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

L. N. Hannivoort1,†, H. E. M. Vereecke1,†,* , J. H. Proost1, B. E. K. Heyse2, D. J. Eleveld1, T. W. Bouillon3, M. M. R. F. Struys1,2 and M. Luginbühl4

1Department of Anaesthesiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands, 2Department of Anaesthesia, Ghent University, Gent, Belgium, 3Consulting Scientist, Arlesheim, Switzerland, and 4Department of Anaesthesiology, Spital Tiefenau, University of Bern, Bern, Switzerland

*Corresponding author. E-mail: h.e.m.vereecke@umcg.nl

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 ($C_{eSEVO}$, $C_{ePROP}$, and $C_{eREMI}$); (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% ($Ce50$; $ss$) 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.

Accepted: February 25, 2016

© The Author 2016. Published by Oxford University Press on behalf of the British Journal of Anaesthesia. All rights reserved. For Permissions, please email: journals.permissions@oup.com
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. Recent attempts to measure analgesia, based on the variability of the processed EEG signal or on changes in the autonomic nervous system as measured by pulse plethysmography, were only partly successful. Similar decreasing accuracy was found for the propofol effect-site concentration (\(C_{ePROP}\)) as a measure of drug effect in the presence of opioids.

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. More recently, Bouillon and colleagues 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 normalized and calibrated adequate 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, 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. 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 (\(C_{eSEVO}, C_{ePROP}, \) and \(C_{eREMI}\)), current hypnotic effect monitors, such as the EEG-derived bispectral index (BIS; Coviden, Boulder, CO, USA) and two measures of the EEG-derived spectral entropy, state entropy and response entropy (SE and RE; GE Healthcare, Helsinki, Finland), and newer analgesic effect monitors, such as the BIS-derived composite variability index (CVI; Coviden) and pulse plethysmography-derived surgical pleth index (SPI; GE Healthcare).

**Methods**

We performed a response surface analysis of the pooled raw data from three previously published studies on interactions between sevoflurane, propofol, and remifentanil. 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, sevoflurane–propofol, and sevoflurane–remifentanil were administered using a modified cross-over design according to Short and colleagues. Propofol and remifentanil were administered as computer-controlled infusions targeting effect-site or plasma concentrations using the pharmacokinetic and pharmacodynamic models by Schneider and colleagues, Schneider and Minto, respectively. While Bouillon and colleagues used targeted plasma concentrations and observed an equilibration time of 15 min, Schumacher and colleagues and Heyse and colleagues 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 Schneider and Minto models were confirmed in the propofol–remifentanil study by means of repetitive blood sample analysis for propofol and remifentanil published previously. 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; Coviden) by Bouillon and colleagues, BIS (Version...
The pharmacodynamic model

The synergistic interactions between propofol and remifentanil and between sevoflurane and remifentanil were best described by the modified hierarchical model, whereas the additive interaction between sevoflurane and propofol was best described by the Greco model. We therefore postulated that the interaction of the three compounds could be described by considering any combination of the three drugs as a virtual new drug with the potency of the drugs according to equations (2):

\[ U = \left( \frac{C_{SEVO}}{Ce_{50SEVO}} + \frac{C_{PROP}}{Ce_{50PROP}} \right) \times \left( 1 + \left( \frac{C_{REMI}}{Ce_{REMI}} \right)^{\gamma} \right) \]  

where \( C_{SEVO}, C_{PROP}, \) and \( C_{REMI} \) are the effect-site concentrations of sevoflurane, propofol, and remifentanil, respectively, \( Ce_{50SEVO} \) and \( Ce_{50PROP} \) are the effect-site concentrations of sevoflurane and propofol, respectively, resulting in an apparent decrease of the \( Ce_{50SEVO} \) and \( Ce_{50PROP} \) by 50% and \( \gamma \) is the slope parameter of the concentration-effect relationship of sevoflurane and propofol; \( \gamma_o \) is the slope parameter of propofol.

According to the parameter estimates of the original studies (Table 1), our hypothesis was that \( Ce_{50REMI} \) by a factor of 2 or an apparent decrease of the \( Ce_{50SEVO} \) and \( Ce_{50PROP} \) by 50% and \( \gamma \) was the steepness of the concentration-effect relationship of the opioid.

