Response Surface Modeling of the Interaction between Propofol and Sevoflurane

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Background: Propofol and sevoflurane display additivity for γ-aminobutyric acid receptor activation, loss of consciousness, and tolerance of skin incision. Information about their interaction regarding electroencephalographic suppression is unavailable. This study examined this interaction as well as the interaction on the probability of tolerance of shake and shout and three noxious stimulations by using a response surface methodology.

Methods: Sixty patients preoperatively received different combined concentrations of propofol (0–12 μg/ml) and sevoflurane (0–3.5 vol.%) according to a crisscross design (274 concentration pairs, 3 to 6 per patient). After having reached pseudo-steady state, the authors recorded bispectral index, state and response entropy and the response to shake and shout, tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy. For the analysis of the probability of tolerance by logistic regression, a Greco interaction model was used. For the separate analysis of bispectral index, state and response entropy suppression, a fractional E_{max} Greco model was used. All calculations were performed with NONMEM V (GloboMax LLC, Hanover, MD).

Results: Additivity was found for all endpoints, the $Ce_{50, PROP}$/$Ce_{50, SEVO}$ for bispectral index suppression was 3.68 μg · ml^{-1}/1.53 vol.%, for tolerance of shake and shout 2.34 μg · ml^{-1}/1.03 vol.%, tetanic stimulation 5.34 μg · ml^{-1} / 2.11 vol.%, laryngeal mask airway insertion 5.92 μg · ml^{-1} / 2.55 vol.%, and laryngoscopy 6.55 μg · ml^{-1}/2.83 vol.%.

Conclusion: For both electroencephalographic suppression and tolerance to stimulation, the interaction of propofol and sevoflurane was identified as additive. The response surface data can be used for more rational dose finding in case of sequential and coadministration of propofol and sevoflurane.

⊕ 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).

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data can be used for more rational dose finding in case of sequential and coadministration of propofol and sevoflurane.

INDUCTION of anesthesia is classically done by intravenous administration of a hypnotic and maintenance of anesthesia with volatile anesthetics. Coadministration of propofol and sevoflurane during maintenance might even have potential because of the antiemetic effect of propofol, myocardial protection by sevoflurane,[1,2] and favorable emergence resulting from lower administered amounts of each drug compared to monotherapy. However, the type and extent of their interaction has not yet been fully described.[3-5] Such interaction data will also be required for the emerging predictive drug displays when their use is expanded to volatile agents.[6,7]

The purpose of this study was to investigate the interaction between propofol and sevoflurane with regard to electroencephalographic suppression measured *via* bispectral index (BIS), state entropy (SE), response entropy (RE) and tolerance to clinically relevant stimuli of increasing intensity with response surface methodology. The null hypothesis is that propofol lowers the concentration of sevoflurane to (1) tolerate a specific stimulation and to (2) obtain a certain electroencephalographic parameter value and *vice versa* in an additive fashion.

Materials and Methods

Subjects

After obtaining Institutional Review Board approval (Ghent University Hospital Ethics' Committee, Gent, Belgium) and obtaining written informed consent, 60 American Society of Anesthesiologists status I or II patients, aged 18 to 60 yr, and scheduled to undergo surgery requiring general anesthesia were included. Exclusion criteria were weight less than 70% or more than 130% of ideal body weight, neurologic disorder, diseases involving the cardiovascular system (hypertension, coronary artery disease, prior acute myocardial infarction, any valvular and/or muscular disease involving decrease in ejection fraction, arrhythmias, which are either symptomatic or require continuous medication/pacemaker/automatic implantable cardioverter defibrillator), pulmonary disease, gastric diseases, endocrinology diseases and recent use of psychoactive medication, including alcohol. The complete study was executed in a quiet operation room before the start of the surgical procedure.

Study Design

This study was performed as a randomized, prospective, open-label study. After the unpremedicated patients arrived in the operating room, standard monitoring (electrocardiogram, noninvasive blood pressure, SpO_2 using a Datex S/5 Anesthesia Monitor [GE Healthcare, Helsinki, Finland]) was applied, and a large forearm vein was cannulated. Spectral entropy and BIS electrodes were placed on the forehead. The BIS sensor was always positioned on the righthand side, and the M-entropy sensor was positioned on the lefthand side. Thereafter, the patients were preoxygenated with $6\,1 \cdot min^{-1}\,O_2$ for 5 min by using a tight-fitting face mask, which also served to sample end-tidal carbon dioxide.

All equipment was standard clinical equipment routinely used in the operating room for clinical anesthesia. All medical devices are approved for the purposes applied in the study. All drugs and the way of administration, either alone or in combination, are approved for clinical use under the studied conditions. No "out of label" drug applications were used (European situation).

Drug Administration

Technical Aspects. Propofol was administered by using a target-controlled infusion technique based on a three compartment model and an effect-site compartment as published by Schnider *et al.*[8,9] Propofol infusion was administered by using an Alaris Asena pump (Cardinal Health, Basingstoke, United Kingdom). RUGLOOP II TCI driver (Demed, Temse, Belgium) steered the pump at infusion rates between 0 and $1,200\,ml \cdot hr^{-1}$ *via* an RS-232 interface. Sevoflurane was administered in 50% O_2 and 50% air by using a standard out-of circle vaporizer and a standard breathing circuit of an ADU anesthesia workstation (Datex/Ohmeda, GE Healthcare).

Dosing Regimen. The study design was a modification of the crisscross design proposed by Short *et al.*[10] The choice of propofol/sevoflurane concentration pairs was based on a simulation study; before signing off on the protocol we ran 40 study simulations with 60 patients each.[11] Of those 40 studies, 20 were performed to assess the robustness of the design regarding the continuous BIS response, and 20 were performed for quantal/ordered categorical responses. Modified Minto interaction models[12] were parameterized for the simulation of (1) BIS suppression and (2) arousability and tolerance of laryngoscopy as published.[13,14] Each set of 20 studies consisted of 10 and 10 studies for mildly synergistic ($\beta = 1.6$) and additive behavior, respectively. Virtual individuals were distributed according to a modified crisscross design covering concentrations up to 3.5% sevoflurane and 12 μg/ml propofol (steady state effect site conditions). The typical values, standard errors, and the interindividual variability of the parameters were estimated with the identical control files used for simulation. With the exception of random number generation for the

simulation of quantal responses, all calculations were performed with NONMEM V (GloboMax LLC, Hanover, MD). Bias and precision of the parameter values were evaluated, and models were compared with the likelihood ratio test ($P < 0.01$). For BIS suppression, the pharmacodynamic parameters could be identified with small bias ($\pm$ 20% of the simulation input) in 20 of 20 studies. The type of interaction was always identified correctly with high significance levels ($P < 0.001$). For the quantal responses, arousability and tolerance of laryngoscopy with an additive model underlying the simulations, the type of interaction was identified as additive 9 times out of 10 and misidentified as synergistic once. With a synergistic model underlying the simulations, the type of interaction was identified as synergistic 8 times out of 10 and misidentified as additive twice. In summary, we concluded that with a crisscross design and 60 individuals, parameters describing combined BIS suppression can be reliably estimated. We accepted the presented residual risk of false estimation for our clinical study, and we randomized 60 patients to receive specific combinations of propofol and sevoflurane as simulated and described in the next paragraph.

In half of the patients, propofol was held constant, and sevoflurane was stepwise increased; in the other half, sevoflurane was held constant and propofol was stepwise increased (fig. 1, A and B). For each of the 12 escalating combinations 5 patients were included. To study the boundaries of the response surface (single drug without interaction), 5 patients were given sevoflurane only (0.7 to 3.5 vol.%) and 5 were given propofol only (2–12 μg/ml) during the study period. Based on the simulation study,[11] the maximum Ce_{SEVO} was set at 3.5 vol.%, and maximum Ce_{PROP} was set at 12 μg/ml. A maximum of five steps was used to explore a single slice of the response surface.

No other drugs were given except for a possible 0.1-mg bolus of phenylephrine if mean arterial blood pressure dropped below 50 mmHg.

