Sevoflurane Remifentanil Interaction

Comparison of Different Response Surface Models

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ABSTRACT

Background: Various pharmacodynamic response surface models have been developed to quantitatively describe the relationship between two or more drug concentrations with their combined clinical effect. We examined the interaction of remifentanil and sevoflurane on the probability of tolerance to shake and shout, tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy in patients to compare the performance of five different response surface models.

Methods: Forty patients preoperatively received different combined concentrations of remifentanil (0–12 ng/ml) and sevoflurane (0.5–3.5 vol.%) according to a criss-cross design (160 concentration pairs, four per patient). After having

What We Already Know about This Topic

- A number of response surface models have been developed to describe the relationship between the concentrations of two drugs and their combined clinical effects

What This Article Tells Us That Is New

- When the pharmacodynamic interactions between sevoflurane and remifentanil on various hypnotic and noxious endpoints were characterized by five commonly used interaction models, they were best described by models that assumed no opioid effect when opioid was given alone to patients
- The reduced Greco, scaled C50o hierarchical, and fixed C50o hierarchical models fitted the data reasonably well, but the Minto and Greco models did not

reached pseudosteady state, the response to shake and shout, tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy was recorded. For the analysis of the probability of tolerance, five different interaction models were tested: Greco, Reduced Greco, Minto, Scaled $C50_O$ Hierarchical, and Fixed $C50_O$ Hierarchical model. All calculations were performed with NONMEM VI (Icon Development Solutions, Ellicott City, MD).

Results: The pharmacodynamic interaction between sevoflurane and remifentanil was strongly synergistic for both the hypnotic and the analgesic components of anesthesia. The Greco model did not result in plausible parameter estimates. The Fixed $C50_O$ Hierarchical model performed slightly better than the Scaled $C50_O$ Hierarchical and Reduced Greco models, whereas the Minto model fitted less well.

Conclusion: We showed the importance of exploring various surface model approaches when studying drug interactions. The Fixed $C50_O$ Hierarchical model fits our data on sevoflurane remifentanil interaction best and appears to be an appropriate model for use in hypnotic-opioid drug interaction.

P HARMACODYNAMIC response surface models are three or more dimensional structures that have been developed to quantitatively describe the relationship be-

tween two or more drug concentrations with their combined clinical effect. Response surface models are powerful representations of drug interactions, because they combine information about any isobole and the concentration-response curve of any combination of the drugs involved.[1,2] Using the mathematically defined response surface, the corresponding drug effect for any two or more drug concentrations of the interacting drugs can be predicted.[1,3]

Various methodological approaches to response surface models are found in the literature. Bol *et al.* further developed a previously published response surface model by Greco *et al.* to describe the interaction between dexmedetomidine and midazolam in rats.[4,5] The Greco model can be considered as the basic approach to describe quantal response surface models, since it is the original and most simple model for drug interaction. As this model assumes identical slope factors and identical maximal effects for the single concentration effect courses of the interacting drugs, Minto *et al.* extended the Greco model to make the response surface modeling more flexible. They defined a variable (originally called θ) as the proportion of one drug in the combination of two potentially interacting drugs.[1] More recently, Bouillon *et al.* developed a novel mechanistic approach to the interaction between opioids and hypnotics. Using the knowledge that analgesia represents a drug action on ascending neuropathways and that hypnosis is a cortical response that balances the ascending noxious stimulus against drug-induced cortical suppression, they quantified opioid-hypnotic drug interaction in a sequential (also called hierarchical) model.[6] As some of the authors of the original paper thought that the initial form of their hierarchical model was overparameterized,[2] they designed a less complex form of the model, hereby called the Fixed $C50_O$ Hierarchical model,[7] which is now applied in one of the commercially available drug interaction displays (Smart Pilot View, Dräger, Lübeck, Germany). In contrast to the Greco and Minto models, the Scaled $C50_O$ and Fixed $C50_O$ Hierarchical models approach comes more close to the clinical pharmacological and physiologic reality.

To characterize the interaction between sevoflurane and remifentanil in blunting responses to verbal (Observer's Assessment of Alertness/Sedation scale) and painful stimuli (pressure algometry, electrical tetanic stimulus, and thermal stimulation), Manyam *et al.* constructed a response surface for each pharmacodynamic response using a Logit model approach and found synergy between sevoflurane and remifentanil for all responses.[8] As this study suffered from nonsteady-state conditions at the moment of measurements, the authors reevaluated their data using effect-site sevoflurane concentrations and a Greco model instead of a Logit approach.[9] Accounting for the lag time between sevoflurane effect-site concentration and end-tidal concentration improved the predictions of responsiveness during anesthesia but had no effect on predicting a response to a noxious stimulus in the recovery room. They concluded that models may be useful in predicting events of clinical interest but large-

scale evaluations with numerous patients are needed to better characterize model performance. Also, they did not test if other response surface models would describe the data more accurately.

The aim of this study was to quantify the pharmacodynamic interaction between sevoflurane and remifentanil in patients and to investigate the performance of different interaction models to predict the likelihood of response. Quantal responses to different clinically relevant hypnotic and noxious stimuli were studied.

Materials and Methods

This study used a similar study design as our previously published report.[10]

Subjects

After obtaining Institutional Review Board approval (Ghent University Hospital Ethics Committee, Gent, Belgium) and prospective trial registration at ClinicalTrials.gov (NCT00522587), as well as written informed consent, 40 American Society of Anesthesiologists status I or II patients, aged 18 to 60 yr, and scheduled to undergo surgery requiring general anesthesia, were included. Patients were allowed to take their usual medication. 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 myocardial disease involving decrease in ejection fraction, arrhythmias, which are either symptomatic or require continuous medication/pacemaker/automatic internal cardioverter defibrillator), pulmonary diseases, gastric diseases, endocrinologic diseases, and recent use of psychoactive medication or more than 20 g of alcohol daily. 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 monitors (electrocardiogram, noninvasive blood pressure, SpO₂), M-entropy using a Datex S/5 Anesthesia Monitor (GE Healthcare, Helsinki, Finland) and bispectral index using a Aspect A-2000 monitor (Covidien, Norwood, MA) were connected, and a large forearm vein was cannulated. Thereafter, the patients were preoxygenated with 6 l/min O_2 at a $F_I = 1.0$ for 5 min, using a tight-fitting facemask, which also served to sample exhaled air for end-tidal carbon dioxide measurement. 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 "off label" drug applications were used (European situation). Vital signs as well as end-tidal sevoflurane concentrations, respiratory data (tidal volume, minute volume, end-tidal carbon dioxide), and infusion related data

(predicted concentrations, amounts infused) were continuously recorded on a computer hard disk using RUGLOOP II data recording software (Demed, Temse, Belgium).

Drug Administration

Technical Aspects. Remifentanil was administered by using a target-controlled infusion technique based on a three-compartment model and an effect-site compartment as published by Minto *et al.*[11,12] Remifentanil infusion was administered by using an Alaris Asena pump (Carefusion, Basingstoke, United Kingdom). RUGLOOP II TCI driver (Demed) controlled the pump at infusion rates between 0 and 1,200 ml/h *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). In all steps, the sevoflurane vaporizer was set to maximum until 80% of the target concentration was reached, then it was turned down to the target setting. A fresh gas flow above minute ventilation was used throughout the study.

