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Mass Spectrometry Provides Warning of Carbon Monoxide Exposure Via *Trifluoromethane*

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Background: **The chemical breakdown of isoflurane, enflurane, or desflurane in dried carbon dioxide absorbents may produce carbon monoxide. Some mass spectrometers can give false indications of enflurane during anesthetic breakdown.**

Methods: **During clinical anesthesia with isoflurane or desflurane, the presence of carbon monoxide in respiratory gas was confirmed when enflurane was inappropriately indicated by a clinical mass spectrometer that identified enflurane at mass to charge ratio = 69. *In vitro,* isoflurane, enflurane, or desflurane in oxygen was passed through dried carbon dioxide absorbents at 35, 45, and 55°C. Gases were analyzed by gas chromatography and by mass spectrometry.**

Results: **Mass spectrometry identified several clinical incidents in which 30–410 ppm carbon monoxide was measured in respiratory gas. Trifluoromethane was produced during *in vitro* breakdown of isoflurane or desflurane. Although these inappropriately indicated quantities of "enflurane" correlated ($r^2 > 0.95$) to carbon monoxide concentrations under a variety of conditions, this ratio varied with temperature, anesthetic agent, absorbent type, and water content.**

Conclusions: **Trifluoromethane causes the inappropriate indication of enflurane by mass spectrometry, and indicates isoflurane and desflurane breakdown. Because the ratio of carbon monoxide to trifluoromethane varies with conditions, this technique cannot be used to quantitatively determine the amount of carbon monoxide to which a patient is exposed. If *any* warning of anesthetic breakdown results from this technique then remedial steps should be taken immediately to stop patient exposure to carbon monoxide. No warning can be provided for the breakdown of enflurane by this technique. (Key words: Anesthetics, inhalational: desflurane; enflurane; isoflurane. Compounds: baralyme; halogenated hydrocarbons; soda lime. Gases: carbon dioxide; carbon monoxide. Gas phase compounds: trifluoromethane. Monitoring, intraoperative: mass spectrometry.)**

INTRAOPERATIVE carbon monoxide exposure has been reported during closed- or semiclosed-circuit anesthesia.[1] Recent studies have shown that carbon monoxide is produced *via* chemical decomposition of isoflurane, enflurane, or desflurane, by dry carbon dioxide absorbents.[2] In two cases of intraoperative carbon monoxide exposure during isoflurane anesthesia,[3] the presence of enflurane was indicated by a magnetic sector mass spectrometer, although enflurane had not been administered to these patients. The operating room mass spectrometer indicated the presence of enflurane based on the detection of fragmentation products of respiratory gases, with a mass to charge ratio (m/z) = 69. Trifluoromethane has been shown to result from the degradation of isoflurane and desflurane,[4] and is responsible for these false readings of enflurane. Therefore, warning of anesthetic decomposition and the production of carbon monoxide may be possible using current anesthesia monitoring instrumentation. The purpose of this study was to determine the usefulness of this technique to identify the presence of carbon monoxide during clinical conditions.

Methods

Separate human and *in vitro* studies were conducted to determine the relationship between carbon monoxide production from anesthetic breakdown in dry carbon dioxide absorbents and erroneous indications of the presence of enflurane *via* mass spectrometry.

Human Study

With the approval of our institutional human research committee, permission was obtained to analyze respi-

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ratory gases for carbon monoxide in the event that the presence of enflurane was indicated during isoflurane or desflurane anesthesia, hence indicating a possible exposure to carbon monoxide. Analysis for gas phase carbon monoxide was performed as indicated later. Patient monitoring was performed with either of two magnetic sector mass spectrometers (MGA 1100, Marquette Electronics, Milwaukee, WI). Mass to charge ratio (m/z) = 69 was used for the identification of enflurane. Proper calibration of the MGA 1100 mass spectrometers was verified using calibration gases dictated by the manufacturer's instructions. Patient display was performed with the Advantage 2000 monitor (Marquette Electronics, Milwaukee, WI) or Tramscope 12 C monitor (Marquette Electronics, Milwaukee, WI). Carboxyhemoglobin concentrations were determined (ABL 520, Radiometer Copenhagen, Copenhagen, Denmark) if the anesthesiologist deemed that sufficient exposure to carbon monoxide was suspected to warrant further investigation on clinical grounds.

