Dr. Mariyaselvam has been selected as a National Health Service Innovation Accelerator Fellow and National Health Service Clinical Entrepreneur Fellow to support the implementation of the Venner WireSafe. Both have ownership rights to the intellectual property and hope to be involved with supporting and advising on the commercialization of the Venner WireSafe, and may benefit financially alongside its clinical success, subject to future negotiation and agreement.

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References

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Pharmacokinetic Pharmacodynamic Perspective on the Detection of Signs of Neural Inertia in Humans

To the Editor: We read with great interest the paper, “Investigation of Slow-wave Activity Saturation during Surgical Anesthesia Reveals a Signature of Neural Inertia in Humans” by Warnaby et al.1 The authors claim to have found experimental evidence for neural inertia in humans on the basis of a difference in the modeled slow-wave activity between induction and emergence from propofol anesthesia. As the authors state, up to recently, neural inertia has only been observed in animals,2 and evidence was lacking on the importance of this phenomenon in humans.

In parallel to Warnaby et al., our group recently conducted a clinical study to investigate this phenomenon in healthy volunteers.3 Our analysis suggested, among other things, that the ability to detect signs of neural inertia depends on the design of the study. Inspired by the work of Warnaby et al., we would like to show how the drug titration scheme may influence the detection of neural inertia and could lead to false positive results.

In studies with anesthetic agents, effect-site target-controlled infusion is frequently used to control delivery of the drug. Effect-site target-controlled infusion systems calculate the optimal infusion regimen required to achieve the target effect-site concentration as fast as possible. These systems depend heavily on population pharmacokinetic models and their associated estimate for the rate-constant for equilibration between the plasma and effect-site concentrations. Clinical trial design is usually optimized with respect to this rate-constant for equilibration, such that pharmacodynamic endpoints are measured only after the predicted effect-site concentrations have reached a steady-state. The rate-constant for equilibration of 0.260 min–1 integrated into the Diprifusor system (AstraZeneca Ltd., United Kingdom) suggests a rapid effect-site equilibration. Presumably based on this knowledge, Warnaby et al. chose to change the target effect-site every 2 min during the induction phase of the study. For the emergence phase, the authors simply stopped the propofol infusion.

However, reported rate-constants for equilibration in the literature vary substantially. For example, for propofol-induced changes in Bispectral Index (Covidien, USA), reported rate-constants for equilibration range between 0.17 min–14 and 0.79 min–1.5 In our opinion, this uncertainty should be taken into account when designing a study; failing to do so may lead to false conclusions.

To substantiate our claim, we simulated the propofol infusion scheme used by Warnaby et al. (details with respect to the propofol infusion are found in the supplementary materials from an earlier paper from the same group9). Hereeto, the Marsh model7 and the associated rate-constant for equilibration of 0.260 min–1 were used to calculate predicted arterial and effect-site concentrations. Predicted effect-site concentrations (Ce) were used to calculate a hypothetical drug effect according to equation 1 with a gamma (γ) and a concentration producing half-maximum effect (C50) which were 2 and 1.5 μg/ml, respectively.

\[
Effect = \frac{C_e^\gamma}{C_e^\gamma + C_{50}^\gamma}
\]

Subsequently, the model in equation 1 was fitted to the simulated data for the induction and emergence phase separately to estimate the γ and C50. This process was repeated with different values for the rate-constant for equilibration. Besides the study design described by Warnaby et al., we also evaluated the drug infusion scheme that was used in our study.3

The results of the simulations are shown in figure 1. This figure clearly shows that the C50 for induction and emergence depend on the rate-constant for equilibration. More specifically, if the wrong rate-constant for equilibration is used, the estimated C50 for induction increases, whereas that for emergence decreases. For example, in Warnaby et al., a 30% difference between estimated induction and emergence C50 is expected when the rate-constant for equilibration is 0.160 min–1, but none if it is 0.260 min–1. Thus, neural inertia is an apparent artefact of the experiment. In addition,
some trial designs may be less sensitive to the rate-constant for equilibration used. For example, in our study design, this situation would only result in a 4% difference between the predicted C_{so} values. This would likely lead to no difference between induction and emergence C_{50}'s, which, in this case, is the correct conclusion.

Our simulations show that data indicating the existence of neural inertia (higher estimated C_{so} for induction vs. emergence) may occur because of poor trial design. Given the range of rate-constants for equilibration reported in the literature, it seems pivotal to take the uncertainty associated with the rate-constant for equilibration into account when designing a study. Failing to do so will lead to false positive results. A more precise definition of neural inertia, and methodologic framework for studying this in clinical practice, is necessary to conclude whether neural inertia exists in humans and is of clinical importance.

Fig. 1. The estimated concentration producing half-maximum effect (C_{so}) for the induction (solid lines) and emergence phase (dashed lines) according to the rate-constant for equilibration (k_{e0}) that was used to generate the hypothetical drug effect. The different colors show the dependence of the C_{so} on the k_{e0} for the trial design by Warnaby et al. (blue lines) and the design that was used in our study on neural inertia (red lines).

Competing Interests
Dr. Struys's research group/department received grants and funding from The Medicines Company (Parsippany, New Jersey), Masimo (Irvine, California), Fresenius (Bad Homburg, Germany), Acacia Design (Maastricht, The Netherlands), and Medtronic (Dublin, Ireland), and honoraria from The Medicines Company, Masimo, Fresenius, Baxter (Deerfield, Illinois), Medtronic, and Demed Medical (Temse, Belgium). Dr. Struys serves as director and editorial board member of the British Journal of Anaesthesia and as senior editor for Anesthesia & Analgesia. The remaining authors declare no competing interests.

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References
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.

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 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

References


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Competing Interests

The author declares no competing interests.