

REVIEW ARTICLE

The mechanisms of carbon monoxide production by inhalational agents

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Summary

Carbon monoxide can be formed when volatile anaesthetic agents such as desflurane and sevoflurane are used with anaesthetic breathing systems containing carbon dioxide absorbents. This review describes the possible chemical processes involved and summarises the experimental and clinical evidence for the generation of carbon monoxide. We emphasise the different conditions that were used in the experimental work, and explain some of the features of the clinical reports. Finally, we provide guidelines for the prevention and detection of this complication.

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It has long been known that inhalation anaesthetic agents are broken down and that carbon monoxide (CO) can be formed by that breakdown in the presence of carbon dioxide (CO₂) absorbents. Initial anecdotal reports suggested that soda lime and Baralyme* absorbent (Table 1) could produce CO from inhaled anaesthetics. The first cases involved enflurane [1] and isoflurane [2]. Thirty-one cases of intra-operative CO poisoning were described, with some CO concentrations exceeding 1000 parts per million and carboxyhaemoglobin (COHb) concentrations reaching 30% or more. With desflurane, COHb concentrations of 32% were reported [3, 4]. *In vitro* experiments showed that with dried absorbents, CO production was in the following order: desflurane > enflurane > isoflurane and was trivial with halothane and sevoflurane [5]. Degradation appears to be inversely related to the water content of the absorbent and occurs more with Baralyme than with soda lime. It was shown *in vitro* that the rehydration of desiccated Baralyme prevents CO formation from desflurane [6]. A difluoromethoxy group is a structural requirement for halo ether degradation to CO [7]. The typical case of CO poisoning is the first patient on a Monday morning (Monday morning disease), when after the weekend an anaesthetic machine is used through

which high gas flows had been maintained, resulting in drying of the absorbent.

CO production

Early studies found that sevoflurane was less stable than might be desired and that it breaks down at a rate determined by temperature: 13% over 1 h at 40 °C and 56% at 60 °C [8]. Baralyme produced a four-fold greater degradation of sevoflurane than did soda lime (0.66 ml.min⁻¹ vapour vs. 0.17 ml.min⁻¹), inducing a slight delay at the start of anaesthesia [9]. Degradation to compound A was inhibited by chilling the soda lime canister to 26 °C [10]. Baralyme dehydration increased and soda lime dehydration decreased the concentration of compound A in an *in vitro* model [11]. Until 2000 it was thought that the breakdown of sevoflurane was more or less associated with the production of compound A and that among the inhalation anaesthetics, CO production was mainly associated with desflurane. Indeed, in pigs anaesthetised with desflurane, high COHb concentrations were found when the CO₂ absorbent was partially dried [12]. With dehydrated Baralyme, peak CO concentrations of 37 000 ± 3500 parts per million and COHb concentrations of > 80% were found. It came as a surprise when Holak *et al.* reported that, with sevoflurane in

*Baralyme was withdrawn from the market in August 2004.

Table 1 Brand and composition of CO₂ absorbents mentioned in this review.

Brand	Company	NaOH (%)	KOH (%)	Ca(OH) ₂ (%)	CaCl ₂ (%)	Ba(OH) ₂ (%)
Baralyme	Chemetron, St. Louis, MO	–	5.3	74	–	11
Soda lime	Several	2–4	1–3	94	–	–
Drägersorb 800	Dräger, Lübeck, Germany	2	3	79	–	–
DrägerSorb Free	Dräger, Lübeck, Germany	3–5	–	74–82	3–5	–
Sofnolime	Molecular product, Thaxed, UK	3	–	< 75	–	–
Amsorb	Armstrong, Coleraine, Northern Ireland	–	–	83	0.7	–
AmsorbPlus	Armstrong, Coleraine, Northern Ireland	–	–	83.2	0.7	–

specific experimental circumstances *in vitro*, the generation of 11 000 parts per million CO occurred, followed by an explosion and fire when the canister temperature exceeded 200 °C [13]. It is therefore of interest to review all the known *in vitro* and *in vivo* assessments concerning the production of CO, particularly with sevoflurane, and to describe the scarce clinical data on this problem.

