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ANESTHESIOLOGY

Population Pharmacodynamics of Propofol and Sevoflurane in Healthy Volunteers Using a Clinical Score and the Patient State Index

A Crossover Study

Merel H. Kuizenga, M.D., Pieter J. Colin, Ph.D., Koen M. E. M. Reyntjens, M.D., Daan J. Touw, Ph.D., Hasan Nalbat, R.N., Froukje H. Knotnerus, R.N., Hugo E. M. Vereecke, M.D., Ph.D., Michel M. R. F. Struys, M.D., Ph.D.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Hypnotic drug effects can be assessed as the presence or absence of standard clinical endpoints, such as tolerance to calling the person by name and tolerance to shake and shout
- Antinociceptive drug effects can be assessed as the presence or absence of tolerance to tetanic stimulus
- The Patient State Index is a processed, electroencephalographic-derived index that is considered by some to be a drug-independent representation of the depth of sedation and anesthesia

What This Article Tells Us That Is New

- A four-period randomized sequence crossover study determined the concentration–effect relationships for both propofol and sevoflurane, both with and without remifentanil coadministration, with effects measured as tolerance to standard stimuli and by the Patient State Index
- The sevoflurane Patient State Index values associated with a 50% probability of tolerance to the standard stimuli were higher for than those for propofol
- Adding a 2 ng · ml^{-1} predicted effect-site remifentanil concentration increased all Patient State Index values associated with a 50% probability of tolerance to the standard stimuli, but 4 ng · ml^{-1} produced additional effects only during propofol administration

ABSTRACT

Background: The population pharmacodynamics of propofol and sevoflurane with or without opioids were compared using the endpoints no response to calling the person by name, tolerance to shake and shout, tolerance to tetanic stimulus, and two versions of a processed electroencephalographic measure, the Patient State Index (Patient State Index-1 and Patient State Index-2).

Methods: This is a reanalysis of previously published data. Volunteers received four anesthesia sessions, each with different drug combinations of propofol or sevoflurane, with or without remifentanil. Nonlinear mixed effects modeling was used to study the relationship between drug concentrations, clinical endpoints, and Patient State Index-1 and Patient State Index-2.

Results: The C_{50} values for no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation for propofol (μg · ml^{-1}) and sevoflurane (vol %; relative standard error [%]) were 1.62 (7.00)/0.64 (4.20), 1.85 (6.20)/0.90 (5.00), and 2.82 (15.5)/0.91 (10.0), respectively. The C_{50} values for Patient State Index-1 and Patient State Index-2 were 1.63 μg · ml^{-1} (3.7) and 1.22 vol % (3.1) for propofol and sevoflurane. Only for sevoflurane was a significant difference found in the pharmacodynamic model for Patient State Index-2 compared with Patient State Index-1. The pharmacodynamic models for Patient State Index-1 and Patient State Index-2 as a predictor for no response to calling the person by name, tolerance to shake and shout, and tetanic stimulation were indistinguishable, with Patient State Index$_{50}$ values for propofol and sevoflurane of 46.7 (5.1)/68 (3.0), 41.5 (4.1)/59.2 (3.6), and 29.5 (12.9)/61.1 (8.1), respectively. *Post hoc* C_{50} values for propofol and sevoflurane were perfectly correlated (correlation coefficient = 1) for no response to calling the person by name and tolerance to shake and shout. *Post hoc* C_{50} and Patient State Index$_{50}$ values for propofol and sevoflurane for tolerance to tetanic stimulation were independent within an individual (correlation coefficient = 0).

Conclusions: The pharmacodynamics of propofol and sevoflurane were described on both population and individual levels using a clinical score and the Patient State Index. Patient State Index-2 has an improved performance at higher sevoflurane concentrations, and the relationship to probability of responsiveness depends on the drug used but is unaffected for Patient State Index-1 and Patient State Index-2.

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It remains unclear how to quantitatively compare the pharmacodynamics of propofol and sevoflurane in the absence or presence of opioids in a patient during anesthesia. Comparing the concentration–effect relationships for various specific hypnotic–opioid drug combinations might be interesting to clinicians when titrating combined hypnotics during anesthesia or when switching between drugs during a case.[1,2]

Anesthesia can considered to be the combination of the hypnotic drug effect producing loss of consciousness and the analgesic drug effect (antinociception) inhibiting

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induced noxious stimuli (nociception).[1] Hypnotic drug effects can be measured using clinical endpoints such as no response to calling the person by name or tolerance to shake and shout, derived from the Modified Observer's Assessment of Alertness/Sedation Scale,[3–5] as seen in table 1. For the assessment of the balance between nociception and antinociception, one can use the relationship between movement in response to a tetanic stimulus and the combined hypnotic–analgesic drug concentrations, expressed as tolerance to tetanic stimulus.[6–8]

Anesthetic drug effects between and within individuals can also be quantified using processed, electroencephalographic-derived indices.[9] The Patient State Index (Masimo, USA) is such an index and is calculated by a proprietary algorithm based on a combination of quantitative electroencephalographic parameters and recorded from a four-channel frontal electroencephalographic monitor (SedLine; Masimo).[10–14] Patient State Index values range between 100 (awake condition) and 0 (full suppression of electroencephalography), with a recommended target range between 25 and 50 for surgical anesthesia conditions. Patient State Index-1 has been clinically available for many years[10] and has been described in various studies.[10–15] Like most conventional electroencephalographic-based depth of anesthesia monitors, Patient State Index-1 suffers from intermittent electromyographic noise that interferes with the electroencephalography, leading to the need to limit the electroencephalographic frequency band of interest during index calculations,[16–18] difficulty in calculating an index value with low-power electroencephalography, and significant index variability at baseline that limits the interpretation of the effects of low drug concentrations.[19,20] Recently, a new generation of the Patient State Index (Patient State Index-2) was introduced to deal with limitations of Patient State Index-1 and characterize electroencephalographic behavior in many different frequency bands. During online electroencephalographic signal processing, raw electroencephalographic waves from the four frontal channels are captured independently, and parallel signal processing engines are applied to compute an electroencephalographic-derived parameter including Patient State Index that is less influenced by electromyography. Additionally, adaptive signal processing with band-independent features empowers the algorithm during periods of low-power electroencephalography.[21]

Table 1. Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale

5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild shaking of the shoulder
1	Does not respond to mild shaking of the shoulder but responds to trapezius squeeze
0	Does not respond to a noxious trapezius squeeze

The aim of this four-period randomized sequence crossover study was to describe the concentration–effect relationship of four different anesthetic regimens, being propofol and sevoflurane with and without remifentanil coadministration, as measured by no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation and by two different versions of the Patient State Index. To eliminate potential sources of interindividual variability caused by differences in brain structures, each participant was submitted to all drug combinations. The ability of the Patient State Index to predict different levels of responsiveness was also investigated. In addition, we compared the behavior of the Patient State Index-1 *versus* the new Patient State Index-2.

Materials and Methods

Study Design

For this study, data from a previously published trial,[22] registered at ClinicalTrials.gov (identifier NCT02043938) and approved by the Institutional Review Board of the University Medical Center Groningen (NL43238.042.13) were reanalyzed. The specific details of the clinical study are described in full elsewhere.[22] This manuscript adheres to the applicable Consolidated Standards of Reporting Trials guidelines.

In brief, 36 healthy volunteers (American Society of Anesthesiologists physical status class I), stratified by age, sex, and remifentanil concentration (table 1 of the Supplemental Digital Content, http://links.lww.com/ALN/C53) were included. Written informed consent was obtained from all subjects before inclusion. Exclusion criteria were weight less than 70% or more than 130% of ideal body weight, pregnancy, neurologic disorder, diseases involving the cardiovascular, pulmonary, gastric, and endocrinologic system or recent use of psychoactive medication or intake of more than 20 g of alcohol daily.

Each volunteer was scheduled to receive four sessions of anesthesia with different drug combinations in a random order, with an interval of at least 1 week between

This article is featured in "This Month in Anesthesiology," page 1A. This article is accompanied by an editorial on p. 1199. This article has a related Infographic on p. 17A. This article has an audio podcast. This article has a visual abstract available in the online version. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). Part of this study was presented as a poster titled "Comparison between Two Versions of the Patient State Index® during Propofol and Sevoflurane Anesthesia, with or without Remifentanil" at Euroanaesthesia, the European Anaesthesiology Congress, June 4, 2017, in Geneva, Switzerland.

