Nitric Oxide 89 (2019) 93–95

Contents lists available at ScienceDirect

Nitric Oxide

journal homepage: www.elsevier.com/locate/yniox

Delivery of carbon monoxide via halogenated ether anesthetics

ARTICLE INFO

Keywords:
Anesthetics
CORM
Carbon monoxide
Heme oxygenase
Desflurane
Sevoflurane
Organ transplantation

Letter to the Editor

The therapeutic potential of carbon monoxide (CO) has been well-characterized over the past decades [1]. Organ transplantation is an exemplary unmet medical need where CO has emerged as a protective agent [2]. Translational efforts have focused on CO inhalation protocols, carboxyhemoglobin infusion, heme oxygenase (HO) induction, and local delivery of CO-releasing molecules (CORMs); however, a clinical breakthrough has yet to emerge [3]. Interestingly, halogenated ether anesthetics (HEAs) (Fig. 1) have been linked to elevated intraoperative carboxyhemoglobin (COHb) levels [4,5]. A recent randomized clinical trial indicated patients receiving HEAs have demonstrated improved graft survival prognosis relative to patients receiving a different anesthetic. While it is unclear if CO is related to this finding, the link may warrant investigation.

CO is produced endogenously by several enzymatic and non-enzymatic reactions. HO is the premier source of CO via oxidative metabolism of heme with the greatest activity occurring in the spleen during erythrocyte cycling [6]. The average non-smoker maintains a COHb level below 2% whereas a smoker is below 5% with higher levels being attributed to exogenous sources [7]. Though highly variable, the fatal limit for healthy individuals may be as high as 50% COHb [8]. Incidentally, kidney grafts have been successfully transplanted from donors that had died of CO poisoning [9,10]. Despite CO carrying a ghastly reputation for deadly toxicity, numerous preclinical models have demonstrated profound therapeutic effects upon induction of HO or delivery of CO [1].

In the context of transplant surgery, preclinical data indicates CO ameliorates ischemia-reperfusion injury (IRI) [11], attenuates delayed graft function [12], and carries numerous other anti-inflammatory effects [13]. In parallel to preclinical CO data, the HEAs have numerous reports of beneficial effects against IRI [14], inhibiting lipopolysaccharide induced inflammation [15], and reducing renal transplant complications [16,17]. Clinical trials evaluating CO as a protective agent in organ transplantation have failed to meet endpoints which is thought to be due to subtherapeutic dosing [3]. The therapeutic window, however, has remained elusive due to significant variation across preclinical models. Whereas preclinical models have experimental flexibility, stringent safety constraints have prevented physicians from attaining high COHb levels in humans. Interestingly, a widely used general anesthetic, desflurane, has been associated with significantly increased intraoperative COHb levels ranging between 7% and 36% when administered through dried carbon dioxide absorbents [18]. Though 36% COHb is an extraordinary case, it seems possible that anesthesia protocols utilizing HEAs can be optimized to deliver a CO payload to achieve high COHb levels in a clinical setting.

The phenomenon of CO being liberated from HEAs within an anesthesia machine apparatus has been well-documented [4]. The proposed mechanism for desflurane is specifically dependent upon a reaction with partially dried carbon dioxide absorbents ($< 4.8\%$ water for soda lime and $< 9.7\%$ water for Baralyme) whereby the anesthetic degrades to form CO and a halogenated methane molecule (Scheme 1) [19,20]. Trihalomethanes undergo metabolic biotransformation to form CO [21], thus each mole of ether has the potential to generate 2 M equivalents of CO. Furthermore, HEAs have been characterized as HO-1 inducers which accelerate endogenous CO production [22]. As the anesthetic apparatus can be used as a closed breathing system, CO exhaled by a patient is repeatedly inspired. The combination of CO gas inhalation, CO prodrug delivery, induction of HO-1, and negligible pulmonary excretion appears to stage HEAs as an ideal CO/HO therapeutic candidate.

A team at the University Medical Center Groningen recently initiated the Volatile Anesthetic Protection of Renal Transplants (VAPOR) project which aims to improve graft survival. The first phase consisted of a randomized trial to evaluate the prognosis of sevoflurane versus propofol anesthesia in kidney transplantation from living donors. After two years, patients initially receiving sevoflurane demonstrated a significantly lower acute rejection rate [23]. The second phase of VAPOR (ClinicalTrials.gov: NCT02727296) is evaluating the effectiveness of sevoflurane in graft survival originating from deceased donors [24].