Laboratory studies with small amounts of soda lime and strict temperature control

In an early effort to analyse the production of CO, barrels of simple 30-ml syringes were used with the open ends sealed with rubber corks, pierced with a needle through which gases were passed [5]. Dried and partially dried (1.4–9.7% water) absorbents (soda lime and Baralyme) were examined. Desflurane, enflurane and isoflurane were analysed at 25–45 °C, and halothane and sevoflurane at 45–60 °C. The magnitude of CO production was in the order: desflurane ≥ enflurane > isoflurane ≥ halothane = sevoflurane. Completely dry soda lime produced more CO than partially dry soda lime. Baralyme produced more CO than soda lime. An increased, controlled absorbent temperature increased CO production. At 60 °C the peak CO concentrations were only 79 parts per million with 3.6% sevoflurane (Table 2). In another study, sealed 20.7-ml vials were used which contained desiccated absorbent and a filter paper onto which anaesthetics were injected for volatilisation [7]. CO formation from desflurane, enflurane and isoflurane was greater with Baralyme (containing 4.6% potassium hydroxide) than with soda lime (containing only 2.5%

potassium hydroxide), probably through greater base-catalysed difluoromethoxy proton removal with potassium than sodium hydroxide (Fig. 1). Sevoflurane and halothane formed only negligible amounts of CO. These two laboratory studies with only small amounts of absorbents did not indicate any real problem from CO production with sevoflurane.

In vitro studies using clinical absorber systems

In more clinically relevant studies, larger amounts of CO₂ absorbents were studied in standard canisters with no control of absorbent temperature. Halothane, enflurane and isoflurane were assessed in a Dräger ISO system filled with completely dried CO₂ absorbent [14]. Peak CO of 3500 parts per million was recorded with enflurane and isoflurane. Although maximal CO concentrations of only 450 parts per million were found with halothane, the temperature increased to 50 °C and more. Interestingly, it took about 75 min to attain a measurable halothane concentration. These findings suggest that halothane is absorbed in dried soda lime, with an exothermic chemical reaction between the absorbent and the anaesthetic. In an almost identical study, desflurane, enflurane, isoflurane and sevoflurane were passed through completely dried Drägersorb 800 soda lime for 2–3 days [15]. In contrast to the hydrated CO₂ absorbent, with the dried absorbent a temperature increase was found with all the anaesthetics and was more pronounced with sevoflurane (120–130 °C) than with the other anaesthetics (desflurane 56–58 °C). Water condensation at the inspiratory valve was also noticed with sevoflurane and later also in the

Table 2 Peak CO concentrations in laboratory experiments.

Reference	Inhalation agent	Peak CO concentration (parts/10 ⁶)	Temperature	CO ₂ absorbent
Fang (1995) [5]	3.6% sevoflurane	79	60 °C	Soda lime
Strauss (1996) [14]	Enflurane/isoflurane	3500	52.1 °C	Soda lime
Stabernack (2000) [23]	Desflurane	36 000		Dried Baralyme
Wissing (2001) [25]	5% sevoflurane	1600	130 °C	Drägersorb 800
Holak (2003) [13]	2.1% sevoflurane	11 000	> 110 °C	Dried Baralyme

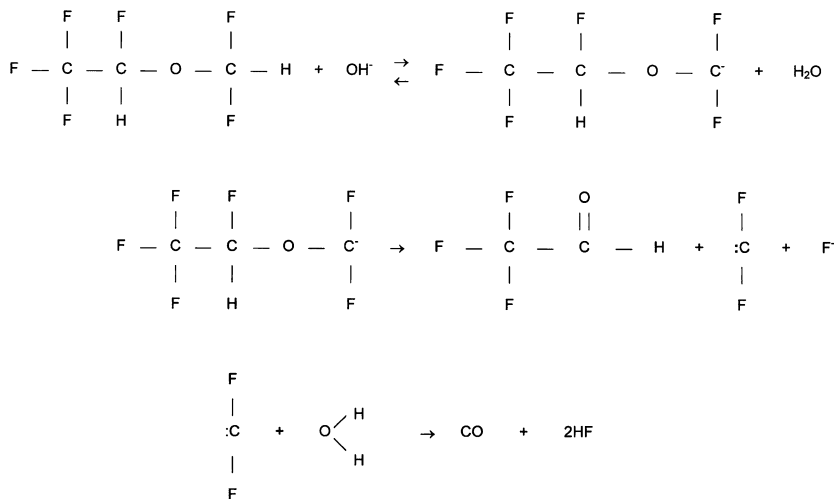


Figure 1 Simplified mechanism of carbon monoxide (CO) formation from desflurane (Baxter); the source of CO is the -CF₂ moiety.