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sessions. Randomization was performed before each session by drawing a sealed envelope. Any volunteer withdrawing from the study before finishing all sessions was replaced by a newly recruited volunteer. The four sessions were named "propofol," "sevoflurane," "remifentanil with step-dose propofol," and "remifentanil with step-dose sevoflurane."

An arterial line for blood sampling was placed before any drug was administered. Propofol and remifentanil were administered through an intravenous line by a Fresenius Base Primea docking station (Fresenius-Kabi, Germany) carrying two Fresenius module dynamic pressure system pumps, controlled by RUGLOOPII software (Demed, Belgium). RUGLOOPII steers the pumps and their infusion rates as target-controlled infusions to achieve desired target concentrations using pharmacokinetic–pharmacodynamic models consisting of three-compartment pharmacokinetic models linked to an effect site compartments. For propofol, the effect-site concentration was predicted by the pharmacokinetic–pharmacodynamic model of Schnider *et al.*[23,24] For remifentanil, the pharmacokinetic–pharmacodynamic model published by Minto *et al.*[25,26] was used to predict the effect-site concentration. Sevoflurane was titrated using the closed-loop algorithm of the Zeus ventilator (software version 4.03.35; Dräger Medical, Germany) to target and maintain a constant end-tidal sevoflurane concentration over time.

Each session followed an identical titration procedure. After 2 min of baseline monitoring, a stepwise infusion of anesthetic drugs was administered. For the propofol group, the initial effect-site concentration was set to 0.5 $\mu g \cdot ml^{-1}$ followed by consecutive steps to target concentrations of 1, 1.5, 2.5, 3.5, 4.5, 6, and 7.5 $\mu g \cdot ml^{-1}$. For the sevoflurane group, the initial end-tidal sevoflurane concentration was set to 0.2 vol % followed by consecutive end-tidal sevoflurane concentration of 0.5, 1, 1.5, 2.5, 3.5, 4, and 4.5 vol %. After the predicted effect-site concentration for the propofol group or end-tidal sevoflurane concentration reached the target at each step, an equilibration time of 12 min was maintained to allow optimal equilibration between plasma or end-tidal concentration and the corresponding effect-site concentration. For the sessions with remifentanil, the same procedure was executed, although 2 min before propofol or sevoflurane was started, an effect-site concentration of 2 or 4 $ng \cdot ml^{-1}$ was targeted according to the stratification and maintained during the entire study.

After the 12 min of equilibration time, an additional minute of baseline electroencephalographic and hemodynamic measurements was maintained before assessing subject responsiveness using the Modified Observer's Assessment of Alertness/Sedation scale (table 1). No response to calling the person by name corresponded to an Observer's Assessment of Alertness/Sedation score of less than 3 and tolerance to shake and shout corresponded to a score of less than 2. For the analyses, response to the stimulus was considered as 0 and tolerance as 1. After assessing subject responsiveness, an arterial blood sample was obtained for analysis of plasma propofol and/or remifentanil concentrations.[22,27] For sevoflurane, the measured end-tidal sevoflurane concentration at this steady-state condition was recorded. A graphical representation of the sequence of events can be found in the supplemental data of the original study.[22] An electrical stimulus was applied for a maximum duration of 30 s, as described before,[22] 2 min after assessing subject responsiveness, and tolerance/motor responsiveness to tetanic stimulation was scored, again followed by 2 min to observe a possible response to the stimulus.

In each session, all volunteers started with spontaneous ventilation *via* a tight-fitting face mask connected to an anesthesia ventilator (Zeus, software version 4.03.35; Dräger Medical). End-tidal sevoflurane, carbon dioxide, and oxygen concentrations were monitored using the gas analyzer of the anesthesia ventilator.

When needed, respiratory support was applied to secure an unobstructed airway, adequate oxygenation (oxygen saturation measured by pulse oximetry of more than 92%), and CO_2 (35 to 45 mmHg) homeostasis. Throughout the study, oxygen saturation (measured by pulse oximetry), electrocardiogram, and blood pressure (measured noninvasively at 1-min intervals using a Philips IntelliVue MP50 vital signs monitor, Philips Medizin Systeme, Germany) were monitored.

Patient State Index-1 and Patient State Index-2 were derived from *post hoc* running proprietary software (Masimo) and extracted from raw electroencephalographic-waveforms that were recorded throughout the study using a frontal bilateral electrode (SedLine Sensor; Masimo). The electrode was attached on the forehead according to the manufacturer's guidelines and connected to a Masimo root monitor (model RDS-7; Masimo) running the SedLine brain function software (Masimo).

Pharmacodynamic Modeling

Nonlinear mixed effects modeling was used to study the relationship between measured concentrations, the two versions of the Patient State Index (Patient State Index-1 and Patient State Index-2) and clinical endpoints (no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation). For continuous dependent variables (Patient State Index-1 and Patient State Index-2), models were fitted to the data using the first-order conditional estimation routine in NONMEM (version 7.3; Icon Development Solutions, USA). For binary dependent variables (no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation), the LAPLACE estimation routine was used.

A sigmoid E_{max} model, as shown in equation 1, was used to describe the nonlinear relationship between Patient State Index (PSI) and the measured plasma propofol and end-tidal sevoflurane concentrations (C).

$$PSI = PSI_0 - \frac{E_{max} \times C^{\gamma}}{C_{50}{}^{\gamma} + C^{\gamma}} \quad (1)$$

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In this model, Patient State Index is related to the measured propofol or sevoflurane concentration according to a nonlinear function with γ defining the steepness of the concentration–effect relationship. PSI_0 is the baseline Patient State Index when no drug is present and E_{max} is the maximum drug effect. The C_{50} is the concentration that produces 50% of the maximal drug effect. The two versions of the Patient State Index, being Patient State Index-1 and Patient State Index-2, were modeled simultaneously.

For the clinical endpoints (no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation), the sigmoid E_{max} model described the probability of observing the respective clinical outcome. These probabilities are naturally bound between 0 and 1; hence the baseline term and the E_{max} term in equation 1 were *a priori* forced to 0 and 1. In these models C_{50} and Patient State $Index_{50}$ denote the concentration or the Patient State Index value corresponding to a 50% probability of observing the clinical outcome measure.

Interindividual variability around the population typical parameters was assumed according to a multivariate log normal distribution with mean 0 and variances ω^2. Correlations between off-diagonal elements were explored. For continuous dependent variables, residual unexplained variability was described using additive error models.

Accounting for the Hypnotic–Opioid Interaction

In our analysis we assumed that differences existed between the remifentanil groups (0, 2 and 4 ng · ml^{-1}). To account for these differences, we introduced an interaction term on the C_{50} and the Patient State $Index_{50}$. Equations 2 and 3 illustrate the parameterization for the interaction on C_{50} (the same parameterization applies in the case of Patient State $Index_{50}$).

$$C50' = C50 \times (1 + INT) \quad (2)$$

$$INT = \theta_1 \times (1 + \theta_2) \quad (3)$$

In these equations, θ_1 and θ_2 are 0 for all volunteers not receiving remifentanil. θ_1 denotes the proportional difference in C_{50} between the 0 and 2 ng·ml^{-1} remifentanil groups. θ_2 denotes the proportional difference in C_{50} between the 2 and 4 ng · ml^{-1} remifentanil groups. Both θ_1 and θ_2 are estimated from the data. In case there is a (strong) influence of remifentanil on the C_{50} or Patient State $Index_{50}$, the estimate for θ_1 will be significantly different from 0. Moreover, if the influence is different between the volunteers in the 4 ng · ml^{-1} and those in 2 ng · ml^{-1} group, θ_2 will be significantly higher than 0.

Testing for Differences between Patient State Index-1 and Patient State Index-2

We tested for potential differences in the estimated parameters derived for both Patient State Index algorithms. Therefore, as shown in equation 4, additional parameters were added to the model. This doubles the number of parameters to be estimated.

$$TV = TV_{PSI-2} \times (1 + \theta_{\Delta PSI}) \quad (4)$$

In equation 4, a population typical parameter (TV), such as E_{max}, C_{50}, Patient State $Index_{50}$, *etc.*, was composed of a parameter denoting the estimate for the Patient State Index-2 model (TV_{PSI-2}) and a parameter describing the proportional difference in the estimate when switching from Patient State Index-2 to Patient State Index-1 ($\theta_{\Delta PSI}$). A $\theta_{\Delta PSI}$ significantly different from 0 indicates a difference between the two versions of the Patient State Index algorithm for that particular estimated parameter.

