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Probability to tolerate laryngoscopy and noxious stimulation response index as general indicators of the anaesthetic potency of sevoflurane, propofol, and remifentanil

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Abstract

Background: The probability to tolerate laryngoscopy (P_{TOL}) and its derivative, the noxious stimulation response index (NSRI), have been proposed as measures of potency of a propofol–remifentanil drug combination. This study aims at developing a triple drug interaction model to estimate the combined potency of sevoflurane, propofol, and remifentanil in terms of P_{TOL}. We compare the predictive performance of P_{TOL} and the NSRI with various anaesthetic depth monitors.

Methods: Data from three previous studies (n=120) were pooled and reanalysed. Movement response after laryngoscopy was observed with different combinations of propofol–remifentanil, sevoflurane–propofol, and sevoflurane–remifentanil. A triple interaction model to estimate P_{TOL} was developed. The NSRI was derived from P_{TOL}. The ability of P_{TOL} and the NSRI to predict observed tolerance of laryngoscopy (TOL) was compared with the following other measures: (i) effect-site concentrations of sevoflurane, propofol, and remifentanil (Ce_{SEVO}, Ce_{PROP}, and Ce_{REMI}); (ii) bispectral index; (iii) two measures of spectral entropy; (iv) composite variability index; and (v) surgical pleth index.

Results: Sevoflurane and propofol interact additively, whereas remifentanil interacts in a strongly synergistic manner. The effect-site concentrations of sevoflurane and propofol at a P_{TOL} of 50% (Ce50; SE) were 2.59 (0.13) vol % and 7.58 (0.49) μg ml^{-1}. A Ce_{REMI} of 1.36 (0.15) ng ml^{-1} reduced the Ce50 of sevoflurane and propofol by 50%. The common slope factor was 5.22 (0.52). The P_{TOL} and NSRI predict the movement response to laryngoscopy best.

Conclusions: The triple interaction model estimates the potency of any combination of sevoflurane, propofol, and remifentanil expressed as either P_{TOL} or NSRI.

Key words: drug interactions; laryngoscopy; propofol; remifentanil; sevoflurane

† Both authors contributed equally to this study and should both be regarded as first author.

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Editor's key points

- The probability to tolerate laryngoscopy (P_{TOL}) and its derivative, noxious stimulation response index (NSRI), may be useful to quantify and compare the potency of volatile and i.v. anaesthetics, but it is not clear whether or not there are differences in the interactions of an opioid with a volatile anaesthetic and with an i.v. anaesthetic.
- A triple interaction model, which was developed using data from previous studies, indicated that sevoflurane and propofol interact additively, whereas remifentanil interacts in a strongly synergistic manner.
- The triple interaction model can estimate the potency of any combination of sevoflurane, propofol, and remifentanil.

Adequate anaesthesia can be defined as the combination of an accurate level of hypnosis with sufficient analgesia to avoid response to a noxious stimulation, where 'response' includes a variety of modalities, such as movement, haemodynamic response, or arousal. Most contemporary anaesthetic depth monitors are based on the processed EEG and correlate mainly with hypnotic drug effect; however, they do not reliably predict a response to noxious stimulation.[1 2] Recent attempts to measure analgesia, based on the variability of the processed EEG signal[3] or on changes in the autonomic nervous system as measured by pulse plethysmography,[4 5] were only partly successful. Similar decreasing accuracy was found for the propofol effect-site concentration (Ce_{PROP}) as a measure of drug effect in the presence of opioids.[1 2]

For decades, the probability of response to skin incision, defined as the minimal alveolar concentration (MAC), has been used to quantify and compare the potency of volatile agents.[6–9] More recently, Bouillon and colleagues[10] defined tolerance of laryngoscopy (TOL) as an absence of movement response to laryngoscopy, and they proposed the probability to tolerate laryngoscopy (P_{TOL}) as an alternative to MAC when using propofol instead of volatile agents. For ergonomic reasons and in order to cope with the clinical conformity of standard depth of anaesthesia monitoring, Luginbühl and colleagues[11] normalized and calibrated P_{TOL} towards a new index called the noxious stimulation response index (NSRI). The NSRI is a numerical depth of anaesthesia indicator that is directly derived from P_{TOL} and was first described for propofol and remifentanil anaesthesia. The NSRI and P_{TOL} are therefore interchangeable; they merely differ in scale. The NSRI is scaled between 100 (when no anaesthetic drugs are administered) and zero (indicating extensive combined drug effects), whereas P_{TOL} scales from zero to one.

