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Response surface modelling of the pharmacodynamic interaction between propofol and remifentanil in patients undergoing anaesthesia

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Summary

This study describes the pharmacodynamic interaction between propofol and remifentanil. Sixty patients who were scheduled for elective surgery under general anaesthesia (30 males/30 females) were enrolled. Patients were randomly allocated to receive one of 15 combinations of drug levels. Baseline electroencephalograms (EEGs) were recorded for 5 minutes prior to administering the drugs. Patients received a target-controlled infusion at one of four predefined doses of propofol (high, 3 μg/mL; medium, 1.5 μg/mL; low, 0.5 μg/mL; or no drug) and of remifentanil (high, 6 or 8 ng/mL; medium, 4 ng/mL; low, 2 ng/mL; or no drug). The occurrence of muscle rigidity, apnoea, and loss of consciousness (LOC) was monitored, and EEGs were recorded during the drug administration phase. Electroencephalographic approximate entropy (ApEn) and temporal linear mode complexity (TLMC) parameters at baseline and under steady state conditions were calculated off-line. Response surfaces were developed to map the interaction between propofol and remifentanil to the probability of occurrence for quantal responses (muscle rigidity, apnoea, LOC) and ApEn and TLMC measurements. Model parameters were estimated using non-linear mixed effects modelling. The response surface revealed infra-additive and synergistic effects for muscle rigidity and apnoea, respectively. The effects of the combined drugs on LOC and EEG parameters (eg, ApEn and TLMC) were additive. The C_{50} estimates of remifentanil (ng/mL) and propofol (μg/mL) were 9.11 and 130 000 for muscle rigidity, 8.99 and 6.26 for apnoea, 13.9 and 3.04 for LOC, 23.4 and 10.4 for ApEn, and 14.8 and 6.51 for TLMC, respectively. The probability of occurrence for muscle rigidity declined when propofol was combined with remifentanil.

KEYWORDS
interaction, propofol, remifentanil

1 | INTRODUCTION

Propofol and remifentanil are a popular combination of hypnotic and analgesic agents used for total intravenous anaesthesia. The rapid intravenous administration of a high dose of remifentanil during the induction of anaesthesia may cause severe rigidity of the thoracic and abdominal muscles, making spontaneous ventilation extremely difficult.[1,2] The incidence of opioid-induced rigidity is related to drug dose and the rate of administration.[3] However,

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the exact mechanism underlying this effect remains unknown.[3,4] Opioid-induced rigidity involves the activation of spinal motoneurons, which is mediated by diverse mechanisms, including the cerulospinal noradrenergic mechanism, cerulospinal glutamatergic pathway and *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors in the spinal cord.[5] Similarly, several receptors and structures in the central nervous system, such as gamma-aminobutyearsic acid receptors (activation) and NMDA receptors (inhibition),[6] play important roles in the diverse effects of propofol. For example, propofol can be used to treat opioid-induced pruritus, possibly via the suppression of spinal neural structures.[7] Opioid-induced muscle rigidity can be prevented by pretreatment with sedatives and hypnotics, including propofol.[8-10] Therefore, we postulated that propofol attenuates opioid-induced rigidity via one or more spinal or supra-spinal mechanisms.

Propofol and remifentanil may produce apnoea. However, to the best of our knowledge, no information is available on the pharmacodynamic interactions between these drugs in relation to apnoea or muscle rigidity. Extensive studies on the pharmacodynamic interactions between propofol and remifentanil in relation to the level of consciousness, bispectral index (BIS) and electroencephalographic approximate entropy (ApEn) have been performed.[11-13] However, the BIS is insensitive to clinically relevant opioid concentrations[11,14,15], and ApEn is heavily dependent on the length of the recording.[16] Temporal linear mode complexity (TLMC) measures the complexity of the temporal linear mode in a single-channel electroencephalogram (EEG) irrespective of the length of the recording.[17] The appropriateness of TLMC as a surrogate measure of the effects of remifentanil and sevoflurane on the central nervous system was evaluated in our preliminary studies.[17,18] However, little is known about the usefulness of TLMC for quantifying the effect of propofol and remifentanil on the central nervous system.

This study constructed response surfaces for the probability of occurrence for muscle rigidity, apnoea and loss of consciousness (LOC) and compared the response surface parameters for ApEn and TLMC across clinically relevant concentrations of propofol and remifentanil administered to surgical patients.

2 | RESULTS

Dangerous haemodynamic instabilities, including bradycardia and hypotension, occurred at the highest target concentration of remifentanil despite the repeated administration of atropine and/or ephedrine. Propofol and/or remifentanil concentrations were maintained for at least 15 minutes after reaching pseudo-steady states in the absence of other noxious or surgical stimuli. Therefore, the high remifentanil concentration of 8 ng/mL administered to some patients was reduced to 6 ng/mL, and 19 drug level combinations were studied (Table 1). The mean (range) age, weight, and height of patients were 50 years (21-69 years), 60 kg (41.6-85.4 kg), and 162.5 cm (144.5-187.2 cm), respectively.

TABLE 1 Combinations of the effect-site concentrations of propofol and remifentanil, and patient allocation

		Number of patients	
Propofol μg/mL)	Remifentanil (ng/mL)	Male (n=30)	Female (n=30)
0 (n=12)	2	2	2
	4	2	2
	6	1	2
	8	1	-
0.5 (n=16)	0	2	2
	2	2	2
	4	2	2
	6	1	2
	8	-	1
1.5 (n=16)	0	2	2
	2	2	2
	4	2	2
	6	2	1
	8	-	1
3 (n=16)	0	2	2
	2	2	2
	4	2	2
	6	2	1
	8	-	1

