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Response Surface Modeling of Remifentanil–Propofol Interaction on Cardiorespiratory Control and Bispectral Index

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Background: **Since propofol and remifentanil are frequently combined for monitored anesthesia care, we examined the influence of the separate and combined administration of these agents on cardiorespiratory control and bispectral index in humans.**

Methods: **The effect of steady-state concentrations of remifentanil and propofol was assessed in 22 healthy male volunteer subjects. For each subject, measurements were obtained from experiments using remifentanil alone, propofol alone, and remifentanil plus propofol (measured arterial blood concentration range: propofol studies, 0–2.6 μg/ml; remifentanil studies, 0–2.0 ng/ml). Respiratory experiments consisted of ventilatory responses to three to eight increases in end-tidal P_{CO_2} (P_{ETCO_2}). Invasive blood pressure, heart rate, and bispectral index were monitored concurrently. The nature of interaction was assessed by response surface modeling using a population approach with NONMEM. Values are population estimate plus or minus standard error.**

Results: **A total of 94 responses were obtained at various drug combinations. When given separately, remifentanil and propofol depressed cardiorespiratory variables in a dose-dependent fashion (resting $\dot{V}_i$: 12.6 ± 3.3% and 27.7 ± 3.5% depression at 1 μg/ml propofol and 1 ng/ml remifentanil, respectively; $\dot{V}_i$ at fixed P_{ETCO_2} of 55 mmHg: 44.3 ± 3.9% and 57.7 ± 3.5% depression at 1 μg/ml propofol and 1 ng/ml remifentanil, respectively; blood pressure: 9.9 ± 1.8% and 3.7 ± 1.1% depression at 1 μg/ml propofol and 1 ng/ml remifentanil, respectively). When given in combination, their effect on respiration was synergistic (greatest synergy observed for resting $\dot{V}_i$). The effects of both drugs on heart rate and blood pressure were modest, with additive interactions when combined. Over the dose range studied, remifentanil had no effect on bispectral index even when combined with propofol (inert interaction).**

Conclusions: **These data show dose-dependent effects on respiration at relatively low concentrations of propofol and remifentanil. When combined, their effect on respiration is strikingly synergistic, resulting in severe respiratory depression.**

THE COMBINED administration of opioids and anesthetics for induction and maintenance of anesthesia is common practice. The anesthetic is given to lose consciousness, prevent awareness, and reduce movement responses in the patient; the opioid is given to suppress somatic, stress, and adrenergic responses to surgical stimulation. An important advantage of combining an opioid and an anesthetic is the synergistic increase in these desired effects, with consequently the need for less drugs to attain the goal of adequate anesthesia relative to the amount of drug needed when only a single agent (*i.e.*, an anesthetic) is given.[1] Since this is not only true for patients who are ventilated but also for patients who maintain their own breathing (for example, during minimal, moderate, and deep sedation), it is of interest to address the issue of the effect of drug combinations on respiration. While it is known that anesthesia induces many side effects, it is acknowledged that respiratory depression is potentially life-threatening.[2] Therefore, we studied the effect of the opioid remifentanil and intravenous anesthetic propofol on the cardiorespiratory control. This combination of drugs is frequently used in patients receiving monitored anesthesia care for minor (without additional regional anesthesia) and major (with additional regional anesthesia) surgery. Knowledge on the quantitative and qualitative (additive *vs.* synergistic) nature of their interaction is clinically important and may lead to specific dosing regimens aimed at the titration of sedation/analgesia *versus* respiratory effect.

To study the remifentanil–propofol interaction, we used the technique of response surface modeling.[3–7] This technique allows the observation of the concentration-effect relation among infinite combinations of remifentanil and propofol over the whole surface area in three-dimensional space. We previously made successful use of this technique to quantify the interactive effects of sevoflurane and alfentanil on cardiorespiratory control.[6]

Methods

Subjects and Apparatus

Twenty-two healthy male volunteers (aged 19–25 yr) participated in the protocol after approval was obtained from the local Human Ethics Committee (Commissie Medische Ethiek, Leiden University Medical Center, Leiden, The Netherlands). Oral and written consent was obtained from all volunteers.

An intravenous catheter was inserted in the left antecubital vein (for drug infusion) and an arterial line was placed in the right radial artery (for blood sampling) in each volunteer upon arrival at the laboratory. Subsequently, electrodes for electroencephalogram monitor-

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ing (BIS® Sensor, Aspect Medical Systems, Newton, MA) were placed on the head as specified by the manufacturer and the subjects rested for 20 to 30 min. Next a face mask was applied over the mouth and nose. Gas flow was measured with a pneumotachograph connected to a pressure transducer and electronically integrated to yield a volume signal. Corrections were made for the changes in gas viscosity due to changes in oxygen concentration of the inhaled gas mixtures. The pneumotachograph was connected to a T-piece. One arm of the T-piece received a gas mixture from a gas mixing system consisting of three mass-flow controllers (Bronkhorst High-Tec, Veenendaal, The Netherlands). A personal computer provided control signals to the mass-flow controllers so that the composition of the inspired gas mixtures could be adjusted to force end-tidal oxygen and carbon dioxide concentrations ($P_{ET}O_2$ and P_{ETCO_2}) to follow a specified pattern in time. The O_2 and CO_2 concentrations of inspired and expired gases and the arterial hemoglobin-O_2 saturation (Spo_2) were measured with a Datex Multicap gas monitor and Datex Satlite Plus pulse oximeter, respectively (Datex-Engstrom, Helsinki, Finland).

The electroencephalogram was recorded using an A-2000 monitor with software version 3.3 (Aspect Medical Systems). The monitor computed the bispectral index over 2-s epochs. We averaged the bispectral index values during 1 min-intervals and used data points obtained at 3-min intervals.

Study Design

Resting ventilation and P_{ETCO_2} (*i.e.*, without any inspired CO_2), blood pressure, heart rate, bispectral index, and the ventilatory response to hypercapnia were measured before and during infusion of remifentanil, propofol, and the combined infusion of these agents. Initially control (*i.e.*, without the administration of any agent) values were obtained. Next, the infusion of remifentanil was started and cardiorespiratory and bispectral index parameter values were obtained at steady state blood target concentrations. After this set of experiments, the infusion was terminated and the subject rested for 1 h. Next, the infusion of propofol was started and cardiorespiratory and bispectral index parameter values were obtained at steady state blood target concentrations. Subsequently, parameter values were obtained during the combined administration of remifentanil and propofol. In some subjects, two to three experiments were performed at different propofol–remifentanil combinations. The subjects were randomly assigned to a fixed scheme of target concentrations of remifentanil and propofol. The scheme was designed ensuring that, in the applied dose ranges, evenly spread data points were obtained.

Ventilatory Response to Hypercapnia

The ventilatory response to CO_2 was obtained by using the "dynamic end-tidal forcing" technique.[8,9] After assessment of resting variables, three to eight increases in P_{ETCO_2} were applied to obtain data points for the steady-state ventilatory response. The increases varied from 3 to 19 mmHg. The increased P_{ETCO_2} readings lasted at least 8 min. When on-line analysis revealed that a ventilatory steady-state had not been reached, the duration of hypercapnia was extended. The order of increases was arbitrarily chosen. All hypercapnic studies were performed at a background of moderate hyperoxia ($P_{ET}O_2$ 120 mmHg).

The increased P_{ETCO_2} and the corresponding $\dot{V}_i$ breath-to-breath data were averaged over 10-breaths. Data points were obtained at the end of the P_{ETCO_2} increase. This procedure yielded three to eight steady-state data points. We expressed $\dot{V}_i$ as a linear function of P_{ETCO_2}:

$$\dot{V}_i = S(P_{ET}CO_2 - B) \quad (1)$$

where S is the ventilatory CO_2 sensitivity and B the extrapolated P_{ETCO_2} at zero $\dot{V}_i$. Parameters S and B were determined by linear regression of $\dot{V}_i$ on P_{ETCO_2}.

