DECOMPOSITION OF VOLATILE ANESTHETICS IN SODA LIME

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SUMMARY

Soda lime mediated decomposition products of volatile anesthetics - halothane, enflurane, isoflurane and sevoflurane - and the degree of degradation, toxicity and concentration in an anesthetic circuit equipped with a model lung are described. These anesthetics undergo decomposition by soda lime as follows: halothane decomposes to yield difluorochlorobromoethylene and trifluorochloroethane; enflurane decomposes to yield 1-chloro-1,2-difluorovinyl difluoromethyl ether; isoflurane decomposes to yield 2,2-difluoro-1-chlorovinyl difluoromethyl ether and fluoroform; sevoflurane decomposes to yield fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether, fluoromethyl 2-methyl-2,2-difluoro-1-(difluoromethylene)ethyl ether, two isomers of fluoromethyl 2-methoxy-2-fluoro-1-(trifluoromethyl)vinyl ether and fluoromethyl 2,2-difluoro-1-(difluoromethoxy ethyl)vinyl ether. Almost all degraded compounds of these volatile anesthetics are produced by elimination of hydrofluoride from adjacent carbon atoms by soda lime.

KEY WORDS

anesthetics, carbon dioxide, soda lime, decomposition, dehydrofluorination

INTRODUCTION

During general anesthesia using a semi-closed or closed anesthetic circuit, some or all of the expired gas is re-inhaled by the patient and soda lime is used to absorb carbon dioxide in the expired gas. Volatile anesthetics - halothane, enflurane, isoflurane and sevoflurane - come into contact with soda lime during general anesthesia using a semi-closed or closed anesthetic circuit, so it is essential that volatile anesthetics are stable in soda lime.

Earlier studies showed that these volatile anesthetics and trichloroethylene are decomposed by soda lime as follows: Trichloroethylene decomposes to yield a toxic amount of dichloroacetylene /1/; Halothane decomposes to yield difluorochlorobromoethylene and trifluorochloroethane /2/; Enflurane decomposes to yield 1-chloro-1,2-difluorovinyl difluoromethyl ether /3/; Isoflurane decomposes to yield 2,2-difluoro-1-chlorovinyl difluoromethyl ether and fluoroform /4/; Sevoflurane decomposes to yield fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether, fluoromethyl 2-methyl-2,2-difluoro-1-(difluoromethylene)ethyl ether, two isomers of fluoromethyl 2-methoxy-2-fluoro-1-(trifluoromethyl)vinyl ether and fluoromethyl 2,2-difluoro-1-(difluoromethoxy ethyl)vinyl ether /5/. Almost all degraded compounds of these volatile anesthetics are produced by elimination of hydrofluoride from adjacent carbon atoms by soda lime.

Although some products, for example, dichloroacetylene and difluorochlorobromoethylene, are very toxic, except for dichloroacetylene, the toxicity of these compounds is clinically negligible because the concentration of the degradation products produced during anesthesia is lower than the toxic amount. However, it is important to know the mechanism of degradation, the compounds produced and their toxicities in order to predict degradation products when a new volatile anesthetic is used for clinical anesthesia.

In this report, the degradation products of the volatile anesthetics, halothane, enflurane, isoflurane and sevoflurane, by soda lime, the mechanisms of degradation and the toxicity of the degradation products are summarized.

CHEMISTRY OF SODA LIME AND ANESTHETICS

Soda lime as a carbon dioxide absorbent consists of 94 percent calcium hydroxide, 5 percent sodium hydroxide, 1 percent potassium hydroxide and an activator. Small amounts of silica are added, producing calcium and sodium silicate, which hardens the soda lime and reduces dust formation. The efficacy of absorption by soda lime varies inversely with its hardness; therefore, little silicate is used in contemporary soda lime. Sodium hydroxide is the active component for the carbon dioxide absorptive properties of soda lime. The absorption of carbon dioxide by soda lime is a chemical, not physical, process /6/. Carbon dioxide combines with water to form carbonic acid, which reacts with the hydroxides to form sodium (or potassium) carbonate and water. Calcium hydroxide accepts the carbonate to form calcium carbonate and sodium (or potassium) hydroxide.

Volatile anesthetics, such as trichloroethylene, halothane, sevoflurane, isoflurane and enflurane, are halogenated ethers or haloalkanes having one or more hydrogen atom(s) in their structure. Generally, when hydrogen atoms in hydrocarbon molecules are replaced by halogens, the anesthetic potential increases. The greater the number of halogens, the greater the anesthetic potential. The halogens, in order of their potential to increase anesthetic ability by substituting for hydrogen, are bromine, chlorine, and fluorine, and the order of their potential to increase the toxicity of the compound is the same. However, if all hydrogen atoms in the molecule are replaced by halogens, the anesthetic potential is lost. Therefore, anesthetics in general clinical use have at least one hydrogen atom and one or more halogens in the methyl group of the molecule /7/.