General Modeling Strategy

First, a full model was constructed. This model accounted for the hypnotic–opioid interaction as described under "Accounting for the Hypnotic–Opioid Interaction." For the pharmacodynamic models for Patient State Index, the full model also included additional terms to quantify the difference in model parameters between Patient State Index-1 and Patient State Index-2, as described under "Testing for Differences between Patient State Index-1 and Patient State Index-2." Next, this saturated model was simplified by removing nonsignificant parameters. An increase of the objective function value of less than 3.84, corresponding to a value of $P < 0.05$, was considered nonsignificant and led to the removal of the tested parameter.

All models were fitted to the data using PsN[28] and Pirana[29] as back and/or front end to NONMEM. The numerical and graphical assessment of the goodness of fit was conducted in R (R Foundation for Statistical Computing, Austria).

Statistical Analysis

To determine an appropriate sample size, the sample of 36 volunteers was based on previous expertise in pharmacokinetic–pharmacodynamic modeling in our group and what has been used by others in similar study conditions considering the population variability on age and sex. Statistical significance was set at $P < 0.05$ unless stated otherwise. All model parameters are reported as typical values with associated relative standard errors.

Results

The Consolidated Standards of Reporting Trials flow diagram of the screening and inclusion methodology of the 36 healthy volunteers included in the analysis is provided elsewhere.[22] In total, 107 volunteers were assessed for eligibility. Of these 107 volunteers, 20 did not meet the inclusion criteria, 17 declined to participate, and 2 were excluded for other reasons, leaving 68 volunteers confirmed to be eligible. Of these 68 volunteers, 44 were allocated to the

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intervention, but 8 discontinued it because of the commitment/load of the four sessions. In total, 36 volunteers completed the study and were analyzed. There were no missing data from these 36 volunteers. The subject demographics are shown in table 2 of the Supplemental Digital Content (http://links.lww.com/ALN/C53).

In total, 891 no response to calling the person by name/tolerance to shake and shout and 781 tolerance to tetanic stimulation observations were included in the analysis. Measured arterial propofol and remifentanil concentrations and end-tidal sevoflurane concentrations were used as surrogates for their respective effect-site concentrations in the analysis. In total, 655 arterial blood samples were drawn during the stepwise titration procedure. From these samples, 451 propofol and 204 remifentanil concentrations were measured. From the continuously measured end-tidal sevoflurane concentration, only those exactly matching the timing of the Modified Observer's Assessment of Alertness/Sedation Scale and tolerance to tetanic stimulation observations were retained in the dataset, constituting a total of 440 measurements.

Relation between No Response to Calling the Person by Name, Tolerance to Shake and Shout, Tolerance to Tetanic Stimulation, and Propofol or Sevoflurane Concentrations

Figure 1 shows the raw data of the steady-state, measured plasma propofol and end-tidal sevoflurane concentration *versus* the no observed response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulus. Box plots are used to show the distribution of the measured concentrations in the different groups. The predicted probability of achieving no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation at a specific steady-state, measured plasma propofol and end-tidal sevoflurane concentration in the absence or presence of a specific effect-site concentration (remifentanil) is shown in figure 2. Table 2 describes the parameter estimates (and associated relative standard errors) for the pharmacodynamic model shown in figure 2 relating no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation to the steady-state, measured plasma propofol (in $\mu g \cdot ml^{-1}$) and end-tidal sevoflurane concentrations (in vol %) and the influence of remifentanil $2 ng \cdot ml^{-1}$ (θ_1) and $4 ng \cdot ml^{-1}$ (θ_2) on the estimated C_{50} values. In the propofol + $2 ng \cdot ml^{-1}$ remifentanil group, we found 32.7% (relative standard error, 20.5%), 28.0% (relative standard error, 15.1%), and 72.2% (relative standard error, 7.0%) decreases in the C_{50} for no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation, respectively, whereas a target effect-site concentration (remifentanil) of $4 ng \cdot ml^{-1}$ led to decreases in the C_{50} of 66.3% (relative standard error, 49.6%), 84.1% (relative standard error, 27.7%), and 22.4% (relative standard error, 36.6%) for no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation, respectively. In contrast to the results for propofol, the addition of remifentanil 2 or $4 ng \cdot ml^{-1}$ did not significantly affect the C_{50} for no response to calling the person by name during sevoflurane anesthesia. For tolerance to shake and shout and tolerance to tetanic stimulation, effect-site concentration (remifentanil) $2 ng \cdot ml^{-1}$ decreased the C_{50} 26.4% (relative standard error, 21.1%) and 56.0% (relative standard error, 10.6%), respectively. Adding more remifentanil did not alter these C_{50} values for sevoflurane further. Table 2 also shows the interindividual variability for the various C_{50} values and the correlation between the C_{50} values for no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation when giving propofol or sevoflurane. During model building, it was found that the interindividual variability around the population typical C_{50} values for propofol and sevoflurane were highly correlated within an individual for no response to calling the person by name and tolerance to shake and shout, as represented by the value of 1 in table 2. Simplification of the random effects model to a single interindividual variability term for both propofol and sevoflurane lead to a nonsignificant increase in the model's objective function value, being +0.9 and +2.9 for no response to calling the person by name and tolerance to shake and shout, respectively. On the other hand, for tolerance to tetanic stimulation, we found that interindividual variability in C_{50} values for propofol and sevoflurane were independent within an individual. Removal of the correlation coefficient (ρC_{50}) had a marginal impact on the model's goodness of fit (ΔOFV +2.9).

Relation between Patient State Index-1 or Patient State Index-2 and Propofol or Sevoflurane Concentrations

The pharmacodynamic relationship between the two versions of Patient State Index for each volunteer and the steady-state, measured plasma propofol and end-tidal sevoflurane concentration for each effect-site concentration (remifentanil) coadministration are shown in figure 3. The *two left columns* show the individual responses for Patient State Index-1 (*dark gray*) or Patient State Index-2 (*light gray*) and a nonparametric smooth to the data (in *blue* for Patient State Index-1 or *red* for Patient State Index-2). For all propofol groups, increasing propofol concentrations resulted in a monotonically decreasing Patient State Index-1 and Patient State Index-2. For sevoflurane, a clear paradoxical response is observed at higher concentrations for Patient State Index-1. The *two right columns* show the individual *post hoc* expected responses for Patient State Index-1 (*dark gray*) or Patient State Index-2 (*light gray*) and the typical population expectation (in *blue* for Patient State Index-1 or *red* for Patient State Index-2) as calculated by NONMEM using the pharmacodynamic model. The biphasic response at higher sevoflurane concentrations results in a difference between the pharmacodynamic models for Patient State Index-1 and Patient State Index-2. No differences for propofol are observed. Table 3 lists the parameter estimates (and associated relative standard errors) for the

