Remifentanil–sevoflurane interaction models of circulatory response to laryngoscopy and circulatory depression

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Background. Sevoflurane and remifentanil are commonly combined to produce the hypnotic and analgesic effects required for clinical anaesthesia. Previous studies have characterized interactions between several i.v. drugs and inhalation agents. Aiming to extend this effort, we developed two new mathematical models to characterize the interactions manner and strength between sevoflurane and remifentanil.

Methods. Sixty-five adult Chinese patients undergoing elective operations received a target-controlled infusion of remifentanil (0–10 ng ml−1) and inhaled sevoflurane (0.3–3.4 vol.%) at various randomly selected target concentration pairs. After reaching pseudo-steady-state drug levels, the circulatory response to laryngoscopy and any circulatory depression (a side-effect) were observed for each pair of target concentrations. The pharmacodynamic interactions between sevoflurane and remifentanil were investigated by response surface methodology. NONMEM software was used to estimate the model parameters.

Results. The response surface models revealed significant synergy between sevoflurane and remifentanil. When the target remifentanil concentration was increased from 0 to 10 ng ml−1, the C50,sevo decreased from 2.6 to 0.38 vol.% for the prevention of circulatory response to laryngoscopy and from 3.53 to 1.46 vol.% for the induction of circulatory depression.

Conclusions. The new models can be used to characterize the interactions between these two drugs both qualitatively and quantitatively. Remifentanil significantly decreased the amount of sevoflurane required to eliminate patient response to clinical stimuli, thus reducing the likelihood of side-effects, specifically circulatory depression.

Keywords: anaesthetics volatile, sevoflurane; analgesics opioid, remifentanil; model, mathematical; model, pharmacodynamic

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Modern anaesthetic drugs are often co-administered to efficiently create the desired anaesthetic state and to avoid the adverse effects. For example, the induction and maintenance of anaesthesia may involve a hypnotic to achieve and maintain loss of consciousness, and an opioid to blunt the response to noxious stimulation. One of the advantages of combining an opioid and a hypnotic over the use of single agent is the synergistic increase in a desired anaesthetic effect.1 It is important to quantitatively understand the pharmacodynamic interactions of these agents to optimize drug dosing. Various quantitative approaches have been developed to describe drug interactions.2–6

The anaesthetic state consists of both a hypnotic and an analgesic component and therefore cannot be considered as a single universum of the drug effect. Somatic responses (e.g. movement) and circulatory responses [e.g. heart rate (HR) and mean arterial blood pressure (MABP)] may be used as perioperative pharmacodynamic endpoints. Various hypnotic–analgesic interaction models have been described.7–19 Minto and colleagues7 described a

Editor’s key points

- This study investigates the pharmacodynamic interaction of sevoflurane and remifentanil as described by the probabilities of no response to laryngoscopy and occurrence of circulatory depression using response surface modeling.
- Remifentanil reduces the amount of sevoflurane required to prevent circulatory response to laryngoscopy and occurrence of circulatory depression in a synergistic manner.
- The synergistic effect is bigger for the prevention of circulatory response to laryngoscopy than for the occurrence of circulatory depression.
mathematical approach based on response surface methods for evaluating drug–drug interactions between several i.v. anaesthetic drugs. This method is an extension of previous models, such as the ones proposed by Greco and colleagues and Short and colleagues. Minto co-workers hypothesized that any given ratio of two drugs behaves as a ‘new drug’ with its own sigmoidal concentration–response relationship. The Minto model has been applied in various studies focusing on either multiple i.v. anaesthetic drugs or opioid-volatile anaesthetic synergy. By using the Minto model, they introduced terms of normalized concentrations of drug A, drug B, and the ‘new drug’ such as $U_A$, $U_B$, and $U_{50}$. Dahan and colleagues made two modifications to the Minto model. First, drug interactions were taken into account by a function $I(Q)$ for which they chose a spline with two interpretable parameters. Secondly, they chose a general linear dose–response relationship for the model. The introduction of the $I(Q)$ function which was considered variation in the cubic-spline approach is reasonable; however, the response surface model established by Dahan and his colleagues is appropriate for continuous data at lower concentration pairs of alfentanil and sevoflurane.

