THE DEHYDROFLUORINATED PRODUCT OF SEVOFLURANE BY SODA LIME REACTS WITH ETHANOL TO PRODUCE TWO PRODUCTS

Kohyu Fujii, Toshiharu Az-ma and Osafumi Yuge

Department of Anesthesiology and Critical Care Medicine, Hiroshima University School of Medicine, Kasumi 1-2-3, Minami-ku, Hiroshima, Japan

SUMMARY

Dehydrofluorinated sevoflurane produced by soda lime reacted with methanol to produce methoxylated compounds. It is expected that dehydrofluorinated sevoflurane may react with ethyl alcohol in a patient who has recently ingested alcohol. In a closed vessel system and a model lung with circle absorber, sevoflurane, soda lime and ethanol were reacted at 25°C. The breakdown products of sevoflurane in the gas phase were analyzed by gas chromatography and mass spectrometry. The ethoxylated compounds of dehydrofluorinated sevoflurane [fluoromethyl 2-ethoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether] and its dehydrofluorinated compound [fluoromethyl 2-ethoxy-2,2-fluoro-1-(trifluoromethyl)vinyl ether] were detected in the mixture of sevoflurane and soda lime in the presence of ethanol. In the closed vessel, the concentrations of these compounds were 69.4±6.6 ppm and 79.3±8.8 ppm, respectively, at 120 min in the presence of 11.2 mg/l of ethanol. These concentrations were dependent on the ethanol concentration. These compounds were also detected in the closed anesthetic circuit having a model lung by 180 minutes of circulation of 1.5% sevoflurane and 0.56 mg/l of ethanol with 200 ml/min carbon dioxide gas through soda lime: 24.2±4.0 ppm and 21.4±0.9 ppm, respectively. Dehydrofluorinated sevoflurane reacts with ethanol at concentrations that are within the range that may be encountered in a patient who has recently ingested alcohol to produce an ethoxylated compound, and this ethoxylated compound undergoes dehydrofluorination by soda lime.

KEY WORDS

anesthetics, volatile, sevoflurane, carbon dioxide, soda lime, decomposition, dehydrofluorination, ethoxylation

INTRODUCTION

Sevoflurane [fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether] is a newly developed halogenated inhalational anesthetic. It has been reported that sevoflurane reacts with soda lime. Methanol is produced by hydrolysis and reacts with the defluorinated products of sevoflurane in the degradation process /1/. Alcohols in the anesthetic circuit might react with the defluorinated products of sevoflurane.

We occasionally anesthetize a drunken man whose blood ethanol concentration is ~0.12-5 mg/ml and expired gas concentration is ~0.125-2.5 mg/l. Ethanol might react with the defluorinated products of sevoflurane to produce new degradation products. We tested the stability of ethanol with the defluorinated products of sevoflurane.

METHODS AND MATERIALS

Reagents

Wako lime Ace® (Wako Pure Chemical; Osaka, Japan) was used as soda lime. Analytical grade ethanol was purchased from Katayama Chemical (Osaka, Japan). Sevoflurane was obtained from Maruishi Pharmaceutical (Osaka, Japan).

Gas chromatography and mass spectrometry

A Hewlett Packard HP-9860 Series II gas chromatograph was used equipped with a column DB-624 (30 m x 0.55 mm; J&W Scientific, CA, USA; column temp. 70°C), split type injection port (150°C) and a flame ionization detector at 100°C. A helium carrier stream of 15 ml/min was used. The concentrations of the products were calculated as the area percentage against sevoflurane. The determination of sevoflurane and ethanol concentrations was done using the pure compounds as standards.

A Shimadzu GCMS-QP1000 mass spectrometer was used for qualitative analysis. The ion source temperature was set at 250°C and ionizing energy at 70 eV.

Degradation of sevoflurane by soda lime in a closed vessel

Sevoflurane (1 μl) and soda lime (0.769±0.014 g; n=10) were allowed to react with and without ethanol (5.6, 11.2 or 28.0 mg/l) in a 14 ml test tube having a butyl rubber cap at 25°C for 2 hours. The reaction was started by the addition of 1 μl sevoflurane.

