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Electroencephalogram and Anesthetics

To the Editor:

I was intrigued by the article by Warnaby *et al.*, who reported that electroencephalographic slow-wave activity saturation is observed for both intravenous and volatile anesthetics.[1] Furthermore, they found that opiates reduced the concentration of anesthetic at which slow-wave saturation was observed. In contrast, they reported that muscle relaxants did not alter the anesthetic concentration at which electroencephalographic slow-wave saturation occurred. Their results may lead to the erroneous conclusion that muscle relaxants do not alter the electroencephalographic effects of anesthetics. By comparison, our own study in dogs demonstrated that pancuronium neuromuscular blockade potentiated electroencephalographic burst suppression elicited by isoflurane.[2] This effect on electroencephalography was reversed by the administration of neostigmine. Furthermore, the description of electroencephalographic burst suppression by Warnaby *et al.* as an "artefactual disturbance" greatly obscures this issue. Most certainly, electroencephalographic burst suppression is not an artefactual disturbance, as multiple reports confirm that dose-dependent electroencephalographic burst suppression is elicited by a wide variety of anesthetic agents of diverse chemical structure.[3] For all of these anesthetics, electroencephalographic burst suppression is associated with a dose-related decrease in cerebral metabolic rate. Indeed, altered electroencephalographic burst suppression in elderly patients confirms the accepted principal of age-related shifts in the pharmacodynamics of volatile anesthesia.[4,5] It should also be noted that in their clinical study, Warnaby *et al.* failed to control for dose, timing, or even the identity of muscle relaxants. They also fail to explain why values of N in their own work, cited by this article, do not always agree with values of N reported in the original publications.

Competing Interests

The author declares no competing interests.

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In Reply:

We thank Colin *et al.* and Schwartz for their interest in our recently published work in Anesthesiology.[1] In the referenced manuscript, we fitted slow-wave activity drug dose-response curves to electroencephalographic data acquired during anesthesia in a propofol healthy volunteer study and three patient studies. By applying these techniques to induction and emergence, we presented two distinct, but related, findings.

First, as described by Schwartz, we confirmed that our experimental finding of slow-wave activity saturation[2] also occurs during surgical anesthesia. While we entirely agree that exploration of the transition to burst suppression is important, this was not the focus of our article. Slow-wave activity saturation occurs at considerably lower levels of anesthesia than burst suppression (fig. 1G of Warnaby *et al.*[1])—hence why the presence of burst suppression was considered to be artefactual in the fitting of slow-wave activity–concentration curves. Furthermore, we did not imply that muscle relaxants have no influence on the electroencephalogram, only that they had no influence on the slow-wave activity saturation parameters (*i.e.,* the power and concentration of slow-wave activity saturation, defined by the electroencephalographic dose-response curve fit). Neuromuscular blocking

drugs certainly influence the electroencephalogram and, in particular, frequencies above 20 Hz,[3] but we are unaware of any evidence that neuromuscular blockade potentiates burst suppression in humans. The prerequisites for inclusion of patient data in our analyses were specified in the Materials and Methods section. Any small discrepancies in N were due to the original data not meeting the criteria for inclusion in this different analysis with different criteria.

Second, as discussed by Colin *et al.*, we presented evidence of neural inertia in humans. We agree that there is a wide variation across individuals in the time taken for the drug to move from the blood and "activate" its effect site, and this is one of the many weak links in the use of population pharmacokinetic models. However, it is important to remember that the equilibration rate parameter (ke_0) is an abstract parameter that depends on the elimination of hysteresis for its estimation, therefore providing potential for circularity in this argument. We strongly argue that this single exponential diffusion term is poor at capturing the complexity of the many processes involved. This single parameter is expected to subsume a multiplicity of biologic processes including: (1) chemical diffusion from blood to brain, (2) molecular binding to various receptor targets, (3) disturbance of neuronal function, (4) impairment of neural network dynamics, and (5) the resultant change in behavior.

As shown by the modeling of our experimental propofol infusion regime in the letter from Colin *et al.*, it is mathematically inevitable that a value of the equilibration rate constant can be chosen so that the EC50 of induction equals the EC50 of emergence. However, based on our findings that were obtained using the commonly accepted population-based equilibration rate constant values, we would argue that the shape of the drug concentration effect curve is a better indicator of neural inertia in an individual than the EC50. As an illustration, we ran a drug concentration–effect simulation with two different processes for induction and emergence (fig. 1, *blue curves*). The addition of a suitable equilibration rate constant will make the EC50 of induction and the EC50 of emergence equal (fig. 1, *red curves*). However, we believe it is the failure of the induction and emergence curves to overlay that is a true marker that induction and emergence are not equivalent processes. The EC50 is ultimately a single point on the population-generated curve and, as such, is not particularly meaningful for assessing such a complex phenomenon within an individual.