Dosing Regimen. The study design was a modification of the criss-cross design proposed by Short *et al.*[3] The choice of the sevoflurane/remifentanil concentrations pairs were based on the sevoflurane Ce50 ($Ce50_{sevo}$) to suppress the response to skin incision (= minimal anesthetic concentration, MAC) of 1.85%[13] and a remifentanil Ce50 (= remifentanil concentration reducing the MAC_{SEVO} by 50%) of 1.5 ng/ml[14]:

$$\text{opioid effect} = Ce_{REMI}/(Ce50_{REMI} + Ce_{REMI})$$

$$Ce_{SEVO(norm)} = (Ce_{SEVO}/Ce50_{SEVO})/(1-\text{opioid effect})$$

where opioid effect is the relative effect of remifentanil on $Ce50_{SEVO}$, Ce_{REMI} is the effect-site concentration of remifentanil, Ce_{SEVO} is the effect-site concentration of sevoflurane, and $Ce_{SEVO(norm)}$ is the effect-site concentration of sevoflurane normalized to MAC, taking into account the opioid effect.

We randomized 40 patients to receive specific combinations of sevoflurane and remifentanil as simulated and described in the next paragraph. Before induction the subjects were randomly assigned to receive four prespecified pairs of sevoflurane and remifentanil concentrations. In half of the patients, remifentanil was held constant, and sevoflurane was stepwise increased; in the other half, sevoflurane was held constant and remifentanil was stepwise increased (table 1). For each of the 10 escalating combinations, three patients were included. To study the boundaries of the response surface (single drug without interaction), five patients were given sevoflurane only (0.7 to 3.5 vol.%) and five were given remifentanil (2–12 ng/ml) during the study period. The maximum Ce_{SEVO} was set at 3.5 vol.%, and maximum Ce_{REMI} was set at 12 ng/ml. A maximum of four 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.

Table 1. Concentration Grid of Study Design

Patients (n)	Remifentanil (ng/ml)	Sevoflurane (vol.%)	MAC Multiples (Minimum–Maximum)
5	0	0.7, 1.5, 2.5, 3.5	0.4–1.9
3	1	0.7, 1.5, 2.5, 3.5	0.6–3.2
3	2	0.5, 1.5, 2.5, 3.5	0.6–4.4
3	3	0.5, 1.0, 1.5, 2.5	0.8–4.1
3	4	0.5, 1.0, 1.5, 2.5	1.0–5.0
3	6	0.5, 0.75, 1.0, 1.5	1.4–4.1

Patients (n)	Sevoflurane* (vol.%)	Remifentanil (ng/ml)	MAC Multiples (Minimum–Maximum)
5	0.5	2, 4, 8, 12	0.6–2.4
3	0.75	0, 4, 8, 12	0.4–3.6
3	1.0	0, 1, 4,10	0.5–4.1
3	1.5	0, 1, 3, 6	0.8–4.1
3	2.0	0, 1, 2, 4	1.1–4.0
3	2.5	0, 1, 2, 4	1.4–5.0

* A 0 vol.% sevoflurane group has been omitted for ethical reasons; with 0.5 vol.% sevoflurane, a minimum of 1 ng/ml remifentanil is administered.

MAC = minimal anesthetic concentration.

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) verbal and nonpainful tactile stimuli according to the Observer's Assessment of Alertness/Sedation (OAA/S score)[15] (an OAA/S score less than 2 was considered as tolerant); (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 Macintosh-type blade (HEINE Optotechnik GmbH & Co KG, Herrsching, Germany). Verbal response, 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 to minimize interobserver variability. If there was no response to the first stimulus, the next stimulus was applied 1 min after the response assessment of the first. 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.

Pharmacodynamic Analysis of Quantal Responses

The four quantal responses, defined as tolerance to shaking and shouting, tolerance to a 5 s tetanic stimulus, tolerance to LMA insertion, and tolerance to laryngoscopy were modeled using five interaction models: Greco model,[4,5] Reduced Greco model,[2,16] Minto model,[1] Scaled $C50_O$ Hierarchical model,[6] and Fixed $C50_O$ Hierarchical model.[2,7] Details of the models can be found in the appendix.

An OAA/S score of 0–1 was considered as tolerant to shaking and shouting, and a score of 2–5 as responsive.

For remifentanil, the targeted effect-site concentration after 12 min of equilibration was considered as the steady-state concentration taking into account the reported[11,12] age-dependent equilibration half-time of 0.94, 1.32, and 2.20 min for 20, 50, and 80 yr, respectively, and was used as the remifentanil effect-site concentration (Ce_{REMI}) in the 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 the steady state concentration, and was used as sevoflurane effect-site concentration (Ce_{SEVO}) in the analysis. To reduce data noise in Ce_{REMI} and Ce_{SEVO}, the median value of 11 measurements at 5 s intervals during 1 min preceding the assessment of the OAA/S score were used. The duration of equilibration of 12 min was five times the reported equilibration half-life for sevoflurane of 2.4 min.[17]

In the current data set it was observed in several cases that the patient was tolerant to a stimulus, whereas the same patient was responsive to the preceding, *a priori* considered less intense stimulus. Therefore the approach described by Bouillon *et al.*[6] and by Schumacher *et al.*,[10] combining the observed responses to the four stimuli into a single value, could not be applied. Instead the observed response to each stimulus was compared to the probability of that response according to the model, irrespective of the response to the other stimuli.

Parameter Estimation

The model parameters were estimated using NONMEM VI version 2.0 (Icon Development Solutions, Ellicott City, MD), using FOCE LAPLACE and LIKELIHOOD options.

Platform was Windows XP (Microsoft, Redmond, WA) and compiler was G95. For all parameters interindividual variability was either assumed to be absent, or to have a log-normal distribution. A single value for the individual deviation from the typical value (η in NONMEM) was used for Ce50 of sevoflurane and remifentanil for all stimuli, in accordance with the assumption that this value reflects the sensitivity of that individual for hypnotic and opioid drugs.

Model building was performed starting with the simplest form of each model, and expanding the model with interaction terms and interindividual variability until the decrease of the objective function value (OFV) was not statistically significant using the chi-square test. The best fitting model was selected using Akaike Information Criterion, calculated as OFV + 2p, where p is the number of parameters in the model. The NONMEM analysis was performed with various values for initial estimates and boundary values. The results were accepted as valid only if both minimization and covariance step were successful, unless stated otherwise.

To evaluate the final model a bootstrap analysis was performed, based on 1,000 sets of 40 patients each, randomly selected from the available 40 patients, using a custom program written in C. Results were analyzed in Excel (Microsoft). In addition, log-likelihood profiles were calculated for each population parameter, and the 95% CIs were obtained from these data assuming a chi-square distribution with one degree of freedom and $P = 0.025$, resulting in a critical difference of 5.02 in the OFV.

Several performance measures were calculated from the prediction errors, *i.e.*, the difference between the predicted probability of tolerance minus the observed response (0 for responsive, 1 for tolerant): mean prediction error, mean absolute prediction error, and root mean squared error. In addition, the prediction error score was calculated as the percentage of mispredicted responses, *i.e.*, if tolerant, P < 0.5, or if responsive, P > 0.5.

Statistical Analysis

All model parameters are reported as typical values with relative standard errors in % within parentheses, and clinical data are given as mean and SD or as median and range, when appropriate.

Results

In total, 40 patients (26 females, 14 males) were included in this study. The demographics are as follows: body weight: 66 ± 11 kg, height: 172 ± 8 cm, age: 30 ± 11 yr. All patients were classified as American Society of Anesthesiologists status I.

Data

In total, the data sets contained 159 periods of testing (40 patients with 4 periods per patient, minus 1 missing period where no stimulus was given). According to the protocol escalating stimulus intensity was assumed in the order of shaking and shouting, tetanic stimulation, LMA insertion, and laryngoscopy. In 74 cases a stimulus was not applied for ethical reasons, because the patient was responsive to the preceding less intense stimulus at the same concentrations of sevoflurane and remifentanil. The patient was then considered a responder to more intense stimuli for data analysis. In 14 other cases a stimulus was not given for other reasons (such as severe hemodynamic changes), although the patient was tolerant to the preceding stimulus. In the data analysis these data were treated as missing values.