Study using a closed anesthetic circuit with a model lung

The absorbent canister was filled with 800 g of soda lime which was placed in the closed anesthetic circuit with a five liter rubber bag as a model lung. The system was filled with 1.5% of sevoflurane in oxygen, and 200 ml/min of carbon dioxide was fed to the model lung of the anesthetic circuit. After addition of 10 μg of ethanol (0.56 mg/l in the gas phase) to the circuit, the system was ventilated with an Aika ventilator (Aika Co., Tokyo, Japan) for 3 hours under the following conditions: respiratory rate of 12 times/min and tidal volume of 500 ml. The concentrations of ethanol and sevoflurane in gaseous samples from the bag were measured by gas chromatography.

Statistical analysis

Student's t-test was used for statistical analysis of the results, with a p-value of less than 0.05 being considered as significant.

RESULTS

Degradation of sevoflurane by soda lime in a closed vessel

After reaction two decomposition products (compound X and compound Y) were detected with a retention time of 3.6 and 4.8 min by gas chromatography with two minor peaks (Fig. 1). After reaction without soda lime, these compounds were not detected (Fig. 1). As shown in Fig. 2, the six strong peaks of the fragment ions in the mass spectra of compound X were m/z 33 (CH_2F), 45 (CH_3CH_2O), 51 (CHF_2), 69 (CF_3), 95 ($CH_3CH_2OCF_2$), 131 (CF_3CHOCH_2F). The structure of substance X was determined to be $CH_3CH_2OCF_2(CF_3)$-

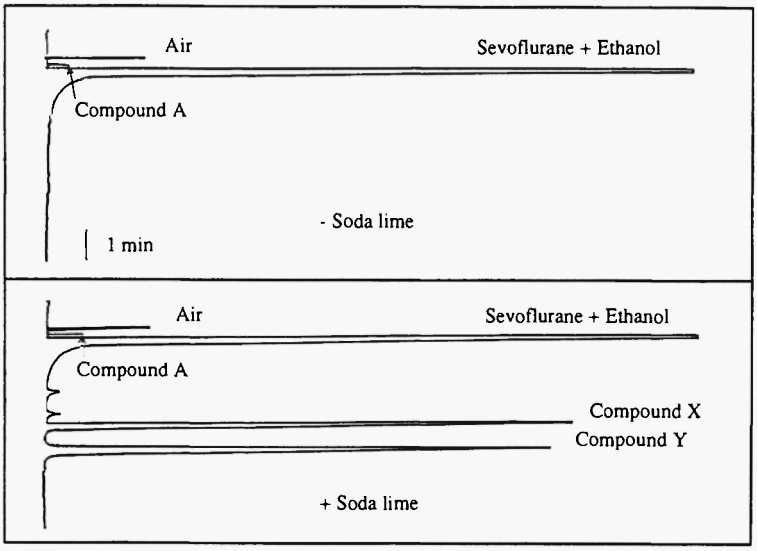

Fig. 1: Gas chromatogram of the gas phase in the closed vessel in which sevoflurane had reacted with ethanol and soda lime. After reaction, two decomposition products (compound X and compound Y) were detected with a retention time of 3.6 and 4.8 min by gas chromatography. After reaction without soda lime, these compounds were not detected.

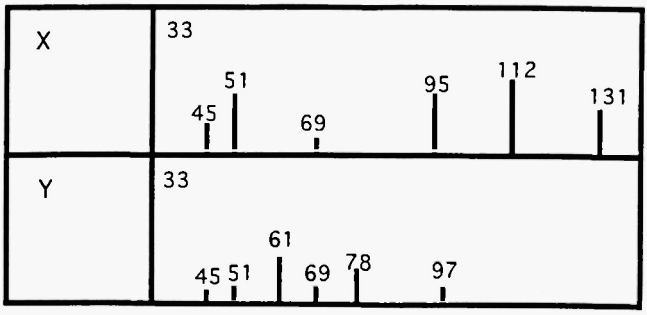

Fig. 2: Mass spectrogram of the two decomposition products. Compound X is the substance detected with a retention time of 3.6 min and compound Y is the substance detected with a retention time of 4.8 min by gas chromatography. The six strong peaks of the fragment ions in the spectrum of compound X were m/z 33 (CH_2F), 45 (CH_3CH_2O), 51 (CHF_2), 69 (CF_3), 95 ($CH_3CH_2OCF_2$), 131 (CF_3CHOCH_2F). The six strong peaks of the fragment ions in the spectrum of substance Y were m/z 33 (CH_2F), 45 (CH_3CH_2O), 61 ($COCH_2F$), 69 (CF_3), 78 ($CH_3CH_2OCH_2F$), 97 (CF_3CO).