breathing tubing. With dried CO₂ absorbent and sevoflurane, no sevoflurane could be detected for about 20 min, followed by a short-lasting overshoot (about twice the vapour dial). An irritating smell was also noticed. In a Dräger circle system, sevoflurane 8% in O₂ 6 l.min⁻¹ was washed into the canister in which there was previously dried Drägersorb 800 (containing potassium hydroxide (KOH)) or Sofnolime (KOH free) CO₂ absorbent [16]. With dry soda lime, sevoflurane could not be measured before 3 min but compound A and methanol were detectable after only 1 min, with an absorbent peak temperature of 110 °C. Formaldehyde was detected only with dry soda lime. Significant interaction with inhalation anaesthetics was not observed if the water content of the CO₂ absorbent was >5%. Sevoflurane degradation was aggravated by high KOH content of the lime. It was suggested that clinical airway irritation might be caused by formic acid, which is

generated with methanol by the Cannizzaro reaction (Fig. 2), in which certain aldehydes may undergo in concentrated alkali: one molecule of the aldehyde is reduced to the corresponding alcohol and another molecule is simultaneously oxidised to the salt of a carboxylic acid.

Animal studies

Baralyme was ‘conditioned’ by passing a 5 l.min⁻¹ O₂ flow through the canister for 40 h [17]. Pigs were anaesthetised with a rebreathing circuit containing the dehydrated Baralyme and using sevoflurane, aiming at an end-tidal concentration of 3.0–3.2%. Compound A peaked at a concentration of 357 parts per million and the Baralyme temperature at 310 °C. However, in one experiment the temperature rose very rapidly, reaching 401 °C after 80 min, the absorbent began to melt, smoulder and smoke appeared in the circuit. CO

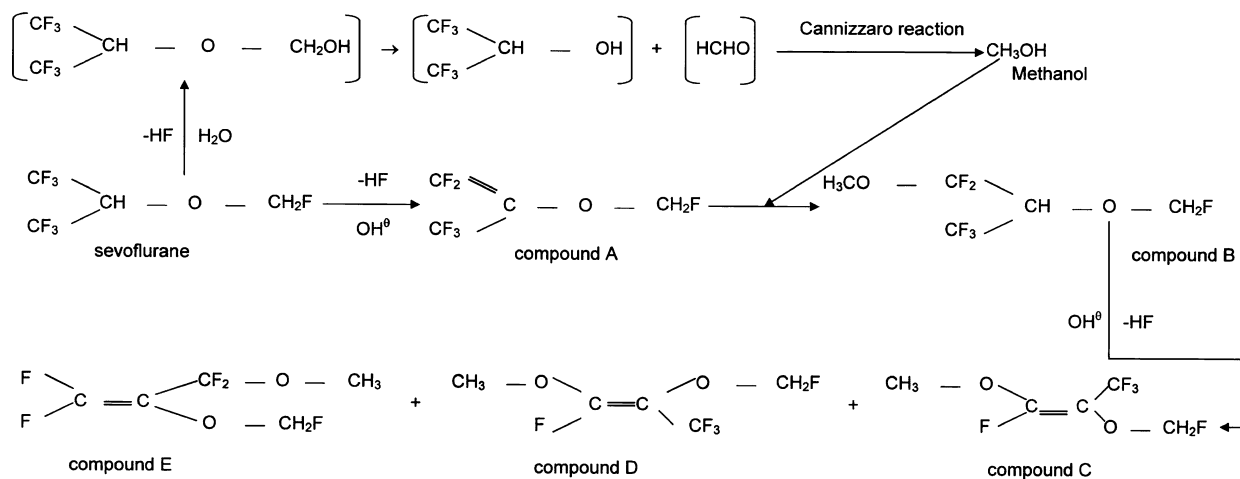


Figure 2 Cannizzaro reaction showing the production of methanol (from Morio *et al.* [21], with permission).

concentrations were not analysed. In the study by Frink *et al.* [12] Baralyme or soda lime dried for 24 or 48 h was used while anaesthetising pigs with desflurane in a conventional circle system. Extremely high COHb concentrations of >80% were found with Baralyme dried for 48 h. For CO₂ absorbents dried for 24 h, peak CO concentrations of 8800–13 600 parts per million were reached. Peak COHb concentrations of 73% for Baralyme and 53% for soda lime were recorded with absorbent temperatures of 50 °C. Sevoflurane was not assessed in this study.

