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Indirect Detection of Intraoperative Carbon Monoxide Exposure by Mass Spectrometry during Isoflurane Anesthesia

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INTRAOPERATIVE exposure of a patient to carbon monoxide appears to be uncommon but is a potentially lethal complication of inhalation anesthesia. The passage of difluoromethyl-ethyl ethers, such as isoflurane, enflurane, and desflurane, through dry carbon dioxide absorbents has been shown to result in carbon monoxide production and anesthetic destruction.[1] The true incidence of carbon monoxide exposure during clinical anesthesia is unknown, and no adequate means to detect intraoperative exposure exists at this time. We present two cases in which abnormalities evident *via* mass spectrometry led to the identification of increased carboxyhemoglobin concentrations in patients receiving isoflurane anesthesia without other risk factors for carbon monoxide exposure.

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Case Reports

Case 1

On a Monday morning, a 26-yr-old, 65-kg man underwent bifrontal and bitemporal electroencephalographic grid placement for cortical mapping of intractable seizures. The patient's only medication was 900 mg gabapentin twice daily. The patient had no other medical problems, was a nonsmoker, and had no known preoperative exposure to carbon monoxide. Induction of general anesthesia was performed with thiopental, fentanyl, and pancuronium. Ventilation *via* face mask with isoflurane in oxygen was performed before intubation. After tracheal intubation, anesthesia was maintained with isoflurane in oxygen at 1 l/min and nitrous oxide at 2 l/min. A circle system was used with Baralyme (Chemtron Medical Division, Allied Healthcare Products, St. Louis, MO), the standard carbon dioxide absorbent at our hospital. Gas monitoring was performed with a properly maintained and calibrated MGA 1100 Marquette Gas Analysis system (Milwaukee, WI).

During the surgical procedure, the mass spectrometer indicated that a mixture of isoflurane and enflurane was present, although isoflurane was the only halogenated agent administered to the patient. Anesthetic gas concentrations at this time are shown in table 1. Initially, the possibility was raised that the isoflurane vaporizer was contaminated with enflurane, although this was unlikely because enflurane had not been stocked in our hospital for nearly 6 months. The vaporizer was drained intraoperatively and refilled from a new, unopened bottle of isoflurane, while temporarily maintaining anesthesia with boluses of propofol. To quickly reestablish the previous end-tidal anesthetic concentrations, the fresh gas flows were increased to 4 l/min of oxygen and 4 l/min of nitrous oxide. Only isoflurane was indicated on the mass spectrometer during this period of increased gas flows. The fresh gas flow rates were reduced to 2 l/min of nitrous oxide and 1 l/min of oxygen after the desired end-tidal concentration (6.0–7.5 mmHg) of isoflurane was obtained. Shortly thereafter, the mass spectrometer again indicated that a mixture of isoflurane and enflurane was present. A small portion of isoflurane

Table 1. Gas Concentrations

	Before Intubation		Intubation + 15 min		Intubation + 45 min	
	Inspired	Expired	Inspired	Expired	Inspired	Expired
Patient 1						
Isoflurane (mmHg)	6.8	5.2	3.0	3.0	0.8	1.5
Enflurane (mmHg)	0	0	2.2	2.2	5.2	6.8
N_2O (mmHg)	9.0	9.0	486	474	504	495
	Intubation + 5 min				Intubation + 30 min	
	Inspired	Expired			Inspired	Expired
Patient 2						
Isoflurane (mmHg)	9.8	6.8			3.8	3.0
Enflurane (mmHg)	0	0			2.2	3.0
N_2O (mmHg)	399	375			504	501

was drained from the vaporizer, and the vapor was tested on another port of the mass spectrometer, which indicated that only isoflurane was present. Blood oximetry was subsequently performed on this patient using a properly calibrated and maintained ABL 520 Blood Gas System (Radiometer Medical, Copenhagen, Denmark), which revealed a carboxyhemoglobin concentration of 8.3%. At the time of this case presentation, the association of carbon monoxide production by dry carbon dioxide absorbent had not been published.‖ Because the actual means of carbon monoxide production was not known at that time, it was postulated that a possible mechanism for the carbon monoxide production was that isoflurane was metabolized to carbon monoxide because of hepatic microsomal enzyme induction from long-term anticonvulsant use.[2] Because of that postulate, isoflurane was discontinued, and the lungs were ventilated with 100% O_2 while anesthesia was maintained with propofol and opioids. Five minutes after isoflurane was discontinued and end-tidal concentrations of isoflurane were no longer displayed on the monitor, halothane was indicated for 1 min at inspired and expired partial pressures of 43.5 and 75 mmHg, respectively. The patient's carboxyhemoglobin concentration decreased to 4.2% in 1 h and 2.6% in 2 h. Pulse oximetry indicated an Sp_{O_2} of 99% during the entire anesthetic.

