Issues in Anesthetic Degradation and Toxicity

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ANESTHETIC DEGRADATION

"Out of sight, out of mind" is perhaps the most apt phrase to describe where the carbon dioxide absorbent resides in the universe of considerations and concerns of the average anesthesia practitioner. While certainly understandable, relative to issues like patient, surgical and anesthetic considerations, and even the more visible and vital parts of the anesthesia machine, the CO_2 absorbent is nonetheless not inert, and not immune from safety considerations. Indeed, the last decade has witnessed considerable concern about the consequences and safety of volatile anesthetic interactions with CO_2 absorbents. All currently used volatile anesthetics interact with CO_2 absorbents and undergo degradation. This lecture will highlight the mechanism, consequences, safety considerations, and prevention, of volatile anesthetics interaction with and degradation by CO_2 absorbents.

CO_2 Absorbents

Understanding the composition of CO_2 absorbents is essential to understanding their interaction with volatile anesthetics. The Table below lists the approximate composition of several absorbents, based on several publications and manufacturers' information. The earlier versions of most absorbents contained the strong bases potassium hydroxide (KOH) and/or sodium hydroxide (NaOH).

Composition of carbon dioxide absorbents (weight%)

CO_2 absorbent	$Ca(OH)_2$	KOH	NaOH	$Ba(OH)_2$	$CaCl_2$	H_2O
Baralyme®	69	5	-	10	-	15
Sodalime I	76	2	2	-	-	19
Sodalime II	76	-	2	-	-	19
Drägersorb Free®	74–82	-	<2	-	3–5	14–18
Amsorb®	>75	-	-	-	0.7	14
Amsorb Plus®	>75	-	-	-	0.7	14

All currently used volatile anesthetics undergo chemical degradation, within the anesthesia machine, by CO_2 absorbents which contain the strong bases sodium and/or potassium hydroxide. Sevoflurane degradation results in the formation of a haloalkene called 'compound A'. Desflurane, enflurane and isoflurane are degraded to carbon monoxide (CO). Under very extreme circumstances, sevoflurane can also be degraded to CO.

The two most important factors which determine anesthetic degradation are the content and identity of strong base in the absorbent, and the degree of hydration (or conversely, desiccation). KOH causes more degradation than NaOH, hence absorbents containing more KOH will cause more degradation. Baralyme®, which contains more KOH, caused more anesthetic degradation than other absorbents. Absorbents only degrade anesthetics to CO when they lose their water of hydration (dry out). Hence, the most important messages for a practitioner are:

1) Use a CO_2 absorbent which does not contain strong base whenever possible.
2) Never let an absorbent which does contain strong base dry out (become desiccated).

Sodasorb brand of soda lime (WR Grace) was reformulated in January 2000, and the potassium hydroxide was removed. Amsorb®, which contains no strong base, was introduced in approximately 1999, and replaced within the past few years by a reformulated version which has greater CO_2 absorbing capacity. Baralyme® was withdrawn from the market by its manufacturer in August, 2004. Any Baralyme® held by distributors was to be removed. The manufacturer stated that they would pursue development of a new CO_2 absorbent, and that they would not manufacture, distribute, promote, market, sell, commercialize, donate, develop or license Baralyme® or any similar product containing potassium hydroxide.

Absorbents can become desiccated when the fresh gas flow is left on (usually at high flows, several L/min) for more than a day or two. The longer the flow of gas through an absorbent, the more desiccated it becomes. A typical 'set-up' for a potentially disastrous scenario involving anesthetic degradation is a machine which is left on over a weekend. That is why many problems have occurred at (but are not limited to) the first case of the day. Anesthesia

machines in less frequently used locations (radiology, OB) are at greater risk for desiccation. It is crucial to understand that there is no indicator in a CO_2 absorbent which shows when it has become desiccated or partially desiccated. This is unlike the indicator (typically turning from colorless to blue) which shows when the CO_2 absorbing capacity is exhausted. Therefore, if using an absorbent which contains strong base, it is important to turn off the anesthesia machine at end of day, and especially over a weekend; replace the absorbent if there is any suspicion that it is desiccated, consider changing the CO2 absorbent at regular intervals (ie on Mondays); and educate anesthesia technicians or other OR personnel that there is nothing wrong with condensation in a CO_2 absorbent canister, and there is no need to turn on the fresh gas flow at the end of a day to 'dry out' the absorbent. **Nevertheless, the absolute safest way to prevent anesthetic degradation is to use a CO_2 absorbent which does not contain strong base.**

