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Resisting neural inertia: an exercise in floccinaucinihilipilification?

Douglas J. Eleveld[1], Pieter J. Colin[1], Anthony R. Absalom[1] and Michel M. R. F. Struys[1,2,*]

[1]Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands and [2]Department of Basic and Applied Medical Sciences, Ghent University, Ghent, Belgium

*Corresponding author. E-mail: m.m.r.f.struys@umcg.nl

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In their article in this issue of the *British Journal of Anaesthesia*, Proekt & Kelz[1] refer to an aphorism attributed to Confucius that 'the hardest thing of all is to find a black cat in a dark room, especially if there is no cat'. Proving that something is impossible, also known as a negative proof, can be very useful in science. It can put to rest further attempts to find a solution, avoiding a considerable waste of scientific resources, and enabling research groups to direct their time and efforts towards more beneficial endeavours. Negative proofs lay bare our misunderstandings about the foundations of the models and methods we use, helping us discard incorrect notions so we can improve our methods.

Pharmacometrics is a branch of science that aims to quantify the relationship between the dose of a drug and the resulting clinical effect. The study of this relationship can be logically divided into three aspects: (1) *pharmacokinetics* defined as the time course of the relationship between the given dose/s of a drug and the resulting plasma concentration; (2) pharmacodynamics defined as the relationship between the drug plasma concentration, the effect-organ concentration, or both, and the clinical effect, and (3) the *linkage* between pharmacokinetics and pharmacodynamics which is required when blood plasma is not the site of drug effect. Classically, compartmental mammillary models are used to describe the pharmacokinetics, and sigmoidal maximal effect (Emax) models are used to describe pharmacodynamics. When plasma is not the site of drug effect, a typical delay between the time course of plasma concentration and drug effect is observed, and this is the case for anaesthetic drugs. Until recently, this hysteresis has been assumed to be caused by an equilibration delay between plasma and effect-site concentrations, the linkage component of pharmacometrics mentioned above. This is described mathematically by the effect-site equilibration rate constant k_{e0}. An important assumption underlying pharmacodynamics, and in particular the methods used to estimate the k_{e0} for the hypnotic drugs, is that loss and recovery of consciousness occur at the same drug concentration in the biophase, or effect-site. The most common approach is to estimate the value for k_{e0} such that the 'hysteresis curve collapses'.[2]

The above assumption is incompatible with a concept causing some controversy in the anaesthetic literature known as neural inertia. This term describes the proposed propensity of brain function to resist state changes.[3,4] One corollary of this concept is that the effects of anaesthetic drugs are 'path-dependent' (i.e. effects depend on the direction of change of effect-site concentrations). When a person is conscious, but effect-site hypnotic drug concentrations are increasing, the brain is postulated to resist loss of consciousness, whereas when a person is unconscious and effect-site concentrations are decreasing, the brain will resist return of consciousness. The implication is that effect-site concentrations will be higher at the moment of loss of consciousness than at the moment of recovery of consciousness, and that there might be a range of effect-site drug concentrations at which a patient could be either conscious or unconscious, depending on their previous state.

The work of Proekt & Kelz suggests that at least part of this hysteresis is the result of neural inertia, the degree of which differs for different drugs.[3,5–8] This plausibility of this assertion is strengthened by their recent findings that even under steady-state conditions in animal models there can be fluctuations in responses to stimuli, and that the system shows a bi-stable state (i.e. if one response is positive, then the subsequent one is more likely to also be positive).[5] This situation, in which a single effect-site concentration can be associated with consciousness or unconsciousness, is evocative of the Schrodinger cat quantum superposition thought experiment.[7]

We recently used non-linear mixed effects modelling of the pharmacodynamic relationships among effect-site propofol and sevoflurane concentrations and clinical effect.[4] The study design was such that we could assume that the effect-site concentrations were equivalent to the measured plasma or end-tidal concentrations of the two drugs, respectively. We found that adjustment of the C50 parameter by a path-dependent inertia factor did not improve the model fit for

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propofol (and only did do so in certain circumstances for sevoflurane). This suggests that there is no neural inertia with propofol.[4]