We entirely agree with Colin *et al.* that a more precise definition of "neural inertia" is required, as there are many subtleties that need to be further elucidated.[4] Originally proposed by Friedman *et al.*,[5] a neural component of the observed hysteresis is inferred through genetic and pharmacologic modification in animals also using behavioral state changes as a read-out. We would like to point out that, even using the disputed average population propofol model parameters, we did not find much evidence of neural inertia for behavioral response. This is similar to the result obtained in the recent associated paper by Kuizenga *et al.*[6]

Importantly, we did find strong hysteresis in our brain-based measurement of electroencephalographic slow-wave

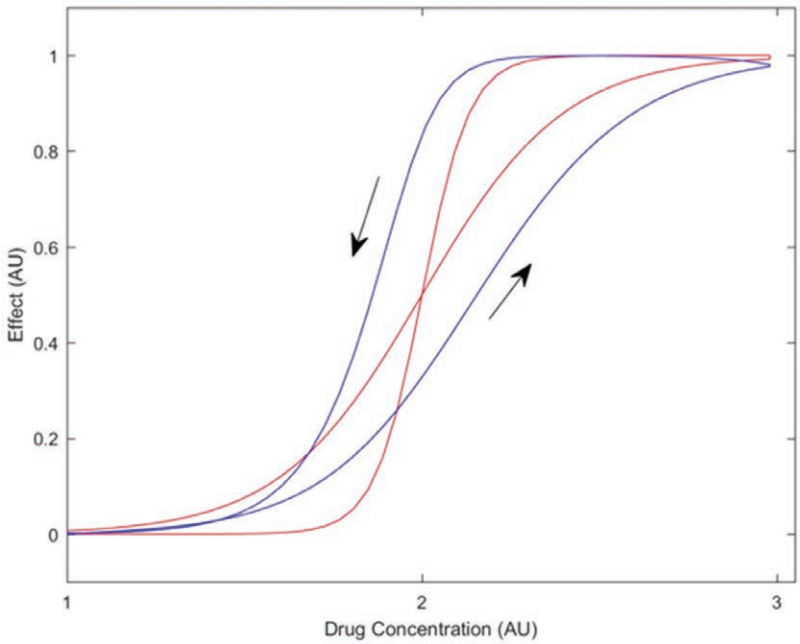

Fig. 1. Simulation of drug concentration-response curves for induction and emergence from anesthesia. The raw processes are indicated by the *blue curves*, with *arrows* showing the direction of change (*i.e.,* induction = *up arrow*, emergence = *down arrow*). The addition of a equilibration rate constant of 0.25 results in the EC50 of induction and EC50 of emergence being equal (*i.e.*, EC50 induction = EC50 emergence, *red curves*). The resulting figure-of-eight loops indicate failure to properly describe the different process driving induction and emergence. This example highlights the inadequacy of a single equilibration rate constant to model the biologic situation.

activity. In particular, the identification of abrupt slow-wave emergence trajectories in some individuals indicates a higher resistance to brain state changes on emergence, *i.e.,* these individuals have a higher degree of neural inertia. This quite marked interindividual hysteresis is lost unless within-subject analyses are performed as we have done. Furthermore, our categorization of abrupt (rather than graded) emergence trajectories takes into account three factors: the electroencephalographic brain state, behavioral state, and hypnotic drug concentrations. While we acknowledge that the use of population-based propofol effect concentrations is a minor limitation, these abrupt trajectories were also identified in the clinical studies using the more accurate measurement of end-tidal volatile agent concentrations.

We believe our findings provide additional support to Kelz and coworkers' hypothesis that a neural effect contributes to anesthetic hysteresis, further highlighting that this is not purely a pharmacokinetic issue. Based on our findings, we proposed a more general definition of neural inertia as "a tendency of the central nervous system to resist transitions between conscious and unconscious states" in the article's Discussion. This allows for inclusion of different brain state transitions, as inferred by electroencephalographic methods, functional brain imaging, and/or behavior. While Colin *et al.* have tended to focus on pharmacokinetic mechanisms and behavioral read-outs, the shortcomings of which for assessing true neural inertia are elegantly detailed by Proekt and Kelz,[4] we suggest our systems-level approach is more suitable and indicates that both disruption of neuronal function and impairment of neural network dynamics play a key role in neural inertia.

Competing Interests

Dr. Warnaby and Irene Tracey were listed as inventors on patent applications filed by Oxford University Innovation, the technology transfer company of the University of Oxford (Oxford, United Kingdom; formerly Isis Innovation) on perception loss detection using slow-wave activity saturation. The remaining author declares no competing interests.

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Risks of Impaired Organ Protection with Inhibiting Transient Receptor Potential Vanilloid 1

To the Editor:

With great interest we recently read the manuscript by Garami *et al.*,[1] which illustrates how the transient receptor potential vanilloid 1 antagonists, AMG 517 and ABT-102, prevent anesthesia-induced hypothermia and simultaneously decrease opioid requirements for postoperative hyperalgesia in rodents. These preclinical data suggest that transient receptor potential vanilloid 1 antagonists may be useful as opioid-sparing modalities for analgesia intraoperatively and postoperatively while also providing hyperthermia to pharmacologically counteract anesthetic-induced hypothermia. This finding is novel and may lead the way to developing new opioid-sparing drugs to be used perioperatively. However, it would be of benefit if the authors may comment on some of the potential shortcomings we see of using transient receptor potential vanilloid 1 antagonists during surgery and the potential strategies to overcome these barriers we outline below.

For example, intravenous administration of transient receptor potential vanilloid 1 antagonists may also block endogenous mechanisms of organ protection. It is important to recognize that untreated transient receptor potential vanilloid 1 knockout mice or mice treated with a transient receptor potential vanilloid 1 inhibitor subjected to ischemia-reperfusion injury using an isolated heart model produce impaired functional recovery compared to wild-type transient receptor potential vanilloid 1 mice.[2] Further, in a deoxycorticosterone acetate–salt hypertension model, ablation of transient receptor potential vanilloid 1 gene in the C57BL/6 mice exacerbates renal damage compared to deoxycorticosterone acetate–salt-treated wild-type mice, indicating that transient receptor potential vanilloid 1 may constitute a protective mechanism against end-organ damage induced by hypertension.[3] Additionally, transient receptor potential vanilloid 1 channel activation reduces organ