Case 2

On a Monday morning, a 40-yr-old, 90-kg man underwent lumbar disk excision under general anesthesia. The patient was taking no medications at the time of surgery, was a nonsmoker, and had no known preoperative exposure to carbon monoxide. Induction of general anesthesia was performed with propofol, fentanyl, and vecuronium. After tracheal intubation, anesthesia was maintained with isoflurane in oxygen and nitrous oxide.

The mass spectrometer indicated that only isoflurane was present for the first 5 min, but after 10 min, the mass spectrometer indicated that the gas composition had changed to a mixture of isoflurane and enflurane, as depicted in table 1. About 1 h elapsed after the initial indication of "enflurane." When the carbon dioxide absorbent was replaced with fresh Baralyme, "enflurane" was no longer indicated at the same fresh gas flow rates. Ten minutes later, blood oximetry with the ABL 520 analyzer revealed a carboxyhemoglobin concentration of 6.9%. The patient's carboxyhemoglobin concentration was measured after 100% O_2 had been administered for 30 min in the recovery room and had decreased to 4.5%. Pulse oximetry indicated an Sp_{O_2} of 99% during the entire anesthetic.

Discussion

These two patients had increased intraoperative carboxyhemoglobin concentrations. The occurrence of these events on Monday mornings is consistent with previous case reports for intraoperative carbon monoxide exposure and is also consistent with the Anesthesia Patient Safety Foundation report of chemical decomposition of difluoromethyl-ethyl ethers in dry carbon dioxide absorbents.‖ Fang *et al.*[1] have shown that Baralyme can produce higher carbon monoxide concentrations than soda lime at any given water content during the breakdown of isoflurane, enflurane, and desflurane. Although the current case reports lack gas phase detection of carbon monoxide, clinical monitors cannot detect carbon monoxide.

The respiratory gas analysis used for these patients was a time-shared magnetic sector mass spectrometer with continuous infrared carbon dioxide monitoring. The process by which the mass spectrometer identifies gases is complex. First, the gases are subjected to an ionizing beam of electrons in a high vacuum. The resulting ions are separated by their mass to charge ratios as they are bent by a magnetic field. Electrodes are located in the vacuum chamber corresponding to the

‖ Fang ZX, Eger EI: Source of toxic CO explained: -CHF2 anesthetic + dry absorbent. Anesthesia Patient Safety Foundation Newsletter 9: 25–36, 1994.

mass to charge ratios of interest. When an ion strikes the electrode, current flow is produced and is quantified by the accompanying electronic circuitry. A mathematical algorithm is used to determine the proportions of the identifiable gases based on the current flows at each of the detectors, as well as empiric calibration data that define the expected current flow for each identifiable gas species. Molecules may be hit by the electron beam at different locations and may fragment into smaller molecules, ions, and uncharged radicals. This results in the potential for multiple fragmentation products from any individual large molecule. The MGA 1100 mass spectrometer senses only the charged fragments (ions) that are aimed at the electrodes by the magnetic field. The MGA 1100 mass spectrometer (Milwaukee, WI) measures at mass to charge ratios of 4 (He^+), 12 (C^+ for CO_2), 28 (N_2^+), 32 (O_2^+), 44 (N_2O^+), 69 (enflurane fragmentation products), 87 (isoflurane fragmentation products, although some spectrometers use mass to charge ratio of 89 or 91), and 117 (halothane fragmentation products, although some spectrometers use a mass to charge ratio of 128). MGA 1100 spectrometers designed to identify desflurane have a channel for mass to charge ratio of 101 instead of the helium channel. The selectivity of each channel of the MGA 1100 mass spectrometer is believed to be $\pm$ <1 atomic mass unit in the lower range of molecular weights but may be as high as $\pm$1 or 2 atomic mass units at mass to charge ratios of 60 to 80, and increases with increasing molecular weight.#

Measurements from gases not specifically designed for detection by the system may result in false readings. Chlorofluorocarbon propellants from aerosol inhalers have been incorrectly identified as both carbon dioxide and isoflurane, and the propellants have effects on the reported concentrations of other halogenated anesthetics.[3–5] Trichloromonofluoromethane and dichlorodifluoromethane, two propellants in albuterol aerosol inhalers,[3] have potential fragmentation products of C^+ with mass to charge ratio of 12; $CClF_2^+$ with mass to charge ratios of 85 and 87; CCl_2F^+ with mass to charge ratios of 101, 103, and 105; and $CCl_2F_2^+$ with mass to charge ratios of 120, 122, and 124. These fragments have multiple molecular weights because chlorine has two stable isotopes with molecular weights of 35 and 37, in an atomic ratio of approximately 3 to 1. The fragments with mass to charge ratios of 85 and 87 may interfere with the identification of isoflurane, which is measured in the range of 87 to 91. Similarly, the fragments of mass 101 to 105 and 120 to 124 may interfere with identification of desflurane and halothane, respectively. Because the C^+ fragment may be produced by any carbon-containing parent molecule, interference with the detection of carbon dioxide or other organic molecules may result.