Manyam and colleagues have analysed the interactions between sevoflurane and remifentanil by using logistic regression method. In our preliminary study, to retain the feature of quantitative analysis of interactions, the response surface methodology was here applied to investigate sevoflurane and remifentanil interactions. We preliminarily combined the Minto and Dahan models to create our response surface model in which each of the model parameters is given its physiological meaning and estimation takes place within a clinical reasonable range. Several effects such as loss of responsiveness, loss of response to painful stimuli, and other endpoints for sevoflurane and remifentanil combination have previously been reported. We choose the probabilities of no response to laryngoscopy and occurrence of circulatory depression (a side-effect) for patients as the pharmacodynamic effects.

**Materials and methods**

**Patient selection and monitoring**

Data were collected between 2007 and 2009. After approval from the local Medical Ethics Committee (Peking University, Beijing, China, IRB00001052-06078), 65 adult patients (30 men and 35 women, aged 20–50 years) were enrolled. All participants gave written informed consent. All enrolled patients had an American Society of Anaesthesiologists physical status of I (ASA I), were non-smokers, deviated from their ideal body weight by no more than 25%, and were scheduled to undergo elective surgeries. Patients with a history of significant alcohol or drug abuse, a history of allergy to opioids, a history of cardiac, pulmonary, or renal disease, or a history of chronic drug use or medical illness known to alter the pharmacokinetics or pharmacodynamics of opioids or inhalation anaesthetics and patients with oesophageal reflux or hiatal hernia were excluded.

After 8 h of fasting, patients received an i.v. catheter for fluid and drug administration. In each patient, inspired and expired sevoflurane concentration, expired carbon dioxide concentration, pulse oximetry, and a five-lead electrocardiogram were measured. Non-invasive blood pressure was measured every 3 min (Anaesthesia Monitor, PHILLIPS Intellivue MP60, Germany).

**Study design and drug delivery**

This was a prospective, open-label, randomized, parallel group study using a slices design as described by Short and colleagues to assess the drug–drug interactions. Patients received no premedication. The primary drug in this study was sevoflurane. The concentration of sevoflurane was maintained at no more than two minimal alveolar concentration (the end-tidal concentration of volatile anaesthetic where there is a 50% probability of moving in response to a skin incision), ranging from 0.3 to 3.4 vol.%. Each patient was randomly assigned to one of 13 different sevoflurane concentration study groups ($n=5$ each). The assigned concentrations of sevoflurane were 0.3, 0.5, 0.7, 0.9, 1.1, 1.3, 1.5, 1.7, 2.0, 2.3, 2.6, 3.0, and 3.4 vol.% for the 13 groups, respectively.

The patients were studied in two phases, single drug and drug combination, the second phase taking place immediately after the first. In the first phase, the patients received sevoflurane alone at a fixed concentration. Thereafter, the second phase commenced with the administration of remifentanil. Remifentanil was administrated as target-controlled infusion (TCI) using a computer-controlled infusion device (Orchestra Base Primea, Fresenius Vial, France). The pump was programmed with the remifentanil pharmacokinetic parameters reported by Minto and colleagues. The TCI concentration of remifentanil for every patient was increased from 0 to 10 ng ml$^{-1}$ in a stepwise ascending fashion (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 ng ml$^{-1}$), so that interactions could be characterized throughout the entire concentration range. Because of ethical issues, patient compliance and the fact that remifentanil caused sufficient sedation and analgesia, the concentration of remifentanil for TCI was no more than 10 ng ml$^{-1}$. If the patient had no pharmacodynamic effect at remifentanil concentration of 10 ng ml$^{-1}$, the probability was recorded as 0.

Anesthesia was induced with sevoflurane and oxygen, first during spontaneous ventilation. Ventilation was assisted if the tidal volume was too small to provide adequate end-tidal sampling for the measurement of anaesthetic concentrations. The inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration at a constant value according to a pre-selected concentration. This concentration was maintained for at least 15 min. Sevoflurane was administered with oxygen (3 litre min$^{-1}$) and fresh air (3 litre min$^{-1}$) through a tight-fitting mask, using a standard breathing circuit and anaesthesia machine (Penlon Prima, Abingdon, UK).
Measurement of drug effects

After reaching a pseudo-steady state (at least 5 min after achieving the target effect site concentration of remifentanil or 10 min after achieving a stable end-tidal concentration of sevoflurane), a sequence of noxious stimuli (laryngoscopy and tracheal intubation) was conducted. The circulatory response to laryngoscopy and any circulatory depression (a side-effect) were selected to assess the drug–drug interactions between sevoflurane and remifentanil.