Remifentanil and Propofol Administration, Blood Sampling and Assays

Propofol and remifentanil were administered using target controlled infusion (TCI) systems. For propofol, we used a palm-top computer (Psion, London, UK) programmed with a three-compartment propofol pharmacokinetic data set to control an infusion pump (Becton Dickinson, St. Etienne, France).[10,11] For remifentanil, we used a custom built infusion pump that was programmed with a remifentanil pharmacokinetic data set (Remifusor, University of Glasgow, Glasgow).[12] These systems allow a specified target plasma concentration of remifentanil and propofol to be rapidly achieved and maintained. Hypercapnic studies were performed ~10 min after blood remifentanil and propofol had reached their target concentrations. Since this equals more than five to 10 times the remifentanil and propofol blood-effect-site equilibration half-lifes, we assumed that brain and blood remifentanil and propofol concentrations were in equilibrium.

Before and after changes in target drug concentrations, arterial blood samples for determination of remifentanil and propofol concentrations were collected. Blood for propofol determination was collected in syringes containing potassium oxalate. Propofol concentrations were determined by reverse-phase high performance liquid chromatography.[13] Samples for the determination of blood remifentanil concentrations were collected into tubes containing sodium heparin and immediately transferred to tubes containing 50% citric acid (to inactivate esterases) before freezing at −20°C. The assay method is based on tandem mass spectrometry detection.[14]

Response Surface Modeling

Analysis was performed on the following variables: resting inspired minute ventilation ($\dot{V}_i$) and P_{ETCO_2} (*i.e.*, without any inspired CO_2), slope of the hypercapnic ventilatory response (S), ventilation at a fixed P_{ETCO_2} of 55 mmHg ($\dot{V}_{55}$, calculated from S and B), mean arterial pressure (MAP), heart rate (HR), and bispectral index. The basis of the pharmacodynamic model is similar to the previously published model.[6] The single-drug concentration-effect (*C-E*) relationship is given by

$$E(C) = E_0 \cdot \left\{ 1 - \left[\frac{C}{C_{50}} \right]^{\gamma} \cdot \frac{1}{2} \right\} \quad (2)$$

where E_0 is the baseline drug effect, C_{50} the value of C that gives 50% depression, and γ a nonlinearity parameter; notice that the model is linear when $\gamma = 1$. A straightforward extension for two concomitantly administered drugs (C_r = remifentanil concentration, C_p = propofol concentration) is obtained by respecting Loewe additivity[15]:

$$E(C_r, C_p) = E_0 \cdot \left\{ 1 - \left[\frac{C_r}{C_{50,r}} + \frac{C_p}{C_{50,p}} \right]^{\gamma} \cdot \frac{1}{2} \right\} \quad (3)$$

Note that isoboles in the C_r-C_p plane are straight lines, irrespective of the value of γ. Deviations from additivity can be modeled as:

$$E(C_r, C_p) = E_0 \cdot \left\{ 1 - \left[\frac{C_r}{C_{50,r}} + \frac{C_p}{C_{50,p}} \right]^{\gamma(Q)} \cdot \frac{1}{2} \cdot I(Q) \right\} \quad (4)$$

with $I(Q)$ a smooth function (spline) with a parameter denoting maximum interaction I_{max} at $I(Q_{max})$ and $Q = U_r/(U_r+U_p)$, $U_r = C_r/C_{50,r}$, $U_p = C_p/C_{50,p}$. To limit the number of parameters $\gamma(Q)$ was either a constant or a linear function going from γ_r at $Q = 1$ to γ_p at $Q = 0$. Since the concentration ranges used in the study for most variables lie below the C_{50}s, these parameters will be poorly estimated leading to wide asymmetric confidence intervals. A remedy would be to use C_{10}s or C_{25}s but one does not know the optimal parameters beforehand. In fact, it is better to use parameters that are centered according to the study design:

$$E(C_r, C_p) = E_0 \cdot \left\{ 1 - \left[\frac{C_r}{C_{h,r}} \cdot \lambda_r^{1/\gamma(Q)} + \frac{C_p}{C_{h,p}} \cdot \lambda_p^{1/\gamma(Q)} \right]^{\gamma(Q)} \cdot I(Q) \right\} \quad (5)$$

where $C_{h,r}$ and $C_{h,p}$ the values of C_r and C_p midway in the measured concentrations range, and Q redefined to be $Q = U_r/(U_r+U_p)$, $U_r = C_r/C_{h,r}$, $U_p = C_p/C_{h,p}$; λ_r and λ_p denote the degree of depression from E_0 when $C_r = C_{h,r}$ and $C_p = 0$ and *vice versa*, respectively. For variable P_{CO_2}, which increases from E_0, the model used was the same as equation 5, except the minus sign was replaced by a plus sign.

Parameter Estimation and Model Selection

The above model has the following parameters to be estimated: E_0, λ_r, λ_p, I_{max}, Q_{max}, γ_r, and γ_p. The following situations are of special interest:

- $I_{max} = 1$, $Q_{max} = 0.5$ denoting additivity;
- $I_{max} \neq 1$, $Q_{max} = 0.5$ denoting symmetric interaction;
- $I_{max} \neq 1$, $Q_{max} \neq 0.5$ denoting asymmetric interaction.

Notice that when $Q_{max} = 0.5$ we could use the Minto parabolic function of Q instead of the spline $I(Q)$.[5] Furthermore, when two drugs are pharmacodynamically equivalent apart from a difference in potency, we would expect a symmetric interaction (since Q is based on normalized concentrations). For each of the above three cases, there are five situations that describe (non)linearity:

- $\gamma_r = \gamma_p = 1$ denoting linearity;
- $\gamma_r = \gamma_p \neq 1$ denoting nonlinearity described by one parameter;
- $\gamma_r \neq 1$ and $\gamma_p = 1$ denoting nonlinearity for drug *R* and linearity for *P*;
- $\gamma_r = 1$ and $\gamma_p \neq 1$ denoting linearity for drug *R* and nonlinearity for *P*;
- $\gamma_r \neq 1$ and $\gamma_p \neq 1$ denoting nonlinearity described by two parameters.

This results in a total of fifteen models to be investigated (fig. 1). NONMEM was used to estimate the parameter values.[16] Since the models are nonnested, the likelihood ratio criterion is not applicable so the Akaike Information-theoretic Criterion (AIC) was used instead[16]: AIC = $-2LL + 2P$, where $-2LL$ is the minimum value of the objective function calculated by NONMEM and P denotes the number of parameters. The model with the lowest *AIC* is considered "best." The population analysis was done with the assumption of lognormally distributed model parameters and constant relative (except for P_{CO_2} where it was assumed to be additive) normally distributed intraindividual error.