In Vitro *Study*

Barium hydroxide lime (Baralyme, Chemtron, St. Louis, MO) was dried by the passage of dry oxygen at 10 l/min at room temperature until 5.2% water remained (partially dried), or until a constant weight was obtained. Soda lime (SODA LIME, Puritan Bennett, Lenexa, KS) was also dried to constant weight at room temperature in dry oxygen. Drying the absorbents to constant weight required several days under these conditions. A 275-ml aluminum cylinder surrounded by a water jacket served as a reaction chamber, and was filled with 200 g dried barium hydroxide lime. The temperature of the reaction chamber was maintained at 45–48°C (Concha Therm III Servo Controlled Heater #380-80, Respiratory Care, Arlington Heights, IL). Temperature was monitored by a thermocouple (2100 Telethermometer, Yellow Springs Instruments, Yellow Springs, OH) or glass/mercury thermometer placed into the barium hydroxide lime. The flow rate of gas through the reaction chamber was 300 $ml \cdot min^{-1}$. At the beginning of each experiment, dried or partially dried barium hydroxide lime was placed into the reaction chamber and allowed to reach the desired temperature. Oxygen (100%; control), or isoflurane (1.0%; Isoflurane Vapor 19.1 vaporizer, Draegerwerk, Luebeck, Germany), enflurane (1.2%; Enflurane Vapor 19.1 vaporizer, Draegerwerk), or desflurane (4.0%; Ohmeda Tec 6 Desflurane vaporizer, Madison, WI) in dry oxygen was passed through the reaction chamber. Gas samples were taken from the inlet and the outlet of the reaction chamber for analysis. Data were selected to show maximal values for carbon monoxide concentration, and were assessed by analysis of variance to verify statistically significant differences between inlet and outlet concentrations.

Additional experiments were conducted where isoflurane (1–5%) or desflurane (4 to 10%) in dry oxygen was passed through the reaction chamber at 35 ± 1, 45 ± 1, or 55 ± 5°C, and at flow rates of 30 $ml \cdot min^{-1}$ to 2,500 $ml \cdot min^{-1}$ to obtain various degrees of reaction. Barium hydroxide lime (dried or partially dried) or soda lime (dried) were changed at appropriate time intervals to test the clinical mass spectrometer analysis of the reacted gases at varying degrees of absorbent exhaustion. These data were assessed by analysis of variance and regression lines were determined between the apparent but misidentified concentration of "enflurane," and the concentration of carbon monoxide. Statistical differences between the slopes of the regression lines were compared by the test of two slopes simple regression with zero intercept model. Significance was determined at $P < 0.05$.

Analysis for various chemical constituents was performed by gas chromatography, mass spectrometry, or gas chromatography/mass spectrometry. Carbon monoxide content was determined by gas chromatography (QuinTron Model 225 Gas Chromatograph, Milwaukee, WI) using a 13× molecular sieve and thermal conductivity detector. Helium was used as the carrier gas at a flow rate of 300 $ml \cdot min^{-1}$ with the columns at room temperature. Calibration was performed with 3,000 ppm carbon monoxide in air (Airco, Milwaukee, WI). Continuous display of the mass spectrum of the reaction products from m/z = 10–200 was determined by a specially adapted clinical quadrapole mass spectrometer (Random Access Mass Spectrometer, Marquette Electronics, Milwaukee, WI). Selected samples reacted with dried barium hydroxide lime also were analyzed on a 5890 Series II Gas Chromatograph/5989A MS Engine Mass Spectrometer system (Hewlett Packard, Palo Alto, CA). An HP-FFAP capillary column (cross-linked polyethylene glycol film) 25-m long, 0.32-mm ID, and 0.52 μm film thickness was used for gas separation. The mass spectra of some of the compounds were identified by comparison to authentic standards or the Wiley 138 Mass Spectra Library.‖

‖ Wiley Mass Spectra Library, John Wiley & Sons, Licensed to Hewlett Packard Company, Palo Alto, California, 1991.