2.1 | Rigidity and apnoea

Muscle rigidity occurred in five patients who received higher concentrations of remifentanil in combination with lower concentrations of propofol (Figure 1A). Muscle rigidity did not occur in patients administered propofol at the effect-site concentration of 3 μg/mL, irrespective of the target remifentanil concentration. The ratio of $C_{50,propofol}$ and the interaction term for hybrid potency (A, $Interaction_{potency}$) was estimated to be −25.8 in the interaction model for muscle rigidity. Therefore, $Interaction_{potency}$ (A) can be expressed as follows:

$$A = -\frac{C_{50,propofol}}{25.8}$$

By definition, U_{50} and Q are expressed as follows:

$$U_{50} = 1 - A \cdot Q + A \cdot Q^2$$

$$Q = \frac{U_P}{U_P + U_R}$$

Therefore, substituting A with $-\frac{C_{50,propofol}}{25.8}$ gives the following equation for U_{50}:

$$U_{50} = 1 + \frac{C_{50,propofol}}{25.8}\left(\frac{U_P}{U_P + U_R}\right) - \frac{C_{50,propofol}}{25.8}\left(\frac{U_P}{U_P + U_R}\right)^2$$
$$= 1 + \frac{C_{50,propofol}}{25.8}\left(\frac{\frac{PROP}{C_{50,propofol}}}{\frac{PROP}{C_{50,propofol}} + \frac{REMI}{C_{50,remifentanil}}}\right) - \frac{C_{50,propofol}}{25.8}\left(\frac{\frac{PROP}{C_{50,propofol}}}{\frac{PROP}{C_{50,propofol}} + \frac{REMI}{C_{50,remifentanil}}}\right)^2$$
$$= 1 + \frac{1}{25.8}\left(\frac{1}{\frac{1}{C_{50,propofol}} + \frac{REMI}{C_{50,remifentanil} \cdot PROP}}\right) - \frac{1}{25.8}\left(\frac{\frac{PROP}{C_{50,propofol}}}{\frac{1}{C_{50,propofol}^2} + \frac{REMI^2}{PROP \cdot C_{50,remifentanil}^2} + 2\frac{REMI}{C_{50,propofol} \cdot C_{50,remifentanil}}}\right)$$

where U_{50} is the hybrid potency for remifentanil and propofol, and PROP and REMI are the effect-site concentrations of propofol and remifentanil, respectively. Assuming that $C_{50,propofol}$ is very large and $\frac{1}{C_{50,propofol}}$ approaches zero, U_{50} can be calculated as follows:

$$U_{50} = 1 + \frac{1}{25.8}\left(\frac{1}{\frac{REMI}{C_{50,remifentanil} \cdot PROP}}\right) - \frac{1}{25.8}\left(\frac{\frac{PROP}{C_{50,propofol}}}{\frac{REMI^2}{PROP \cdot C_{50,remifentanil}^2} + 2\frac{REMI}{C_{50,propofol} \cdot C_{50,remifentanil}}}\right) \quad (1)$$
$$= 1 + \frac{1}{25.8} \cdot \frac{PROP \cdot C_{50,remifentanil}}{REMI} - \frac{1}{25.8}\left(\frac{PROP^2 \cdot C_{50,remifentanil}^2}{REMI^2 \cdot C_{50,propofol} + 2 \cdot PROP \cdot REMI \cdot C_{50,remifentanil}}\right)$$
$$= 1 + \frac{1}{25.8} \cdot \frac{PROP \cdot C_{50,remifentanil}}{REMI}$$

Therefore, the U_{50} for muscle rigidity is independent of $C_{50,propofol}$ and is a function of the effect-site concentrations of propofol and remifentanil, and $C_{50,remifentanil}$.

The observed occurrence of apnoea is shown in Figure 1B. Apnoea was induced by remifentanil as doses of 6 ng/mL or higher in combination with lower concentrations of propofol (0 and 0.5 μg/mL). Propofol administered without remifentanil did not induce apnoea, but remifentanil administered without propofol induced apnoea in one patient. The effect-site concentrations of propofol and remifentanil were significant factors for the probability of occurrence for apnoea in logistic regression analyses (P=.01 for remifentanil and P < .001 for propofol).

Table 2 summarizes the estimated pharmacodynamic parameters for the probability of the occurrence of muscle rigidity and apnoea. The inclusion of separate steepness parameters for propofol and remifentanil did not reveal significant improvements in either model.

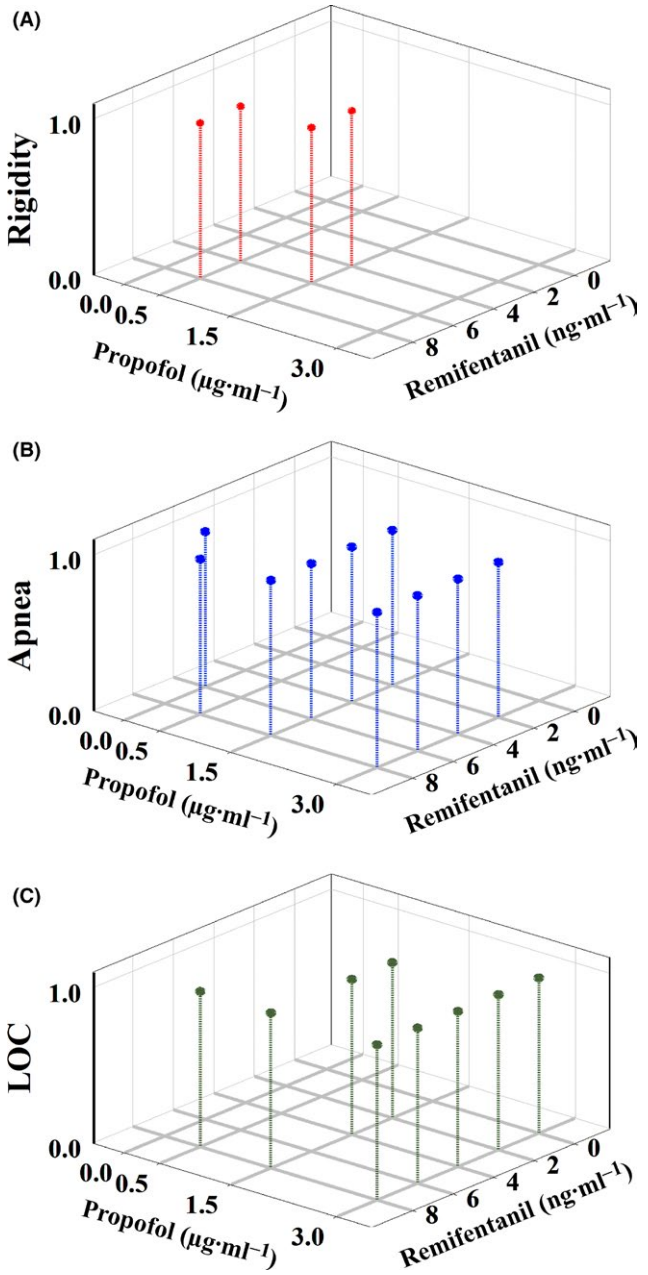

FIGURE 1 Observed occurrence of muscle rigidity (n=5, A), apnea (n=22, B) and loss of consciousness (LOC, n=16, C) in response to different combinations of the effect-site concentrations of propofol and remifentanil. 1: events occurred, 0: events did not occur

