The Pharmacodynamics of Hypnotic and Analgesic Drug Combinations as Measured by Clinical and Electroencephalographic Effects

Thesis submitted to obtain the degree of

Doctor in Medical Sciences

Bjorn Heyse

UNIVERSITEIT GENT

FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

The Pharmacodynamics of Hypnotic and Analgesic Drug Combinations as Measured by Clinical and Electroencephalographic Effects

Thesis submitted to obtain the degree of Doctor in Medical Science

Bjorn Heyse

Promotor : Prof. Dr. Luc De Baerdemaeker
Co-Promotor : Prof. Dr. Michel M.R.F. Struys

Table of Contents

Dankwoord

Na het afronden van mijn opleiding geneeskunde vatte ik de opleiding “Anesthesie en Reanimatie” aan. Van bij de start werd deze in goede banen geleid door Prof. Dr. Eric Mortier. Onder zijn alziend oog en dat van zijn collega’s stafleden, werden mijn jaargenoten en ikzelf de klinische vaardigheden die ons vak vereist, aangeleerd. De wetenschappelijke gangmakers binnen onze dienst waren op dat ogenblik Prof. Dr. Michel Struys, Dr. Hugo Vereecke en Dr. Luc De Baerdemaeker. Hun prikkelend enthousiasme rond wetenschap zorgde ervoor dat ik, al vanop “jonge” leeftijd, de mogelijkheid om te participeren aan onderzoek als een meerwaarde zag. En van het één kwam het ander… Na het beëindigen van mijn opleiding anesthesie had ik het geluk te kunnen aansluiten bij een toffe equipe. Anderzijds kreeg ik de kans om naast het vele klinische werk ook wat aan wetenschappelijk onderzoek te doen. Prof. Dr. Vereecke en Prof. Dr. De Baerdemaeker werden mijn steun en toeverlaat om deze wetenschappelijke ambitie verder vorm te geven. Zowel op theoretisch, technisch, organisatorisch als praktisch vlak kon ik met elke vraag bij hen terecht. De verandering der levenslopen had er intussen voor gezorgd dat ik, ondanks de afstand tussen Gent en Groningen, eveneens kon rekenen op een *ally* in het hoge noorden : Prof. Dr. Struys. Zonder deze vier mensen had ik zelfs niet kunnen dromen van een doctoraat. Daarom : ongelofelijk bedankt !!!

Een thesis maken is teamwerk. En het team dat ik nodig had was groot, heel groot. Ik wil mijn diensthoofd, Prof. Dr. Wouters, maar ook alle stafleden van onze dienst bedanken voor hun inzet. Zij zorgden ervoor dat ik vrijgesteld werd van klinische taken zodat ik ongestoord kon werken en stonden me, te gepasten tijde, bij met praktische en professionele ondersteuning. Ik mag natuurlijk ook mijn medeauteurs niet vergeten : voor het verwerken van de data, uitschrijven van de bevindingen, voor de talrijke discussies, voor de heldere uitleg, enz… Zonder jullie was deze thesis natuurlijk onbestaande.

Voor elke patiënt had ik, vóór aanvang van chirurgie, een tweetal uur onderzoek nodig in de operatiezaal. Wetende dat de zaal, met of zonder studie, toch om 16 uur dicht moest, wil ik de collega’s van de snijdende disciplines danken voor hun geduld en kalmte ! Ook de verpleegkundigen ben ik het één en ander verschuldigd : het kan niet makkelijk zijn om tijdens dergelijk onderzoek, waarbij absolute stilte in de zaal vereist is, aan alle willetjes van een veeleisende anesthesist te voldoen. Vervolgens wil ik ook het secretariaat van onze dienst danken voor de administratieve ondersteuning.

Het doornemen van dit werk was vermoedelijk een hele opdracht. Ik wens dan ook de leden van de examencommissie te danken voor hun constructieve en to the point opmerkingen.

Maar ondanks het grote belang van alle vooraf genoemde personen zijn er toch nog enkele mensen die ik buitengewoon veel verschuldigd ben… Mijn ouders : voor alle wijze raad, het luisterend oor en voor de geboden mogelijkheden… van welke aard dan ook. Mijn echtgenote : voor alle steun en begrip, in makkelijke en moeilijkere tijden. En vooral Bo en Oona : voor alle geduld, omdat ik er zoveel niet geweest ben wanneer ik er wel had moeten zijn…. Ik hoop dat het resultaat ook voor jullie alle moeite waard was.

Chapter 1 Introduction and aims

It has always been challenging to describe the phenomenon “anesthesia”. For nearly a century, and inspired by the single drug anesthesia, the state of general anesthesia has been described as a multi-featured phenomenon with one underlying mechanism, and, to be common for all general anesthetics with diverse chemical structures, this mechanism is supposed to be non-specific.[1,2] Using this theory, anesthesia is based on unitary non-specific mechanisms of anesthetic actions, one anesthetic may be replaced freely by another. In the case of anesthetic combinations, the anesthetic effect of mixtures is expected to be additive. The problem with the classic concept of the state of anesthesia became obvious when neuromuscular blocking agents, opioids, and barbiturates began to be widely used in combination with inhaled anesthetics.

It took until 1957, when Woodbridge described anesthesia by quoting its components : Amnesia, Analgesia, Akinesia and Attenuation of autonomic responses and sensory reflex blockade.[3] In 1998, Peter Glass described an eminent paradigm shift of the definition of general anesthesia.[4] He depicts the latter as a balance between a state of unconsciousness of the brain, mediated by hypnotics and on the other hand a form of inhibition of the noxious stimuli reaching the brain. This inhibition can be mediated by the action of opioids at the opioid receptors situated in the spinal cord or by local anesthetics on peripheral nerves. Since then, general anesthesia can be described by its two components : the “hypnotic” and the “analgesic” component.

The hypnotic component of anesthesia can be measured by using intermittent clinical endpoints (e.g. a response from the patient to a verbal command)[5,6] or by continuous measures of cerebral drug effect (e.g. spontaneous or evoked electro-encephalographic monitoring).[7,8] The analgesic component of anesthesia is the net physiological result of the simultaneously opposing effects of nociception and anti-nociception mediated by medication. Controlling the hypnotic component of anesthesia is rather easy as more hypnotic drug will result in a more extensive cerebral drug effect. In contrast, the balance between nociception and anti-nociception is more complex and more difficult to control as anesthesiologists can only manage anti-nociception. The nociceptive part is the result of varying noxious stimuli during the surgical procedure. Dichotomous measures (e.g. movement of the patient in response of a tactile or noxious stimulus) or continuous measures (e.g. arousal responses measured by electro-encephalographic alterations or changes at the level of the autonomic nervous system such as heart rate or blood pressure changes) of the analgesic component of anesthesia will always be the result of both anti-nociception and nociception (if present).[9]

Each drug given to control one of the components of anesthesia is governed by a specific dose-response relation. This relation can be divided into a pharmacokinetic and a pharmacodynamic part. The pharmacokinetic relation describes the time course of the plasma concentration of this drug after a given dose. The pharmacodynamic relation depicts the connection between that specific plasma concentration and the resulting clinical effect. As the site of drug effects is mostly outside the plasma, hysteresis or a delay between the

plasma concentration and the effect arises. This can be modeled by using a virtual effect-site concentration or biophase. For every effect-site concentration there is a corresponding effect without time delay.

It is apparent that when administering two (or more) drugs to a patient in an attempt to control both components of anesthesia, these drugs will interact which each other at both the kinetic and dynamic level. Although kinetic interaction nearly always exists, we will focus in this thesis on the pharmacodynamic interactions solely hereby accepting the fact that a kinetic interaction will always result in a dynamic one. Classically, pharmacodynamic drug interactions are described as additive, synergistic or antagonistic (see Figure 1).[10]

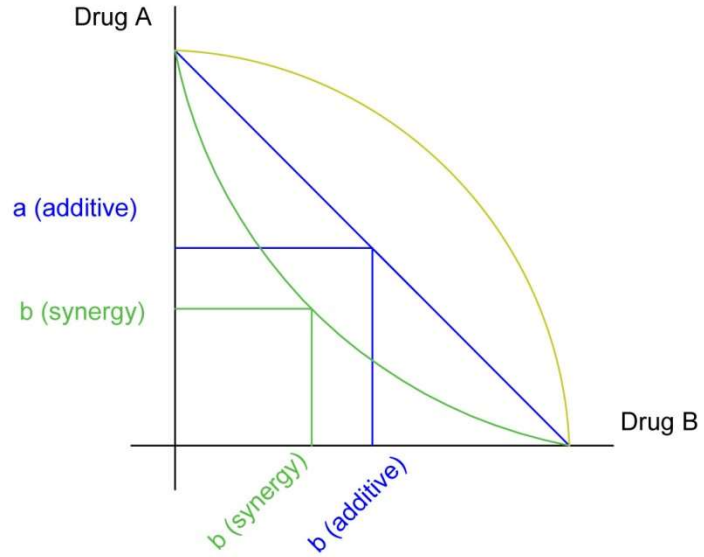


Figure 1

Isoeffective doses of a two drug combination

Classical isobolographic representation of the pharmacodynamic drug interaction between two drugs, A and B with the corresponding doses a and b. Each point in an isobole represents a dose combination of A and B, resulting in an equal effect. If the drugs have an additive relationship the isobole is a straight line (blue curve). If the isobole deviates away from the origin, indicating that more drug is needed to achieve an equal effect, the relation is infra-additive (yellow curve). If, in the opposite, the isobole bends towards the origin, the interaction is synergistic (green curve).[11]

The classical two-dimensional representation of a drug interaction can only depict one level of combined drug effect. If one wants to study the entire range of drug effect (between no effect and maximal effect, respectively E_0 and E_{max}) a three dimensional study design and representation is required as shown in Figure 2. This representation is called "response surface drug model". (see Chapter 2).

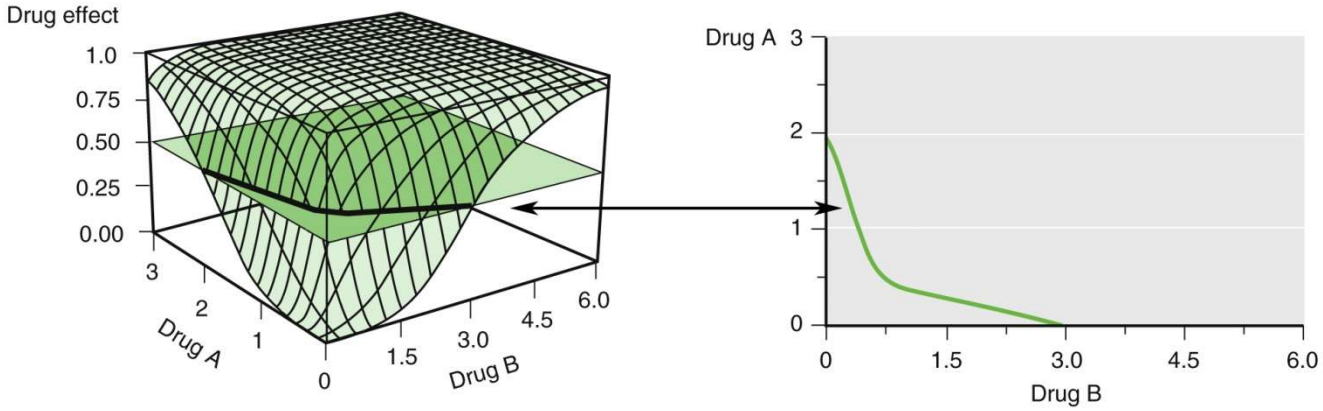


Figure 2

Relationship between a response surface and a standard isobologram

A three dimensional response surface offers the possibility to characterize the full concentration-response relation. In fact, an isobologram is a horizontal section of the response surface (e.g., 50% drug effect as in the right part of the picture). *(Modified from Miller's Anesthesia, 8th ed., Chapter 33, used with permission.)*

In order to study the drug interaction for both hypnotic and analgesic components of anesthesia, we have to document the drug interactions between these two. As such, we focused in this thesis on the interaction between hypnotics and opioids. Previously, others described interactions between propofol-fentanyl,[12–14] propofol-midazolam-alfentanil,[11,15] propofol-alfentanil-nitrous oxide,[16] propofol-alfentanil[17–19], propofol-opioids,[20,21] propofol-remifentanil,[22–27] desflurane-fentanyl,[28] desflurane-remifentanil,[29] sevoflurane-fentanyl,[30–32] sevoflurane-remifentanil,[33,34] isoflurane-fentanyl[35–37], isoflurane-alfentanyl,[36] isoflurane-sufentanyl,[38] isoflurane-remifentanil,[39]... and hereby also described various surface modeling strategies for pharmacodynamic interactions.

During anesthesia, volatile anesthetics such as sevoflurane (with or without nitrous oxide) are frequently combined with opioids such as remifentanil. Therefore, we aimed at describing the relationship between those two (or three) drugs. The published knowledge on these drug interactions can be considered incomplete. Previously, Manyam and colleagues developed a response surface model for various pharmacodynamic responses using a Logit model approach and found synergy between sevoflurane and remifentanil for all responses.[40] Unfortunately, as this study suffered from nonsteady-state conditions at the moment of the observations, these researchers improved their data using calculated effect-site sevoflurane concentrations and a specific surface model instead of a Logit approach.[41] Accounting for the lag time between sevoflurane effect-site concentration and end-tidal concentration improved the predictions of responsiveness during anesthesia but had no effect on the accuracy of prediction of a response to a noxious stimulus in recovery. They concluded that models may be useful in predicting events of clinical interest, but large-scale evaluations with numerous patients are needed to better characterize the interaction.

As a result, we aimed in this thesis to enlarge the knowledge on the interaction between sevoflurane, nitrous oxide and opioids using both dichotomous and continuous measures of drug effect. Secondly, we hypothesized that the applied surface model approach might influence the resulting interaction and has to be explored during the model development. Thirdly, we aimed at using a response surface interaction model to develop a new predictive anesthetic state index.

Initially, we studied the interaction between sevoflurane and remifentanil using tolerance to shake and shout, tolerance to a tetanic stimulus, tolerance to the insertion of a laryngeal mask and tolerance to laryngoscopy as clinical measures. Additionally, we studied the influence of the various surface modeling approaches on the interaction model using these data (Chapter 3). We also studied the response surface model approach during sevoflurane-remifentanil interaction using various EEG and autonomic nervous system derived continuous measures with or without noxious stimulus ("the pharmacodynamics shift") (see Chapter 4). As nitrous oxide is still used to supplement inhaled anesthetics such as sevoflurane, we analyzed the triple interaction between nitrous oxide, sevoflurane and opioids on the hypnotic and analgesic component of anesthesia using the response surface approach (Chapter 5).

In an attempt to use drug interaction models as the input of a predictive anesthetic state index, we developed the NSRI (noxious stimulation response index). The NSRI is proposed to predict, based on the effect-site concentrations of an opioid and an anesthetic, the likelihood of response to a noxious stimulus, being the tolerance to laryngoscopy (Chapter 6). More recently, we enlarged and adapted the original NSRI to deal with triple interaction models estimating the potency of any combination of sevoflurane, propofol and remifentanil in terms of the probability to tolerate laryngoscopy (Chapter 6).

In order to assist the less experienced reader, we added a chapter (see Chapter 2) to explain the basic and theoretical concepts used in our studies.

Chapter 2 Basic principles and review of the literature

Anesthesiologists combine several agents in order to achieve multiple goals simultaneously. Rapid loss of consciousness during induction, adequate depth of anesthesia during maintenance, analgesia during surgery and afterwards, fast emergence, hemodynamic stability and control of the respiratory depression are some of the challenges. To redeem these objectives, intravenous drugs, inhaled anesthetics, opioids, neuromuscular blocking agents and locoregional techniques are routinely combined. Nowadays these drugs are usually administered using standard dosing regiments, the clinical evolution of the patient, and the clinical experience of the anesthesiologist.

Optimisation of combing anesthetic drugs to obtain a predefined level of anamnestic and analgetic effect requires the ability to measure these effects. Furthermore, thorough knowledge of multiple single drug dose response relationships is needed to adjust the dose of the administered medications to achieve the intended effects. Additionally, well-defined interaction models are nessecary to estimate the effects of the applied drugs on eachother.

1 Measuring the effect

11 Continuous parameters

General anesthesia can be achieved by an extremely diverse group of drugs. Nevertheless, the mechanisms of action to produce a reversible loss of consciousness are still a mystery.[1] EEG monitors have been used in different anesthetic states in an effort to gain insights into the working principle of anesthetics. It revealed that, with increasing depth of anesthesia, there was a progressive increase in low frequency, high amplitude activity and a decrease in the high frequency activity.[42,43] This observation has led to a search for an objective, reproducible and continuous measure of cerebral hypnotic drug effect and subsequently to the development of monitors that interpret the changes in neurophysiologic endpoints.[44] The major advantage of this technology is the availability of continuous information on the cerebral state even during conditions during which patients have lost all responses to a verbal or painful stimulus.

111 The Bispectral index

The bispectral index (BIS, Covidien) is an empirically derived complex parameter, derived from a raw EEG signal measured with a specific sensor taped on the forehead. Three different processing techniques including bispectral analysis, power spectral analysis, and time domain analysis are used to calculate disparate descriptors from the collected EEG signal. Each descriptor is designed to discriminate different EEG signals corresponding with different levels of anesthesia. Consequently, they all have a specific range at which they

perform best. A proprietary algorithm combines these different descriptors to optimize the correlation between the obtained EEG signal and the clinical effects of anesthesia.[43,44] A schematic depiction can be found in Figure 3.[45]

The resulting dimensionless number ranges between 100 (fully awake) and 0 (isoelectric EEG). A BIS value between 40 and 60 indicates an appropriate level for general anesthesia. There are numerous studies that demonstrate a good correlation between clinical hypnotic effects and BIS.[6,22,25,46–49] Although there is a good correlation between BIS and the level of hypnosis, there are many potentially confounding variables.[43]

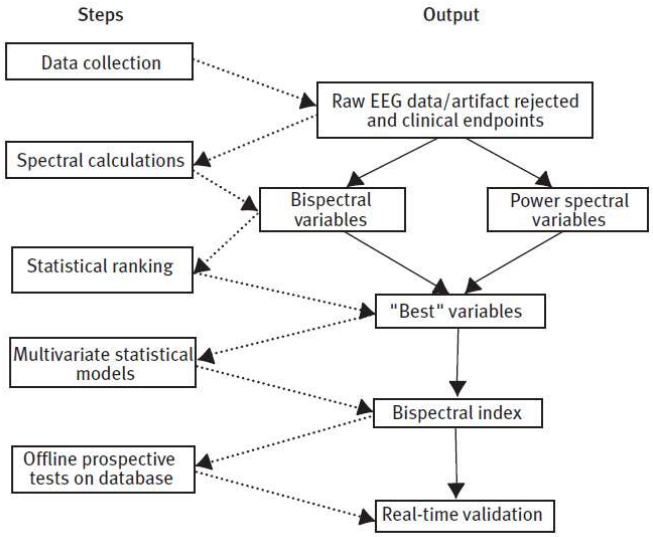


Figure 3

Development process of the BIS.

(modified from Bispectral Guidelines, Aspect ®, Natick, USA)

112 Entropy

In the context of information theory, entropy describes the irregularity, the randomness or the unpredictability of a signal. A completely predictable signal such as a fixed magnitude or a sine wave gives an entropy of zero. If a signal exists of sequential, but randomly chosen values, following unknown values are difficult to estimate and therefore such a signal has high entropy. Absolute scales like amplitude or frequency of a signal have no influence on regularity or predictability of that signal, and will not affect entropy. The idea of using entropy to estimate the depth of anesthesia originates form the preposition that the irregularity within an EEG signal decreases with increasing levels of anesthetic drugs in the brain. To quantify this “amount of order” in the EEG, different entropy concepts have been applied.[50–52]

To define entropy in real time, a time window or "epoch" is needed. The optimal length of the epoch is related to the frequency range of interest. Estimation of lowest frequency variations in the signal must be feasible and therefore the time window must be sufficiently long. Since the EEG signal consist of a wide frequency range, a set of window lengths is chosen in order to achieve an optimal balance between time and reliability to estimate accurate data. This way short epochs for high frequency ranges result in a short response time and long epochs ensure accurate data even for low frequency ranges.[52]

With spectral entropy, it is possible to calculate the contribution of a defined frequency range to the total entropy. EEG derived from the forehead of a patient contains a considerable amount of electric noise created by muscle activity or frontal electromyographic activity (EMG). During anesthesia, the EEG signal dominates the frequencies lower than 30 Hz. At higher frequencies, an exponential decrease in EEG power is noted and EMG dominates the signal.[24,52]

The first commercial available monitor based on spectral entropy is the Datex-Ohmeda S/5 Entropy Module (GE Healthcare, Helsinki, Finland). This monitor generates two indices, the State Entropy (SE) and the Response Entropy (RE). Response Entropy is calculated from the signals in the 0.8 to 47 Hz range, and thus enclosing both the EEG and EMG dominant part of the spectrum. The response time of RE is very fast, typically less than two seconds. In analogy of the BIS, this is reflected in a dimensionless number between 0 and 100. EMG activity is especially noted during the awake state. The epochs of RE are selected in such way that very fast response times are achieved. Considering the two latter, the objective of RE is to provide an indicator of arousal. However, RE can also be affected by other confounding factors, for example neuromuscular blocking agents.[53–55]

The range from 0.8 to 32 Hz excludes the EMG dominant part of the spectrum and the entropy calculated from this frequency range is called State Entropy (SE). Therefore, the State Entropy value is always less or equal to the Response Entropy value, with a maximum value of 91. In an attempt to create a stable indicator of the effects of hypnotics on the cortex, the epochs of SE are determined to remove transient fluctuations from the data. So SE tries to reflect the cortical state of the patient more precisely but with a bigger time delay than RE. The clinically relevant target range for both entropy values is 40 - 60.