Sevoflurane is among the HEAs capable of delivering CO [25]. Pediatric patients receiving either low flow desflurane or sevoflurane with fresh carbon dioxide absorbents had an increase of ~0.25% COHb after 1 h of dosing [26]. Likewise, with fresh lime soda there was a ~0.25%

https://doi.org/10.1016/j.niox.2019.05.006
Received 6 January 2019; Received in revised form 4 April 2019; Accepted 21 May 2019
Available online 22 May 2019
1089-8603/

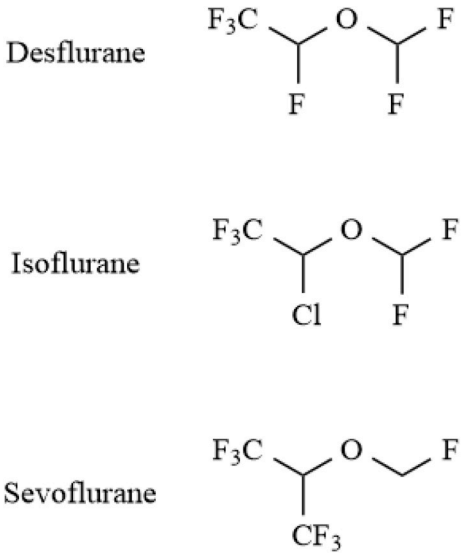
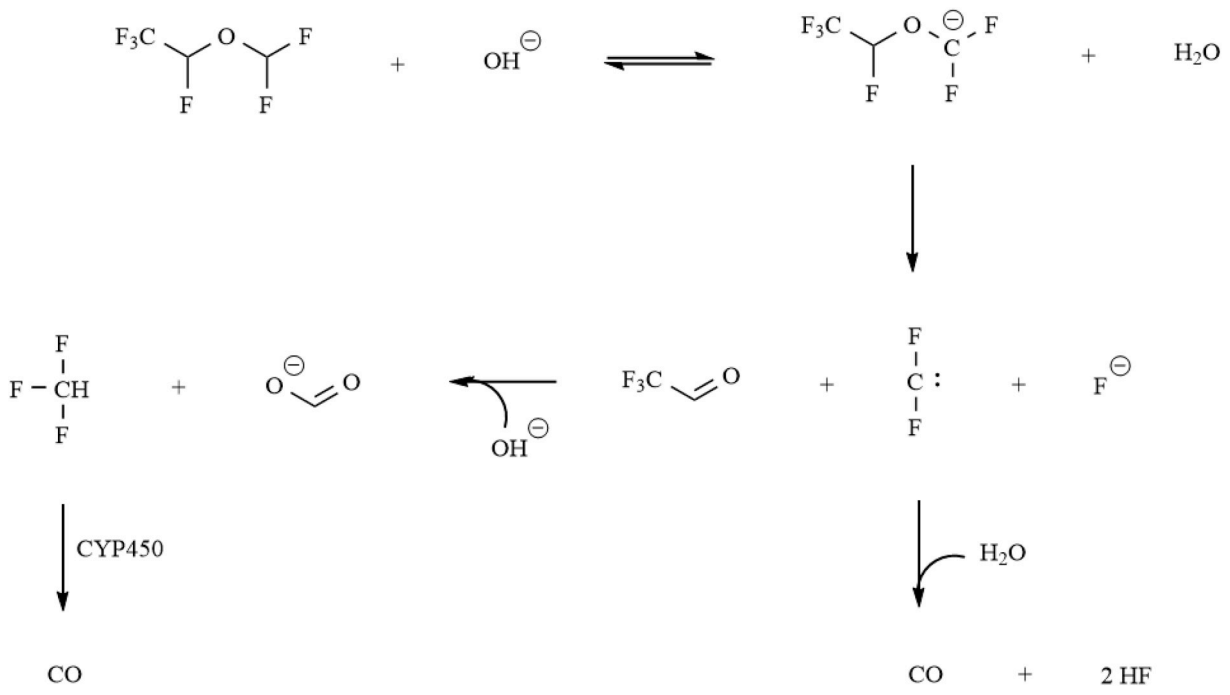


Fig. 1. Exemplary halogenated ether anesthetic structures.



Scheme 1. Proposed mechanism for carbon monoxide liberation from desflurane. Adopted from Baxter et al. [20].

COHb increase in both low-flow and minimal-flow desflurane administration [27]. Though low dose CO is linked to therapeutic effects [28], these observations appear to reinforce the requirement of dehydrated absorbents for significant CO production. The vendor and hydration status of absorbents [29], fresh gas flow rate and ventilator rate [25] are key variables affecting CO production and, in principle, could be leveraged to optimize CO delivery.

Desflurane has been in medical service for nearly 30 years [30]. The HEAs overcome many of the pharmaceutical development and regulatory hurdles for clinical translation faced by most therapeutic CORM candidates. Given the widespread use of HEAs in human and veterinary medicine, there appears to be opportunity for research and clinical trials to determine if the HEA-COHb relationship correlates to enhanced graft survival along with other improved surgical outcomes.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.niox.2019.05.006.

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