Model Stability Assessment Using the Bootstrap

When, according to *AIC* criterion, a model is chosen for a certain effect parameter, that choice is not associated with a measure of confidence in that model. One would like to be more certain that the choice is not an artifact of particular individuals in the current data set, and that when a new data set would be obtained, the same model would be chosen. A way to generate surrogate data sets is given by the method of the bootstrap.[17] Basically, a bootstrap data set is formed by selecting, with replacement, the data from individuals until a set is obtained with the same total number of individuals. This data set is then subject to the same fitting procedure, and by repeating the process N times, N parameter estimate sets are obtained with N selections of one of the fifteen models. From the parameter estimates confidence intervals and histograms can be constructed. The impact of con-

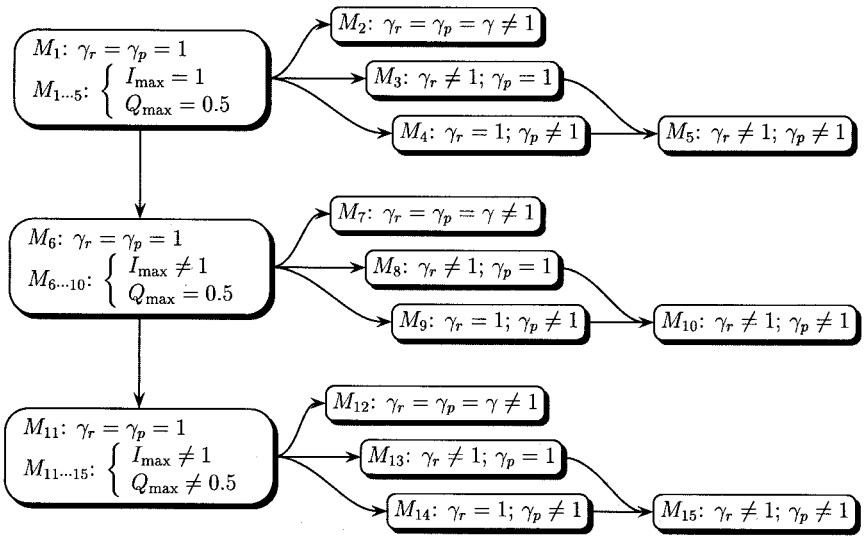

Fig. 1. Schematic representation of the 15 different pharmacodynamic model (M) possibilities. Models 1 to 5: additive interaction between propofol (p) and remifentanil (r) with different values for γ_r and γ_p per model; models 5 to 10: nonadditive interactions at a value of Q_{max} equal to 0.5 (*i.e.*, symmetric interactions) with different values for γ_r and γ_p per model; models 11 to 15: nonadditive interactions at a value of Q_{max} not equal to 0.5 (nonsymmetrical interactions) with different values for γ_r and γ_p per model.

straining certain parameters to fixed values, and therefore identifiability, can then be studied visually. The number of times a model is selected is a measure of our confidence in the model. In our analysis N was set at 1000.

The bootstrap procedure was implemented in a C++ program that generates bootstrap data sets, NONMEM control files with appropriately fixed parameters, runs NONMEM and reads back the estimated parameter values and the minimum value of the objective function. When NONMEM returned an error status regarding parameter boundary problems (despite carefully chosen initial conditions and boundaries) or rounding errors, the model that was fitted was deemed to be not supported by the data. This, in principle, gives a bias towards the simpler models. Furthermore, to have a feasible procedure with respect to computer time, we opted not to investigate all possibilities for the statistical model. Initially, interindividual variability was assumed to be present only on parameters E_0, λ_r, and λ_p. When the number of times the corresponding variance was estimated to be negligible exceeded $N/2$, this variability term was removed and the bootstrap redone. Confidence intervals were obtained in the traditional way (*i.e.*, estimate $\pm$ 1.96 $\cdot$ SE) and the bootstrap BC_a (bias-corrected and accelerated) method.[17]

Results

All 22 subjects completed the protocol without major-nor-respiratory- side effects. The durations of the studies ranged from 3 to 4 h per subject. A total of 94 responses were obtained at different drug combinations. The range of the measured arterial remifentanil was 0–2 ng/ml. For propofol all measured concentrations were in the range of 0–2.0 μg/ml except one (2.6 μg/ml). Consequently $C_{h,r}$ and $C_{h,p}$ were set to 1 ng/ml and 1 μg/ml, respectively, in the pharmacodynamic model.

A typical example of respiratory studies in one subject is given in figure 2. Its shows the control response (no drugs given) with a slope of 2.4 $l \cdot min^{-1} \cdot mmHg^{-1}$, the effects of 1.5 μg/ml propofol (a 66% reduction of the slope of the $\dot{V}_i$-CO_2 response to 0.8 $l \cdot min^{-1} \cdot mmHg^{-1}$) and 1 ng/ml remifentanil (a parallel shift of the response curve with a slope of 2.2 $l \cdot min^{-1} \cdot mmHg^{-1}$) alone, and the effect of that drug combination, which was greater than the sum of the effects of either drug alone (a > 90% depression of the slope to 0.2 $l \cdot min^{-1} \cdot mmHg^{-1}$).

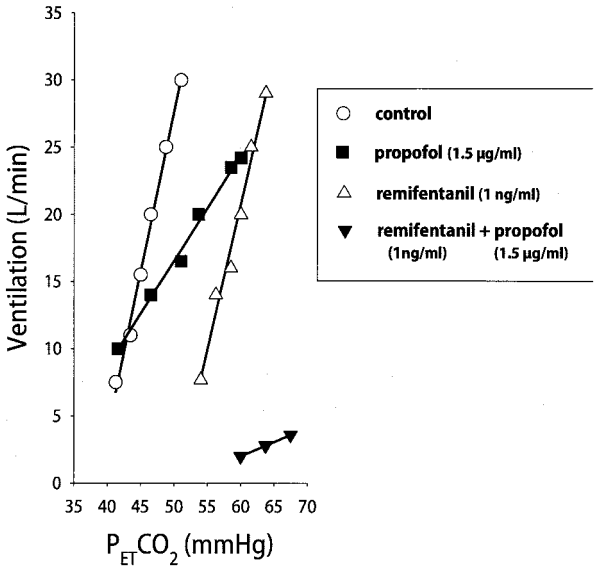

Fig. 2. Four ventilatory carbon dioxide response curves of one subject. The control response had a slope of 2.4 l/min per mmHg. While propofol decreased the slope to 0.8 l/min per mmHg, remifentanil caused a parallel shift to higher P_{CO_2} values of about 12 mmHg (slope = 2.2 l/min per mmHg). The combined administration yielded both a reduction in slope of the response curve (slope = 0.2 l/min per mmHg) and a rightward shift of about 20 mmHg. These observations suggest synergy on the slope of hypercapnic response and ventilation at a fixed P_{ETCO_2}.

Table 1. Results of the Bootstrap-based Model Selection

	Model																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Nonlinear*	Interaction†
Resting $\dot{V}_i$, l/min	0	0	0	1	1	68	531‡	81	74	46	3	145	12	5	33	929	998
$\dot{V}_{55}$, l/min	0	28	32	1	22	0	431‡	37	0	268	0	128	1	0	47	1,000	912
Resting P_{ETCO_2}, mmHg	53	29	56	11	41	130	357‡	150	35	68	10	31	13	7	9	717	810
S, l· min^{-1}· $mmHg^{-1}$	22	81	16	24	16	3	357‡	18	4	261	1	106	2	3	86	974	841
Heart rate, beats/min	156	240‡	133	121	20	69	210	7	8	0	6	10	0	1	0	769	311
MAP, mmHg	664‡	3	13	6	11	140	81	9	18	2	3	23	4	11	1	193	292

The analysis was performed on 1,000 data sets created by the bootstrap method and based on 22 original studies. The values are the number of times that that specific model was chosen by Akaike's Information Criterion. The corresponding model was used in the analysis of the original data set.

* Total number of times that a nonlinear model (models 2–5 + 7–10 + 12–15) was chosen. † Total number of times that a nonadditive interaction model (models 6–15) was chosen. ‡ indicates the most frequently chosen numbers.

MAP = mean arterial pressure; $Petco_2$ = end-tidal pressure of carbon dioxide; S = slope of the hypercapnic ventilatory response; $\dot{V}_{55}$ = ventilation at a fixed $Petco_2$ of 55 mmHg; $\dot{V}_i$ = inspired minute ventilation obtained without any inspired carbon dioxide.