As for BIS, various papers concluding that there is a good correlation between the hypnotic state and entropy have been published.[7,22,24,49,51,54]

113 Surgical Pleth Index

Although different EEG derived parameters, such as BIS and entropy, have been validated as measures of the hypnotic component of anesthesia, their ability to estimate the analgesic component of anesthesia accurately, is limited.[7,48,56,57] Injury, trauma or surgery results in a stress response, mediated by autonomic, metabolic and hormonal changes. Since those changes will influence other physiological parameters like heart rate, blood pressure, levels of circulating catecholamines, etc… various physiological measures have been studied with

the objective to reflect the balance between nociception and anti-nociception. One of them, the Surgical Pleth Index (formerly known as the Surgical Stress Index[58], GE Healthcare, Helsinki, Finland), is a multivariate numerical index, ranging between 0 and 100. A value of 100 indicates a high stress level, values between 20 and 50 have been proposed as adequate analgesia.[59] It is based on the pulse wave amplitude of photoplethysmography (PPGA) and the heart beat interval (HBI) derived from the photoplethysmographic waveform. To decrease the inter-individual variability that is not related to surgical stress, the two parameters are normalized using histogram transformation.[58,60] Furthermore, this normalization procedure adjusts the individual values so that they are in a scale between 0 and 100. In the following formula $PPGA_{norm}$ and HBI_{norm} are respectively the normalized PPGA and HBI.

Equation 1

$$\boldsymbol{SPI = 100 - (0.7 \times PPGA_{norm} + 0.3 \times HBI_{norm})}$$

Published data show that SPI is capable of detecting noxious stimuli and the influence of analgesics on it.[61–65] However, other factors like pacing, drugs affecting the heart rate[66], intravascular volume status[67,68], posture[69], etc … may influence the measured variables and consequently the SPI.

114 Composite Variability Index

Alterations in BIS values in response to noxious stimulation have been extensively documented. Different authors have reported that these responses can be blunted with the addition of opioids or higher doses of hypnotics.[57,70,71] These findings gave birth to the idea that the magnitude of the fluctuations in BIS values in response to noxious stimulation may provide a direct measure of antinociception. Analysis of a retrospective dataset yielded the Composite Variability Index (CVI), a weighted combination of 3 variables : sBIS, sEMG, and BIS.[72] sBIS and sEMG are respectively the standard deviations of BIS and EMG signal over the previous 3 minutes, and are computed every second. So CVI should be regarded as an index scaled between 0 and 10 representing the total variability in a single measure. The function describing the Composite Variability Index (CVI) algorithm has the following form :

Equation 2

$$\boldsymbol{CVI = 10 \times \left(\frac{1}{1 + e^{-(\alpha_1 sBIS + \ _2 sEMG + \alpha_3 BIS + \alpha_4)}} \right)}$$

Artifact removal and preprocessing of BIS and EMG, as well as the specific weights, α_i, are proprietary and unpublished. As for other indices, confounding variables like the application of neuromuscular blocking drugs, may impede the interpretation. Some authors even question the usefulness of this parameter as an index of the balance between nociception and anti-nociception.[9]

12 Dichotomous parameters

The Observer's Assessment of Alertness/Sedation (OAA/S) Scale was developed to measure the level of alertness in sedated patients.[5] This scale is assessed by applying progressively more intense stimuli, ranging from a moderate speaking voice to physical shaking until a response is observed. shows the five levels of the OAAS scale.[73] In order to have the possibility to assess the response to moderate noxious stimuli (trapezius squeeze), a level 0 was added later as a modification of the scale (Modified OAAS).[74] The Observer's Assessment of Alertness/Sedation Scale has been used in numerous articles to validate the performance of depth of anesthesia monitors such as BIS[7,75] or AAI.[56] Responses to verbal commands are defined by an OAAS scale of 3 – 5. Responses to tactile or noxious stimuli are defined by the lower levels 0 – 2. The OAAS scale is one of the few scales whose reliability has been documented.[5,6] Nevertheless, in certain conditions, patients might not respond to the verbal and tactile stimuli, although awake. Furthermore the highest practically feasible frequency of assessments of a patient's degree of sedation is approximately every 10 seconds.[73]

Table 1

The Observer's Assessment of Alertness Sedation (OAAS) scale.

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic reponse to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

The results from an OAA/S score can be seen as dichotomous data since each assessment will result in a present or absent response. To test the extent of an analgesic effect, different painful stimuli can be applied which may be or may not be followed by a response. Throughout the literature multiple noxious stimuli such as tetanic stimulus applied to the forearm, laryngeal mask placement, and others have been used to estimate the influence of an analgesic effect. In the current literature laryngoscopy has been routinely applied as a standard noxious stimulus.[26,27,37,40,41,76]

2 Single drug dose-response relationship

To better understand the full dose response relationship for two drugs it is necessary to elaborate on the single drug dose relationship.

For each drug, the relation between an administered dose and effect, summarized in Figure 4[77], can be divided into three parts: pharmacokinetics, pharmacodynamics and the coupling of them. The relationship between the dose and the resulting blood concentration is described in the pharmacokinetic phase. The Pharmacodynamic phase depicts the association between the blood concentration of a drug and the clinical effect. Stated otherwise : pharmacokinetics is "what the body does to the drug" whereas pharmacodynamics can be described as "what the drug does to the body". The coupling between the pharmacokinetics and dynamics is the final step which involves taking into account hysteresis by defining a (virtual) effect stie concentration and invoking a k_{e0}.

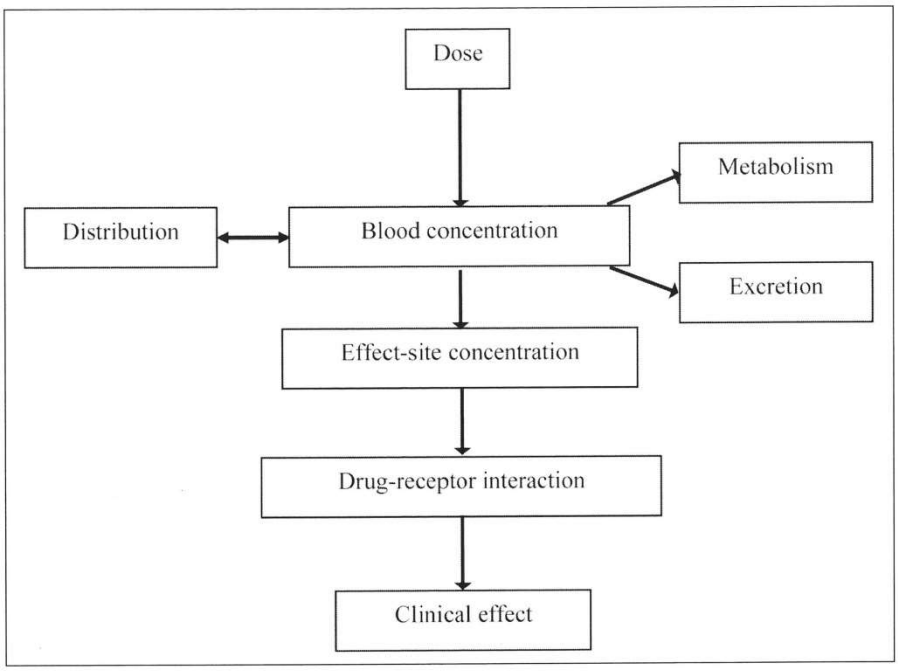


Figure 4

Schematic representation of the pharmacokinetic and dynamic processes determining the relationship between administered dose and resulting clinical effect.

When drugs are injected, they are distributed to different groups of tissues, where they are taken up. The speed and amount of the uptake is depending on multiple factors : tissue perfusion, concentration differences, permeability characteristics, lipid solubility, etc ... Drugs can be bound at different binding sites and if the drug is metabolized biotransformation occurs, with or without formation of active metabolites. The drugs (and metabolites) are also distributed to the eliminating organs, so clearance starts immediately. The time course of the drug concentration is affected by all those factors. To make a description of the time course of the drug concentration, compartment models have been created. Compartments are mathematical concepts which do not correspond to a physiological or anatomical volumes but they can be used as parameters to make a model. Many drugs used in anesthesia distribute extensively into different body tissues. The

concentration changes over time of these drugs are often poorly described by a single compartment advocating the use of multi-compartment models.[78–81]

The concept can be illustrated graphically (Figure 5) if we replace a compartment by a barrel of water. The drug concentration could be the height of the water in the barrel. The amount of water added to the barrel represents the amount of drug administrated to the patient. A hole made in the barrel represents drug elimination. Multi-compartment models can be depicted as a system with multiple barrels connected by small hoses of different diameters.[82,83] There are several ways to parameterize compartment models. It can be described by rate constants and volumes of the compartments. Otherwise it can be expressed using a poly-exponential equation.

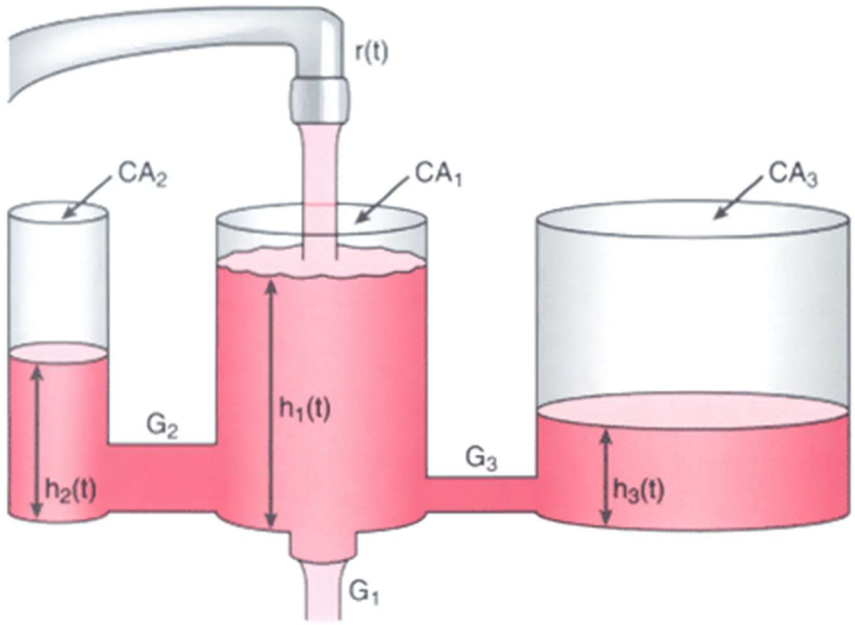


Figure 5

Hydraulic model analogy of three-compartment pharmacokinetic model.

The height, hi (t), represents the water level in each compartment. Each bucket is characterized by a cylindrical area, CAi , and the pipes connecting the buckets to each other or to the outside world are characterized by a conductance, Gi . Water enters bucket 1 at the rate r(t) and leaks irreversibly through G1.
From Hughes MA, Glass PS, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 76:334–341, 1992.

Apart from the difficulties in calculating the dosage scheme to obtain a constant blood concentration, this is not the anesthesiologist's target. Anesthetics have their intended effect in the brain, not in the blood. It is well known that after an intravenous bolus dose, it takes time to establish an effect : the drug must be transported to the tissue, diffuse to the cytoplasm, bind to a receptor, and give rise to a process which can evoke an effect. Each step will delay the time course of the effect. In contrast to non-anesthetic drugs, where the delay between administration and peak effect may not be so important, the lag time has a

huge impact on the modelling of the effect of anesthetics. To avoid this problem the effect compartment with a corresponding effect-site compartment was introduced.[84–86] For any concentration in this virtual compartment there is, by definition, a corresponding effect without time delay between the effect-site concentration and the effect. Like the other compartments, the concentration in the effect-site compartment can be described by rate constants (k_{e0}). To avoid influence of the effect-site compartment on the estimates of the rate constants, the volume is, by convention, zero. In order to obtain accurate estimates of the effect and reproducible effect-site concentrations most pharmacodynamic studies tend to use steady state conditions.[78]

The relation between a single drug concentration and the effect can be described by the Hill equation or sigmoidal E_{max} model.[87]

Equation 3

$$E = E_0 + E_{max}\left(\frac{C^{\gamma}}{EC_{50}{}^{\gamma} + C^{\gamma}}\right)$$

E_0 represets the baseline effect, E_{max} represents the maximum effect, C is the durg concentration, EC_{50} is the drug concentration for which 50% of maximum effect is obtained and γ defines the steepness and is called the "Hill coefficient of sigmoidicity". While E_{max} is a measure of the drug efficacity, C_{50} provides a measure of drug potency. Since the baseline effect for anesthetic agents is normally equal to zero, E_0 is frequently omitted (Figure 5).

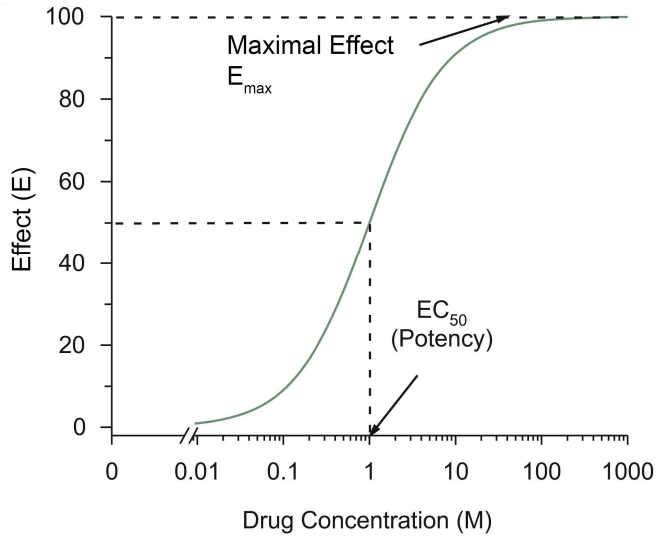


Figure 5

Sigmoidal E_{max} curve

The potency of inhaled anesthetics is often described using the minimal alveolar concentration (MAC). This parameter, introduced by Eger et al. reflects the alveolar concentration at which 50 % of subjects are unresponsive to a standard surgical stimulus[88].

Consequently, it is rather a description of a quantal response in the population than a quantification of the magnitude of effect like the C_{50}.

3 Interaction

The word synergism originates from the Greek words sun (= together) and ergon (=work). They were combined in the mid-19th century to the Greek word "sunergos". An intuitive pharmacological definition is that synergism occurs between two agents when the observed effect of a combination is more than what would be predicted from the sum of the individual effects from each agent. Antagonism can be determined as the opposite of synergism : the resulting effect of the combination of drugs will be less than in additive conditions. If drugs are additive the effect is equal to the sum of the individual effects of each agent.[10,89]

Interaction may occur at different levels, even before absorption or delivery (eg physical drug interactions). Drug interactions may also involve the pharmacokinetics, the pharmacodynamics or both processes. An example could be the interaction of propofol and midazolam : they have an interaction on the pharmacokinetic level by reducing the clearance of each other. They both act on the gamma-aminobutyric acid (GABA) receptors resulting in a pharmacodynamic interaction as well[90,91].

31 Isobolograms and response surfaces

The full dose-response relationship for two drugs can be displayed using a three dimensional representation. Every combination of the two drugs (represented on the X and the Y axis, respectively drugs A and B) corresponds with a point on the vertical Z axis, the height of which is the drug effect. Together, all these points will form a response-surface representing the relation between the effect and the administered combination of drugs.[11,92] There are multiple steps between the administration of a drug and the effect, resulting in significant interindividual differences. In order to describe the effect of interaction it is mandatory that patients receive comparable doses of each drug or, stated otherwise, that the concentration of the drugs is expressed in terms of effect-site concentration.

Multiple mathematical models have been used to clarify interaction characteristics. The result of these models can be presented in various graphs. In an isobologram, the concentrations of two drugs are represented on the axes of a two dimensional figure. Each point in the isobole represents a dose combination of the studied drugs, resulting in an equal effect. If the drugs have an additive relationship the isobole is a straight line. If the isobole deviates away from the origin, indicating that more drug is needed to achieve an equal effect, the relation is infra-additive. If, in the opposite, the isobole bends towards the origin, the interaction is synergistic.[11] Although isobolograms are valuable tools that can demonstrate the equal effect for a scala of drug concentrations, it must be clear that isobolograms have significant shortcommings. First, the extent of interaction is not necessarily a constant in the total range of effect : drugs could exert synergism in the high effect range and show antagonism in the low effect range.[93] This problem can be partially

circumvented by simultaneous plotting isobolograms of different levels of effect in one graph : a “multiple isobologram”. Secondly, in certain interactions, the isobologram indicates both antagonism and synergy in different regions of the curve.[94,95]

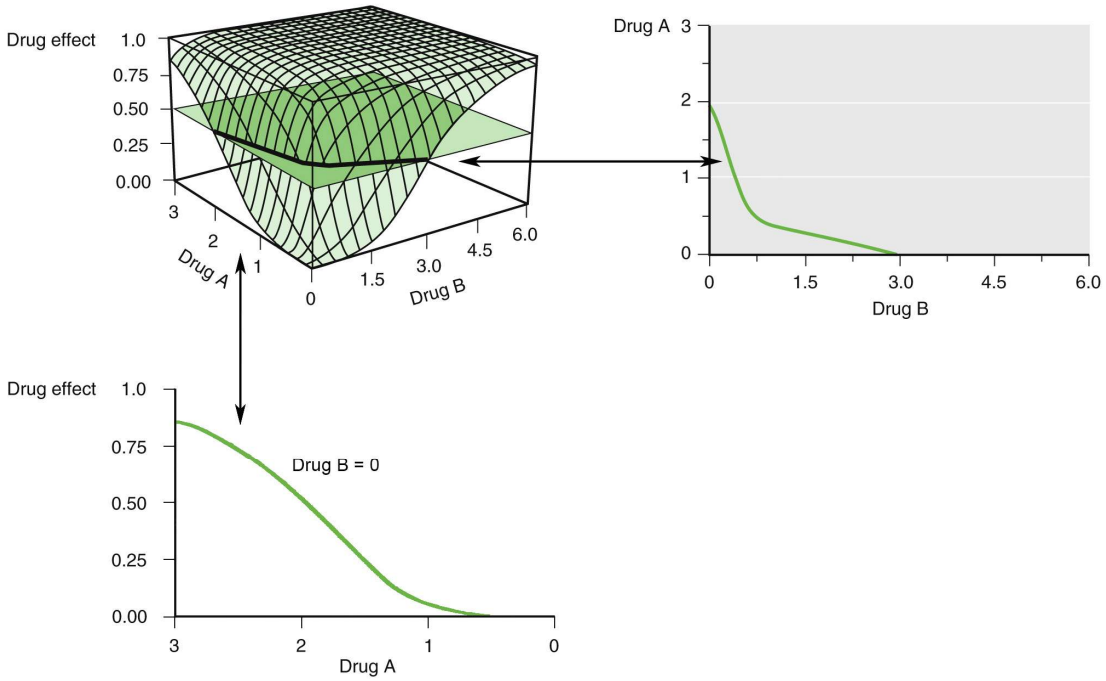


Figure 6

Relationship between a response surface and a standard isobologram

A three dimensional response surface offers the possibility to characterize the full concentration-response relation. In fact, an isobolgram is a horizontal section of the response surface (e.g., 50% drug effect as in the right part of the picture). A vertical section of the response surface yields to a dose response curve of one drug combined with a fixed concentration of the second drug.
(Modified from Miller’s Anesthesia, 8th ed., Chapter 33, used with permission.)