The hybrid steepness parameter γ(Q) in this model is approximated by the following equation:

$$\gamma(Q) = \gamma_R - (\gamma_P - \gamma_R - B) \cdot Q + B \cdot Q^2$$

where γ_R and γ_P are the steepness parameters of remifentanil and propofol, respectively, and B is an interaction term for the hybrid steepness parameter. Therefore, we determined a single steepness parameter for both models. Figure 2A and B shows the response surfaces for the probability of occurrence for muscle rigidity and apnoea, respectively. The response surface for muscle rigidity shows an infra-additive behaviour in which the probability of occurrence for rigidity

TABLE 2 Response surface parameters (relative standard error) on the probability of the occurrence of muscle rigidity, apnea and loss of consciousness (LOC)

	Rigidity	Apnea	LOC
$C_{50,propofol}$, μg/mL	130 000* (126.2)	6.26 (7.7)	3.04 (16.9)
$C_{50,remifentanil}$, ng/mL	9.11 (28.4)	8.99 (24.9)	13.9 (31.7)
γ	3.1 (41.9)	7.13 (27.3)	3.4 (27.5)
$Interaction_{potency}$	−5060* (16.2)	1.86 (22.7)	-

$C_{50,propofol}$, effect-site concentration of propofol associated with 50% probability of the occurrence of muscle rigidity, apnea and LOC; $C_{50,remifentanil}$, effect-site concentration of remifentanil associated with 50% probability of the occurrence of muscle rigidity, apnea and LOC; γ, slope of the combined normalized dose of propofol and remifentanil-probability of the occurrence of muscle rigidity, apnea and LOC curves; $Interaction_{potency}$ <0, infra-additive interaction, >0; synergistic interaction, (-), additive interaction between propofol and remifentnail. Naïve pooled data approach with first-order estimation method was used. Residual random variability was modeled using an additive error model. *Which suggest that propofol does not induce muscle rigidity.

decreases with an increase in the effect-site propofol concentration. Figure 3A and B show the hybrid potencies for muscle rigidity and apnoea, respectively. The hybrid potency for muscle rigidity increased with increasing effect-site concentrations of propofol for combinations of clinically relevant effect-site concentrations of propofol and remifentanil. The U_{50} for apnoea exhibited a synergistic feature as demonstrated by the fact that the Q value of 0.5 produced the largest decrease in U_{50}.

2.2 | LOC

Figure 1C shows the occurrence of LOC. The effect-site concentrations of propofol and remifentanil were found to be significant factors related to the probability of occurrence for LOC in logistic regression analyses (P=.01 for remifentanil and P < .001 for propofol). Table 2 summarizes the estimated pharmacodynamic parameters for the probability of occurrence for LOC. The interactive effect of propofol and remifentanil on the probability of occurrence for LOC did not exhibit significant synergy. Only a single steepness parameter was estimated for propofol and remifentanil because the model was not significantly improved by estimating separate steepness parameters.

Figure 2C shows the response surfaces for the probability of occurrence for LOC. The U_{50} for LOC remained constant at 1 (Figure 3), and propofol did not interact with remifentanil in relation to the probability of occurrence for LOC.

2.3 | ApEn and TLMC

Figure 4 shows the observed ApEn and TLMC results relative to the different combinations of effect-site concentrations of propofol and remifentanil. Both drugs reduced the complexity and entropy parameters of the electroencephalographic signals to a similar extent. The stability of the baseline TLMC values was slightly better than that of the baseline ApEn values. The fractional decrease from baseline to the minimum TLMC values was also slightly larger and more stable than that of the ApEn values. However, the ApEn values at LOC were more stable than the TLMC values (Table 3). The usefulness of TLMC was comparable to that of ApEn as a surrogate measure for quantifying the effect of propofol and remifentanil on the central nervous system. Table 4 shows the parameters of the response surface models relating the effects of propofol and remifentanil to the ApEn and TLMC values. The interactive effect of propofol and remifentanil on both electroencephalographic measures of the drugs' effects was additive. The relative standard errors for the pharmacodynamic parameters were well below 50%, indicating that the parameters were determined with appropriate precision. Estimating separate steepness parameters for propofol and remifentanil failed to improve the model. TLMC and ApEn values that corresponded to the effect-site concentration of remifentanil that was associated with a 50% probability of the occurrence of muscle rigidity without the administration of propofol were 0.474 and 0.346, respectively. The median weighted residual and median absolute weighted residual were −0.03 (%) and 6.27 (%) for TLMC and 0.00 (%) and 5.07 (%) for ApEn, respectively. Figure 5 shows the response surfaces for ApEn and TLMC.

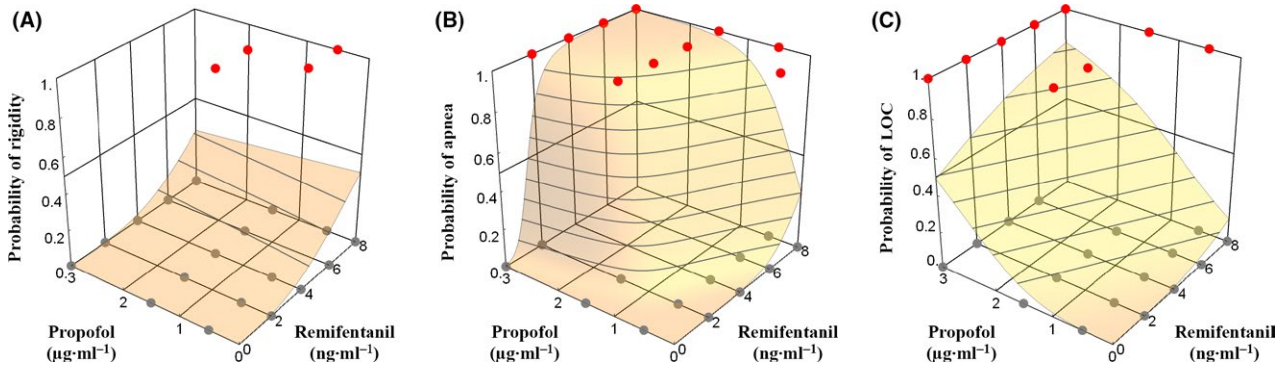

FIGURE 2 Response surfaces describing the interactive effect of propofol and remifentanil on the probability of the occurrence of muscle rigidity (A), apnea (B) and loss of consciousness (LOC, C) in response to different combinations of the effect-site concentrations of propofol and remifentanil (red circles indicate that events occurred, and gray circles indicate that events did not occur)