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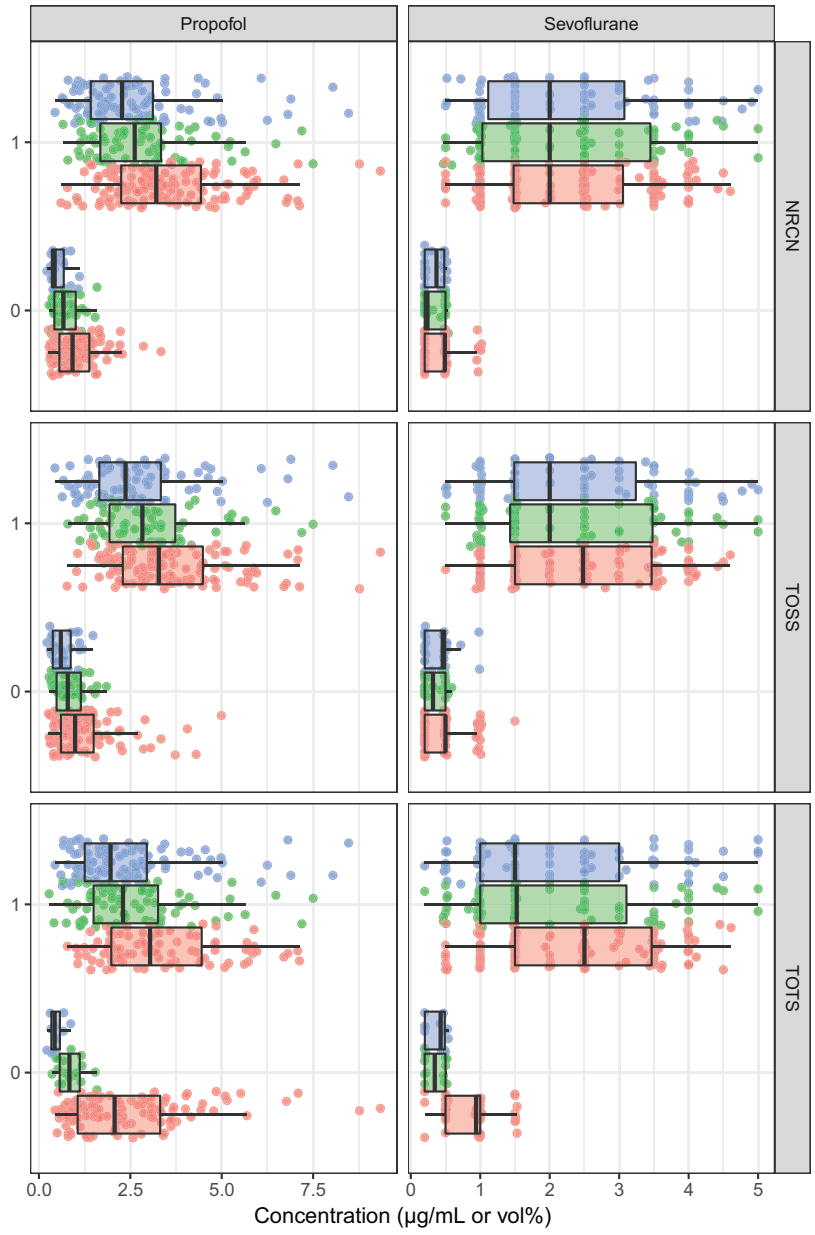

Fig. 1. Steady-state, measured plasma propofol (µg · ml^{-1}) and end-tidal sevoflurane concentration (vol %) *versus* observed response (defined as 0) or no response (defined as 1) to calling the person by name (NRCN), tolerance to shake and shout (TOSS), and tolerance to tetanic stimulation (TOTS). Box plots are used to show measured concentrations in the different remifentanil groups. Individual observations are shown with *circles* and are scattered and offset against the *y* axis to increase visibility. *Red*, *green*, and *blue* are used for the 0, 2, and 4 ng · ml^{-1} remifentanil groups, respectively.

pharmacodynamic models for the Patient State Index-2 and Patient State Index-1 related to the steady-state, measured plasma propofol (in µg · ml^{-1}) and end-tidal sevoflurane concentration (in vol %; C) and the influence of remifentanil 2 ng · ml^{-1} (θ_1) and 4 ng · ml^{-1} (θ_2) on the estimated C_{50} values. For propofol, the estimated drug effect parameters were not significantly different between Patient State Index-1 and Patient State Index-2. In contrast, for sevoflurane, significant differences in the estimated drug effect parameters were obtained for E_{max} and γ. The E_{max} of Patient State Index-1 was 15.2% (relative standard error, 17.1%) lower than the E_{max} of Patient State Index-2. The γ of Patient State Index-1 was 42.2% (relative standard error, 57.4%) higher than that of Patient State Index-2. At baseline (in the awake state), the Patient State Index-1 has a higher interindividual variability and has a higher overall

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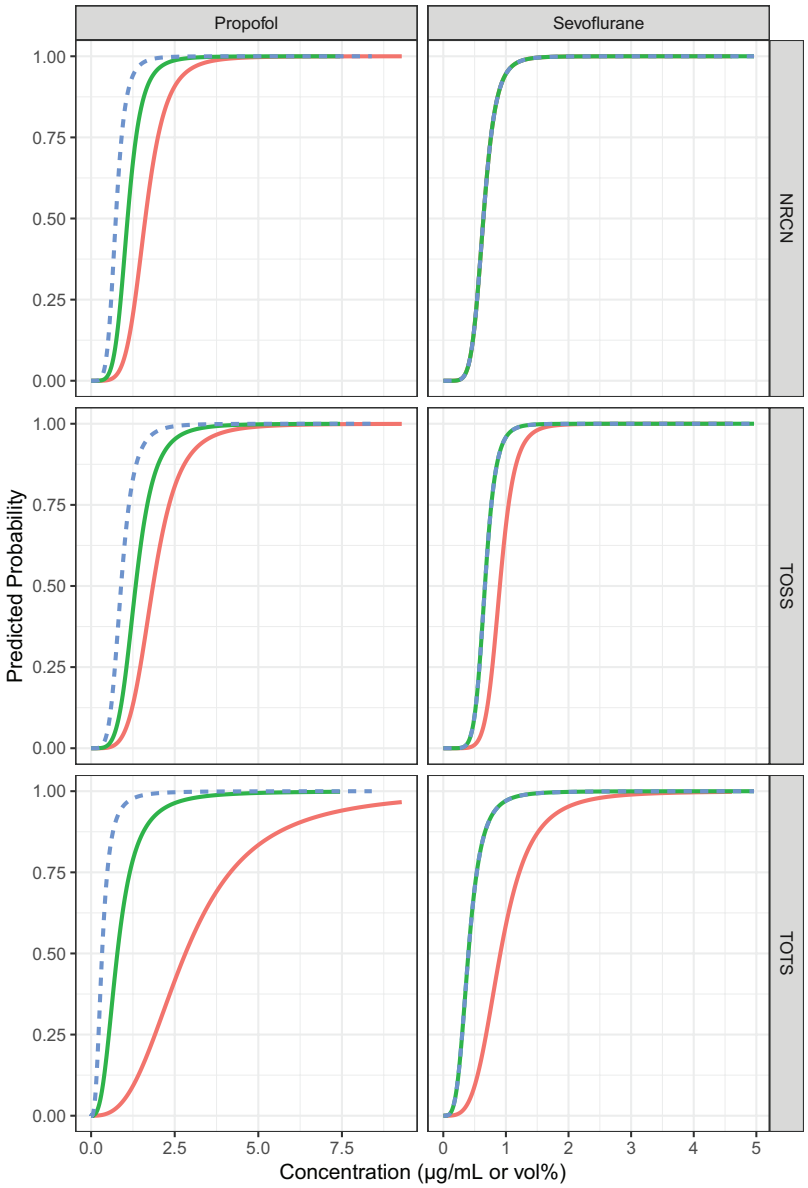

Fig. 2. Steady-state, measured plasma propofol (μg · ml^{-1}) and end-tidal sevoflurane concentration (vol %) *versus* predicted probabilities for no response to calling the person by name (NRCN), tolerance to shake and shout (TOSS), and tolerance to tetanic stimulation (TOTS). *Solid red*, *solid green*, and *dashed blue lines* are used for the predicted probabilities in the 0, 2, and 4 ng · ml^{-1} remifentanil groups.

residual unexplained variability than Patient State Index-2. The ability of Patient State Index-2 to detect the interaction between hypnotics and opioids is not affected compared with Patient State Index-1. The addition of remifentanil lowered the C_{50} of propofol significantly for both models to a similar degree. In the propofol + 2 ng · ml^{-1} remifentanil group, we found a 13.5% (relative standard error, 20.8%) decrease in the C_{50} (from 1.63 to 1.41 μg · ml^{-1}), whereas a target effect-site concentration (remifentanil) of 4 ng · ml^{-1} led to a decrease in the C_{50} of 81.6% (relative standard error, 62.3%). In contrast to the results for propofol, the addition of remifentanil 2 or 4 ng · ml^{-1} did not significantly affect the C_{50} of sevoflurane (1.22 vol %) in both Patient State Index-1 and Patient State Index-2 models.