An extension of this method is a three dimensional graph wherein the drug concentrations are represented in the horizontal axes and the observed effect in the vertical axis. It has the advantage that it offers the possibility to characterize the full concentration-response relation. In fact isoboles are a horizontal section of the response surface. Vertical sections parallel to one of the axes results in a dose response curve fore one drug combined with a constant concentration of the second drug. Sections passing through the vertical axis and one of the horizontal axes describe the dose response curve for one of the drugs solely. A vertical section through the origin of the coordinate system returns a dose response curve for one specific drug ratio. Dose response curves from these different vertical sections can be described mathematically with a “Sigmoidal E_{max} model”. Analogous to the technique of plotting multiple isobolograms in one graph, “multiple dose response curves” can be plotted. In that case several dose-response curves are plotted in the same graph, each with a different fixed concentration of the second drug.[96,97] Vertical sections trough the origin result in a Hill-curve, illustrating the effect versus the dose of a certain drugratio.[89,98]

Although this model for representing drug interactions was first proposed in 1872 by Fraser reporting the antagonism between atropine and physostigmine, technical limitations and the fact that more complex mathematical approaches are advocated to generate a 3D surface yielded that the technique fell into disuse for several years.[95,96,99] Despite its shortcomings, the intuitively attractive and in many circumstances easily usable isobologram, became very popular for many years. In 1990, Greco induced a revival of the response surface and in the following ten years the response surface became the gold standard.[10,11,89] Eight years later, Glass described an eminent paradigm shift of the definition of general anesthesia.[4] He depicted the latter as a balance between a state of unconsciousness of the brain, mediated by hypnotics and on the other hand a form of inhibition of the noxious stimuli reaching the brain. This inhibition can be mediated by the action of opioids at the opioid receptors situated in the spinal cord or by local anesthetics on periferal nerves. With this idea in mind, a more physiological based concept, specifically mirroring the interaction between opioids and hypnotics, called the hierarchical model, was introduced in 2004.[26]

32 Additivity, synergy and infra-additivity

The concepts additive, synergistic and antagonistic interactions are intuitively easy to understand. The knowledge of the effects evoked by the application of single drugs allows us to estimate the effect if two of those drugs are combined. If the observed effect is more pronounced than expected it is called synergistic. If the observed effect is equal to the estimation than it is termed additive. In case of a less pronounced effect than expected from addition we name it antagonistic. However, the problem is how to define "simple additivity"… Moreover, the definition of "no interaction" is fundamental, since this will influence the nature of the interaction.[100] Two commonly used concepts defining "no interaction" deserve a closer look : Loewe additivity and the Bliss independence. Originally, both models were designed to describe simple enzyme reactions and both are equally logic, reasonable and theoretically underpinned.[101,102]

321 Loewe additivity

The concept of Loewe's additivity is inseparable from the isobologram approach and is based on the idea that one drug cannot interact with itself.[103] A straightforward way to clarify the concept of Loewe additivity is a sham experiment : presume that we administer a combination of drug A and drug B simultaneously, knowing that drug B is a dilution of drug A. The effect evoked by the combination of drugs A and B will result in a straight line isobole, or the isobole defining "no interaction", illustrating the basic principle : one agent cannot interact with itself. This imaginary experiment also illustrates the limitations of the concept. Drugs A and B could have different maximal effects or they could have different slopes in their dose-response relation making the isobole of "no interaction" a curved line.[100] Furthermore, in this concept, both drugs have the same site and mechanism of action.[89,104] Loewe additivity can be described mathematically by the following equation :

Equation 4

$$Interaction\ Index = \frac{d_A}{D_A} + \frac{d_B}{D_B}$$

In this equation d_A and d_B are the doses of drug A and B in a mixture evoking a specified effect (eg. 50 % of maximal effect). D_A and D_B are, respectively, the doses of drug A and B, that evoke an equal effect when given alone. If the interaction index equals 1 there is no interaction or there is an additive situation. If the interaction index is less than 1, there is synergism and if the interaction index is more than 1 antagonism is noted.

322 Bliss independence

Bliss independence is based on probabilistic independence. It implies that, if there is no interaction, two drugs behave completely independent from each other or they don't cooperate biologically, chemically or physically. This can be explained with the following example : assume that dose d_A from drug A has an effect E_A. Similary, the response of drug B alone is E_B. Since the two drugs behave independently and the effects of drug A are already present, drug B can only elicit an effect on the remaining possible response : $1 – E_A$. In case of an additive interaction the additional effect of drug B will be $(1-E_A) \times E_B$. Therefore the total effect due to the combination of drug A and drug B, presuming additive effect, will be $E_A + E_B (1 – E_A)$ which equals $E_A + E_B – E_A \times E_B$.[105] If the observed effect resulting from the combination of drug A and drug B, is more pronounced than the effect in case of Bliss independence, the interaction is called synergistic. If, in contrast, the observed effect is less pronounced the interaction is called antagonistic.[106] As for Loewe additivity, the maximal effect of both drugs has to be equal. In contrast to the concept of Loewe additivity, Bliss independence is not consistent with an isobolographic approach.[107]

33 Interaction models in anesthesiology

The graphical representation of an interaction is the result of a mathematical model. Today, several models have been proposed to describe hypnotic-opioid drug interaction.

As described in the previous section, a vertical section of the response surfaces results in a so-called "Sigmoid E_{max} model". The Hill-equation (Equation 5) is widely used to describe the relationship between the effect (E) and the drug concentration (C).

Equation 5

$$E = E_{max}\left(\frac{C^{\gamma}}{EC_{50}{}^{\gamma} + C^{\gamma}}\right)$$

EC_{50} is the drug concentration for which 50% of maximum effect is obtained and γ defines the slope and is called the "Hill coefficient of sigmoidicity".[87] Regarding the same effect, large differences in potency between various drugs can exist. This can be overcome by using normalized concentrations : for two drugs with different potency the maximal effect corresponds with a normalized concentration equal to 1. In mathematical terms the normalized concentration, U, is the concentration divided by the EC_{50}. This transforms Equation 5 into :

Equation 6

$$E = E_{max}\frac{\left(\frac{C}{EC_{50}}\right)^{\gamma}}{1 + \left(\frac{C}{EC_{50}}\right)^{\gamma}} = E_{max}\frac{U^{\gamma}}{1 + U^{\gamma}}$$

With little rearrangement of the formula the effect can be expressed as a percentage of the maximal effect or as a probability of no response for dichotomous data.

Equation 7

$$P = E/E_{max} = \frac{U^{\gamma}}{1 + U^{\gamma}}$$

If the probability or an extent of effect are predefined, U can be calculated from this formula. In case of drug interaction U can be replaced by the appropriate equation, obtained from the interaction model. Regarding interaction between opioids and hypnotics, different models have been proposed : the logistic regression model, the Greco model, the reduced Greco, the Minto model, the Hierarchical model and finally the modified Hierarchical model.

331 The logistic regression model

The logit is a term used in mathematics to describe the negative natural logarithm of the odds ratio. Drug- response models of single drugs are frequently modelled using a logistic regression model using the logit as a linear function of drug concentration. This responds in

Equation 8

$$log_e(odds\ ratio) = ln\left(\frac{P}{1-P}\right) = \beta_0 + \beta_1 \cdot (C)$$

where P is the probability of effect and where β_0 and β_1 are modelled parameters. After some algebra and substituting β_0 with $-\gamma \cdot \ln(C_{50})$ and β_1 with γ it results in Equation 7. Several drug interactions have been modelled by making use of an extension of a logistic regression model for single drug responses.[18,28,31] However, the multiple logistic regression approach has several shortcomings, advocating other modelling techniques, based on accepted pharmacodynamic principles.[11]

332 The Greco model

The Greco model is a response surface model based on an extrapolation of the equations describing the 50 % effect isobole of Loewe.[10] It was designed with the objective to provide a quantitative assessment of drug interaction. The model is characterized by an "interaction" or "non-additivity" parameter α, reflecting the type and magnitude of interaction :

Equation 9

$$1 = U_A + U_B + \alpha\, U_A\, U_B$$

U_A and U_B are respectively the normalized effect site concentrations of drug A and B. If α = 0 there is additivity (or no interaction). If α is positive, synergism exists and the isobole bends toward the origin. If α is negative the interaction can be described as antagonistic. Keeping the 50% effect in mind and applying this in Equation 7, U equal to 1, is obtained. After extrapolation to the whole spectrum, U symbolizes the normalized effect site concentration of the drug combination yielding to :

Equation 10

$$U = U_A + U_B + \alpha\, U_A\, U_B$$

The Greco model has some constraints : Firstly, the Hill coefficient γ is a constant for all drug combinations of A and B. Inherently the slope factor of the dose response curve for the single drugs should be similar. Secondly, the maximal effect of both drugs should be identical. Thirdly, the interaction parameter α is a constant for the entire range of effect and consequently does not allow different levels of interaction at different levels of effect.

It is well known that opioids cannot reliably produce amnesia or hypnosis.[108,109] This phenomenon will yield to unrealistic high estimations of the opioid EC_{50}, making the assumption regarding the equal maximal effect, hard to accept. In situations where one drug of the two drug combination has only a modulating effect on the other drug but no

effect by itself, Greco proposes a reduced, but fundamentally different form of his model.[10] This transforms Equation 10 to :

Equation 11

$$U = U_A + \alpha\, U_A\, U_B$$

In analogy with the pervious equation U is the normalized effect site concentration of the drug combination, U_A, U_B, are respectively the normalized effect site concentration of the hypnotic (U_H) and the opioid (U_O), α is the interaction parameter. In this concept absence of a direct hypnotic effect of the opioids is postulated. Consequently, the hypnotic effects of opioids are presumed a potentiation of the hypnotic drug. However, circumventing this problem creates another : α and U_O can never be estimated independently.[97] With exception of the restriction concerning the maximal effect, it is clear that the reduced form of the model suffers from the same limitations as the original model.

333 The Minto model

The Minto model introduces a new parameter, θ, representing a concentration ratio of the studied drugs.[11] Then for every θ, a classic Sigmoidal E_{max} model is made, resulting in a response surface. In this concept every ratio of the studied drugs is considered as a new drug, for which a dose response curve is made.

Equation 12

$$\theta = \frac{B}{A + B}$$

After normalization of the drug concentration, Equation 12 becomes :

Equation 13

$$\theta = \frac{U_B}{U_A + U_B}$$

As reflected by the formula θ is a dimensionless number between 0 (only drug A) and 1 (only drug B). The drug concentration is equal to $U_A + U_B$. If we apply this concept and combine it with Equation 6 the following formula emerges :

Equation 14

$$E = E_0 + (E_{max} - E_0)\, \frac{\left(\frac{U_A + U_B}{U_{50}(\theta)}\right)^{\gamma(\theta)}}{1 + \left(\frac{U_A + U_B}{U_{50}(\theta)}\right)^{\gamma(\theta)}}$$

In this formula E_0 is the baseline effect, E_{max} the peak effect, the drug concentration is equal to $U_A + U_B$ and γ(θ) is the slope for that specific drug ratio θ. The best description of the term $U_{50}(\theta)$ is provided in Minto's report : "$U_{50}(\theta)$ is the potency of the drug combination at ratio θ relative to the normalized potency of each drug by itself."[11]

The true significance of this statement is easier to understand when it is illustrated with examples : suppose only drug B is present in a concentration evoking an effect equal to 50% of the maximal effect. It is clear that the concentration of B is equal to $C_{50,B}$. Since drug A is absent, θ must be equal to 1. Furthermore, U_A must be 0 and U_B must be 1, making the total drug concentration $U_A + U_B$ equal to 1. If we substitute the different parameters from Equation 14 with this data, it becomes clear that $U_{50}(\theta)$, must be equal to 1. If the same method of deduction is used with the assumption that only drug A is present in a concentration $C_{50,A}$, then $U_{50}(\theta) = 1$ is found again.

Now imagine a situation in which drug A and drug B are present in a concentration equal to ½ C_{50} of that drug, being ½ $C_{50,A}$ and ½ $C_{50,B}$. In this case θ = 0,5, U_A = 0,5, U_B = 0,5 and the total concentration $U_A + U_B = 1$. If the combination is additive they should elicit an effect equal to 50% of the maximal effect, since they are both present in exactly one half of the concentration that would evoke an effect of 50% in the case that they were administered alone. In the case of additivity at θ = 0,5, $U_{50}(\theta)$ is equal to 1. However, if there is synergy at this drug ratio θ, the effect resulting of this concentration will be more than 50% of the maximal effect. Stated another way : when drugs A and B are combined in ratio θ, lower concentrations of drugs A and B than the respective concentrations ½ $C_{50,A}$ and ½ $C_{50,B}$ will be sufficient to evoke 50 % of maximal effect. This will result in $U_{50}(\theta) < 1$. In summary : if the value of $U_{50}(\theta)$ is equal to 1 the effect is additive at drug ratio θ, if the value of $U_{50}(\theta) > 1$ the effect is antagonistic at drug ratio θ and finally if $U_{50}(\theta) < 1$ the interaction is synergistic for drug combination θ.

The basic principle of the Minto model is a θ for every drug combination and a corresponding sigmoidal E_{max} model for that θ. Consequently there is an E_{max}, an U_{50}, and an γ for every drug ratio θ. Minto describes this parameters of the model using fourth-order polynomials. Using the formulae (Equation 15), $E_{max}(\theta)$, $U_{50}(\theta)$ or γ(θ) can be calculated for every θ, if f(θ) is replaced. β_0, β_1, β_2, β_3, β_4 are estimated from the data.

Equation 15

$$f(\theta) = \beta_0 + \beta_1 \theta + \beta_2 \theta^2 + \beta_3 \theta^3 + \beta_4 \theta^4$$

Fortunately, a lot of interactions can be described by a less complex quadratic function, resulting in a isobole with a simple inward or outward curvature and simplifying Equation 15 to :

Equation 16

$$f(\theta) = \beta_0 + \beta_1 \theta + \beta_2 \theta^2$$

It also needs only one coefficient to be estimated from the data. This can be illustrated by applying Equation 16 for $U_{50}(\theta)$. When only drug A is present, and thus $\theta = 0$, this will yield to $U_{50}(\theta) = U_{50}(0) = U_{50,A} = \beta_0$. When only drug B is present and consequently $\theta = 1$, it will yield to $U_{50}(\theta) = U_{50}(1) = U_{50,B} = \beta_0 + \beta_1 + \beta_2$ (cfr. Appendix 1). Combining those equations results in

Equation 17

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

Equation 17 states that if $\beta_{2,\,U50}$ is 0, then $U_{50}(\theta) = 1$. Applying this in Equation 14 makes clear that the interaction will be additive. In case that $\beta_{2,\,U50}$ is positive, $U_{50}(\theta)$ must be less than one because θ is a number between 0 and 1. Substituting this in Equation 14 reveals a greater effect than expected with $U_{50}(\theta)$ equal to 1, and consequently synergy. It is clear that if the data would yield to a negative $\beta_{2,\,U50}$ the interaction is infra-additive.

This model is very versatile, even allowing modeling of triple drug interaction. In that case a θ for every drug can be defined as the proportion of each drug present. Accordingly $\theta_A + \theta_B + \theta_C = 1$. Like in the two drug model, for every fixed ratio of θ_A and θ_B, a sigmoidal relation between concentration and effect exists. Equation 13 and Equation 14 can be rewritten as :

Equation 18

$$\boldsymbol{\theta_A = \frac{U_A}{U_A + U_B + U_C}}$$

Equation 19

$$\boldsymbol{E = E_0 + (E_{max} - E_0)\,\frac{\left(\frac{U_A + U_B + U_C}{U_{50}(\theta_A, \theta_B)}\right)^{\gamma(\theta_A,\theta_B)}}{1 + \left(\frac{U_A + U_B + U_C}{U_{50}(\theta_A, \theta_B)}\right)^{\gamma(\theta_A,\theta_B)}}}$$

Despite the tremendous flexibility, the Minto model has limitations. When the polynomials, describing the interaction, are a quadratic function, both drugs have to be able to exert the same maximum effect. Furthermore the quadratic function tends to produce a “dip” in the isoboles estimated by the model.

334 The Hierarchical model

Greco already suggested a comprehensive mechanistic mathematical approach could be beneficial. In 2004 Bouillon publishes the hierarchical model.[26] The concept of the model is mainly based on the balance between a state of unconsciousness of the brain, mediated by hypnotics and on the other hand a form of inhibition of the noxious stimuli reaching the brain. Hereby making use of the neuro-physiological insights in general anesthesia proposed by Glass.[4]

Analgetics are considered to have an effect on the spine, the midbrain and the thalamus, thereby attenuating the response of a noxious stimulus. Hypnotics are supposed to generate cortical suppression resulting in a balance between ascending noxious stimuli and drug induced cortical suppression. A graphical representation of the model resembles Figure 7.

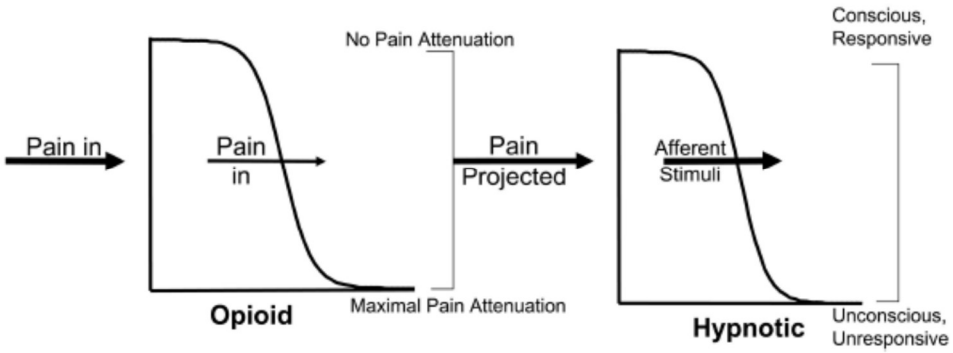


Figure 7

Hierarchical model of opioid–hypnotic drug interaction. Painful stimulus is first attenuated by the action of opioids. The potency of the opioids in attenuating pain decreases (e.g., shifts to the right) with increasingly painful stimulation. The attenuated signal then projects to the cortex, where hypnotics act to modulate the probability of response. Similar to opioids, the ability of the hypnotic to attenuate the response is shifted rightward with increasing stimulus.[26]

The intensity of the stimulus will influence the concentration of the opioid needed to attenuate the stimulus.[110] This is reflected in the following relation :

Equation 20

$$\boldsymbol{PostOI = PreOI \times \left(1 - \frac{O^{\gamma}}{O^{\gamma} + (O_{50} \times PreOI)^{\gamma}}\right)}$$

In this formula, PreOI represents the intensity of the afferent noxious stimulus, O is the opioid concentration and PostOI stands for postopioid intensity which is the intensity of the stimulus after attenuation of the stimulus due to the influence of opioids. O_{50} is the concentration of opioids that results in a reduction of the postopioid intensity of 50%. γ is the steepness of the relation between the opioid concentration and the degree of attenuation of the stimulus. By multiplying the preopioid intensity with the O_{50}, the influence of the potency of the opioids to blunt responses and the influence of the stimulus intensity becomes apparent.

In the next hierarchical level the postopioid intensity is transferred to the cortex. Here the central nervous depressant characteristics of the hypnotics counteract the incoming stimulus in an attempt to avoid arousal. Mathematically this can be expressed as :

Equation 21

$$P_{NR} = \frac{H^{\varphi}}{H^{\varphi} + (H_{50} \times PostOI)^{\varphi}}$$

Where P_{NR} is the probability of non-responsiveness to a certain stimulus, H is the concentration of the hypnotic drug, H_{50} is the concentration resulting in a 50% P_{NR} when the postopioid intensity is equal to 1, and ϕ is the slope of the relation between the concentration and the probability of non-responsiveness. In this perspective, the O_{50} must be seen as opioid concentration resulting in a 50% reduction of the concentration of hypnotics compared with the concentration of the hypnotic without opioids, to obtain the same effect.

In this concept, it is obvious that the postopioid intensity has to exceed 0, even in the unstimulated patient. Furthermore, after some mathematics, it becomes clear that the only difference between a model for the probability of no response to shaking and shouting ($P_{hypnosis}$) and a model for the probability of no response to laryngoscopy ($P_{laryngoscopy}$) is the estimate of the preopioid intensity of the stimulus (cfr. Equation 22, Appendix 2

Equation 22

$$U = \frac{U_H}{PreOI}\left(1 + \frac{{U_O}^{\gamma}}{PreOI^{\gamma}}\right)$$

If different stimuli result in an equal effect then U must be equal in the two conditions, consequently this results in different O_{50}'s (or H_{50}'s) for the different stimuli. Or stated otherwise : the potency of opioids and hypnotics can be set in relation to the preopioid stimulus intensity. This makes it possible to compare the intensities of different stimuli by comparing the respective C_{50}'s.