Carbon Monoxide Toxicity

Concerns about anesthesia-related carbon monoxide (CO) toxicity are founded on actual clinical experience. CO production from volatile anesthetic degradation in anesthesia circuits is a safety issue which has necessitated changes in clinical practice and product labeling. Desflurane, enflurane, and isoflurane are degraded to CO by desiccated and partially desiccated absorbents which contain strong base. Desflurane produces the highest CO concentration, followed by enflurane and isoflurane. Under very rare conditions, sevoflurane can also be degraded, forming large amounts of CO. Higher CO formation occurs with higher CO_2 absorbent temperature, Baralyme vs soda lime, and higher anesthetic concentration. No anesthetic is degraded to CO by fully hydrated absorbents, or by absorbents not containing strong base.

A common scenario for CO exposure is a first case on Monday morning, using an anesthesia machine idled for 2 days with fresh gas flowing. Current EPA limits for CO exposure are 35 and 9 ppm for 1- and 8-hour exposures, respectively. Several cases of CO poisoning with desflurane, enflurane, isoflurane, or sevoflurane, with some CO concentrations > 1000 ppm, and toxic COHb levels of 30% have been described. A prospective analysis showed that the incidence of CO exposure was 0.5% for the first case of the day (2.9% in remote locations other than operating rooms) with an overall incidence of 0.3%.

CO toxicity is dependent on inhaled CO concentration and exposure duration. Toxic effects of CO are well-described. CNS consequences include headache, nausea, vomiting, dizziness, visual/motor disturbances, diminished consciousness, and delayed neuropsychologic sequelae. Intraoperative and postoperative detection of CO toxicity is extremely difficult. Pulse oximetry cannot detect either COHb or true arterial oxyhemoglobin (O_2Hb) desaturation because pulse oximeters cannot distinguish between COHb and O_2Hb. Mental status changes are masked or mimicked by typical postoperative patient symptoms (neadache, nausea, vomiting).

Practitioners are cautioned by the FDA to replace carbon dioxide absorbent which they suspect may be desiccated. Some prophylactically change absorbent at predetermined intervals.

"Compound A" Formation

Sevoflurane degradation results in the formation of 'compound A'. This occurs with both 'wet' and desiccated absorbents containing strong base. Factors increasing compound A formation include higher CO_2 absorbent temperature, higher sevoflurane concentration, use of Baralyme® vs soda lime, lower fresh gas flows, and higher CO_2 production. Negligible amount of compound A are formed by absorbents not containing strong base. In surgical patients, peak inspired compound A concentrations during low-flow and closed circuit sevoflurane anesthesia average 8-24 ppm and 20-32 ppm with soda lime and Baralyme, respectively. Total compound A exposures average 80 ppm-hr for 3-4 MAC-hr sevoflurane.

Compound A is nephrotoxic in rats. It causes proximal tubular necrosis and elevations in serum BUN and creatinine, and increased urine protein excretion. The threshold for renal injury in rats is approximately 330 ppm-hr.

