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Analysis of pharmacodynamic interaction of sevoflurane and propofol on bispectral index during general anaesthesia using a response surface model

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Background. Propofol and sevoflurane act on the GABA_A receptor, modulating the function of this receptor in an additive manner. The pharmacodynamic interaction of both drugs considering their effect on EEG activity analysed by the bispectral index (BIS) was identified as additive, but this has not been studied in a clinical setting. The objective of this study was to analyse the pharmacodynamic interaction of propofol and sevoflurane on BIS using a surface response model in patients undergoing general anaesthesia with i.v. induction and inhalation maintenance.

Methods. We performed a prospective study in 24 patients undergoing general anaesthesia with propofol induction and sevoflurane maintenance. Anaesthetic depth was measured with a BIS VISTA Bilateral monitor. Propofol biophase concentration was determined using a three-compartment pharmacokinetic model, and sevoflurane end-tidal concentration was measured continuously. The response surface model described by Minto and colleagues was used to analyse the interaction. Statistical analysis was performed with Excel 2002 and SPSS v11.0.

Results. The mean value of $U_{50}(\theta)$ was 0.956 (sd 0.029) in the overall estimated data, and remained within the predefined range for all ratios $\theta$ of the drugs, fulfilling the criterion of additivity. The median of the weighted residuals between the actual BIS value and the BIS value predicted by the model was −5.926%.

Conclusions. Under the study conditions, it was confirmed that sevoflurane and propofol have an additive effect on BIS, with no evidence suggesting the existence of a synergistic effect for the concentrations of both drugs typically used in clinical practice.

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Combinations of drugs that produce similar effects on some components of anaesthesia are commonly used, resulting in pharmacodynamic interactions between them. These interactions can be of various types as a result of the chemical heterogeneity of the compounds and their action on different sites of action. There are three types of interaction: synergistic, additive, or infra-additive, when the combined effect of both drugs is greater, equal, or less than the sum of the effects of either drug alone, respectively. Synergistic interactions can be useful because they allow lower doses of each drug to be used, and therefore have the possibility to reduce the side-effects.

A common combination in clinical practice is to perform induction with an i.v. drug (such as propofol) and to continue maintenance with an inhaled agent (such as sevoflurane). Propofol and sevoflurane act on the GABA_A receptor, at least for part of their actions, and appear to modulate the function of this receptor in an additive manner. Clinically, there appears to be an additive effect for loss of consciousness and movement to stimulus with these drugs. Recently, Schumacher and colleagues demonstrated an additive effect of propofol and sevoflurane on EEG suppression analysed by the bispectral index (BIS) and entropy in a controlled setting. However, this
interaction has not been studied in real-life clinical conditions.

The objective of this study was to analyse the pharmacodynamic interaction of propofol and sevoflurane on BIS to confirm if this action is additive using a surface response model in patients undergoing a standard procedure under general anaesthesia with i.v. induction and inhalation maintenance.

Methods

Patients

A prospective, observational, non-randomized study was conducted in 24 patients undergoing general anaesthesia at the Hospital Xeral-Cies of Vigo, after approval by the Clinical Research Ethics Committee of Galicia and signature of informed consent by the participants. We included ASA I–III patients more than 18 yr of age of both sexes undergoing any type of surgical procedure under general anaesthesia with tracheal intubation and a planned duration of more than 1 h, excluding surgery in the head region, patients with severe weight disturbances (body mass index >35% or <15%), pregnancy, altered levels of consciousness, neurological disorders with unilateral or bilateral cortical involvement, or allergy to any of the drugs used in the study.

All patients received standard monitoring (ECG, SaO2, non-invasive arterial pressure, and expired gases), and additional monitoring was used if required by the patient’s circumstances or surgery. They all received premedication with midazolam 15 mg kg\(^{-1}\) and fentanyl 3 mg kg\(^{-1}\). Induction was performed with propofol 2 mg kg\(^{-1}\) and cisatracurium 0.1 mg kg\(^{-1}\) was used as a neuromuscular blocking drug. After the trachea was intubated and at the anaesthetist’s discretion, ventilation was controlled artificially (Datex Aestiva, Finland) with 50/50 oxygen/air mixture, adjusting ventilatory parameters for an E\(_{\text{tc}}\) of 0 \pm 2

In each patient, the three basic variables of the model (CePROPO, \(U_{\text{SEVO}}\), and BIS) were determined in six periods, the first at 8 min post-induction and then every 5 min.