335 The Modified Hierarchical model

In 2010, the hierarchical model was modified in order to increase parsimony and adopting the simplest formulation of the formulae, while retaining it's essential features.[27] The original and the modified hierarchal opioid-hypnotic interaction models are compared in Figure 8 (respectively part A and B). Because unconscious anesthetized patients do not feel pain, these terms are replaced by "stimulus". Secondly, because the data of the original study[26] estimated the slope factor almost equal to 1, the model was collapsed to a fractional E_{max} model. Mathematically this can be expressed with the following formula :

Equation 23

$$PostOI = PreOI \times \left(1 - \frac{O}{O + O_{50}}\right)$$

Where PostOI is the stimulus intensity after attenuation by the opioid, PreOI is the intensity of the incoming stimulus, O is the effect-site opioid concentration and O_{50} is the effect-site opioid concentration associated with a 50% reduction of preopioid intensity. Therefore, the O_{50} *does not* represent the opioid concentrations associated with half maximal effect on the probability of tolerating the stimulus but it is the ability to increase the effectiveness of the hypnotic by altering the respective C_{e50} of the hypnotic.

Independent estimation of the preopioid intensities or C_{50}'s for different intensities of stimuli is not possible with the hierarchical model. If only one stimulus is investigated the preopioid intensity can be fixed to 1. If more stimuli are investigated other preopioid intensities can be compared to a reference stimulus with the intensity of 1.

In the original model, the multiplication of the C_{50} of the opioid with the preopioid pain intensity was believed to be necessary to account for the fact that higher opioid concentrations are needed to attenuate more severe pain. Although not obvious, this behavior is also displayed by the modified model. It is therefore the absolute value of postopioid intensity and the C_{50} of the hypnotic that determine the concentration of hypnotic needed to achieve a certain probability of non-responsiveness for a certain preopioid stimulus strength.

The next hierarchical step in the modified model, the calculation of probability of tolerance to an incoming stimulus for a certain postopioid intensity, is unchanged compared to the original model (cfr. Equation 21).

Under the assumption that the opioid potency (O_{50}) is identical for fractional suppression of stimuli of different strength and secondly that preopioid intensity of the reference stimulus is 1, the ratio of the respective H_{50}'s can be set in relation to the relative strength of the different stimuli. This fixed opioid potency explains that the Modified Hierarchical model is sometimes called "the Fixed C_{50} model" in contrast to "the Scaled C_{50} model" or Hierarchical model.

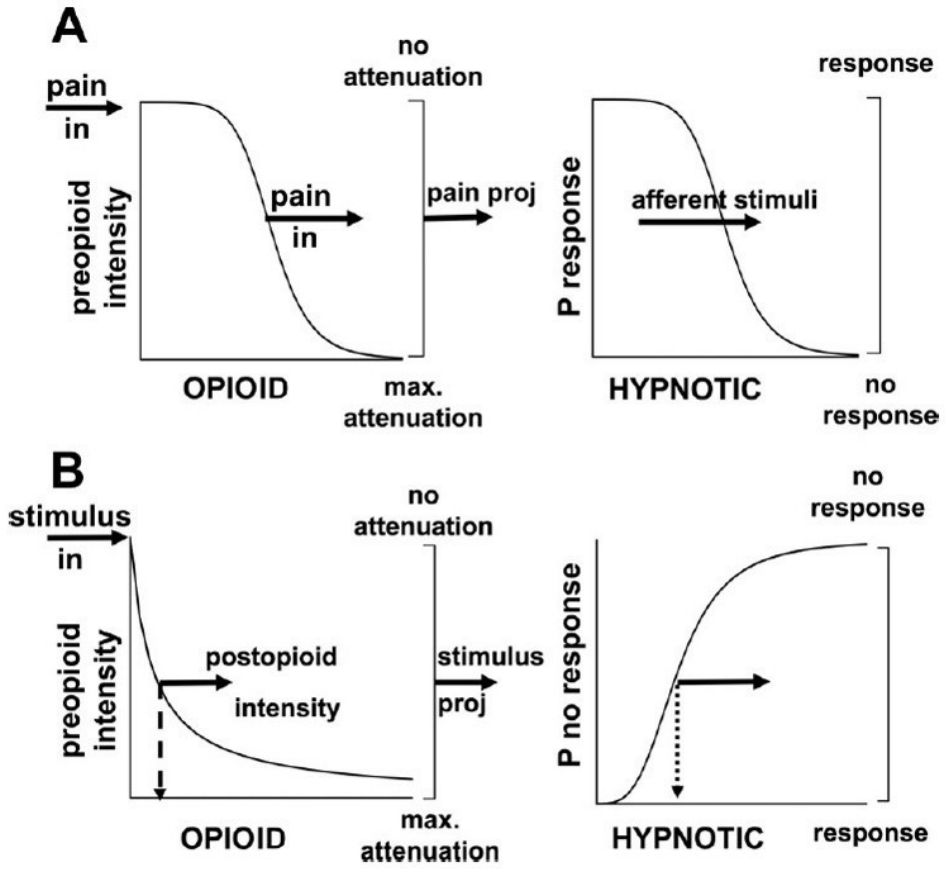


Figure 8

Comparison of the original and the modified hierarchal opioid– hypnotic interaction model. The endpoint of the opioid–hypnotic interaction is the probability of response (Presponse, original model, A) or nonresponse to a stimulus (Pnonresponse, modified model,B). The incoming stimulus is attenuated by the presence of an opioid. Presponse or Pnonresponse is dependent on the strength of the attenuated stimulus, the hypnotic drug concentration, and the hypnotic drug concentration associated with a 50% probability of response/nonresponse (C50hypnotic). In the original model (A), the incoming stimulus ("pain in") of a strength-labeled preopioid intensity on the y-axis is attenuated by the opioid (on the x-axis) according to a negative Emax model resulting in an afferent stimulus with a strength that is a fraction of preopioid intensity. The pre-opioid stimulus intensity and the slope parameter of this Emax model are estimated from the data. The projected pain ("pain proj") refers to the intensity of the attenuated stimulus transmitted to the central nervous system (also labeled as "afferent stimuli" in the original model). Presponse is estimated from a negative Emax model. In the modified model (B), the terms pain in and pain proj are replaced by "stimulus in" and "stimulus proj," respectively because unconscious anesthetized patients do not feel pain. Attenuation of preopioid intensity follows a fractional Emax model with a fixed slope constant of 1. The C50opioid (dashed arrow) is the opioid concentration reducing the strength of preopioid intensity by 50%. Pnonresponse is estimated with a positive Emax model, including the parameters postopioid intensity, current hypnotic drug concentration (x-axis), and the C50hypnotic (dotted arrow).[27]

In summary the differences between the modified and the original hierarchical model are :

- In the modified model the slope of the relation between postopioid intensity and opioids is equal to 1.
- In the modified model the preopioid intensity has no influence on the O_{50}

- In the modified model the preopioid intensity of the reference stimulus is equal to 1.

The principle that different H_{50}'s correspond with different strengths of stimuli has been the basis of the development of the Noxious Stimulation Response Index (NSRI). This index is proposed to predict the likelihood of response to a noxious stimulus, and uses the modified hierarchical model to correlate the effect site concentrations of the hypnotics and opioids to correlate these with the probability of non-responsiveness to laryngoscopy.

4 Developing models and response surfaces : efficient trial design

Short and coworkers studied the influence of different study designs on the number of patients needed to describe an entire response surface adequately. To do that, they created, depending on the study design, virtual plasma, effect-site concentrations and effects by applying different pharmacokinetic, pharmacodynamic and interaction models on data of virtual patients.[12,111–113] A well-defined variability was added each step of the process to generate realistic data (as would be elicited in real patients). The simulated data where then modelled, depending on the study design and secondly on the number of included virtual patients. The models, best describing the simulated data, originating from different study designs and different numbers of included patients, were then compared with each other and with the known, predefined model. By handling this way, the authors were able to select the design that resulted in the most robust model with the least patients needed to develop the model.

In the crisscross design, drug A was held constant at a variety of steady state concentrations in half of the patients. Simultaneous incremental doses of drug B were given up to maximum effect. In the other half of the patients, drug B was held constant and the concentration of drug A was augmented up to maximum effect. This approach seems to be the most efficient to determine the original response surface, using the least number of patients. Furthermore, it had also some additional advantages : more than other study designs it mimics the way drugs are used clinically; concentrations of one drug are usually altered in response to clinical circumstances. Compared to other designs, the crisscross design has the advantage that the data of each patient will frequently intersect parts of the surface covered by data originating from other patients, so outliers are less able to skew the surface. The symmetrical design seems to be better able to discriminate a skewed surface accurately.

5 References

1. Franks, N. P. General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. *Nat. Rev. Neurosci.* **9,** 370–386 (2008).
2. Cantor, R. S. Breaking the Meyer-Overton rule: predicted effects of varying stiffness and interfacial activity on the intrinsic potency of anesthetics. *Biophys. J.* **80,** 2284–2297 (2001).
3. Woodbridge, P. D. CHANGING CONCEPTS CONCERNING DEPTH OF ANESTHESIA. *Anesthesiology* **18,** (1957).
4. Glass, P. S. A. Anesthetic Drug Interactions: An Insight into General Anesthesia - Its Mechanism and Dosing Strategies. *Anesthesiology* **88,** (1998).
5. Chernik, D. A. *et al.* Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J. Clin. Psychopharmacol.* **10,** 244–51 (1990).
6. Liu, J., Singh, H. & White, P. F. Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. *Anesth. Analg.* **84,** 185–9 (1997).
7. Vanluchene, a L. G., Struys, M. M. R. F., Heyse, B. E. K. & Mortier, E. P. Spectral entropy measurement of patient responsiveness during propofol and remifentanil. A comparison with the bispectral index. *Br. J. Anaesth.* **93,** 645–54 (2004).
8. Heyse, B. *et al.* Comparison of contemporary EEG derived depth of anesthesia monitors with a 5 step validation process. *Acta Anaesthesiol. Belg.* **60,** 19–33 (2009).
9. Sahinovic, M. M. *et al.* Accuracy of the composite variability index as a measure of the balance between nociception and antinociception during anesthesia. *Anesth. Analg.* **119,** 288–301 (2014).
10. Greco, W. R., Park, H. S. & Rustum, Y. M. Application of a new approach for the quantitation of drug synergism to the combination of cis-diamminedichloroplatinum and 1-beta-D-arabinofuranosylcytosine. *Cancer Res.* **50,** 5318–27 (1990).
11. Minto, C. F. *et al.* Response surface model for anesthetic drug interactions. *Anesthesiology* **92,** 1603–16 (2000).
12. Smith, C. *et al. The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision. Anesthesiology* **81,** (1994).
13. Billard, V., Moulla, F., Bourgain, J. L., Megnigbeto, A. & Stanski, D. R. *Hemodynamic response to induction and intubation. Propofol/fentanyl interaction. Anesthesiology* **81,** (1994).
14. Kazama, T., Ikeda, K. & Morita, K. *The pharmacodynamic interaction between propofol and fentanyl with respect to the suppression of somatic or hemodynamic responses to skin incision, peritoneum incision, and abdominal wall retraction. Anesthesiology* **89,** (1998).
15. Vuyk, J., Hennis, P. J., Burm, A. G., de Voogt, J. W. & Spierdijk, J. *Comparison of*

midazolam and propofol in combination with alfentanil for total intravenous anesthesia. Anesthesia and analgesia **71,** (1990).

16. Vuyk, J. *et al.* Pharmacodynamics of alfentanil as a supplement to propofol or nitrous oxide for lower abdominal surgery in female patients. *Anesthesiology* **78,** 1036–1045; discussion 23A (1993).

17. Vuyk, J. *et al. The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. Anesthesiology* **83,** (1995).

18. Vuyk, J. *et al.* Pharmacodynamic interaction between propofol and alfentanil when given for induction of anesthesia. *Anesthesiology* **84,** 288–299 (1996).

19. Schwilden, H. *et al. Testing and modelling the interaction of alfentanil and propofol on the EEG. European journal of anaesthesiology* **20,** (2003).

20. Vuyk, J., Mertens, M. J., Olofsen, E., Burm, A. G. & Bovill, J. G. Propofol anesthesia and rational opioid selection: determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. *Anesthesiology* **87,** 1549–1562 (1997).

21. Vuyk, J. Pharmacokinetic and pharmacodynamic interactions between opioids and propofol. in *Journal of Clinical Anesthesia* **9,** (1997).

22. Bruhn, J. *et al.* Correlation of approximate entropy, bispectral index, and spectral edge frequency 95 (SEF95) with clinical signs of 'anesthetic depth' during coadministration of propofol and remifentanil. *Anesthesiology* **98,** 621–7 (2003).

23. Röpcke, H., Könen-Bergmann, M., Cuhls, M., Bouillon, T. & Hoeft, A. Propofol and remifentanil pharmacodynamic interaction during orthopedic surgical procedures as measured by effects on bispectral index. *J. Clin. Anesth.* **13,** 198–207 (2001).

24. Vanluchene, A. L. G. *et al.* Spectral Entropy as an Electroencephalographic Measure of Anesthetic Drug Effect. *Anesthesiology* **101,** 34–42 (2004).

25. Bouillon, T. *et al.* Non-steady state analysis of the pharmacokinetic interaction between propofol and remifentanil. *Anesthesiology* **97,** 1350–62 (2002).

26. Bouillon, T. W. *et al.* Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. *Anesthesiology* **100,** 1353–72 (2004).

27. Luginbühl, M. *et al.* Noxious stimulation response index: a novel anesthetic state index based on hypnotic-opioid interaction. *Anesthesiology* **112,** 872–80 (2010).

28. Sebel, P. S. *et al.* Reduction of the MAC of desflurane with fentanyl. *Anesthesiology* **76,** 52–9 (1992).

29. Albertin, A. *et al.* The effect of adding two target-controlled concentrations (1-3 ng mL -1) of remifentanil on MAC BAR of desflurane. *Eur. J. Anaesthesiol.* **23,** 510–516 (2006).

30. Katoh, T. & Ikeda, K. The effects of fentanyl on sevoflurane requirements for loss of consciousness and skin incision. *Anesthesiology* **88,** 18–24 (1998).

31. Katoh, T. *et al.* The effect of fentanyl on sevoflurane requirements for somatic and sympathetic responses to surgical incision. *Anesthesiology* **90,** 398–405 (1999).

32. Katoh, T. *et al.* Fentanyl augments block of sympathetic responses to skin incision during sevoflurane anaesthesia in children. *Br. J. Anaesth.* **84,** 63–6 (2000).

33. Albertin, A., Casati, A., Bergonzi, P., Fano, G. & Torri, G. *Effects of two target-controlled concentrations (1 and 3 ng/ml) of remifentanil on MAC(BAR) of sevoflurane. Anesthesiology* **100,** (2004).

34. Olofsen, E., Sleigh, J. W. & Dahan, A. *The influence of remifentanil on the dynamic relationship between sevoflurane and surrogate anesthetic effect measures derived from the EEG. Anesthesiology* **96,** (2002).

35. McEwan, A. I. *et al.* Isoflurane minimum alveolar concentration reduction by fentanyl. *Anesthesiology* **78,** 864–9 (1993).

36. Westmoreland, C. L., Sebel, P. S. & Gropper, A. *Fentanyl or alfentanil decreases the minimum alveolar anesthetic concentration of isoflurane in surgical patients. Anesthesia and analgesia* **78,** (1994).

37. Syroid, N. D. *et al.* Response surface model predictions of emergence and response to pain in the recovery room: An evaluation of patients emerging from an isoflurane and fentanyl anesthetic. *Anesth. Analg.* **111,** 380–386 (2010).

38. Brunner, M. D. *et al. MAC reduction of isoflurane by sufentanil. British journal of anaesthesia* **72,** (1994).

39. Lang, E. *et al. Reduction of isoflurane minimal alveolar concentration by remifentanil. Anesthesiology* **85,** (1996).

40. Manyam, S. C. *et al.* Opioid-volatile anesthetic synergy: a response surface model with remifentanil and sevoflurane as prototypes. *Anesthesiology* **105,** 267–78 (2006).

41. Johnson, K. B. *et al.* An evaluation of remifentanil-sevoflurane response surface models in patients emerging from anesthesia: model improvement using effect-site sevoflurane concentrations. *Anesth. Analg.* **111,** 387–94 (2010).

42. Brown, E. N., Lydic, R. & Schiff, N. D. General anesthesia, sleep, and coma. *N. Engl. J. Med.* **363,** 2638–50 (2010).

43. Dahaba, A. a. Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. *Anesth. Analg.* **101,** 765–73 (2005).

44. Bruhn, J., Myles, P. S., Sneyd, R. & Struys, M. M. R. F. Depth of anaesthesia monitoring: what's available, what's validated and what's next? *Br. J. Anaesth.* **97,** 85–94 (2006).

45. Bard, J. W. The BIS monitor: a review and technology assessment. *AANA J.* **69,** 477–83 (2001).

46. Glass, P. S. *et al.* Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* **86,** 836–47 (1997).

47. Katoh, T., Suzuki, A. & Ikeda, K. Electroencephalographic derivatives as a tool for predicting the depth of sedation and anesthesia induced by sevoflurane. *Anesthesiology* **88,** 642–50 (1998).

48. Struys, M. M. R. F. *et al.* Ability of the bispectral index, autoregressive modelling with exogenous input-derived auditory evoked potentials, and predicted propofol concentrations to measure patient responsiveness during anesthesia with propofol and remifentanil. *Anesthesiology* **99,** 802–12 (2003).

49. Schmidt, G. N. *et al.* Comparative evaluation of the Datex-Ohmeda S/5 Entropy Module and the Bispectral Index monitor during propofol-remifentanil anesthesia. *Anesthesiology* **101,** 1283–90 (2004).

50. Bruhn, J., Röpcke, H. & Hoeft, A. Approximate entropy as an electroencephalographic measure of anesthetic drug effect during desflurane anesthesia. *Anesthesiology* **92,** 715–26 (2000).

51. Bruhn, J., Lehmann, L. E., Röpcke, H., Bouillon, T. W. & Hoeft, A. Shannon Entropy Applied to the Measurement of the Electroencephalographic Effects of Desflurane. *Anesthesiology* **95,** 30–35 (2001).

52. Viertiö-Oja, H. *et al.* Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. *Acta Anaesthesiol. Scand.* **48,** 154–61 (2004).

53. Hans, P., Giwer, J., Brichant, J. F., Dewandre, P.-Y. & Bonhomme, V. Effect of an intubation dose of rocuronium on Spectral Entropy and Bispectral Index responses to laryngoscopy during propofol anaesthesia. *Br. J. Anaesth.* **97,** 842–7 (2006).

54. Vereecke, H. E. M., Vanluchene, A. L., Mortier, E. P., Everaert, K. & Struys, M. M. R. F. The effects of ketamine and rocuronium on the A-Line auditory evoked potential index, Bispectral Index, and spectral entropy monitor during steady state propofol and remifentanil anesthesia. *Anesthesiology* **105,** 1122–34 (2006).

55. Aho, A. J., Lyytikäinen, L.-P., Yli-Hankala, A., Kamata, K. & Jäntti, V. Explaining Entropy responses after a noxious stimulus, with or without neuromuscular blocking agents, by means of the raw electroencephalographic and electromyographic characteristics. *Br. J. Anaesth.* **106,** 69–76 (2011).

56. Struys, M. M. R. F. *et al.* Performance of the ARX-derived auditory evoked potential index as an indicator of anesthetic depth: a comparison with bispectral index and hemodynamic measures during propofol administration. *Anesthesiology* **96,** 803–16 (2002).

57. Guignard, B., Menigaux, C., Dupont, X., Fletcher, D. & Chauvin, M. *The effect of remifentanil on the bispectral index change and hemodynamic responses after orotracheal intubation. Anesthesia and analgesia* **90,** (2000).

58. Huiku, M. *et al.* Assessment of surgical stress during general anaesthesia. *Br. J. Anaesth.* **98,** 447–55 (2007).

59. Chen, X. *et al.* Comparison of surgical stress index-guided analgesia with standard clinical practice during routine general anesthesia: a pilot study. *Anesthesiology* **112,** 1175–83 (2010).