Volatile anesthetics have halogen and hydrogen atoms in adjacent carbon atoms as described above. Therefore, volatile anesthetics react with soda lime, a base, as catalyst, to eliminate halogen and hydrogen from adjacent carbon atoms and to produce a double bond. Some anesthetics may undergo further decomposition, rather than elimination, by soda lime, such as substitution or methoxylation.

HALOTHANE

Halothane, 2-chloro-2-bromo-1,1,1-trifluoroethane ($CHClBrCF_3$), is widely used in clinical anesthesia. Its structure is a halogenated

ethane which has three fluorines, one bromine, one chlorine and one hydrogen atom in the molecule. In reaction with soda lime, halothane undergoes degradation to produce 2-bromo-2-chloro-1,1-difluoroethylene (H-1 in Fig. 1) and 2-chloro-1,1,1-trifluoroethane (H-2 in Fig. 1) /2/. One is a dehydrofluorinated product, and the other is a compound substituted product.

After 5 hours ventilation of a model lung attached to a closed anesthetic circuit filled with 1-3% of halothane, 1.5-4.5 ppm of 2-bromo-2-chloro-1,1-difluoroethylene is detected in the gas phase of the circuit. 2-Chloro-1,1,1-trifluoroethane is also detected at 0.4-1.2 ppm /2/.

Inhalation of around 100 ppm of 2-bromo-2-chloro-1,1-difluoroethylene caused renal injury in rats /8/. This compound undergoes further biodegradation and is excreted in urine as S-(2-bromo-2-chloro-1,1-difluoroethyl)-N-acetyl-L-cysteine /9/. S-(2-bromo-2-chloro-1,1-difluoroethyl)glutathione and S-(2-bromo-2-chloro-1,1-difluoroethyl)-L-cysteine are putative intermediates in the metabolism of 2-bromo-2-chloro-1,1-difluoroethene and are analogs of nephrotoxic and cytotoxic S-haloalkyl glutathione and cysteine conjugates. Finkelstein *et al.* /10/ have reported that both S-conjugates were nephrotoxic in Fischer 344 rats and caused diuresis, and increases in urine glucose and protein concentrations, in blood urea nitrogen concentrations, in kidney/body weight ratios and in serum glutamate-pyruvate transaminase activities. Both S-conjugates also produce severe morphological changes in the kidneys, especially in the proximal tubules, and in the livers of animals. Both S-conjugates are cytotoxic to LLC-PK1 cells, as shown by lactate dehydrogenase release into the medium /10/.

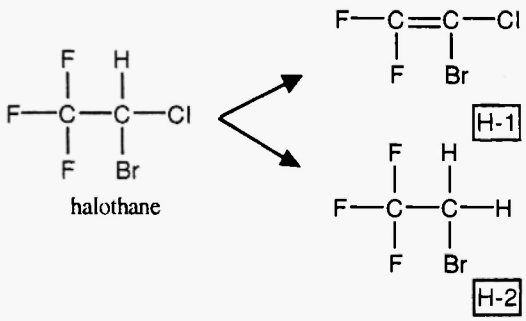

Fig. 1: Decomposition of halothane.

The inhalation of 4.3% of 2-chloro-1,1,1-trifluoro ethane causes spasm. Fifty percent lethal concentration (LC_{50}) of this compound is 15% /8/.

ENFLURANE

Enflurane, 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether ($CHClFCF_2OCHF_2$), is a halogenated ethyl methyl ether. This compound has both halogen and hydrogen atoms adjacent to the carbon atom of the ethyl radical. Enflurane could react with soda lime by eliminating hydrofluoride. Grodin *et al.* /11/ reported that soda lime absorbs enflurane, but it is generally believed that enflurane does not react with soda lime and has no decomposition product /12/. However, after 3 hours incubation of enflurane with soda lime at 50°C and 100°C in a closed vessel in a dry oven, one decomposition product was detected, but not when incubated without soda lime /3/. Since the concentration of the product increased with time in a temperature dependent manner, the substance detected is not an impurity but a product of a chemical reaction. It was determined from the mass spectrogram that the decomposition product was 1-chloro-1,2-difluorovinyl difluoromethyl ether (Fig. 2).