Results

Anesthetic destruction occurred when isoflurane, enflurane, or desflurane was passed through the reactor; this was confirmed by decreases in specific spectral peaks measured by all three mass spectrometers. Gas chromatography was used to quantify the maximal concentrations of carbon monoxide produced by anesthetic destruction, as shown in table 1. Trifluoromethane was identified by gas chromatography mass spectrometry when isoflurane or desflurane was reacted, but not when enflurane was reacted. Although trace amounts of other compounds were noted, carbon monoxide and trifluoromethane were the only gas phase compounds produced in large quantities during anesthetic breakdown in this study. Whenever trifluoromethane was present, the Random Access Mass Spectrometer quadrapole mass spectrometer showed marked increase in the size of the mass spectral peak at m/z = 69. The MGA 1100 mass spectrometer indicated apparent enflurane, which is measured by the relative strength of the signal produced by ions having m/z = 69. In subsequent *in vitro* experiments with isoflurane and desflurane at different concentrations and conditions, the apparent "% enflurane" as measured by the MGA 1100 was plotted against the carbon monoxide concentrations. The plots shown in figures 1 and 2 show the regression lines for data points resulting from plotting measured carbon monoxide concentrations against apparent enflurane values. The breakdown of isoflurane produced a greater apparent value of enflurane for the same carbon monoxide concentration as compared to desflurane. Greater apparent enflurane values for the same carbon monoxide concentrations also resulted at higher temperatures, higher water content (for barium hydroxide lime), and for barium hydroxide lime *versus* soda lime.

Clinical Data

Enflurane was indicated during the anesthesia of four patients receiving isoflurane. Barium hydroxide lime was the carbon dioxide absorbent in all four cases. Carbon monoxide was measured in the patient breathing circuit in three of these cases, and from the carbon dioxide absorbent canister immediately after removal of the canister from the breathing circuit in one case. The range of carbon monoxide concentrations measured in the breathing circuit was 30–410 ppm. The total duration of patient exposure to carbon monoxide in these cases was less than 15 min, and blood gas analysis showed that carboxyhemoglobin concentrations of all patients were less than 1.5%.

Table 1. Maximum Carbon Monoxide Concentrations (Mean ± SE) Indicated during the First 10 min or Anesthetic Breakdown at 300 ml · min^{-1} with Air-dried Barium Hydroxide Lime at 45°C

Method	ppm Carbon Monoxide by Gas Chromatography
1.0% isoflurane	833 ± 11
1.2% enflurane	4,480 ± 88
4% desflurane	19,250 ± 250

Discussion

The warning of the presence of carbon monoxide depends on the simultaneous production of carbon monoxide and trifluoromethane during chemical decomposition of isoflurane and desflurane. The presence of gases for which clinical mass spectrometers were not specifically designed may result in false readings.[5–7] For example, clinical mass spectrometers will misidentify carbon monoxide as nitrogen because both