60. Gonzalez, R. & Woods, R. *Digital image processing*. (2002).

61. Gruenewald, M. *et al.* Influence of different remifentanil concentrations on the performance of the surgical stress index to detect a standardized painful stimulus during sevoflurane anaesthesia. *Br. J. Anaesth.* **103,** 586–93 (2009).

62. Wennervirta, J. *et al.* Surgical stress index as a measure of nociception/antinociception balance during general anesthesia. *Acta Anaesthesiol. Scand.* **52,** 1038–45 (2008).

63. Chen, X. *et al.* Correlation of surgical pleth index with stress hormones during propofol-remifentanil anaesthesia. *ScientificWorldJournal.* **2012,** 879158 (2012).

64. Struys, M. M. R. F. *et al.* Changes in a surgical stress index in response to standardized pain stimuli during propofol-remifentanil infusion. *Br. J. Anaesth.* **99,** 359–67 (2007).

65. Ahonen, J., Jokela, R., Uutela, K. & Huiku, M. Surgical stress index reflects surgical stress in gynaecological laparoscopic day-case surgery. *Br. J. Anaesth.* **98,** 456–61 (2007).

66. Höcker, J. *et al.* Surgical stress index in response to pacemaker stimulation or atropine. *Br. J. Anaesth.* **105,** 150–4 (2010).

67. Bonhomme, V. *et al.* Comparison of the surgical Pleth Index™ with haemodynamic variables to assess nociception-anti-nociception balance during general anaesthesia. *Br. J. Anaesth.* **106,** 101–11 (2011).

68. Hans, P., Verscheure, S., Uutela, K., Hans, G. & Bonhomme, V. Effect of a fluid challenge on the Surgical Pleth Index during stable propofol-remifentanil anaesthesia. *Acta Anaesthesiol. Scand.* **56,** 787–96 (2012).

69. Ilies, C. *et al.* The effect of posture and anaesthetic technique on the surgical pleth index. *Anaesthesia* **67,** 508–13 (2012).

70. Röpcke, H. *et al.* Surgical stimulation shifts EEG concentration-response relationship of desflurane. *Anesthesiology* **94,** 390–9; discussion 5A (2001).

71. Menigaux, C. *et al.* Esmolol prevents movement and attenuates the BIS response to orotracheal intubation. *Br. J. Anaesth.* **89,** 857–62 (2002).

72. Mathews, D. M., Clark, L., Johansen, J., Matute, E. & Seshagiri, C. V. Increases in electroencephalogram and electromyogram variability are associated with an increased incidence of intraoperative somatic response. *Anesth. Analg.* **114,** 759–70 (2012).

73. Jensen, E. W., Litvan, H., Struys, M. & Martinez Vazquez, P. Pitfalls and challenges when assessing the depth of hypnosis during general anaesthesia by clinical signs and electronic indices. *Acta Anaesthesiol. Scand.* **48,** 1260–7 (2004).

74. Litvan, H. *et al.* Comparison of auditory evoked potentials and the A-line ARX Index for monitoring the hypnotic level during sevoflurane and propofol induction. *Acta Anaesthesiol. Scand.* **46,** 245–51 (2002).

75. Struys, M. *et al.* Clinical usefulness of the bispectral index for titrating propofol target effect-site concentration. *Anaesthesia* **53,** 4–12 (1998).

76. Schumacher, P. M. *et al.* Response Surface Modeling of the Interaction between Propofol and Sevoflurane. *Anesthesiology* **111,** (2009).

77. Absalom, A. R. & Struys, M. M. R. F. *Overview of Target Controlled Infusions and Total Intravenous Anesthesia*. (Academia Press, 2007).

78. Minto, C. F. *et al.* Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* **86,** 10–23 (1997).

79. Schnider, T. W. *et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology* **88,** (1998).

80. Gepts, E. *et al.* Linearity of pharmacokinetics and model estimation of sufentanil. *Anesthesiology* **83,** 1194–1204 (1995).

81. Marsh, B., White, M., Morton, N. & Kenny, G. N. Pharmacokinetic model driven infusion of propofol in children. *Br. J. Anaesth.* **67,** 41–48 (1991).

82. Evers, A. S. & Maze, M. *Anesthetic Pharmacology Physiologic Principles and Clinical Practice*. (Churchill Livingstone, 2004).

83. Hughes, M. A., Glass, P. S. & Jacobs, J. R. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology* **76,** 334–41 (1992).

84. Hull, C. J., Van Beem, H. B., McLeod, K., Sibbald, A. & Watson, M. J. A pharmacodynamic model for pancuronium. *Br. J. Anaesth.* **50,** 1113–23 (1978).

85. Sheiner, L. B., Stanski, D. R., Vozeh, S., Miller, R. D. & Ham, J. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. *Clin. Pharmacol. Ther.* **25,** 358–71 (1979).

86. Wakeling, H. G., Zimmerman, J. B., Howell, S. & Glass, P. S. Targeting effect compartment or central compartment concentration of propofol: what predicts loss of consciousness? *Anesthesiology* **90,** 92–7 (1999).

87. Goutelle, S. *et al.* The Hill equation: a review of its capabilities in pharmacological modelling. *Fundam. Clin. Pharmacol.* **22,** 633–48 (2008).

88. Eger, E. I., Saidman, L. J. & Brandstater, B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. *Anesthesiology* **26,** 756–63 (1965).

89. Greco, W. R., Bravo, G. & Parsons, J. C. The search for synergy: a critical review from a response surface perspective. *Pharmacol. Rev.* **47,** 331–85 (1995).

90. Vuyk, J., Lichtenbelt, B. J., Olofsen, E., van Kleef, J. W. & Dahan, A. Mixed-effects modeling of the influence of midazolam on propofol pharmacokinetics. *Anesth. Analg.* **108,** 1522–30 (2009).

91. Lichtenbelt, B. J. *et al.* Propofol reduces the distribution and clearance of midazolam. *Anesth. Analg.* **110,** 1597–606 (2010).

92. Short, T. G., Ho, T. Y., Minto, C. F., Schnider, T. W. & Shafer, S. L. Efficient Trial Design for Eliciting a Pharmacokinetic– Pharmacodynamic Model–based Response Surface

Describing the Interaction between Two Intravenous Anesthetic Drugs. *Anesthesiology* **96,** 400–408 (2002).

93. Loewe, S. Antagonisms and antagonists. *Pharmacol. Rev.* **9,** 237–42 (1957).

94. Berenbaum, M. Isobolographic, Algebraic, and Search Methods in the Analysis of Multiagent Synergy. *Int. J. Toxicol.* **7,** 927–938 (1988).

95. Fraser, T. R. Lecture on the Antagonism between the Actions of Active Substances. *Br. Med. J.* **2,** 485–7 (1872).

96. Prichard, M. N. & Shipman, C. A three-dimensional model to analyze drug-drug interactions. *Antiviral Res.* **14,** 181–205 (1990).

97. Bouillon, T. W. Hypnotic and opioid anesthetic drug interactions on the CNS, focus on response surface modeling. *Handb. Exp. Pharmacol.* 471–87 (2008). doi:10.1007/978-3-540-74806-9_22

98. Gessner, P. K. Isobolographic analysis of interactions: an update on applications and utility. *Toxicology* **105,** 161–79 (1995).

99. Fraser, T. R. Lecture on the Antagonism between the Actions of Active Substances. *Br. Med. J.* **2,** 457–9 (1872).

100. Lee, S.-I. Drug interaction: focusing on response surface models. *Korean J. Anesthesiol.* **58,** 421–434 (2010).

101. Fitzgerald, J. B., Schoeberl, B., Nielsen, U. B. & Sorger, P. K. Systems biology and combination therapy in the quest for clinical efficacy. *Nat. Chem. Biol.* **2,** 458–466 (2006).

102. Jonker, D. M., Visser, S. A. G., van der Graaf, P. H., Voskuyl, R. A. & Danhof, M. Towards a mechanism-based analysis of pharmacodynamic drug-drug interactions in vivo. *Pharmacol. Ther.* **106,** 1–18 (2005).

103. Alex S. Evers, Maze, M. & Kharasch, E. D. *Anesthetic Pharmacology: Basic Principles and Clinical Practice*. (Cambridge University Press, 2011).

104. Goldoni, M. & Johansson, C. A mathematical approach to study combined effects of toxicants in vitro: Evaluation of the Bliss independence criterion and the Loewe additivity model. *Toxicology in Vitro* **21,** 759–769 (2007).

105. Berenbaum, M. C. Criteria for analyzing interactions between biologically active agents. *Adv. Cancer Res.* **35,** 269–335 (1981).

106. Zhao, W. *et al.* A New Bliss Independence Model to Analyze Drug Combination Data. *J. Biomol. Screen.* **19,** 817–821 (2014).

107. Tallarida, R. J. Revisiting the isobole and related quantitative methods for assessing drug synergism. *J. Pharmacol. Exp. Ther.* **342,** 2–8 (2012).

108. Wong, K. C. Narcotics are not expected to produce unconsciousness and amnesia. *Anesth. Analg.* **62,** 625–6 (1983).

109. Hug, C. C. Does opioid 'anesthesia' exist? *Anesthesiology* **73,** 1–4 (1990).

110. Ausems, M. E., Hug, C. C., Stanski, D. R. & Burm, A. G. Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. *Anesthesiology* **65,** 362–73 (1986).

111. Scott, J. C. & Stanski, D. R. Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamic evaluation. *J. Pharmacol. Exp. Ther.* **240,** 159–166 (1987).

112. Bührer, M., Maitre, P. O., Hung, O. & Stanski, D. R. Electroencephalographic effects of benzodiazepines. I. Choosing an electroencephalographic parameter to measure the effect of midazolam on the central nervous system. *Clin. Pharmacol. Ther.* **48,** 544–554 (1990).

113. Short, T. G., Plummer, J. L. & Chui, P. T. Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil. *Br. J. Anaesth.* **69,** 162–7 (1992).

114. Nieuwenhuijs, D. J. F. *et al.* Response surface modeling of remifentanil-propofol interaction on cardiorespiratory control and bispectral index. *Anesthesiology* **98,** 312–322 (2003).

115. Struys, M. M. R. F., Sahinovic, M., Lichtenbelt, B. J., Vereecke, H. E. M. & Absalom, A. R. Optimizing intravenous drug administration by applying pharmacokinetic/pharmacodynamic concepts. *Br. J. Anaesth.* **107,** 38–47 (2011).

116. Schumacher, P. M. *et al.* Time-Based Online Display of a Noxious Stimulus Response Index Based on Pharmacological Data. **107,** A17 (2007).

117. Heyse, B. *et al.* Sevoflurane remifentanil interaction: comparison of different response surface models. *Anesthesiology* **116,** 311–23 (2012).

118. Heyse, B. *et al.* A response surface model approach for continuous measures of hypnotic and analgesic effect during sevoflurane-remifentanil interaction: quantifying the pharmacodynamic shift evoked by stimulation. *Anesthesiology* **120,** 1390–9 (2014).

119. Luginbuehl, M. *et al.* Noxious Stimulation Response Index. *Anesthesiology* **112,** 872–880 (2010).

120. Heyse, B. *et al.* Sevoflurane Remifentanil Interaction. *Anesthesiology* **116,** 311–323 (2012).

121. Kreuer, S. *et al.* Application of Bispectral Index and Narcotrend index to the measurement of the electroencephalographic effects of isoflurane with and without burst suppression. *Anesthesiology* **101,** 847–54 (2004).

122. Kreuer, S., Bruhn, J., Larsen, R., Bialas, P. & Wilhelm, W. Comparability of Narcotrend index and bispectral index during propofol anaesthesia. *Br. J. Anaesth.* **93,** 235–40 (2004).

123. Kreuer, S. *et al.* Comparative pharmacodynamic modeling using bispectral and narcotrend-index with and without a pharmacodynamic plateau during sevoflurane anesthesia. *Anesth. Analg.* **106,** 1171–81, table of contents (2008).

Chapter 3 Sevoflurane Remifentanil Interaction

Comparison of Different Response Surface Models

Bjorn Heyse, M.D., Johannes H. Proost, Pharm.D., Ph.D., Peter M. Schumacher, M.Sc., Ph.D., Thomas W. Bouillon, P.D. Dr. med., Hugo E. M. Vereecke, M.D., Ph.D., Douglas J. Eleveld, Ph.D., Martin Luginbühl, M.D., Ph.D., Michel M. R. F. Struys, M.D., Ph.D.

Anesthesiology 2012; 116:311–23

ABSTRACT

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

Methods: Forty patients preoperatively received different combined concentrations of remifentanil (0–12 ng/ml) and sevoflurane (0.5–3.5 vol.%) according to a criss-cross design (160 concentration pairs, four per patient). After having reached pseudosteady state, the response to shake and shout tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy was recorded. For the analysis of the probability of tolerance, five different interaction models were tested : Greco, Reduced Greco, Minto, Scaled $C50_O$ Hierarchical, and Fixed $C50_O$ Hierarchical model. All calculations were performed with NONMEM VI (Icon Development Solutions, Ellicott City, MD).

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

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

This article is accompanied by an Editorial View. Please see :
Shafer SL : All models are wrong. ANESTHESIOLOGY 2012; 116:240–1.

Pharmacodynamic response surface models are three or more dimensional structures that have been developed to quantitatively describe the relationship between two or more drug concentrations with their combined clinical effect. Response surface models are powerful representations of drug interactions, because they combine information about any isobole and the concentration-response curve of any combination of the drugs involved.[1,2] Using the mathematically defined response surface, the corresponding drug effect for any two or more drug concentrations of the interacting drugs can be predicted.[1,3]

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

To characterize the interaction between sevoflurane and remifentanil in blunting responses to verbal (Observer's Assessment of Alertness/Sedation scale) and painful stimuli (pressure algometry, electrical tetanic stimulus, and thermal stimulation), Manyam *et al.* constructed a response surface for each pharmacodynamic response using a Logit model approach and found synergy between sevoflurane and remifentanil for all responses.[8] As this study suffered from nonsteady-state conditions at the moment of measurements, the authors reevaluated their data using effect-site sevoflurane concentrations and a Greco model instead of a Logit approach.[9] Accounting for the lag time between sevoflurane effect-site concentration and end-tidal concentration improved the predictions of responsiveness during anesthesia but had no effect on predicting a response to a noxious stimulus in the recovery room. They concluded that models may be useful in predicting events of clinical interest but largescale evaluations with numerous patients are needed to better characterize model performance. Also, they did not test if other response surface models would describe the data more accurately.

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

1 Materials and Methods

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

11 Subjects

After obtaining Institutional Review Board approval (Ghent University Hospital Ethics Committee, Gent, Belgium) and prospective trial registration at ClinicalTrials.gov (NCT00522587), as well as written informed consent, 40 American Society of Anesthesiologists status I or II patients, aged 18 to 60 yr, and scheduled to undergo surgery requiring general anesthesia, were included. Patients were allowed to take their usual medication. Exclusion criteria were weight less than 70% or more than 130% of ideal body weight, neurologic disorder, diseases involving the cardiovascular system (hypertension, coronary artery disease, prior acute myocardial infarction, any valvular and/or myocardial disease involving decrease in ejection fraction, arrhythmias, which are either symptomatic or require continuous medication/pacemaker/automatic internal cardioverter defibrillator), pulmonary diseases, gastric diseases, endocrinologic diseases, and recent use of psychoactive medication or more than 20 g of alcohol daily. The complete study was executed in a quiet operation room before the start of the surgical procedure.

12 Study Design

This study was performed as a randomized, prospective, open-label study. After the unpremedicated patients arrived in the operating room, standard monitors (electrocardiogram, noninvasive blood pressure, Sp_{O2}), M-entropy using a Datex S/5 Anesthesia Monitor (GE Healthcare, Helsinki, Finland) and bispectral index using a Aspect A-2000 monitor (Covidien, Norwood, MA) were connected, and a large forearm vein was cannulated. Thereafter, the patients were preoxygenated with 6 l/min O_2 at a F_I 1.0 for 5 min, using a tight-fitting facemask, which also served to sample exhaled air for end-tidal carbon dioxide measurement. All medical devices are approved for the purposes applied in the study. All drugs and the way of administration, either alone or in combination, are approved for clinical use under the studied conditions. No “off label” drug applications were used (European situation). Vital signs as well as end-tidal sevoflurane concentrations, respiratory data (tidal volume, minute volume, end-tidal carbon dioxide), and infusion related data (predicted concentrations, amounts infused) were continuously recorded on a computer hard disk using RUGLOOP II data recording software (Demed, Temse, Belgium).

13 Drug Administration

131 Technical Aspects.

Remifentanil was administered by using a target-controlled infusion technique based on a three-compartment model and an effect-site compartment as published by Minto *et al.*[11,12] Remifentanil infusion was administered by using an Alaris Asena pump (Carefusion, Basingstoke, United Kingdom). RUGLOOP II TCI driver (Demed) controlled the pump at infusion rates between 0 and 1,200 ml/h *via* an RS-232 interface. Sevoflurane was administered in 50% O_2 and 50% air by using a standard out of circle vaporizer and a standard breathing circuit of an ADU anesthesia workstation (Datex/Ohmeda, GE Healthcare). In all steps, the sevoflurane vaporizer was set to maximum until 80% of the

target concentration was reached, then it was turned down to the target setting. A fresh gas flow above minute ventilation was used throughout the study.

132 Dosing Regimen.

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

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

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

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

We randomized 40 patients to receive specific combinations of sevoflurane and remifentanil as simulated and described in the next paragraph. Before induction the subjects were randomly assigned to receive four prespecified pairs of sevoflurane and remifentanil concentrations. In half of the patients, remifentanil was held constant, and sevoflurane was stepwise increased; in the other half, sevoflurane was held constant and remifentanil was stepwise increased (table 1). For each of the 10 escalating combinations, three patients were included. To study the boundaries of the response surface (single drug without interaction), five patients were given sevoflurane only (0.7 to 3.5 vol.%) and five were given remifentanil (2–12 ng/ml) during the study period. The maximum Ce_{SEVO} was set at 3.5 vol.%, and maximum Ce_{REMI} was set at 12 ng/ml. A maximum of four steps was used to explore a single slice of the response surface. No other drugs were given, except for a possible 0.1 mg bolus of phenylephrine if mean arterial blood pressure dropped below 50 mmHg.

14 Assessment of Clinical Response

For each concentration step, the clinical response was assessed 12 min after reaching the target concentrations to allow for plasma effect-site equilibration. The patient was exposed to the following series of stimuli with increasing intensity: (1) verbal and nonpainful tactile stimuli according to the Observer's Assessment of Alertness/Sedation (OAA/S score)[15] (an OAA/S score less than 2 was considered as tolerant); (2) a tetanic stimulus of the ulnar nerve for 5 s by using the standard neurostimulator used in the clinical setting to test the level of muscle relaxation (100 Hz, 60 mA, Tristim NS3A peripheral nerve stimulator; Life Tech, Houston, TX); (3) insertion of a laryngeal mask airway (LMA size 3 for women and 4 for men, LMA Unique®, The Surgical Company, Amersfoort, The Netherlands); (4) laryngoscopy aiming at full visualization of the vocal chords by using a size-3 curved Macintosh-type blade (HEINE Optotechnik GmbH & Co KG, Herrsching, Germany). Verbal response, eye opening, grimacing, coughing, withdrawal, or any other purposeful or nonpurposeful movement, including jaw clenching and bucking after a stimulus, were defined as a response. Absence of a response implied tolerance of the stimulus and was labeled 0, and presence of a

response implied no tolerance of the stimulus and was labeled 1 in the case report form. All assessments were performed by one investigator to minimize interobserver variability. If there was no response to the first stimulus, the next stimulus was applied 1 min after the response assessment of the first. The assessment at each drug concentration level was stopped as soon as a response was observed or the patient tolerated laryngoscopy. If there was no response to laryngoscopy at the highest predefined drug combination, data acquisition was stopped, and the patient's trachea was intubated after the administration of 0.9 mg/kg rocuronium.