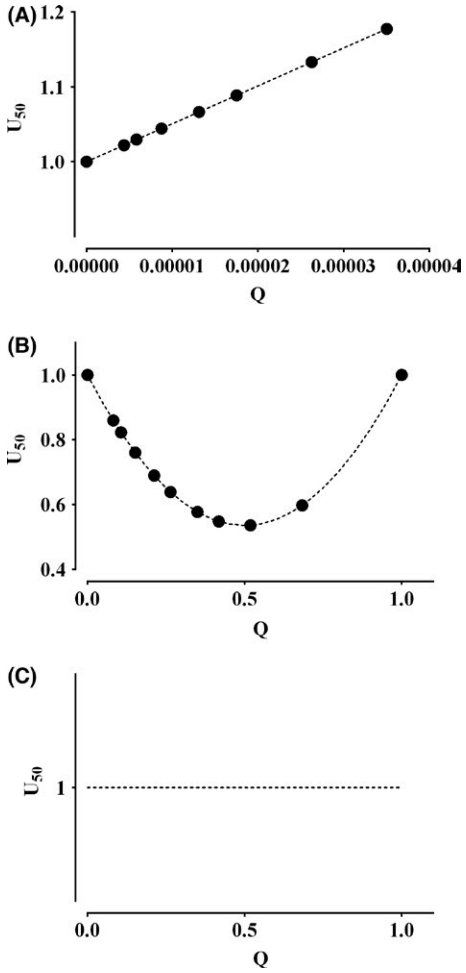

FIGURE 3 Interactions for the potency (U_{50}) of the combined normalized propofol and remifentanil dose-effects curve. A, muscle rigidity; B, apnea; C, loss of consciousness, electroencephalographic approximate entropy and temporal linear mode complexity. Solid circles in A and B: *Q* values calculated from the effect-site concentrations of combinations of propofol and remifentanil tested in this study. $Q = U_{propofol} / (U_{remifentanil} + U_{propofol})$, $U_{propofol\ or\ remifentanil}$ = [effect-site concentration of propofol or remifentanil]/[effect-site concentration associated with the 50% maximal propofol or remifentanil effect]

3 | DISCUSSION

This study constructed response surfaces for muscle rigidity, apnoea and LOC and compared the response surface parameters for ApEn and TLMC across clinically relevant combinations of effect-site concentrations of propofol and remifentanil in surgical patients. The major findings are outlined below:

1. The rapid administration of a high dose of remifentanil induces muscle rigidity, but propofol may reduce the chance of its occurrence. Propofol in combination with remifentanil reduces the probability of occurrence for muscle rigidity. The hybrid potency for the probability of occurrence for muscle rigidity was proportional to the propofol concentration and inversely proportional to the remifentanil concentration, as described by the following equations:

$$U_{50} = 1 + \frac{1}{25.8} \cdot \frac{\mathrm{PROP} \cdot C_{50,\mathrm{remifentanil}}}{\mathrm{REMI}}$$

where U_{50} is the hybrid potency for remifentanil and propofol, and PROP and REMI are the effect-site concentrations of propofol and remifentanil, respectively.
2. The interactive effect between propofol and remifentanil for apnoea was synergic.
3. The interactive effect between propofol and remifentanil for LOC was additive, as determined by patient responsiveness to verbal commands.
4. The interactive effects between propofol and remifentanil on ApEn and TLMC were additive.

This study modelled the pharmacodynamic interaction between propofol and remifentanil using the empirical response surface model described by Minto et al.[19] The model makes no assumptions about the mechanism underlying the interaction between propofol and remifentanil. However, Minto et al. assumed that the concentration-response relationship for each of the interacting drugs could be described using a direct pharmacodynamic model.[19] The pharmacodynamic interaction between the two drugs has been well described by the Minto model in several studies.[20-22] The Minto model is subject to interactive effects between propofol and remifentanil on muscle rigidity. A simple sigmoid model for the effects of remifentanil was also evaluated for its ability to predict the occurrence of muscle rigidity. However, this simple pharmacodynamic model did not perform better in estimating Ce_{50} (186-189 ng/mL). This estimated Ce_{50} value was unreasonable because it was approximately 10-15 times higher than the clinically relevant range. Therefore, it is unlikely that the simple sigmoid model for the effects of remifentanil is better than the interaction model in describing the probability of occurrence for muscle rigidity under conditions in which propofol and remifentanil are co-administered. The mechanism for how propofol decreases the probability of occurrence for muscle rigidity is not well understood, but it may be related to the inhibition of NMDA receptors, which are frequently involved in opioid-induced muscle rigidity and are related the effects of propofol. Further research is needed to fully ascertain the inhibitory mechanism of propofol on opioid-induced muscle rigidity. To the best of our knowledge, no studies have evaluated the probability of occurrence for muscle rigidity in relation to remifentanil concentrations. The effect-site concentration of remifentanil associated with a 50% probability of occurrence for muscle rigidity was 9.11 ng/mL, and the probability of occurrence for muscle rigidity declined when propofol was combined with remifentanil. These results provide information that clinicians can use in determining dosing strategies for the use of propofol and remifentanil to avoid the occurrence of muscle rigidity during the induction of anaesthesia. The relationship between muscle rigidity occurrence rates and the age or frailty of patients is not understood. Patient age and ASA PS (American Society of Anesthesiologists Physical Status) did not significantly differ between patients with and without muscle rigidity in this