Relation between Patient State Index-2 and No Response to Calling the Person by Name, Tolerance to Shake and Shout, and Tolerance to Tetanic Stimulation for Propofol and Sevoflurane

During model building and using a likelihood ratio test at the 5% level of significance, the estimated model parameters

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Table 2. Parameter Estimates for the Pharmacodynamic Models Relating the NRCN, TOSS, and TOTS to the Steady-state, Measured Plasma Propofol and End-tidal Sevoflurane Concentration and the Influence of Remifentanil on the Model

		NRCN		TOSS		TOTS	
		Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane
Drug effect	C_{50}	1.62 (7.00)	0.64 (4.20)	1.85 (6.20)	0.90 (5.00)	2.82 (15.5)	0.91 (10.0)
	γ	5.26 (14.6)	6.40 (16.1)	4.75 (13.1)	7.68 (14.2)	2.82 (10.7)	3.82 (12.7)
Remifentanil interaction	θ_1	−0.327 (20.5)	NS $P = 0.314$	−0.280 (15.1)	−0.264 (21.1)	−0.722 (7.00)	−0.560 (10.6)
	θ_2	0.663 (49.6)	NS $P = 0.710$	0.841 (27.7)	NS $P = 1.00$	0.224 (36.6)	NS $P = 0.693$
IIV	C_{50}*	16.8 (71.8)		16.1 (50.8)		71.4 (29.1)	29.5 (43.4)
	ρC_{50}	1		1		NS $P = 0.132$	

The values indicate parameter estimates and associated relative standard error (%). Steady-state, measured plasma propofol in μg · ml^{-1}. End-tidal sevoflurane concentration in vol %. Remifentanil 2 ng · ml^{-1} (θ1) and 4 ng · ml^{-1} (θ2).

*The *P* value for the likelihood-ratio test leading to the exclusion of the parameter is included in the table, calculated according to: $\sqrt{e^{\omega}-1}*100\%$.

C_{50}, the concentration producing 50% probability of NCRN, TOSS, or TOTS; γ, the steepness/slope of the concentration–effect relationship; IIV, interindividual variability, modeled using a log normal distribution with variance ω^2; ρC_{50}, the correlation between the C_{50} values for propofol and sevoflurane; NRCN, no response to calling the person by name; NS, parameter not significant at the 5% level of significance as assessed by likelihood-ratio testing; TOSS, tolerance to shake and shout; TOTS, tolerance to tetanic stimulus.

for Patient State Index-1 and Patient State Index-2 as predictors for no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation were indistinguishable. Consequently, both Patient State Index-1 and Patient State Index-2 result in indistinguishable box plots in figure 4, curves in figure 5, and parameter estimates in table 4. As such, only Patient State Index-2 results are shown. Figure 4 shows the raw data of the observed Patient State Index-2 *versus* the no observed response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulus. Box plots are used to show the distribution of Patient State Index-2 in the different groups. The predicted probability of achieving no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation at a specific Patient State Index-2 in the absence or presence of a specific effect-site concentration (remifentanil) is shown in figure 5. Table 4 describes the parameter estimates for the pharmacodynamic model shown in figure 4 relating no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation to Patient State Index-2 and the influence of remifentanil 2 ng · ml^{-1} (θ_1) and 4 ng · ml^{-1} (θ_2) on the estimated Patient State Index$_{50}$ values. For no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation, a significant decrease in Patient State Index$_{50}$ was found when coadministering an effect-site concentration (remifentanil) of 2 ng · ml^{-1} with propofol or sevoflurane. Patient State Index$_{50}$ only decreased further at effect-site concentration (remifentanil) of 4 ng · ml^{-1} for tolerance to shake and shout and tolerance to tetanic stimulation during propofol administration. Table 4 also shows the interindividual variability for the various Patient State Index$_{50}$ values and the correlation between the Patient State Index$_{50}$ values for no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation within an individual when giving propofol or sevoflurane. During model building, it was found that within an individual, Patient State Index$_{50}$ values for propofol and sevoflurane were moderately correlated, as represented by the values of 0.65 and 0.58. In contrast, for tolerance to tetanic stimulation, we found that Patient State Index$_{50}$ values for propofol and sevoflurane were independent within an individual.

Discussion

Because in this trial the same group of volunteers received four different anesthetic regimens in steady-state conditions, our results offer a unique possibility to directly compare the pharmacodynamics of propofol *versus* sevoflurane with and without remifentanil coadministration at both a population and an individual level.

Relation between No Response to Calling the Person by Name, Tolerance to Shake and Shout, Tolerance to Tetanic Stimulation, and Propofol or Sevoflurane Concentrations

The pharmacodynamic relation between no response to calling the person by name, tolerance to shake and shout, tolerance to tetanic stimulation, and the steady-state, measured plasma propofol or end-tidal sevoflurane concentration could be described by a classical nonlinear relation. The model parameter values are in agreement with others for no response to calling the person by name and tolerance to shake and shout but mostly lower than others for tolerance to tetanic stimulation.[7,30–32] However, comparing our C_{50} values with those from other studies is not that relevant, because the results are influenced by observer differences for clinical scores and differences in device and stimulation characteristics for tolerance

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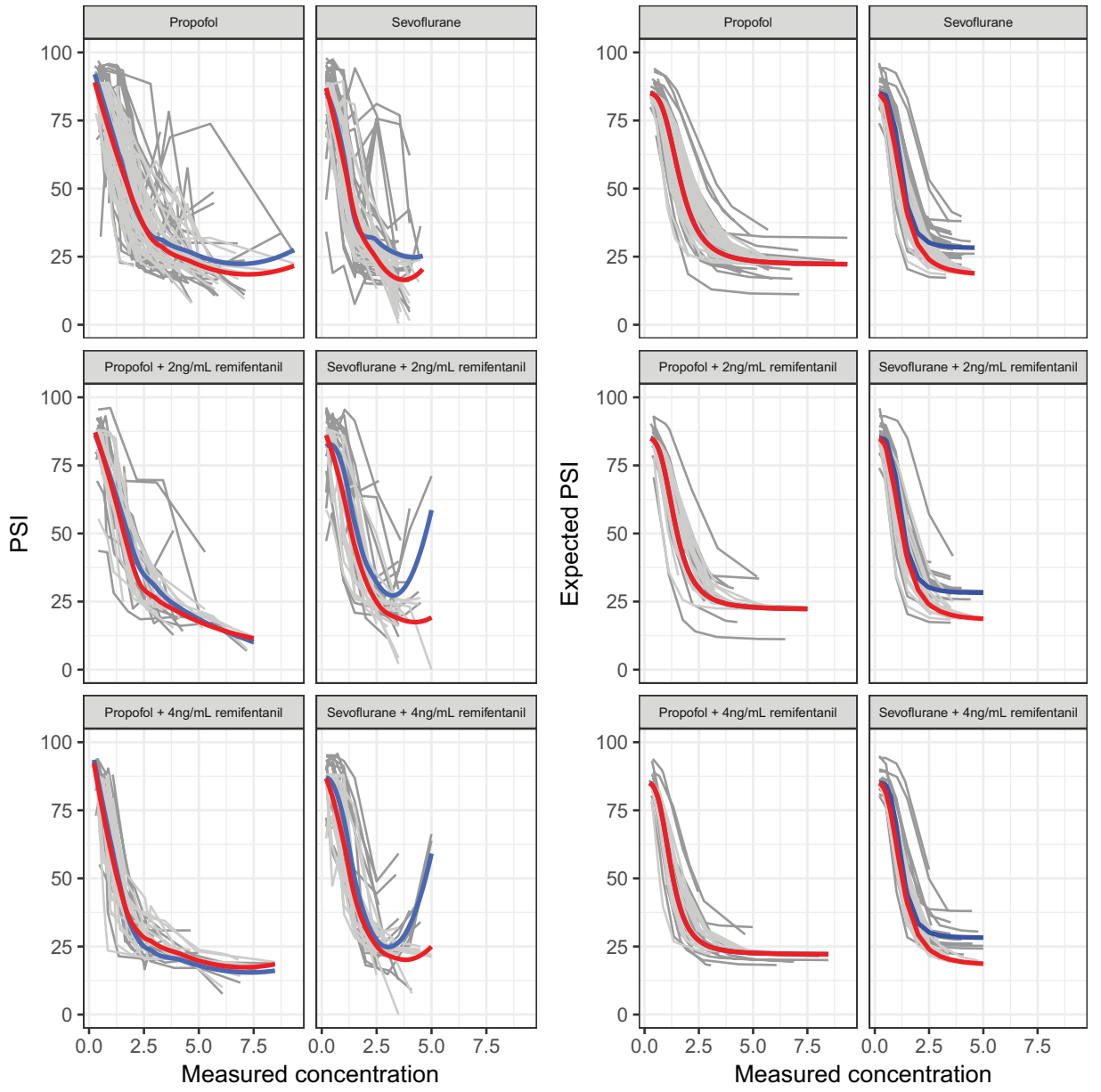