Response surface model

For the interaction model, we used as a variable the concentration of propofol in the biophase (CePROPO) in \(\mu g \cdot ml^{-1}\). Using the dose and time of administration of propofol in each patient in the induction phase, CePROPO was determined by the RUGLOOP v.3.28 program (Demed, Temse, Belgium), using the three-compartment pharmacokinetic model defined by Marsh and colleagues, corrected by Schneider to adjust the time to peak effect to 1.6 min.\(^9\)

For analysis of the interaction, we used the response surface model described by Minto and colleagues. This model provides a more complete quantitative analysis and graphical representation of the interaction between two or three drugs than that provided by an isobologram. The model is based on two fundamental concepts: first, the combination of two drugs is considered to act like a single drug with a certain concentration–effect relationship; secondly, the properties of this single drug are dependent on the ratio of the concentrations of the two drugs.\(^10\)

The concentrations of each drug are normalized to the corresponding \(C_{50}\) (the concentration that produces 50% of maximal effect, and which is related to its potency):

\[
U_{\text{SEVO}} = \frac{U_{\text{SEVO}}}{C_{50,\text{SEVO}}} \quad U_{\text{PROPO}} = \frac{C_{\text{PROPO}}}{C_{50,\text{PROPO}}}
\]  

where \(U_{\text{SEVO}}\) and \(U_{\text{PROPO}}\) are the normalized concentrations of the two drugs and \(C_{50,\text{SEVO}}\) and \(C_{50,\text{PROPO}}\) the concentration of each drug that produces 50% of maximal effect.

The normalized concentrations are used to define a new variable \(\theta\), which represents the ratio of sevoflurane and propofol:

\[
\theta = \frac{U_{\text{SEVO}}}{U_{\text{PROPO}} + U_{\text{SEVO}}}
\]

The value of \(\theta\) ranges from 0 to 1. If only sevoflurane is administered, \(U_{\text{PROPO}}=0\) and hence \(\theta=1\). Conversely, if only propofol is administered, \(U_{\text{SEVO}}=0\) and hence \(\theta=0\). When equal normalized concentrations of both drugs are administered, \(\theta=0.5\).

The relationship between the effect (\(E\)) and the concentration of the drugs is described with a sigmoidal model using the Hill equation. Substituting the above terms into the Hill equation, the following function is obtained:

\[
E = E_0 + (E_{\text{max}}(\theta)) - E_0 \left( \frac{((U_{\text{SEVO}} + U_{\text{PROPO}})/U_{50}(\theta))^{\gamma(\theta)}}{1 + ((U_{\text{SEVO}} + U_{\text{PROPO}})/U_{50}(\theta))^{\gamma(\theta)}} \right)
\]

where \(E\) is the effect, \(E_0\) the baseline effect with no drug,
Interaction of sevoflurane and propofol on BIS

$E_{\text{max}}(\theta)$ the maximal effect of the drug at ratio $\theta$, $U_{50}(\theta)$ are the normalized units of concentration (or potency of the drug combination) at ratio $\theta$ of both drugs that produce 50% of the maximal effect, and $\gamma(\theta)$ is the slope of the concentration–response relation at ratio $\theta$. Each ratio of both drugs ($\theta$) can have its own $E_{\text{max}}$, $U_{50}$, and $\gamma$, and hence each of the ratios behaves as a new drug with its own sigmoidal concentration–response relation.

