Mathematical Modeling of Carbon Monoxide Exposures from Anesthetic Breakdown

Effect of Subject Size, Hematocrit, Fraction of Inspired Oxygen, and Quantity of Carbon Monoxide

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Background: Carbon monoxide (CO) is produced by reaction of isoflurane, enfurane, and desflurane in desiccated carbon dioxide absorbents. The inspiratory CO concentration depends on the dryness and identity of the absorbent and anesthetic. The adaptation of existing mathematical models to a rebreathing circuit allows identification of patient factors that predispose to more severe exposures, as identified by carboxyhemoglobin concentration.

Methods: From our companion study, the authors used quantitative in vitro CO production data for 60 min at 7.5% desflurane or 1.5% isoflurane at 1 l/min fresh gas flow. The carboxyhemoglobin concentration was calculated by iteratively solving the Coburn Forster Kane equation modified for a rebreathing system that incorporates the removal of CO by patient absorption. Demonstrating good fit of predicted carboxyhemoglobin concentrations to published data from animal and human exposures validated the model. Carboxyhemoglobin concentrations were predicted for exposures of various severity, patients of different sizes, hematocrit, and fraction of inspired oxygen.

Results: The calculated carboxyhemoglobin concentrations closely predicted the experimental results of other investigators, thereby validating the model. These equations indicate the severity of CO poisoning is inversely related to the hemoglobin quantity of a subject. Fraction of inspired oxygen had the greatest effect in patients of small size with low hematocrit values, where equilibrium and not the rate of uptake determined carboxyhemoglobin concentrations.

Conclusion: This model predicts that patients with low hemoglobin quantities will have more severe CO exposures based on the attainment of a higher carboxyhemoglobin concentration. This includes patients of small size (pediatric population) and patients with anemia.

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the end of each 1-min interval, additional CO was added to the circuit based on the production data obtained in the absence of a subject, which is summarized in the Web-based electronic supplement to this article.

Clinical validation of the model was performed using CO production data that most closely resembled those described in previous publications. The carboxyhemoglobin concentration was calculated for clinically relevant conditions to demonstrate the predicted effects of absorbent drying, anemia, patient size, and fraction of inspired oxygen (FI\textsubscript{O}\textsubscript{2}) on simulated CO exposures. These assumed approximate 1.2-min alveolar concentrations of isoflurane or desflurane and 1 l/min fresh gas flow.

Statistical Analysis
Correlation coefficients and mean differences between experimental and calculated data were performed with StatView (Abacus Concepts, Berkeley, CA). No statistical analyses were performed for calculated data.

Results
Validation
Figure 1 demonstrates that the calculated carboxyhemoglobin concentrations show a good fit to the experimental data of Frink et al. (n = 10; r\textsuperscript{2} = 0.961; mean difference between calculated and experimental carboxyhemoglobin = 2.2%). For the exposure reported by Berry et al., this model predicted carboxyhemoglobin concentration within 2% of the measured value (n = 1) but also predicted a peak carboxyhemoglobin concentration of 42% before interventions to stop and treat the exposure. For the experiment by Bonome et al. (not shown), the calculated and experimental data (n = 9) have an r\textsuperscript{2} = 0.876 with a mean difference between calculated and experimental data of 6.9% carboxyhemoglobin.

Clinically Relevant Extrapolations
Figure 2 shows that, in an average-sized adult human, 24 h or more of absorbent drying results in carboxyhemoglobin concentrations that are associated with rapid development of severe poisoning, and 48 h or more of drying can result in lethal concentrations of CO with 7.5% desflurane. Similar but less severe trends exist with isoflurane, with later peak carboxyhemoglobin concentrations. Figures 3 and 4 show that the carboxyhemoglobin concentration is inversely related to hematocrit and patient size.

The effect of FI\textsubscript{O}2 is shown in figure 5. This effect demonstrates that initially there is little difference in carboxyhemoglobin concentration during the first 15–20 min of exposure during these conditions, but later in the exposure there is considerable difference as a result of FI\textsubscript{O}2.

Fig. 1. Data used to validate the predicted carboxyhemoglobin (COHb) concentrations. These data show a good fit to the experimental data of Frink et al. (n = 10; r\textsuperscript{2} = 0.961; mean difference between calculated and experimental carboxyhemoglobin = 2.2%). For the exposure reported by Berry et al. this model predicted carboxyhemoglobin concentration within 2% of the measured value (n = 1) but also predicted a peak carboxyhemoglobin concentration of 42% before interventions to stop and treat the exposure.