After incubation of enflurane with potassium hydroxide, sodium hydroxide or calcium hydroxide at 50°C and 100°C for 3 hours, the same compound was produced. The concentrations were 21 ppm and 14,783 ppm with potassium hydroxide, 3 ppm and 1,190 ppm with sodium hydroxide, and 0 ppm and 25 ppm with calcium hydroxide, respectively. Incubation of enflurane with silica, which is included in soda lime, in a closed vessel under the same conditions, did not produce this compound /3/. These findings suggest that potassium hydroxide, which constitutes 1% of soda lime by weight, serving as an activator, plays an important role in this reaction.

enflurane

Fig. 2: Decomposition of enflurane.

After circulating 5% enflurane with 200 ml/min carbon dioxide gas through soda lime in the closed anesthetic circuit with a model lung for 8 hours, 1-chloro-1,2-difluorovinyl difluoromethyl ether was detected in the gas phase at a maximum concentration of 1.29 ppm at 420 min /3/. As the toxicity of this compound is unclear, further investigation is needed.

ISOFLURANE

Isoflurane, 2-chloro-1,1,1-trifluoroethyl difluoromethyl ether (CF_3-$CHClOCHF_2$) is an isomer of enflurane. This compound has fluorine and hydrogen atoms on adjacent carbons in the ethyl group of this compound. After 3 hours incubation of isoflurane with soda lime in a closed vessel, two degradation products were detected. One was 2-chloro-1,1-difluorovinyl difluoromethyl ether (1-1 in Fig. 3) and the other was fluoroform (1-2 in Fig. 3) /4/.

After 3 hours incubation of isoflurane with soda lime in a closed vessel at 50, 100 and 140°C in a dry oven, fluoroform was produced at 6 ppm, 348 ppm and 1017 ppm respectively, and 2-chloro-1,1-difluorovinyl difluoromethyl ether was produced at 7 ppm, 145 ppm and 315 ppm respectively. After incubation of isoflurane without soda lime for 3 hours at 140°C, trifluoroacetyldifluoromethyl ether was produced. These products were not found in the gas phase in a closed anesthetic circuit attached to a soda lime canister after 3 hours ventila-

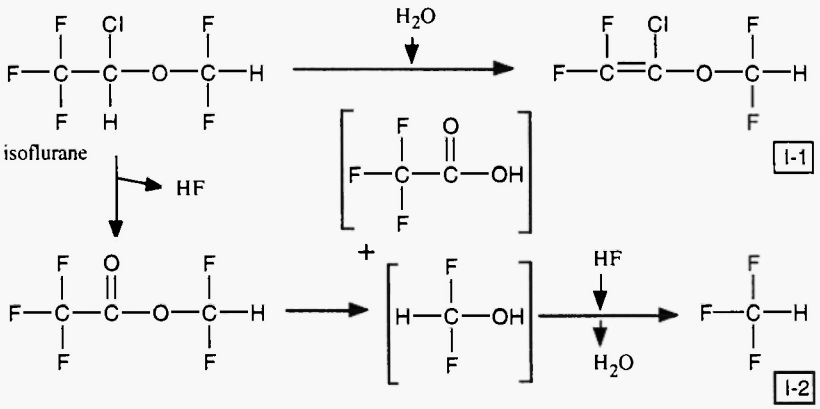

Fig. 3: Decomposition of isoflurane.

tion of a model lung with 1.2% isoflurane, but these products may have been present at <0.1 ppm, the detection limit in gas chromatography. It is presumed that 2-chloro-1,1-difluorovinyl difluoromethyl ether is produced by the dehydrofluorination of isoflurane /4/.

It is known that fluoroform is narcotic in high concentrations and non-toxic /13/. The determination of toxicity of 2-chloro-1,1-difluorovinyl difluoromethyl ether remains to be determined. The breakdown products of isoflurane require further study to assess their toxicity.

SEVOFLURANE

Sevoflurane, fluoromethyl-2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether ($CH(CF_3)OCH_2F$) is a halogenated methyl propyl ether. This compound has hydrogen and fluorine atoms on the adjacent carbons of the propyl radical. Five degradation products by soda lime have been detected *in vitro* (Fig. 4). Two of them have been detected in a closed anesthetic circuit. One is the dehydrofluorinated compound, $CF_2=C-(CF_3)OCH_2F$ (S-1 in Fig. 4), and the other is the methoxylated compound of the dehydrofluorinated compound, $CH_3OCF_2CH(CF_3)OCH_2F$ (S-2 in Fig. 4) /5/.

During circulation of 1%, 2%, and 3% sevoflurane through a carbon dioxide canister in a closed anesthetic circuit for 8 hours, peak concentrations of the dehydrofluorinated compound were 13.3±0.27, 30.2±0.10 and 42.1±1.07 ppm at 2 hours, respectively. The concentration of the methoxylated compound did not exceed 2 ppm. The temperature of the soda lime was 43.3±2.8°C at 1 hour and increased gradually to 47.9±1.5°C after 8 h /5/.

