

Issues Regarding Propofol Concentrations within the Clinical Range

To the Editor:

Recently, Gleason *et al.*¹ have demonstrated that propofol at concentrations of 2×10^{-5} to 2×10^{-4} M relaxes guinea pig tracheal rings in organ baths in response to noradrenergic noncholinergic-mediated electrical field stimulation; these researchers have adopted the concentrations of propofol within this clinical range. The plasma concentration of propofol during the induction of anesthesia in humans has been reported as up to 3×10^{-5} M, and burst suppression doses of propofol for cerebral protection are up to 6×10^{-5} M.²⁻⁴ Effective concentrations of propofol (2×10^{-5} to 2×10^{-4} M) in the study by Gleason *et al.* are probably much higher than those with clinical relevance if considering plasma-free concentrations calculated from both above clinical plasma concentrations of propofol and the substantial binding of this compound to plasma proteins (97–98%).^{1,3} Therefore, it seems still unknown whether propofol actually protects against irritant-induced bronchoconstriction in those with the clinical condition. It would be helpful for clinicians to interpret their results if any future study is capable of showing the higher tissue uptake of propofol by the lung in their experimental condition.

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In Reply:

We thank Drs. Kinoshita and Matsuda for their interest in our study.¹ In that work, we did not seek to determine

whether propofol protects against irritant-induced bronchoconstriction in the clinical situation established by previous clinical studies^{2,3} and clinical experience. In contrast, we sought to identify signaling pathways of irritant-induced bronchoconstriction against which propofol might be effective.

We demonstrated that, at the same concentration, propofol was more effective at attenuating contractions induced by nonadrenergic, noncholinergic nerve stimulation or tachykinins compared with contractions induced by cholinergic nerve stimulation or acetylcholine.¹ This focus was selected because previous clinical studies⁴⁻⁶ suggested that propofol's protective airway effects were *via* blockade of cholinergic mechanisms.

Drs. Kinoshita and Matsuda are concerned about our comparison of *in vitro* bath concentrations of propofol with those measured in plasma. Comparing clinically measured plasma concentrations of a drug with concentrations achieved at a cellular level *in vitro* remains challenging. *In vivo*, although the majority of propofol is bound to serum proteins, extensive lung extraction of propofol has been demonstrated.⁷ *In vitro*, drug concentrations at the level of the airway smooth muscle cell rely on tissue diffusion, and there is no benefit from microvascular delivery of the drug to the tissue as occurs *in vivo*. Thus, different factors *in vitro* and *in vivo* dictate the drug concentrations achieved at the level of the airway smooth muscle cell. A direct comparison cannot be made until airway smooth muscle cellular concentrations are measured during *in vivo* and *in vitro* deliveries of propofol—a study that has yet to be done.

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Opioid Modeling of Central Respiratory Drive Must Take Upper Airway Obstruction into Account

To the Editor:

The elegant modeling of the dynamic effects of remifentanyl on respiratory depression by Olofson *et al.* is a useful contribution to our understanding of opioid effects on respiratory control.¹ The authors' incorporation of non-steady state changes in opioid concentration and the addition of propofol to induce apnea help in their goal to reproduce real-life conditions in patients receiving opioids and sedatives. This is particularly relevant when considering morbidity and mortality incurred by patients in general care ward settings who receive opioids and sedatives.² However, we believe that the model neglects important considerations that simulate real-life clinical situations relating to predisposed patients whose depth of sedation is sufficient to induce loss of consciousness and upper airway obstruction.

Olofson *et al.* used end-tidal carbon dioxide (ETCO₂) and remifentanyl concentrations as inputs to the model and measured ventilation as an output. The study's stated objective is to build a model that predicts apnea at finite opioid and hypnotic concentrations under dynamic conditions. Our concern is that at concentrations of sedation commensurate with loss of responsiveness, as occurred in this study, partial or complete airway collapse could preclude sampled ETCO₂ from being an accurate reflection of the arterial carbon dioxide, and thereby a valid input to the model. As it stands, the model assumes a patent upper airway. The authors acknowledge that, close to apnea, the ETCO₂, used by the model to set the ventilation gain *G* (equation 6), is likely to be falsely low. The authors account for the inaccuracy of this model input by assigning a residual error to the ETCO₂ and modeling it as a probability density function, in addition to ignoring values less than 37.5 torr. Low and unpredictable ETCO₂ values are common in the periapneic period, as shown during the 15-min breathing after the period of apnea in 8 of 10 study subjects receiving remifentanyl and propofol (fig. 3, original article). It is feasible that an upper airway obstructive component could contribute to these events. Consequently, the model could break down in obstruction-prone subjects for both the ETCO₂ input (fig. 5F, original article) and minute ventilation (fig. 5E, original article) output during the periapneic period, the precise time for which the model is designed to provide insights.

Hillman *et al.* have shown that an abrupt increase in the tendency of the upper airway to collapse at the point of loss of consciousness with propofol in healthy volunteers can be

attributed to a precipitate decrease in tone of the primary upper airway dilator, the genioglossus muscle.³ Hajiha *et al.* recently demonstrated that opioids cause a dose-related suppression of tonic brainstem stimulatory input to the genioglossus in rats.⁴ Thus, apart from their suppression of central respiratory drive, opioids and other sedatives can also precipitate upper airway obstruction. The authors use the term *apnea* (cessation of airflow) throughout the article as synonymous with suppression central respiratory drive (a central apnea), without considering obstruction (an obstructive apnea). This is an important omission, and the distinction is critical in understanding the time course and relative contributions of upper airway collapse and reduced central respiratory drive to ventilatory failure. It has important implications for our ability to monitor, diagnose, and prevent respiratory decompensation. Thus, ambiguity in the models' critical inputs during the periapneic periods and failure to account for airway obstruction in modeling respiratory responses to opioid/propofol infusion detract from its use.

We believe the model would be improved by including components that account for the complex interactions between the respiratory control mechanisms and airway patency, as eloquently described by Younes.⁵ Consistent with standard control theory, we would divide the overall (closed-loop) gain of the system into a controller gain and a plant gain. White describes controller gain as the ventilatory responsiveness to hypercapnia or hypoxia, whereas plant gain reflects the effectiveness of any given concentration of ventilatory drive in eliminating carbon dioxide.⁶ As obstructive hypopneas and apneas develop, a ramped-up controller gain from accumulating PaCO₂ may be attenuated by a negative plant gain from an obstructed airway. In these patients, the ability to rescue themselves from a fatal decompensation, either through a central nervous system arousal or sufficient chemical drive, to cause reflex opening of their airway is a tenuous dynamic that only can be simulated by a model that includes all these components. A metric relating to propensity for upper airway obstruction, perhaps related to critical closing pressure, should be among these.^{3,7} We also commend the approach of Bouillon *et al.*, who uses PaCO₂ as the dependent variable in modeling remifentanyl-induced ventilatory depression, with a method that takes carbon dioxide kinetics into account.⁸

We are keen to encourage such an approach because root-cause analysis of a case series of postoperative patients found dead in bed on the ward by one of us (F.O.) found serosanguinous pulmonary edema not to be an uncommon autopsy finding. Although nonspecific, a potential explanation for this finding is negative pressure pulmonary edema secondary to upper airway obstruction, with fatal consequences.

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