$CHOCH_2F$, an ethoxylated compound of dehydrofluorinated sevoflurane (compound A). The six strong peaks of the fragment ions in the spectra of substance Y were m/z 33 (CH_2F), 45 (CH_3CH_2O), 61 ($COCH_2F$), 69 (CF_3), 78 ($CH_3CH_2OCH_2F$), 97 (CF_3CO). The structure of substance Y was determined to be $CH_3CH_2OCF(CF_3)COCH_2F$, dehydrofluorinated compound X.

After 120 min reaction with 11.2 mg/l ethanol in a test tube, the concentrations of compound X and compound Y increased with time up to 69.4±6.6 and 79.3+8.8 ppm (means ± sd, n=6), respectively. However, compound A reached a plateau at 7.8±1.1 ppm (mean ± sd, n=6) after 60 minutes of reaction. In the reaction without ethanol, compounds X and Y were not detected, and the concentration of compound A was slightly higher than with ethanol (Fig. 3).

The formation of these compounds depended on the concentration of ethanol. The amount of compound X produced was 29.6±4.5 ppm, 47.1±2.6 ppm, and 68.4±6.2 ppm (means ± sd, n=6) after 60 min reaction with 5.6 mg/l, 11.2 mg/l, and 28.0 mg/l of ethanol, respectively. The amount of compound Y produced was 29.4±4.9 ppm, 50.4±6.0 ppm and 72.7±8.4 ppm (means ± sd, n=6) after 60 min reaction with 5.6 mg/l, 11.2 mg/l, and 28.0 mg/l of ethanol, respectively.

Study using a closed anesthetic circuit with a model lung

Compounds X and Y were detected, and their concentrations increased with time up to 24.2±4.0 and 21.4±0.9 ppm (means ± sd, n=6) at 180 minutes, respectively (Fig. 4). Compound A was also detected after 30 minutes of ventilation, and then the concentration gradually decreased. The temperature inside the canister increased during ventilation, reaching 41.7±1.3°C (n=3) by the end of ventilation.

DISCUSSION

We showed that ethanol reacts with dehydrofluorinated sevoflurane degraded by soda lime to produce $CH_3CH_2OCF_2(CF_3)CHOCH_2F$ and $CH_3CH_2OCF(CF_3)COCH_2F$. The former is an ethoxylated compound of dehydrofluorinated sevoflurane, the latter is its dehydrofluorinated compound. The formation of an alkene by elimination of HX (X= halogen atom) from an alkyl halide under ionic conditions is a well known reaction.

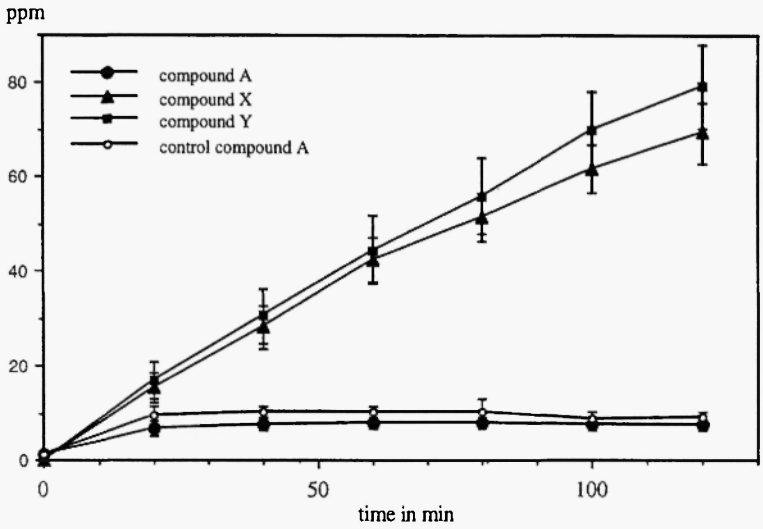

Fig. 3: Time course of concentrations of compound A, compound X and compound Y. Sevoflurane (final concentration: 1.2%) and soda lime (0.769±0.014 g; n=10) were allowed to react with or without ethanol (final concentration: 11.2 mg/l) in a 14 ml test tube with a butyl rubber cap at 25°C for 2 hours. The reactions were started by the addition of sevoflurane. Control compound A: compound A produced in the reaction mixture without ethanol (mean ± sd; n=3).

