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## Putting the Brakes on Anesthetic Breakdown

HOW many articles do we read in ANESTHESIOLOGY that may actually change our clinical practice? In this issue, Murray *et al.*<sup>1</sup> present data that may solve an important clinical problem and resolve a controversy that has contentiously divided the specialty for several years.

Currently used carbon dioxide (CO<sub>2</sub>) absorbents can degrade halothane and sevoflurane to haloalkenes (BCDFE and compound A, respectively), which are nephrotoxic in rats, although clinically significant renal effects of haloalkene formation in surgical patients have not been found.<sup>2-4</sup> Currently used CO<sub>2</sub> absorbents can also degrade some anesthetics (desflurane, enflurane, and isoflurane) to carbon monoxide (CO), resulting in occasional patient exposures to toxic CO concentrations.<sup>5</sup> Rare instances of severe CO poisoning, and in at least one case, known patient injury has been reported after desflurane administration.<sup>6-8\*</sup> Anesthetic degradation and associated concerns regarding patient safety have necessitated changes in clinical practice and product labeling and have been the focus of more than 100 laboratory and clinical reports, several editorials in this journal,<sup>9-13</sup> scholarly debates, public and private arguments and letters, anesthetic manufacturers' marketing and lobbying campaigns, and hearings by the Food and Drug Administration and international regulatory agencies.

This Editorial View accompanies the following article: Murray JM, Renfrew CW, Bedi A, McCrystal CB, Jones DS, Fee JPH: Amsorb: A new carbon dioxide absorbent for use in anesthetic breathing systems. *ANESTHESIOLOGY* 1999; 91:1342-8.

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\* Food and Drug Administration, Spontaneous Reporting System.

The central focus of the issue is chemical degradation of volatile anesthetics by the strong bases in CO<sub>2</sub> absorbents. The initial step in anesthetic degradation is removal of a labile proton. Strong alkali bases such as potassium (in particular) and sodium hydroxide are required to initiate the reaction that forms CO, whereas weaker divalent hydroxides such as barium hydroxide do not catalyze the reaction.<sup>14</sup> Hence, barium hydroxide lime (which contains potassium but not sodium hydroxide) forms more CO than does soda lime (which contains less potassium hydroxide and some sodium hydroxide). Similarly, barium hydroxide lime causes greater sevoflurane degradation to compound A than does soda lime.

Additional factors that influence anesthetic degradation to CO include anesthetic structure (a difluoromethoxy moiety, as found in desflurane, enflurane, and isoflurane, is required for CO formation), absorbent temperature (higher temperatures increase CO formation), and absorbent water content (CO formation requires partially dried or fully desiccated absorbents).<sup>14-16</sup> Additional factors that influence formation of compound A include absorbent water content and temperature, CO<sub>2</sub> production, and fresh gas flow rates, with greater formation of compound A at lower flows.<sup>17</sup>

As a result of concerns over the renal effects of compound A formation and the influence of fresh gas flow rates, and concerns over CO formation and the critical role of absorbent water on CO production, the Food and Drug Administration has made specific recommendations regarding product labeling. The original package label for sevoflurane contained a warning stating that, because of limited clinical experience, flow rates less than 2 l/min were not recommended. In October 1998, this was revised to suggest that flow rates of 1 l/min were acceptable but should not exceed 2 minimum alveolar concentration-hour, and

## EDITORIAL VIEWS

flow rates less than 1 l/min were not recommended. The package label for anesthetics such as desflurane and isoflurane was changed† to include a precaution that when a practitioner suspects that the CO<sub>2</sub> absorbent may be desiccated, it should be replaced.

The fallacy in the latter warning, of course, is that we have no clue when CO<sub>2</sub> absorbents become partially dried or fully desiccated. Absorbents contain a dye that does indicate when the CO<sub>2</sub> scavenging capacity is exhausted, but none that indicates when drying or desiccation has occurred. Unless a CO monitor is installed on an anesthesia machine or CO-hemoglobin concentrations are routinely measured, there is no way to reliably detect CO exposure or CO poisoning. We cannot rely on clinical signs of CO toxicity, and pulse oximeters are grossly insensitive.