Table 2. Comparison of OFV, AIC, Parameter Values, and Measures of Performance between the Models, Including Interindividual Variability

—	Reduced Greco		Minto		Scaled C50O Hierarchical		Fixed C50O Hierarchical	
—	—	%SE	—	%SE	—	%SE	—	%SE
OFV	285.285	—	311.035	—	280.925	—	276.789	—
Number of parameters	7	—	8	—	8	—	8	—
ΔAIC$	6.496	—	34.246	—	4.136	—	0	—
$C50_O$ (ng/ml)	2.28	14%	14.3	12%	—	—	1.69	21%
$C50_O$ _TOSS (ng/ml)	—	—	—	—	1.47	21%	—	—
$C50_O$ _TTET (ng/ml)	—	—	—	—	1.46*	—	—	—
$C50_O$ _TLMA (ng/ml)	—	—	—	—	1.90§	—	—	—
$C50_O$ _TLAR (ng/ml)	—	—	—	—	1.81¶	—	—	—
$C50_H$ _TOSS (vol%)	1.40	8%	1.31	9%	1.55	7%	1.47	7%
$C50_H$ _TTET (vol%)	1.41	8%	1.40	9%	1.54	7%	1.48	7%
$C50_H$ _TLMA (vol%)	2.02	8%	1.91	9%	2.00	7%	2.09	8%
$C50_H$ _TLAR (vol%)	1.93	8%	1.89	9%	1.91	7%	2.00	8%
γ_O	—	—	—	—	0.704	12%	0.718	12%
γ	6.94	11%	9.32	11%	7.28	11%	7.41	12%
β_{C50}	—	—	1.47	15%	—	—	—	—
IIV($C50_H$)	21%	37%	26%	38%	19%	38%	20%	38%
MPE (%)	−0.1	—	−0.2	—	−0.1	—	−0.1	—
MAPE (%)	11.2	—	11.8	—	11.3	—	11.0	—
RMSE(%)	22.7	—	23.2	—	23.0	—	22.6	—
PES (%)	6.9	—	6.6	—	7.7	—	7.6	—

* Calculated from $C50_H$ _TTET * $C50_O$ _TOSS/$C50_H$ _TOSS. § Calculated from $C50_H$ _TLMA * $C50_O$ _TOSS/$C50_H$ _TOSS. ¶ Calculated from $C50_H$ _TLAR * $C50_O$ _TOSS/$C50_H$ _TOSS. $ Difference between AIC of the model and AIC of the best model (Fixed $C50_O$ Hierarchical model).

γ_O = model parameter reflecting the steepness of the concentration-effect relationship for the opioid; γ = model parameter reflecting the steepness of the concentration-effect relationship; β_{C50} = model parameter reflecting the interaction in the Minto model; %SE = the standard error expressed in % of the typical value; AIC = Akaike's information criterion; $C50_H$ = effect-site concentration of the hypnotic with 50% effect to tolerance to shaking and shouting (TOSS), tolerance to tetanic stimulation (TTET), tolerance to laryngeal mask airway insertion (TLMA), and tolerance to laryngoscopy (TLAR); $C50_O$ = effect-site concentration of the opioid with 50% effect; IIV = interindividual variability, calculated as the square root of interindividual variance, multiplied by 100%; MAPE = mean absolute prediction error, MPE = mean prediction error; OFV = objective function value; PES = prediction error score, or the percentage of mispredicted responses; RMSE = root mean squared error.

Model Selection

The Greco model did not result in plausible parameter estimates; both $Ce50_{REMI}$ and α became very large, whereas the OFV was higher than for the Reduced Greco model (data not shown). If the parameters were allowed to take very large values, the OFV approached that of the Reduced Greco model, and the ratio $Ce50_{REMI}/\alpha$ approached $Ce50_{REMI}$ of the Reduced Greco model. Therefore the original Greco model was not further considered. The Akaike Information Criterion of the Minto model was markedly higher than for the other models, and the estimated $Ce50_{REMI}$ was above the highest remifentanil concentration applied. Compared with the other models, the Akaike Information Criterion of the Fixed $C50_O$ Hierarchical model was the lowest, indicating the best-fitting model.

Allowing variation of the $Ce50_{REMI}$ and the slope parameters among the different stimuli in the modeling process did not significantly reduce the OFV. Even estimating a different $Ce50_{REMI}$ for the nonnoxious shaking and shouting compared with the $Ce50_{REMI}$ for tetanic stimulation, LMA insertion, and laryngoscopy did not result in a significant improvement of the OFV. In the final model a common $Ce50_{REMI}$ and common slope parameters for all stimuli were obtained, whereas the $Ce50_{SEVO}$ was stimulus specific (table 2).

Inclusion of interindividual variability in each parameter was tested either alone or in combinations. In all cases interindividual variability was the same for each stimulus. The results have been summarized in table 2. For all models, inclusion of interindividual variability in $Ce50_{SEVO}$ significantly improved the OFV (P < 0.01); but not interindividual variability of other parameters. We performed a covariate analysis on patient weight, height, age, gender, and order of administration of remifentanil and sevoflurane. None of these covariates did improve the fit significantly.

The Reduced Greco model is identical with the Fixed $C50_O$ Hierarchical model if γ_O is fixed to 1, and therefore both models may be compared using the likelihood ratio. Given the reduction of 8.5 in OFV it can be concluded that the Fixed $C50_O$ Hierarchical model fits significantly better to the data than the Reduced Greco model. The Scaled $C50_O$ and Fixed $C50_O$ Hierarchical models cannot be compared using the likelihood ratio, because both models have the same number of parameters. However, the reduction of 4.1

Table 3. Median and 95% Nonparametric CIs of Parameters for the Fixed C50$_O$ Hierarchical Model with Interindividual Variability Obtained by Bootstrap Analysis (Using 1,000 Replicate Datasets) and from Log-likelihood Profiles

—	C50$_O$ (ng/ml)	C50$_H$ TOSS (vol%)	C50$_H$ TTET (vol%)	C50$_H$ TLMA (vol%)	C50$_H$ TLAR (vol%)	γ_O	γ	IIV C50$_H$
NONMEM								
Typical value	1.69	1.47	1.48	2.09	2.00	0.718	7.41	20%
Bootstrap analysis								
Median	1.67	1.47	1.49	2.09	2.00	0.713	7.65	19%
2.5%	0.80	1.29	1.25	1.76	1.69	0.464	6.14	11%
97.5%	2.55	1.70	1.78	2.51	2.37	0.981	10.70	26%
Log-likelihood profiles								
2.5%	0.99	1.25	1.26	1.77	1.69	0.543	5.81	12%
97.5%	2.59	1.73	1.75	2.48	2.37	0.925	9.54	30%

γ_O = model parameter reflecting the steepness of the concentration-effect relationship for the opioid; γ = model parameter reflecting the steepness of the concentration-effect relationship; C50$_H$ = effect-site concentration of the hypnotic with 50% effect to tolerance to shaking and shouting (TOSS), tolerance to tetanic stimulation (TTET), tolerance to laryngeal mask airway insertion (TLMA), and tolerance to laryngoscopy (TLAR); C50$_O$ = effect-site concentration of the opioid with 50% effect; IIV = interindividual variability, calculated as the square root of interindividual variance, multiplied by 100%.

in the OFV indicates that the Fixed C50$_O$ Hierarchical model fits better to the data.

The differences between the four models with respect to the performance measures were rather small (table 2).