In table 1 the results of the bootstrap based model selection are given. For all respiratory variables, model 7 seemed best fitted to describe the data (*i.e.*, nonlinear relationship between drugs and effect, synergistic interaction, $Q_{max} = 0.5$; *i.e.*, indicating that interaction was symmetric) (fig. 1). The population estimates ± SE and 95% confidence intervals –as derived from the NONMEM analysis– of the response surfaces are given in table 2 and for resting $\dot{V}_i$, resting P_{ETCO_2}, $\dot{V}_{55}$ and S in figures 3–6. At 1 ng/ml and 1 μg/ml, remifentanil and propofol caused ~28% and 13% depression of resting ventilation, respectively. Combining propofol and remifentanil at these same blood concentrations caused 58% depression (equation 4), indicating the synergistic nature of the interaction. Similar observations were made for resting P_{ETCO_2}, $\dot{V}_{55}$ and S, although the synergistic interaction strength was less (I_{max} resting $\dot{V}_i$ = 1.9 *vs.* I_{max} resting P_{ETCO_2}, $\dot{V}_{55}$ and S = 1.2–1.3). At the combined infusion of 1 μg/ml propofol and 1 ng/ml remifentanil the depression of $\dot{V}_{55}$ was 82% (equation 4); the corresponding values for resting P_{ETCO_2} and S were 23% and 69%, respectively.

In order to get an indication of the spread of data points over the surface as well as on the goodness of fit, we included bubble plots that show the distance of individual measured data points from the population surface (*i.e.*, residuals) (figs. 3–6). These plots show evenly spread data over the tested dose ranges and the absence of overt misfits.

The values of baseline mean arterial pressure and heart rate (values before any drug was given) indicate that the subjects were free of agitation or stress during the studies (table 2). The effects of remifentanil and propofol on MAP and HR rate were not as remarkable as their effects on the respiratory variables: depression at 1 ng/ml remifentanil and 1 μg/ml propofol ranged from 4 to 12% (table 2). The effect of their combination was expected from the concentration-response curve of the individual agents (*i.e.*, additive interaction or $I_{max} = 1$, linear dose-effect relationship for MAP, nonlinear relationship for HR, table 1).

The BIS® monitor was unable to unearth any sedative effect of remifentanil in the dose range we studied (inert

Table 2. Population Pharmacodynamic Estimates

	Resting $\dot{V}_i$, l/min	Resting P_{ETCO_2}, mmHg	S, l· min^{-1}· $mmHg^{-1}$	$\dot{V}_{55}$, l/min	MAP, mmHg	HR, beats/min	BIS
Baseline value	9.4 ± 0.3	41.2 ± 0.1	1.87 ± 0.01	31.4 ± 1.5	93.0 ± 1.6	64.1 ± 1.8	—
$\dot{V}_i$ 95% CI	8.8–10.0	41.0–41.4	1.84–1.89	28.4–34.4	89.8–96.2	60.4–67.7	—
λ Remifentanil, %	27.7 ± 3.5	15.4 ± 1.2	20.0 ± 5.4	57.7 ± 3.5	3.7 ± 1.1	10.6 ± 2.7	—
$\dot{V}_i$ 95% CI	20.7–34.7	13.0–17.8	9.2–30.8	51.0–65.0	1.5–5.9	5.2–16.0	—
λ Propofol, %	12.6 ± 3.3	4.2 ± 0.9	51.0 ± 4.5	44.3 ± 3.9	9.9 ± 1.8	11.9 ± 3.1	18.9 ± 1.4
$\dot{V}_i$ 95% CI	6.0–19.2	2.4–6.0	42.0–60.0	37.0–52.0	6.3–13.5	5.7–18.1	16.1–21.7
I_{MAX}	1.9 ± 0.2	1.3 ± 0.2	1.3 ± 0.1	1.2 ± 0.1	1	1	—
$\dot{V}_i$ 95% CI	1.5–2.3	0.9–1.7	1.1–1.5	1.04–1.38	—	—	—
Q_{MAX}	0.5	0.5	0.5	0.5	0.5	0.5	—
γ	0.5 ± 0.1	0.7 ± 0.1	0.4 ± 0.1	0.4 ± 0.05	1	0.3 ± 0.1	1
$\dot{V}_i$ 95% CI	0.3–0.7	0.5–0.9	0.2–0.6	0.27–0.47	—	0.1–0.5	—
$C_{50,R}$, ng/ml	3.3	5.4	8.6	0.7	—	—	—
$C_{50,P}$, μg/ml	15.8	34.3	1.0	0.7	—	—	2.7

Values are population estimate ± SE and 95% confidence intervals as derived from the NONMEM analysis. I_{MAX} and Q_{MAX} are interaction parameters (see text): I_{MAX} values greater than one indicate synergy, and I_{MAX} values equal to one indicate additivity. $C_{50,R}$ and $C_{50,P}$ are extrapolated values.

λ = percent decrease at 1 ng/ml remifentanil and 1 μg/ml propofol; BIS = bispectral index; HR = heart rate; MAP = mean arterial pressure; S = slope of the hypercapnic ventilatory response; $\dot{V}_{55}$ = ventilation at a fixed $Petco_2$ of 55 mmHg; $\dot{V}_i$ = inspired minute ventilation obtained without any inspired carbon dioxide.

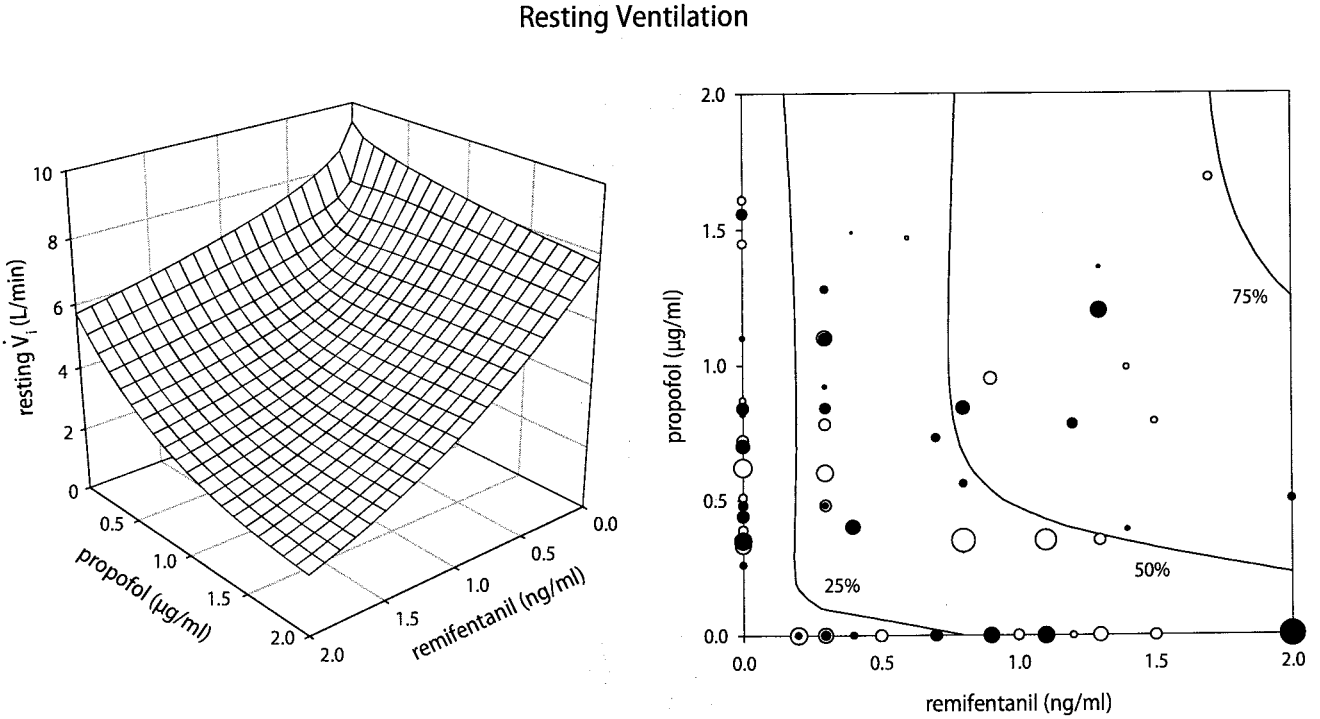

Fig. 3. Response surface modeling of the interaction of remifentanil and propofol on resting ventilation. (*Left*) Population response surface showing that the propofol–remifentanil interaction is synergistic (I(max) = 1.9 ± 0.2). Also, the dose-response relationships between drugs and effect was not linear (for both drugs $\gamma = 0.5 \pm 0.1$). (*Right*) Individual data points and 25, 50 and 75% isoboles. Open circles denote data point above the surface, closed circles denote data points below the surface. The area of the circles is proportional to the distance from that data point to the surface.

interaction) (fig. 7). Furthermore, the effect of propofol on the bispectral index was independent of the remifentanil concentration. The propofol–bispectral index relationship was linear with 19% depression of the bispectral index at 1 μg/ml plasma level.