The article by Proekt & Kelz[1] in the *BJA* caught our eye, because it offers the potential for a negative proof for neural inertia. Their study investigated whether the pharmacokinetic–pharmacodynamic (PK-PD) modelling techniques used in our study are a valid method of proving the presence or absence of neural inertia. Their major claim is that the effect-compartment model used ubiquitously in anaesthetic PK-PD research is ill-suited for this purpose, when used for simple on-off study designs and for more complex study designs using multiple step up-step down approaches.[1,4,9] The underlying issue is that existing PK-PD modelling studies have relied on an effect-site rate constant (k_{e0}) that estimates the rate of equilibration between plasma and the effect-site or biophase where the anaesthetic effect is triggered. As the effect-site is a theoretical rather than an anatomical concept, and the exact site of action is unknown, the true value of k_{e0} cannot be known because the drug concentrations cannot be measured by sampling. Instead k_{e0} is determined from the data by collapsing the hysteresis loop, and as such it is unconstrained by other physiological properties. As long as k_{e0} is unconstrained, a k_{e0} value can always be found that explains hysteresis purely in terms of a plasma-effect-site equilibration delay.

To illustrate their claims, we performed PK-PD simulations with the presence of neural inertia assumed. We used a two-compartment mammillary PK model with central and peripheral volumes of 10 and 15 L with elimination and inter-

