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Lack of Degradation of Sevoflurane by a New Carbon Dioxide Absorbent in Humans

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Background: **Potent inhaled anesthetics degrade in the presence of the strong bases (sodium hydroxide or potassium hydroxide) in carbon dioxide (CO_2) absorbents. A new absorbent, Amsorb (Armstrong Medical Ltd., Coleraine, Northern Ireland), does not employ these strong bases. This study compared the scavenging efficacy and compound A production of two commercially available absorbents (soda lime and barium hydroxide lime) with Amsorb in humans undergoing general anesthesia.**

Methods: **Four healthy volunteers were anesthetized on different days with desflurane, sevoflurane, enflurane, and isoflurane. End-tidal carbon dioxide ($ETco_2$) and anesthetic concentrations were measured with infrared spectroscopy; blood pressure and arterial blood gases were obtained from a radial artery catheter. Each anesthetic exposure lasted 3 h, during which the three fresh (normally hydrated) CO_2 absorbents were used for a period of 1 h each. Anesthesia was administered with a fresh gas flow rate of 2 l/min of air:oxygen (50:50). Tidal volume was 10 ml/kg; respiratory rate was 8 breaths/min. Arterial blood gases were obtained at baseline and after each hour. Inspired concentrations of compound A were measured after 15, 30, and 60 min of anesthetic administration for each CO_2 absorbent.**

Results: **Arterial blood gases and $ETco_2$ were not different among three CO_2 absorbents. During sevoflurane, compound A formed with barium hydroxide lime and soda lime, but not with Amsorb.**

Conclusions: **This new CO_2 absorbent effectively scavenged CO_2 and was not associated with compound A production.**

CARBON dioxide (CO_2) absorbents cause all potent inhaled anesthetics to degrade.[1,2] The initial step in this degradation is removal of a labile proton. Most commercial absorbers contain the alkali bases, potassium or sodium hydroxide. Degradation of the anesthetics is slightly greater with absorbents containing a higher composition of potassium hydroxide.[3] Barium hydroxide lime (Baralyme; Collins Medical Inc., Braintree, MA) contains 12% barium hydroxide and 6% potassium hydroxide and degrades the anesthetics to a greater extent than does soda lime (which contains less potassium hydroxide and some sodium hydroxide).[4] The reaction of halothane and sevoflurane with carbon dioxide absorbents results in degradation of these anesthetics to haloalkenes.[5–7] Halothane degrades to form trace amounts of BCDFE (2-bromo-2-chloro-1,1-difluoroethene), and sevoflurane degrades to form trace amounts of compound A (2-(fluoromethoxy)-1,1,3,3,3-pentafluoro-1-propene). Although clinically significant renal effects of haloalkene formation in surgical patients have not been reported, these haloalkenes have been shown to be nephrotoxic in rats.[8,9] Desflurane, enflurane, and isoflurane degradation to carbon monoxide occurs when the CO_2 absorbent is dehydrated (approximately 90% of the water content must be removed).[3,10]

Recently, a new absorbent, Amsorb (Armstrong Medical Ltd., Coleraine, Northern Ireland), has been described that does not seem to be associated with the degradation of current volatile anesthetics.[11] *In vitro* testing shows no compound A formation when Amsorb is exposed to 2% sevoflurane at a fresh gas flow (FGF) of 1 l/min and no carbon monoxide formation when desflurane, isoflurane, or enflurane is administered through dehydrated CO_2 absorbents.[11] The essential change in the new absorbent is the removal of the strong bases (KOH and NaOH) from the absorbent. Calcium hydroxide forms the bulk of the absorbent (70%). Calcium chloride (0.7%) is a humectant along with two setting agents, calcium sulfate (0.7%) and polyvinyl pyrrolidine (0.7%). The moisture content is 14.5% by weight and is similar to soda lime and barium hydroxide lime.

This study extends the laboratory studies with the new absorbent, Amsorb, by evaluating its scavenging efficacy in human volunteers anesthetized with sevoflurane, enflurane, isoflurane, and desflurane. Sevoflurane degradation to compound A also was determined. Comparisons were made with commercially available CO_2 absorbents, soda lime, and barium hydroxide lime.