Thus, \( SF = 0 \) if \( C_{SEVO} = 0 \) and \( SF = 1 \) if \( C_{PROP} = 0 \) and \( SF \) is a zero and one for mixtures of sevoflurane and propofol.
The purpose of the model developed from the data is to predict $P_{TOL}$ of random individuals in a population. Similar to the MAC, a $P_{TOL}$ of 50% is the concentration where 50% of a population tolerates laryngoscopy without movement response (TOL). The individual concentration–response of the ‘typical subject’ was therefore not the focus of the study, and inter-individual variability was not included in the parameter estimation (naive pooling approach).

**Selection of the final model and parameter estimation**

In the first step, the data from each study were separately fitted to the model [equations (1)–(6)] in order to determine the effect of considering only TOL instead of the whole series of stimuli as previously published. In the second step, a fit of the pooled TOL data was performed. In the pooled fit, the parameters $C_{e,S}^{SEVO}, C_{e,S}^{PROP}, C_{e,S}^{REMI}, \gamma_s$, and $\eta$ were estimated assuming that the parameters $C_{e,S}^{REMI}$, $\eta$, and $\gamma_s$ were identical for the two hypnotics sevoflurane and propofol. Then we tested whether different values for $C_{e,S}^{REMI}$, $\eta$, or $\gamma_s$ for sevoflurane and propofol significantly improved the fit. In addition, we tested whether $\gamma_s$ was significantly different from one. The results were accepted as valid only if both minimization and covariance steps were successful, unless stated otherwise.

The model parameters were estimated using NONMEM 7.2.0 (Icon Development Solutions, Hanover, MD, USA), using the Laplace method. The software was installed on a GNU Fortran 95 compiler (http://gcc.gnu.org) with Windows XP operating system (Microsoft, Redmond, WA, USA). PLT Tools (PLTsoft, San Francisco, CA, USA) was used as graphical user interface.

To determine the final model, non-parametric 95% confidence intervals (CIs) were calculated, using a bootstrap analysis based on 2000 sets, stratified according to the original studies. Assuming a $\chi^2$ distribution with one degree of freedom, an improvement of the objective function value of 3.84, corresponding to a $P$ value of <0.05, was considered significant.

The $P_{TOL}$ was calculated from equation (1) and NSRI from equation (7):

$$\text{NSRI} = 1 + \left( \frac{P_{TOL}}{1 - P_{TOL}} \right)^{-1}$$

where $s$ is a constant ($s=0.63093$).

For further information on the transformation of $P_{TOL}$ to NSRI, see Supplementary File 2.

**Model evaluation**

The data of responders and non-responders were plotted together with the 50 and 90% isoboles, derived from the original models, and the final model for visual inspection of the goodness of fit. Additionally, we plotted the observed $P_{TOL}$ against the $P_{TOL}$ predicted by all models to compare the ability of the final model for $P_{TOL}$ with the previously published models. The observed $P_{TOL}$ was obtained from the raw data according to the following procedure. For each observation (response or no response to laryngoscopy), the predicted $P_{TOL}$ was calculated from the effect-site concentrations and model parameters (Table 1) using equations (1) and (2). Then the predicted $P_{TOL}$ of each observation and the related true response (0 or 1) were sorted with increasing value of predicted $P_{TOL}$. The observed $P_{TOL}$ was defined as the average of the response of the index observation and the next 10 observations with a lower and a higher predicted $P_{TOL}$. The observed $P_{TOL}$ is thus a moving average over 21 observations, where the missing values at the lower and upper end were omitted. The resulting plots allow a visual inspection of the goodness of fit, as shown in Supplementary File 3. The mean absolute prediction error (MAPE) was calculated as the mean of the absolute value of the difference between the observed and predicted $P_{TOL}$. For clarification to the reader, the ‘observed $P_{TOL}$’ is used only for this specific model validation. Otherwise in this work, $P_{TOL}$ always refers to the ‘predicted $P_{TOL}$’.

In a second validation, we used the raw data of two original studies for parameter estimation and the raw data of the third study for model validation, as shown in the Supplementary File 4.