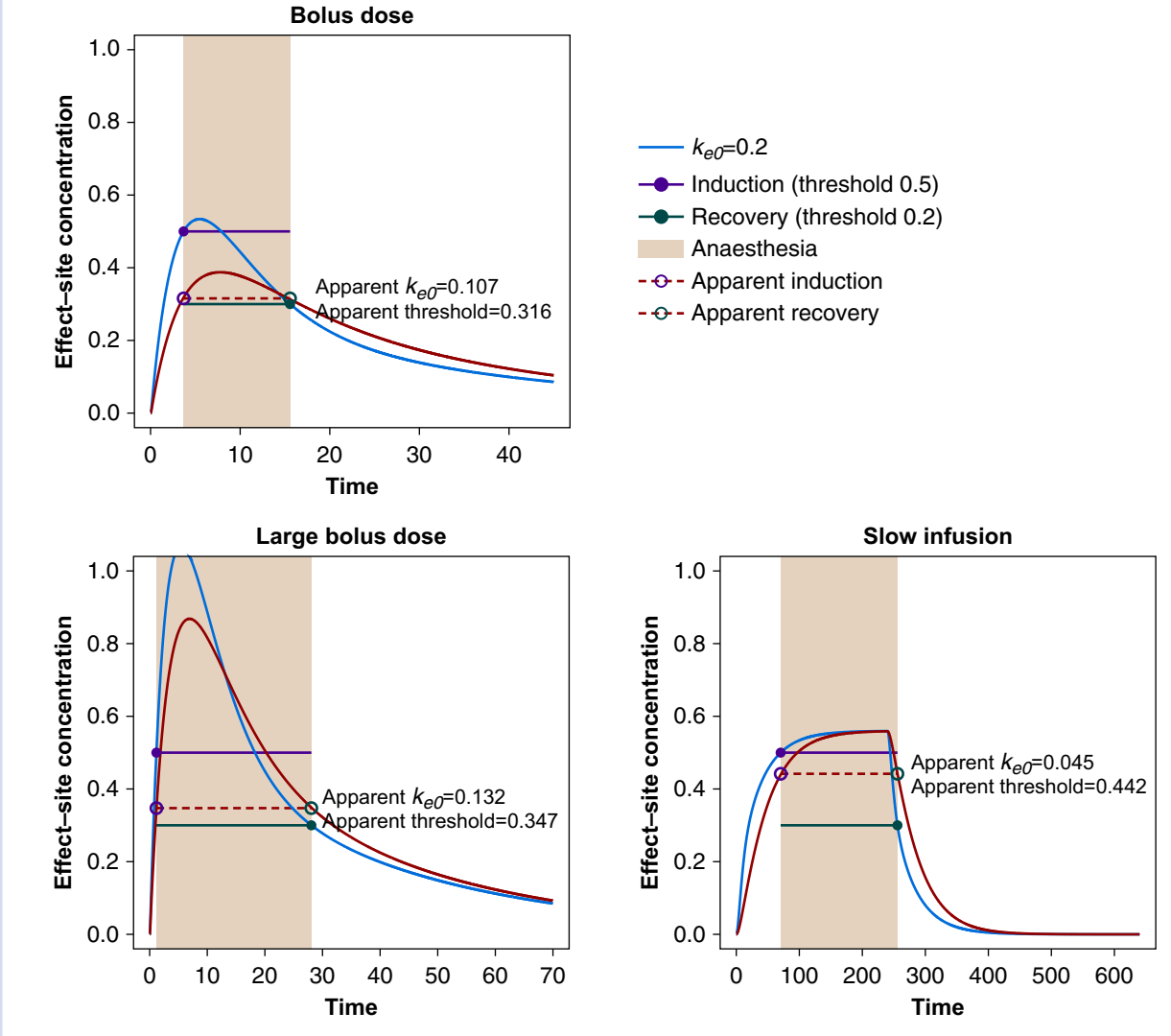

Fig. 1. Pharmacokinetic–pharmacodynamic (PK-PD) simulations of neural inertia and simulation to detect its presence with an 'unconstrained' k_{e0}. The grey line shows the true effect compartment concentration which induces anaesthesia when it exceeds 0.5 and recovery occurs when it is below 0.3. For each simulation, an apparent k_{e0} and singular threshold (i.e. absence of neural inertia) can be found that replicates the time of induction and recovery. We note that the apparent k_{e0} values and thresholds differ with dose and dosing rate. This may be useful information to detect neural inertia using PK-PD models.

compartmental clearances of 1. The k_{e0} value was fixed at 0.2 and the effect-site concentration at loss of responsiveness was assumed to be 0.5 and that at recovery 0.3. The results of the simulations for a bolus dose, a large bolus dose, and a slow infusion are shown in Fig 1. The grey line shows the effect-site concentration using a k_{e0} of 0.2 and the red and blue points indicate the moments of induction and recovery of anaesthesia.

The period of time while the individual remains unresponsive is shaded green. This is the period after the effect-site concentration has exceeded 0.5 but before it has diminished below 0.3. For each of these simulations, a k_{e0} could be found (black line) that resulted in loss and return of consciousness at the same time, but at the same effect-site concentration (i.e. the absence of neural inertia). Thus, the claim of Proekt & Kelz[1] appears correct: even if neural inertia exists, an unconstrained effect-site rate constant can result in the same experimental observations, thereby suggesting the absence of neural inertia.

We noticed from these simulations that to satisfy a condition of absent neural inertia, the apparent k_{e0} values differ across dosing methods. If an experiment was conducted in which an individual was administered a drug in these different ways, then a single apparent k_{e0} value would be unable to collapse all of the hysteresis loops. This inability could be taken as evidence for neural inertia. It remains to be seen whether such a study design is practically possible given the various measurement uncertainties. However, this does show that the observations of Proekt & Kelz[1] do not necessarily apply to all possible PK-PD study designs.

Anaesthetists witness the delay between injecting hypnotics i.v. and the onset/offset of drug effect every day in clinical practice, however proof that this delay is only governed by pharmacokinetics or by more complex phenomena also including neural dynamics is still lacking in humans. The clinical relevance of neural inertia during drug titration using principles of pharmacokinetics and pharmacodynamics is also unknown. Although it has been shown in animals that at a fixed drug concentration around the EC_{50} (population-based effect-site concentration for 50% of drug effect)[5] a subject can be either anaesthetised or awake, no information on the additional effect of neural dynamics on hysteresis is available at clinical levels of anaesthetic drug effect, more likely to be at EC_{95}.[10] If future research can prove that anaesthetic hysteresis in humans is significantly larger than that caused by the delay in equilibration between the plasma and effect-site concentrations, then we will have to re-evaluate and redesign pharmacometric study methods. Proekt & Kelz[1] suggest a method of studying neural inertia by exposing human subjects to either volatile or i.v. anaesthetic concentrations close to MAC-awake or EC_{50} awake at pharmacokinetic equilibrium similar to their animal experiments.[5] These experiments would be extremely difficult to execute, as a stimulus-free setting is required (no noise, no tubes, no BP cuff inflating, etc.) to avoid bias in the data.