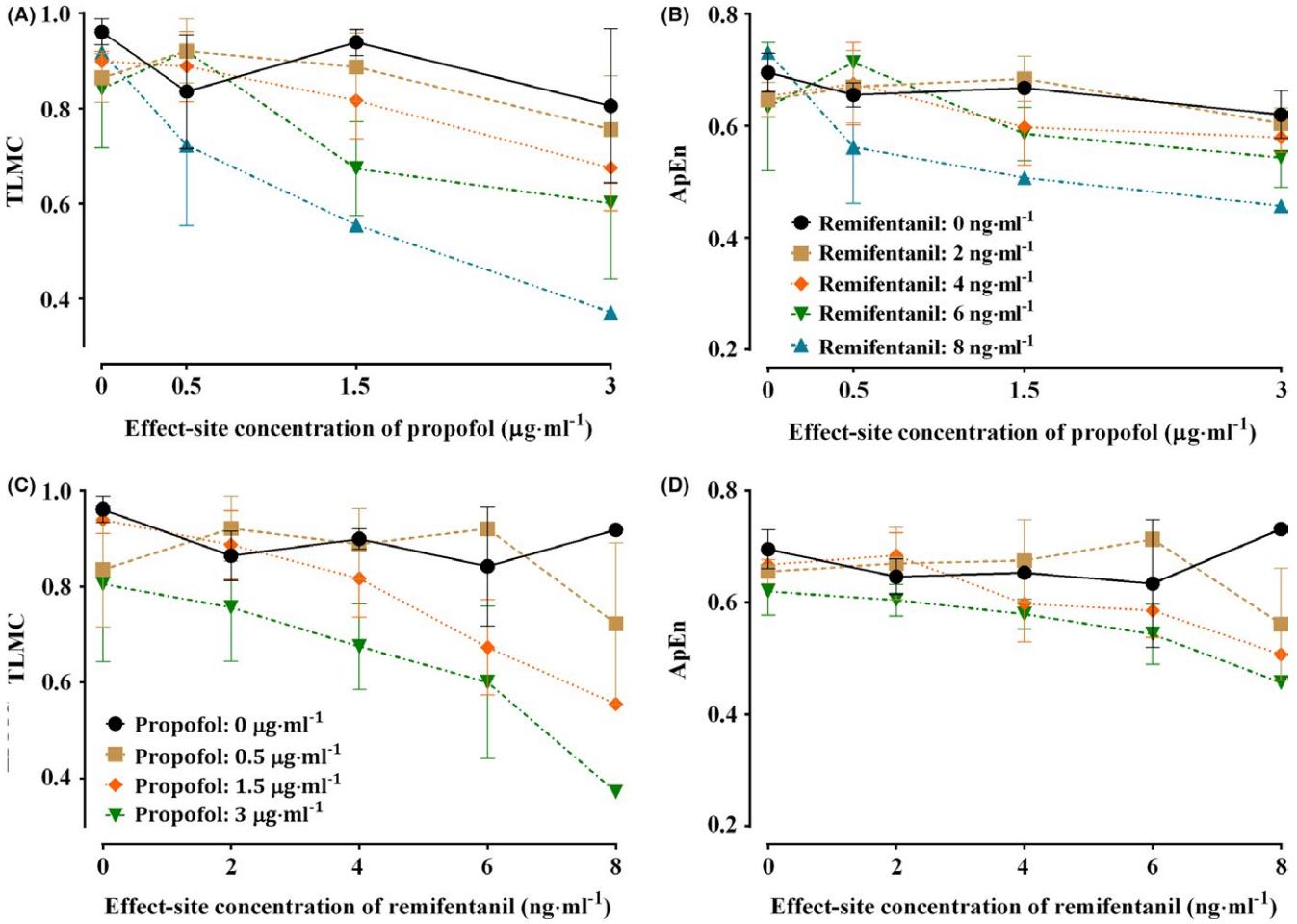

FIGURE 4 Observed electroencephalographic approximate entropy (ApEn) and temporal linear mode complexity (TLMC) values in response to combinations of the effect-site concentrations of propofol and remifentanil. Data are presented as the mean±SD

TABLE 3 Baseline values, fractional decreases from baseline to median maximal values and values at loss of consciousness (LOC) of temporal linear mode complexity (TLMC) and approximate entropy (ApEn)

	TLMC	ApEn
Baseline value (E_0)	0.96 ± 0.03 (2.84)	0.70 ± 0.03 (4.93)
Fractional decrease from baseline (%)	15.98 ± 9.80 (91.80)	14.67 ± 9.70 (99.90)
Values at LOC	0.68 ± 0.17 (25.08)	0.57 ± 0.07 (12.51)

Data are expressed as means±SD (CV%). CV, coefficient of variation = SD/mean × 100 (%).

study. Nieuwenhuijs et al. found dose-dependent effects on respiration at relatively low concentrations of propofol (0-2 μg/mL) and remifentanil (0-2 ng/mL), and the effect of their combination on respiration was found to be strikingly synergistic and to result in severe respiratory depression.[15] Therefore, the respiratory system was most severely depressed in a synergistic manner at clinically relevant concentrations of propofol and remifentanil when co-administered. The morphologic shape of the surface model for LOC revealed an interesting association between the probability of occurrence for LOC and the drug combinations administered. The surface was skewed toward the axis for analgesia, indicating that the occurrence of LOC has a greater component related to hypnosis than analgesia. This finding indicates that remifentanil, at clinically relevant concentrations, does not induce LOC, which is supported by our previous observation that the Ce_{50} of remifentanil for ApEn was 21.4 ng/mL in a 50-year-old volunteer.[23] The $C_{50,remifentanil}$ for ApEn found in a study by Bouillon et al. was 13.1 ng/mL.[11] Kern et al. evaluated the interaction between propofol and remifentanil on the sedative response, considered an event to have occurred if the subject's OAA/S (Observer Assessment of Alertness/Sedation) score was 1, 2, or 3, in which case the interaction was synergic for sedation.[24] This result is inconsistent with our LOC results, which revealed an additive interaction between the two agents. This discrepancy may be explained by differences in the target endpoint. The hypnotic state associated with an OAA/S score of 3 is much deeper than the state associated with patients that give no response to verbal command. Additionally, this discrepancy may have resulted from different predefined combinations of doses for the two drugs. Mertens et al. developed a response surface over a wider range of propofol and remifentanil concentrations and suggested a synergic interactive effect of these drugs on the return of consciousness.[25]

TABLE 4 Response surface parameters (relative standard error) with the results (median, 2.5-97.5 percentile) of 2000 replicates of nonparametric bootstrap for the interaction of propofol and remifentanil on electroencephalographic approximate entropy (ApEn) and temporal linear mode complexity (TLMC)

	ApEn	TLMC
E_0	0.691 (0.7), (0.69, 0.68-0.70)	0.948 (1.4), (0.949, 0.935-0.961)
$C_{50,propofol}$, μg/mL	10.4 (26), (10.4,7.2-18.8)	6.51 (5.5), (6.55, 5.29-9.74)
$C_{50,remifentanil}$, ng/mL	23.4 (23.5), (23.2, 15.9-29.8)	14.8 (5.7), (14.6, 11.5-23.9)
γ	1.93 (24.7), (1.97, 1.35-2.89)	2.54 (9.8), (2.57, 1.54-3.66)
$Interaction_{potency}$	-	-

ApEn, electroencephalographic approximate entropy; TLMC, electroencephalographic temporal linear mode complexity; E_0, baseline effect when no drug is present; $C_{50,propofol}$, effect-site concentration associated with 50% maximal propofol effect; $C_{50,remifentanil}$, effect-site concentration associated with 50% maximal remifentanil effect; γ, slope of the effect-site concentration of drug-effects curve; $\gamma_{remifentanil}$, slope of the effect-site concentration of remifentanil-effects curve. $Interaction_{potency}$ (-), additive interaction between propofol and remifentanil. Naïve pooled data approach with first-order estimation method was used. Residual random variability was modeled using an additive error model.