Assessment of Clinical Response

For each concentration step, the clinical response was assessed 12 min after reaching the target concentrations to allow for plasma effect-site equilibration. The patient was exposed to the following series of stimuli with increasing intensity: (1) mild prodding and saying his or her name in a loud voice ("shake and shout," corresponding to the Observer's Assessment of Alertness/Sedation score less than 2); (2) a tetanic stimulus of the ulnar nerve for 5 s by using the standard neurostimulator used in the clinical setting to test the level of muscle relaxation (100 Hz, 60 mA, Tristim NS3A peripheral nerve stimulator; Life Tech, Houston, TX); (3) insertion of a laryngeal mask airway (LMA size 3 for women and 4 for men, LMA Unique® [The Surgical Company, Amersfoort, The Netherlands]); (4) laryngoscopy aiming at full visualization of the vocal chords by using a size-3 curved
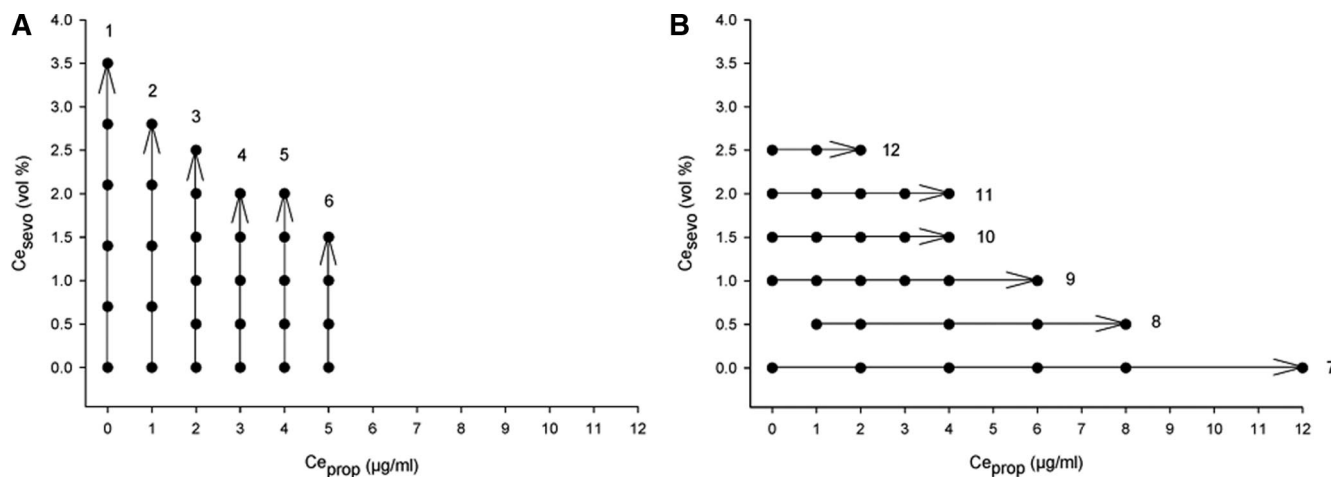
Fig. 1. Concentration grid of crisscross study design. (*A*) Escalating combinations 1 to 6, where propofol was held constant and sevoflurane was step-wise increased. (*B*) Escalating combinations 7 to 12, where sevoflurane was held constant and propofol was step-wise increased. Each escalating combination was tested in five patients, including combinations 1 and 7, which are the one-drug-only schemes.

Macintosh-type blade (HEINE Optotechnik GmbH & Co. KG, Herrsching, Germany). Verbal acknowledgment, eye opening, grimacing, coughing, withdrawal, or any other purposeful or nonpurposeful movement, including jaw clenching and bucking after a stimulus, were defined as a response. Absence of a response implied tolerance of the stimulus and was labeled 0, and presence of a response implied no tolerance of the stimulus and was labeled 1 in the case report form. All assessments were performed by one investigator (J.D.) to minimize interobserver variability. If there was no response to the first stimulus, the next stimulus was applied 10 s after the response assessment of the first. Between LMA insertion and laryngoscopy, this interval was at least 15 s. The assessment at each drug concentration level was stopped as soon as a response was observed or the patient tolerated laryngoscopy.

If there was no response to laryngoscopy at the highest predefined drug combination, data acquisition was stopped, and the patient's trachea was intubated after the administration of 0.9 mg/kg rocuronium.

Data Acquisition and Management

Spectral entropy (M-Entropy, GE Healthcare) parameters SE and RE and the bispectral index (Version 4.0, A-2000 BIS® monitor; Aspect Medical, Newton, IL) were derived from the frontal electroencephalographic (At-Fpzt). The smoothing time of the BIS® monitor was set at 15 s. For both monitors, burst suppression ratio was recorded as the secondary endpoint. All data were recorded electronically by using RUGLOOP II software (Demed) with a 5-s time interval. *Post hoc*, a moving median filter of 1-min length was applied to all electroencephalographic parameter data and to heart rate and blood pressure data. These artifact-filtered data were subsequently used for modeling.

Statistical Analysis

For propofol, the targeted effect-site concentration after 12 min of equilibration was considered as a pseudo-steady state concentration and was used as propofol effect-site concentration (Ce_{PROP}) in our analysis. For sevoflurane, the alveolar concentration measured by the S5 Anesthesia Monitor (GE Healthcare) *via* end-expiratory measurement after 12 min of equilibration was considered as a pseudo-steady state concentration and used as sevoflurane effect-site concentration (Ce_{SEVO}) in our analysis (5 times $t_{1/2}(ke0)$ of 2.4 min).[15]

Dependent variables were divided into quantal responses (tolerance of shake and shout, tetanic stimulus, insertion of laryngeal mask airway, and laryngoscopy) and continuous responses as measured by SE, RE, and BIS.

Pharmacodynamic Analysis of the Quantal Responses

We defined the probability of tolerance of shaking and shouting (TOSS) as P_{TOSS}, tolerance of a 5-s tetanic stimulus (TTET) as P_{TTET}, tolerance of laryngeal mask airway (TLMA) insertion as P_{TLMA}, and tolerance of laryngoscopy (TLAR) as P_{TLAR}. The model applied was the response surface model as described by Greco *et al.*[16] This common pharmacodynamic drug interaction model describes the drug effect as the sum of each drug's contribution after normalizing the effect-site concentration to the single drug's potency or Ce_{50} value plus an additional term for interaction scaled by the factor ε (not to be confused with NONMEM epsilon). This can be expressed as:

$$U = \frac{Ce_{PROP}}{Ce_{50,\,PROP}} + \frac{Ce_{SEVO}}{Ce_{50,\,SEVO}} + \varepsilon * \frac{Ce_{PROP}}{Ce_{50,\,PROP}} * \frac{Ce_{SEVO}}{Ce_{50,\,SEVO}} \quad (1)$$

where U is the combined drug potency, Ce_{PROP} and Ce_{SEVO} are the propofol and sevoflurane effect-site concentrations, $Ce_{50,\,PROP}$ and $Ce_{50,\,SEVO}$ are the propofol

and sevoflurane effect-site concentrations with 50% of effect, respectively.

For quantal response data, this interaction model can be introduced into a logistic pharmacodynamic model:

$$UN = U^{slope} \qquad (2)$$

$$P_{tolerance} = UN/(1 + UN) \qquad (3)$$

Where *tolerance* can be TOSS, TTET, TLMA, or TLAR, respectively. *Slope* is the steepness of the relation between the drug combination and the probabilities.

Initially, separate models were fitted to each of the quantal responses (TOSS, TTET, TLMA, TLAR). The resulting Ce_{50} and slope values were later used to check the plausibility of the parameter values estimated from a combined analysis with a common slope. For the combined estimation, the dependent variable and related probability were defined as:

0 = Reacts to shake and shout with

$$P = (1 - P_{TOSS}) * (1 - P_{TTET}) * (1 - P_{TLMA}) * (1 - P_{TLAR}) \qquad (4a)$$

1 = Tolerates shake and shout, reacts to tetanic stimulus with

$$P = P_{TOSS} * (1 - P_{TTET}) * (1 - P_{TLMA}) * (1 - P_{TLAR}) \qquad (4b)$$

2 = Tolerates tetanic stimulus and reacts to LMA insertion with

$$P = P_{TOSS} * P_{TTET} * (1 - P_{TLMA}) * (1 - P_{TLAR}) \qquad (4c)$$

3 = Tolerates LMA insertion and reacts to laryngoscopy with

$$P = P_{TOSS} * P_{TTET} * P_{TLMA} * (1 - P_{TLAR}) \qquad (4d)$$

4 = Tolerates laryngoscopy with

$$P = P_{TOSS} * P_{TTET} * P_{TLMA} * P_{TLAR} \qquad (4e)$$

Pharmacodynamic Analysis of the Continuous Electroencephalographic Variables

For the continuous data BIS, SE, and RE, a negative sigmoidal E_{max} model was used:

$$Effect = E_0 - (E_0 - REST) * UN/(1 + UN) \qquad (5)$$

Effect is the combined effect on BIS of the two drugs, E_0 is the effect when no drugs are given, UN is explained in Equation 2. REST is a required additional parameter related to the different properties of propofol and sevoflurane in suppressing the BIS in the examined concentration range. The selected interpolation approach is the same as when modeling the interaction of two drugs that exhibit different E_{max} values as described by Minto *et al.* The authors recommended interpolation of the

E_{max} for different ratios of the interacting drugs normalized to their potency.[12] For BIS and both spectral entropy variables, the concentration effect relation can be described by a negative sigmoid E_{max} model down to values where burst suppression occurs.

The interpolation factor REST was empirically defined as a function of the two drugs:

$$REST = REST_0 * \left(\frac{Ce_{SEVO}}{Ce_{50,SEVO}} \middle/ \left(\frac{Ce_{SEVO}}{Ce_{50,SEVO}} + \frac{Ce_{PROP}}{Ce_{50,PROP}} \right) \right)^{\lambda} \qquad (6)$$

whereby the exponential λ and $REST_0$ were also estimated during the modeling process. For propofol alone, *REST* is zero; for sevoflurane alone, *REST* equals to $REST_0$, corresponding to the nonsuppressible BIS. For drug combinations Equation 6 gives an interpolated value for *REST*.

If REST becomes negligible, the negative sigmoidal E_{max} model as defined in Equation 5, becomes a fractional sigmoid E_{max} model.

Parameter Estimation

The model parameters were estimated by using NONMEM V (GloboMax LLC). For all parameters, interindividual variability was permitted by using a log-normal distribution:

$$P_i = P_{TV} e^{\eta_i} \qquad (7)$$

where P_i is the parameter value in the ith patient, P_{TV} is the typical value of the parameter in the population, and η is a random variable with a mean of 0 and a variance of ω^2. Individual variability is reported as ω, the SD of η in the log domain, which is approximately the coefficient of variation in the standard domain. For the quantal responses, a single η for propofol and a single η for sevoflurane were estimated across all stimuli, in line with the notion that a patient requiring high doses to suppress consciousness will also require high doses for tolerance of laryngoscopy, compared to the respective population mean. Residual intraindividual variability of the continuous variables was modeled by using a standard additive error model (see Supplemental Digital Content 1, a document that contains the final control files for all endpoints, http://links.lww.com/ALN/A541).

