BJA

British Journal of Anaesthesia, ■ (■): 1–12 (2017)

doi: 10.1016/j.bja.2017.11.072
Advance Access Publication Date: xxx
Clinical Investigation

CLINICAL INVESTIGATION

Neural inertia in humans during general anaesthesia: fact or fiction?

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Part of this study was presented as a poster at Euroanaesthesia, the European Anaesthesiology Congress, 2017, Geneva, Switzerland.

Abstract

Background: Neural inertia is defined as the tendency of the central nervous system to resist transitions between arousal states. This phenomenon has been observed in mice and *Drosophila* anaesthetized with volatile anaesthetics: the effect-site concentration required to induce anaesthesia in 50% of the population (C_{50}) was significantly higher than the effect-site concentration for 50% of the population to recover from anaesthesia. We evaluated this phenomenon in humans using propofol or sevoflurane (both with or without remifentanil) as anaesthetic agents.

Methods: Thirty-six healthy volunteers received four sessions of anaesthesia with different drug combinations in a step-up/step-down design. Propofol or sevoflurane was administered with or without remifentanil. Serum concentrations of propofol and remifentanil were measured from arterial blood samples. Loss and return of responsiveness (LOR-ROR), response to pain (PAIN), Patient State Index (PSI) and spectral edge frequency (SEF) were modeled with NONMEM®.

Results: For propofol, the C_{50} for induction and recovery of anaesthesia was not significantly different across the different endpoints. For sevoflurane, for all endpoints except SEF, significant differences were found. For some endpoints (LOR and PAIN) the difference was significant only when sevoflurane was combined with remifentanil.

Conclusions: Our results nuance earlier findings with volatile anaesthetics in mice and *Drosophila*. Methodological aspects of the study, such as the measured endpoint, influence the detection of neural inertia. A more thorough definition of neural inertia, with a robust methodological framework for clinical studies is required to advance our knowledge of this phenomenon.

Clinical trial registration: NCT 02043938.

Keywords: anaesthesia, general; anaesthesia, inhalation; anaesthesia, intravenous; consciousness monitors; unconsciousness/drug effects

Editorial decision: August 25, 2017; **Accepted:** August 25, 2017

Editor's key points

- Neural inertia, evident in differences in anaesthetic concentration at loss and recovery of consciousness, has been demonstrated in animal models
- Neural inertia involving multiple endpoints was investigated in human volunteers undergoing induction and emergence from propofol or sevoflurane anaesthesia with or without co-administered remifentanil
- Evidence for neural inertia was found for sevoflurane, greater in the presence of remifentanil, but not for propofol

Clinical observations give the impression that the relationship between hypnotic effect and hypnotic drug concentration at the effect site is different during induction and recovery of anaesthesia, resulting in a different effect-site concentration at loss (LOR) and return of responsiveness (ROR). To explain this phenomenon, Friedman and colleagues[1] introduced the concept of neural inertia, the tendency of the central nervous system to resist transitions between arousal states. They found that mice and flies, anaesthetized using steady-state titration of isoflurane or halothane, showed ROR at significantly lower volatile agent concentrations compared with the concentrations found at LOR. As a result, their concentration–response curves for the recovery phase shifts to the left compared with induction. Causality of this phenomenon was suggested, including a potential role for adrenergic effects and genetic predisposition.[1] If neural inertia is an intrinsic neurophysiological entity of neurones, neural networks or brain tissue, then the accompanying difference in concentration–response relationship between induction and recovery should exist for various hypnotic drugs and should be consistent across species.

The aim of this four-period randomized sequence crossover study was to evaluate the animal findings on neural inertia in humans using various pharmacodynamic endpoints frequently used in clinical practice (LOR–ROR, response to noxious stimulation, two derived electroencephalographic indices) during stepwise increasing and decreasing pseudo steady-state concentrations of propofol or sevoflurane with or without remifentanil. For this, we developed pharmacodynamic models for each endpoint and tested if adding model parameters describing neural inertia would result in a better fit of the data. Additionally, the influence of remifentanil on neural inertia was studied.

Methods

This study was registered at Clinical Trials.gov (Identifier NCT02043938) and approved by the Institutional Review Board of the University Medical Center Groningen (NL43238.042.13). All medical devices used in this study are approved for the purposes applied in the study. They are also clinically used in our hospital and are CE labelled. All drugs and the route of administration, either alone or in combination, are approved for clinical use under the studied conditions. No 'off-label' drug applications were used based on European regulations.

Screening, inclusion, exclusion, randomization

We included, in an age- and sex-stratified way (Table 1), 36 healthy volunteers (ASA physical status 1) with normal cognitive function. Volunteers were recruited by QPS (Groningen, The Netherlands), a certified contract research organization supporting preclinical and clinical drug development. Written informed consent was obtained from all volunteers prior to inclusion.

Exclusion criteria were weight <70% or >130% of ideal body weight, pregnancy, neurological disorder, diseases involving the cardiovascular, pulmonary, gastric, or endocrinological system, recent use of psychoactive medication, or intake of >20 g of alcohol daily. No ethnic-based criteria were applied in the selection.

The volunteers were scheduled to receive four sessions of anaesthesia with different drug combinations administered in a random order with a minimal interval of 1 week between sessions. Randomization was performed before each session by drawing a closed envelope. Any volunteer withdrawing from the study before finishing all sessions was replaced by a new recruited volunteer. The four sessions are named 'propofol alone' (Group P), 'sevoflurane alone' (Group S), 'propofol combined with remifentanil' (Group PR), and 'sevoflurane combined with remifentanil' (Group SR). During the sessions with remifentanil an effect-site concentration of 2 or 4 ng ml^{-1} was targeted. Inclusions were stratified according to age, sex and the targeted effect-site concentration of remifentanil (Ce_{REMI}). (Table 1).

Preparation, safety procedures and airway management

The study was executed in a quiet research unit near the operating rooms of the University Medical Center Groningen that was exclusively equipped for this study. This included all mandatory monitoring, airway management tools, and personnel to guarantee safe administration of anaesthetic drugs. All volunteers fasted for at least 6 h before the start of the drug administration. No premedication was administered. The volunteer was placed in a supine position and asked to relax and close their eyes before measurements started. An anaesthetic team, consisting of an experienced nurse anaesthetist and a board-certified anaesthetist, observed the volunteer throughout the study, and were responsible for drug administration, airway, and breathing support. An additional

Table 1 Stratification of 36 volunteers according to age, sex, and remifentanil effect-site concentration (Ce_{REMI}). Group P, propofol alone; Group S, sevoflurane alone; Group PR, propofol with remifentanil; Group SR, sevoflurane with remifentanil

Ce_{REMI}	0 ng ml^{-1} (Group P and S)	2 ng ml^{-1} (50% of Group PR and SR)	4 ng ml^{-1} (50% of Group PR and SR)
Age (yr)	Male/female	Male/female	Male/female
18–35	6/6	3/3	3/3
35–50	6/6	3/3	3/3
50–70	6/6	3/3	3/3
Total number of males/females	18/18	9/9	9/9