Anesthesiology
67:779–781, 1987

# *Stability of Sevoflurane in Soda Lime*

*David P. Strum, M.D.,* Brynte H. Johnson, M.S.,† Edmond I. Eger II, M.D.‡*

**Stability of a halogenated volatile anesthetic is important because of the potential toxicity associated with the breakdown products. The authors enclosed 100 ml of gas containing sevoflurane with 100 g of soda lime in a 581-ml flask for periods up to 24 h. The rate of degradation of sevoflurane by soda lime was several-fold greater than previously reported, and the degradation was temperature-dependent. At 22° C, soda lime degraded 6.5% of the sevoflurane per hour. The rate increased by 1.6% per hour per degree rise in temperature, reaching 57.4% degradation per hour at 54° C. In contrast, isoflurane was not degraded by soda lime. Halothane did not degrade at 22° C or 37° C, but did degrade (2.2% per hour) at 54° C. (Key words: Anesthetics, volatile: halothane; isoflurane; sevoflurane. Soda lime, anesthetic degradation: soda lime; temperature. Water, anesthetic degradation.)**

IT IS IMPORTANT to determine the physical stability of a volatile halogenated anesthetic because an unstable anesthetic may degrade to toxic compounds *in vitro*[1–3]§ and *in vivo*.[4] Sevoflurane is a new inhaled anesthetic whose low stability and, hence, ability to produce a rapid induction of and recovery from anesthesia recommend its application.[5,6] Initial tests of the stability of sevoflurane in soda lime suggested that, although it is not as stable as currently available agents, the degree of instability is minor.[5] Wallin *et al.* recirculated 5% sevoflurane for 7 h in a closed system with soda lime at a maximum temperature of 50° C. They found that the condensate of the remaining vapor contained 99.8% sevoflurane and 0.18% of $CF_2{=}C(CF_3)\text{-}O\text{-}CFH_2$. When liquid sevoflurane was sealed in a glass vial with soda lime and heated to 70° C for 3 h, only 2.7% of the remaining liquid was identified as breakdown products, sevoflurane constituting the other 97.3%.

Because neither experiment in the Wallin study attempted to account for the net loss of sevoflurane, we decided to reevaluate the stability of this anesthetic in comparison with isoflurane and halothane. We also studied the stability of sevoflurane in a buffered aqueous solution because this agent reportedly decomposes slowly in water.[5]

## Materials and Methods

Three groups of five, 581-ml flasks were filled with fresh soda lime (Sodasorb®). Ten ml of distilled water were added to each flask and the flask sealed with a Teflon® stopper pierced with a needle capped with a one-way stopcock. The flasks were evacuated and 100 ml of a mixture of approximately 1.9% sevoflurane, 1.3% isoflurane, and 0.7% halothane were added to each flask. The pressure in each flask was allowed to reach ambient pressure by the admission of room air. For sampling, 10 ml of gas were taken from each flask and the concentration of each anesthetic determined by gas chromatography. The column of the gas chromatograph was composed of 10% S.F. 96 on Chromasorb WHP, 68/80-mesh, 0.32 cm by 4.6 m, and was maintained at 30° C. A carrier stream of nitrogen flowing at 45 ml/min was delivered through the column to a flame ionization detector at 200° C, supplied by hydrogen at 40ml/min and by air at 280 ml/min. The first group of five flasks was maintained at 22° C (room temperature), and the gas in the flasks serially sampled at 75, 150, 250, 550, and 1440 min. The second group was placed in a water bath at 37° C, and gas serially sampled at 75, 120, 240, 480, and 1440 min. The third group was placed in an oven at 54° C, and gas serially sampled at 75, 150, 250, 550, and 1440 min.

The concentrations of each anesthetic at each temperature were plotted against time for the three groups of flasks. Assuming a logarithmic decay, we applied regression analysis to the data for individual anesthetics at each temperature. The regression equations did not include the values for the determinations at time zero (the first sample). We performed a *t* test on the deviation from zero of the slope of each regression equation.