The objective function for the analysis was –2 log likelihood (–2LL). The interaction parameters were tested for significance by comparing –2LL when ε (Equation 1) equals 0 (= additive model) with the –2LL when ε was not fixed to 0 (= synergistic model). Significance level for hypothesis tests was 0.01 (chi-square test) or a 6.84 difference in the –2LL adding one parameter for nested models.

The goodness of fit for the models was also assessed by visual inspection of the distribution of residual errors for each of the continuous endpoints.

Table 1. Demographic Data

	Median (Range)
Weight, kg	66.0 (50–102)
Height, cm	172.5 (150–190)
Age, yr	29.5 (18–58)
Gender, female/male	33/27

All model parameters are reported as typical values with standard errors, and clinical data are given as median with range.

Results

All patients completed the study; table 1 shows the demographic data. Figure 2 shows the actual concentration grid with some distribution of the sevoflurane end-tidal measurements taken after the equilibration phase just before stimulation. No phenylephrine had to be given because of blood pressure drops below 50 mmHg.

Quantal Response Modeling

In total, we obtained 274 stimulus response observations in all patients with an average of 4.6 observations for each patient (range 3 to 6). The distribution of responses to the different stimuli are displayed in figure 3. On the basis of available data, using $P \leq 0.01$ and 0 being excluded from the 95% interval of the typical value of the interaction parameter, a synergistic model was not found to be superior to an additive model for any endpoint.

This finding was confirmed in a fit of the combined model to all responses to stimulation. Therefore, additive interaction was concluded. Table 2 displays the parameters of the population fit for the combined analysis of

all quantal responses. The Ce_{50} values for the tolerance of the different stimulations are reflecting the relative strength of the stimulations; the constant C_{50} ratio reflects that the relative potencies of propofol and sevoflurane are approximately constant, regardless of the type of stimulation (nonpainful/painful/airway manipulation).

Figure 3 displays the observed and predicted responses (typical value ± SD) to the applied stimuli *versus* the sum of the normalized drug concentrations (combined potency TOSS = $(Ce_{PROP}/2.34) + (Ce_{SEVO}/1.03)$, where the denominators are the respective Ce_{50} values for tolerance of TOSS). The response surfaces for the probabilities of TOSS, TTET, TLMA, and TLAR are shown in figure 4A–4D. Figure 5 compares the isoboles at the probability levels of 5% (P_5), 50% (P_{50}), and 95% (P_{95}) for the additive and synergistic models. This representation shows that the models only differ very slightly, confirming also visually that the higher complexity of the synergistic model is not justified for the description of our data.

Modeling of BIS, SE, RE

Independent modeling and hypothesis testing of the concentration response relationship for BIS, SE, and RE was performed. Six different structural models were tested for BIS, SE, and RE: an additive and synergistic fractional E_{max} model (acc. to Equation 5, REST = 0), an additive and synergistic negative sigmoidal E_{max} model (acc. to Equation 5), and an additive and synergistic interpolated negative sigmoidal E_{max} model (acc. to Equations 5 and 6). For BIS, the interpolated, additive sigmoidal E_{max} model was selected as our final model. For SE and RE, a simple additive fractional E_{max} model resulted in the best fit. Using $P \leq 0.01$ and 0 being
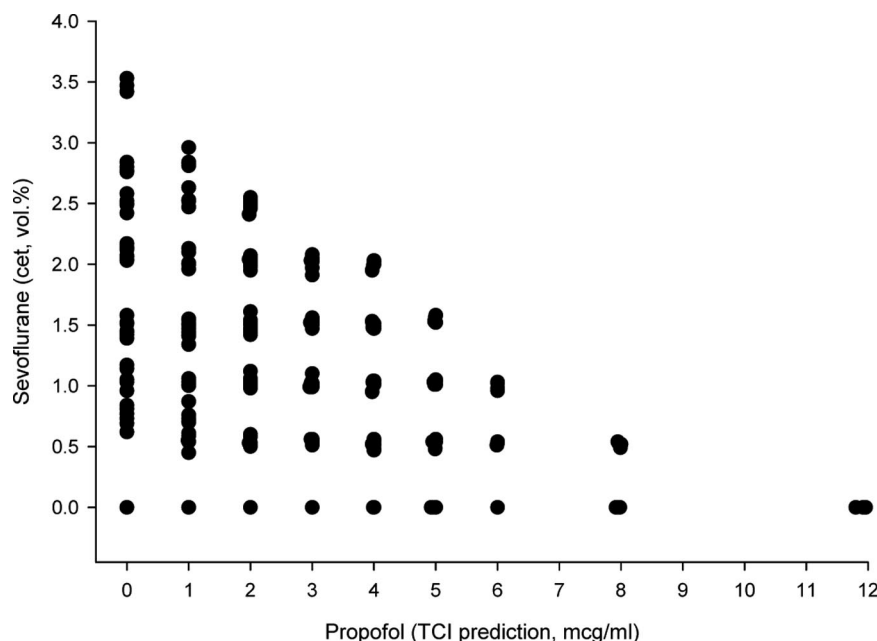
Fig. 2. Actual concentration grid with end-tidal measurements and effect site predictions (target-controlled infusion [TCI] prediction) after equilibration: some variability can be observed in the measurements as compared to the study grid in fig. 1.
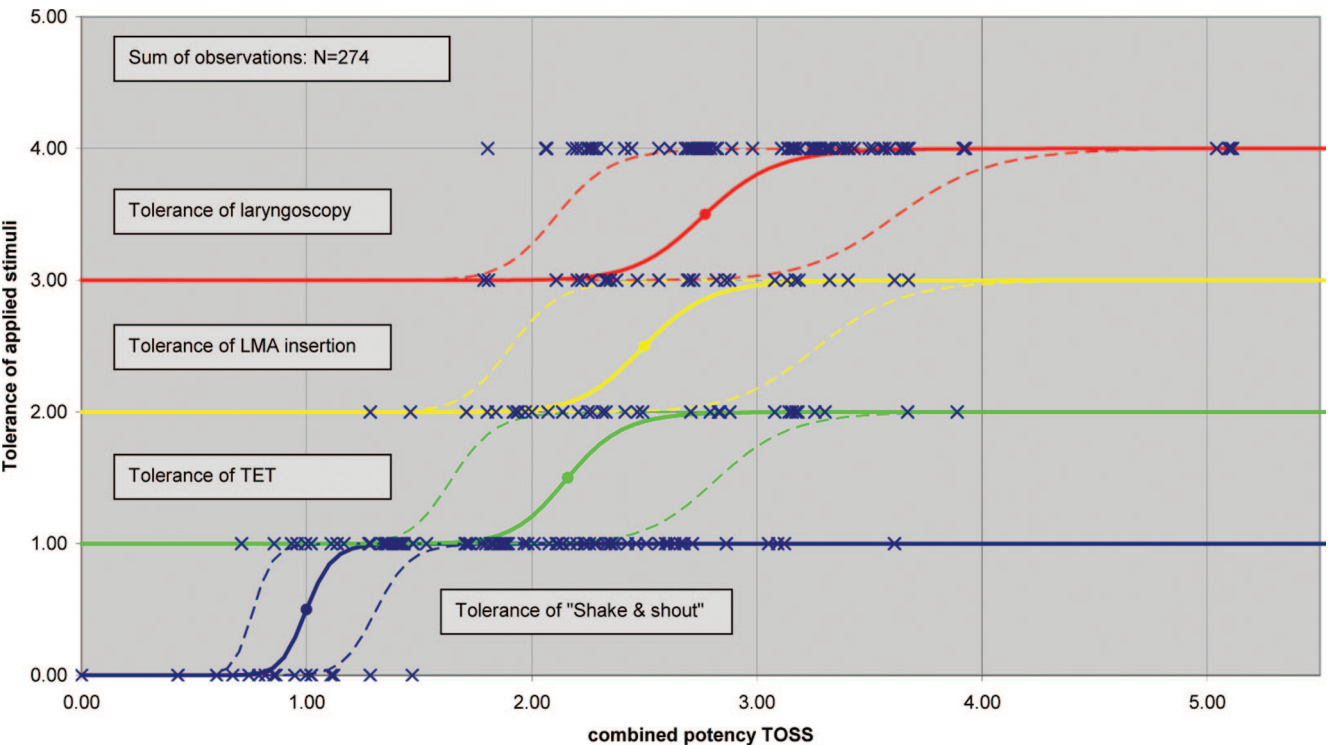
Fig. 3. Summary of the quantal response analysis of the final model showing all 274 responses (marked as *x*) and the predicted concentration response curves (*solid lines*). The responses were scored as follows: 0 = reacts to shake and shout (30 observations); 1 = tolerates shake and shout (TOSS), but reacts to stronger stimuli (98 observations); 2 = tolerates tetanic stimulation (TET), but reacts to stronger stimuli (37 observations); 3 = tolerates laryngeal mask (LMA) insertion, but reacts to stronger stimuli (26 observations); 4 = tolerates laryngoscopy (83 observations). Between-subject variability (± SD) is shown as *dashed lines*. This plot graphically relates the different Ce_{50}s to the TOSS Ce_{50}, which is scaled to 1 by using the normalized sum of concentrations (combined potency) notation according to Equation 1 and parameterized as per table 2.

excluded from the 95% interval of the typical value of the interaction parameter, a synergistic model was not found to be superior to an additive model for any of the processed electroencephalographic endpoints. All model parameters are presented in table 3.