Fig. 3. Relationship between Patient State Index (PSI)-1 or PSI-2 and the steady-state measured plasma propofol (μg · ml^{-1}) or end-tidal sevoflurane (vol %) concentration during various effect-compartment targeted remifentanil (ng · ml^{-1}) coadministrations. The *two left columns* show the individual responses for PSI-1 (*dark gray*) or PSI-2 (*light gray*) and a nonparametric smooth (in *blue* for PSI-1 or *red* for PSI-2). The *two right columns* show the individual *post hoc* expected responses for PSI-1 (*dark gray*) or PSI-2 (*light gray*) and the typical population expectation (in *blue* for PSI-1 or *red* for PSI-2) as calculated by NONMEM using the pharmacodynamic model.

to tetanic stimulation. Because we used a crossover design, it is much more interesting to quantify the ratio between C_{50} values for no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation between propofol and sevoflurane (without remifentanil), being 1.62 μg · ml^{-1}/0.64 vol %, 1.85 μg · ml^{-1}/0.90 vol %, and 2.82 μg · ml^{-1}/0.91 vol %, respectively. As an example using tolerance to shake and shout, this means that a clinician can expect tolerance to shake and shout in 50% of his patients when titrating a propofol steady-state concentration of 1.85 μg · ml^{-1} or a steady-state end-tidal concentration of sevoflurane of 0.90 vol %, resulting in ratio of 2.05. This also means that a clinician titrating the propofol effect at a steady-state concentration of 1.85 μg · ml^{-1} can theoretically produce a similar

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Table 3. Final Parameter Estimates for the Pharmacodynamic Model for the PSI-2 and PSI-1 *versus* the Steady-state, Measured Plasma Propofol and End-tidal Sevoflurane Concentration and the Influence of Remifentanil on the Model

		PSI-2		PSI-1	
		Propofol	Sevoflurane	Propofol	Sevoflurane
Baseline	E_0	85.1 (0.8)		$P = 0.508$	
Drug effect	E_{max}	63.1 (1.9)	67.2 (2.3)	$P = 0.163$	–0.152* (17.1)
	C_{50}	1.63 (3.7)	1.22 (3.1)	$P = 0.952$†	$P = 0.952$†
	γ	3.41 (5.6)	3.23 (6.7)	$P = 0.749$	0.422* (57.4)
Remifentanil interaction	θ_1	–0.135 (20.8)	$P = 1.00$	$P = 0.771$	—
	θ_2	0.816 (62.3)	$P = 1.00$	$P = 0.593$	—
IIV	E_0‡	$P = 0.874$		6.64 (38.6)	
	C_{50}‡	25.8 (22.2)	20.1 (24.3)	26.2 (21.9)	28.0 (23.1)
	ρC_{50}	0.54 (25.5)		0.69 (17.1)	
RUV	$\sigma_{Additive}$§	8.54 (5.0)		12.7 (5.1)	

The values indicate parameter estimates and associated relative standard error (%). The dash (—) denotes a situation where the difference between PSI-1 and PSI-2 could not be tested because the parameter was already excluded from the PSI-2 model. Steady-state, measured plasma propofol in μg · ml^{-1}. End-tidal sevoflurane concentration in vol %. Remifentanil 2 ng · ml^{-1} (θ1) and 4 ng · ml^{-1} (θ2).

*Parameters are expressed as relative differences *versus* parameters estimates obtained for PSI-2. †These parameters were removed from the model simultaneously. ‡Statistical significance was set at $P < 0.05$, calculated according to: $\sqrt{e^{\omega} - 1} * 100\%$. §Expressed as SD.

C_{50}, the concentration which produces 50% of the maximal drug effect; E_0, the baseline measurement of the pharmacodynamic endpoint when no drug is present; E_{max}, the maximum drug effect; γ, the steepness/slope of the concentration–effect relationship; IIV, interindividual variability, by assuming a log normal distribution of C_{50}, with η_i being an individual realization from this distribution with variance ω^2; PSI, Patient State Index; ρC_{50}, the correlation between the C_{50} values for propofol and sevoflurane; RUV, the residual unexplained variability ($\sigma_{Additive}$).

hypnotic effect as measured with tolerance to shake and shout when switching to a sevoflurane steady-state concentration of 0.90 vol %. As such, these values become clinically useful to help the clinician optimizing drug titration when switching between propofol and sevoflurane. Our propofol and sevoflurane ratios are close to the observations made by Schumacher *et al.*[7] when studying the interaction between propofol and sevoflurane, being 2.05 and 3.09 for tolerance to shake and shout and tolerance to tetanic stimulation, respectively.

Because of the absence of analgesic properties for propofol, we found a difference between propofol and sevoflurane in the influence of remifentanil on the C_{50} values for the various clinical endpoints. For propofol, significant decreases in the propofol C_{50} for no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation were found at increasing effect-site concentration (remifentanil) as also found by Kern *et al.*[30] For sevoflurane, the influence of remifentanil on the sevoflurane C_{50} values was variable, ranging from no influence for no response to calling the person by name to an effect of effect-site concentration (remifentanil) of 2 ng · ml^{-1} for tolerance to shake and shout and tolerance to tetanic stimulation without an additional effect when increasing effect-site concentration (remifentanil) to 4 ng · ml^{-1}. Heyse *et al.*[32] studied the interaction between sevoflurane and remifentanil and also found differences in the synergy between various clinical endpoints. In addition, Heyse *et al.*[32] showed that above a effect-site concentration (remifentanil) of 4 ng · ml^{-1}, the interaction no longer increases.

Relation between Patient State Index-1 or Patient State Index-2 and Propofol or Sevoflurane Concentrations

As shown in figure 3, both Patient State Index-1 and Patient State Index-2 decreased with increasing measured plasma propofol or end-tidal sevoflurane concentrations. For propofol, we found no significant differences between Patient State Index-1 and Patient State Index-2 in the model parameters of the concentration–effect relationship, independent of the addition of remifentanil. In contrast, for sevoflurane with or without remifentanil, we found an improved monotonic relationship of the concentration–effect curve for Patient State Index-2 compared with Patient State Index-1. This was also reflected in a significant difference between Patient State Index-1 and Patient State Index-2 in two model parameters, E_{max} and γ, even though the C_{50} values were similar for both indices. In combination with the decreased variability for Patient State Index-2 at baseline (suggesting a better signal-to-noise ratio in awake individuals), our findings indicate that Patient State Index-2 has improved characteristics to serve as a continuous pharmacodynamic measure of cortical electrical activity during both propofol and sevoflurane anesthesia. Paradoxical increases, especially during administration of higher concentrations of inhaled anesthetics, have been described before and must be taken into consideration during processed electroencephalographic algorithm development to avoid incorrect anesthetic management under electroencephalographic monitoring.[33–35]

We are aware of only two articles that have used pharmacodynamic modeling to compare the concentration–effect relationship between propofol or sevoflurane and the Patient