Table 1. Concentration Grid of Study Design

Patients (n)	Remifentanil (ng/ml)	Sevoflurane (vol.%)	MAC Multiples (Minimum–Maximum)
5	0	0.7, 1.5, 2.5, 3.5	0.4–1.9
3	1	0.7, 1.5, 2.5, 3.5	0.6–3.2
3	2	0.5, 1.5, 2.5, 3.5	0.6–4.4
3	3	0.5, 1.0, 1.5, 2.5	0.8–4.1
3	4	0.5, 1.0, 1.5, 2.5	1.0–5.0
3	6	0.5, 0.75, 1.0, 1.5	1.4–4.1
Patients (n)	**Sevoflurane* (vol.%)**	**Remifentanil (ng/ml)**	**MAC Multiples (Minimum–Maximum)**
5	0.5	2, 4, 8, 12	0.6–2.4
3	0.75	0, 4, 8, 12	0.4–3.6
3	1.0	0, 1, 4,10	0.5–4.1
3	1.5	0, 1, 3, 6	0.8–4.1
3	2.0	0, 1, 2, 4	1.1–4.0
3	2.5	0, 1, 2, 4	1.4–5.0

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

MAC = minimal anesthetic concentration

15 Pharmacodynamic Analysis of Quantal Responses

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

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

For remifentanil, the targeted effect-site concentration after 12 min of equilibration was considered as the steady-state concentration taking into account the reported[11,12] age-dependent equilibration half-time of 0.94, 1.32, and 2.20 min for 20, 50, and 80 yr,

respectively, and was used as the remifentanil effect-site concentration (Ce_{REMI}) in the analysis. For sevoflurane, the alveolar concentration measured by the S5 Anesthesia Monitor (GE Healthcare) *via* end-expiratory measurement after 12 min of equilibration was considered as the steady state concentration, and was used as sevoflurane effect-site concentration (Ce_{SEVO}) in the analysis. To reduce data noise in Ce_{REMI} and Ce_{SEVO}, the median value of 11 measurements at 5 s intervals during 1 min preceding the assessment of the OAA/S score were used. The duration of equilibration of 12 min was five times the reported equilibration half-life for sevoflurane of 2.4 min.[17]

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

16 Parameter Estimation

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

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

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

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

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

17 Statistical Analysis

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

2 Results

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

21 Data

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

22 Model Selection

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

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

Inclusion of interindividual variability in each parameter was tested either alone or in combinations. In all cases interindividual variability was the same for each stimulus. The results have been summarized in table 2. For all models, inclusion of interindividual variability in $Ce50_{SEVO}$ significantly improved the OFV ($P < 0.01$); but not interindividual variability of other parameters. We performed a covariate analysis on patient weight,

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

	Reduced Greco		Minto		Scaled C50O Hierarchical		Fixed C50O Hierarchical	
—	—	%SE	—	%SE	—	%SE	—	%SE
OFV	285.285	—	311.035	—	280.925	—	276.789	—
Number of parameters	7	—	8	—	8	—	8	—
ΔAIC$	6.496	—	34.246	—	4.136	—	0	—
$C50_O$ (ng/ml)	2.28	14%	14.3	12%	—	—	1.69	21%
$C50_O$ _TOSS (ng/ml)	—	—	—	—	1.47	21%	—	—
$C50_O$ _TTET (ng/ml)	—	—	—	—	1.46*	—	—	—
$C50_O$ _TLMA (ng/ml)	—	—	—	—	1.90§	—	—	—
$C50_O$ _TLAR (ng/ml)	—	—	—	—	1.81¶	—	—	—
$C50_H$ _TOSS (vol%)	1.40	8%	1.31	9%	1.55	7%	1.47	7%
$C50_H$ _TTET (vol%)	1.41	8%	1.40	9%	1.54	7%	1.48	7%
$C50_H$ _TLMA (vol%)	2.02	8%	1.91	9%	2.00	7%	2.09	8%
$C50_H$ _TLAR (vol%)	1.93	8%	1.89	9%	1.91	7%	2.00	8%
γ_0	—	—	—	—	0.704	12%	0.718	12%
γ	6.94	11%	9.32	11%	7.28	11%	7.41	12%
β_{C50}	—	—	1.47	15%	—	—	—	—
IIV($C50_H$)	21%	37%	26%	38%	19%	38%	20%	38%
MPE (%)	0.1	—	0.2	—	0.1	—	0.1	—
MAPE (%)	11.2	—	11.8	—	11.3	—	11.0	—
RMSE(%)	22.7	—	23.2	—	23.0	—	22.6	—
PES (%)	6.9	—	6.6	—	7.7	—	7.6	—

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

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

height, age, gender, and order of administration of remifentanil and sevoflurane. None of these covariates did improve the fit significantly.

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

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

Table 3. Median and 95% Nonparametric CIs of Parameters for the Fixed $C50_O$ Hierarchical Model with Interindividual Variability Obtained by Bootstrap Analysis (Using 1,000 Replicate Datasets) and from Log-likelihood Profiles

—	$C50_O$ (ng/ml)	$C50_H$ TOSS (vol%)	$C50_H$ TTET (vol%)	$C50_H$ TLMA (vol%)	$C50_H$ TLAR (vol%)	γ_O	γ	IIV $C50_H$
NONMEM								
Typical value	1.69	1.47	1.48	2.09	2.00	0.718	7.41	20%
Bootstrap analysis								
Median	1.67	1.47	1.49	2.09	2.00	0.713	7.65	19%
2.5%	0.80	1.29	1.25	1.76	1.69	0.464	6.14	11%
97.5%	2.55	1.70	1.78	2.51	2.37	0.981	10.70	26%
Log-likelihood profiles								
2.5%	0.99	1.25	1.26	1.77	1.69	0.543	5.81	12%
97.5%	2.59	1.73	1.75	2.48	2.37	0.925	9.54	30%

γ_O = model parameter reflecting the steepness of the concentration-effect relationship for the opioid; γ = model parameter reflecting the steepness of the concentration-effect relationship; $C50_H$ = effect-site concentration of the hypnotic with 50% effect to tolerance to shaking and shouting (TOSS), tolerance to tetanic stimulation (TTET), tolerance to laryngeal mask airway insertion (TLMA), and tolerance to laryngoscopy (TLAR); $C50_O$ = effect-site concentration of the opioid with 50% effect; IIV = interindividual variability, calculated as the square root of interindividual variance, multiplied by 100%.

The results of the final model, *i.e.*, Fixed $C50_O$ Hierarchical model with interindividual variability in $Ce50_{SEVO}$, were checked by performing a bootstrap analysis, based on 1,000 sets; 994 sets resulted in a successful minimization, and 983 sets gave a successful covariance step. The results of the bootstrap analysis were in good agreement with the NONMEM results (table 3). Also, the CIs estimated from the bootstrap analysis and from the log-likelihood profiles were comparable (table 3). The log-likelihood profiles for the parameters of the Fixed $C50_O$ Hierarchical model are depicted in figure 1.

23 Response Surface and Isoboles

The response surfaces for the probabilities of tolerance to each stimulus are shown in figure 2. Figure 3 compares the isoboles for 50% probability of tolerance to the four stimuli for the four models. Figure 4 shows the isoboles for 50% probability of tolerance to the four stimuli for the Fixed $C50_O$ Hierarchical model and the observed responses. Figure5 compares the isoboles for 50% probability of tolerance to the four stimuli for the four models. In figure 6, the isoboles for 5%, 50%, and 95% probability of tolerance to the four stimuli for the Fixed $C50_O$ Hierarchical model are shown. Figure 7 shows the isoboles for 95% probability of tolerance to laryngoscopy for the four models, illustrating the clinical significant difference between the Minto model and the three other models.

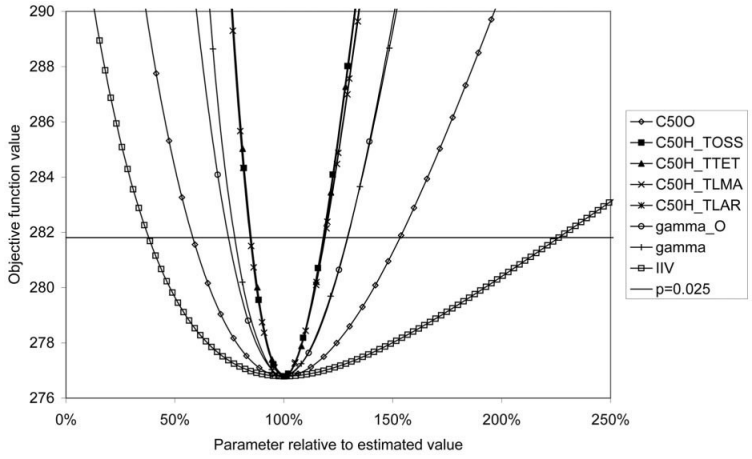


Fig. 1. Log-likelihood profiles for the parameters of the Fixed $C50_O$ Hierarchical model, expressed as a percentage of the estimated value. The *horizontal line* represents the significance level on a chi-square distribution (*P* 0.025). Note that the profiles of the $C50_H$ for the four stimuli are almost the same. IIV interindividual variability; TLAR tolerance to laryngoscopy; TLMA tolerance to laryngeal mask airway insertion; TOSS tolerance to shaking and shouting; TTET tolerance to tetanic stimulation.

3 Discussion

As expected, the pharmacodynamic interaction between sevoflurane and remifentanil was strongly synergistic for both the hypnotic and the analgesic components of anesthesia, as illustrated by tolerance to shake and shout, tetanic stimulation, LMA insertion, and laryngoscopy.[2,6,7] The main finding of this study is the validity of the Fixed $C50_O$ Hierarchical model[2,7] assuming an identical Ce50 and slope parameter for the opioid and an identical slope parameter of the hypnotic for different stimuli, but keeping different $Ce50_{hypnotic}$ for different stimuli. The model is thus validated not only for the propofol-remifentanil but also for the sevoflurane-remifentanil combination. The flexibility of the Fixed $C50_O$ Hierarchical model where only the $Ce50_{opioid}$, the $Ce50_{hypnotic}$ and slope parameters for the opioid and hypnotic are needed as input parameters, is of importance for the parsimonious description of the interaction and therefore very useful in the context of anesthesia drug displays.

The Minto model with a $Ce50_{REMI}$ of 14.3 ng/ml was statistically inferior, whereas the original Greco model did not even support a reliable estimation of the $Ce50_{REMI}$ (estimated values above 50 ng/ml). This is in agreement with the clinical experience that in the absence of a hypnotic drug opioids do not suppress the response to stimulation, at least at clinically reasonable opioid concentrations. The Hierarchical models are semi-mechanistic models that have been developed to detect synergism for the combination of an analgesic and a hypnotic drug using a simple reconstruction of neuropathic pathways, as opposed to other more generalistic models. These Hierarchical models, as well as the Reduced Greco model, assume no relevant opioid effect if given alone, and therefore these models fitted better to the data than the Greco and Minto models. The differences between the Reduced Greco model, Scaled $C50_O$ Hierarchical model, and Fixed $C50_O$ Hierarchical model were rather small, and each of these three models fitted reasonably well to the data. However, the OFV and Akaike Information Criterion unequivocally showed that the Fixed $C50_O$ Hierarchical model fit best to our data.

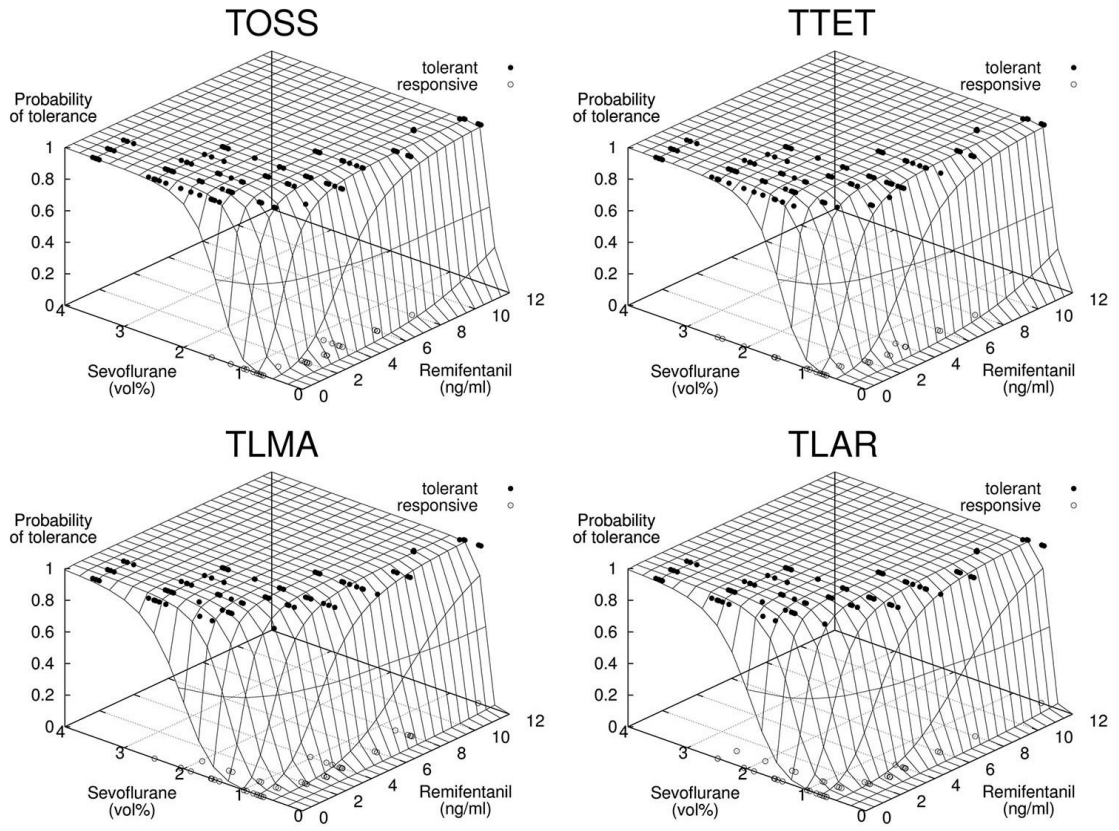


Fig. 2. Response surface for probability of tolerance to shaking and shouting, tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy for the Fixed $C50_O$ Hierarchical model. The *solid lines* at probability 0.5 represents the 50% isoboles. TLAR = tolerance to laryngoscopy; TLMA = tolerance to laryngeal mask airway insertion; TOSS = tolerance to shaking and shouting; TTET = tolerance to tetanic stimulation.

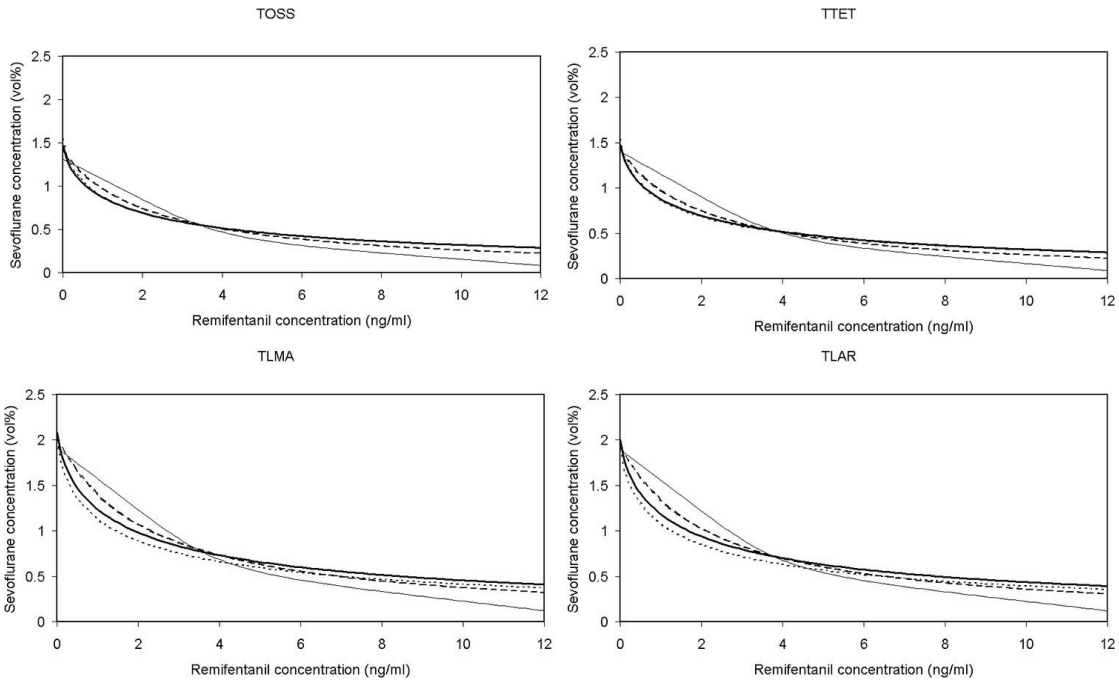


Fig. 3. Isoboles for 50% probability of tolerance to shaking and shouting, tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy for four models (*dashed line* = Reduced Greco, *thin solid line* = Minto, *dotted line* = Scaled $C50_O$ Hierarchical, *thick solid line* Fixed $C50_O$ Hierarchical). Note that the isoboles of shaking and shouting and tetanic stimulation are almost the same for the Scaled $C50_O$ and Fixed $C50_O$ Hierarchical models, and that the isobole of the Scaled $C50_O$ Hierarchical model is

obscured by that of the Fixed $C50_O$ Hierarchical model. TLAR = tolerance to laryngoscopy; TLMA = tolerance to laryngeal mask airway insertion; TOSS = tolerance to shaking and shouting; TTET = tolerance to tetanic stimulation.

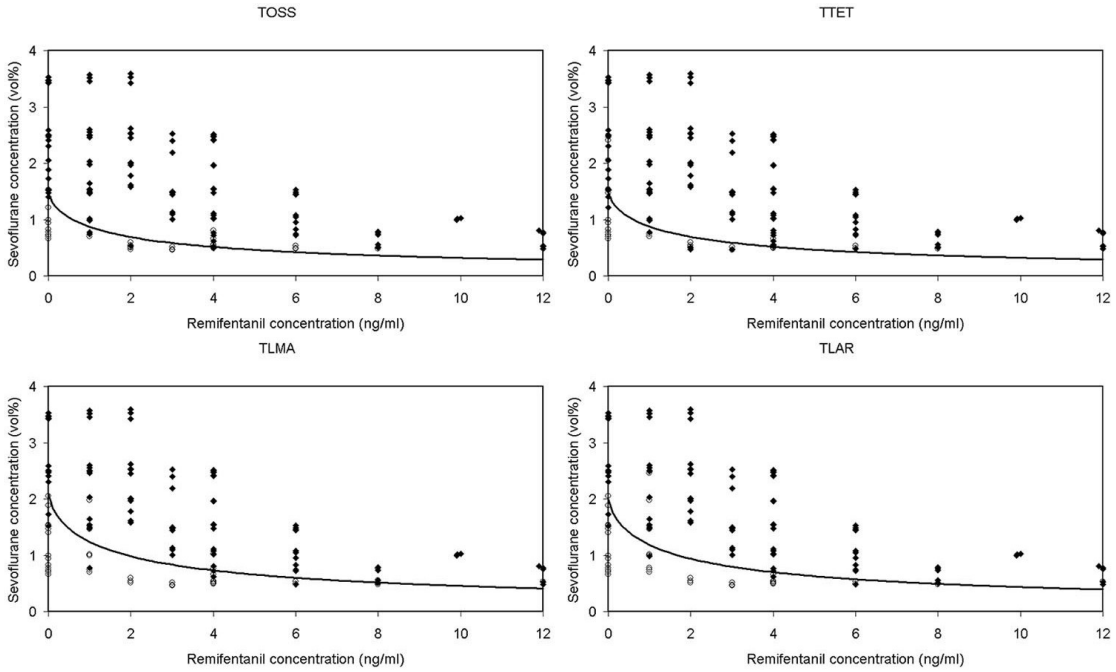


Fig. 4. Isoboles for 50% probability of tolerance to shaking and shouting, tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy for the Fixed $C50_O$ Hierarchical model, with observed responses (*open circles* = responsive, *closed squares* = tolerant). TLAR = tolerance to laryngoscopy; TLMA = tolerance to laryngeal mask airway insertion; TOSS = tolerance to shaking and shouting; TTET = tolerance to tetanic stimulation.