The range of concentrations for the combined doses of propofol and remifentanil that are assessed is highly important and should be adjusted in relation to the endpoints that are being explored for the interaction between these agents. Furthermore, the interaction behaviours, such as synergy, additivity or infra-additivity, may primarily depend on the range of doses when these drugs are co-administered. Several well-designed studies on the pharmacodynamic interactions between propofol and remifentanil have been performed. Response surfaces constructed over wider ranges of propofol (up to 12 μg/mL) and remifentanil (up to 80 ng/mL) concentrations exhibited considerable synergy for blunting the responses to noxious stimuli and sedation.[11,24] Bouillon et al. observed that the synergistic interactive effect of propofol and remifentanil on the depth of consciousness as determined by the patient's response to shouting and shaking was substantial only up to remifentanil concentrations of 4 ng/mL. The remifentanil concentrations used in this study were up to 8 ng/mL, and the observed additive behaviours in relation to LOC may have been due to the lower maximum concentrations of propofol applied.[25] The TLMC and ApEn values were observed within a relatively narrow range in this study compared with the values from previous studies,[17,23] and these limited data may be insufficient to develop an adequate surface model. However, the additive interactions demonstrated by the processed electroencephalographic parameters were consistent with the results of an earlier study.[11] Some reports have demonstrated synergistic interactive effects for propofol and remifentanil on BIS,[26-28] but significant changes in EEGs induced by opioids generally occur at higher opioid concentrations than those used in practice. The effect-site concentrations of remifentanil administered alone associated with a half-maximal effect for ApEn have been shown to be approximately 20 ng/mL or higher,[23] which is similar to the results of the present study. Therefore, remifentanil had little effect on the two electroencephalographic parameters assessed in this study. These different interactive behaviours in relation to LOC and processed electroencephalographic parameters may be explained by the fact that LOC is a quantal and precipitous response and the depression of processed electroencephalographic parameters is a gradual response.

There are several limitations of this study that should be considered. First, the predefined propofol effect-site concentrations (*Ce*) in this study did not cover the entire therapeutic range that is used for general anaesthesia. The target range for propofol was 0-12 μg/mL in previous studies of response surface models.[11,24] However, the range of propofol concentration in this study was determined based on several clinical factors. The mean (SD) effect-site concentration associated with a 95% probability of occurrence for a LOC was 2.22 (0.44) μg/mL for the long-chain triglyceride propofol (Diprivan; AstraZeneca, London, United Kingdom),[29] and we titrated the target *Ce* values of propofol within a range of 2.5-3 μg/mL during the maintenance of general anaesthesia based on these findings. We performed deterministic simulations using Asan Pump software to calculate the total amount and infusion rate of propofol 15 minutes after target *Ce*-controlled infusions of 4, 5, and 6 μg/mL in a hypothetical subject weighing 65 kg using the modified Marsh model,[30,31] and the infusion rates at each target *Ce* were 11.4, 14.2, 17.1 mg/kg/h, respectively. Infusion rates of propofol during the maintenance of general anaesthesia range from 6 to 12 mg/kg/h.[32] The full therapeutic range of propofol concentrations was not covered in this study, but our findings are applicable to the range of propofol concentrations that are used in clinical situations. Second, the occurrence rate of muscle rigidity was low because of the relatively low concentration of remifentanil, and five data points may be insufficient to develop a robust surface model. Increasing remifentanil concentrations above 8 ng/mL dramatically increases the occurrence rate of rigidity, and there is a possibility that some patients may be awake and unable to move or breathe spontaneously. Therefore, administering higher doses of remifentanil may be unethical. The occurrence rate of muscle rigidity was low in our study, and we constructed response surface models in haemodynamically stabilized patients.

In conclusion, consciousness levels may be depressed in an additive manner at clinically relevant concentrations of propofol and remifentanil when co-administered, and apnoea may be induced in a synergistic manner. Finally, propofol may reduce the occurrence of muscle rigidity caused by the rapid administration of a high dose of remifentanil.

4 | METHODS

4.1 | Patients

The Asan Medical Center Institutional Review Board approved the study protocol (approval number: 2012–0184), which was registered at an international clinical trials registry platform (http://cris.

