxicity to more than 100,000 patients in Japan is only somewhat reassuring. There may be pharmacogenetic differences in the susceptibility to toxicity in such diverse populations as those in the United States and in Japan. Also, low-frequency toxic events are very difficult to detect; one has only to recall that halothane hepatotoxicity was not appreciated until several million halothane anesthetics had been administered.

In summary, the two studies[1,2] in this month's issue of ANESTHESIOLOGY do little to establish the safety of sevoflurane in humans. I believe that a great deal more work should be required before the drug is released for clinical practice in the United States.

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