The results of the final model, *i.e.*, Fixed C50$_O$ Hierarchical model with interindividual variability in Ce50$_{SEVO}$, were checked by performing a bootstrap analysis, based on 1,000 sets; 994 sets resulted in a successful minimization, and 983 sets gave a successful covariance step. The results of the bootstrap analysis were in good agreement with the NONMEM results (table 3). Also, the CIs estimated from the bootstrap analysis and from the log-likelihood profiles were comparable (table 3). The log-likelihood profiles for the parameters of the Fixed C50$_O$ Hierarchical model are depicted in figure 1.
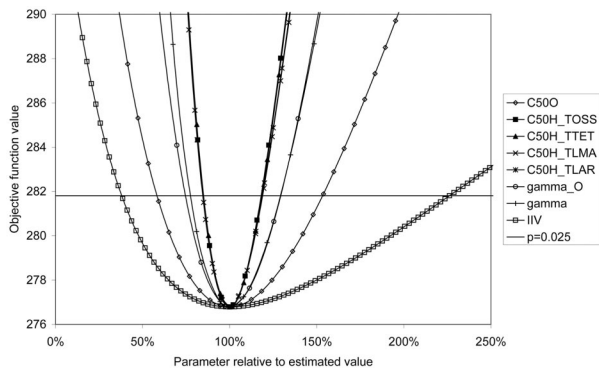
Fig. 1. Log-likelihood profiles for the parameters of the Fixed C50$_O$ Hierarchical model, expressed as a percentage of the estimated value. The *horizontal line* represents the significance level on a chi-square distribution ($P = 0.025$). Note that the profiles of the C50$_H$ for the four stimuli are almost the same. IIV = interindividual variability; TLAR = tolerance to laryngoscopy; TLMA = tolerance to laryngeal mask airway insertion; TOSS = tolerance to shaking and shouting; TTET = tolerance to tetanic stimulation.

Response Surface and Isoboles

The response surfaces for the probabilities of tolerance to each stimulus are shown in figure 2. Figure 3 compares the isoboles for 50% probability of tolerance to the four stimuli for the four models. Figure 4 shows the isoboles for 50% probability of tolerance to the four stimuli for the Fixed C50$_O$ Hierarchical model and the observed responses. Figure 5 compares the isoboles for 50% probability of tolerance to the four stimuli for the four models. In figure 6, the isoboles for 5%, 50%, and 95% probability of tolerance to the four stimuli for the Fixed C50$_O$ Hierarchical model are shown. Figure 7 shows the isoboles for 95% probability of tolerance to laryngoscopy for the four models, illustrating the clinical significant difference between the Minto model and the three other models.

Discussion

As expected, the pharmacodynamic interaction between sevoflurane and remifentanil was strongly synergistic for both the hypnotic and the analgesic components of anesthesia, as illustrated by tolerance to shake and shout, tetanic stimulation, LMA insertion, and laryngoscopy.[2,6,7] The main finding of this study is the validity of the Fixed C50$_O$ Hierarchical model[2,7] assuming an identical Ce50 and slope parameter for the opioid and an identical slope parameter of the hypnotic for different stimuli, but keeping different Ce50$_{hypnotic}$ for different stimuli. The model is thus validated not only for the propofol-remifentanil but also for the sevoflurane-remifentanil combination. The flexibility of the Fixed C50$_O$ Hierarchical model where only the Ce50$_{opioid}$, the Ce50$_{hypnotic}$ and slope parameters for the opioid and hypnotic are needed as input parameters, is of importance for the parsimonious description of the interaction and therefore very useful in the context of anesthesia drug displays.

The Minto model with a Ce50$_{REMI}$ of 14.3 ng/ml was statistically inferior, whereas the original Greco model did not even
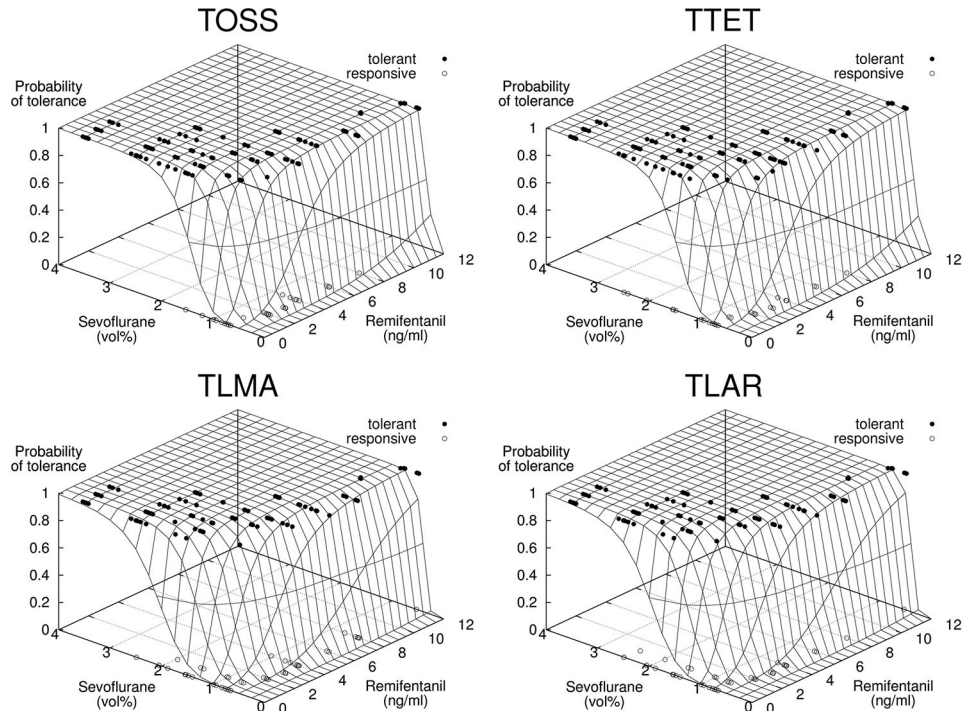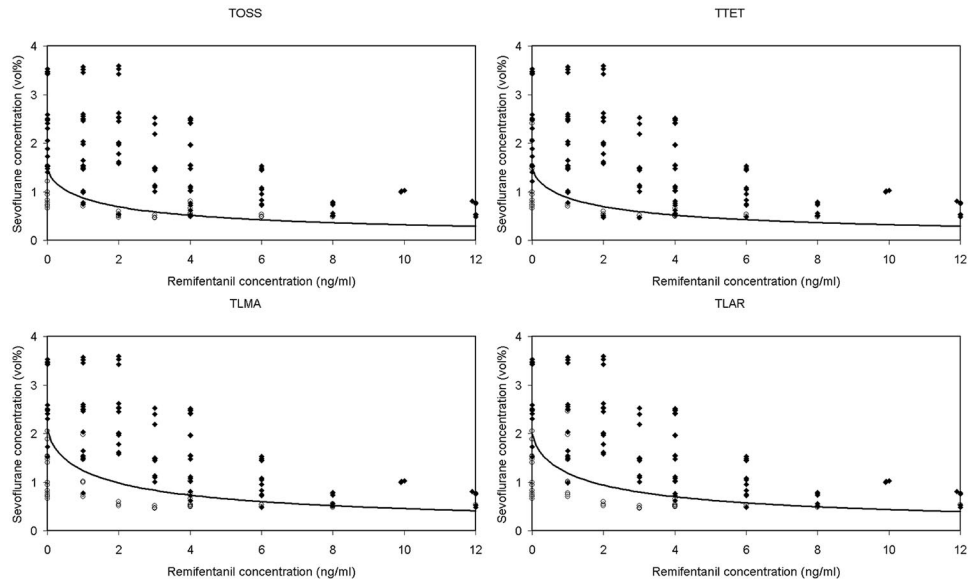
Fig. 2. Response surface for probability of tolerance to shaking and shouting, tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy for the Fixed C50$_O$ Hierarchical model. The *solid lines* at probability 0.5 represents the 50% isoboles. TLAR = tolerance to laryngoscopy; TLMA = tolerance to laryngeal mask airway insertion; TOSS = tolerance to shaking and shouting; TTET = tolerance to tetanic stimulation.