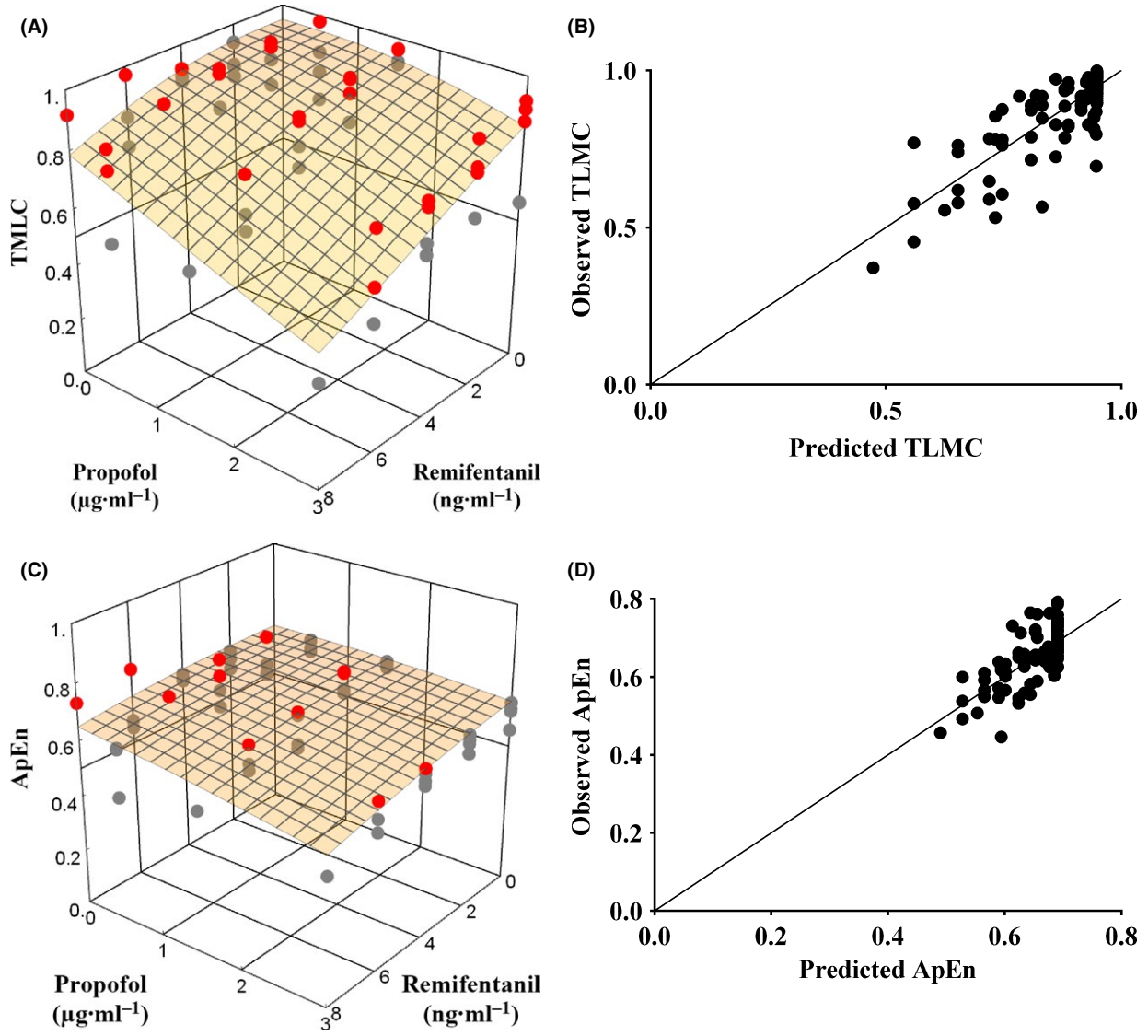

FIGURE 5 Response surface describing the interactive effect of propofol and remifentanil on electroencephalographic temporal linear mode complexity (TLMC, A) and approximate entropy (ApEn, C) in response to different combinations of the effect-site concentrations of propofol and remifentanil. Red circles represent observed values above the surface and gray circles represent observed values below the surface. Predicted TLMC (B) and ApEn (D) values plotted against individually observed values. Solid lines represent the line of identity

nih.go.kr, KCT0001776). Written informed consent was obtained from all patients. Sixty patients (30 males and 30 females) who were considered to have ASA PS (American Society of Anesthesiologists Physical Status) grades of 1 or 2 and were scheduled for elective surgery under general anaesthesia were randomly allocated to one of the 15 predetermined combinations of drug levels. Each predetermined combination of drugs was administered to two male and two female patients. All patients were informed of the procedure and agreed that they may be awake and unable to move or breathe spontaneously for a brief period of time. Patients were excluded from the study if they had a known allergy to propofol (Diprivan; AstraZeneca), abnormal and clinically significant laboratory findings, a history of habitual psychoactive drug use, smoking, ischaemic heart disease or neurological disorders, or any evidence of being pregnant.

4.2 | Study design and drug administration

Patients received a target effect-site concentration controlled infusion at one of four predefined doses of propofol (high, 3 μg/mL; medium, 1.5 μg/mL; low, 0.5 μg/mL; or no drug) and of remifentanil (high, 6 or 8 ng/mL; medium, 4 ng/mL; low, 2 ng/mL; or no drug). Drugs were administered via a Pilot anaesthesia pump 2 (Master TCI; Fresenius Vial S.A., Brezins, France) driven by an Asan Pump (version 2.1; Bionet Co. Ltd., Seoul, Korea) running on a commercially available personal computer. The Asan Pump was programmed with the propofol pharmacokinetic parameters reported by Marsh et al.,[31] in which the k_{e0} value was adjusted using the t_{peak} method,[33] and the remifentanil pharmacokinetic parameters reported by Minto et al.[34] All patients had fasted from the previous midnight. Premedications were omitted to avoid effects on the EEG. An

18-gauge angiocatheter was placed in a vein of the volar surface of the forearm. All patients received oxygen via a nasal cannula at a flow rate of 2 L/min in the operating room and were monitored using electroencephalography (WEEG32; Laxtha, Daejeon, Korea), electrocardiography, pulse oximetry, end-tidal carbon dioxide partial pressure measurements, non-invasive blood pressure measurements (Datex-Ohmeda S/5; Planar Systems, Inc., Beaverton, OR, USA) and BIS monitors (Aspect 2000; Aspect Medical Systems, Inc., Newton, MA, USA). These data, except BIS data, were continuously downloaded to personal computers using RS232C cables until the end of the study. Baseline EEGs were acquired for 5 minutes, and then each patient received propofol and remifentanil. Target effect-site concentrations of propofol and remifentanil were increased by 0.5 μg/mL and 1 ng/mL, respectively, every 1 minute. The predefined levels of both drugs were maintained for at least 15 minutes after reaching pseudo-steady states. The highest level of remifentanil was set to 8 ng/mL as long as systolic blood pressure and heart rate were maintained at >80 mmHg and >45 b.p.m., respectively, during stepwise increases in the target concentrations of the drugs. The target concentration of remifentanil was decreased to 6 ng/mL if hemodynamic stability was not maintained with intravenous administrations of ephedrine (5 mg) and/or atropine (0.5 mg). All measurements and assessments were performed after a new pseudo-steady state for remifentanil was achieved. Ephedrine or atropine was administered to maintain systolic blood pressure at > 80 mmHg and heart rate at >45 b.p.m. for other combinations of drug doses without changing the predetermined doses of both drugs.

Respiratory parameters, including end-tidal carbon dioxide partial pressure and tidal volume, were monitored through a tight-fitting face mask (Vital Signs, Totowa, NJ, USA) during the administration of propofol and/or remifentanil. If apnoea continued for longer than 10 seconds, the lungs were manually ventilated with 100% oxygen via the facemask to maintain an end-tidal carbon dioxide concentration of 35-45 mmHg. The study was discontinued immediately if muscle rigidity occurred or we were not able to ventilate the patient's lungs adequately because of difficult airway, and stepwise increases of 1 μg/mL in the target concentration of propofol, to induce a BIS <60, and an intravenous bolus injection of vecuronium (0.15 mg/kg) were administered to ensure adequate ventilation. Target concentrations of remifentanil were increased or decreased by 1-7 ng/mL. Once anaesthetized, the patient's trachea was intubated, and surgery commenced as scheduled.