**Assessment of prediction probability**

The prediction probability ($P_K$) is based on multiple comparisons of two data points from the total data set, to investigate the degree of association between each predictor and the observed tolerance. A $P_K$ value of 0.5 implies no association, thus a poor prediction probability; a value of one implies complete association, thus an excellent prediction probability. 25 26

We used $P_K$ to assess the performance of predicted $P_{TOL}$, its derivative, NSRI, and the observed BIS, SE, RE, CVI, and SPI to predict TOL. For comparison, the $P_K$ values of the single drug concentrations ($C_{e,SEVO}, C_{e,PROP},$ and $C_{e,REMI}$) were also determined. Using single drug concentrations as estimates of the likelihood of tolerance does not take into account the effect of simultaneously administered drugs; therefore, we hypothesized that they are less accurate than the predicted $P_{TOL}$ as a result of this limitation.

The drug concentrations, their related variables, and the monitor records immediately before the stimulus series were used as independent variables to predict the response. To ensure that the predicted $P_{TOL}$ and its derivative, NSRI, are independent of the observed $P_{TOL}$, the calculation of $P_K$ for $P_{TOL}$ and NSRI was performed by a two-fold cross-validation procedure. The total data set was divided into two subsets, each containing 60 patients, randomly drawn from the propofol–remifentanil10 (10 patients), sevoflurane–propofol12 (30 patients), and sevoflurane–remifentanil13 (20 patients) studies. In each subset, a population interaction model was modelled and used for calculating $P_{TOL}$ and NSRI in the other subgroup. The parameter estimates for calculating $P_{TOL}$ and NSRI from one subgroup were thus used to validate the prediction in the other subgroup.

Bootstrapping (1000 replicates) was used to determine 95% CIs of the $P_K$ values for each predictor and also the difference between the $P_K$ values of each combination of two predictors. Significance was achieved if the 95% CI of the difference did not include zero ($P<0.05$).

All $P_K$ calculations were performed in Excel 2003 (Microsoft) using VBA macros.

**Statistical analysis**

In all patients, we were able to compare the predictive performance of predicted $P_{TOL}$, NSRI, $C_{e,SEVO}, C_{e,PROP}, C_{e,REMI}$, and BIS to predict TOL ($P_K$ performance comparison 1). In data obtained from the sevoflurane–propofol and the sevoflurane–remifentanil studies, SE and RE were additionally available as predictors ($P_K$ performance comparison 2). In the data obtained from the sevoflurane–remifentanil study, SPI and CVI were also evaluated, as predictors of TOL ($P_K$ performance comparison 3). Results of each performance comparison should be seen as a separate test of performance because the data sets are different.

Statistical significance is set to $P<0.05$ unless stated otherwise. All model parameters are reported as typical values with
ss within parentheses. Clinical data are given as mean and so or as median and range, when appropriate.

Results

Study population

The characteristics of the populations of the three studies were comparable. The mean (range) weight was 69 (50–120), 66 (50–102), and 64 (50–103) kg in the propofol–remifentanil,10 the sevoflurane–propofol,12 and the sevoflurane–remifentanil13 trial, respectively. The mean height was 159 (155–194), 172 (150–190), and 172 (157–186) cm, the mean age 34 (20–43), 30 (18–58), and 26 (18–54) yr, and the gender ratio (female/male) 10/10, 33/27, and 26/14, respectively.

Common response surface of sevoflurane, propofol, and remifentanil

The results of the reanalysis of the three studies by separate and pooled analysis of the laryngoscopy data are summarized in Table 1, together with the results reported in the original papers. The separate reanalysis of each study gave slightly different results from those reported in the original paper, because only the laryngoscopy data were included and because inter-individual variation of the parameter estimates was not included in our analysis.