Sedation was measured by OAA/S score first. If OAA/S scale level 1 was reached, the patient was non-responsive to calling and shaking, which was defined as loss of consciousness. After patients achieved non-responsive status, laryngoscopic stimulus was performed. Direct laryngoscopy was applied using a Macintosh laryngoscope to attain Cormack grade I or II and maintained for 5 s at each pair of target concentrations. The maximum intensity of the laryngoscopy stimulus was set as the value reported by Kern and colleagues. HR and MABP were recorded before induction of anaesthesia. If the HR and MABP in response to laryngoscopy increased by no more than 10% from their pre-stimulation level, the patient was considered to have experienced no circulatory response and the measurement of effect was recorded as 1. If a circulatory response was observed, the effect was recorded as 0. When patients were considered non-responsive to laryngoscopy stimuli, tracheal intubation was performed. Table 1 shows the rating of airway conditions and intubation responses. Patients who achieved score II or less for all the items of observation were considered non-responsive to intubation. Circulatory depression was defined as an MABP of ≤ 50 mm Hg or HR of ≤ 45 bpm. The occurrence of effect in these cases was recorded as 1 and absence as 0. All assessments were performed by one investigator to minimize the inter-observer variability.

Raw data organization

Each patient randomly received a fixed dose of sevoflurane combined with a low to high dose of remifentanil for a target concentration of 0–10 ng ml⁻¹. The measurement of effect was recorded as binary response (0 or 1). The modelling was done with the probabilities which were calculated out of the five individual binary responses in each sevoflurane subgroup. In each sevoflurane subgroup, the actually measured end-tidal sevoflurane concentrations were averaged to obtain sevoflurane–remifentanil concentration pairs.

Novel response surface model development

The response–surface modelling approach was used to model the pharmacodynamic drug–drug interactions. This is a multivariate technique that mathematically fits the experimental domain studied using the theoretical design through a response function. Response–surface methodology is generally used for two principal purposes: to provide a description of the response pattern in the region of the observations and to assist the search for the optimal dose ratio to achieve the desired effect. The three-dimensional model can characterize the dose–response relationship between combinations of drugs. It is also mathematically consistent with models of the concentration–response relationships of single drugs.

One condition for additive interaction was developed both by Greco and Berenbaum (see Appendix) for two drugs acting in a sigmoid manner, pharmacodynamics can be described by the Hill equation. Minto and colleagues have proposed a model that could characterize the drug–drug interactions quantitatively (see Appendix). Dahan and colleagues made some modifications to the Minto model (see Appendix). They introduced a function I(Q) to describe the type of drug–drug interaction. For this equation, they chose a spline with two interpretable parameters of I_max and Q_max. I_max is the maximum value of the drug–drug interactions, and Q_max is the value of Q at which the interaction function I(Q) attains I_max. The Dahan model was found to be a suitable model for describing drug interaction as measured by continuous data such as the bispectral index (BIS) and HR, and when only for relatively low concentrations of alfentanil.

We incorporated Dahan’s concept of I(Q) into the Minto model to create a preliminary new model. For the probability data, we constructed a response–surface model for each pharmacodynamic response, as follows:

$$ P = \frac{(U_s + U_r)^2}{(1/I(Q))^2 + (U_s + U_r)^2} $$

Here, P represents the probability that there will be no circulatory response to laryngoscopy or that circulatory depression will occur, γ is the steepness of the concentration vs response probability, and s and r stand for sevoflurane.