Clinical information

In a large clinical trial of patients having low-flow anaesthesia, no evidence of accidental CO intoxication was found when the CO₂ absorbent was properly maintained [18]. Severe CO poisoning during desflurane anaesthesia has been reported [19]: in a 24-year-old woman during 5% desflurane anaesthesia in the presence of dehydrated Baralyme, the S_pO₂ decreased to 93% and HbO₂ to 63%, and 36% COHb was found. She recovered completely after immediate replacement of the Baralyme. Five cases were reported in which sevoflurane reacted with accidentally dried soda lime [20]. In a 14-year-old girl, despite a vapour concentration of 8% sevoflurane on the dial, an effective circuit concentration of less than 1% was found; the insufflation pressure was high at 45 cm H₂O and the O₂ saturation decreased to 81%, followed by coughing, tachycardia and cyanotic skin colouration. Arterial blood gas analysis revealed a COHb concentration of 4.4% (Table 3). The soda lime turned dark blue and subsequent analysis showed a water concentration of only 1.3%. The girl had to be ventilated for 1 day, and had coughing and mild dyspnoea for some days, but she had recovered completely by the 9th day. In a 2-year-old boy, induction with 4% sevoflurane by mask produced intense coughing and, despite an increase to 7% sevoflurane, induction was not successful in the next 15 min, with coughing and extreme salivation. It was noticed that the CO₂ absorbent had turned blue and that the canister was extremely hot, while a pungent smell

escaped. An arterial sample revealed a COHb concentration of 8.4%, which decreased to 3.4% after 3 h ventilation. Subsequent analysis of the soda lime showed that it was completely dry, as it had not been changed for 3 weeks. In another 2-year-old boy, induction with 7% sevoflurane by mask produced intense coughing and salivation. The breathing gases had an irritating smell, the breathing tubes were hot and water vapour was generated. The CO₂ absorber felt overheated and the CO₂ absorbent turned blue; subsequent analysis showed a water content of 0.5%. In two inductions with sevoflurane 2.5% in boys weighing 18 and 22 kg, less than the expected concentrations were found: in the first, changing to isoflurane resolved the problem, while in the second, a blue colouration of the CO₂ absorbent was noticed; the O₂ saturation was unchanged. After changing the CO₂ absorber, anaesthesia progressed without problems. It was found that the CO₂ absorbent in the induction room had not been changed for 3 weeks. All the above-mentioned cases fortunately recovered, thanks to early diagnosis and appropriate measures. They clearly show that in routine clinical practice, sevoflurane reacts with accidentally desiccated CO₂ absorbents by absorption and/or destruction of the anaesthetic and with intense heat generation. In another published case, a 46-year-old woman could not be induced with 5% sevoflurane, but the temperature of the absorbent canister increased sharply and the Dräger sorb 800 absorbent turned blue, with condensing water visible in the tubing. Subsequent analysis showed a water content of < 1% [21].

Studies in the last 5 years with more modern CO₂ absorbents

During the last 5 years, the particular importance of the chemical composition and brand of the CO₂ absorbent has been recognised. The strong alkali hydroxides, KOH and sodium hydroxide (NaOH), were held responsible for the decomposition of inhalation anaesthetics and elimination of these substances have made the CO₂ absorbent safer, as tested in a study published in 1999 [22]. That study, using barrels of 30-ml syringes, demonstrated

Table 3 Published clinical reactions with sevoflurane.

Patient (age or body weight, sex)	Inspired sevoflurane	Clinical problems	Oxygenation	Absorbent characteristics
14 year, ♀	8%	Coughing, tachycardia	O ₂ sat = 81%; COHb = 4.4%	Blue; H ₂ O = 1.3%
2 year, ♂	7%	Coughing, salivation	COHb = 8.4%	Blue, hot; dry
2 year, ♂	7%	Coughing, salivation	O ₂ saturation normal	Blue; H ₂ O = 0.5%
18 kg, ♂	2.5%	Concentration not reached		
22 kg, ♂	2.5%	Concentration not reached	O ₂ saturation normal	Light blue; hot
46 year, ♀	5%	Concentration not reached		Blue, hot; H ₂ O < 1%

that NaOH and KOH are the primary determinants of the degradation of desflurane to CO, and that they modestly augment the production of compound A from sevoflurane. Elimination of these bases in the desiccated lime decreased CO production 10-fold and decreased compound A by 41%. In a further study, it was shown that absorbents differ enormously in their capacity to produce compound A and CO [23]. Again, 30-ml barrels immersed in water at 45 °C (at 80 °C for lithium hydroxide (LiOH)) were used. The highest CO production with desflurane was found with Baralyme (36 100 parts per million) dried for 24 h; minimal or no CO occurred with dried Amsorb (containing no NaOH or KOH) and LiOH. In an *in vitro* experiment, it was found that when exposed to desflurane, enflurane or isoflurane, dehydrated Amsorb produced only minimal CO (1.2, 2.3 and 1.5 parts per million, respectively) [24]. Unfortunately, in these last three studies, the production of CO with sevoflurane was not assessed. When different inhalation agents were passed from bottom to top through a Dräger ISO canister filled with Drägersorb 800 (containing NaOH and KOH) dried for at least 72 h, intense CO formation was noticed with desflurane, enflurane and isoflurane [25]. A smaller but significant production of 1600 parts per million CO was found with 5% sevoflurane, at or after the canister temperature increased to 130 °C. This temperature increase was much higher than with the other anaesthetics. CO production ceases when heat reaches its maximum at the outlet of the canister. The temperature increase seems to precede the production of CO with sevoflurane. In another report, it was suggested that CO could be formed as a reaction product from hexafluoroisopropanol, postulated as an intermediate of sevoflurane degradation [26]. In pigs it has been shown that dried Amsorb (NaOH- and KOH-free absorbent), in contrast to classic soda limes, produced minimal if any CO with desflurane and isoflurane [27]. Sevoflurane was not examined in this context, but dried Amsorb caused negligible formation of compound A with sevoflurane. Consistent with the lack of compound A formation, dehydrated Amsorb did not increase COHb concentrations [27]. During an *in vitro* study with two new-generation absorbents, DrägerSorb Free and Amsorb Plus, it was found that with desflurane, no CO was formed with either dehydrated absorbent [28], but regrettably sevoflurane was not examined for CO production.