Figure 6A–6C show the response surfaces of the final models and the diagnostic plots measured *versus* predicted values. The isoboles of the different models at various levels of effect are displayed in figure 7A–7C.

Discussion

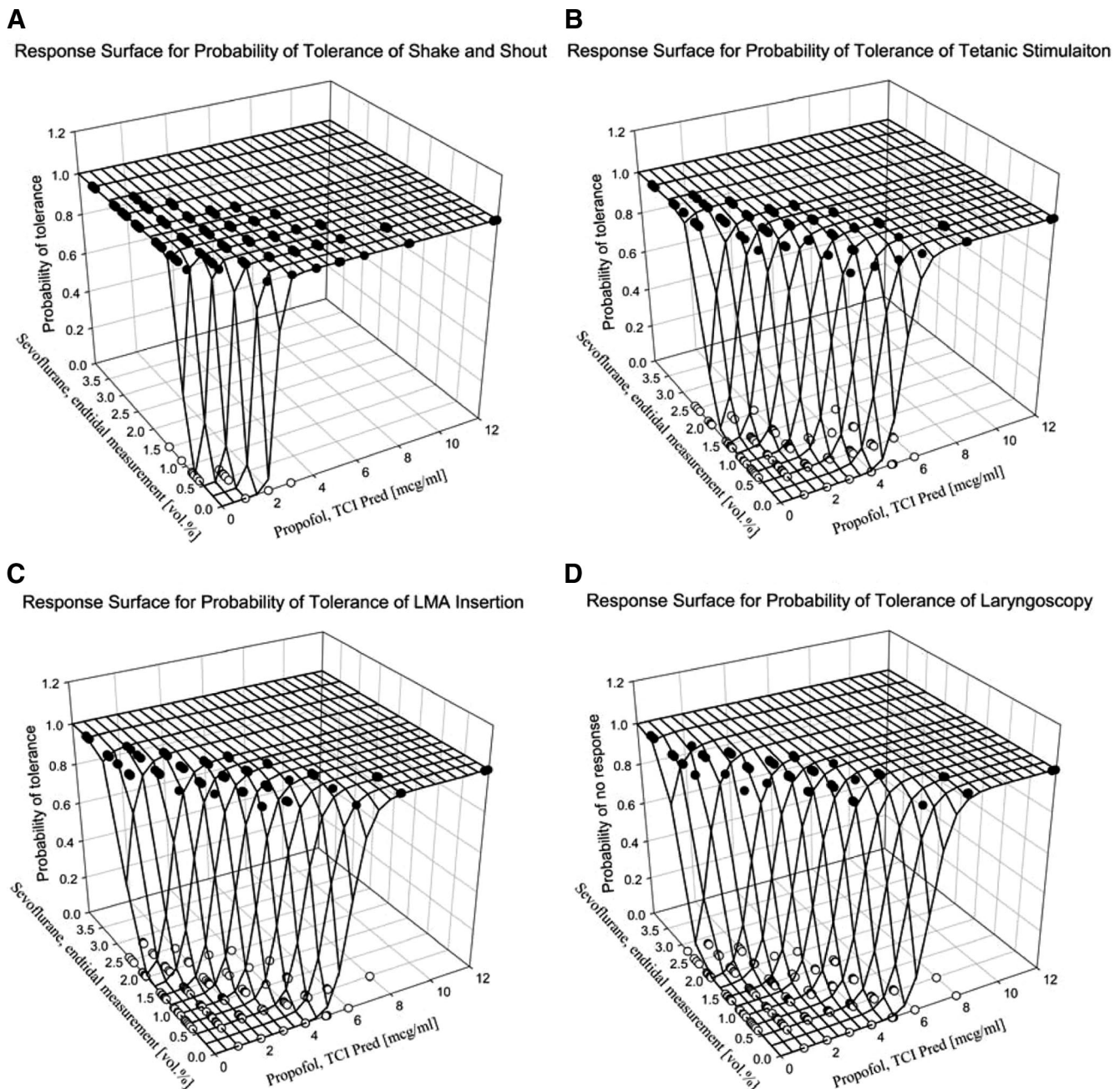This investigation was intended to quantify, under approximately steady-state conditions, the interaction between propofol and sevoflurane with regard to clinically relevant endpoints defined by tolerance to a series of stimuli with increasing intensity. In addition, the combined central nervous system suppressant drug effect was quantified by using three processed electroencephalographic variables, BIS, SE, and RE. These clinical and electroencephalographic endpoints have been used and validated in various previous interaction studies.[14,17,18] At a significance level of 0.01, we could unequivocally accept our null-hypothesis that propofol lowers the concentration of sevoflurane to (1) tolerate a specific clinical stimulation and to (2) obtain a certain processed electroencephalographic effect and *vice versa* in an additive fashion.

Table 2. Population Modeling Results for Quantal Responses

Parameter	TOSS	TTET	TLMA	TLAR	CV%
$Ce_{50,\ PROP}$, $\mu g/ml$	2.34 (0.22)	5.34 (0.43)	5.92 (0.45)	6.55 (0.51)	31%
$Ce_{50,\ SEVO}$, vol.%	1.03 (0.07)	2.11 (0.13)	2.55 (0.16)	2.83 (0.19)	32%
Ce_{50} ratio, vol.% · ml · μg^{-1}	0.44	0.40	0.43	0.43	—
Slope P_{TV}	17.6 (2.69)	17.6 (2.69)	17.6 (2.69)	17.6 (2.69)	—

Population Ce_{50} parameters and slope typical value parameter (P_{TV}) for propofol and sevoflurane with (standard errors) from the combined analysis of all quantal responses: tolerance to shake and shout (TOSS) (Observer's Assessment of Alertness/Sedation Scale less than 2), tolerance to tetanic stimulation (TTET), tolerance to laryngeal mask airway insertion (TLMA), and tolerance to laryngoscopy (TLAR). CV% is the between-subject coefficient of variation. The numerical ratio between the sevoflurane and propofol Ce_{50} values is shown for all quantal responses (according to Equation 1, $Ce_{50,\ PROP}$ and $Ce_{50,\ SEVO}$ are the propofol and sevoflurane effect-site concentrations with 50% of effect, respectively).

A

Response Surface for Probability of Tolerance of Shake and Shout

B

Response Surface for Probability of Tolerance of Tetanic Stimulaiton

C

Response Surface for Probability of Tolerance of LMA Insertion

D

Response Surface for Probability of Tolerance of Laryngoscopy

Fig. 4. Full response surfaces for the probability of quantal responses: probability of tolerance of (*A*) shake and shout, (*B*) tetanic stimulation, (*C*) laryngeal mask airway (LMA) insertion, and (*D*) laryngoscopy. The responders are shown at the bottom as *open circles*, and the nonresponders at the roof side as *filled circles*. The response surfaces are shown as a function of measured end-tidal sevoflurane and predicted propofol effect site concentration (TCI Pred).

Propofol and sevoflurane both enhance the function of the γ-aminobutyric acid type A receptor in neurons and in recombinant systems.[19,20] Recently, Sebel *et al.* showed in a laboratory investigation that response surface modeling of the potentiation of γ-aminobutyric acid type A responses by propofol and sevoflurane revealed that the two anesthetics modulated the receptor function in an additive manner, suggesting that these drugs have converging pathways of action on the γ-aminobutyric acid type A receptor with separate binding sites.[4] In an accompanying paper by Harris *et al.*, additivity be-

tween propofol and sevoflurane with regard to loss of consciousness and immobility to surgical incision was found.[3] An editorial by Hemmings and Antognini accompanied the two papers.[21] They warned to oversimplify the molecular action, but concluded that the clinical findings are useful for more rational dosing.