Table 1 Rating of airway conditions and intubation responses

<table>
<thead>
<tr>
<th>Observation items</th>
<th>Score</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaw mobility</td>
<td></td>
<td>Fully relaxed</td>
<td>Mild resistance</td>
<td>Tight, but opens</td>
<td>Closed</td>
</tr>
<tr>
<td>Glottis view</td>
<td></td>
<td>Full</td>
<td>Half</td>
<td>Posterior cornu, arytenoids</td>
<td>Blind</td>
</tr>
<tr>
<td>Vocal cord position</td>
<td></td>
<td>Open</td>
<td>Midposition</td>
<td>Moving, not open</td>
<td>Closed</td>
</tr>
<tr>
<td>Coughing movement</td>
<td></td>
<td>None</td>
<td>One or two coughs</td>
<td>Three or more coughs</td>
<td>Bucking/movement</td>
</tr>
</tbody>
</table>
and remifentanil, respectively. Each of the two drug combinations could be expressed as a unique ratio of $U_s$ and $U_r$ in terms of $Q$:

$$Q = \frac{U_s}{U_s + U_r}$$  (2)

where $Q$ ranges from 0 (remifentanil only) to 1 (sevoflurane only). It is the drug concentration ratio of sevoflurane and remifentanil normalized by their respective $C_{50}$.

$$U_s = \frac{C_{sevo}}{C_{sevo,50}}$$  (3)

$$U_r = \frac{C_{remi}}{C_{remi,50}}$$  (4)

Here $C_{sevo}$ and $C_{remi}$ are the concentrations of sevoflurane and remifentanil, respectively, and $C_{sevo,50}$ and $C_{remi,50}$ are the corresponding concentrations at half of the maximum effect. Any given ratio of the two drugs is treated as a new drug.

**Parameter estimation**

To quantitatively evaluate the relationship between the probability of response and corresponding combination ratio of sevoflurane and remifentanil, five parameters in the response surface model need to be estimated: $C_{50,sevo}$, $C_{50,remi}$, $\gamma$, $I_{\text{max}}$ and $Q_{\text{max}}$. All the parameters were estimated using the NONMEM program (version VI, level 1, ICON, Ellicott City, MD, USA).

Inter-individual variability (IIV) was expressed using a log-normal variance model:

$$\theta_i = \theta_{TV,i} \cdot \exp(\eta_i)$$  (5)

Here $\theta_i$ is the $i$th basic pharmacodynamic parameter for the $i$th individual, $\theta_{TV,i}$ is the typical value of the $i$th population parameter, and $\eta_i$, which is normally distributed with a mean of 0, and variance of $\sigma_i^2$, is a random variable for the $i$th individual in the $j$th parameter.

An additive model was used to describe the residual variability, representing the variance between the values observed and those predicted by the model:

$$DV_{\text{obs}} = DV_{\text{pred}} + \varepsilon$$  (6)

Here $DV_{\text{obs}}$ and $DV_{\text{pred}}$ refer to observed and predicted probabilities, while $\varepsilon$ is a randomly distributed variable with a mean of 0 and variances of $\sigma^2$, accounting for the residual variability.

**Statistical analysis**

The model was developed using the first-order (FO) method because the preceding analysis showed that FO conditional estimation (FOCE) and FOCE with interactions (FOCEI) were not successful. Unless otherwise specified, all statistical procedures and graphics were performed or generated using R (version 2.10.1). When comparing two models with different numbers of parameters, the $F$-test was used as suggested by NONMEM (version VI, level 1, ICON, Ellicott City, MD, USA). If the decrease in the objective function value (OFV) is $> 3.84$ ($P < 0.05$, degree of freedom = 1), it was considered significantly different.

As described in our model, if $I(Q) = 1$ for any value of $Q$, the interaction is characterized as additive. It is supra-additive if $I(Q) > 1$ and infra-additive if $I(Q) < 1$. To characterize the manner of interaction between sevoflurane and remifentanil, we compared the OFV of the additive model (value of $I_{\text{max}}$ fixed at 1) to that of the non-additive model ($I_{\text{max}}$ estimated simultaneously with the other parameters) during the modelling process. Bootstrap analysis and visual predictive checks (VPCs) were performed for the final models. 95% confidence intervals (CIs) for the parameter estimates based on 1000 bootstrap iterations and evaluation of the prediction of the final model based on 1000 VPC simulations were performed by Perl-speaks-NONMEM (version 3.2.12), respectively.