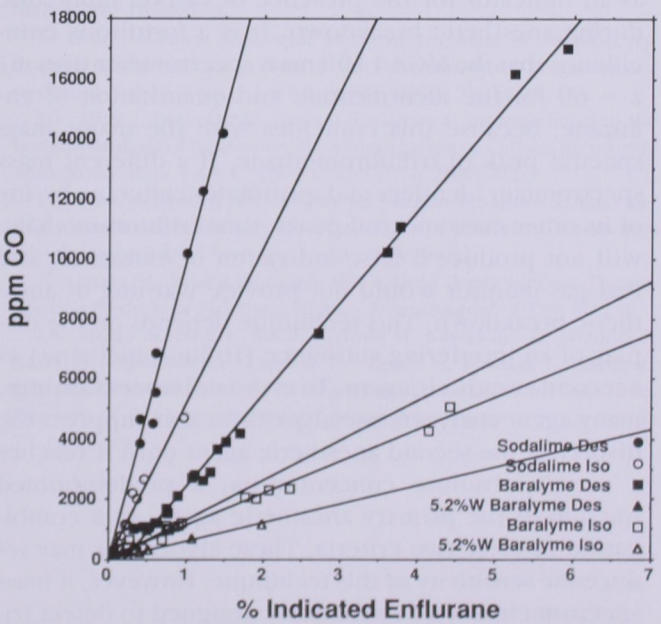

Fig. 1. Parts per million carbon monoxide *versus* percent indicated enflurane for isoflurane and desflurane reacted at 45°C under different absorbent conditions. All regression lines are statistically different from each other, and all have r^2 values > 0.95.

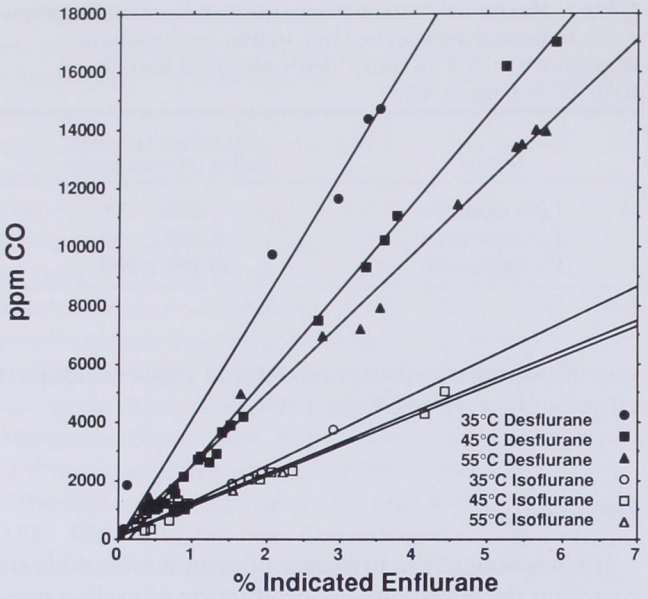

Fig. 2. Temperature effect on the ratio of parts per million carbon monoxide to percent indicated enflurane for isoflurane and desflurane reacted in dried barium hydroxide lime. All regression lines have r^2 values > 0.95 and all are statistically different from each other except isoflurane at 45°C and 55°C.

gases possess mass spectra with m/z values of 28 and, therefore, mass spectrometers cannot reliably be used as an indicator for the presence of carbon monoxide during anesthetic breakdown. It is a fortuitous coincidence that the MGA 1100 mass spectrometer uses m/z = 69 for the identification and quantitation of enflurane, because this coincides with the major mass spectral peak of trifluoromethane. If a different mass spectrometer identifies and quantitates enflurane by any of its other mass spectral peaks, then trifluoromethane will not produce a false indication of enflurane, and that gas monitor would not provide warning of anesthetic breakdown. This technique depends on the display of an interfering substance (trifluoromethane) as a second anesthetic agent. To avoid nuisance warnings, many agent analyzers use algorithms that suppress the display of the second anesthetic agent until it reaches a certain absolute concentration, a predetermined fraction of the primary anesthetic agent, or a combination of these two criteria. These algorithms may reduce the sensitivity of this technique. However, if mass spectrometers were specifically designed to detect trifluoromethane, the sensitivity of this technique could be increased. Warning of the presence of carbon monoxide will not result from this technique if trifluoromethane is not simultaneously produced; this might occur with the endogenous production of carbon monoxide, or during the breakdown of enflurane, because enflurane does not produce trifluoromethane. However, under the conditions of this study, this technique has provided warning of anesthetic breakdown with breathing circuit concentrations of carbon monoxide as low as 30 ppm. Equilibrium carboxy-hemoglobin concentrations for 30 ppm carbon monoxide in room air are less than 5%,[8] and would be lower with the higher inspired oxygen concentrations commonly used during clinical anesthetics.