Finally, we examined the rate of degradation of sevoflurane in water at a *p*H of 7.0. Fifteen-hundred and forty milliliters of distilled water were buffered to a *p*H of 7.0 with a 25 mM phosphate buffer (total liquid volume 1,600 ml), and placed in a 2,100 ml glass flask sealed with a Teflon® stopper pierced with a needle having a one-way stopcock. Fifty ml of air were evacuated from the flask and 100 ml of 2.0% sevoflurane added. To detect leakage, we added 0.5 ml of nitrous oxide to the flask as a marker. The flask was shaken vigorously and placed in a water bath at 37° C. After 85 min, we took the first of six, 20 ml sample of gas. Samples were taken after 540, 1,740, 2,640, 4,260, and 5,820 min. Each sample was taken after the flask was shaken vigorously. The concentration of sevoflurane in

* Research Fellow.
† Research Specialist.
‡ Professor of Anesthesia.

Received from the Department of Anesthesia, University of California, San Francisco, California. Accepted for publication June 23, 1987. Supported in part by National Institutes of Health grant PO1AG03014-05, and in part by Anaquest.

Address reprint requests to Dr. Eger: Department of Anesthesia, University of California, Room 1386 HSE, Third and Parnassus Avenues, San Francisco, California 94143.

§ Karis JH, O'Neal FO, Menzer DB. Toxicity of ultraviolet (UV) irradiated halothane in mice (abstract). Anesthesiology 53:S45, 1980

TABLE 1. Rate of Anesthetic Degradation (%/h)

| Temperature | Sevoflurane | Isoflurane | Halothane |
|---|---|---|---|
| 22° C | 6.46 ± 0.87* | 0.04 ± 0.00 | 0.83 ± 0.00 |
| 37° C | 31.04 ± 0.48* | 0.06 ± 0.00 | 0.52 ± 0.00 |
| 54° C | 57.36 ± 2.05* | 0.30 ± 0.00 | 2.21 ± 0.00* |

* These values are statistically different from 0 ($P < 0.05$).

each sample was determined using gas chromatography. The concentration of nitrous oxide in each sample was analyzed by gas chromatography using a molecular sieve column and an electron capture detector.

## Results

Isoflurane did not degrade significantly at any temperature (table 1, fig. 1). That is, the slope for concentration of isoflurane *versus* time did not deviate from zero. Similarly, halothane did not undergo significant degradation at 22° C or 37° C, but did degrade slowly at 54° C (table 1). In contrast, sevoflurane degraded at all temperatures (table 1, figs. 1, 2). The rate of degradation was linearly related to the temperature (table 1, fig. 3), increasing by 1.6% per hour per degree increase in temperature. At 54° C, the rate of degradation of sevoflurane was 26 times more rapid than that of halothane. In the flask containing sevoflurane in a solution of buffered water, there was no detectable loss of sevoflurane or nitrous oxide over a 4-day period.