Since Harris *et al.* used Dixon's up-down titration method,[22] they could only determine the 50% isobole (propofol and sevoflurane concentration at which 50% of patients lost consciousness and moved to skin incision [= EC_{50}s]). Moreover, they evaluated the respective ef-
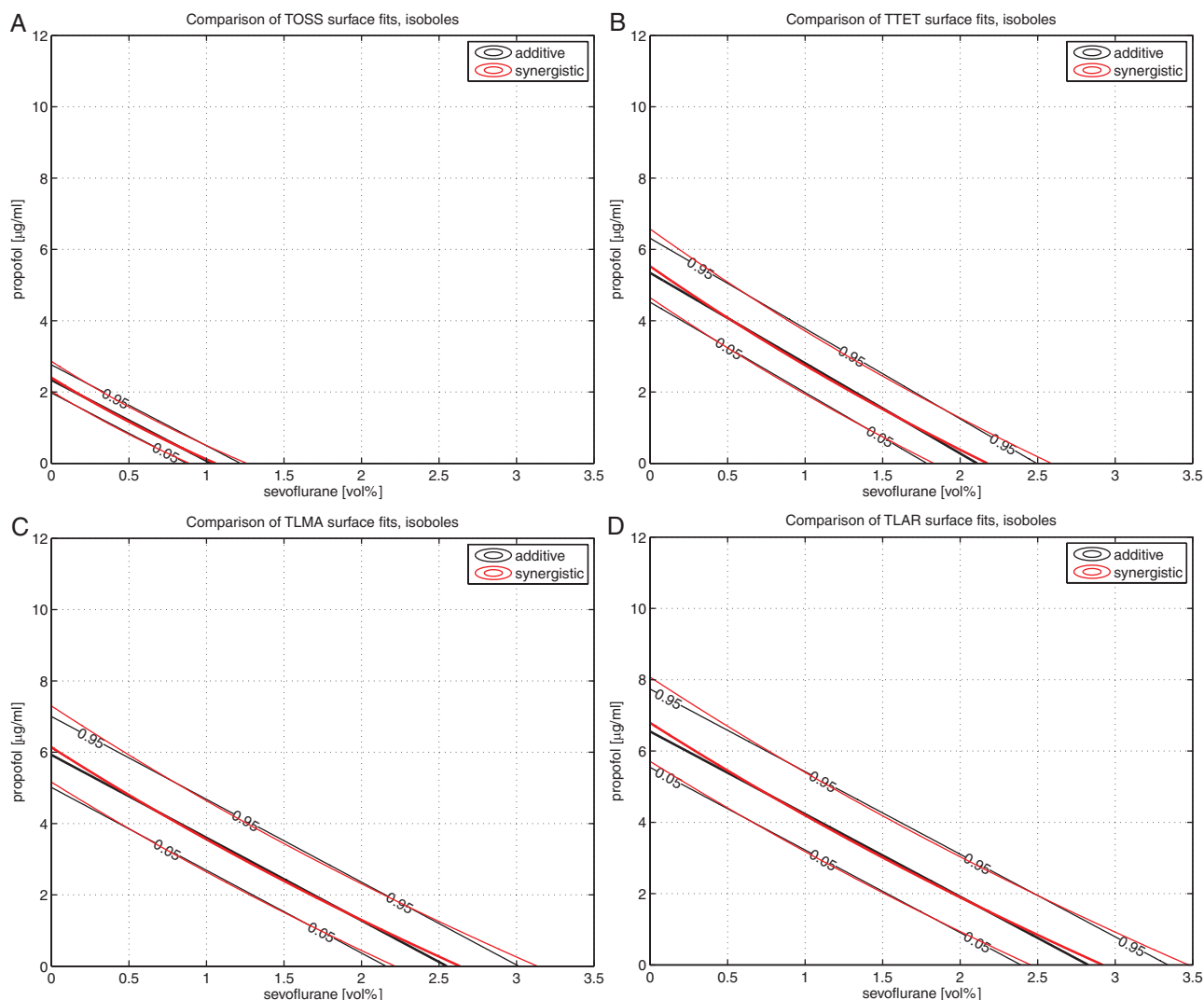
Fig. 5. Comparison of the isoboles at the probability levels of 5% (P_5), 50% (P_{50}), and 95% (P_{95}) for the additive (*black lines*) and synergistic (*red lines*) models. The additive model was selected as the final model. (*A*) TOSS, tolerance of shake and shout; (*B*) TTET, tolerance of tetanic stimulation; (*C*) TLMA, tolerance of laryngeal mask airway insertion; (*D*) TLAR, tolerance of laryngoscopy.

fect at a single sevoflurane concentration, only the propofol target concentrations were up- and down-titrated, and the axis intercept values (single drug situation) were derived from historical data by Kodaka *et al.*[23]

For these reasons, it appeared justified to investigate the propofol-sevoflurane interaction by using a more general and robust approach. Our crisscross study design[10] covered the entire clinically relevant concentration range, enabling us to apply response surface methodology and provide guidelines for rational anesthetic drug dosing for suppression of multiple stimuli and electroencephalographically guided anesthesia at any level/isobole. Our study confirms the additive interaction found by previous authors for the 50% isobole[3] and extends it to the entire response surface.

Our ranking of the stimuli from easiest to most difficult to suppress and then performing them in this order could be a possible source of bias. Because of ethical reasons, it was not possible to administer the stimuli in

a random order, nor did we attempt to expose a person reacting to loud voice to laryngoscopy to ascertain that he/she would react to a stronger stimulus too. We therefore performed a simulation study to assess the amount of potential bias that can be expected from such a design. The conclusion from this simulation study described in appendix 1 is that in the setting of our study bias is constrained to a range of ± 4% and on average 0 %.

Our model building process for the quantal responses was a two-step approach. We initially estimated separate response surfaces to the responses to single stimuli, ascertaining that (1) the Ce_{50} values were discernible, (2) the Ce_{50} values were in identical order for both drugs, and (3) an additive response was displayed for all response categories, which was a testable hypothesis and by no way certain because the stimuli differed regarding quality (painless arousal, painful, airway manipulation) and the neuroanatomical pathways involved (au-

Table 3. Population Modeling Results for Bispectral Index (BIS), State Entropy (SE), and Response Entropy (RE)

	BIS	SE	RE
Baseline (E_0) P_{TV}	94.5 (2.40)	88.6 (2.20)	98.2 (2.35)
Baseline CV%	3.2	—	—
$Ce_{50, PROP}$ P_{TV}, μg/ml	3.68 (0.19)	3.87 (0.24)	3.71 (0.24)
$Ce_{50, PROP}$ CV%	20.0	27.2	28.3
$Ce_{50, SEVO}$ P_{TV}, vol.%	1.53 (0.09)	1.99 (0.08)	1.98 (0.08)
$Ce_{50, SEVO}$ CV%	19.2	14.1	17.3
Slope P_{TV}	2.23 (0.10)	2.75 (0.14)	2.72 (0.24)
$REST_0$ P_{TV}	21.5 (3.18)	—	—
λ P_{TV}	3.49 (0.79)	—	—
Ce_{50} ratio, vol.% · ml · μg^{-1}	0.42	0.51	0.53

P_{TV} = typical population value with (standard error); CV = between subject coefficient of variation for all parameters estimated: Baseline (E_0), Ce_{50} values for propofol and sevoflurane, slope and interpolation parameters $REST_0$ and λ for BIS. The Ce_{50} Ratio describes the potency ratio between propofol and sevoflurane (according to Equation 1, $Ce_{50, PROP}$ and $Ce_{50, SEVO}$ are the propofol and sevoflurane effect-site concentrations with 50% of effect, respectively).

ditory, peripheral sensory, and cranial nerves). The results of this interim analysis enabled us to conclude that the isoboles would not cross, which is essential for the applied parameterization. It was also noted that the interindividual variability of Ce_{50} values could not be estimated for all stimuli in the separate analyses. For logistic regression type analyses, this invariably leads to the underestimation of the steepness of the surface.[24] The next iteration of the model building process was focused on model reduction and stabilization. Pooling data from the response to all stimuli turned the modeling problem from assessing unconnected binary responses into assessing an ordered categorical response. This paradigm necessitated introduction of one single term for the interindividual variability of all Ce_{50} values for each drug, implying the assumption that sensitivity to a drug relative to the population mean is uniformly equal regardless of stimulus, *i.e.*, a subject who needs less sevoflurane than the typical subject for tolerance of shake and shout also needs less for tolerance of tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy. This simplification profoundly increased the stability of parameter estimates while maintaining an excellent fit.