Discussion

The main findings of our study are as follows. (1) In the dose range tested, remifentanil (0–2 ng/ml) and propofol (0–2.6 μg/ml) caused a dose-dependent depression of respiration, as observed by an increase in resting P_{ETCO_2} and decreases in resting $\dot{V}_i$, slope of the $\dot{V}_i$-CO_2 response and ventilation at a fixed P_{ETCO_2} of 55 mmHg. (2) While remifentanil shifts the $\dot{V}_i$-CO_2 response curve in a parallel fashion to higher P_{ETCO_2} levels, propofol reduces the slope of the response rather than shifting its position (pivot point at resting $\dot{V}_i$). (3) When combined, the depressant effect of propofol and remifentanil on resting $\dot{V}_i$, resting P_{ETCO_2}, S, and $\dot{V}_{55}$ is synergistic, with the greatest synergy observed for resting $\dot{V}_i$. (4) The depressant effect of remifentanil and propofol on blood pressure and heart rate is modest, when given separately; when combined their depressant effect is additive. (5) The bispectral index is sensitive to propofol but not to remifentanil, even when these agents are combined.

Pharmacodynamic Modeling

The Model. Similar to our previous study,[6] we used an asymmetric sigmoid function to describe the dose–effect relations. The function may be linear ($\gamma = 1$) or nonlinear ($\gamma \neq 1$). The advantages of this approach have been discussed previously.[6] In short, in contrast to classic sigmoid pharmacodynamic models, such as the inhibitory sigmoid E_{max} model,[18] our model predicts apnea at and above certain finite drug concentrations; it can predict negative responses above certain drug concentrations (for example, negative responses may occur when testing the effect of opioids on the ventilatory response to hypoxia)[6,19]; and finally, linear respiratory dose-responses may occur in limited dose ranges.[20] Interaction was modeled as suggested by Minto *et al.*,[5] which is based on the following two ideas: (1) the combination of two drugs should be regarded as one new drug with its own properties, and (2) that these properties depend only on the concentration ratio Q. As before, interaction was defined by the function $I(Q)$, for which we chose a spline (for details see ref. 6). Furthermore, the two drugs used in this study have dissimilar mechanisms of action so that we would not expect their γ to be equal at equipotent concentrations. Therefore, we also included the possibility of a linear $\gamma(Q)$. To our surprise $\gamma_r = \gamma_p = \gamma$ for all tested variables.

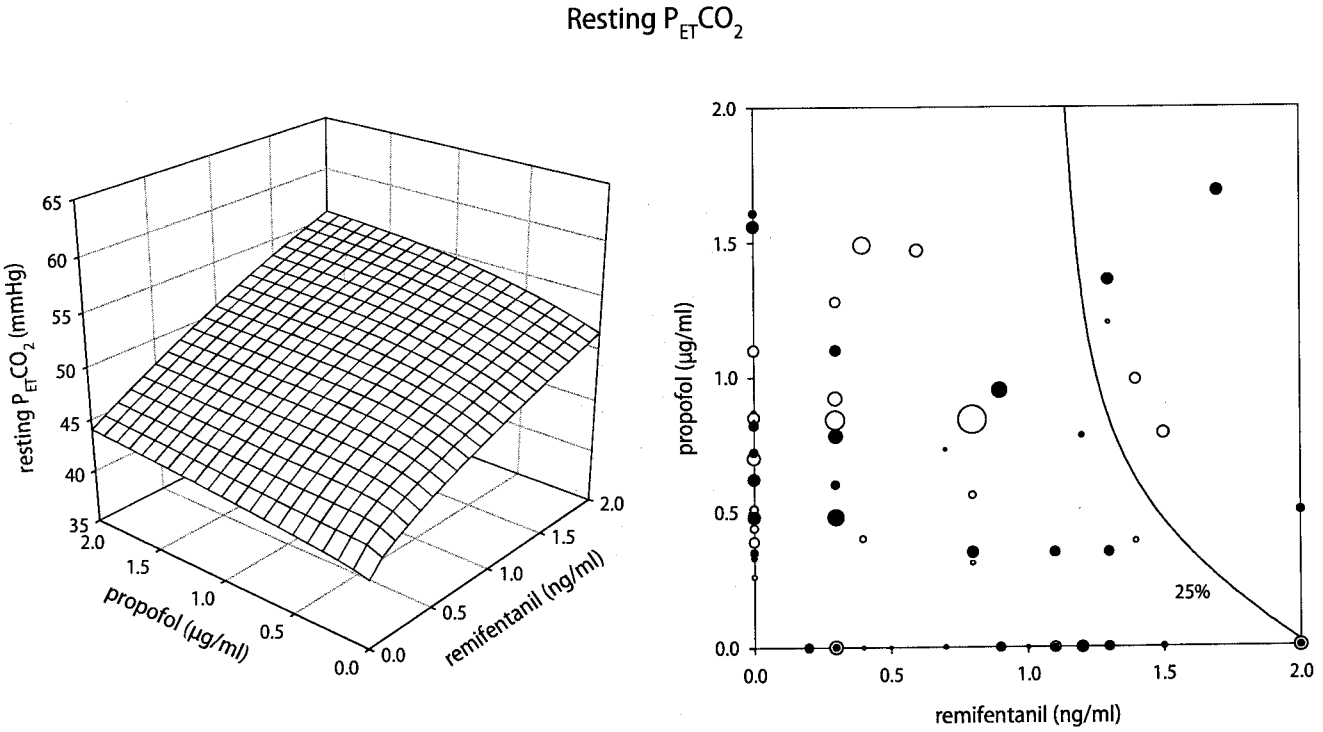

Fig. 4. Response surface modeling of the interaction of remifentanil and propofol on resting end-tidal carbon dioxide concentration (P_{ETCO_2}). (*Left*) Population response surface showing that the propofol–remifentanil interaction is synergistic (I(max) = 1.3 ± 0.2). The dose-response relationships between drugs and effect was not linear (for both drugs $\gamma = 0.7 \pm 0.1$). Note that the *x* and *y* axes are different from the other response surface plots with the origin now facing the reader. (*Right*) Individual data points and 25% isobole. Open circles denote data point above the surface, closed circles denote data points below the surface. The area of the circles is proportional to the distance from that data point to the surface.

Parameterization

Frequently, pharmacodynamic models incorporate C_{50}s to describe and compare potencies. Since, in our study, the applied concentration ranges are less than the C_{50}s, these parameters are poorly estimated with wide and asymmetric confidence intervals. In order to overcome this problem, we introduced the parameter λ, which is the percentage depression at the concentration midway in the plasma concentration range (equation 4).

Bootstrap Model Selection

The method of the bootstrap was applied here to assess the stability of the model selection based on *AIC*. Confidence in a model is then expressed as the number of times a model is chosen. Note that this confidence is not equivalent with the type I or type II error in traditional hypothesis testing. In the space of two nested models, however, the *AIC* is closely related to the type I error and the model selection percentage closely related to the power of the test.[21] When NONMEM produced an error message concerning boundary errors, the model that was tested was most probably overparameterized and would not be selected by *AIC* anyway.