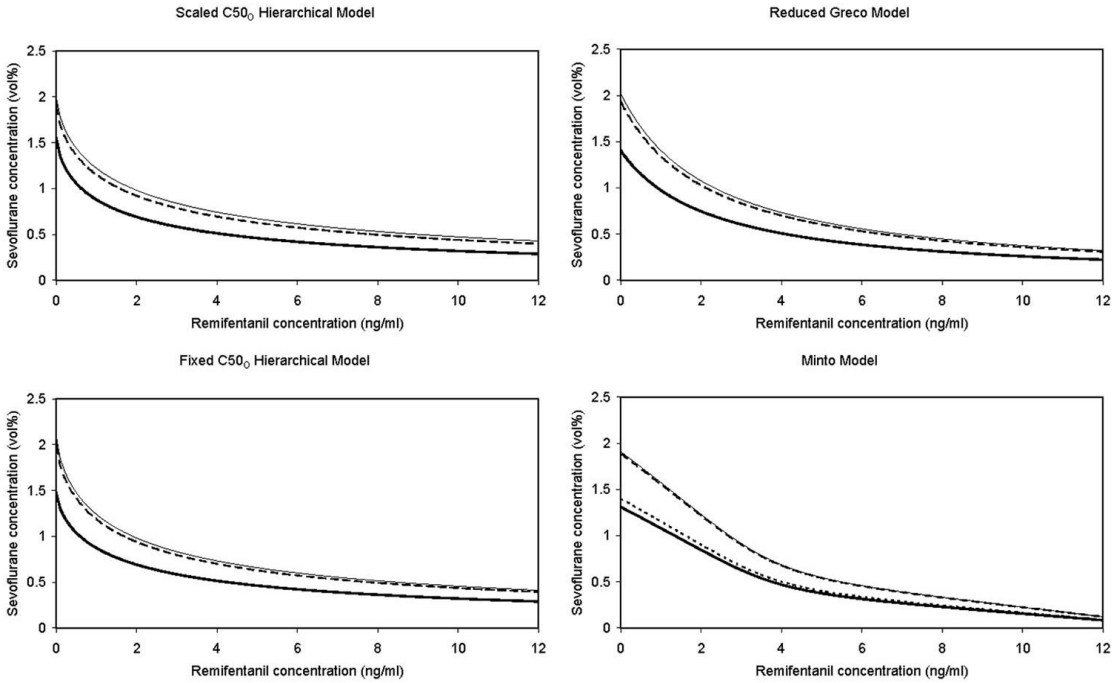


Fig. 5. Isoboles for 50% probability of tolerance to shaking and shouting (*thick solid line*), tetanic stimulation (*dotted line*), laryngeal mask airway insertion (*thin solid line*), and laryngoscopy (*dashed line*) for the Reduced Greco model, Minto model, Scaled $C50_O$ Hierarchical model, and Fixed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

The conclusions with respect to the best fitting model should not be translated to interactions of different classes of drugs. Each of these models is an empirical model that needs to be validated for each application. The Reduced Greco and both Hierarchical models are applicable when one of the drugs does not exert an effect when given alone, as is the case for the sevoflurane-remifentanil combination studied in this investigation. For other drug combinations where both drugs can exert a full effect, the original Greco model and the Minto model may be appropriate. For combinations where one of the drugs can only exert a partial effect, a modified version of the Minto model seems appropriate.

To evaluate the clinical relevance of the observed differences between the models, the isoboles for 95% probability of tolerance to laryngoscopy for the four models are shown in figure 7. At a fixed remifentanil concentration of 3 ng/ml, the sevoflurane concentration predicted by the Minto, Reduced Greco, Scaled $C50_O$ Hierarchical, and Fixed $C50_O$ Hierarchical model is 1.59, 1.27, 1.08, and 1.19 vol.%, respectively. This illustrates the deviating characteristics of the Minto model, and the relatively small differences between the Reduced Greco and both Hierarchical models. Clinicians aim at titrating their drugs during anesthesia at least at a level of 95% probability of tolerance, so at a specific remifentanil concentration, applying the Minto model would result in the use of a clinically relevant higher sevoflurane concentration than when using the other models.

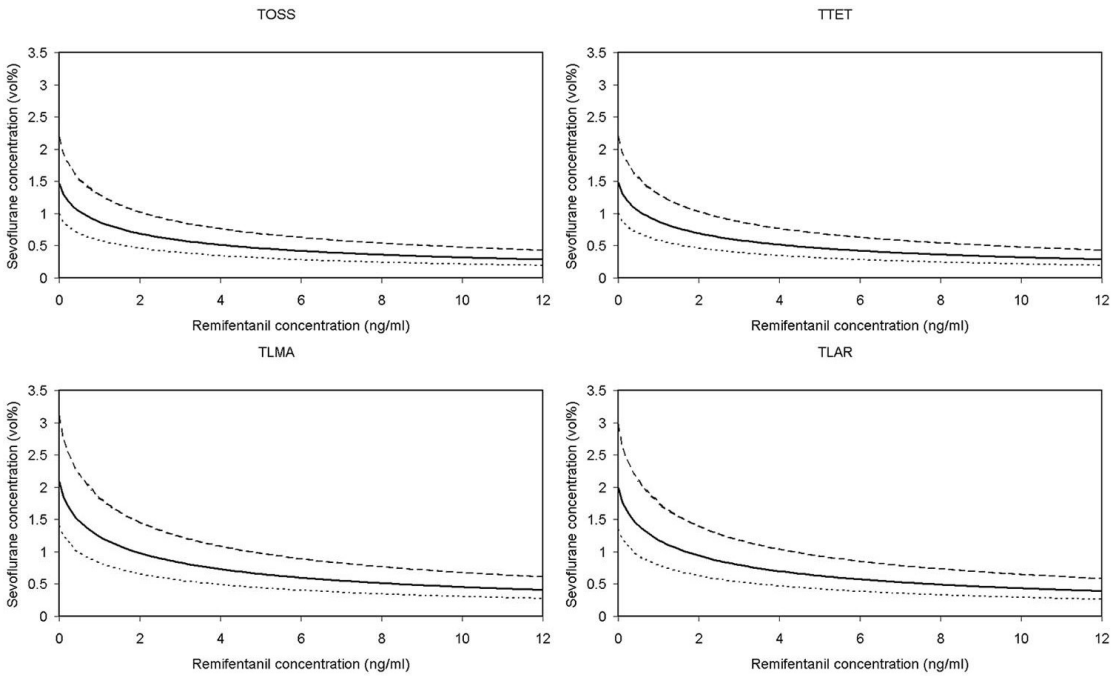


Fig. 6. Isoboles for 5% (*dotted line*), 50% (*thick solid line*), and 95% (*dashed line*) probability of tolerance to shaking and shouting, tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy for the Fixed $C50_O$ Hierarchical model. TLAR = tolerance to laryngoscopy; TLMA = tolerance to laryngeal mask airway insertion; TOSS = tolerance to shaking and shouting; TTET = tolerance to tetanic stimulation.

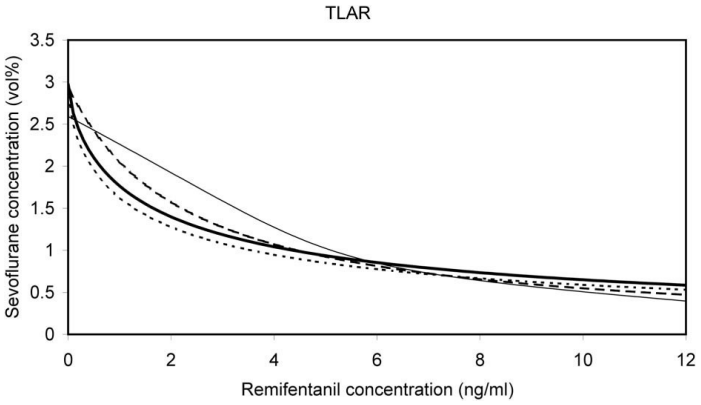


Fig. 7. Isoboles for 95% probability of tolerance to laryngoscopy for four models (dashed line = Reduced Greco, thin solid line = Minto, dotted line = Scaled $C50_O$ Hierarchical, thick solid line = Fixed $C50_O$ Hierarchical). TLAR = tolerance to laryngoscopy.

Response surfaces or interaction isoboles are used in anesthetic drug displays as reference to interpret the current effect-site concentrations estimated in the patient. The parameter estimates of the model are therefore crucial. According to the Fixed $C50_O$ Hierarchical model, the Ce50s of the hypnotic are used to rank different stimuli according to their intensity. The $Ce50_{SEVO}$ for tolerance of shaking and shouting (nonnoxious) and tetanic stimulation (noxious) were similar. The $Ce50_{SEVO}$ for tolerance of LMA insertion and for laryngoscopy were also similar but substantially higher. In the previous study on the interaction of sevoflurane and propofol performed with the same stimuli by the same investigators,[10] the Ce50 values for sevoflurane for tolerance to shake and shout, tetanic stimulation, LMA insertion, and laryngoscopy were 1.03, 2.11, 2.55, and 2.83 vol.% respectively, which is markedly different from that found in the present study (1.47, 1.48, 2.09, and 2.00 vol.%, respectively). Furthermore, the slope reported by Schumacher *et al.* was 17.6, whereas in the present study it was 7.41. To elucidate the cause of these differences, the data points of the previous and the current study where sevoflurane was given alone were reanalyzed (table 4). The parameter estimates obtained from the "sevoflurane alone" data of the two studies still differ, although the difference is smaller and the order of the Ce50s was similar in both studies. We can only speculate why the $Ce50_{SEVO}$ for tolerance to shake and shout was lower and the $Ce50_{SEVO}$ for tolerance to laryngoscopy was higher in the previous compared to the current study. Age, weight, and height were similar in the two studies. Classification of the subjects in responders and nonresponders was similar (a response was assumed if there was an observed response to a given stimulus, and if there was a response to a lower intensity stimulus and when the subsequent higher intensity stimulus was not applied). The pattern and current intensity of the electrical stimulus was also the same. The individual airway anatomy of the patients may affect the force to be applied during LMA insertion and the pressure applied with the laryngoscope to visualize the vocal cords. This may explain in part the difference between the Ce50s for tolerance to LMA insertion and laryngoscopy but not the difference between Ce50s for tolerance to shake and shout and tetanic stimulation.

A synergistic interaction between sevoflurane and remifentanil for both the hypnotic and analgesic stimuli using surface modeling was also found previously.[8,9] However, their parameter estimates differ markedly from those of the current study. Several reasons may explain this discrepancy: Whereas Manyam *et al.* used a logistic regression model, Johnson used the Greco model in his reanalysis of the same data. In the study of Manyam *et al.* the stimuli were given 5 min after achieving a stable end-tidal sevoflurane concentration, whereas in our study the equilibration was allowed for 12 min, which is five times the

reported equilibration half-life for sevoflurane of 2.4 min.[17] To compensate for this disequilibrium, Johnson *et al.*[9] used an estimated effect-site concentration to describe the hysteresis with the end-tidal concentration. The $Ce50_{REMI}$ for OAA/S1 during emergence (no return of consciousness) reported by Johnson *et al.* was 50.9 ng/ml, which is far above the investigated concentration range applied and may thus not be reliable, although it reflects the weak hypnotic potency of opioids. The $Ce50_{REMI}$ for tolerance of tibial pressure was 1.3 ng/ml, which is in the range of the common $Ce50_{REMI}$ in the current study as well as in the previous studies.[2,6,7] In our study the $Ce50_{REMI}$ estimated with the Reduced Greco model was 2.28 ng/ml for OAAS1 (table 2), which is lower than the value calculated from the ratio Ce50/reported by Johnson *et al.* (50.9/9.4 5.4 ng/ml).

Table 4. Comparison of Results from Data in the Absence of Remifentanil and Propofol in the Present Study (19 Patients with 34 Observations for Each Stimulus) and Schumacher Study (28 Patients with 45 Observations for Each Stimulus), without and with Interindividual Variability in $C50_H$

—	Present Study without IIV		Present Study with IIV		Schumacher without IIV		Schumacher with IIV	
—	Typical Value	%SE	Typical Value	%SE	Typical Value	%SE	Typical Value	%SE
$C50_H$ _TOSS (vol%)	1.25	10%	1.32	9%	0.955	9%	1.00	**
$C50_H$ _TTET (vol%)	1.57	9%	1.61	9%	2.17	6%	2.26	**
$C50_H$ _TLMA (vol%)	2.00	9%	2.01	9%	2.37	6%	2.55	**
$C50_H$ _TLAR (vol%)	2.09	9%	2.11	9%	2.52	6%	2.85	**
γ	5.96	17%	10.0	27%	7.96	18%	49.5*	**
IIV ($C50_H$)	—	—	22%	54%	—	—	32%	**

* Value reached boundary. ** Covariance matrix not calculated.

γ = model parameter reflecting the steepness of the concentration-effect relationship; %SE = the standard error expressed in % of the typical value; $C50_H$ = effect-site concentration of the hypnotic with 50% effect to tolerance to shaking and shouting (TOSS), tolerance to tetanic stimulation (TTET), tolerance to laryngeal mask airway insertion (TLMA), and tolerance to laryngoscopy (TLAR); IIV = interindividual variability, calculated as the square root of interindividual variance, multiplied by 100%.

Whereas Johnson *et al.* reported a different slope for OAAS1 (5.2) and tolerance of tibial pressure (2.7), we did not find a significant difference between the slopes for the different stimuli, and in our final model the common slope was 7.4. It seems that the data from Manyam, reanalyzed by Johnson and our data are difficult to compare because of the different methodology and the different endpoints used.

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

Current interaction displays use two different stimuli and the related interaction models as reference to quantify the anesthetic potency of a given combination of a hypnotic (propofol or volatile) and an opioid. The Fixed $C50_O$ Hierarchical model appears to be the most appropriate to define the reference lines or numbers to guide the clinician in rational dosing. The two stimuli used in interaction displays as reference must be clearly different in

intensity, *i.e.*, significantly differ in their $Ce50_{hypnotic}$. According to the present and previous data, "shaking and shouting" and "laryngoscopy" with their clearly distinct Ce50s, are therefore reasonable reference stimuli representing a superficial (near loss of consciousness) and a deeper state of anesthesia needed for surgery.

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

4 Appendix: Binary Response Models

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

$$\boldsymbol{P = \frac{U^{\gamma}}{1 + U^{\gamma}}} \qquad \textit{(A1)}$$

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

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

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

$$\boldsymbol{U_O = \frac{C_O}{C50_O}} \qquad \textit{(A2)}$$

$$U_H = \frac{C_H}{C50_H}$$

(A3)

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

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

41 Greco Model

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

$$U = U_O + U_H + \alpha \cdot U_O \cdot U_H$$

(A4)

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

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

42 Reduced Greco Model without Effect of the Opioid Alone

In the case of the interaction of opioids with hypnotics, the effect of the opioid alone on *P* may be too small to accurately assess the $C50_O$ (i.e., the actual value of $C50_O$ is very high). The Greco model can then be easily modified by leaving out the term U_O from Eq. A4, creating

$$U = U_H + \alpha \cdot U_O \cdot U_H$$

(A5)

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

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

(A6)

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

$$\boldsymbol{U = U_H + \left(1 + \alpha' \cdot C_O\right)}$$

(A7)

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

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

(A8)

$$\boldsymbol{U = U_H + (1 + U_O)}$$

(A9)

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

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

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

43 Minto Model

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

$$\boldsymbol{\theta} = \frac{\boldsymbol{U_H}}{\boldsymbol{U_O} + \boldsymbol{U_H}}$$

(A10)

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

$$\boldsymbol{U_{50}(\theta) = 1 - \beta_{U_{50}} \cdot \theta \cdot (1 - \theta)}$$

(A11)

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

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

(A12)

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

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

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

(A13)

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

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

44 Hierarchical Model

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

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

(A14)

And A15,

$$\boldsymbol{postopioid\_intensity = preopioid\_intensity \cdot \left(1 - \frac{C_O{}^{\gamma_O}}{(C50_O \cdot preopioid\_intensity)^{\gamma_O} + C_O{}^{\gamma_O}}\right)}$$

(A14)

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

Eq. A14 corresponds to the general Eq. A1 if

$$\boldsymbol{U = \frac{U_H}{postopioid\_intensity}}$$

(A16)

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

$$\boldsymbol{U = \frac{U_H}{preopioid\_intensity} \cdot \left(1 + \left(\frac{U_O}{preopioid\_intensity}\right)^{\gamma_O}\right)}$$

(A17)

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

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

$$\boldsymbol{U = U_H \cdot (1 + U_O{}^{\gamma_O})}$$

(A17)

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

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

45 Scaled $C50_O$ Hierarchical Model

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

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

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

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

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

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

46 Fixed $C50_O$ Hierarchical Model

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

$$C50_{Oi} = C50_{O1}$$

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

This constraint is identical to omitting preopioid_intensity from the denominator of Eq. A15. From these constraints and Eq. A18 it follows that the Fixed $C50_O$ Hierarchical model is an extension of the Reduced Greco model, *i.e.*, by adding an exponent γ_O to U_O in Eq. A9 and with a common parameter $C50_O$ for all stimuli. Note that in the Fixed $C50_O$ Hierarchical model proposed by Bouillon[2] γ_O was assumed to be 1 (equation on page 481 of that paper), making the model identical to the Reduced Greco model. The number of model parameter is identical to that of the Scaled $C50_O$ Hierarchical model ($C50_O$, γ, γ_O, and N values for $C50_{Hi}$).

47 Relationships between Models

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

The Greco model and the Minto model as commonly implemented assume an effect of the opioid given alone, whereas the other models assume that the opioid alone has no effect on the response to a stimulus;

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

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

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

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

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

5 References

1. Minto CF, Schnider TW, Short TG, Gregg KM, Gentilini A, Shafer SL: Response surface model for anesthetic drug interactions. *Anesthesiology* 2000; 92:1603–16
2. Bouillon TW: Hypnotic and Opioid Anesthetic Drug Interactions on the CNS, Focus on Response Surface Modelling, Modern Anesthetics, Handbook of Experimental Pharmacology 182. Berlin: Heidelberg, Springer-Verlag; 2008
3. Short TG, Ho TY, Minto CF, Schnider TW, Shafer SL: Efficient trial design for eliciting a pharmacokinetic-pharmacodynamic model-based response surface describing the interaction between two intravenous anesthetic drugs. *Anesthesiology* 2002; 96:400–8
4. Greco WR, Park HS, Rustum YM: Application of a new approach for the quantitation of drug synergism to the combination of cis-diamminedichloroplatinum and 1-beta-D-arabinofuranosylcytosine. Cancer Res 1990; 50:5318–27
5. Bol CJ, Vogelaar JP, Tang JP, Mandema JW: Quantification of pharmacodynamic interactions between dexmedetomidine and midazolam in the rat. J Pharmacol Exp Ther 2000; 294: 347–55
6. Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, Shafer SL: Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. *Anesthesiology* 2004; 100: 1353–72
7. Luginbühl M, Schumacher PM, Vuilleumier P, Vereecke H, Heyse B, Bouillon TW, Struys MM: Noxious stimulation response index: A novel anesthetic state index based on hypnotic-opioid interaction. *Anesthesiology* 2010; 112:872–80
8. Manyam SC, Gupta DK, Johnson KB, White JL, Pace NL, Westenskow DR, Egan TD: Opioid-volatile anesthetic synergy: A response surface model with remifentanil and sevoflurane as prototypes. *Anesthesiology* 2006; 105:267–78
9. Johnson KB, Syroid ND, Gupta DK, Manyam SC, Pace NL, LaPierre CD, Egan TD, White JL, Tyler D, Westenskow DR: An evaluation of remifentanil-sevoflurane response surface models in patients emerging from anesthesia: Model improvement using effect-site sevoflurane concentrations. Anesth Analg 2010; 111:387–94
10. Schumacher PM, Dossche J, Mortier EP, Luginbuehl M, Bouillon TW, Struys MM: Response surface modeling of the interaction between propofol and sevoflurane. *Anesthesiology* 2009; 111:790–804
11. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I Model development. *Anesthesiology* 1997; 86:10–23
12. Minto CF, Schnider TW, Shafer SL: Pharmacokinetics and pharmacodynamics of remifentanil. II Model application. *Anesthesiology* 1997; 86:24–33
13. Lang E, Kapila A, Shlugman D, Hoke JF, Sebel PS, Glass PS: Reduction of isoflurane minimal alveolar concentration by remifentanil. *Anesthesiology* 1996; 85:721–8
14. Katoh T, Kobayashi S, Suzuki A, Iwamoto T, Bito H, Ikeda K: The effect of fentanyl on sevoflurane requirements for somatic and sympathetic responses to surgical incision. *Anesthesiology* 1999; 90:398–405

15. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL: Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with intravenous midazolam. J Clin Psychopharmacol 1990; 10:244–51
16. Mertens MJ, Olofsen E, Engbers FH, Burm AG, Bovill JG, Vuyk J: Propofol reduces perioperative remifentanil requirements in a synergistic manner: Response surface modeling of perioperative remifentanil-propofol interactions. *Anesthesiology* 2003; 99:347–59
17. Rehberg B, Bouillon T, Zinserling J, Hoeft A: Comparative pharmacodynamic modeling of the electroencephalography slowing effect of isoflurane, sevoflurane, and desflurane. *Anesthesiology* 1999; 91:397–405
18. McEwan AI, Smith C, Dyar O, Goodman D, Smith LR, GlassPS: Isoflurane minimum alveolar concentration reduction by fentanyl. *Anesthesiology* 1993; 78:864–9
19. Brunner MD, Braithwaite P, Jhaveri R, McEwan AI, GoodmanDK, Smith LR, Glass PS: MAC reduction of isoflurane by sufentanil. Br J Anaesth 1994; 72:42–6
20. Westmoreland CL, Sebel PS, Gropper A: Fentanyl or alfentanil decreases the minimum alveolar anesthetic concentration of isoflurane in surgical patients. Anesth Analg 1994; 78: 23–8
21. Katoh T, Ikeda K: The effects of fentanyl on sevoflurane requirements for loss of consciousness and skin incision. *Anesthesiology* 1998; 88:18–24

Chapter 4 A Response Surface Model Approach for Continuous Measures of Hypnotic and Analgesic Effect during Sevoflurane–Remifentanil Interaction data.