The LC_{50} of the dehydrofluorinated compound in Wistar rats is 1,090 ppm in males and 1,050 ppm in females exposed for 1 h, and 420 ppm in males and 400 ppm in females exposed for 3 h. The chronic toxicity of the dehydrofluorinated compound in Wistar rats was studied by exposing rats 24 times, for 3 h each, to initial concentrations of 30, 60, or 120 ppm in a ventilated chamber. At all concentrations, there were no apparent effects other than a loss of body weight in females (at 120 ppm) on the final day. The dehydrofluorinated compound did not induce mutation in the reverse (Ames) test at less than 2,500 μg/dish (culture medium 2.7 ml) with activation by S-9 mixture, and below 1,250 μg/dish (culture medium 2.7 ml) without activation, in four strains of *S. typhomurium* and in one strain of *E. coli*. Exposure of

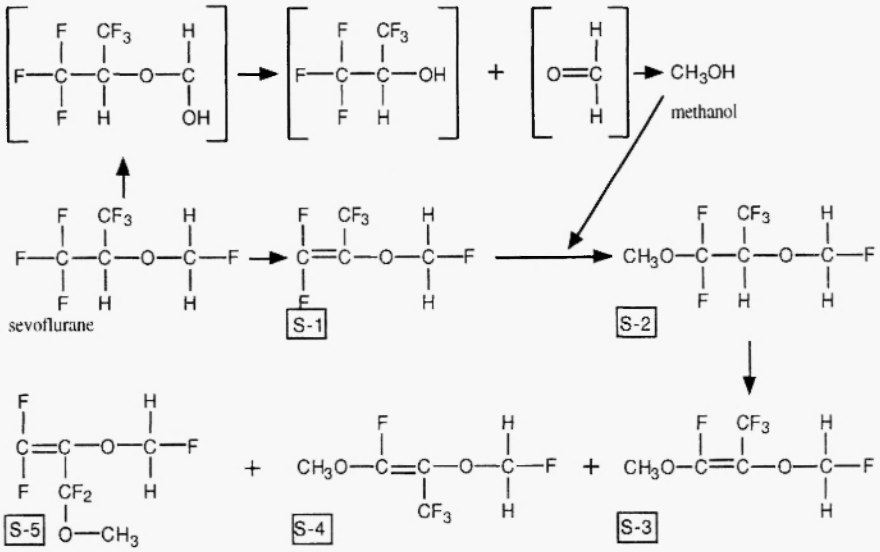

Fig. 4: Decomposition of sevoflurane.

fibroblasts to 7,500 ppm of compound A (the dehydrofluorinated compound) for 1 hour did not induce structural change. In a study of acute toxicity of the methoxylated compound, there was no toxicity in Wistar rats after 3 h exposure at 2,400 ppm. The reverse (Ames) test for the methoxylated compound was negative at 625-1,250 µg/dish /14/.

These degradation compounds may undergo further defluorination in the liver after inhalation. It is suspected that the excretion of fluoride is higher than the excretion of hexafluoroisopropanol-glucuronide, which is produced through the degradation of sevoflurane by elimination of a molecule of fluorine, by the liver microsomal oxidase system /15/.

CONCLUDING REMARKS

Formation of an alkene by elimination of HX (H: hydrogen, X: halide) from adjacent carbon atoms of an alkyl halide under ionic conditions to form a double bond is a well-known reaction. Almost all volatile anesthetics have a methyl halide group in these molecules,

which may be attacked by soda lime. The mechanism of elimination of HX from an alkyl halide in the anesthetic molecule may be as follows: in the initial phase, the base (hydroxide) is partially joined to the beta-hydrogen of the methyl halide group in the anesthetic molecule; a double bond starts to form between the two carbon atoms of the methyl group; the halogen atom is loosened by the attachment of the base to carbon, and the charge is distributed between the attaching group and the halogen atom. In the terminal phase, the base separates from one carbon atom and the halogen separates from the other carrying with it a full negative charge.

In this article, the soda lime-mediated decomposition products of volatile anesthetics and their degree of degradation and toxicity are described. However the toxicity of some compounds has not been determined because these reaction products are not expected to cause toxicity clinically. The main degradation products have a double bond. The pi-electron in the double bond may react with biological molecules. Further investigation of the toxicity of these compounds is needed.

Volatile anesthetics are different from other drugs which depend on metabolism for elimination from the body, as they are eliminated mainly by expiration. Therefore, anesthetics are required to be biologically and chemically stable. There is room for improvement of the soda lime mixture, including the system of carbon dioxide removal; the degree of degradation of anesthetics is dependent on the composition of the soda lime.

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