**Results**

Out of the total 65 patients, 57 completed the study and 8 patients were excluded during the experiment because of difficulties with assisted ventilation. A total of 164 paired pharmacodynamic responses were obtained at various treatment levels for laryngoscopy and 142 paired responses were obtained for the probability of cardiovascular depression (a side-effect). The experimental phase of remifentanil

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimates from final model (NONMEM estimate)</th>
<th>Estimate</th>
<th>RSE (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No circulatory response to laryngoscopy</td>
<td>C_{50.sevo} (vol.%)</td>
<td>2.60</td>
<td>3.44</td>
<td>2.40–2.82</td>
</tr>
<tr>
<td></td>
<td>C_{50.remI} (ng ml^{-1})</td>
<td>46.2</td>
<td>13.4</td>
<td>24.2–50.2</td>
</tr>
<tr>
<td></td>
<td>$\gamma$</td>
<td>6.59</td>
<td>10.2</td>
<td>3.96–9.40</td>
</tr>
<tr>
<td></td>
<td>$I_{\text{max}}$</td>
<td>3.40</td>
<td>6.59</td>
<td>2.47–3.61</td>
</tr>
<tr>
<td></td>
<td>$Q_{\text{max}}$</td>
<td>0.75</td>
<td>2.75</td>
<td>0.68–0.83</td>
</tr>
<tr>
<td>Inter-individual variability (% CV)</td>
<td>$C_{50,remI}$</td>
<td>40.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual error (so additive)</td>
<td>$\Sigma$</td>
<td>0.029</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulatory depression (side-effect)</td>
<td>C_{50.sevo} (vol.%)</td>
<td>3.53</td>
<td>3.00</td>
<td>3.22–3.85</td>
</tr>
<tr>
<td></td>
<td>C_{50.remI} (ng ml^{-1})</td>
<td>94.7</td>
<td>3.19</td>
<td>70.4–106.0</td>
</tr>
<tr>
<td></td>
<td>$\gamma$</td>
<td>4.91</td>
<td>4.30</td>
<td>4.51–5.71</td>
</tr>
<tr>
<td></td>
<td>$I_{\text{max}}$</td>
<td>1.95</td>
<td>3.62</td>
<td>1.79–2.19</td>
</tr>
<tr>
<td></td>
<td>$Q_{\text{max}}$</td>
<td>0.85</td>
<td>0.96</td>
<td>0.78–0.86</td>
</tr>
<tr>
<td>Inter-individual variability (% CV)</td>
<td>$C_{50,remI}$</td>
<td>35.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual error (so additive)</td>
<td>$\sigma$</td>
<td>0.053</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig 1 Observed and predictions of the relationship between sevoflurane and remifentanil and probability of pharmacodynamic effects. (a) Response surface for the absence of circulatory response to laryngoscopic stimuli. (b) Response surface for circulatory depression (side-effect). The points represent raw probabilities. (c) Concentration–response curve of plot (a). (d) Concentration–response curve of plot (b).
infusion was between 30 and 140 min. All patients breathed adequately upon awakening, and none of the patients reported awareness or severe muscle rigidity for any intraoperative event.

Pharmacodynamic endpoints of the prevention of circulatory response to laryngoscopy, and the occurrence of side-effect circulatory depression, were analysed using the response surface model, as described in equation (1). For laryngoscopy and side-effect, the data were found to be best characterized by a synergistic model. When the interaction term $I_{\text{max}}$ was not fixed at 1 (additive interaction) but was estimated simultaneously with other parameters, the OFV decreased significantly from $2^{386}$ to $2^{386}$ for the response to laryngoscopy and from $2^{546}$ to $2^{633}$ for circulatory depression, which is considered as highly significant. Table 2 shows the parameter estimates for the final synergistic models. The %RSEs for all parameters were <60%. This indicated that estimates were reliable. The introduction of IIV to all model parameters did not successfully converge and the estimated values of IIV in other parameters were very small. The model residual variability (random effects) of laryngoscopy and side-effects was small with SD of 0.029 and 0.053, respectively.

Pharmacodynamic models were developed using the calculated probabilities in each sevoflurane subgroup. The three-dimensional surface was found to describe this probability adequately. Figure 1A and B shows the three-dimensional response surface for the prevention of circulatory response to laryngoscopy and of circulatory depression with a varying ratio of sevoflurane and remifentanil combinations. Figure 1C and D shows a cross section of the three-dimensional surface. In these plots, the three-dimensional surface appears to bow towards the reader. At $Q_{\text{max}}=0.75$, the surface showing the response to laryngoscopy appears to plateau. This bowing causes the conventional isobologram to deviate from the straight line of additivity towards the origin. The profiles of the interactions were characterized by the function $I(Q)$. The relationship between $I(Q)$ and the levels of
Table 3 Decreases in required amount of sevoflurane in response to increasing concentrations of remifentanil.