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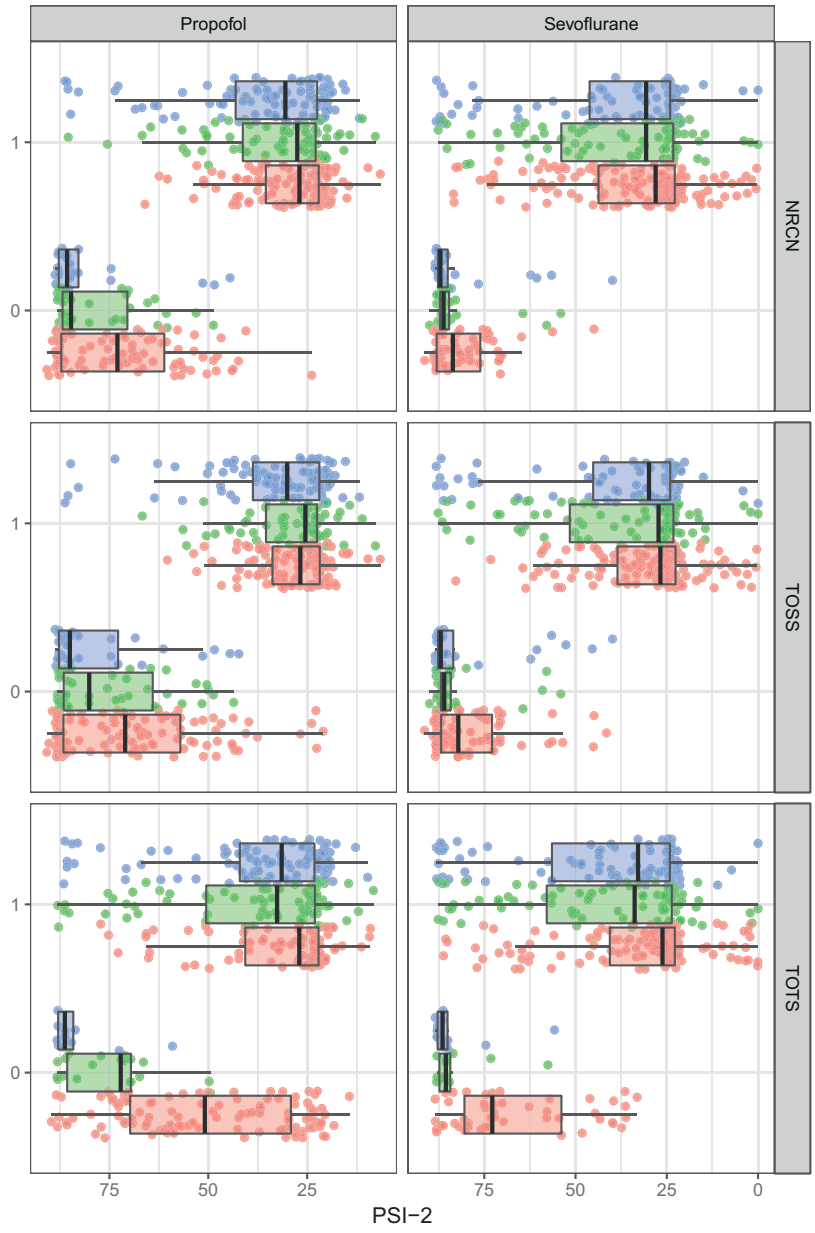

Fig. 4. Patient State Index (PSI)-2 *versus* no observed response to calling the person by name (NRCN), tolerance to shake and shout (TOSS), and tolerance to tetanic stimulation (TOTS) during propofol and sevoflurane administration. Box plots are used to show the distribution of the PSI-2 index in the different remifentanil groups. Individual observations are shown with *circles* and are scattered and offset against the *y* axis to increase visibility. *Red*, *green*, and *blue* are used for the 0, 2, and 4 ng · ml^{-1} remifentanil groups, respectively.

State Index-1. Soehle *et al.*[13,14] obtained C_{50} values of 1.38 μg · ml^{-1} and 0.77 vol % for propofol and sevoflurane, respectively, which are considerably lower for sevoflurane compared with our C_{50} values; the difference is probably related to differences in sample selection and methodology. More relevant and similar to the clinical endpoints, we compared C_{50} values for both Patient State Index-1 and Patient State Index-2 between propofol and sevoflurane in the same sample of volunteers on both a population and an individual level.

Relation between Patient State Index-2 and No Response to Calling the Person by Name, Tolerance to Shake and Shout, and Tolerance to Tetanic Stimulation for Propofol and Sevoflurane

We found indistinguishable results in the model parameters for Patient State Index-1 and Patient State Index-2 in relation to no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic

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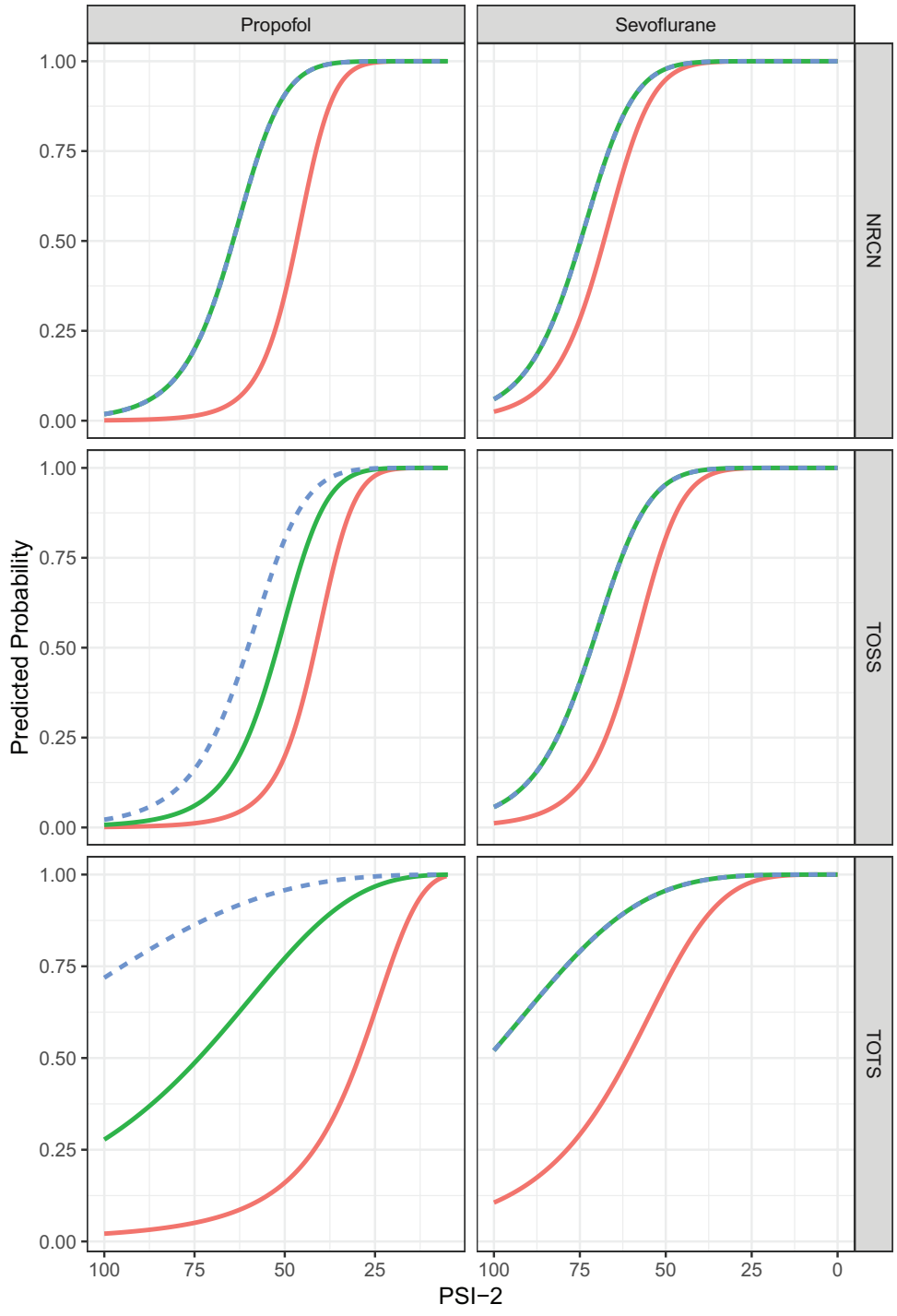

Fig. 5. Patient State Index (PSI)-2 *versus* predicted probabilities for no response to calling the person by name (NRCN), tolerance to shake and shout (TOSS), and tolerance to tetanic stimulation (TOTS) during propofol and sevoflurane administration. *Solid red*, *solid green*, and *dashed blue lines* are used for the predicted probabilities in the 0, 2, and 4 ng·ml^{-1} remifentanil groups.

stimulation, and as such, we only present results for Patient State Index-2. Although improvements in concentration–effect relationship for Patient State Index-2 were observed, particularly for sevoflurane, this did not influence the correlation between Patient State Index and no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation. Therefore, no adaptation is required for the clinician when switching to

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Table 4. Parameter Estimates for the Pharmacodynamic Models Relating the NRCN, TOSS, and TOTS to PSI-2 and the Influence of Remifentanil 2 ng·ml^{-1} (θ_1) and 4 ng·ml^{-1} (θ_2) on the Model

		NRCN		TOSS		TOTS	
		Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane
Drug effect	PSI_{50}	46.7 (5.10)	68.0 (3.00)	41.5 (4.10)	59.2 (3.60)	29.5 (12.9)	61.1 (8.10)
	γ	9.04 (19.8)	9.49 (17.8)	7.50 (13.7)	8.42 (14.7)	3.14 (10.5)	4.33 (9.60)
Remi interaction	θ_1	0.377 (21.6)	0.100 (40.4)	0.254 (18.5)	0.210 (25.2)	1.50 (30.2)	0.668 (27.5)
	θ_2	NS $P = 0.063$	NS $P = 0.906$	0.777 (80.1)	NS $P = 1.00$	1.38 (57.5)	NS $P = 0.856$
IIV	PSI_{50}*	17.0 (38.9)	10.3 (38.8)	15.2 (39.6)	13.2 (42.4)	55.6 (35.7)	28.2 (19.1)
	ρPSI_{50}	0.65 (50.8)		0.584 (40.9)		NS $P = 0.297$	

The values indicate parameter estimates and associated relative standard errors (%).