support a reliable estimation of the Ce50$_{REMI}$ (estimated values above 50 ng/ml). This is in agreement with the clinical experience that in the absence of a hypnotic drug opioids do not suppress the response to stimulation, at least at clinically reason-

able opioid concentrations. The Hierarchical models are semi-mechanistic models that have been developed to detect synergism for the combination of an analgesic and a hypnotic drug using a simple reconstruction of neuropathic pathways, as op-
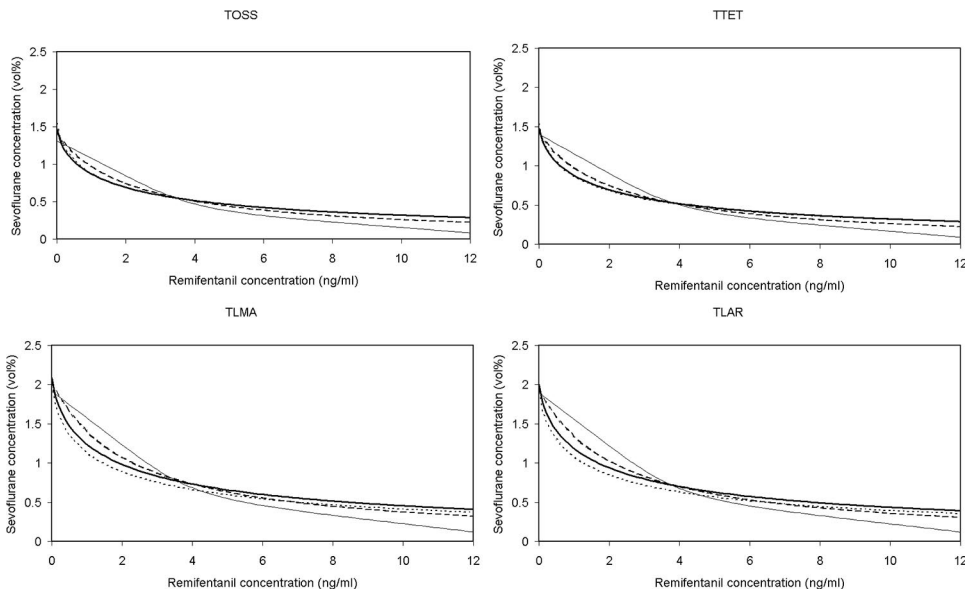
Fig. 3. Isoboles for 50% probability of tolerance to shaking and shouting, tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy for four models (*dashed line* = Reduced Greco, *thin solid line* = Minto, *dotted line* = Scaled C50$_O$ Hierarchical, *thick solid line* = Fixed C50$_O$ Hierarchical). Note that the isoboles of shaking and shouting and tetanic stimulation are almost the same for the Scaled C50$_O$ and Fixed C50$_O$ Hierarchical models, and that the isobole of the Scaled C50$_O$ Hierarchical model is obscured by that of the Fixed C50$_O$ Hierarchical model. TLAR = tolerance to laryngoscopy; TLMA = tolerance to laryngeal mask airway insertion; TOSS = tolerance to shaking and shouting; TTET = tolerance to tetanic stimulation.
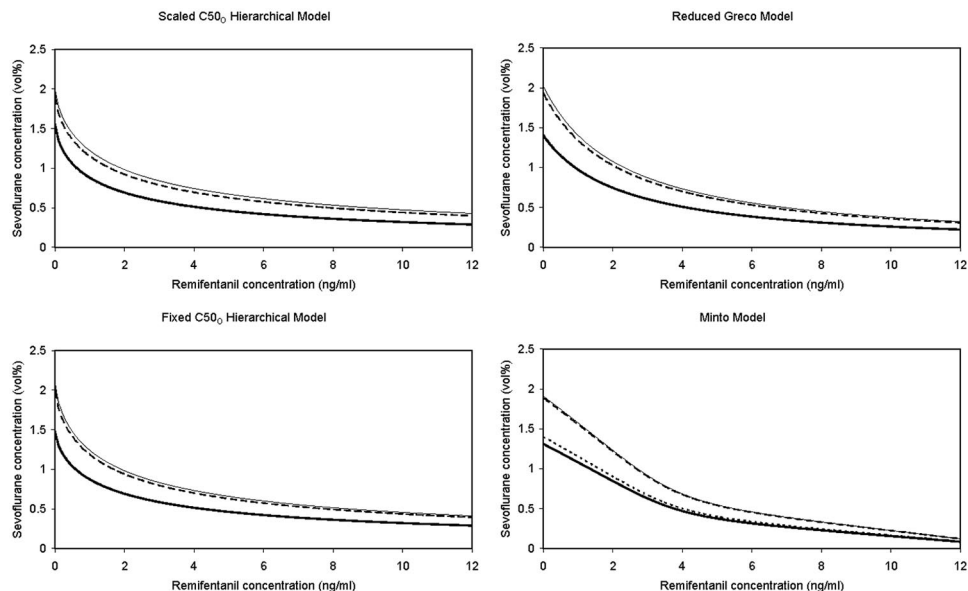
Fig. 4. Isoboles for 50% probability of tolerance to shaking and shouting, tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy for the Fixed C50$_O$ Hierarchical model, with observed responses (*open circles* = responsive, *closed squares* = tolerant). TLAR = tolerance to laryngoscopy; TLMA = tolerance to laryngeal mask airway insertion; TOSS = tolerance to shaking and shouting; TTET = tolerance to tetanic stimulation.

posed to other more generalistic models. These Hierarchical models, as well as the Reduced Greco model, assume no relevant opioid effect if given alone, and therefore these models fitted better to the data than the Greco and Minto models. The differences between the Reduced Greco model, Scaled C50$_O$ Hierarchical model, and Fixed C50$_O$ Hierarchical model were rather small, and each of these three models fitted reasonably well to the data. However, the OFV and Akaike Information

Criterion unequivocally showed that the Fixed C50$_O$ Hierarchical model fit best to our data.

The conclusions with respect to the best fitting model should not be translated to interactions of different classes of drugs. Each of these models is an empirical model that needs to be validated for each application. The Reduced Greco and both Hierarchical models are applicable when one of the drugs does not exert an effect when given alone, as is the case