We consider TOSS as a surrogate for loss of consciousness because it includes the Observer's Assessment of Alertness/Sedation Scale ratings below 2.[25] TTET, TLMA, and TLAR reflected the probability of response to a noxious stimulus and airway manipulation in the absence of antinociceptive drugs. Obviously, TOSS was obtained at much lower concentrations than TTET, TLMA, and TLAR (fig. 3), illustrating the requirement for much higher concentrations of hypnotic-anesthetic drugs to suppress the response to noxious stimuli. For any of these endpoints, propofol and sevoflurane acted additively. The Ce_{50} values for TOSS are supported by the following previous findings: The $Ce_{50, PROP}$ (2.34 μg/ml) is consistent with the findings of Bouillon *et al.* (2.16 μg/ml) from a response surface analysis.[14] Kodaka *et al.*[23] reports 2.7 and 2.9 μg/ml using Dixon's up-down method[22] for female and male patients,
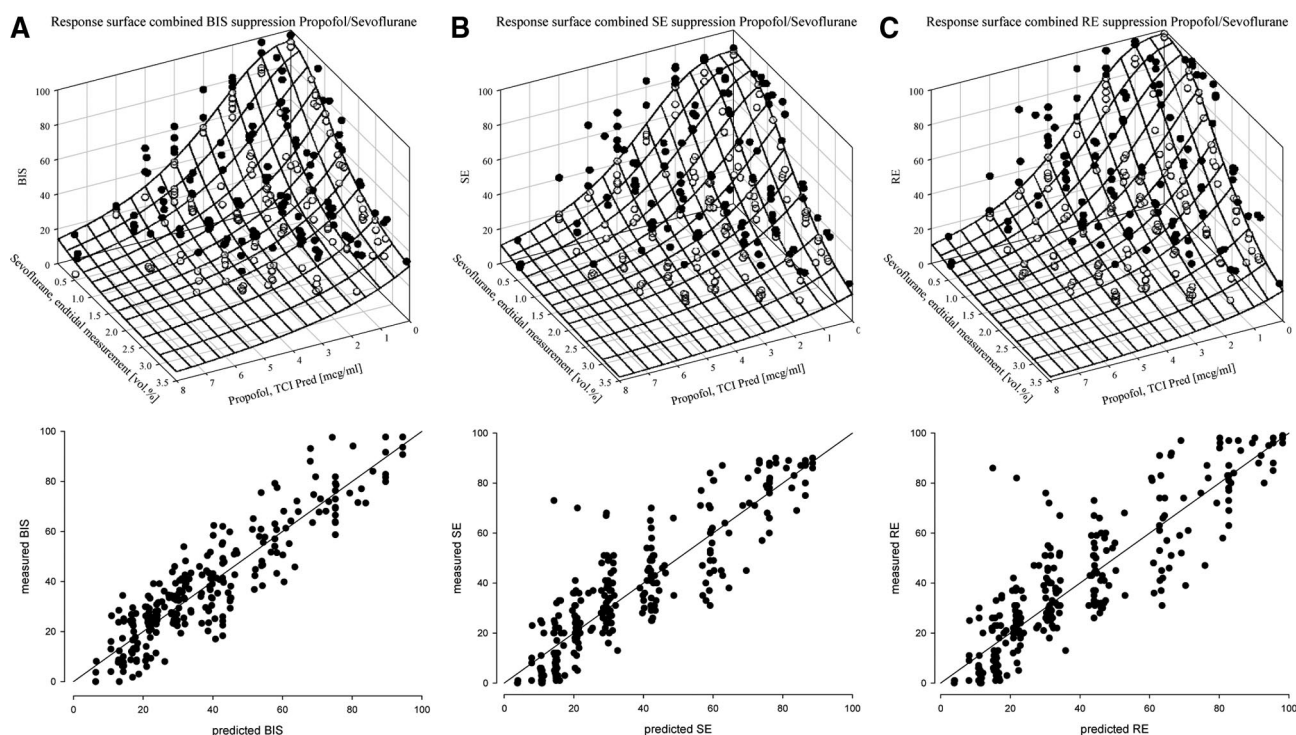
Fig. 6. Full response surfaces for electroencephalographic endpoints and measured *versus* predicted goodness of fit plots: (*A*) bispectral index (BIS), (*B*) Spectral Entropy (SE); (*C*) Response Entropy (RE). Measured values above the surface are shown as *filled circles* and below the surface as *open circles*. The response surfaces are shown as a function of measured end-tidal sevoflurane and predicted propofol effect site concentration (TCI Pred).
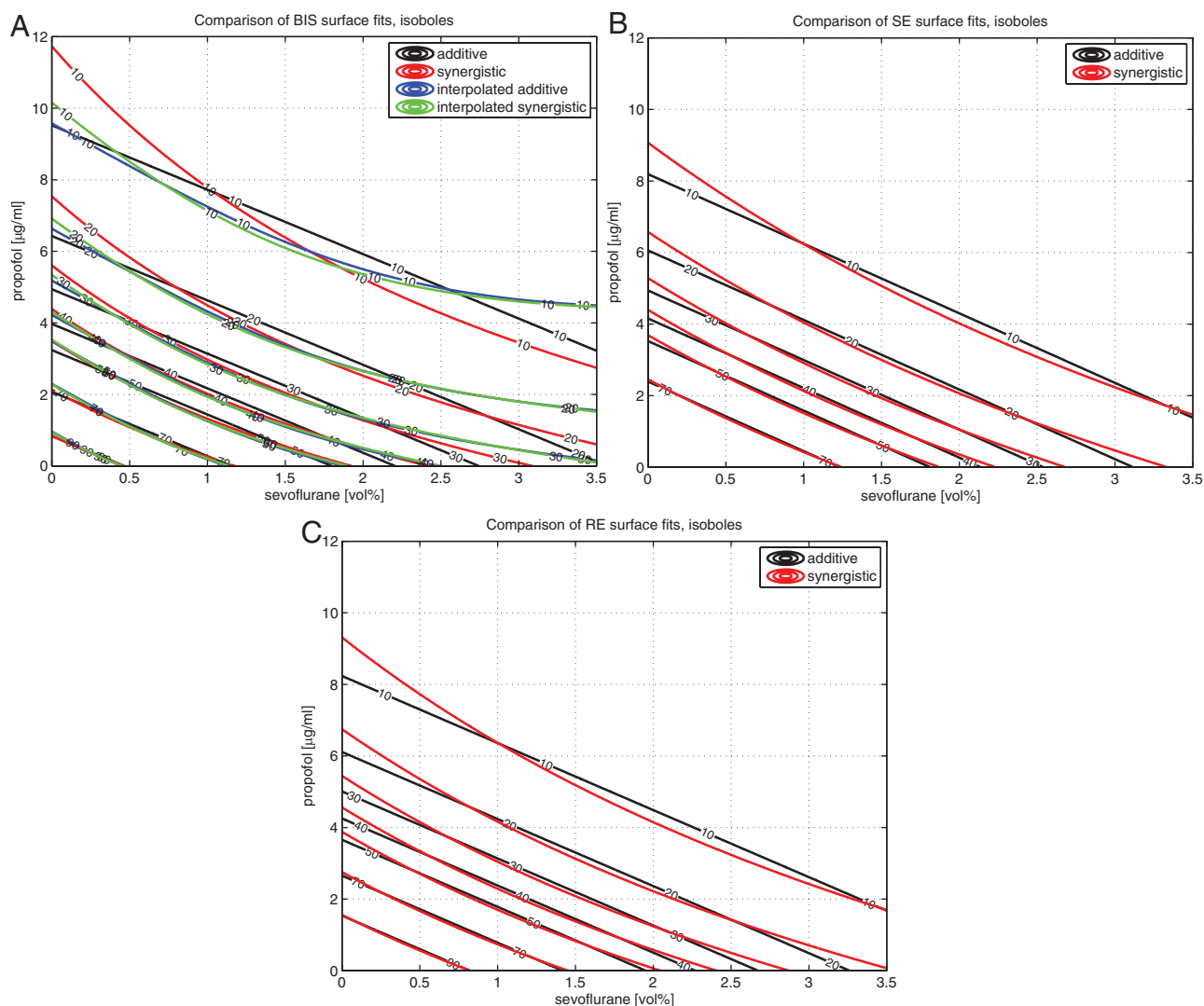
Fig. 7. Comparison of the different models for the electroencephalographic endpoints, (A) bispectral index (BIS), (B) Spectral Entropy (SE), and (C) Response Entropy (RE), by using isoboles for processed electroencephalographic values of 10, 20, 30, 40, 50, 70, and 90. The interpolated additive was selected as the final model for BIS, and the additive model was selected as the final model for SE/RE.

respectively. The $Ce_{50, SEVO}$ of 1.03 vol.% is consistent with the value of 0.88 vol.% (average of male and female patients) reported by Kodaka *et al.*[23] When comparing the 50% isobole at the single midpoint examined by Harris *et al.* at a sevoflurane end-tidal concentration of 0.45 vol.%, we predict a corresponding propofol concentration of 1.29 μm/ml, which is within both the 95% confidence interval of the experimental data and the prediction of the additive model of Harris *et al.*[3]

All evidence considered we believe to have accurately captured the interaction between propofol and sevoflurane with regard to suppression of consciousness.

Unfortunately, only limited data are available to compare our Ce_{50} values for tolerance of the noxious/airway stimuli.

Our $Ce_{50, SEVO}$ TTET was 2.11 (0.16) vol.% and compares well with the 1.83 (0.15) vol.% reported by Katoh *et al.*[26] and 2.22 (0.29) vol.%, by Higuchi *et al.*[27] Manyam

et al. found a value of 3.4 vol.%, substantially higher than any of the other reported values.[28] In part, this could be explained by the non-steady state condition after an equilibration period of only 5 min that they used. The $Ce_{50, PROP}$ found for TTET of 5.34 μg/ml is higher than the 4.1 μg/ml that was reported by Struys *et al.* in a previous study.[29] However, the tetanic stimulation in this study was limited to 2 s as compared to 5 s used by us, which may explain the difference in the Ce_{50} values.

Our $Ce_{50, SEVO}$ for TLMA was 2.55 (0.24) vol.%, whereas Nishina reported 2.0 (0.16) vol.% for children between 3 and 11 yr.[30] The Ce_{50}s for tolerance of insertion of a classic LMA in adults reported by Kodaka *et al.* were 2.36 (0.22) vol.% of sevoflurane and 3.14 (0.33) μg/ml propofol, whereas the corresponding values for insertion of a ProSeal® LMA were significantly higher.[31] Although there is good agreement among the $Ce_{50, SEVO}$, their $Ce_{50, PROP}$ based on model predictions according to

Gepts[32] and modified by Marsh[33] was substantially lower than our value (5.9 μg/ml) which is based on model predictions according to Schnider.[8,9] Kodaka's $Ce_{50, PROP}$ for LMA insertion was not confirmed in other studies,[34–37] reporting values between 4.3 μg/ml[35] and 8.72 μg/ml.[37] All these studies differ in regard to the pharmacokinetic models, equilibration times, premedication, study population, type of laryngeal mask airway, the exact definition of the patient's response to LMA insertion and its grading. Within the context of all these studies, we consider our $Ce_{50, PROP}$ finding for LMA insertion as plausible.