Until now, specific P_{TOL} results have been found in three different drug interaction studies, resulting in separate response surface models for propofol–remifentanil,[10] sevoflurane–propofol,[12] and sevoflurane–remifentanil.[13] In order to use P_{TOL} (and NSRI) as general probabilistic parameters to represent the lack of responsiveness to a noxious stimulation in both i.v. and volatile anaesthesia conditions, supplemented with opioids, one needs to solve the problems of whether synergy of remifentanil with propofol is stronger than synergy with sevoflurane and whether the slope of the propofol–remifentanil and the sevoflurane–remifentanil response surfaces are different. This may be clarified by developing a triple interaction surface model, merging the information from the previously published dual drug models,[10 12 13] hereby also rescaling and expanding previously published P_{TOL} and NSRI scales.

For clinicians, a general P_{TOL} and its derivative, NSRI, would enable estimation of the concentration of sevoflurane that is equipotent to a given propofol concentration when used in combination with remifentanil.

The primary purpose of the present study was to define a triple interaction response surface model to express the potency of any combination of sevoflurane, propofol, and remifentanil in terms of P_{TOL} and NSRI by merging the raw data from three previously published studies.[10 12 13] The secondary purpose was to test the ability of P_{TOL} and NSRI, calculated with the new triple interaction model parameters, to predict the observed TOL. We compared the performance of P_{TOL} and NSRI with other measures, such as single drug effect-site concentrations of sevoflurane, propofol, and remifentanil (Ce_{SEVO}, Ce_{PROP}, and Ce_{REMI}), current hypnotic effect monitors, such as the EEG-derived bispectral index (BIS; Covidien, Boulder, CO, USA)[14] and two measures of the EEG-derived spectral entropy, state entropy and response entropy (SE and RE; GE Healthcare, Helsinki, Finland),[15] and newer analgesic effect monitors, such as the BIS-derived composite variability index (CVI; Covidien)[3 16] and pulse plethysmograph-derived surgical pleth index (SPI; GE Healthcare).[5]

Methods

We performed a response surface analysis of the pooled raw data from three previously published studies on interactions between sevoflurane, propofol, and remifentanil.[10 12 13 17] The Ethics' Committees from these original studies (Ghent University Hospital, Gent, Belgium and Stanford University, Stanford, CA, USA) both agreed that the anonymized original databases could be re-used for this analysis. As the original studies were executed and published long before the introduction of the public registration requirements, no registration of the original studies was possible.

The characteristics of the study populations are summarized in Supplementary File 1 and in the Results section. The study design and drug administration protocol have been described in detail in each of the studies. Briefly, combinations of propofol–remifentanil,[10] sevoflurane–propofol,[12] and sevoflurane–remifentanil[13 17] were administered using a modified criss-cross design according to Short and colleagues.[18] Propofol and remifentanil were administered as computer-controlled infusions targeting effect-site or plasma concentrations using the pharmacokinetic and pharmacodynamic models by Schnider[19 20] and Minto,[21 22] respectively. While Bouillon and colleagues[10] used targeted plasma concentrations and observed an equilibration time of 15 min, Schumacher and colleagues[12] and Heyse and colleagues[13 17] applied target effect-site concentrations with an equilibration time of 12 min. Sevoflurane was titrated to achieve predetermined end-tidal concentrations using an ADU ventilator with an integrated AS3 monitor (GE Healthcare). These equilibration times are considered sufficient for all drugs to allow equilibration between the plasma and effect-site concentration. Acceptable prediction errors of the Schnider and Minto models were confirmed in the propofol–remifentanil study by means of repetitive blood sample analysis for propofol and remifentanil published previously.[23] A steady state for sevoflurane was confirmed through end-tidal measurements of sevoflurane concentrations. In all three studies, after equilibration of plasma and effect-site concentrations, a series of stimuli was applied and the presence or absence of movement response recorded. However, only TOL was used in our final analysis after initial model validation (see Results section).

The following drug effect monitors were used: BIS (BIS Version 3.22, A1000; Covidien) by Bouillon and colleagues;[10] BIS (Version