Fig. 2. The predicted effect of various barium hydroxide lime drying times on the carboxyhemoglobin (COHb) saturation in a 70-kg patient receiving an anesthetic at 1,000 ml/min fresh gas flow, a hematocrit of 42%, tidal volume of 15 ml/kg, respiratory rate of 10 breaths/min, and fraction of inspired oxygen of 40%. Solid lines 1, 2, 3, 4, and 5 represent complete desiccation, 66-, 48-, 24-, and 14-h drying time, respectively, at 10 l/min with 7.5% end-tidal desflurane. Note that highly dried absorbent rapidly produces carboxyhemoglobin concentrations in the lethal range. Dashed lines 6, 7, 8, 9, and 10 represent complete desiccation, 66-, 48-, 24-, and 14-h drying time, respectively, at 10 l/min with 7.5% end-tidal isoflurane.
Discussion

Validation of the Model
Existing published data were used to validate this model, which predicts the data of Berry et al.\textsuperscript{12} and Frink et al.\textsuperscript{5} well. The fit is not as good in comparison to the data of Bonome et al.,\textsuperscript{6} where a different anesthesia machine was used with a different circuit configuration, and the assumptions of gas flow patterns used in this model were knowingly incorrect.

Effect of Anesthetic and Degree of Desiccation
The results shown in figure 2 explain clinical observations that the most severe exposures to CO result from desflurane on Monday mornings when 66 h or more of absorbent desiccation have occurred at 10 l/min. An important extrapolation is that, with 24 h or less of absorbent desiccation in a 70-kg subject anesthetized with 1.5% isoflurane, this model predicts carboxyhemoglobin concentrations similar to those seen in smokers. This may not provoke the suspicion of intraoperative CO poisoning solely on the basis of the carboxyhemoglobin concentration, but with ischemic heart disease, even low carboxyhemoglobin concentrations can produce morbidity.\textsuperscript{13-16}

\textbf{Effect of Size and Hematocrit}
These two factors are related because both determine the quantity of hemoglobin, which determines both carboxyhemoglobin concentrations and the quantity of CO removed from the breathing circuit. The effect of size is
more complex than the effect of hematocrit because smaller patients have proportionately smaller lungs and a lower diffusing capacity of CO.

Effect of Fraction of Inspired Oxygen

It is important to note that greater $FIO_2$ was less effective at preventing a rapid increase in carboxyhemoglobin concentrations than that predicted in a prior study using the CFK equation unmodified for uptake by the patient. CO exposures in an anesthesia machine are unique in that a small quantity of CO is produced compared with environmental exposures. CO absorbed by the subject is removed from the breathing circuit, and this reduces the partial pressure, driving it to bind with hemoglobin. In a physically large patient with a relatively small CO exposure, equilibrium is never achieved. A high $FIO_2$ has minimal benefit because the CFK equation predicts that the uptake of CO is rate limited. Fortunately, physically large nonanemic patients are predicted to rarely experience a potentially lethal exposure to CO unless desflurane reacts with extremely dry absorbents. Conversely, a small patient with a low hematocrit will more rapidly attain equilibrium concentrations of carboxyhemoglobin, and a large protective effect of high $FIO_2$ is predicted.

Limitations of the Model

Conditions that result in hemoglobin desaturation in arterial blood cannot be modeled because the CFK equation requires that hemoglobin be saturated with either or both CO or oxygen. This model also requires that breathing circuit configuration to be the same as that postulated in Methods because only then will the fraction of gas rebreathed and eliminated from the circuit be adequately modeled. Validation of this model was performed against historical data where assumptions were required for the missing or unpublished data. Nevertheless, this model can be used to provide reasonable predictions of carboxyhemoglobin concentrations in a variety of situations likely to be encountered clinically.

The physiologic effects of CO poisoning cannot be predicted by this model. The physical status of an actual patient during anesthesia may mitigate or exacerbate any physiologic effect of CO. Patients with coronary artery disease may be injured by relatively small CO exposures that do not appear severe by carboxyhemoglobin concentrations.

References

10. Woehlck HJ: Predicting the severity of carbon monoxide poisoning at varying $FIO_2$. Anesthesiology 1998; 88:1126–7

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