The Holak *in vitro* study is the most convincing report of the possible dangers of CO generation with sevoflurane and dry CO₂ absorbents [13]. The study simulated respiration by the addition of CO₂ to an artificially ventilated circuit. Baralyme that had been desiccated for at least 1 week was examined, together with sevoflurane at a

2.1% end-tidal concentration (1 MAC). No significant degree of anaesthetic breakdown or CO production was noticed with normally hydrated Baralyme. Desiccated absorbent produced measurable sevoflurane breakdown; 1 MAC could not be obtained with 2 l.min⁻¹ fresh gas flow, despite a vaporiser output of 8%. Under other conditions, CO concentrations of 239–542 parts per million were recorded. Most clinically relevant, CO concentrations did not occur until the absorbent temperature exceeded 80 °C. The absorbent in the upper canister turned blue. In one particular condition, the upper canister was heated to >110 °C and turned blue within 10 min. An exponential increase in CO concentration began, exceeding 11 000 parts per million after 50 min. Somewhat later, an explosion occurred, together with a flash of light in the breathing circuit. Just before the explosion, formaldehyde and methanol were detected but were not quantified. Interestingly, at no time did the infrared gas monitor detect an erroneous anaesthetic. Holak suggests that CO production depends on the temperature of the absorbent and that 80 °C may be the temperature threshold for important CO production [13]. It is likely that methanol, formaldehyde, CO and sevoflurane all contributed to the development of a flammable gas mixture. In a recent *in vitro* study [29], desiccated Baralyme was used in an artificially ventilated circuit. With desflurane and isoflurane (1.5 and 3.0 MAC, respectively) the canister temperature increased to a maximum of 100 °C. However, with sevoflurane (1.5 MAC) the temperature increased to over 200 °C and, in two of five runs, flames appeared in the anaesthetic circuit.

The general problem of CO generation with inhalation agents

It is now evident that in particular circumstances CO can be formed during sevoflurane administration. A dry CO₂ absorbent seems to be essential for this occurrence, and from the published data, it appears that Baralyme is the most reactive absorbent. Although Baralyme is now an outmoded CO₂ absorbent and is not used in Europe, other absorbents are also reactive. Formal studies are still needed on all the newer NaOH- and KOH-free CO₂ absorbents. Holak's report [13] was so important that it provoked the sending of a 'Dear doctor' letter in the USA by the makers of sevoflurane, pointing to the clinical importance of the problem and stressing the need to avoid using dry CO₂ absorbent. An unusually delayed rise or unexpected decline of inspired sevoflurane concentration compared to the vaporiser setting may be associated with excessive heating of the CO₂ absorbent canister. Lack of significant colour change should not be taken as an assurance of adequate hydration of the CO₂ absorbent.

Measures to prevent accidental drying of the CO₂ absorbent in clinical use

Firm guidelines on the use of anaesthetic machines should prevent accidental drying of the CO₂ absorbent contained in the canister of the breathing circuit [20, 30]. After the anaesthetic, the gas flows should be turned off completely, particularly at the end of the day. The CO₂ absorbent should be changed routinely regardless of the state of the colour indicator and certainly if the machine has not been used for some time. Flushing of the breathing circuit with fresh gas before use will not prevent CO exposure [31]. If the gas flow has not been shut off during the night or weekend, the absorbent should be replaced in both canisters [32]. If excessive heat from the CO₂ absorbent canister is noted, the absorbent should be replaced and the patient monitored for CO exposure. There is also a case for using low-flow anaesthesia techniques to preserve the water contained in the CO₂ absorbent.

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