We found a $Ce_{50, PROP}$ for TLAR of 6.55 μg/ml, whereas 6.62 μg/ml and 5.6 μg/ml were reported by Bouillon *et al.*[14] and Kern *et al.*[38] respectively. Our study and the one of Bouillon *et al.* used the Schnider model[8,9] for propofol predictions, whereas Kern *et al.* used the model described by Tackley *et al.*,[39] which could explain the slight difference found. For sevoflurane, there is little information on the Ce_{50} value for tolerance of laryngoscopy alone (without intubation) so far. Manyam *et al.* reported a value of 2.6 vol.% in their sevoflurane-remifentanil interaction study.[28] This value compares well with our finding of 2.83 vol.%; however, as mentioned above, their measurement was not at steady state, so those findings should be interpreted with care. The sevoflurane Ce_{50} for tolerance of tracheal intubation including laryngoscopy was reported at 3.55 vol.% (95% CI 3.3–3.8) by Katoh *et al.*[40] For isoflurane, a Ce_{50} for tolerance of tracheal intubation of 1.89 (0.10) vol.% was found, which can be related to the Ce_{50} of laryngoscopy of 1.07 (0.07) vol.% reported in the same study by Zbinden *et al.*[41] Assuming that the ratio of the two Ce_{50} is the same for sevoflurane as for isoflurane (*i.e.*, 0.6) a sevoflurane Ce_{50} laryngoscopy in the range of 2.1 vol.% would be expected. This is substantially lower than 2.83 vol.% that we found in our data. However, Zbinden *et al.* defined only gross purposeful movement and Katoh *et al.* in addition bucking as a response. In our study, coughing, jaw clenching, and any other sort of movement were also considered as a response; accordingly, the $Ce_{50, SEVO}$ to abolish all these responses is higher than extrapolated from those other studies. In an older minimum alveolar concentration (MAC) study using halothane Yakaitis *et al.* found a ratio of 1.3 between MAC intubation and MAC laryngoscopy.[42] By using this ratio and the MAC intubation from Katoh and colleagues,[40] one could extrapolate a MAC laryngoscopy for sevoflurane of 2.73 vol.%, well within the 95% CI of our actual finding.

Although skin incision is the classic stimulus to assess the potency of anesthetic drugs or drug combinations, we selected LMA insertion and laryngoscopy as clinical stimuli. The main reason was that these stimuli are repeatable in the same subject (skin incision is not) so that we obtained crossovers in every patient for almost every

quantal endpoint, hereby adding power to the study.[24] LMA insertion and laryngoscopy are clinically relevant stimuli that have been used in previous studies on propofol and remifentanil.[14,38] With this design, we were able to do a population analysis and estimate Ce_{50}s and slopes for any stimulus with high precision.

To analyze the central nervous system suppressant effect of propofol and sevoflurane, we studied three different processed electroencephalographic measures. Both the BIS and spectral entropy have been used extensively to quantify cerebral drug effects for propofol and sevoflurane, after single administration and in combination with opiates.[13,43–49] When administering propofol or sevoflurane alone, our typical values for $Ce_{50, PROP}$ for BIS, SE, and RE are in the range with those found by others. Mourisse *et al.*[43] revealed a typical value (CV%) for $Ce_{50, PROP}$ of 2.56 (21%) μg/ml when using BIS, whereas Vanluchene *et al.*[13] found typical values (CV%) of 4.92 (34%), 4.68 (36%), and 4.55 (35%) for BIS, SE and RE, respectively. For $Ce_{50, SEVO}$, our results are very close to others. Mourisse *et al.*[43] found a typical value (CV%) for $Ce_{50, SEVO}$ of 1.33 (19%) vol.%, and Ellerkmann *et al.*[44] reported values (mean $\pm$ SD) of 1.45 $\pm$ 0.59, 1.60 $\pm$ 0.51, and 1.55 $\pm$ 0.51 vol.% for BIS, SE, and RE, respectively.

For the three separately analyzed measures of cerebral drug effect, a synergistic interaction model did not improve the fit to the data compared to an additive model ($P < 0.01$). Figure 7 visualizes the response surfaces for the different BIS, SE, and RE fits as an isobolographic representation of BIS, SE, and RE values between 10 and 90. For SE and RE values in the clinical range, differences between additive and synergistic model fits are hardly visible and well within the variability of the surface parameters (data not shown). For the lower values, the differences are a bit more pronounced.

For BIS, we encountered that, in the given concentration range of propofol, the lowest values of BIS were on average around 10; for sevoflurane, the lowest values were on average around 35. To be able to construct a reasonable response surface from these inherent 'mismatch' to suppress BIS over the examined concentration ranges, a "nonsuppressible BIS" (REST) factor was included into the model and estimated (as explained in the Materials and Methods section). The interpolated additive negative E_{max} model revealed the best data fit. Although we are aware of the possibility to decrease BIS, SE, or RE values to zero with sevoflurane or propofol, we did not observe these levels at the highest concentrations administered in our study, and we felt that it was clinically and ethically unacceptable to go beyond these limits.

We used a tight-fitting facemask to optimize sevoflurane administration, and we measured and controlled carbon dioxide and tidal volumes during spontaneous ventilation to ensure accurate ventilation. If required,

manual breathing support was allowed. To ensure a pseudo-steady state condition between end-tidal and effect-site concentration, we waited 12 min for equilibration based on equilibration time constants $t_{1/2}(ke0)$ as described previously: 2.4 min for the spectral edge frequency at the 95% of the electroencephalographic power spectrum,[15] 1.45 min for BIS and 2.9 min to abolish blink reflex,[43] and 2.8 min to abolish tetanic stimulus-induced withdrawal reflex.[50] The 12-min equilibration time was then selected as the four to five times $t_{1/2}(ke0)$ to be within 94–97% of the steady state value. A very recent publication by Kennedy *et al.* found 3.4 min for $t_{1/2}(ke0)$ for BIS.[51] This would result in an equilibration to still above 90% of steady state after 12 min. For propofol, an effect compartment target-controlled infusion technique was used to ensure pseudosteady state conditions within the 12 min waiting time.[8,9] We did not measure propofol plasma concentrations; however, we applied the model from Schnider *et al.*, which has been validated and applied in a number of previous studies.[3,46,52]

Interestingly, the ratios between the Ce_{50}s of sevoflurane and propofol found for the different endpoints are similar except for SE and RE, averaging 0.43 vol.% · ml · μg^{-1}. Therefore it was attempted to model the quantal response data with a fixed Ce_{50} ratio for the quantal endpoints, only estimating the ratio and the Ce_{50}s for propofol. Using the Akaike Information Criterion,[53] the more complex model was significantly better in describing the data ($P < 0.01$). Therefore, modeling fixed Ce_{50} ratios *versus* individual Ce_{50} values for each drug and stimulus was considered inferior.

However, in the clinical setting, the Ce_{50} ratio of 0.43 vol.% · ml · μg^{-1} could be used to easily calculate combined drug potency in steady state. A propofol target-controlled infusion with a target of 2 μg/ml combined with 1 vol.% sevoflurane would give an equivalent of 1.86 vol.% sevoflurane or approximately 1 MAC. Myocardial protection by volatile anesthetics has been demonstrated in clinical trials[1,2]; it is therefore possible that sevoflurane/propofol coadministration will be performed more frequently in the future. For sevoflurane, an endothelial protection against ischemia–reperfusion injury has been shown already with sedative concentrations.[54]

In transient situations, such as during induction, the calculation of the combined potency has to include the kinetics of propofol and sevoflurane and is therefore no longer a simple scaled addition and requires the use of computer-based calculation and visualization tools. A drug display frontend could be used for such a visualization.[7]

Limitations of the Study

All stated Ce_{50} values for propofol are based on model predicted values and not measured drug con-

centrations. The true effective concentrations during stimulation are therefore unknown and only approximated by the model. We examined response to stimulation during pseudo-steady state, when individual variability is smaller than variability after bolus. The institutional review board would not have approved an arterial line for drug sampling, so we were restricted to using predicted concentrations, which is scientifically limiting. However, from a practical point of view, it makes sense to report predicted concentrations for propofol because this is what many clinicians see in their everyday practice when using target-controlled infusions of propofol. Also, the Ce_{50} values found for the different endpoints are in good agreement with other studies, and some of them actually used measured concentrations.

In conclusion, we identified the Ce_{50} values of and additivity for sevoflurane and propofol regarding electroencephalographic suppression, tolerance of shake and shout, tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy by using response surface methodology. The resulting pharmacodynamic parameters were determined with high precision and are in agreement with those obtained from single drug and 50% isobole studies. They can be used to optimize the sequential and/or concomitant administration of propofol and sevoflurane.

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Appendix 1: Bias Simulation Study

With this simulation, the possible bias in case of ordered categorical measurements as used in this study was estimated. Stimuli of increasing strength were applied until there was a response from the patient at the given drug combination. This design implies increasing Ce_{50}s to tolerate the different stimuli, and it is *a priori* unknown what bias has to be expected if two Ce_{50}s are the same or not differing much.

A software was developed in Matlab (The Mathworks Inc., Natick, MA) for simulation of the study design. For simplification, one drug only was assumed, which, however, is not a limitation for bias estimation. One Ce was defined at $Ce1 = 3.5$ drug units, and then a log-normal distribution was assumed for the population. The variance of this distribution was an input parameter to the simulations. The second Ce was defined *via* a multiplication factor β, yielding a $Ce2 = Ce1 * \beta$. β itself was again assumed as log-normally distributed, the variance also an input to the simulations. A random population of n patients was then generated by using the above mentioned distribution. A fixed n = 60 was assumed, but this could also have been an additional input parameter for the simulation.