In the pooled analysis of the laryngoscopy data from the three studies, we could not confirm the hypothesis that Ce50REM and γ are different for sevoflurane and propofol. In addition, γRE was not significantly different from one. When the Ce50REM was allowed to vary between sevoflurane and propofol, the parameter estimates were 1.37 and 1.33 ng ml⁻¹, respectively, with an ‘improvement’ of the NONMEM objective function of 0.018. When γ was allowed to vary between sevoflurane and propofol, the parameter estimates (ss) were 5.55 (0.74) and 4.71 (0.87), respectively, with an improvement of the NONMEM objective function of 0.420. As a result, the data of the three studies can be well described with only four model parameters (Ce50SEVO, Ce50PROP, Ce50REM, and γ), with good precision (i.e. the ss values were smaller than in the original papers and in the separate analysis; Table 1). Equation (2) may therefore be simplified to:

\[
U = \left(\frac{Ce_{50SEVO}}{Ce_{50SEVO} + Ce_{50PROP}}\right) \times \left(1 + \frac{Ce_{REM}}{Ce_{REM}}\right)
\]  

also known as the reduced Greco model.7 17 Equation (8) is thus the final model of the combined effect of sevoflurane, propofol, and remifentanil.

The CIs calculated from the bootstrap analysis are presented in Table 1. In order to calculate P_TOL using equation (1), U was calculated using equation (8) by entering the parameter estimates of the pooled analysis in the formula (Table 1). Figure 1 shows the presence or absence of TOL as a function of U.

Model evaluation

The 50 and 90% TOL isoboles and the raw data of responders and non-responders are shown in Figure 2A–C. The MAPE was calculated for the following three models: (i) a model as published (i.e. computed from the raw data of each single study including the response to all applied stimuli); (ii) a model reanalysed from the data of each single study including the response to laryngoscopy only; and (iii) the final model computed from the pooled data of all three studies including response to laryngoscopy only. For propofol–remifentanil, the MAPEs of the predicted P_TOL of the resulting models were 1.8, 2.3, and 3.9%, respectively. For sevoflurane–propofol, the MAPEs were 14.6, 6.8, and 6.9%, and for sevoflurane–remifentanil, the MAPEs were 5.3, 3.0, and 4.1%, respectively. Thus, the MAPE values of the triple interaction model are close to those of the separate reanalysis of each study and are lower than those obtained from the published models, except for propofol–remifentanil, where MAPE is low for all models. The reason for the rather large MAPE for the sevoflurane–propofol data is visible in Figure 1. In the absence of remifentanil, the maximal U was only 1.56, which was only little above the range of U where responders and non-responders were observed. A plot of observed vs predicted P_TOL allowing for a visual inspection of the goodness of fit is presented in Supplementary File 3. The result of the cross-validation based on parameter estimation from the raw data of two studies and validation with the raw data of the third study is presented in Supplementary File 4.

Prediction probability

Table 2 shows the results for Pₚ to assess the performance of P_TOL, its derivative, NSRI, and the observed BIS, SE, RE, CVI, and SPI to predict TOL. For comparison, the Pₚ values of the single drug concentrations (Ce_{SEVO}, Ce_{PROP} and Ce_{REM}) were also determined and are shown in Table 2.

Discussion

With a pooled analysis of data from three previously published studies of similar design on dual drug interactions, a triple interaction model was developed to describe the anaesthetic potency of combinations of sevoflurane, propofol, and remifentanil in terms of P_TOL and its derivative, the NSRI. The model that fits the data best can be interpreted as an extension of the hierarchical hypnotic–opioid interaction model published previously.10 11 13 25 We found that the interaction between sevoflurane and propofol is additive when their concentrations are normalized to their respective effect-site concentration inducing TOL in 50%
of the population. This is a confirmation of earlier work. Remifentanil has a strong but equally synergistic effect on sevoflurane and propofol. In contrast to original publications, the pooled analysis did not support different Ce50 values for remifentanil nor different slope factors for sevoflurane and propofol. This is not surprising, because the se values of both parameters were ~20% in the study by Heyse and colleagues and ~40% in the study by Bouillon and colleagues for Ce50, and the 95% CIs for the slopes were overlapping in all three studies. As such, our common Ce50EMI and slope are within the se of the values published previously (Table 1).