<table>
<thead>
<tr>
<th>Remifentanil targeted concentration, ng ml(^{-1})</th>
<th>(C_{\text{50,sevo}}), no circulatory response to laryngoscopy, vol.%</th>
<th>(C_{\text{50,sevo}}), circulatory depression (side-effect), vol.%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.6</td>
<td>3.57</td>
</tr>
<tr>
<td>1</td>
<td>1.62</td>
<td>2.86</td>
</tr>
<tr>
<td>2</td>
<td>0.92</td>
<td>2.44</td>
</tr>
<tr>
<td>3</td>
<td>0.73</td>
<td>2.14</td>
</tr>
<tr>
<td>4</td>
<td>0.65</td>
<td>1.94</td>
</tr>
<tr>
<td>5</td>
<td>0.58</td>
<td>1.75</td>
</tr>
<tr>
<td>6</td>
<td>0.52</td>
<td>1.65</td>
</tr>
<tr>
<td>7</td>
<td>0.47</td>
<td>1.57</td>
</tr>
<tr>
<td>8</td>
<td>0.43</td>
<td>1.53</td>
</tr>
<tr>
<td>9</td>
<td>0.41</td>
<td>1.49</td>
</tr>
<tr>
<td>10</td>
<td>0.38</td>
<td>1.46</td>
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</tbody>
</table>

The final model was run through 1000 simulations to evaluate the predictive performance under VPC evaluation. A graphical comparison was made between the observed data and the model-predicted median and 95% prediction interval over sevoflurane concentrations (Fig. 5). The VPC plot demonstrated that the drug interaction described by response surface models had no evident bias.

**Discussion**

Previous studies have demonstrated that remifentanil is a useful supplement to general anaesthesia. Accurate opioid administration during anaesthesia attenuates the adrenocortical responses, and autonomic, somatic to noxious stimuli, and alters the muscle microcirculation in different ways. This study was designed to develop a new mathematical model to describe the characterization of the nature of interactions between sevoflurane and remifentanil both qualitatively and quantitatively and to determine the influence of remifentanil on sevoflurane requirements for the suppression of responses to perioperative stimuli and occurrence of side-effect in adult Chinese patients. Our results suggest that remifentanil reduces the amount of sevoflurane required to prevent circulatory response to laryngoscopy and occurrence circulatory depression (a common side-effect) in a synergistic manner. The synergistic effect is bigger for the desired effect than for the undesired side-effect (Fig. 2c).

Opioid–hypnotic drug interaction studies have traditionally evaluated the effects of adding one or two fixed doses or concentrations of a drug to several defined concentrations of the second drug using an isobologram or demonstrating shifts in parallel dose-response curves. Minto and colleagues described a novel method for drug interaction analysis.
Fig 4 The diagnostic plots of the response surface models with respect to the prevention of circulatory response to laryngoscopic stimuli (left panels) and of circulatory depression (right panels). (A) and (B) Weighted residuals (WRES) vs the individual predicted probability of response surface models and vs concentration of sevoflurane. (C) and (D) Scatter plots of observations vs the population predictions and individual predictions. Circles represent individual observations and the lines represent unity.
Fig 5 Results of visual predictive checks of the final response surface model with respect to the probability of preventing circulatory response to laryngoscopic stimuli (A) and preventing circulatory depression (B). The points represent the median probabilities of observed. The orange lines represent 50% and the orange lines represent 2.5 and 97.5% probabilities of simulated data.
It was used by Diz and his colleagues to describe the pharmacodynamics interaction of sevoflurane and propofol on BIS.18 (Using the Minto model to describe our study converged successfully.) However, the $U_{50}$ (0.1) extrapolated to an unreasonable value about 6.62 (%RSE 10.6). The terms $U_A$ and $U_B$ are related to $C_{50,A}$, $C_{50,B}$, and $U_{50}$ in the Minto model is dependent on them too. It suggests that the terms $U_A$, $U_B$, and $U_{50}$ are not independent of each other, and thus cannot be estimated simultaneously. The recent study conducted by Heyse and colleagues focused on comparison of different response models between sevoflurane and remifentanil.32 Their results showed that the reduced Greco, scaled C50h hierarchical, and fixed C50h hierarchical models fitted the data reasonably well, but the Minto and Greco models did not. Therefore, we modified the Minto model by introducing the spline function of $I(Q)$ to describe the relationship between sevoflurane and remifentanil concentrations with their combined clinical effect. The combined model [equation (1)] was able to describe the pharmacodynamic interactions between sevoflurane and remifentanil appropriately. One thousand simulations per response surface model were performed for the final models. The plots showed that approximately 90% of the measured data were included within 90% of the simulated data envelope (Fig. 5). As a result, the models are defined accurate.