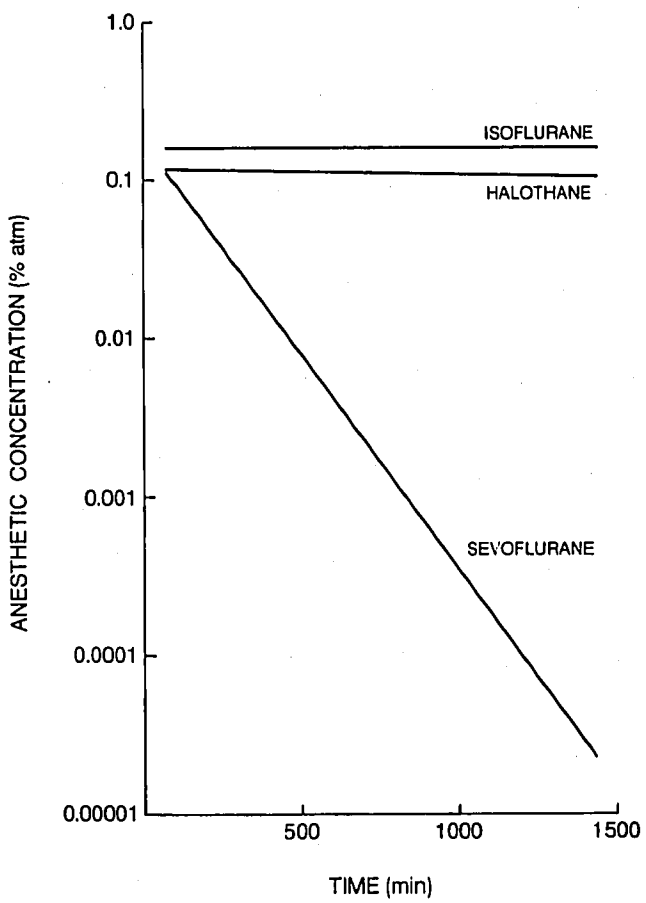


FIG. 1. At 37° C, in the presence of soda lime, sevoflurane degrades more rapidly than halothane or isoflurane. The slope of the regression for halothane or isoflurane after 1 h did not differ from zero. However, the data for all three anesthetics indicate a decrease in concentration during the first hour, which we interpret as the result of absorption of these agents by soda lime.

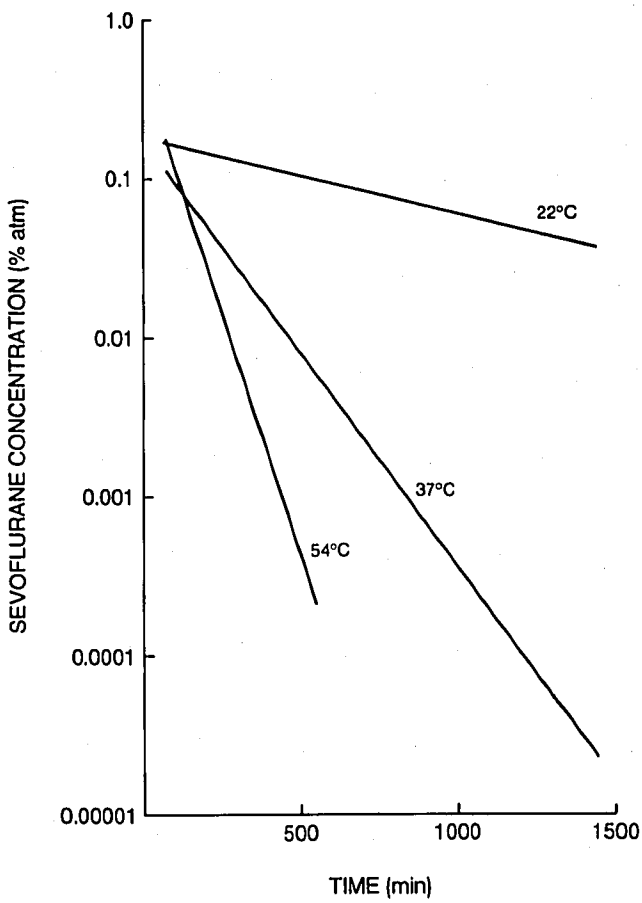


FIG. 2. The rate of degradation of sevoflurane increased eight-fold as the temperature was increased from 22° C to 54° C.

## Discussion

The present study differs from earlier ones in that we examined the disappearance of sevoflurane over time rather than the appearance of degradation products. We found that sevoflurane degraded at a much higher rate than that reported by others.[5] These results differ because earlier investigators did not measure all degradation products. That is, they measured only those products remaining in sevoflurane and not the larger

fraction retained by soda lime. Another potentially important difference is that the present study was done at concentrations of sevoflurane 10–50 times lower than used by Wallin. If the rate of degradation becomes surface area dependent (zero order) at higher concentrations, this may explain the small relative percentage of sevoflurane degraded in Wallin's study.