By definition, when $U_{50}(\theta)<1$, the interaction is synergistic; when $U_{50}(\theta)>1$, the interaction is infra-additive or antagonistic; and when $U_{50}(\theta)=1$, the interaction is additive. However, and considering the variability in measurement of the parameters, a 10% degree of deviation was arbitrarily accepted, and therefore, the definition used in this study for an additive interaction was a $U_{50}(\theta)$ between 0.9 and 1.1, considering the interaction synergistic when $U_{50}(\theta)<0.9$ and infra-additive when $U_{50}(\theta)>1.1$.

Although more complex equations have been used to define the parameters representing the curves that define $E_{\text{max}}(\theta)$, $U_{50}(\theta)$, and $\gamma(\theta)$, it has been demonstrated that most can be described perfectly using second-order polynomial functions. We thus have the following equations:

$$E_{\text{max}}(\theta) = E_{\text{max,SEVO}} + (E_{\text{max,PROPO}} - E_{\text{max,SEVO}} - \beta_{2E}) \theta + \beta_{2E} \theta^2$$

$$U_{50}(\theta) = 1 - \beta_{2U} \theta + \beta_{2U} \theta^2$$

$$\gamma(\theta) = \gamma_{SEVO} + (\gamma_{PROPO} - \gamma_{SEVO} - \beta_{2\gamma}) \theta + \beta_{2\gamma} \theta^2$$

where $\beta_{2E}$, $\beta_{2U}$, and $\beta_{2\gamma}$ are the coefficients that will, respectively, define the relations for $E_{\text{max}}(\theta)$, $U_{50}(\theta)$, and $\gamma(\theta)$ for each value of the ratio $\theta$, and which will be estimated from the data. From equation (5), additivity of the interaction can also be defined when $\beta_{2U}=0$, synergy when $\beta_{2U}$ is positive, and infra-additivity when $\beta_{2U}$ is negative, but considering the previously described percentage of deviation.

For calculation of the parameters, we need to know the $E_0$, $E_{\text{max}}$, $C_{50}$, and $\gamma$ of each of the two study drugs. For this, we used the data from the models in which these values were calculated for each drug separately and considering the effect measured on BIS, which are shown in Table 1.12 13 It should be taken into account that these selected parameters generate an asymmetry in the model, since $E_{\text{max,SEVO}}$ does not reach 0 as in the case of propofol, and the value of BIS for $C_{50,SEVO}$ is 61, unlike the BIS for $C_{50,PROPO}$, which is 50.

### Statistical analysis

To calculate the values of $E$ that allow the surface model to be represented, we entered the equations and the variables in an Excel 2002 worksheet. The 144 observations ($E_{SEVO}$, $C_{PROPO}$, and observed BIS) of the 24 patients (six observations from each patient) were pooled (using the naïve data pooled method). The coefficients were estimated in a two-stage process, first obtaining the coefficients for each observation and then averaging them for the whole sample. Coefficients were calculated with Excel Solver, using a quadratic estimation of non-linear models with Newton’s method.

Statistical analysis was performed with the SPSS v11.0 program. Data are expressed as mean (SD) for quantitative variables, including in some cases the 95% confidence interval of the mean, or as n (%) for qualitative variables. The ability of the model to predict the observations with which it was constructed was determined by the median of the weighted residuals between the observed and predicted BIS values.

### Results

The characteristics of the patients included in the study are shown in Table 2. Twelve of the patients underwent gynaecological surgical procedures (six hysterectomies, five mastectomies, and one laparotomy for a pelvic mass), 11 had general surgical operations (four thyroidectomies/parotidectomies, four sigmoidectomies, and three cholecystectomies), and one had neurosurgery (herniated disc).

Figure 1 shows the values of $E_{SEVO}$, $C_{PROPO}$, and BIS for the six study periods, that is, at 8 min post-induction and then every 5 min. $C_{PROPO}$ decreases after the induction dose, and $E_{SEVO}$ is progressively increased at the anaesthetist’s discretion to achieve an adequate BIS value. Figure 2 shows the actual $E_{SEVO}$ and $C_{PROPO}$ values we have used in the study for constructing the model with their BIS values.