Fig. 5. Isoboles for 50% probability of tolerance to shaking and shouting (*thick solid line*), tetanic stimulation (*dotted line*), laryngeal mask airway insertion (*thin solid line*), and laryngoscopy (*dashed line*) for the Reduced Greco model, Minto model, Scaled C50$_O$ Hierarchical model, and Fixed C50$_O$ Hierarchical model. Note that the isoboles of tolerance to shaking and shouting and tetanic stimulation are almost the same for the Reduced Greco, Scaled C50$_O$ Hierarchical, and Fixed C50$_O$ Hierarchical models, and that the isoboles of tolerance to laryngeal mask airway insertion and laryngoscopy are almost the same for the Minto model.
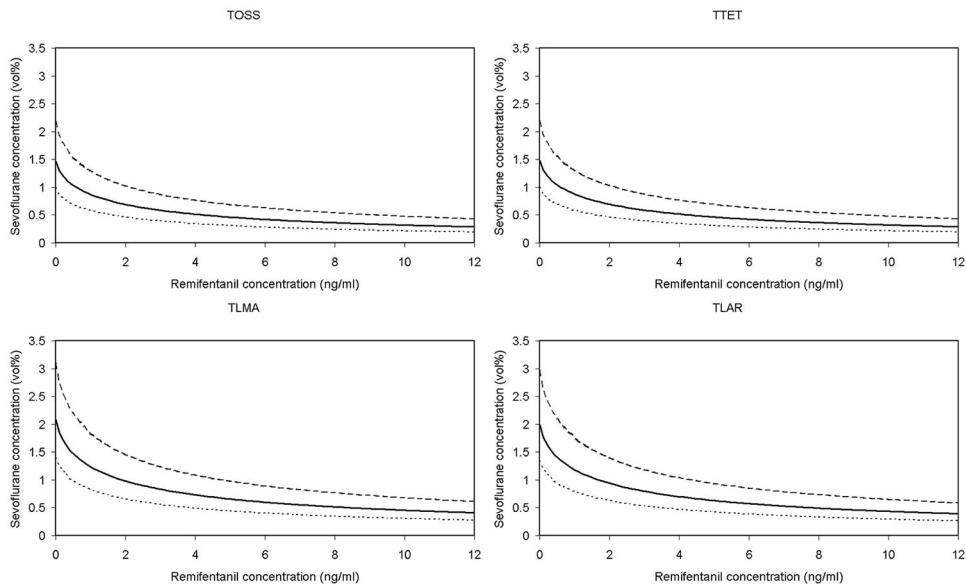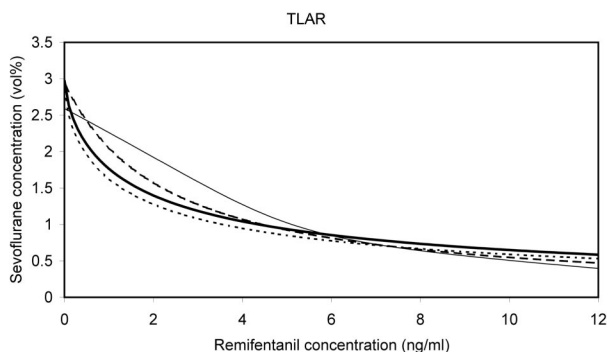
Fig. 6. Isoboles for 5% (*dotted line*), 50% (*thick solid line*), and 95% (*dashed line*) probability of tolerance to shaking and shouting, tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy for the Fixed $C50_O$ Hierarchical model. TLAR = tolerance to laryngoscopy; TLMA = tolerance to laryngeal mask airway insertion; TOSS = tolerance to shaking and shouting; TTET = tolerance to tetanic stimulation.

for the sevoflurane-remifentanil combination studied in this investigation. For other drug combinations where both drugs can exert a full effect, the original Greco model and the Minto model may be appropriate. For combinations where one of the drugs can only exert a partial effect, a modified version of the Minto model seems appropriate.

To evaluate the clinical relevance of the observed differences between the models, the isoboles for 95% probability of tolerance to laryngoscopy for the four models are shown in figure 7. At a fixed remifentanil concentration of 3 ng/ml, the sevoflurane concentration predicted by the Minto, Reduced Greco, Scaled $C50_O$ Hierarchical, and Fixed $C50_O$ Hierarchical model is 1.59, 1.27, 1.08, and 1.19 vol.%, respectively. This illustrates the deviating characteristics of the Minto model, and the relatively small differences between the Reduced Greco and both Hierarchical models. Clinicians

Fig. 7. Isoboles for 95% probability of tolerance to laryngoscopy for four models (*dashed line* = Reduced Greco, *thin solid line* = Minto, *dotted line* = Scaled $C50_O$ Hierarchical, *thick solid line* = Fixed $C50_O$ Hierarchical). TLAR = tolerance to laryngoscopy.

aim at titrating their drugs during anesthesia at least at a level of 95% probability of tolerance, so at a specific remifentanil concentration, applying the Minto model would result in the use of a clinically relevant higher sevoflurane concentration than when using the other models.

Response surfaces or interaction isoboles are used in anesthetic drug displays as reference to interpret the current effect-site concentrations estimated in the patient. The parameter estimates of the model are therefore crucial. According to the Fixed $C50_O$ Hierarchical model, the Ce50s of the hypnotic are used to rank different stimuli according to their intensity. The $Ce50_{SEVO}$ for tolerance of shaking and shouting (nonnoxious) and tetanic stimulation (noxious) were similar. The $Ce50_{SEVO}$ for tolerance of LMA insertion and for laryngoscopy were also similar but substantially higher. In the previous study on the interaction of sevoflurane and propofol performed with the same stimuli by the same investigators,[10] the Ce50 values for sevoflurane for tolerance to shake and shout, tetanic stimulation, LMA insertion, and laryngoscopy were 1.03, 2.11, 2.55, and 2.83 vol.% respectively, which is markedly different from that found in the present study (1.47, 1.48, 2.09, and 2.00 vol.%, respectively). Furthermore, the slope reported by Schumacher *et al.* was 17.6, whereas in the present study it was 7.41. To elucidate the cause of these differences, the data points of the previous and the current study where sevoflurane was given alone were reanalyzed (table 4). The parameter estimates obtained from the "sevoflurane alone" data of the two studies still differ, although the difference is smaller and the order of the Ce50s was similar in both studies. We can only speculate why the $Ce50_{SEVO}$ for tolerance to shake and shout was lower and the $Ce50_{SEVO}$ for tolerance to laryngoscopy was

Table 4. Comparison of Results from Data in the Absence of Remifentanil and Propofol in the Present Study (19 Patients with 34 Observations for Each Stimulus) and Schumacher Study (28 Patients with 45 Observations for Each Stimulus), without and with Interindividual Variability in C50$_H$

—	Present Study without IIV		Present Study with IIV		Schumacher without IIV		Schumacher with IIV	
—	Typical Value	%SE	Typical Value	%SE	Typical Value	%SE	Typical Value	%SE
C50$_H$ _TOSS (vol%)	1.25	10%	1.32	9%	0.955	9%	1.00	**
C50$_H$ _TTET (vol%)	1.57	9%	1.61	9%	2.17	6%	2.26	**
C50$_H$ _TLMA (vol%)	2.00	9%	2.01	9%	2.37	6%	2.55	**
C50$_H$ _TLAR (vol%)	2.09	9%	2.11	9%	2.52	6%	2.85	**
γ	5.96	17%	10.0	27%	7.96	18%	49.5*	**
IIV (C50$_H$)	—	—	22%	54%	—	—	32%	**

* Value reached boundary. ** Covariance matrix not calculated.
γ = model parameter reflecting the steepness of the concentration-effect relationship; %SE = the standard error expressed in % of the typical value; C50$_H$ = effect-site concentration of the hypnotic with 50% effect to tolerance to shaking and shouting (TOSS), tolerance to tetanic stimulation (TTET), tolerance to laryngeal mask airway insertion (TLMA), and tolerance to laryngoscopy (TLAR); IIV = interindividual variability, calculated as the square root of interindividual variance, multiplied by 100%.

higher in the previous compared to the current study. Age, weight, and height were similar in the two studies. Classification of the subjects in responders and nonresponders was similar (a response was assumed if there was an observed response to a given stimulus, and if there was a response to a lower intensity stimulus and when the subsequent higher intensity stimulus was not applied). The pattern and current intensity of the electrical stimulus was also the same. The individual airway anatomy of the patients may affect the force to be applied during LMA insertion and the pressure applied with the laryngoscope to visualize the vocal cords. This may explain in part the difference between the Ce50s for tolerance to LMA insertion and laryngoscopy but not the difference between Ce50s for tolerance to shake and shout and tetanic stimulation.