Characteristics of Parameter Distributions

Parameter distributions can be estimated by constructing histograms of the estimated parameter values from the bootstrap runs. With the parameterization utilizing λs, their distributions were neither wide nor skewed so that the confidence intervals (obtained from the NONMEM population estimates ± 1.96 · SE, table 2) turned out to be equivalent with those obtained from the bootstrap parameter distributions. For example, for $\dot{V}_{55}$ the corresponding bootstrap values are baseline value 29.0–34.0 l/min, λ_r 51.0–67.0%, λ_p 37.0–52.0%, I_{max} 1.08–1.39 and γ 0.22–0.50.

Physiologic and Pharmacological Considerations

Opioids and anesthetics influence respiration by affecting chemical control of breathing, behavioral control of breathing, or, which happens most frequently, by affecting both. Chemical or metabolic control of breathing is coupled to the metabolism and depends on the chemical composition of arterial blood (pH, arterial P_{CO_2}, arterial P_{O_2}) and brainstem interstitial fluid (pH, brain tissue P_{CO_2}) *via* actions at peripheral and central chemoreceptors. Behavioral control of breathing allows adjustment of breathing to speech, pain, sedation, arousal, *et cetera*. We tested two sets of respiratory measures: resting variables (resting $\dot{V}_i$ and resting P_{ETCO_2}) and variables obtained from the ventilatory response to inspired CO_2 (S and $\dot{V}_{55}$). While S and $\dot{V}_{55}$ (note that $\dot{V}_{55}$ determines the position of the ventilatory response slope to CO_2, just like parameter B of equation 1) are predominantly chem-

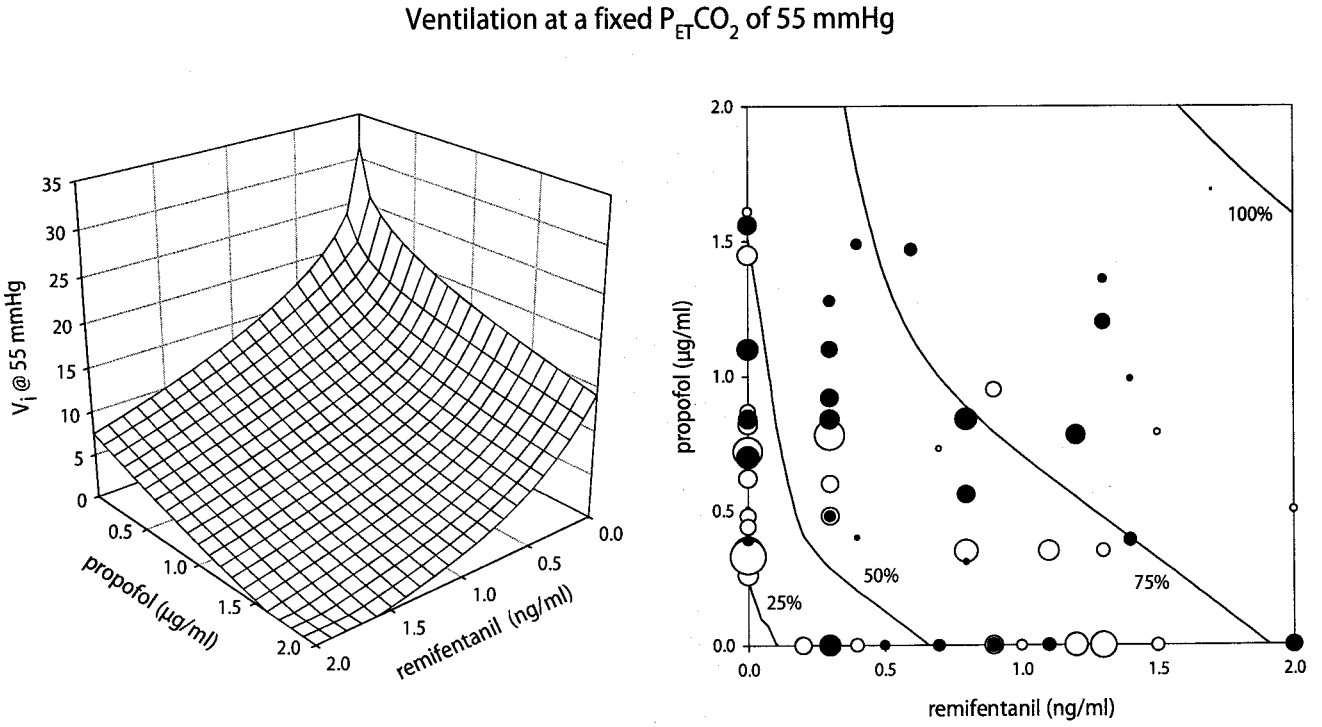

Fig. 5. Response surface modeling of the interaction of remifentanil and propofol on ventilation at a fixed P_{ETCO_2} of 55 mmHg. (*Left*) Population response surface showing that the propofol–remifentanil interaction is synergistic (I(max) = 1.2 ± 0.1). The dose-response relationships between drugs and effect was not linear (for both drugs $\gamma = 0.4 \pm 0.1$). The model predicted apnea to occur at several combinations of propofol and remifentanil, for example, 1.6 ng/ml remifentanil and 2.0 µg/ml propofol or 2.0 ng/ml remifentanil and 1.6 µg/ml propofol. (*Right*) Individual data points and 25, 50, 75 and 100% isoboles. Open circles denote data point above the surface, closed circles denote data points below the surface. The area of the circles is proportional to the distance from that data point to the surface.

ical in nature, resting $\dot{V}_i$ and resting P_{ETCO_2} have both behavioral and chemical components. Attempts have been made to combine all of these 4 variables into a single model.[18] We refrained from such an approach for the obvious reason that blind grouping of data obtained during CO_2 inhalation and resting variables has little physiologic meaning for the above mentioned reasons. Consequently, C_{50}s and time constants may differ for data obtained without and with increased inspired CO_2. We do believe, however, that grouping resting P_{ETCO_2} and resting $\dot{V}_i$ into a single model has obvious advantages. Such a model should be able to predict apnea at some finite opioid concentration and should possibly be independent of inspired CO_2 $\dot{V}_i$-response data. The proposed (sigmoid E_{max}) indirect response model lacks both characteristics.[18] Incorporation of our asymmetric sigmoid function will allow the modeling of apnea. Further -simulation and experimental- studies are needed to explore this matter.

With respect to chemical control of breathing, we tested two agents with distinct respiratory properties and mechanisms of action. The opioid remifentanil caused a parallel shift of the $\dot{V}_i$-CO_2 response towards higher P_{CO_2} values with little effect on the slope (fig. 2). However, the anesthetic/sedative propofol caused a reduction of the slope of the $\dot{V}_i$-CO_2 response curve (S) with little to no effect on the position of the curve at resting P_{ETCO_2} values (fig. 2). We consider the parallel shift of the $\dot{V}_i$-CO_2 response curve a typical µ-opioid effect, and the reduction of the slope a typical effect of a hypnotic/sedative. Previously, we observed large differences in the effect of intravenous morphine on the slope of the $\dot{V}_i$-CO_2 response in men and women,[22,23] with no effect of morphine on the slope in men but a large reduction in women. Taken into account the above, it would be appropriate to suggest that in our previous studies morphine produced greater sedation in women than in men and consequently greater effects on S in women. Indeed, in a recent study in which we assessed the effect of morphine's active metabolite, morphine-6-glucuronide (M6G), on the level of sedation using a numerical rating score, we found greater sedation in women than men while plasma M6G concentrations were equal (R.R. Romberg, B.Sc., A. Dahan, M.D., Ph.D., unpublished observation, January 2002–January 2003). Note however, that our suggestions do not exclude more fundamental sex differences in CNS responses to opioids, such as sex differences in µ-opioid receptor density and affinity in regions involved in ventilatory control and pain response.[24]

In agreement with our previous study,[6] the magnitude of synergy was greatest for resting ventilation. The ob-

