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 studies[4–6] 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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