Similarly, the indication of "enflurane" during these episodes of carbon monoxide exposure does not necessarily indicate that enflurane was present. This merely suggests that there are species present with mass to charge ratios of 69 in the proper proportion to other measured species to satisfy the criteria of the mathematical algorithm for the detection of enflurane. The trifluoromethyl cation, CF_3^+, has a mass to charge ratio of 69 and may result from ionization and fragmentation of a breakdown product of isoflurane, because isoflurane contains a trifluoromethyl moiety. Similarly, when halothane was indicated briefly during case 1, halothane was not present. Halothane has a potential fragmentation product with mass to charge ratio of 117, CF_3-$CHCl^+$, which results from the loss of bromine after ionization. Because isoflurane and halothane share the CF_3-CHCl- moiety, chemical breakdown of isoflurane in the carbon dioxide absorbent may result in a gas species that has fragmentation products after ionization that can be misinterpreted as halothane by the mass spectrometer. Therefore, the indication of enflurane or halothane during isoflurane anesthesia may be a clinically useful indicator of anesthetic breakdown, because new halogenated gases may be produced that can be misinterpreted by the mass spectrometer.

Pulse oximetry did not detect the presence of carboxyhemoglobin in either case. This is consistent with the results of Barker *et al.*,[6] who showed that carboxyhemoglobin concentrations of 70% can be interpreted as an Sp_{O_2} of approximately 90% by a two-wavelength pulse oximeter. The presence of carboxyhemoglobin was confirmed by oximetry with the ABL 520 analyzer, which uses six wavelengths of light. This instrument can provide measurements of total hemoglobin, hemoglobin oxygen saturation, carboxyhemoglobin concentration, and methemoglobin concentration. The measurement of carboxyhemoglobin was considered to be due to the presence of carbon monoxide in the respiratory gases, although no direct test for the presence of carbon monoxide in respiratory gases was available. Carbon monoxide cannot be monitored di-

Corsale D: Personal communication. 1995.

rectly by mass spectrometry because its molecular weight is equivalent to that of nitrogen, a gas usually present in much greater amounts. Detection of carbon monoxide by fragmentation products is not possible by mass spectrometry because carbon dioxide is present in greater amounts and has fragmentation products similar to carbon monoxide.

Additional indirect evidence of intraoperative carbon monoxide exposure is provided by the time course of the decrease in carboxyhemoglobin concentration. Patient 1 had a decrease in carboxyhemoglobin concentration from 8.3% to 4.2% in 1 h and to 2.6% in 2 h. Patient 2 had a decrease from 6.9% to 4.5% after 30 min of breathing 100% O_2. This half-life of approximately 45–60 min in 100% O_2 is consistent with the time course of carbon monoxide saturation in other studies.[7] This provides further evidence that the measurement of carboxyhemoglobin is consistent with actual carbon monoxide exposure and not a laboratory artifact that produced a constant increase in measured carboxyhemoglobin. Although there was no reason to suspect increased preoperative carboxyhemoglobin concentrations, as neither patient was a smoker, extrapolation would yield values of 14–16% COHb at 2.5 h before surgery. This extrapolation is based on a 4-h half-life for COHb in a patient with normal ventilation breathing room air.[7] The addition of supplemental oxygen during surgery would increase the extrapolated values by decreasing the half-life of carboxyhemoglobin. Such levels would be likely to produce symptoms of carbon monoxide poisoning. The absence of preoperative symptoms is consistent with a lack of preoperative exposure to carbon monoxide.

Changing the carbon dioxide absorbent in the second case eliminated the presence of the contaminating gas identified as "enflurane" without alteration of the vaporizer settings or contents. This is also consistent with anesthetic breakdown in the carbon dioxide absorbent, because fresh soda lime or Baralyme has sufficient water to prevent anesthetic breakdown.[1,8] In addition, the reaction was noted only during moderately low-flow anesthesia, when the patient was able to rebreathe gases that have passed through the carbon dioxide absorbent.