Table 3 shows the data measured in the sample, and the estimated values of the coefficients ($\beta_{2E}$, $\beta_{2U}$, and $\beta_{2\gamma}$) with which the model estimations were calculated for the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>56.96 (29–81)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>5/19 (20.8/79.2)</td>
</tr>
<tr>
<td>ASA (I/II/III)</td>
<td>1/19/4 (4.2/79.2/16.7)</td>
</tr>
<tr>
<td>BMI (kg m$^{-2}$)</td>
<td>27.30 (4.94)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>96 (37)</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>132 (42)</td>
</tr>
<tr>
<td>Propofol induction dose (mg kg$^{-1}$)</td>
<td>2.02 (0.66)</td>
</tr>
<tr>
<td>Fentanyl induction dose (µg kg$^{-1}$)</td>
<td>3.10 (0.8)</td>
</tr>
<tr>
<td>Midazolam induction dose (mg kg$^{-1}$)</td>
<td>0.016 (0.009)</td>
</tr>
</tbody>
</table>

### Table 1 Parameters of the values in the reference models used for sevoflurane and propofol. $C_{50,PROPO}$ refers to the concentration at biophase. The effects ($E_0$ and $E_{\text{max}}$) are measured in arbitrary BIS units.

<table>
<thead>
<tr>
<th>C50</th>
<th>E0</th>
<th>Emax</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevoflurane</td>
<td>1.12 (% E$'$)</td>
<td>100</td>
<td>23</td>
</tr>
<tr>
<td>Propofol</td>
<td>4.98 (µg ml$^{-1}$)</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>
predicted values of BIS, $E_{\text{max}}(\theta)$, $U_{50}(\theta)$, and $\gamma(\theta)$. The measured values of $E_{\text{max}}(\theta)$, $U_{50}(\theta)$, and $\gamma(\theta)$ refer to those calculated with the individual coefficients ($\beta_{2E}$, $\beta_{2U}$, and $\beta_{3}$) for each of the cases. As can be seen, the mean value of $U_{50}(\theta)$ was $0.908 (0.290)$ in the individual values and $0.956 (0.029)$ in the overall estimated data, and therefore fulfils the criterion of additivity assumed by us. This is consistent with the $\beta_{2U}$ value of $0.424 (3.528)$, which did not differ significantly from the value of 0. Therefore, the criterion of additivity of the interaction between propofol and sevoflurane is fulfilled under the conditions of this study.

Figure 3 shows the relationship between the concentrations of sevoflurane and propofol with the predicted BIS calculated with the parameters estimated according to the response surface model. The surface does not exhibit the curvature that would appear if the interaction was synergistic or infra-additive. The asymmetry in the surface caused by the different maximal effect for sevoflurane and propofol that we used in the model can also be noted. In Figure 2, we represent the isoboles that produce target BIS values of 40, 50, and 60 according to the model.

The values of $E_{\text{max}}(\theta)$, $U_{50}(\theta)$, and $\gamma(\theta)$ for different ratios (\theta) of sevoflurane and propofol are graphed in Figure 4. The value of $U_{50}(\theta)$ is within the predefined range for all ratios of the drugs, confirming the additive behaviour of the interaction, although it approaches 0.9 for $\theta$ values close to 0.5. As previously explained, because the $E_{\text{max}}$ values of sevoflurane and propofol are different, there is an asymmetry when it is graphed against $\theta$, with $E_{\text{max}}(\theta)=0$ when $\theta=0$ (only propofol is administered) and $E_{\text{max}}(\theta)=23$ when $\theta=1$ (only sevoflurane is administered), according to the specifications of the model. Similarly, the behaviour $\gamma(\theta)$ is also asymmetrical because of the different slopes of the concentration—response curves of sevoflurane and propofol.

The standardized weighted residuals for the difference between the observed BIS and the BIS predicted by the model for the different ratios $\theta$ are graphed in Figure 5. Most of the measurements made were close to $\theta=1$, that is, with a predominant normalized dose of sevoflurane, as explained in the Methods section. The median of the weighted residuals between the actual BIS value and the predicted BIS value was $-5.926\%$.