*The P value for the likelihood-ratio test leading to the exclusion of the parameter is included in the table, calculated according to: $\sqrt{e^{\omega}-1}*100\%$.

γ, the steepness/slope of the PSI-2 effect relationship; IIV, interindividual variability, modeled using a log normal distribution with variance ω^2; NRCN, no response to calling the person by name; NS, parameter not significant at the 5% level of significance as assessed by likelihood-ratio testing; PSI, Patient State Index; PSI_{50}, the Patient State Index-2 index associated with 50% probability of NRCN, TOSS or TOTS; $\rho PSI_{50,}$ the correlation between the Patient State $Index_{50}$ values for propofol and sevoflurane; TOSS, tolerance to shake and shout; TOTS, tolerance to tetanic stimulus.

the new Patient State Index-2. Moreover, it seems that our results do not invalidate earlier publications on the relation between Patient State Index and clinical endpoints.[10–15]

The relationships between Patient State Index-2 and the three clinical endpoints show some fundamental clinical differences between propofol and sevoflurane anesthesia. The Patient State Index-2 values associated with 50% probability (Patient State $Index_{50}$) of no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation are significantly higher for sevoflurane than propofol. Adding remifentanil 2 ng · ml^{-1} increased all Patient State $Index_{50}$ values significantly. However higher effect-site concentration (remifentanil) values showed an additional effect for tolerance to shake and shout and tolerance to tetanic stimulation only during propofol administration. When maintaining a Patient State Index-2 within the range of 25 to 50 as recommended by the company for general anesthesia, there was still a significant risk that the patient could be responsive to one of the clinical endpoints during propofol administration even in the presence of remifentanil. Based on our findings presented in figure 5 and table 4, we recommend lowering the upper range limit towards a Patient State Index-2 value of 35 to maintain a safe level of the hypnotic component of anesthesia when using propofol. When using sevoflurane, the recommended Patient State Index-2 range of 50 to 25 is sufficient to ensure a high probability for the hypnotic endpoints no response to calling the person by name and tolerance to shake and shout. The significant difference in Patient State $Index_{50}$ for tolerance to tetanic stimulation between propofol and sevoflurane also reflects the much higher intrinsic immobilizing capacity of sevoflurane compared with propofol.[36,37] To obtain a similar probability of immobility to noxious stimulus, propofol should inhibit the cortical electrical activity to a much larger extent compared with sevoflurane and therefore requires a higher concentration of propofol, resulting in more electroencephalographic suppression and lower Patient State Index-2 values. The addition of a sufficiently effective concentration of remifentanil during propofol anesthesia is mandatory to ensure immobility after a noxious stimulus.

Originally, Patient State Index-1 was presented as a drug-independent representation of electroencephalographic suppression by some authors.[12,38] Our study clearly indicates that the Patient State Index-2 needs to be interpreted differently depending on the anesthetic drugs used, as suggested by Purdon *et al.*[39] and Schneider *et al.*[40]

Interindividual Variability around C_{50}

Because our study allows direct comparisons between propofol and sevoflurane, we studied variability in C_{50} values and Patient State $Index_{50}$ values within an individual during propofol and sevoflurane administration in the absence or presence of remifentanil. We found that within an individual, C_{50} values for propofol and sevoflurane are perfectly correlated (ρC_{50} = 1) for no response to calling the person by name and tolerance to shake and shout. This means that an individual having a higher or lower C_{50} for propofol *versus* the population typical value also has a higher or lower C_{50} value for sevoflurane. At the same time, this means that the ratio of C_{50} values for no response to calling the person by name and tolerance to shake and shout between propofol and sevoflurane is identical for all individuals and equal to the population ratios of 1.62 μg · ml^{-1}/0.64 vol %, and 1.85 μg · ml^{-1}/0.90 vol %, respectively.

We also showed that C_{50} values for propofol and sevoflurane for Patient State Index-1 (ρC_{50} = 0.69) and Patient State Index-2 (ρC_{50} = 0.54) and Patient State $Index_{50}$ values for no response to calling the person by name (ρC_{50} = 0.65)

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and tolerance to shake and shout (ρC_{50} = 0.58) are positively correlated. This means that, on average, individuals having a higher or lower C_{50} or Patient State $Index_{50}$ for propofol also have a higher or lower C_{50} or Patient State $Index_{50}$ for sevoflurane. A consequence of the correlation coefficient being less than 1 is that the population typical ratio does not apply to all individuals and that some interindividual variability exists in the ratios. For example, for Patient State Index-2 the population typical ratio is 1.63 μg · ml^{-1}/1.22 vol % with individual (*post hoc*) ratios ranging from 0.85 μg · ml^{-1}/1.22 vol % to 2.06 μg · ml^{-1}/1.30 vol %. Similarly, the population typical ratio of Patient State $Index_{50}$ values for Patient State Index-2 was 0.69 with individual ratios ranging from 0.55 to 0.75 for no response to calling the person by name and tolerance to shake and shout, respectively.

Interestingly, no correlation between C_{50} values and Patient State $Index_{50}$ values for propofol and sevoflurane was found for tolerance to tetanic stimulation. This means that an individual having a higher C_{50} for propofol (compared with the population typical value) has an equal probability of having a higher or lower C_{50} for sevoflurane. Consequently, individual ratios vary considerably from the population typical ratios of C_{50} and Patient State $Index_{50}$. The population typical ratios of C_{50} and Patient State $Index_{50}$ are 2.82 μg · ml^{-1}/0.91 vol % and 0.48 and individual ratios range from 0.91 μg · ml^{-1}/0.81 vol % to 5.13 μg · ml^{-1}/0.92 vol % and from 0.22 to 0.84. These correlations between *post hoc* C_{50} and Patient State $Index_{50}$ values for propofol and sevoflurane for these hypnotic-related, clinical, and electroencephalographic endpoints, but not for the spinal reaction-related tolerance to tetanic stimulation, are exciting and might offer new insights into mechanisms of action for sevoflurane *versus* propofol.[41,42]

A limitation of our modeling approach is that we used the predicted effect-site concentrations of remifentanil instead of the measured concentrations. As such, the between-subject variability in the measured concentrations is not considered. Although parameter estimates on the group level are likely unbiased, this approach could possibly have confounded the estimates for the correlations between the C_{50} values and Patient State $Index_{50}$ values. Nevertheless, in our opinion this approach is justified because we did not aim at building a surface-response model, and considering the between-subject variability in the measured concentrations would only increase the complexity of the analysis without leading to different conclusions with respect to the pharmacodynamics of propofol and sevoflurane for no response to calling the person by name, tolerance to shake and shout, tolerance to tetanic stimulation, and Patient State Index.

Conclusions

The pharmacodynamics for propofol and sevoflurane with and without remifentanil coadministration were described on both population and individual levels using clinical scores and Patient State Index. We observed that the interindividual variability around the population typical C_{50} values and Patient State $Index_{50}$ during propofol and sevoflurane administration were significantly correlated within an individual for no response to calling the person by name and tolerance to shake and shout, but not for tolerance to tetanic stimulation. Patient State Index-2 has an improved monotonic concentration–effect relationship and descriptive performance at higher sevoflurane concentrations compared with Patient State Index-1. Finally, the probability of responsiveness for no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation as a function of Patient State Index is drug- and drug combination–specific but is not affected by the version of Patient State Index used.

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Competing Interests

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