Compound A formation during sevoflurane anesthesia in surgical patients has been extensively evaluated and found to have no clinically significant effects. Studies have typically compared low-flow sevoflurane with low-flow isoflurane and/or high-flow sevoflurane. In none of the published studies using low-flow or closed-circuit sevoflurane, were there any differences between anesthetics in postoperative renal function as assessed by the

standard markers of BUN, creatinine, and creatinine clearance, even in the patients with the highest compound A exposures (up to ~400 ppm-hr). In patients undergoing very long procedures, proteinuria was seen in one investigation, but not in any of the others. Proteinuria can also be seen after anesthesia with other agents. Most recently reported were the effects of compound A formation during low-flow sevoflurane anesthesia on patients with preexisting renal insufficiency, a known risk factor for postoperative renal dysfunction. Although these patients are at greater risk, there was no difference between low-flow sevoflurane and isoflurane on postop renal function.

Renal effects of compound A exposure have also been examined in normal human volunteers. Studies compared low-flow sevoflurane and desflurane, or evaluated low-flow sevoflurane alone. The results are highly controversial. Four investigations studied high concentration (3%), moderate (4 hr) or long duration (8hr), low-flow (2 L/min) sevoflurane in fluid restricted, hypotensive volunteers. Eger *et al* reported severe albuminuria, glucosuria and enzymuria, and claimed glomerular, proximal and distal tubular injury. In contrast, Ebert *et al* using the same protocols found no significant effects of low-flow sevoflurane on albuminuria, glucosuria or enzymuria, and no evidence of renal toxicity. Neither found postoperative changes in serum creatinine. Explanations for these profound differences are not apparent, and the relevance of these volunteer studies to surgical anesthesia is unknown. Renal effects of compound A in healthy volunteers remain the only 'controversy' about compound A.

The current labeling for sevoflurane states that flow-flow anesthesia of >2 MAC-hr is not recommended, as are flow rates < 1 L/min. There is not data in patients to support these restrictions, which were written before many low-flow studies were published. This was also written before soda lime was reformulated, Baralyme® was withdrawn from the market, and Amsorb® became available.

Strongly Exothermic Reactions and Fire

The most extreme visual example of the interaction of volatile anesthetics with CO_2 absorbents is the interaction of sevoflurane with extremely desiccated absorbent. Several cases have been reported recently, of extreme heat or fire in the respiratory circuit when sevoflurane was used with desiccated CO_2 absorbent. Most cases occurred with Baralyme®, however it has been reported to have occurred with a soda lime product in Europe. In general, the reaction of sevoflurane with desiccated absorbent generates more heat than the degradation of other anesthetics. In the extreme examples reported, extremely hot CO_2 canisters, melted CO_2 canister plastic, burning respiratory circuit plastic, tracheal burns, and/or contained explosions have occurred. These rare reactions result from the interaction of extremely desiccated absorbent with sevoflurane, and have not been reported for other anesthetics.

Anesthetic destruction

Another consequence of anesthetic degradation by CO_2 absorbent in anesthesia machines is destruction of volatile anesthetic per se, thereby diminishing inspired concentrations. Loss of inspired anesthetic may increase cost and/or adversely affect anesthetic induction or maintenance. Specifically, cases of delayed sevoflurane inhalation induction due to degradation have been reported.

Prevention

Desiccated absorbents, and those containing strong base, degrade volatile anesthetics. The best method to prevent this is to use a CO_2 absorbent which does not contain strong base. If one does use an absorbent which contains strong base, meticulous care should be taken to prevent its desiccation. Desiccated absorbent should be immediately replaced. Absorbents which do not contain strong base do not constitute a risk when they become desiccated.

ANESTHETIC METABOLISM

Anesthetic Hepatotoxicity

Fulminant hepatic necrosis and jaundice after halothane ("halothane hepatitis") is rare (1 in 6,000-35,000 anesthetics) but often fatal. Halothane hepatitis is an immunologic phenomenon initiated by halothane metabolism and the binding of its metabolite to liver proteins forming trifluoroacetylated proteins, which, in susceptible individuals, stimulate the formation of antibodies. Upon subsequent halothane reexposure, these antibodies mediate massive hepatic necrosis. Because the extent of metabolism of enflurane, isoflurane, and desflurane is so much less

than that of halothane, fulminant hepatitis from enflurane, isoflurane, and desflurane is far less common than with halothane. Sevoflurane metabolism is different from that of the other volatile anesthetics, does not result in trifluoroacetylated liver proteins, and immune-based hepatitis after sevoflurane has not been reported. With the disappearance of halothane from clinical practice in developed countries, and lack of hepatotoxicity from either desflurane or sevoflurane, anesthetic hepatotoxicity does not appear to be a significant clinical concern.