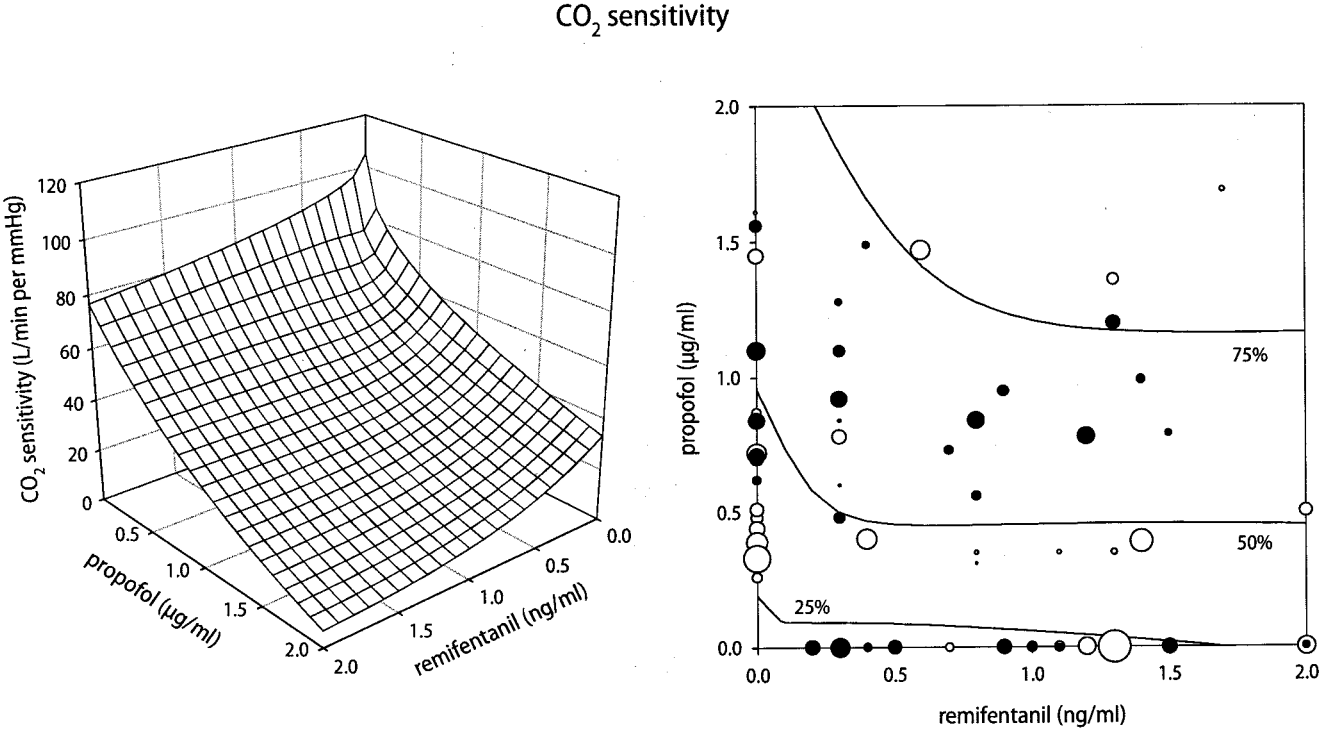

Fig. 6. Response surface modeling of the interaction of remifentanil and propofol on the slope of the ventilatory response to carbon dioxide or CO_2 sensitivity. (*Left*) Population response surface showing that the propofol–remifentanil interaction is synergistic (I(max) = 1.3 ± 0.1). The dose-response relationships between drugs and effect was not linear (for both drugs γ = 0.4 ± 0.1). Note that the effect on slope was predominantly a propofol effect and to a lesser extend a remifentanil effect. (*Right*) Individual data points and 25, 50 and 75% isoboles. Open circles denote data point above the surface, closed circles denote data points below the surface. The area of the circles is proportional to the distance from that data point to the surface.

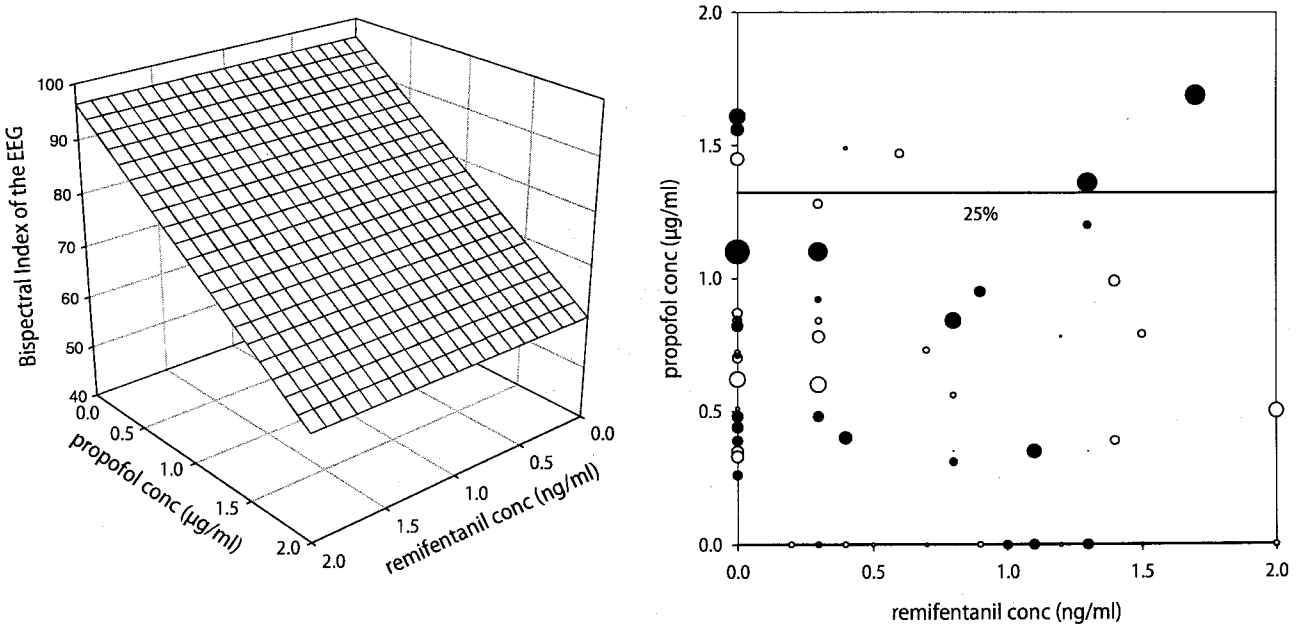

Fig. 7. Response surface modeling of the interaction of remifentanil and propofol on the bispectral index of the electroencephalogram (BIS). (*Left*) Population response surface showing that the propofol–remifentanil interaction is inert since remifentanil had no effect on bispectral index irrespective of the propofol concentrations. Over this dose range, propofol causes a linear decrease in bispectral index with a 25% decrease occurring at 1.4 µg/ml. (*Right*) Individual data points and 25,% isobole. Open circles denote data point above the surface, closed circles denote data points below the surface. The area of the circles is proportional to the distance from that data point to the surface.