The combination of sevoflurane and remifentanil was investigated by Manyam and colleagues9 using a crisscross design advocated by Short and colleagues.11 A logistic regression model for each pharmacodynamic response was developed in healthy volunteers. Their studies suggest that the interactions between these two drugs are synergistic. Our preliminary modelling work showed that this method failed to converge when trying to fit our study data. Our study design is of the ‘slices’ type described by Short and colleagues,11 which produced a skewed surface in a simulation study.

We developed a new model by combining the Minto model with Dahan’s modifications. As the OFVs of the synergistic models were much lower than those of additive models, the synergistic models were chosen to quantitatively characterize drug–drug interactions. $I_{\text{max}}$, the estimated maximum synergistic interaction, was 3.4 between the two drugs at a $Q_{\text{max}}$ of 0.75:0.25 ($U_J:U_I$) as listed in Table 2. Laryngoscopic stimulus testing showed that the probability vs concentration curve moved consistently towards one site following the variations in the target concentration of remifentanil. When the concentration of remifentanil was increased, the intervals of the two-dimensional plot became narrower, suggesting a ceiling effect in the synergistic relationship (Fig. 1c). This trend showed a ceiling effect around 0.75 vol.% sevoflurane and 6.73 ng ml$^{-1}$ remifentanil during sedation, consistent with Manyam’s study.9 Table 2 also showed the $C_{50,\text{remi}}$ for circulatory depression was 94.7 ng ml$^{-1}$, which can be considered extremely high. It means that in the typical concentration range (5–10 ng ml$^{-1}$) of remifentanil alone would produce no circulatory depression. It could be explained by the definition of circulatory depression in the current study being an MABP of ≤50 mm Hg or an HR of ≤45 bpm during the experimental process. Other cut-off values might result in other findings.

When the target concentration of remifentanil was increased from 0 to 10 ng ml$^{-1}$, the concentration of sevoflurane required to prevent a response to laryngoscopy and for circulatory depression to occur decreased accordingly. The $C_{50,\text{sevo}}$ decreased from 2.6 to 0.38 vol.% for no response to laryngoscopy stimuli and from 3.53 to 1.46 vol.% for the occurrence of circulatory depression (Table 3). As shown in Figure 3, there is an advantage when combining sevoflurane and remifentanil. Less sevoflurane is required for intubation if a small amount of remifentanil is added, without an increase of haemodynamic side-effects.

In summary, we characterized the interactions between sevoflurane and remifentanil using a new response surface model. The method was found capable of determining the form of interaction via $I_{\text{max}}$, the maximum interaction point via $Q_{\text{max}}$, and the interaction curve shape via $\gamma$. The preliminary model was found to match the clinical interaction study data well while allowing parameters to describe curve shape properties. However, to explore the optimal dose ratio to achieve desired effect and minimum side-effect in a general anaesthesia with sevoflurane and remifentanil combinations, further validation of the models against an independent data set and extensive simulations will be performed in the future.

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Declaration of interest
None declared.