Various model validation methods were applied and proved that our final model describes the data accurately and represents clinical reality. In Figure 2, the 50 and 90% P TOL isoboles calculated with the triple interaction model and with the previous two-drug interaction models are plotted together with the raw data from the three studies to demonstrate the goodness of fit. Additionally, the clinically used BIS 40 and BIS 60 isoboles as predicted from previous studies are shown. The difference in the shape of the isoboles is related to the difference in Ce50 values and the different slopes between current and previously published models (Table 1). For remifentanil concentrations >2 ng ml⁻¹, the 90% P TOL isobole is between the BIS 40 and BIS 60 isobole, which corresponds to clinical dosing practice. This is consistent with previous data on the sevoflurane–remifentanil interaction by Manyam and colleagues, who demonstrated that the 95% isobole for suppressing response to tetanic stimulation was between the BIS 60 and 70 isobole at remifentanil concentrations greater than ~3 ng ml⁻¹. The additive 50 and 90% isoboles for the sevoflurane and propofol interaction (straight lines) are well above the BIS 40 isobole, which reflects the fact that the EEG-suppressing effect of the two hypnotic drugs is much stronger than the potency to suppress the response to laryngoscopy.

In a general sense, P TOL can be considered an extension of the clinically applied MAC concept. For the first time, the potency of inhaled and i.v. hypnotic drugs can be compared uniformly. Using our triple interaction model, the potency of any combination of sevoflurane, propofol, and remifentanil can be expressed as P TOL or its derivative, NSRI. For example, a Ce REMI of 3 ng ml⁻¹ combined with either a CePROP of 3 µg ml⁻¹ or a Ce REMI of 1.03 vol % will yield a P TOL of 0.7 or an NSRI of 31 and are thus considered equipotent. A more detailed clinical application is shown in Supplementary File S. In a simulated anaesthesia induction with a bolus of propofol and a remifentanil target-controlled infusion, the time when sevoflurane needs to be administered depends on the size of the propofol bolus and the remifentanil concentration. The interaction model allows compensation for the decay of the propofol effect-site concentration by increasing the effect-site concentration of sevoflurane, in order to maintain a predefined total potency of the drugs in terms of P TOL.

In the population, TOL was best predicted by P TOL and NSRI (Table 2), whereas Ce REMI, CePROP, Ce REMI, and BIS were intermediate (0.7) and CePROP was a poor predictor of TOL. In data obtained from the sevoflurane–propofol and the sevoflurane–remifentanil studies, SE and RE were also available and showed a moderate predictive accuracy, similar to BIS. In the data obtained from the sevoflurane–remifentanil study, CVI was found to be a moderately accurate predictor of TOL. The SPI was not able to predict TOL. Both P TOL and NSRI outperformed the other measures in both sub-analyses.

A limitation of our study is that our triple interaction model is based on pooled data from three independently performed two-
drug interaction studies, so no patient was given a combination of all three drugs. As a result, our model neither detects nor excludes a superimposed triple interaction in patients who receive all three drugs simultaneously. In a large triple interaction study on midazolam, propofol, and alfentanil, Minto and colleagues found significant synergistic interactions of each pair of these compounds but no additional triple interaction when three drugs were combined. A significant and relevant triple interaction does not therefore seem likely, considering the additive interaction between sevoflurane and propofol, and the strong and similar synergistic interaction of remifentanil with both hypnotic drugs. Our model does produce predictions about $P_{\text{TOL}}$ when all three drugs are administered simultaneously, and these predictions are open to hypothesis testing. Outside of our model, these predictions are not available because no other triple interaction model exists for these drugs in current literature.

In conclusion, our response surface interaction model allows estimation of the potency of any combination of sevoflurane, propofol, and remifentanil as the probability to tolerate laryngoscopy. The $P_{\text{TOL}}$ and its derivative, the NSRI, are good predictors of TOL and its derivative, the NSRI. The other authors declare no conflicts of interest.

**Funding**

Departmental and institutional funding. Two of the underlying studies were supported by a non-restrictive educational grant from Dräger Medical (Lübeck, Germany).

**References**


**Supplementary material**

Supplementary material is available at British Journal of Anaesthesia online.

**Authors’ contributions**


Acquisition of data: B.H., T.B., M.L., M.M.R.F.S.

Data analysis: J.H.P., D.J.E.


**Declaration of interest**

M.M.R.F.S. and M.L. have received unrestricted educational grants from Dräger Medical, Lübeck, Germany. M.M.R.F.S. is an editor and editorial board member for the British Journal of Anaesthesia but was not involved in the editorial process of this work. The other authors declare no conflicts of interest.