Materials and Methods

Four healthy volunteers (three women and one man) participated; all were classified as American Society of Anesthesiologists physical status I. After Institutional Review Board approval (VA Medical Center and Medical College of Wisconsin, Milwaukee, Wisconsin), healthy volunteers provided informed consent and participated on four occasions. Each session was separated by at least 1 week and consisted of a 3-h exposure to one minimum alveolar concentration (MAC) of a randomly assigned volatile anesthetic (enflurane, sevoflurane, isoflurane, or desflurane). During each hour of the 3-h anesthesia, one of three randomly assigned, fresh, normally hydrated CO_2 absorbents was used in the circuit: Amsorb, soda lime, or barium hydroxide lime.

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Table 1. End-tidal Carbon Dioxide (mmHg) during Anesthesia with Three Different Carbon Dioxide Absorbents

	15 min	30 min	45 min	60 min
Barium hydroxide lime				
Enflurane	41 ± 1	40 ± 2	40 ± 2	40 ± 2
Sevoflurane	38 ± 1	38 ± 2	38 ± 1	38 ± 1
Isoflurane	37 ± 3	37 ± 4	37 ± 4	37 ± 4
Desflurane	37 ± 2	37 ± 2	37 ± 2	37 ± 2
Soda lime				
Enflurane	39 ± 1	39 ± 1	39 ± 2	39 ± 2
Sevoflurane	37 ± 1	37 ± 1	37 ± 0	37 ± 0
Isoflurane	38 ± 4	37 ± 4	37 ± 4	37 ± 4
Desflurane	39 ± 1	39 ± 1	38 ± 1	38 ± 1
Amsorb				
Enflurane	39 ± 1	39 ± 2	39 ± 1	40 ± 1
Sevoflurane	37 ± 0	37 ± 1	37 ± 1	37 ± 1
Isoflurane	37 ± 4	38 ± 4	40 ± 5	39 ± 6
Desflurane	38 ± 2	37 ± 1	37 ± 2	37 ± 2

Mean ± SD.

The volunteers were screened within 1 day before anesthesia. The experimental session began after a radial arterial catheter was placed and standard American Society of Anesthesiology monitors were applied. Thirty milliliters of a nonparticulate antacid were administered. General anesthesia was established with 2.5 mg/kg propofol, and endotracheal intubation was aided with 0.1 mg/kg rocuronium bromide. Mechanical ventilation was established at a tidal volume of 10 ml/kg and a respiratory rate of 8 breaths/min. End-tidal carbon dioxide (ET_{CO_2}) and anesthetic concentrations were monitored *via* infrared spectrometry. Arterial blood gases were obtained at awake baseline and at the end of each hour of the 3-h anesthetic just before switching the absorbent from one to another. Carboxyhemoglobin concentrations were determined by cooximetry. The mean arterial blood pressure was maintained above 60 mm Hg at all times during general anesthesia and aided by head-down tilt, intravenous fluid boluses, and the use of pressors as needed.

During the sevoflurane trial, at an FGF of 2 l/min, compound A was measured at 15, 30, and 60-min intervals for each absorbent. Inspiratory limb gas samples were taken from an airtight stopcock system positioned at the junction of the plastic inspiratory hosing with the anesthesia CO_2 absorber. Samples were drawn into 5-ml syringes, injected into airtight 30-ml glass vials, and mailed overnight to Seattle (the laboratory of Evan Kharasch, M.D., Ph.D., University of Washington, Seattle, WA) for analysis within 36 h of collection. Compound A concentrations were determined by gas chromatography with flame ionization detection using the same validated assay as described previously.[1] The limit of quantification of this assay is 1.5 ppm, and the coefficients of variation are 8.5% (4.4% bias), 8.7% (6.0% bias), and 8.5% (4.4% bias) in standard addition and recovery experiments at compound A concentrations of 4, 9, and 32 ppm, respectively (n = 4).

Statistical Analysis

Data presented are mean ± SD (and ranges, where indicated). Repeated-measures analysis of variance was performed to determine differences among absorbents and anesthetics. A level of significance less than 0.05 was chosen.