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Appendix
Greco and Berenbaum model

The model is a simplification of an additive model,

\[
1 = \frac{[A]}{(E - E_0/E_{max,A} - E)^{1/\gamma_A} \cdot A_{50}} + \frac{[B]}{(E - E_0/E_{max,B} - E)^{1/\gamma_B} \cdot B_{50}}
\]  

(A1)

Here, \([A]/[B]\), \(E_{max,A}/E_{max,B}\), \(\gamma_A/\gamma_B\), and \(A_{50}/B_{50}\) represent the concentration, maximum effect, slope of the Hill function, and concentration at which 50% of each drug's effect occurs when acting alone, respectively. \(E_0\) represents the baseline effect. Equation (1) defines additivity for drug combinations only, while deviations from it (\(<1\) or \(>1\)) can be used to determine whether these interactions are synergistic or infra-additive. When an interaction is synergistic, combination therapy requires fewer or lower doses to produce the same effect relative to either drug alone. Conversely, when an interaction is infra-additive, more or greater doses are required.
Minto model

The Minto model may be described by the following equation:

\[ E = E_0 + (E_{\text{max}}(\theta) - E_0) \cdot \frac{(U_A + U_B)/(U_{50}(\theta))}{1 + ((U_A + U_B)/U_{50}(\theta))} \]  

(A2)

Here \( U_A \) is the normalized concentration of drug A, \( U_B \) is the normalized concentration of drug B, and \( U_{50}(\theta) \) is the number of units \( \theta \) associated with 50% of maximum effect at ratio \( \theta \). Here the term \( U_{50}(\theta) \) is the potency of the drug combination at ratio \( \theta \) relative to the normalized potency of each drug by itself. It is defined by polynomial function for simplicity in their approach. This requires careful explanation. It must be ensured that \( U_{50} \) is always positive in the range of \( 0 \leq U_{50} \leq 1 \). If the polynomial is correlated with multiple drugs, the interactions can be statistically tested based on the polynomial parameter values alone. For drug administered alone at a concentration sufficient to provoke 50% of that drug's effects, the value of \( U_{50} \) must be 1 to keep the two sites of equation (A2) equal to each other.

Dahan model

Dahan and colleagues made two modifications to the Minto model. First, drug interactions were taken into account by a function \( I(Q) \) for which they chose a spline with two interpretable parameters. Secondly, they chose a general linear dose–response relationship for the model. The model can be described by the following equation:

\[ E(C_A,C_S) = E_0 \cdot \left(1 - \frac{[U_A + U_S]}{2 \cdot I(Q)}\right) \]  

(A3)

where \( I(Q) \) is the smooth (spline) function of \( Q \) given by a third-order polynomial

\[ I(Q) = a_0 + a_1 \cdot Q + a_2 \cdot Q^2 + a_3 \cdot Q^3 \]  

(A4)

The term \( Q \) is a function of the two drug combination and could be expressed as below:

\[ Q = \frac{U_A}{(U_A + U_S)} \]  

(A5)

It has parameters \( I_{\text{max}} \) and \( Q_{\text{max}} \). \( I_{\text{max}} \) is the maximum value of the drug–drug interactions, and \( Q_{\text{max}} \) is the value of \( Q \) at which the interaction function \( I(Q) \) attains \( I_{\text{max}} \). When \( I_{\text{max}} \) is close to 1, the interaction is purely additive. An \( I_{\text{max}} \) of less than 1 denotes infra-additive, and an \( I_{\text{max}} \) of more than 1 denotes synergy.

According to the Dahan model, if \( 0 \leq Q \leq Q_{\text{max}} \), the function of \( I(Q) \) can be calculated as follows:

\[ I(Q) = 1 + A \cdot \frac{1 - Q}{3 \cdot Q_{\text{max}}} \cdot Q^3 \]  

(A6)

Otherwise \( (Q_{\text{max}} \leq Q \leq 1) \),

\[ I(Q) = 1 + A \cdot \frac{(1 - Q) \cdot Q_{\text{max}}}{1 - Q_{\text{max}}} - \frac{A}{3 \cdot Q_{\text{max}}} \left[\frac{(1 - Q) \cdot Q_{\text{max}}}{1 - Q_{\text{max}}}\right]^3 \]  

(A7)

Here constant \( A \) is defined as a function of \( I_{\text{max}} \) and \( Q_{\text{max}} \):

\[ A = -\frac{3 \cdot (1 - I_{\text{max}})}{2Q_{\text{max}}} \]  

(A8)

For the spline function there is the condition \( I(0)=I(1)=1 \) (either sevoflurane or remifentanil alone).

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