A synergistic interaction between sevoflurane and remifentanil for both the hypnotic and analgesic stimuli using surface modeling was also found previously.[8,9] However, their parameter estimates differ markedly from those of the current study. Several reasons may explain this discrepancy: Whereas Manyam *et al.* used a logistic regression model, Johnson used the Greco model in his reanalysis of the same data. In the study of Manyam *et al.* the stimuli were given 5 min after achieving a stable end-tidal sevoflurane concentration, whereas in our study the equilibration was allowed for 12 min, which is five times the reported equilibration half-life for sevoflurane of 2.4 min.[17] To compensate for this disequilibrium, Johnson *et al.*[9] used an estimated effect-site concentration to describe the hysteresis with the end-tidal concentration. The Ce50$_{REMI}$ for OAA/S≤1 during emergence (no return of consciousness) reported by Johnson *et al.* was 50.9 ng/ml, which is far above the investigated concentration range applied and may thus not be reliable, although it reflects the weak hypnotic potency of opioids. The Ce50$_{REMI}$ for tolerance of tibial pressure was 1.3 ng/ml, which is in the range of the common Ce50$_{REMI}$ in the current study as well as in the previous studies.[2,6,7] In our study

the Ce50$_{REMI}$ estimated with the Reduced Greco model was 2.28 ng/ml for OAAS≤1 (table 2), which is lower than the value calculated from the ratio Ce50/α reported by Johnson *et al.* (50.9/9.4 = 5.4 ng/ml).

Whereas Johnson *et al.* reported a different slope for OAAS≤1 (5.2) and tolerance of tibial pressure (2.7), we did not find a significant difference between the slopes for the different stimuli, and in our final model the common slope was 7.4. It seems that the data from Manyam, reanalyzed by Johnson and our data are difficult to compare because of the different methodology and the different endpoints used.

Our data are in line with the previous data on MAC reduction for various inhaled anesthetics in the presence of opioids.[13,14,18–21] Whereas studies using multiple stimuli and several combinations of a hypnotic and an opioid in a criss-cross design[6,10] only one stimulus (skin incision) at one randomly assigned combination of the two drugs in one patient was applied in the traditional MAC depression studies. The advantage of the former is a reduction of the number of subjects while maintaining a sufficient number of data points for parameter estimation.

Current interaction displays use two different stimuli and the related interaction models as reference to quantify the anesthetic potency of a given combination of a hypnotic (propofol or volatile) and an opioid. The Fixed C50$_O$ Hierarchical model appears to be the most appropriate to define the reference lines or numbers to guide the clinician in rational dosing. The two stimuli used in interaction displays as reference must be clearly different in intensity, *i.e.*, significantly differ in their Ce50$_{hypnotic}$. According to the present and previous data, "shaking and shouting" and "laryngoscopy" with their clearly distinct Ce50s, are therefore reasonable reference stimuli representing a superficial (near loss of consciousness) and a deeper state of anesthesia needed for surgery.

In conclusion, we confirmed that the pharmacodynamic interaction between sevoflurane and remifentanil was strongly synergistic for both the hypnotic and the analgesic

components of anesthesia. We illustrated the importance of exploring the various surface modeling approaches when studying pharmacodynamic drug interactions as model selection might influence the results. In this particular investigation, the Fixed $C50_O$ Hierarchical model best fits our data on sevoflurane remifentanil interaction and it appears to be an appropriate model for use in hypnotic-opioid drug interaction displays. However, the prediction performance was not essentially different between the Reduced Greco, Scaled $C50_O$ Hierarchical, and Fixed $C50_O$ Hierarchical models.

Appendix: Binary Response Models

The probability of tolerance, P, to a certain stimulus can be expressed as

$$P = \frac{U^\gamma}{1 + U^\gamma} \quad (A1)$$

where U represents the normalized combined potency of one or more drugs and is a function of the drug effect-site concentrations and model parameters, reflecting the relative drug concentration, and γ is the slope parameter reflecting the steepness of the concentration-effect relationship. Different interaction models differ with respect to the functional form of U and γ, as described below.

Eq. A1 is the general form of all binary response models described below, and is used in earlier publications, either explicitly or implicitly, in some cases using different symbols for U and γ (*e.g.*, in Luginbuhl,[7] N and ϕ, respectively).

We focus here on models describing the interaction of an opioid (O) and a hypnotic (H) on the probability of tolerance. For each drug we normalize the effect-site concentrations to the related C50, using

$$U_O = \frac{C_O}{C50_O} \quad (A2)$$

$$U_H = \frac{C_H}{C50_H} \quad (A3)$$

where U_O and U_H are the normalized opioid and hypnotic effect-site concentrations, C_O is the effect-site concentration of the opioid, C_H is the effect-site concentration of the hypnotic, $C50_O$ is the effect-site concentration of the opioid that results in $P = 0.5$ in the absence of the hypnotic, and $C50_H$ is the effect-site concentration of the hypnotic that results in $P = 0.5$ in the absence of opioid.

In the case of multiple stimuli, the parameters for each stimulus may be different. Usually, however, one or more parameters are chosen identical for each stimulus, to allow reliable estimation of parameters from a limited number of observations.

Greco Model
The Greco model is a simplification of the original Greco model, and is an extrapolation from the 50% effect isobole[2,4,5]:

$$U = U_O + U_H + \alpha \cdot U_O \cdot U_H \quad (A4)$$

where U is the total potency, α is a dimensionless interaction parameter ($\alpha = 0$: additive; $\alpha < 0$ infraadditive; $\alpha > 0$: supraadditive), and U_H and U_O are the normalized concentrations of the hypnotic and opioid respectively.

The model has four parameters: $C50_O$, $C50_H$, γ, and α. In the case of multiple (N) stimuli, there are 4.N model parameters; assuming equal values for γ and α for each stimulus, there are 2.N + 2 parameters ($C50_O$ and $C50_H$ for each additional stimulus). The model can be further reduced by assuming a common value for $C50_O$ for each stimulus; in this case there are N + 3 parameters (one additional parameter for each stimulus).

Reduced Greco Model without Effect of the Opioid Alone
In the case of the interaction of opioids with hypnotics, the effect of the opioid alone on P may be too small to accurately assess the $C50_O$ (i.e., the actual value of $C50_O$ is very high). The Greco model can then be easily modified by leaving out the term U_O from Eq. A4, creating

$$U = U_H + \alpha \cdot U_O \cdot U_H \quad (A5)$$

which may be written after rearrangement and replacement of U_O according to Eq. A2:

$$U = U_H \cdot \left(1 + \alpha \cdot \frac{C_O}{C50_O}\right) \quad (A6)$$

The parameters $C50_O$ and α cannot be estimated independently, since only their ratio $\alpha/C50_O$ appears in Eq. A6. Therefore Bouillon[2] replaced the term $\alpha/C50_O$ by a single parameter α', resulting in A7:

$$U = U_H \cdot (1 + \alpha' \cdot C_O) \quad (A7)$$

Alternatively, α may be fixed to 1, resulting in A8, which is equal to A9,

$$U = U_H \cdot \left(1 + \frac{C_O}{C50_O}\right) \quad (A8)$$

$$U = U_H \cdot (1 + U_O) \quad (A9)$$

$C50_O$ may now be interpreted as the concentration of the opioid that decreases $C50_H$ by 50%: If $C_O = C50_O$ ($U_O = 1$), $U = 2 \times U_H$, *i.e.*, the concentration of the hypnotic required to achieve a certain potency U, and thus a certain probability of tolerance *P*, is reduced by a factor 2, compared to the concentration in the absence of the opioid.

Both methods are equivalent and produce identical results. Fixing the term α to 1 instead of introducing another term α' has the advantage that the observed value of $C50_O$ can be directly interpreted as the concentration that decreases $C50_H$ by 50%, whereas the meaning of the term α' in the Bouillon method is more difficult to explain.

There are three model parameters to be estimated in the Reduced Greco model: $C50_H$, γ, and α' in the Bouillon method, and $C50_O$, $C50_H$, and γ in the second method. In the case of multiple (N) stimuli, there are 3.N model parameters; assuming an equal value for γ for each stimulus, there are 2.N + 1 parameters. The model can be further reduced by assuming a common value for $C50_O$ for each stimulus; in this case there are N + 2 parameters.