Several attempts to prevent anesthetic degradation or its consequences have been made, albeit with mixed results. Cooling the soda lime decreased formation of compound A *in vitro* but was less successful in a clinical trial.<sup>18,19</sup> Deuterated sevoflurane was synthesized as a potential alternative to the original molecule.<sup>20</sup> Adding additional water (perhydration) to soda lime or using partly exhausted soda lime did effectively diminish production of compound A<sup>21</sup>; however, these methods lack clinical utility. Molecular sieves are an alternative CO<sub>2</sub> absorbent and do not degrade sevoflurane to compound A<sup>22</sup>; however, they are adversely affected by water vapor and nitrous oxide. Replenishing water in desiccated CO<sub>2</sub> absorbent prevented desflurane degradation to CO,<sup>23</sup> but one must first know that desiccation has occurred. It was recommended that new anesthetics not contain a difluoromethoxy group, to render them unsusceptible to degradation to CO,<sup>14</sup> but this offers no solution to degradation of currently used anesthetics.

In this issue of ANESTHESIOLOGY, Murray *et al.* describe a new CO<sub>2</sub> absorbent that does not contain strong base and report a laboratory investigation showing that the new absorbent does not degrade currently used volatile anesthetics. Like soda lime and barium hydroxide lime, the new absorbent (Amsorb, Armstrong Medical Ltd., Coleraine, Northern Ireland; henceforth referred to as calcium hydroxide lime) contains predominantly calcium hydroxide. By adding calcium chloride to the absorbent to retain water, essential for the proper scavenging of CO<sub>2</sub>, the need for potassium or sodium hydroxide (previously used to retain water) is obviated. The CO<sub>2</sub>

scavenging capacity of calcium hydroxide lime was retained at 85–90% of that of currently used absorbents. In contrast, and of extraordinary importance, is that calcium hydroxide lime did not degrade sevoflurane to compound A, or desflurane, enflurane, or isoflurane to CO, even when desiccated.

This apparent solution to anesthetic degradation is elegant in its simplicity—simply remove the offending strong base. No doubt the actual formulation process was far more complex, particularly the identification of a method to retain absorbent water, and I do not mean to imply that the effort was trivial. In an era of highly technical science, it is almost refreshing to find no molecular biology, no cloning, no receptor assays, no complex computer modeling, no electrophysiology, no outcomes research, no economic analyses, not even organic chemistry. Nevertheless, the contributions to anesthesiology, and the potential clinical implications, are substantial. Of course, the results of this laboratory investigation must be confirmed in clinical evaluations of calcium hydroxide lime to substantiate the scavenging efficacy and lack of anesthetic degradation.

An effective CO<sub>2</sub> absorbent that does not degrade anesthetics is not yet available in the United States. If and when it does reach the market, it could, and should, change the way clinicians deliver inhalation anesthesia, both domestically and worldwide. From a patient-safety perspective, widespread adoption of a nondestructive CO<sub>2</sub> absorbent should be axiomatic. Assuming a reasonable and only marginally increased cost over currently used absorbents, economic arguments against a nondestructive absorbent should be moot: it represents a minute portion of total perioperative costs and might even be more cost-effective after considering medicolegal implications, potentially revised gas flow rates, and the need to replace desiccated absorbents. Use of a nondestructive CO<sub>2</sub> absorbent could lead the Food and Drug Administration to revise its warnings about volatile anesthetic degradation. These changes may affect us all.

**Evan D. Kharasch, M.D., Ph.D.**

Professor of Anesthesiology and Medicinal Chemistry  
(Adjunct)

Departments of Anesthesiology and Medicinal  
Chemistry

University of Washington  
Seattle, Washington 98195

Anesthesiology Service

Puget Sound Veterans Affairs Healthcare System  
Seattle, Washington 98108

kharasch@u.washington.edu

† Bedford RF: Note from the FDA (abstract). ANESTHESIOLOGY 1995; 83:33A.

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