Although the mechanism for carbon monoxide production was not known during the anesthetic for patient 1,‖ switching to high fresh gas flows eliminated the detection of the gas identified as "enflurane." High fresh gas flows may actively dry the carbon dioxide absorbent, but high flows also reduce the rebreathing of gas that has traversed the carbon dioxide absorbent. The gases that have passed through the carbon dioxide absorbent would contain carbon monoxide if anesthetic breakdown with subsequent carbon monoxide production has occurred. This has significant safety implications, because the Anesthesia Patient Safety Foundation has recommended low-flow anesthesia for maintaining humidity and preventing drying of the carbon dioxide absorbent.‖ If the absorbent has been dried previously by inadvertently passing dry gas through the absorbent overnight, low-flow conditions may expose the anesthetics to dry absorbent before sufficient water has accumulated to prevent the anesthetic breakdown. Because rebreathing gas that has passed through the carbon dioxide absorbent is a requirement for patient exposure to carbon monoxide if anesthetic breakdown occurs in a circle system, one should be especially vigilant in observing any indicators of anesthetic breakdown during low-flow anesthesia.

No operating room monitor is available for carbon monoxide, but the detection of mixed halogenated agents during isoflurane anesthesia is a clinically useful finding. If a halogenated gas mixture is noticed by mass spectrometry during isoflurane anesthesia, further investigation into the potential for anesthetic gas breakdown and carbon monoxide exposure should be conducted intraoperatively. Because the breakdown of enflurane and desflurane results in greater levels of carbon monoxide production than that resulting from breakdown of isoflurane,[2] the risk of carbon monoxide exposure from these anesthetics is greater. Future studies should be conducted to determine whether the breakdown of enflurane and desflurane would be revealed by mass spectroscopic analysis. Finally, the ability of other types of gas monitors, such as infrared analyzers or Raman spectroscopy, to detect anesthetic breakdown or carbon monoxide should be determined.

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Epidural Anesthesia Complicating Continuous 3-in-1 Lumbar Plexus Blockade

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CONTINUOUS 3-in-1 lumbar plexus blockade is a safe and reliable technique for providing postoperative analgesia after open knee,[1,2] femoral shaft,[3] or hip surgery.[4,5] Serious complications have been described in only two cases: a severe postoperative femoral neuropathy[6] and an acute compression syndrome of the femoral nerve caused by a subfascial hematoma.[7]

We report a case of epidural anesthesia complicating a continuous 3-in-1 blockade performed to provide postoperative analgesia after elective total hip replacement.

Case Report

A 65-yr-old, 174-cm, 80-kg woman, ASA physical status 2, was admitted for elective right total hip replacement. She was taking propranolol for chronic atrial fibrillation and doxepin for psychotic depression. At the time of surgery, her physical examination and preoperative laboratory investigation results were normal. Her blood pressure was 1,38/80 mmHg, and her heart rate was 64 beats/min. Atrial fibrillation with a slow ventricular response rate was detected by electrocardiography.

The patient was premedicated with 2 mg lormetazepam orally and 0.5 mg atropine intramuscularly.

After administration of oxygen by mask and insertion of a 16-G intravenous catheter, a pulse oximeter, a radial arterial catheter, and an electrocardiogram monitor were applied. Anesthesia was induced intravenously with 15 μg sufentanil, 160 mg propofol, and 100 mg succinylcholine. The trachea was intubated without difficulty with an 8 mm-ID cuffed orotracheal tube, and controlled ventilation was started. Pulmonary auscultation and capnography were normal. Anesthesia was maintained with sufentanil infused at a rate of 0.005 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and a mixture of nitrous oxide (66%) and isoflurane (0.3–0.5%) in oxygen.

Before surgery but under general anesthesia, a continuous 3-in-1 blockade was performed to provide postoperative analgesia. With the patient's verbal informed consent, she was included in a study assessing the relationship between the length of introduction of the 3-in-1 catheter into the psoas compartment and the success rate of the technique. She was the first patient of the group: "as cephalad as possible."

Continuous 3-in-1 blockade was performed following Winnie's landmarks.[8] The femoral artery was located just below the inguinal ligament, and an 18-G short bevelled cannula (Alphaplex set, Sterimed, Saarbrucken, Germany) was inserted just lateral to the artery. The femoral nerve was accurately located with a peripheral nerve stimulator (Anaestim MK III, Meda, Belgium). The needle was removed from the cannula, and a semi-rigid wire composed of a metallic core covered by an external, longer plastic sheath was easily pushed through the cannula into the psoas compartment as far cephalad as possible. The cannula was removed, and a 20-G end-hole catheter was threaded on the wire into the psoas compartment at the same depth (24 cm) using a Seldinger technique. After a negative aspiration test for blood and cerebrospinal fluid and a negative test dose of 3 ml 0.25% bupivacaine with 1/200,000 epinephrine, 37 ml of the same solution were injected. The patient was positioned on her left side, and surgery was started. During the procedure, moderate hypotension (systolic/diastolic blood pressure 80–100/45–55 mmHg) and bradycardia (heart rate 50–65 beats/min) were observed. A total dose of 10 mg ephedrine and 0.25 mg atropine and moderate fluid

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