This population was then subjected to our study design. For the estimation of the *Ce*s, a sampling grid could be specified (also an input for the simulations). For each drug level, the patient was tested with a
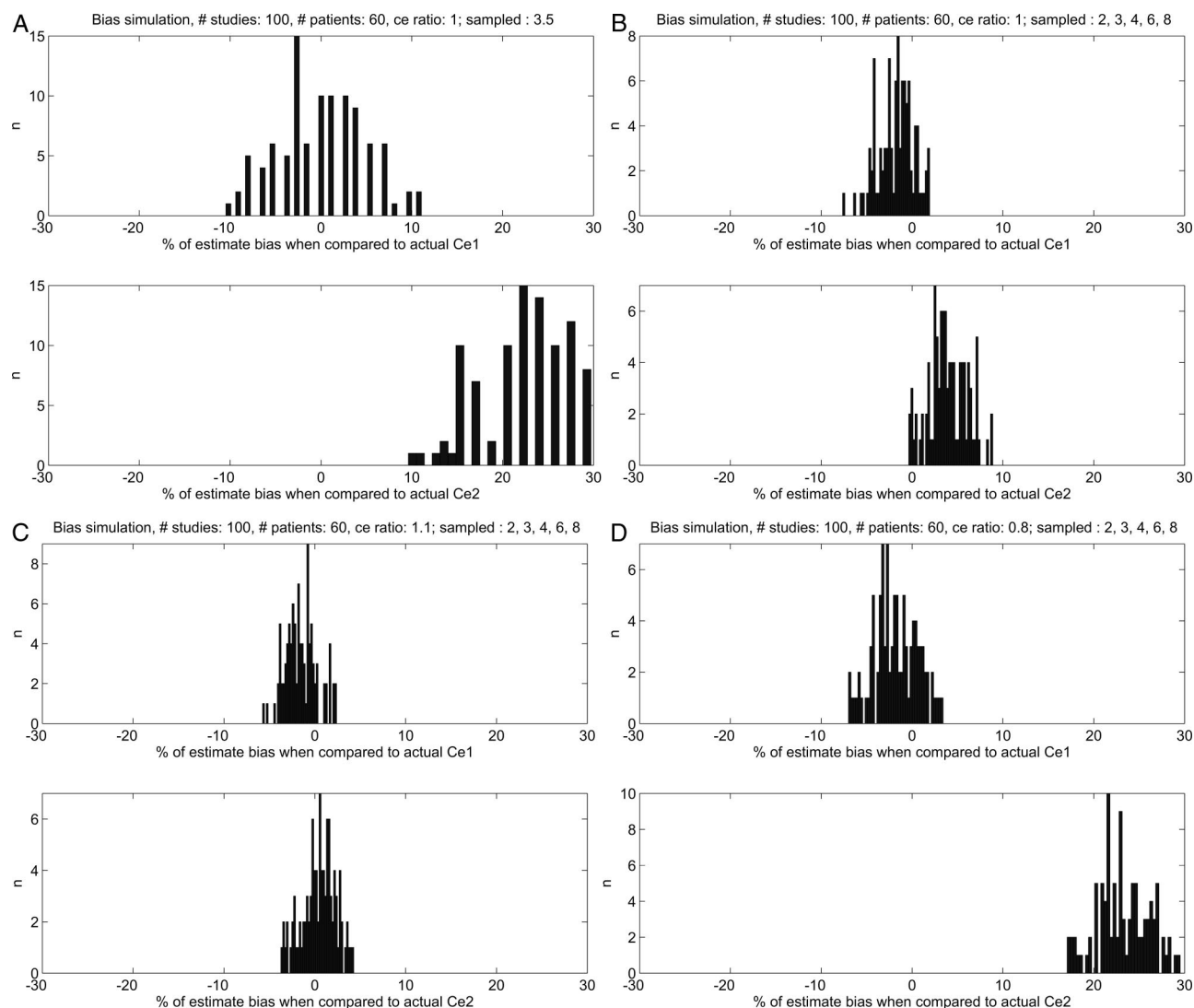
Fig. 8. Case simulations for bias estimation when using the proposed study design with ordered categorical response measurements (see Appendix for details). Each panel shows the distribution of bias from 100 simulated studies, each with 60 virtual patients. (*A*) Bias distribution while assuming no population distribution of the *Ce*s and using only one sample point of 3.5 drug units. (*B*) Bias distribution when both *Ce2* and *Ce1* are 3.5 drug units, but assuming a log-normal population distribution with a variance of 0.5 (Fig. 9) and using sample points at [2 3 4 6 8] drug units. (*C*) Bias distribution when *Ce2* is 10% larger than *Ce1* using the same sampling as for the case shown in *panel B*. (*D*) Bias distribution when the sampling is done in the wrong order (*Ce2* = 0.8 * *Ce1*).

first stimulation. The probability of tolerance was calculated *via* a sigmoid response curve by using the *Ce1* of the specific subject and a steepness factor of 17.6 (corresponding to our slope, table 2). A uniformly distributed random number between 0 and 1 then decided about the response of the virtual patient: tolerance = random number
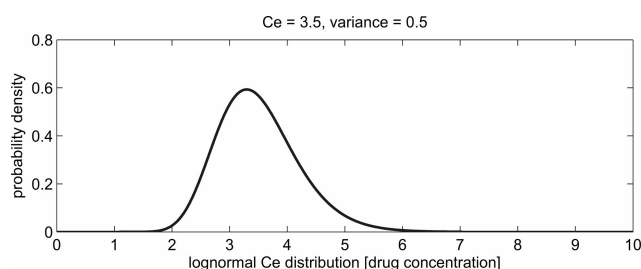
Fig. 9. Log-normal distribution of the simulated population Ce$_{50}$ with a variance of 0.5 (see appendix 1 for details).

below probability of tolerance; no tolerance = random number above probability of tolerance.

If there was no tolerance of the first stimulation, the test for the second stimulation was not done, assuming nontolerance as well (= possible source of bias). In case of tolerance, the sequence was repeated in exactly the same way for the second stimulation (*Ce2*). Of the resulting response data, logistic regression analysis was calculated to estimate both *Ce1* and *Ce2*. For further comparisons and estimation of bias only, the estimated *Ce*s were stored and used.

All of the above steps were then repeated and replicated in *m* studies, using an *m* = 100. With this set of studies – each based on 60 simulated patients – a comparison of bias was made (= 6,000 simulated patients). Bias distribution was calculated on the basis of the following expression:

$$bias_i = \frac{Ce_{i, estimated} - Ce_{i, real}}{Ce_{i, real}} * 100 \qquad (A.1)$$

with $Ce_{i\,real}$ and $Ce_{i\,estimated}$ as the population means of the patients in study i for the real and estimated value of Ce, respectively.

Four case combinations are shown that use different settings for the simulation. For each case, a plot is shown with the distribution of the $bias_i$ as shown in equation A.1 (fig. 8). Each of these cases has different underlying assumptions, ranging from hypothetical to closely corresponding to our study setting.

Case 1 assumes a very small (unrealistic) variance for $Ce1$, $\beta = 1$, with very small variance (basically $Ce1 = Ce2$), sampling only at one drug concentration of 3.5 (equal to $Ce1$); with this hypothetical setting, a huge bias of on average more than 20% has to be expected (fig. 8A).

Case 2 assumes a population distribution with a variance of 0.5 for $Ce1$ (fig. 9), a β as in case 1, and a sampling at drug concentrations [2, 3, 4, 6, 8] drug units; bias is much smaller and can be expected to be around average 4% (fig. 8B).

Case 3 closely corresponds to our clinical study situation; it assumes a population distribution with a variance of 0.5 for $Ce1$, a β of 1.1 corresponding to the smallest difference of approximately 10% as found in the study (typical Ce_{50} values of TLAR compared to TLMA, table 2), and the same sampling as in case 2. On average, the bias disappears and is constrained between $\pm$ 4% (fig. 8C).

Case 4 assumes wrong order sampling, expressed with a $\beta = 0.8$ (assuming that $Ce2$ is 20% smaller than $Ce1$), and same distribution and sampling as in case 3. Not surprisingly, there is a huge bias of on average 25%, and $Ce2$ is estimated to be the same as $Ce1$ (fig. 8D).

Even with identical Ces, bias is relatively small if there is some population distribution of the Ces and when a reasonable sampling is done. Bias is significant when the order of the stimulations is reversed. This could be the case, if the stimulation strength is not known *a priori*, but it could potentially be detected if Ces of different stimulations are found to be equal. If the order is correct and the difference in Ces is 10% and more, no bias was found in our simulations. This is indirectly confirmed by our study with the good estimates for the Ce_{50}s, and the good correlation with other studies that specifically looked at only one stimulation at a time.

■ ANESTHESIOLOGY REFLECTIONS

Cordus' Synthesis of Ether

In 1540 Valerius Cordus (1515–1544; German botanist, pharmacist, and physician) synthesized ether ("sweet oil of vitriol") in his alchemist's still from ethanol ("triply-distilled" wine) and sulfuric acid ("sour oil of vitriol"). His "sweet" mixture floated on water (the volatile diethyl ether portion, which would be vaporized three centuries later as an anesthetic) yet felt greasy to touch (the aromatic diethyl sulfate portion). Hailed later as the Father of Descriptive Botany and of the Legally Sanctioned Pharmacopoeia, Cordus died, possibly from malaria, soon after the 29-year-old's leg was kicked savagely by a horse. The world's first record of the synthesis of ether, *De Artificiosis Extractionibus*, was published 17 years later in a posthumous compilation. In July of 2009, the Wood Library-Museum acquired this "new" tome from 1561 (see above—note its pigskin-quarterbound, antiphonal-vellum-over-pasteboard covers). (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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