Sevoflurane undergoes dehydrofluorination to produce compound A, fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether. Compound A reacts with methanol which is produced from sevoflurane by hydrolysis and Cannizzaro reaction to produce fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether /1/. Ethanol might react with the defluorinated sevoflurane, compound A, to produce compound X and compound Y as follows:

$$(CF_3)_2CHOCH_2F + \text{(soda lime)} \rightarrow CF_2(CF_3)COCH_2F$$

$$CF_2(CF_3)COCH_2F + CH_3CH_2OH \text{ (ethanol)} \rightarrow$$

$$CH_3CH_2OCF_2(CF_3)CHOCH_2F \rightarrow$$

$$CH_3CH_2OCF(CF_3)COCH_2F + HF$$

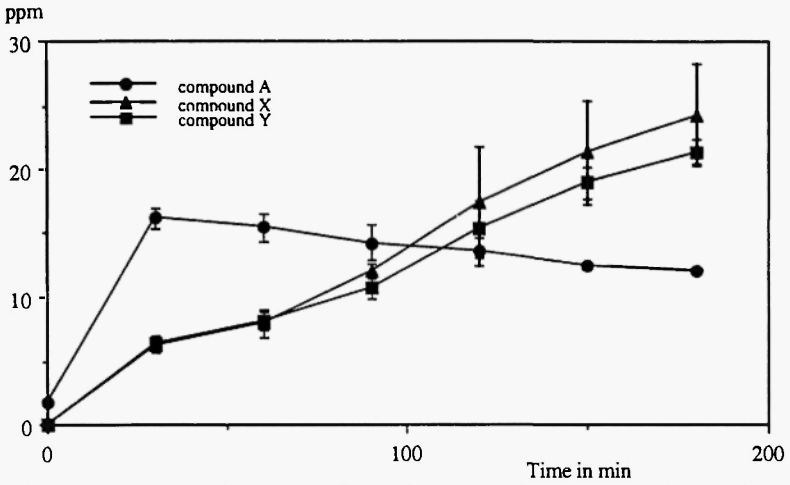

Fig. 4: Time course of concentrations of compound A, compound X and compound Y in the 'anesthetic circuit' in which an absorbent canister filled with 800 g of soda lime and a five liter rubber bag, as a model lung, were ventilated. The system was filled with 1.5% sevoflurane and then 200 ml/min of carbon dioxide was fed to the model lung of the anesthetic circuit. After addition of 10 μg of ethanol (0.56 mg/l) to the circuit, the system was ventilated with an Aika ventilator for 3 hours under the following conditions: respiratory rate of 12 times/min and tidal volume of 500 ml (mean + sd; n=6).

Soda lime, a carbon dioxide absorber, is composed of potassium hydroxide, sodium hydroxide, and calcium hydroxide. Volatile anesthetics, such as trichloroethylene, halothane, sevoflurane, enflurane and isoflurane, are halogenated ethers or haloalkanes which contain hydrogen and halogen atoms. They decompose with the elimination of HX on reaction with soda lime. Trichloroethylene yields a toxic amount of dichloroacetylene /2/. Halothane yields a small amount of difluorochlorobromoethylene which is a toxic compound and is degraded through dehalogenation into trifluorchloroethane /3/. Enflurane is degraded to produce 1-chloro-1,2-difluorovinyldifluoromethyl ether /4/. Isoflurane also undergoes elimination, producing 2,2-difluoro-1-chlorovinyldifluoromethyl ether /5/. Sevoflurane undergoes dehydrofluorination to produce compound A, the LC_{50} (50% lethal concentration) of which is 1,090 ppm in male Wistar rats /6/. Because the molecule contains a π-electron compound Y may react with molecules in the body.

In a closed anesthetic circuit with a model lung, the decomposition products were detected in the gas at a maximum concentration of 20-30 ppm in the presence of 0.56 mg/l of ethanol, and the decomposition products in a heavily drunken man would be higher than this range. However, as the toxicity of these compounds is unclear, further investigation is needed.

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