For now, Proekt & Kelz[1] highlight the weakness of classical PK-PD modelling techniques in investigating neural inertia. This is very important information for researchers. However, their observations do not seem to apply to all possible PK-PD study designs. The search for the existence and clinical relevance of neural inertia in humans is still open to investigation using the classical PK-PD models, provided the study designs are informative. If we consider the aphorism of Proekt & Kelz[1] that the search for neural inertia using effect-site PK-PD models is as difficult as 'finding a black cat in a dark room,' this task is actually quite easy if the room is very small.

Authors' contributions

Wrote manuscript and approval of final manuscript: all authors

Declarations of interest

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Anaesthetic-induced developmental neurotoxicity on (neuro) steroids

Alex S. Evers

Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO, USA

E-mail: eversa@wustl.edu

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Neuroactive steroids alphaxalone and CDNC24 are effective hypnotics and potentiators of GABAA currents, but are not neurotoxic to the developing rat brain by Tesic et al., *Br J Anaesth* 2020:124:603–13, doi: 10.1016/j.bja.2020.01.013

The T-type calcium channel isoform Cav3.1 is a target for the hypnotic effect of the anaesthetic neurosteroid (3β,5β,17β)-3-hydroxyandrostane-17-carbonitrile by Timic Stamenic et al., *Br J Anaesth* 2021:126:245–255, doi: 10.1016/j.bja.2020.07.022

Keywords: alphaxalone; anaesthetic mechanism; apoptosis; calcium channel; gamma-aminobutyric acid; neurosteroid; neurotoxicity

Two decades ago, Jevtovic-Todorovic and colleagues[1] published the seminal observation that neonatal rodents developed neuroapoptosis and long-term cognitive deficits after administration of a mixture of general anaesthetics including midazolam, nitrous oxide, and isoflurane. Subsequent work has confirmed these findings in rodents and extended them to include most of the currently used anaesthetics.[2] The neurotoxic effects of anaesthetics appear to be dependent on the developmental time point of administration, number of exposures, and dose and duration of each exposure.[3,4] Most importantly, studies in non-human primates in which physiological and biochemical parameters can be closely monitored confirm the long-term behavioural changes associated with neonatal anaesthetic administration and do not identify a confounding physiologic variable (i.e. hypotension or hypoxaemia) as the cause of neurotoxicity.[4,5] The results of these animal model studies led the US Food and Drug Administration (FDA) to place a 'black-box' safety warning on a long list of anaesthetic agents regarding their use in neonates.

Human data have been more complex with several epidemiologic studies showing that prolonged and repeated anaesthetic exposures are associated with persistent behavioural changes,[6,7] but prospective trials showing that single brief exposures produce no discernible effect.[8,9] Unfortunately, the critical question of whether long or repeated general anaesthetic exposures are neurotoxic in human neonates is difficult to address, since infants needing general anaesthesia often have underlying conditions and require surgeries that can predispose to cognitive deficits. Efforts to address neurotoxic effects of prolonged and repeated human neonatal exposure to general anaesthesia have focused on the approach of identifying either a non-neurotoxic anaesthetic or a mitigating (neuroprotective) agent that could be used in clinical trials as a comparator to currently used agents.

The search for a non-toxic anaesthetic or mitigating agent would be facilitated by understanding the underlying biochemical mechanisms of anaesthetic-induced developmental neurotoxicity (AIDN) in animals. Regrettably, there is no consensus on mechanism or even whether neuronal apoptosis is causal of the persistent cognitive/behavioural deficits.[10] It is hypothesised that anaesthetic effects on synaptic activity at a critical time in nervous system development promote apoptotic death of neurones and glia, and loss of synaptic connectivity. Since most anaesthetics produce their anaesthetic effect by activating postsynaptic gamma-aminobutyric acid A ($GABA_A$) receptors or blocking *N*-methyl-D-aspartate (NMDA)-type glutamate receptors, these two neurotransmitter receptors have been a major focus of investigation.

Neurosteroids are endogenous brain metabolites of cholesterol that modulate inhibitory neuronal tone and are thought to act as endogenous regulators of mood.[11] The neurosteroids are efficacious modulators of $GABA_A$ receptors that act at specific binding sites to either enhance (3α-OH

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