Anesthetic Nephrotoxicity

Anesthetic nephrotoxicity was first observed with methoxyflurane, which caused high-output renal insufficiency, polyuria, and elevated BUN and creatinine. Methoxyflurane nephrotoxicity is clearly related to its metabolism, possibly to inorganic fluoride. In rats, induction or inhibition of methoxyflurane metabolism and fluoride production produced corresponding increases or decreases in renal toxicity. In humans, there was a significant correlation between methoxyflurane metabolism and the severity of renal dysfunction. No renal effects were observed at peak serum fluoride (F) <40μM; subclinical toxicity was accompanied by peak F of 50-80 μM; mild clinical toxicity was observed at 90-120 μM peak F, and overt nephrotoxicity occurred at 80-175 μM. The fluoride hypothesis was that methoxyflurane toxicity was caused by metabolism, and inorganic fluoride was the renal toxin.

With subsequent introduction of other fluorinated anesthetics, the methoxyflurane toxicity theory was generalized (albeit without supporting data) to all fluorinated anesthetics. A toxicity threshold of 50 μM plasma F evolved as a number of mythic proportions, even though 50 μM F after methoxyflurane were never accompanied by more than subclinical renal toxicity. All new anesthetics have been scrutinized for their potential to generate 50 μM F, and supposedly, renal toxicity.

Anesthetics introduced since methoxyflurane undergo substantially less metabolism. Extents of metabolism are: methoxyflurane (75%), enflurane (8%), isoflurane (0.1-2%), desflurane (0.02-0.2%), and sevoflurane (2-5%). Fluoride concentrations after 2-3 MAC-hr enflurane (20-30 μM), isoflurane (3-8 μM) and desflurane (unchanged) are much less than 50μM, and these anesthetics have no effect on renal function. Prolonged enflurane and isoflurane anesthesia can result in F>50μM, but adverse effects on renal function have not occurred. Approximately 15% of sevoflurane anesthetics result in peak plasma fluoride >50μM, and peak fluoride >100μM can occur with prolonged sevoflurane anesthesia (fluoride concentrations which mirror those after methoxyflurane). Nonetheless, numerous studies and postmarketing surveillance have shown that sevoflurane is not associated with nephrotoxicity. Evan in patients with preexisting renal insufficiency, a known risk factor for postoperative renal dysfunction, there appear to be no differences between the various available volatile anesthetics in their effects on renal function.

These findings are surprising, if the "classical" fluoride hypothesis and 50 μM toxic threshold are applicable to all anesthetics. Indeed, it now appears that they are germane only to methoxyflurane. The absence of renal toxicity with enflurane, isoflurane and sevoflurane despite F>50 μM has led to a rejection of the “classical” fluoride hypothesis. Lack of renal toxicity may be because: 1) the duration of systemic fluoride elevation, or area under the fluoride-time curve, is more important than the peak fluoride concentration, 2) intrarenal anesthetic metabolism may be more important than hepatic metabolism and plasma fluoride concentrations, and human kidneys metabolize methoxyflurane more than other anesthetics.

Most recently, it was shown that fluoride, when administered with other metabolites formed only by methoxyflurane, causes more toxicity than fluoride alone. This suggests a new mechanism of methoxyflurane toxicity. It may explain why increased fluoride formation from methoxyflurane, but not other anesthetics, is associated with renal toxicity. This may have implications for the interpretation of anesthetic defluorination, volatile anesthetics use, and methods to evaluate potential anesthetic toxicity.

None of the currently available volatile anesthetic agents are known to cause clinically significant changes in renal function. Fluoride nephrotoxicity from current anesthetics does not appear to be a concern.

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