### Discussion

Our results confirm that for the concentrations of the drugs used in this study, sevoflurane and propofol have an additive interaction in terms of their effect on BIS. These findings are in line with those published by other authors.\(^5\)\(^6\) Harris and colleagues\(^5\) demonstrated that the interaction between sevoflurane and propofol was additive, but only analysing isobolograms for a single point of concentration of sevoflurane and propofol under steady-state conditions,

### Table 3

<table>
<thead>
<tr>
<th>Values measured</th>
<th>Model estimates</th>
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<tr>
<td>$\gamma(\theta)$</td>
<td>2.982 (0.196) (2.95; 3.014)</td>
</tr>
<tr>
<td>$\beta_{2U}$</td>
<td>1.244 (0.423) (1.172; 1.316)</td>
</tr>
<tr>
<td>$\beta_{2E}$</td>
<td>0.424 (3.528) (0.174; 1.023)</td>
</tr>
<tr>
<td>$\beta_{3}$</td>
<td>0.99 (0.062) (0.98; 1.001)</td>
</tr>
<tr>
<td>$\theta$</td>
<td>0.395 (0.755) (0.835)</td>
</tr>
<tr>
<td>$U_{50}(\theta)$</td>
<td>0.906 (0.541) (0.831; 0.98)</td>
</tr>
<tr>
<td>$U_{\text{max}}(\theta)$</td>
<td>0.795 (0.244) (0.755; 0.835)</td>
</tr>
<tr>
<td>$E_{\text{max}}(\theta)$</td>
<td>1.01 (0.5) (0.93; 1.1)</td>
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<tr>
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</tbody>
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**Fig 1** $\varepsilon_{\text{SEVO}}$ (%), $\text{CePROPO}$ ($\mu$g ml$^{-1}$), and BIS values in the six study periods. The bars represent the mean (sd).

**Fig 2** Topographic view of the actual values of $\varepsilon_{\text{SEVO}}$ (%) and $\text{CePROPO}$ ($\mu$g ml$^{-1}$) used in the study with their BIS values, overlaid on the isoboles that produce target BIS values of 40, 50, and 60.
and analysing consciousness dichotomously as response to verbal stimulus. Although BIS values were recorded in their study, they were not used as a measure of effect as in our study.

Schumacher and colleagues recently demonstrated an additive effect of propofol and sevoflurane on EEG suppression analysed by the BIS and entropy using response surface methodology. They performed a strict crisscross design with different combinations of sevoflurane and propofol before the start of the surgical procedure in a controlled setting, and they also analysed tolerance to clinically relevant stimuli.6

We have used BIS as the only surrogate of depth of anaesthesia (or, more precisely, of the hypnotic level produced by various anaesthetics estimated by EEG analysis) unlike other studies. BIS is a clinically accepted system for monitoring anaesthetic depth, which offers an objective, continuous, reproducible, non-invasive, high-resolution variable. However, the BIS value does not have a direct physiological meaning, and uses an EEG analysis based on an algorithm that includes population data. Therefore, when used as a measure of effect, it should be considered that it is not directly measuring the action of any specific effector system, but reflects the activity of multiple neuronal systems. However, and given the absence of clinically available physiological variables to measure the action of anaesthetics on the central nervous system, we thought it was an analysis that could provide information directly related to clinical practice.

Although both sevoflurane and propofol cause loss of consciousness and reduction of BIS, their effect on BIS values is different. Loss of consciousness has been shown to be associated with different BIS values for both drugs, which may be as a result of their different neurophysiological effects. We have reflected this difference in the model, assuming a BIS of 61 for $C_{50,SEVO}$, and a BIS of 50 for $C_{50,PROPO}$. These data should be interpreted considering that the concept of additivity refers to the concentration of the drugs, not to their effects.