In this study, different concentrations of carbon monoxide are found at the same indicated value of enflurane, depending on type of anesthetic, temperature, and type and degree of hydration of absorbent. This suggests that the ratio of carbon monoxide to trifluoromethane produced during anesthetic destruction varies with the conditions; therefore, the sensitivity of this method also will vary with different conditions likely to occur under clinical situations. The greatest sensitivity of this technique exists with higher temperatures, higher water content, isoflurane rather than desflurane, and barium hydroxide lime rather than soda lime. Because the ratio of carbon monoxide to trifluoromethane varies, this technique cannot be used to quantitatively determine the amount of carbon monoxide that is present. If warning of anesthetic breakdown results from the presence of any amount of trifluoromethane, then remedial steps should be immediately taken to stop patient exposure to carbon monoxide.

Fang *et al.*[2] found that carbon monoxide was produced only in large quantity during the destruction of difluoromethyl ethers (-O-CHF_2), which suggests that the carbon monoxide arises predominantly from the -O-CHF_2 moieties of isoflurane, enflurane, and desflurane. This is consistent with mechanistic studies that infer that dihalomethylene intermediates (-CX_2- where X = any halogen) participate in carbon monoxide production.[9–11] Sevoflurane is a monofluoromethyl ether (-O-CH_2F) and neither possesses a -CX_2- moiety nor produces significant amounts of carbon monoxide during breakdown. Although halothane contains a -CX_2- moiety, this is in a structurally different location than in isoflurane, enflurane, or desflurane. Also, in the current study, the production of trifluoromethane was observed only during destruction of anesthetics containing the CF_3 moiety, namely isoflurane and desflurane, but not enflurane. Although sevoflurane and halothane also contain CF_3 moieties, different chemical pathways that do not result in trifluoromethane production have

been proposed for the chemical reactions of these anesthetics.[12,13] Therefore, with the currently used clinical anesthetics, trifluoromethane production during anesthetic breakdown is accompanied by carbon monoxide production, although during the breakdown of enflurane, carbon monoxide production is not accompanied by trifluoromethane production.

These four cases of intraoperative carbon monoxide exposure, combined with the two cases previously reported from our institution, represent a total of six cases detected by this technique during isoflurane or desflurane anesthesia. During the 10-month period during which these six exposures were detected, a total of 2,316 general anesthetics using isoflurane or desflurane were delivered in operating rooms monitored by mass spectrometry. All cases of carbon monoxide exposure occurred with isoflurane anesthesia during the first general anesthetic of the day in that particular operating room, and the corresponding number of first cases was 1,372. This results in an incidence of 6 of 2,316 or 0.26%, but for first cases, the incidence of carbon monoxide exposure from anesthetic breakdown was 6 of 1,372 or 0.44%.

This study confirms that sufficient quantities of trifluoromethane are produced during the breakdown of isoflurane and desflurane by dried carbon dioxide absorbents to be reported as enflurane by clinical mass spectrometers identifying enflurane at m/z = 69. Because the ratio of carbon monoxide to trifluoromethane varies with conditions that are not likely to be known during clinical anesthesia, this technique cannot be used to quantitatively determine the amount of carbon monoxide to which a patient is exposed. If warning of anesthetic breakdown results from the presence of any amount of trifluoromethane then remedial steps should be immediately taken to stop patient exposure to carbon monoxide. No warning can be provided for the breakdown of enflurane by this technique.

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