Minto Model
The Minto model[1] may be described by the following equations, A10,

$$\theta = \frac{U_H}{U_O + U_H} \quad (A10)$$

where θ is the fraction of the potency of one drug (in this case the hypnotic) to the total potency of both drugs (not to be confounded with the term θ in NONMEM). The value of θ is between 0 and 1 according to the relative contribution of the two drugs to the total potency U_H plus U_O. Equation A11,

$$U_{50} = 1 - \beta_{U50} \cdot \theta \cdot (1 - \theta) \tag{A11}$$

where U_{50} is the potency of two drugs in the combination θ yielding half maximal effect, and β_{U50} is a dimensionless interaction coefficient relating θ (fraction of hypnotic) and $1-\theta$ (fraction of opioid) to U_{50} (higher-order functions of θ may be used to accommodate more complex shapes of interaction). Equation A12,

$$U = \frac{U_O + U_H}{U_{50}} \tag{A12}$$

where U is the potency of the two drugs normalized to U_{50}.

The steepness parameter γ is a model parameter, or a function of the ratio of the drug concentrations (θ) and model parameters ($C50_O$, $C50_H$, γ_O, γ_H, β_γ), and may be written as a linear interpolation between γ_H, and γ_O, and an interaction term analogous to Eq. A11 (higher-order functions of θ may be used to accommodate more complex shapes of interaction): A13,

$$\gamma = \gamma_H \cdot \theta + \gamma_O \cdot (1 - \theta) - \beta_\gamma \cdot \theta \cdot (1 - \theta) \tag{A13}$$

Note that Eqs. A11 and A13 have been rearranged from the corresponding equations in the original paper of the Minto model,[1] to clarify the interaction.

There are four model parameters: $C50_O$, $C50_H$, γ, and β_{U50}, or six model parameters: $C50_O$, $C50_H$, γ_O, γ_H, β_{U50}, and β_γ. In the case of multiple (N) stimuli, there are 4.N (or 6.N) model parameters; assuming an equal value for γ's and β's for each stimulus, there are 2.N + 2 (or 2.N + 4) parameters. The model can be further reduced by assuming a common value for $C50_O$ for each stimulus; in this case there are N + 3 (or N + 5) parameters. In the current implementation using Eq. A1 the Minto model implies that both drugs on their own may yield the maximal effect.

Hierarchical Model

The original Hierarchical model[6,7] may be written as A14,

$$P = \frac{C_H{}^\gamma}{(C50_H \cdot \text{postopioid\_intensity})\gamma + C_H{}^\gamma} \tag{A14}$$

and A15,

postopioid_intensity = preopioid_intensity

$$\cdot \left(1 - \frac{C_O{}^{\gamma O}}{(C50_O \cdot \text{preopioid\_intensity})^{\gamma O} + C_O{}^{\gamma O}}\right), \tag{A15}$$

where postopioid_intensity is the stimulus intensity after attenuation by the opioid, and preopioid_intensity is the intensity of the stimulus in the absence of opioid.

Eq. A14 corresponds to the general Eq. A1 if

$$U = \frac{U_H}{\text{postopioid\_intensity}} \tag{A16}$$

Eqs. A15 and A16 may be combined to eliminate the term postopioid_intensity with A17,

$$U = \frac{U_H}{\text{preopioid\_intensity}} \cdot \left(1 + \left(\frac{U_O}{\text{preopioid\_intensity}}\right)^{\gamma O}\right) \tag{A17}$$

The original Hierarchical model[6] was considered overparameterized.[2] The parameters preopioid_intensity, $C50_H$, and $C50_O$ cannot be estimated uniquely, since the values of $C50_H$, and $C50_O$ can always be adjusted to offset any value of preopioid_intensity.

In the case of a single stimulus, the overparametrization can be solved by fixing preopioid_intensity to 1, reducing Eq. A17 to A18,

$$U = U_H \cdot (1 + U_O{}^{\gamma O}) \tag{A18}$$

Eq. A18 demonstrates that, for single stimulus, the Hierarchical model is a simple extension of the Reduced Greco model, *i.e.*, by adding an exponent γ_O to U_O in Eq. A9, yielding Eq. A18.

In the case of multiple stimuli, the overparametrization can be solved in various ways, leading to different models: the Scaled $C50_O$ and the Fixed $C50_O$ Hierarchical model.

Scaled C50O Hierarchical Model

This approach is consistent with the concept described by Bouillon *et al.*,[6] where the $C50_o$ is multiplied by preopioid intensity to reflect the decreasing potency of opioids in attenuating pain as the intensity of the pain increases.

The Scaled $C50_O$ Hierarchical model constrains $C50_{Oi}$ and $C50_{Hi}$ for i > 1 to:

$C50_{Oi} = C50_{O1} * \text{preopioid\_intensity}_i$

$C50_{Hi} = C50_{H1} * \text{preopioid\_intensity}_i$

In short, the characteristic feature of the Scaled $C50_O$ Hierarchical model is that the stimulus intensity is a factor by which the C50s of both drugs are multiplied.

There are four model parameters: $C50_O$, $C50_H$, γ, and γ_O. In the case of multiple (N) stimuli, there are 4.N model parameters; the constraints on $C50_{Oi}$ and $C50_{Hi}$ reduce the number of free parameters to 3.N + 1; assuming that γ and γ_O are not affected by the type and intensity of the stimulus, there are N + 3 parameters ($C50_{O1}$, γ, γ_O, and N values of $C50_{Hi}$; values of $C50_{Oi}$ for i more than 1 follow from the constraints).

Fixed C50O Hierarchical Model

The modified Hierarchical model proposed by Bouillon[2] introduced a different constraint on $C50_{Oi}$ that is also reasonable and testable: $C50_O$ is the same for all stimuli. Therefore this model is referred to as 'Fixed $C50_O$ Hierarchical model', constraining $C50_{Oi}$ and $C50_{Hi}$ for i > 1 to:

$C50_{Oi} = C50_{O1}$

$C50_{Hi} = C50_{H1} * \text{preopioid\_intensity}_i$

This constraint is identical to omitting preopioid_intensity from the denominator of Eq. A15. From these constraints and Eq. A18 it follows that the Fixed $C50_O$ Hierarchical model is an extension of the Reduced Greco model, *i.e.*, by adding an exponent γ_O to U_O in Eq. A9 and with a common parameter $C50_O$ for all stimuli. Note that in the Fixed $C50_O$ Hierarchical model proposed by Bouillon[2] γ_O was assumed to be 1 (equation on page 481 of that paper), making the model identical to the Reduced Greco model.

The number of model parameter is identical to that of the Scaled $C50_O$ Hierarchical model ($C50_O$, γ, γ_O, and N values for $C50_{Hi}$).

Relationships between Models

The characteristics and relationships between the models can be summarized as follows:

The Greco model and the Minto model as commonly implemented assume an effect of the opioid given alone, whereas the

other models assume that the opioid alone has no effect on the response to a stimulus;

The Reduced Greco model is a reduction of the Greco model; the models are identical if the parameters $C50_O$ and α of the Greco model are infinitely large, and their ratio $C50_O/\alpha$) is equal to $C50_O$ of the Reduced Greco model;

The Reduced Greco model with a common parameter $C50_O$ for all stimuli and the Fixed $C50_O$ Hierarchical model are identical if the parameter γ_O is fixed to 1;

The Scaled $C50_O$ Hierarchical model assumes that the C50 of opioid ($C50_O$) and hypnotic ($C50_H$) are multiplied by a common factor representing the intensity of the stimulus, $i.e.$, the ratio $C50_O/C50_H$ are the same for each stimulus;

The Fixed $C50_O$ Hierarchical model assumes a common $C50_O$ for each stimulus;

For a single stimulus the Fixed $C50_O$ Hierarchical model is identical to the Scaled $C50_O$ Hierarchical model.

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