4.3 | Definitions of pharmacodynamic endpoints

Opioid-induced muscle rigidity was clinically diagnosed.[2,4,35] In this study, muscle rigidity was defined based on clinical features indicating decreasing compliance, such as chest or abdominal wall rigidity, an inability to open the mouth, and an inflation pressure exceeding 40 cmH_20. Apnoea was defined as a cessation of oronasal airflow for a minimum of 10 seconds.[36] LOC was defined as a lack of a response to a verbal command (eg, open your eyes) every 5 seconds.[37]

4.4 | Electroencephalographic measurements

Eleven-channel EEGs (Fp1, Fp2, F3, F4, C3, C4, Cz, P3, P4, O1, O2 referenced by A2, 10-20 system) were recorded continuously, with a sampling frequency of 256 Hz. Conventional disk electrodes were applied, and the skin where the EEG electrodes were attached was wiped with alcohol to maintain impedance at <5 kΩ. Raw electroencephalographic signals were filtered between 0.5 and 30 Hz and divided into epochs of 10 seconds with no overlap. Data were stored on a hard disk for the subsequent off-line calculations of TLMC and ApEn. For the calculation of ApEn, the length of an epoch (N) was 2560, the number of previous values (m) used to predict the subsequent values was 2, and the filtering level (r) was 10% of the SD of the amplitude values. No smoothing techniques were applied in calculating ApEn and TLMC. Serious artifacts were excluded by checking the maximum amplitudes of each epoch. The epoch was excluded if the amplitude was greater than 200 μV, and the effectiveness of artifact rejection was confirmed manually. A single experienced analyst performed the artifact rejection procedure and the analysis of each electroencephalographic parameter. Baseline EEGs were recorded for 5 minutes before the infusion of propofol or remifentanil. Electroencephalographic activity during the infusion of propofol and/or remifentanil was recorded continually for up to 15 minutes after reaching pseudo-steady states at the predefined levels of both drugs. The last 5-minutes segment of each artifact-free EEG was selected, and ApEn and TLMC were calculated off-line. TLMC and ApEn values ranged from 0 to 1. The EEG values (ie, lower TLMC and ApEn values) were lower during anaesthesia with high propofol or remifentanil concentrations than they were with lower concentrations. In our previous study, a P4 montage showed a higher ratio for the average maximal electroencephalographic effect relative to inter-individual baseline variability and lower coefficients of variation for the baseline ApEn values.[23] Therefore, ApEn and TLMC values derived from P4 montages were used. Maximum ApEn or TLMC values calculated from baseline EEGs were used as baseline ApEn or TLMC values (E_0) for each patient. The median ApEn or TLMC value during a pseudo-steady state period was used as the minimum ApEn or TLMC value (E_{max}) for each patient.

4.5 | Pharmacodynamic modelling

The pharmacodynamic model used in this study treats each combination of the potentially interacting agents as if they were a "new" unique drug by normalizing each drug to its potency (reflected by the EC_{50} value; the effect-site concentration associated with 50% of the maximal drug effect) and combining the normalized amounts in a model of the structure shown in the equations below.

Quantal responses, such as muscle rigidity, apnoea and LOC, were modelled using the empirical response surface model described by Minto et al.[19] The model for the probability of event occurrence (1, event occurred; 0, event not occurred) was:

$$P = \frac{\left(\frac{U_R+U_P}{U_{50}(Q)}\right)^{\gamma(Q)}}{1+\left(\frac{U_R+U_P}{U_{50}(Q)}\right)^{\gamma(Q)}}$$

where P is the probability of event occurrence, $C_{50,remifentanil}$ and $C_{50,propofol}$ are the effect-site concentrations of propofol and remifentanil associated with 50% probability of event occurrence, U_P = the effect-site concentration of propofol/$C_{50,propofol}$, U_R = the effect-site concentration of remifentanil/$C_{50,remifentanil}$, $Q = U_P/(U_P+U_R)$, $U_{50}(Q)$ (hybrid potency for the combined agents) = $1 - A{\cdot}Q + A{\cdot}Q^2$ ($A = 0$ signifies an additive interaction, $A > 0$ indicates a synergistic interaction, and A < 0 indicates infra-additive interaction).

Continuous responses, such as ApEn and TLMC, were modelled using the following fractional sigmoid E_{max} model:

$$E = E_0 \times \left(1 - \frac{\left(\frac{U_R+U_P}{U_{50}(Q)}\right)^{\gamma(Q)}}{1+\left(\frac{U_R+U_P}{U_{50}(Q)}\right)^{\gamma(Q)}}\right)$$

where E_0 is the baseline response when no drug is present, E is the response, $C_{50,remifentanil}$ and $C_{50,propofol}$ are the effect-site concentrations of propofol and remifentanil associated with a 50% maximal propofol- and remifentanil-induced electroencephalographic suppressive effect, U_P is the effect-site concentration of propofol/$C_{50,propofol}$, U_R is the effect-site concentration of remifentanil/$C_{50,remifentanil}$, $Q = U_P/(U_P + U_R)$, $U_{50}(Q)$ (hybrid potency for the combined agents) = $1 - A{\cdot}Q + A{\cdot}Q^2$ ($A = 0$ signifies an additive interaction, $A > 0$ indicates a synergistic interaction, and $A < 0$ indicates infra-additive interaction). The response surface was determined from the resulting drug effect in relation to the combination of the two drugs. This approach has been published in detail by Minto et al.[19]

Response surface models were fitted using NONMEM 7 level 2 (ICON Development Solutions, Dublin, Ireland). Inter-individual variations in response surface models could not be successfully estimated with only two combinations of propofol and remifentanil per individual (baseline and pseudo-steady state). Therefore, a naïve-pooled data approach was used. The residual random variability for continuous variables (ApEn and TLMC) was modelled using an additive error model. Residual random variability is reported as σ^2, which is the variance of ε. Different models were evaluated using statistical and graphical methods. The interaction parameters were tested for significance by comparing −2 log likelihood when $A = 0$ (additive interaction) with the −2 log likelihood when A was not fixed equal to 0. An interaction parameter was implemented into the model if the −2 log likelihood decreased by more than 3.84 ($P < .05$, chi-square test). The Akaike Information-theoretic Criterion (AIC)[38] was used to compare non-nested models instead of the likelihood ratio criterion as follows: $AIC = -2LL + 2P$, where $-2LL$ is the minimum value of the objective function produced by NONMEM, and P denotes the number of parameters. The relative standard error was calculated as the standard error divided by the estimate for evaluating the precision of the parameter estimated.[39] R software (version 3.1.2; R Foundation for Statistical Computing, Vienna, Austria) was used for graphical model diagnoses. Models with lower AIC values were considered "better."

The weighted residuals were calculated as (measured − predicted)/predicted. The median weighted residuals and median absolute weighted residuals were calculated to examine the quality of the predictions from the pharmacodynamic models for TLMC and ApEn. A nonparametric bootstrap analysis was used to internally validate the models (fit4NM 3.7.9, Eun-Kyung Lee and Gyu-Jeong Noh, http://www.fit4nm.org/download, last accessed: October 17, 2011).[39] Briefly, 2000 bootstrap replicates were generated via random sampling from the original dataset, with replacement. Parameter estimates were compared with the median parameter values and the 2.5-97.5 percentiles from the nonparametric bootstrap replicates.

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DISCLOSURE

The authors declare that there are no conflicts of interest.

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