We used the term "degraded" throughout this manuscript, while some might argue that "disappearance" is a better word. We prefer "degraded" for two reasons. First, sevoflurane concentration in the flasks decreased logarithmically through four orders of magnitude until it was no longer measurable. By contrast, isoflurane and halothane equilibrated rapidly. This may represent absorption of sevoflurane into an "infinite sink" which paradoxically fails to absorb the remaining two anesthetics; however, we believe it represents degradation. Second, we have observed degradation peaks on the gas chromatographs (unpublished data) from flasks containing the anesthetic mixture, or sevoflurane alone, but not in flasks containing soda lime, isoflurane, or halothane alone. These peaks, although not yet specifically identified, cannot be explained in the context of absorption.

The substantial degradation of sevoflurane raises questions about the potential toxicity of this compound. We have shown that a large fraction of sevoflurane degrades to compounds whose structures and toxicities are unknown. Also, we have not compared the fraction of these compounds escaping from the soda lime with the fraction destroyed by the soda lime. Wallin *et al.* identified two likely breakdown products, fractions of which were not bound by soda lime.[5] One was a condensation product, and the other an olefin ($CF_2=C(CF_3)$-O-$CFH_2$). The double bond of the latter makes it a potentially toxic compound.

The products of the breakdown of sevoflurane require further study to: 1) characterize their structure; 2) determine their affinity for soda lime; 3) assess their toxicity; and 4) explore their production *in vivo*, particularly in alkaline regions of the body, such as the pancreas or small bowel. The data from the Wallin study partially satisfies the first query, and comparison of our results with theirs suggests that most of the breakdown products of sevoflurane are retained by soda lime. The determinations of toxicity and *in vivo* production remain to be explored.

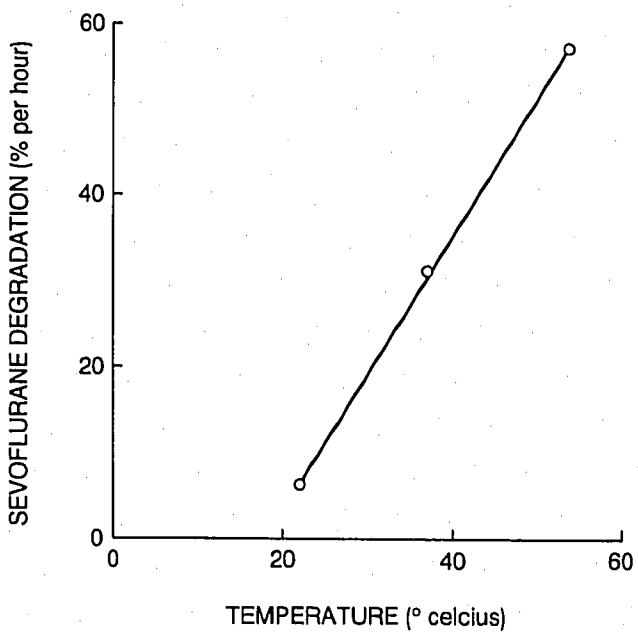


FIG. 3. The rate of degradation of sevoflurane is plotted against temperature, to demonstrate the rectilinear increase in degradation associated with increase in temperature.

## References

1. Bösterling B, Trudell JR: Production of 5- and 15-hydroperoxyeicosatetraenoic acid from arachidonic acid by halothane-free radicals generated by UV-irradiation. ANESTHESIOLOGY 60:209–213, 1984
2. Raventos J, Lemon PG: The impurities in Fluothane®: Their biological properties. Br J Anaesth 37:716–737, 1965
3. Sharp JH, Trudell JR, Cohen EN: Volatile metabolites and decomposition products of halothane in man. ANESTHESIOLOGY 50:2–8, 1979
4. Cohen EN, Van Dyke RA: Metabolism of Volatile Anesthetics. Implications for Toxicity. Reading, Addison-Wesley, 1977
5. Wallin RF, Regan BM, Napoli MD, Stern IJ: Sevoflurane:A new inhalational anesthetic agent. Anesth Analg 54:758–765, 1975
6. Holaday DA, Smith FR: Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. ANESTHESIOLOGY 54:100–106, 1981