Results

With the exception of compound A, there were no significant differences in any variable in response to the four anesthetics and the three absorbents. There were no differences in arterial blood gases at any measurement time for any anesthetic or absorbent. The mean values of pH, partial pressure of oxygen (P_{O_2}), and bicarbonate for all anesthetics and absorbents were 7.4 ± 0.0, 196 ± 24 mm Hg, and 24.6 ± 1.7 mEq, respectively. There were no significant differences in ET_{CO_2}, recorded every 15 min, among the three absorbents exposed to the four different anesthetics (table 1). Arterial CO_2 partial pressure (Pa_{CO_2}) was measured at the end of every hour of exposure to each absorbent and was not different among anesthetics or absorbents (mean, 39.6 ± 2.8 mm Hg). Baseline levels of carboxyhemoglobin were negligible, averaging 0.4%, and did not change with any of the three normally hydrated absorbents when exposed to different anesthetics.

There was significant formation of compound A, detected from the inspired limb, during sevoflurane administration with soda lime and barium hydroxide lime (fig. 1). This contrasted markedly and significantly to the lack of compound A formation when Amsorb was the CO_2 scavenger (fig. 1).

Discussion

This study provides the first clinical evaluation of a novel CO_2 absorbent that does not cause sevoflurane

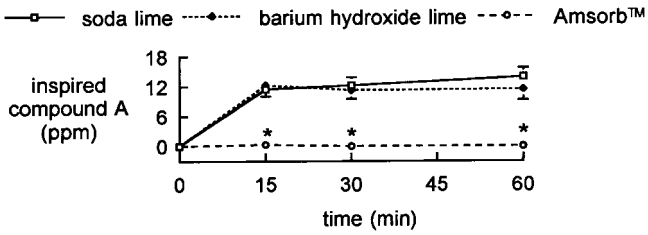

Fig. 1. Compound A concentrations produced from three carbon dioxide absorbents during sevoflurane anesthesia in volunteers (mean ± SEM). Gas samples were taken from the inspired limb of the anesthesia circuit. *Different from barium hydroxide lime or soda lime ($P < 0.05$).

degradation to compound A, presumably because of the absence of sodium and potassium hydroxide as scavenging bases. During 2.4% (1 MAC) sevoflurane in an FGF of 2 l/min, there was no detectable compound A formation when using Amsorb, in contrast to significant concentrations of compound A noted with soda lime and barium hydroxide lime absorbents. The three absorbents were equally effective in scavenging CO_2. We were unable to detect carboxyhemoglobin formation with isoflurane, desflurane, or enflurane, although, for ethical reasons, the experiment was not designed to maximize the potential for carbon monoxide production (*i.e.*, we did not dessicate [remove the normal water content from] the absorbents).

The mechanism of anesthetic degradation by standard CO_2 absorbents recently has been reviewed.[2] The presence of strong bases (sodium hydroxide and potassium hydroxide) in CO_2 absorbents results in removal of a labile proton from the anesthetics and serves as the first step in anesthetic degradation. The formation of compound A with sevoflurane is enhanced by drying and by increasing the temperature of the absorbent. Amsorb does not contain NaOH or KOH. Instead, calcium hydroxide is mixed with calcium chloride. The calcium chloride provides the moisture (water) that is essential for the first step of CO_2 removal (by forming carbonic acid). Subsequently, calcium hydroxide combines with the carbonic acid to form calcium carbonate and regenerates hydrated calcium chloride (or regenerates sodium and potassium hydroxide with conventional absorbents).

Degradation of anesthetics has led to safety concerns, and these concerns have led to considerable discussion and debate in the anesthesia literature.[12–16] In the case of sevoflurane, high concentrations of compound A administration to rodents have resulted in renal injury.[17,18] In one human volunteer study, the use of barium hydroxide lime resulted in transient subclinical renal effects during prolonged sevoflurane administration.[19] However, this was not confirmed in subsequent work.[20,21] Based on theoretical concerns, the Food and Drug Administration has limited potential human exposure to compound A by recommending that FGF less than 1 l/min be avoided to reduce the level of compound A during sevoflurane administration. However, in the majority of countries that use sevoflurane, no FGF restriction has been applied to the use of sevoflurane.

In summary, the formation of compound A during sevoflurane anesthesia with the use of barium hydroxide lime or soda lime absorbent did not occur during sevoflurane anesthesia with Amsorb absorbent. Earlier *in vitro* evaluations also indicate that Amsorb prevented compound A formation at lower FGFs. These findings support the concept that replacement of the strong alkali in the granules of currently used absorbents renders this new absorbent effective in preventing the degradation of sevoflurane to compound A.

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