Classically, it is assumed that the additivity of two drugs implies that they act on the same receptor, and in this regard, these results are consistent with the laboratory study by Sebel and colleagues, in which it is shown that sevoflurane and propofol act in an additive manner on the GABAA receptor, although they probably act on different binding sites. However, the GABAA receptor, although it is fundamental in the action of these drugs, is not the only receptor that explains their anaesthetic action. More recently, it has been shown that additivity may also be possible with drugs that act on different receptors, although the general rule is that drugs that act on different sites of action interact synergistically.

This study has various limitations which are mainly because of the fact that the design chosen was to collect the data from standard anaesthetic procedures with drug doses adjusted to the specific needs of the patient, instead of controlled by the experimental protocol. Therefore, it cannot be interpreted as a laboratory study in which subjects are
subjected to experimental conditions with doses designed to optimize the pharmacodynamic results. \(^6\ ^{14}\) Specifically, our data do not include a wide range of \(E_{\text{SEVO}}\) and \(C_{\text{PRPRO}}\) pairs as in other controlled studies,\(^6\) and consequently our surface parameterization is not so strong. Although this approach limits the study methodology, it has the advantage that patients are not subjected to risks from clinically unjustified doses, and also that the data are obtained in conditions closer to anaesthesia in a real-life context. The use of drug \(C_e\) values predicted by a pharmacokinetic model instead of directly measured in plasma has been used in other studies, and is not considered an important source of error in these models.\(^6\ ^{17}\ ^{20}\ ^{21}\)

One of the limitations is that most of the results were obtained with \(\theta\) values close to 1, that is, with a predominant dose of sevoflurane, without achieving steady-state concentrations, and with low and decreasing doses of propofol. This may limit the ability of the model to predict the effects on BIS at other ratios of both drugs.\(^7\) Our study did not take into account the possible effect of hysteresis on recovery of consciousness with propofol, which may require an adjustment of the value of the slope of the dose–response curve,\(^9\) although this difference in the slope is not as large as would occur if the drug decreasing was sevoflurane.\(^{22}\)

Another limitation is that it did not take into account the effect of the other drugs used in induction (fentanyl and midazolam), which have been demonstrated to have mainly synergistic interactions with propofol and sevoflurane with regard to hypnosis.\(^7\) Low and similar doses were used in all patients, and it was assumed that they had a constant effect on the two study drugs. BIS is relatively insensitive to the doses of opioids typically used in clinical practice,\(^{17}\ ^{21}\) and also to the doses of midazolam we used. The fact that the model predicts BIS values somewhat higher than those observed could be attributable to the

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**Fig 4** Graphs showing the relationship between (a) \(U_{50}(\theta)\), (b) \(E_{\text{max}}(\theta)\), and (c) \(Y(\theta)\) at different normalized concentrations of sevoflurane and propofol expressed by \(\theta\).

**Fig 5** Standardized weighted residuals of the difference between measured and predicted BIS values for different ratios \(\theta\) of sevoflurane and propofol.
effect of these drugs on BIS, and could influence the low $U_{SD}(\theta)$ values (close to the criterion of synergy) which were found at some $\theta$ values.

Even with the above limitations, the model we obtained provides a graphic representation of the whole range of ratios of sevoflurane and propofol used clinically, which agrees with the results in the literature. The values estimated did not produce absurd results, and fulfilled the condition that values of $U_{SD}(\theta)$ and $\gamma(\theta)$ were always positive for the range $0 \leq \theta \leq 1$.7

The model we obtained provides an analysis of the interaction of the two drugs on BIS that may have clinical utility to guide on the expected effect of administering both drugs simultaneously, with the added value that the three basic parameters that are interrelated ($k_{SEVO}$, $C_{PROP}$, and BIS) may be available for monitoring or estimation in the operating theatre with currently existing technology.

In conclusion, we conducted a study on the pharmacodynamic interaction between propofol used in induction and sevoflurane used for maintenance of general anaesthesia, analysing its effect on BIS. Under the study conditions, it was confirmed that both drugs have an additive effect on BIS, with no evidence suggesting the existence of a synergistic effect for the concentrations of both drugs typically used in clinical practice.

Conflict of interest
This paper has not been published in any journal or presented at any congress.

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