**Table 2** Prediction probabilities ($P_{\text{TOL}}$) of all studied measures to detect tolerance of laryngoscopy. Numbers are prediction probabilities according to Smith and colleagues estimated from the data (95% confidence intervals estimated from a bootstrap analysis). The best predictor for each stimulus is highlighted (bold). *P<0.05 compared with $C_{\text{SEVO}}$. †P<0.05 compared with $C_{\text{SEVO}}, C_{\text{PROP}}, C_{\text{REMI}}$, and BIS. ‡P<0.05 compared with $C_{\text{SEVO}}$, $C_{\text{PROP}}, C_{\text{REMI}}$, BIS, SE, and RE. §P<0.05 compared with $C_{\text{SEVO}}, C_{\text{PROP}}, C_{\text{REMI}}$, BIS, SE, RE, CVI, and SPI. $P_{\text{TOL}}$ is the ‘predicted $P_{\text{TOL}}$’ calculated from the effect-site concentrations and model parameters. $C_{\text{SEVO}}, C_{\text{PROP}}$ and $C_{\text{REMI}}$ are the effect-site concentrations of sevoflurane, propofol and remifentanil, respectively; BIS, Bispectral Index; SE, State Entropy; RE, Response Entropy; CVI, Composite Variability Index; SPI, Surgical Plet Index.

<table>
<thead>
<tr>
<th>$C_{\text{SEVO}}$</th>
<th>$C_{\text{PROP}}$</th>
<th>$C_{\text{REMI}}$</th>
<th>BIS</th>
<th>SE</th>
<th>RE</th>
<th>CVI</th>
<th>SPI</th>
<th>$P_{\text{TOL}}$ and NSRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole population (n=120)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.73*</td>
<td>0.46</td>
<td>0.67*</td>
<td>0.71*</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.92† (0.90–0.94)</td>
</tr>
<tr>
<td>(0.68–0.77)</td>
<td>(0.41–0.51)</td>
<td>(0.61–0.72)</td>
<td>(0.66–0.77)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroups sevoflurane–propofol and sevoflurane–remifentanil (n=100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.71*</td>
<td>0.41</td>
<td>0.70*</td>
<td>0.65*</td>
<td>0.69*</td>
<td>0.69*</td>
<td>–</td>
<td>–</td>
<td>0.92‡ (0.89–0.94)</td>
</tr>
<tr>
<td>(0.66–0.76)</td>
<td>(0.35–0.47)</td>
<td>(0.65–0.74)</td>
<td>(0.59–0.71)</td>
<td>(0.63–0.75)</td>
<td>(0.63–0.75)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup sevoflurane–remifentanil (n=40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.76*</td>
<td>–</td>
<td>0.72</td>
<td>0.78§</td>
<td>0.78§</td>
<td>0.77§</td>
<td>0.74</td>
<td>0.57</td>
<td>0.95§ (0.91–0.98)</td>
</tr>
<tr>
<td>(0.68–0.84)</td>
<td></td>
<td>(0.64–0.80)</td>
<td>(0.69–0.86)</td>
<td>(0.68–0.86)</td>
<td>(0.67–0.86)</td>
<td>(0.62–0.84)</td>
<td>(0.48–0.69)</td>
<td></td>
</tr>
</tbody>
</table>
18. Short TG, Ho TY, Minto CF, Schnider TW, Shafer SL. Efficient trial design for eliciting a pharmacokinetic-pharmacodynamic model-based response surface describing the interaction between two intravenous anesthetic drugs. *Anesthesiology* 2002; **96**: 400–8
22. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. *Anesthesiology* 1997; **86**: 24–33
27. Sebel LE, Richardson JE, Singh SP, Bell SV, Jenkins A. Additive effects of sevoflurane and propofol on γ-aminobutyric acid receptor function. *Anesthesiology* 2006; **104**: 1176–83
29. Manyam SC, Gupta DK, Johnson KB, et al. When is a bispectral index of 60 too low? Rational processed electroencephalographic targets are dependent on the sedative-opioid ratio. *Anesthesiology* 2007; **106**: 472–83

Handling editor: T. Asai