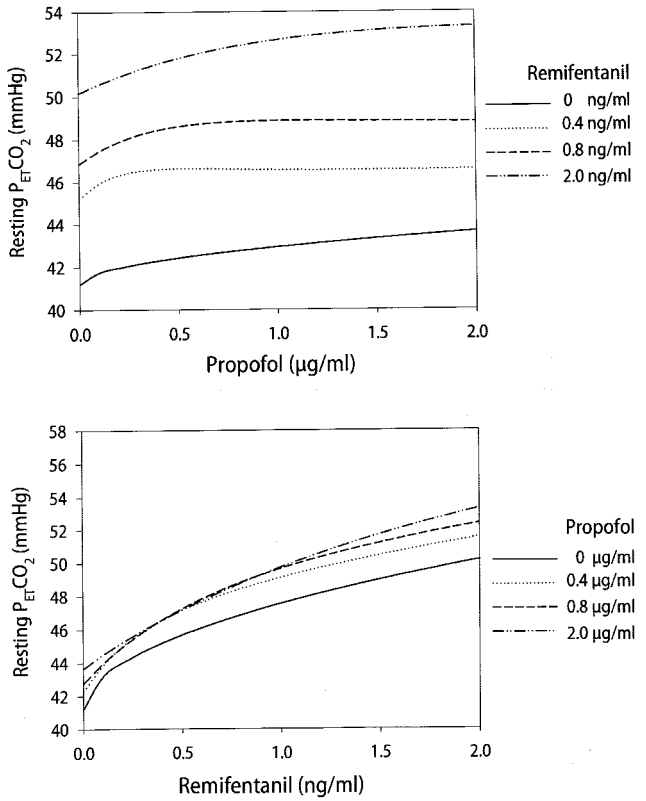

Fig. 8. (*Top*) The influence of the steady-state or effect-site propofol concentration on resting P_{ETCO_2} at various constant remifentanil concentrations. (*Bottom*) The influence of the steady-state or effect-site remifentanil concentration on resting P_{ETCO_2} at various constant propofol concentrations. Changing remifentanil concentrations causes marked reductions in resting end-tidal P_{CO_2}, irrespective of the propofol concentration, while changes in propofol concentrations have less of an effect on resting P_{ETCO_2}, irrespective of the remifentanil concentrations.

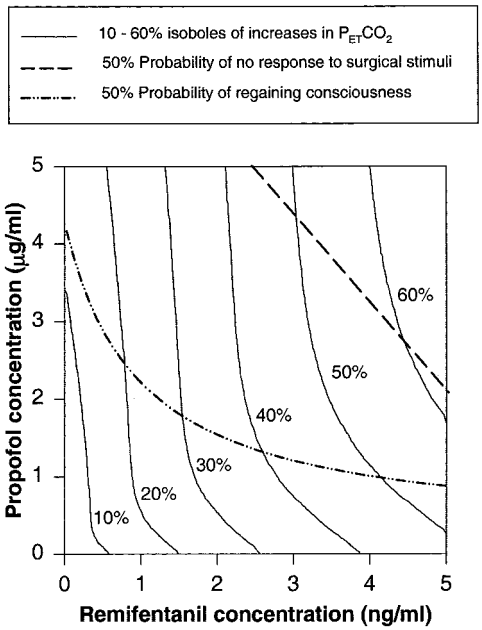

Fig. 9. Comparison of isoboles of respiratory depression (10–60% isoboles for increases in P_{ETCO_2}, data from this study), consciousness and adequate anesthesia (50% probability lines for consciousness and adequate anesthesia in patients undergoing abdominal surgery.

served differences in synergy strength (table 2) may be related to the observation that (in)activation of behavioral control does not have a large effect on the chemoreflexes but does increase resting ventilation by a chemoreflex-independent tonic drive.[25] The effect of propofol and remifentanil on resting ventilation has a behavioral component (the patients falls "asleep") and a chemical component (the direct effect of propofol and remifentanil on carotid bodies and respiratory neurons in the CNS) which leads consequently into a maximal synergistic interaction; the effect of both drugs on CO_2-driven ventilation has much less of a behavioral component and is predominantly chemoreceptor-related, and consequently results in less synergistic interaction. The interactions described here are clinically important since they show marked synergistic interactions on resting ventilation and to a lesser extent on resting CO_2 at low drug concentrations.

Parameter Values

The effects of 1 ng/ml remifentanil and 1 μg/ml propofol on resting $\dot{V}_i$ were considerably less than their effect on $\dot{V}_{55}$ (the ratio of λs is 0.5 for remifentanil and 0.3 for propofol). This is not surprising taking into account the fact that, while resting $\dot{V}_i$ is measured in closed-loop conditions and part of the respiratory depression is offset by the gradual increase in resting P_{ETCO_2}, $\dot{V}_{55}$ is measured in open-loop conditions and the pharmacokinetics and pharmacodynamic of CO_2 (and the effect the tested drugs have on CO_2 pharmacokinetics/pharmacodynamics) have been effectively removed.

The extrapolated C_{50} values from this study correspond well with studies from the literature. For example, the remifentanil C_{50} of $\dot{V}_i$ at an increased and fixed P_{ETCO_2} obtained from a single bolus of 0.5 μg/kg was of the same order of magnitude as our observation (1.1 ng/ml *vs.* 0.7 ng/ml in this study, table 2).[26] Note that, in this latter study, remifentanil concentrations were not measured but obtained from the literature. These C_{50} values are a factor of 10 smaller than those observed for changes in spectral edge frequency of the electroencephalogram,[12] and 4 to 5 times smaller than those observed for 50% probability of adequate anesthesia during abdominal surgery (in combination with 66% nitrous oxide).[27] These findings indicate the higher opioid sensitivity of CNS sites involved in ventilatory control compared to sites involved in behavioral state control and suppression of somatic and autonomic responses. Remifentanil is about 80–100 times more potent than alfentanil in depressing $\dot{V}_{55}$.[6,26] At present we are unaware of any previous respiratory pharmacokinetic or pharmacodynamic data for propofol.

Clinical Considerations

It is difficult to extrapolate the response surfaces to the clinical situation. Propofol and remifentanil are mostly given at a constant rate (resulting in constant plasma levels) with one of the drugs adjusted up as needed for additional analgesia/sedation or down if less respiratory depression is important. Therefore, we calculated the effect of changes in infusion rate (and hence changes in plasma concentration) on changes in resting P_{ETCO_2} (the more easily clinically monitored variable) for propofol at constant remifentanil concentration (fig. 8, top) and remifentanil at constant propofol concentration (fig. 8, bottom). The nonlinear shape of the resting P_{ETCO_2} response surface results in marked differences between these two figures: (1) increasing propofol has little effect on resting P_{ETCO_2} but adding remifentanil however has a marked -synergistic- effect (fig. 8, top); (2) increasing remifentanil increases P_{ETCO_2} regularly with only some potentiation by the addition of propofol (fig. 8, bottom). These graphs indicate that it is safer to titrate the propofol dose with a constant remifentanil background if more or less sedation is needed, but if less respiratory depression is required, then the remifentanil would need to be reduced.

The above applies best to patients who maintain their breathing during anesthesia. In order to extrapolate our findings to postoperative patients, in figure 9, we plotted the 10–60% isoboles of increasing resting P_{ETCO_2} with the isobole for 50% probability of regaining consciousness after general anesthesia for abdominal surgery (and the isobole for 50% probability of no somatic/autonomic response to surgical stimuli). (Data from Martijn Mertens, Ph.D. thesis, Leiden University, 2002.) The plot shows (1) the synergistic interaction between propofol and remifentanil on the 50% probability to "wake-up" after anesthesia (and thus shows in contrast to the bispectral index data (fig. 7) the sedative/hypnotic effect of remifentanil); (2) whether consciousness has been regained or not, ventilation improves best by reducing the remifentanil concentration (*i.e.*, the return of the wakefulness drive is of limited importance at least when the subject is not stimulated or reminded to breathe); (3) without the addition of propofol, remifentanil concentrations up to 2 ng/ml cause only limited respiratory depression and may be applied for postoperative pain relief.

Since, in our study, ventilation and plasma drug levels were at steady state when data points were obtained, we did not get information about the time-course of respiratory effects. Furthermore, especially for rapidly acting drugs, such as remifentanil and propofol, the degree of nonsteady-state respiratory depression may be dependent on the rate of drug infusion. Further studies are needed to study ventilatory dynamics caused by different infusion schemes of opioids and anesthetics.

In conclusion, we observed dose-dependent respiratory depression from propofol and remifentanil. When combined, the respiratory effects were strikingly synergistic with clinically important respiratory depression at already low doses.

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