Quantifying the Pharmacodynamic Shift Evoked by Stimulation

Bjorn Heyse, M.D.,Johannes H. Proost, Pharm.D., Ph.D., Laura N. Hannivoort, M.D., Douglas J. Eleveld, Ph.D., Martin Luginbühl, M.D., Ph.D., Michel M. R. F. Struys, M.D., Ph.D., Hugo E. M. Vereecke,M.D., Ph.D.

Anesthesiology 2014; 120:1390-9

ABSTRACT

Background: The authors studied the interaction between sevoflurane and remifentanil on bispectral index (BIS), state entropy (SE), response entropy (RE), Composite Variability Index, and Surgical Pleth Index, by using a response surface methodology. The authors also studied the influence of stimulation on this interaction.

Methods: Forty patients received combined concentrations of remifentanil (0 to 12 ng/ml) and sevoflurane (0.5 to 3.5 vol%) according to a crisscross design (160 concentration pairs). During pseudo–steady-state anesthesia, the pharmacodynamic measures were obtained before and after a series of noxious and nonnoxious stimulations. For the "prestimulation" and "poststimulation" BIS, SE, RE, Composite Variability Index, and Surgical Pleth Index, interaction models were applied to find the best fit, by using NONMEM 7.2.0. (Icon Development Solutions, Hanover, MD).

Results: The authors found an additive interaction between sevoflurane and remifentanil on BIS, SE, and RE. For Composite Variability Index, a moderate synergism was found. The comparison of pre- and poststimulation data revealed a shift of $C50_{SEVO}$ for BIS, SE, and RE, with a consistent increase of 0.3 vol%. The Surgical Pleth Index data did not result in plausible parameter estimates, neither before nor after stimulation.

Conclusions: By combining pre- and poststimulation data, interaction models for BIS, SE, and RE demonstrate a consistent influence of "stimulation" on the pharmacodynamic relationship between sevoflurane and remifentanil. Significant population variability exists for Composite Variability Index and Surgical Pleth Index.

The first two authors contributed equally to this study and should both be seen as first authors (B.H. and J.H.P.).

Submitted for publication August 2, 2013. Accepted for publication January 14, 2014. From the Department of Anesthesia, Ghent University Hospital, Gent, Belgium (B.H.); Department of Anesthesia, Ghent University, Gent, Belgium (M.M.R.F.S.); Department of Anesthesiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands (J.H.P., L.N.H., D.J.E., M.M.R.F.S., H.E.M.V.); and Department of Anesthesiology, Bern Hospital Network and University of Bern, Bern, Switzerland (M.L.).

Two important components of general anesthesia are hypnosis and analgesia: The hypnotic component may be defined as probability of tolerance to a nonnoxious stimulus (*e.g.*, name calling or shake and shout), whereas the analgesic component (also called: the balance between nociception and antinociception) may be considered as the probability of tolerance to a noxious stimulus.[1] Tolerance means "the absence of a response" being either a somatic response (*e.g.*, movement, sweating, eye opening), a hemodynamic response (increase in heart rate or blood pressure), or an arousal on the electroencephalogram of the frontal cortex, which is a reflection of a decreased cerebral hypnotic drug effect due to an insufficient analgesic effect. This "component" definition is based on the notion that tolerance to verbal and noxious stimulation will be mediated through different neuronal networks, which are located in the higher cortical *versus* subcortical structures of the brain, respectively.[1] These networks are independently affected by the interaction between a hypnotic and an analgesic drug. As an example of this, Heyse *et al*.[2] showed different response surface models for tolerance to nonnoxious and noxious stimulation.

In addition to the dichotomous observations of tolerance to stimulation, several neurophysiology-derived measures of anesthesia effect have been developed to monitor the anesthesia state of the patient in a continuous way. Electroencephalographic measures, such as bispectral index (BIS; Covidien, Boulder, CO), state entropy (SE), and response entropy (RE) (M-Entropy; GE Healthcare, Helsinki, Finland), have a stronger correlation with the hypnotic component than with the analgesic component of anesthesia.[3] More recently, new continuous measures with different neurophysiological background, such as the Surgical Pleth Index (SPI; GE Healthcare) and the Composite Variability Index (CVI; Covidien), attempt to quantify the balance between nociception and antinociception.[4,5] All these continuous surrogate measures of hypnotic or analgesic effect are influenced by the interaction between hypnotic and analgesic drugs and should therefore be studied with this multidrug reality in mind. Eventually, the ultimate goal of continuous monitoring is to effectively counter deviating measurements with an adequate change in the balance between opioids and hypnotics so that better clinical results are obtained. This performance can only be expected if a well-described dose-response relationship exists between the measurements and the applied drug combinations.

To depict this dose-response relationship in the presence of multiple drugs, it is common to use population-derived response surface interaction models.[2] For BIS, SE, RE, CVI, and SPI, the interaction between sevoflurane and remifentanil on continuous measures has not yet been described.

Therefore, the primary goal of this study was to develop response surface models that best describe the dose-response relationship between the combined administration of sevoflurane and remifentanil *versus* BIS, SE, RE, CVI, and SPI. Overall, we hypothesized that the nature of the various interactions should be synergistic for the continuous measures as this is in concordance with the interaction on dichotomous clinical endpoints as described by Heyse *et al*.[2] The secondary goal of the study was to investigate whether noxious stimulation significantly affects the model structure or the model parameters.

1 Materials and Methods

The data presented in this article were collected during a previous study as published by Heyse *et al.*[2] This study presents the results of a secondary analysis focusing on the

continuous measurements of drug effect, whereas the previous study focused on dichotomous endpoints of anesthetic effect (clinical signs of responsiveness). The studied patients, the crisscross study design, and drug administration methods applied in this study have been described elsewhere in detail.[2]

11 Subjects

After obtaining Institutional Review Board (Ghent U niversity Hospital Ethics Committee, Gent, Belgium) approval and prospective trial registration at ClinicalTrials.gov (NCT00522587) and after obtaining written informed consent, 40 patients with American Society of Anesthesiologists status I or II, aged 18 to 60 yr, and scheduled to undergo surgery requiring general anesthesia were included. Exclusion criteria were weight less than 70% or more than 130% of ideal body weight, neurological disorders, diseases involving the cardiovascular system, pulmonary diseases, gastric diseases, endocrine diseases, and recent use of psychoactive medication or use of more than 20 g of alcohol daily. The complete study was executed in a quiet operating room before the start of the surgical procedure.

12 Study Design

This study was performed as a randomized, prospective, open-label study. No participant of the study received premedication. After the patients arrived in the operating room, standard monitors (electrocardiogram, noninvasive blood pressure, and hemoglobin oxygen saturation), M-Entropy using a Datex S/5 Anesthesia Monitor (GE Healthcare), and BIS using an Aspect A-2000 monitor (Covidien) were connected, and a large forearm vein was cannulated. Thereafter, the patients were preoxygenated with 6 l/min of O_2 at an F_I = 1.0 for 5 min using a tightfitting face mask, which also served to sample exhaled air for end-tidal carbon dioxide measurement. Vital signs and end-tidal sevoflurane concentrations, respiratory data (tidal volume, minute volume, and end-tidal carbon dioxide), and infusion-related data (predicted concentrations and infused volumes) were continuously recorded on a computer hard disk using RUGLOOP II data-recording software (Demed, Temse, Belgium).

13 Drug Administration

131 Technical Aspects.

Remifentanil was administered by a target-controlled infusion technique by using RUGLOOP II TCI software (Demed) based on a three-compartment model with an effect-site compartment as published by Minto *et al.*[6,7] Sevoflurane was administered in 50% O_2 and 50% air by using a standard out-of-circle vaporizer and a standard breathing circuit of an ADU anesthesia workstation (Datex/Ohmeda; GE Healthcare).

132 Dosing Regimen.

We randomized 40 patients to receive four prespecified combinations of sevoflurane (0.5 to 3.5 vol%) and remifentanil (0 to 12 ng/ml) according to a modification of the crisscross

design proposed by Short *et al.*[8] In half of the patients, remifentanil was held constant, and sevoflurane was stepwise increased; in the other half, sevoflurane was held constant and remifentanil was stepwise increased. The dosing schedule is shown in table 1 in the study by Heyse *et al*.[2] No muscle relaxants were administered throughout the study.

14 Assessment of Clinical Response

For each concentration step, the clinical response was assessed 12 min after reaching the target concentrations to allow for plasma effect-site equilibration. The patient was exposed to the following series of stimuli, with increasing intensity: (1) verbal and nonpainful tactile stimuli according to the Modified Observer's Assessment of Alertness/ Sedation (OAA/S) score[9]; (2) a tetanic stimulus of the ulnar nerve for 5 s by using the standard neurostimulator; (3) insertion of a laryngeal mask airway (size 3 for women and 4 for men, LMA Unique® [The Surgical Company, Amersfoort, The Netherlands]); and (4) laryngoscopy aiming at full visualization of the vocal cords by using a size-3 curved Macintosh-type blade (HEINE Optotechnik GmbH & Co KG, Herrsching, Germany). All stimuli— including laryngoscopy—were performed by a single anesthesiologist (B.H.) to minimize interindividual variability in stimulation. Between each stimulus, a 1-min delay was maintained to evaluate the somatic responsiveness on each stimulus. If there was no response to a stimulus, the next stimulus was applied 1 min after the response assessment of the previous stimulus.

In this study, we only compared data before OAA/S score (unstimulated state) with data after laryngoscopy (stimulated state). For the data that were obtained in between stimuli, we did not estimate separate models. We could not exclude a bias evoked by influences of the preceding stimulus on the next one. However, by performing simultaneous model estimations on data before and after the sequence of four clinically relevant stimulations, we explore pharmacodynamic differences between a generally "unstimulated" *versus* a "stimulated" anesthesia state.

15 Data Acquisition and Management

151 BIS, SE, and RE.

The spectral entropy monitor (M-Entropy; GE Healthcare) calculated SE and RE. BIS was simultaneously derived from the frontal electroencephalogram (At-Fpzt) by using a quatro BIS™ sensor with four electrodes (Covidien). The smoothing time of the BIS monitor was set at 15 s. All data were recorded electronically using RUGLOOP II software (Demed) with a 5-s time interval.

The median of the recorded values during 1 min before the assessment of the OAA/S score was used for the analysis of the BIS, SE, and RE data.

152 CVI.

The raw electroencephalographic signal was captured by the BIS™ monitor with a 128-Hz sample rate and allowed *post hoc* calculation of CVI. The calculation of CVI has been

described by Mathews *et al*.[5] The CVI is a composite index that combines the variability in BIS with frontal electromyographic changes over time. A high CVI reflects activation of the frontal electromyography and increased input of sensory information from deep brain structures to the cortex. A low CVI reflects an adequate inhibition of this sensory input and adequate analgesia. The CVI was calculated with a 5-s time interval. The median of the recorded values during 1 min before the assessment of the OAA/S score was used for the analysis. In the case that one or more values were missing during the last minute before the assessment of OAA/S score due to a technical reason, the CVI was regarded as a missing value and was not taken into account in the analysis.

153 SPI.

The SPI is derived from plethysmographic pulse wave characteristics combined with heart rate variability and is a surrogate measure of the orthosympathetic and parasympathetic nervous system response to noxious stimulation. The calculation of SPI has been described by Huiku *et al*.[4] The SPI was calculated with a 1-s time interval. The median of the recorded values during 1 min before the assessment of the OAA/S score was used for the analysis. In the case that there were less than seven values during the last minute before the assessment of OAA/S score, the SPI was regarded as a missing value and was not taken into account in the analysis.

154 Data after Stimulation.

A moving median technique was applied on the raw data measured during 1 min after laryngoscopy. For the NONMEM analysis, the highest value of the moving median over several consecutive values was used. By doing so, the effect of single outlier values on the average behavior of each measurement was minimized without losing sensitivity for detecting a relevant response on BIS, SE, RE, CVI, and SPI after stimulation. For measurements that were logged every 5 s (BIS, SE, RE, and CVI), or every second (SPI), we performed the moving median technique over a sequence of respectively five or seven consecutive values. In the case that there were less than five or seven consecutive values during 1 min after application of laryngoscopy, or if laryngoscopy was not applied because the patient was responsive to a previous stimulus (see the study by Heyse *et al*.[2]), the measurement was considered as missing and was not taken into account in the analysis.

155 Pharmacodynamic Analysis of the Continuous Variables

For the continuous data, a negative sigmoid E_{max} model was used[10]:

$$\boldsymbol{Effect = E_0 - (E_0 - REST) \cdot \left(\frac{U^{\gamma}}{1 + U^{\gamma}}\right)} \qquad \textit{(1)}$$

where E_0 is the baseline value in the absence of drug, REST is a nonsuppressible effect (the lowest possible value of the effect variable), U represents the normalized combined potency of one or more drugs, and γ is the slope parameter reflecting the steepness of the concentration–effect relationship.

The normalized combined potency *U* is a function of the drug effect-site concentrations and model parameters, as described in detail in the appendix in the study by Heyse *et al*.[2] The following models were tested:

a. Greco model

$$\boldsymbol{U = \frac{C_{SEVO}}{C50_{SEVO}} + \frac{C_{REMI}}{C50_{REMI}} + \alpha \cdot \frac{C_{SEVO}}{C50_{SEVO}} \cdot \frac{C_{REMI}}{C50_{REMI}}} \quad (2)$$

where C_{SEVO} is the effect-site concentration of sevoflurane, C_{REMI} is the effect-site concentration of remifentanil, $C50_{SEVO}$ is the effect-site concentration of sevoflurane with 50% effect, $C50_{REMI}$ is the effect-site concentration of remifentanil with 50% effect, and α is a dimensionless interaction parameter.

b. Reduced Greco model without effect of the opioid alone

$$\boldsymbol{U = \frac{C_{SEVO}}{C50_{SEVO}} \cdot \left(1 + \frac{C_{REMI}}{C50_{REMI}}\right)} \quad (3)$$

c. Minto model[11]

$$\boldsymbol{U = \frac{\frac{C_{SEVO}}{C50_{SEVO}} + \frac{C_{REMI}}{C50_{REMI}}}{1 - \beta U_{50} \cdot \theta \cdot (1 - \theta)}} \quad (4)$$

where β_{U50} is a dimensionless interaction parameter, and θ is defined by:

$$\boldsymbol{\theta = \frac{\frac{C_{SEVO}}{C50_{SEVO}}}{\frac{C_{SEVO}}{C50_{SEVO}} + \frac{C_{REMI}}{C50_{REMI}}}} \quad (5)$$

d. Hierarchical model

$$\boldsymbol{U = \frac{C_{SEVO}}{C50_{SEVO}} \cdot \left(1 + \left(\frac{C_{REMI}}{C50_{REMI}}\right)^{\gamma_0}\right)} \quad (6)$$

where γ_O is the slope parameter reflecting the steepness of the concentration–effect relationship for remifentanil.

Because each pharmacodynamic endpoint was analyzed separately, the Scaled $C50_O$ and Fixed $C50_O$ Hierarchical models are identical.[2]..

For BIS, SE, and RE, it was assumed that the measure approaches zero for high concentrations of sevoflurane or remifentanil, so REST is zero, reducing the model to a fractional E_{max} model.[10] For CVI and SPI, the nonsuppressible effect REST was modeled as a function of the drug concentrations according to the procedure described by Minto *et al*.[11]:

$$\boldsymbol{REST = REST_{SEVO} \cdot \theta + REST_{REMI} \cdot (1 - \theta) - \beta_{REST} \cdot \theta \cdot (1 - \theta)} \quad \textit{(7)}$$

where $REST_{SEVO}$, $REST_{REMI}$, and β_{REST} are model parameters.

16 Parameter Estimation

The model parameters were estimated using NONMEM 7.2.0 (Icon Development Solutions, Hanover, MD), using first-order conditional estimation. Platform was Windows XP (Microsoft, Redmond, WA) and compiler was G95. For all parameters, interindividual variability was assumed either to be absent or to have a lognormal distribution. It was tested whether a single value for the individual deviation from the typical value (eta in NONMEM) could be used for C50 of sevoflurane and remifentanil, in accordance with the assumption that this value reflects the sensitivity of that individual for hypnotic and opioid drugs. Residual intraindividual variability of the continuous variables was modeled using standard additive or proportional error models.

Parameters were tested for significance by comparing the objective function which is minus two times log-likelihood (−2LL). Significance level for hypothesis tests was 0.01 (chi-square test), or a 6.84 difference in the −2LL adding one parameter for nested models. The goodness-of-fit for the models was also assessed by visual inspection of the predicted *versus* observed plots and the distribution of residuals for each of the continuous endpoints.

Model building was performed starting with the simplest form of each model and expanding the model with parameters and interindividual variability until the decrease of the objective function value was not statistically significant using the chi-square test. In addition, model building was started with the most complex model, reducing the model by fixing parameters to zero. The NONMEM analysis was performed with various values for initial estimates and boundary values. The results were accepted as valid only if both minimization and covariance steps were successful, unless stated otherwise.

To evaluate the final model, a bootstrap analysis was performed, based on 2,000 sets of 40 patients each, randomly selected from the available 40 patients, using a custom program written in c. Results were analyzed in Excel (Microsoft) to obtain nonparametric 95% CIs.

The poststimulation data after laryngoscopy were analyzed by using an identical modeling approach as applied on the prestimulation data. To investigate the effect of the stimulations on the model parameters, we performed a simultaneous fitting of the data before OAA/S (= unstimulated anesthesia state) and after laryngoscopy (= stimulated anesthesia state) in a stepwise model-building process, starting with fixed common parameters for both data sets,

followed by testing the addition of parameters for the difference between before OAA/S and after laryngoscopy.

17 Statistical Analysis

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

2 Results

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

21 Data

In total, the data sets contained 159 periods of testing (40 patients with 4 periods per patient minus 1 missing period where no stimulus was given).

22 Model Development for BIS

Initially, BIS data were analyzed using the Greco, Reduced Greco, Minto, and Hierarchical models, using a fractional E_{max} model (REST = 0). For both the Greco model and the Minto model, the interaction term for C50 did not differ significantly from zero. Similarly, the interaction term for γ in the Minto model did not differ significantly from zero. Consequently, both models yield identical results. The objective function value for the Greco model (808.5) was markedly lower than that for the Reduced Greco model (823.0) and Hierarchical model (822.2), and therefore, the Greco model was considered as the most appropriate method. The additional error model fitted better to the data than the proportional error model, as concluded from the objective function value and diagnostic plots of residuals.

23 Final Model for BIS

The final results for this model are shown in table 1. In the final model, interindividual variability was included in $C50_{REMI}$ and $C50_{SEVO}$ with a common *eta*. The value for C50 for remifentanil (27.3 ng/ml) exceeds the upper range of concentrations in the study (12 ng/ml), but its precision was satisfactory (relative standard error 12%). The response surface of the final model is shown in figure 1. Figure 2 depicts the observed BIS values (filled symbols) and predicted BIS (solid line) *versus* the normalized combined potency U_{BIS}, which has a sigmoidal E_{max} relationship.

24 Model Development for SE and RE

The Greco model was found to be the most appropriate model for SE and RE, in accordance with the best model for BIS.

25 Final Models for SE and RE

The results of the final models are summarized in table 1. The variability in SE and RE is larger than for the BIS data, as reflected in larger relative standard errors, larger interindividual variability, and larger residual SD.

The response surfaces of the final models for SE and RE are shown in figure 1. Figures 3 and 4 depict the observed (filled symbols) and predicted (solid line) SE and RE *versus* the normalized combined potencies U_{SE} and U_{RE}, respectively, which also have a sigmoidal E_{max} relationship.

Table 1. Population Model Estimates for BIS, SE, RE, and CVI

	BIS	SE	RE	CVI
Interaction Model	Greco/Minto	Greco/Minto	Greco/Minto	Reduced Greco
$C50_{REMI}$ (ng/ml)	27.3 (13%) (20.4–37.7)	16.2 (19%) (11.0–27.9)	18.2 (21%) (12.6–31.9)	7.56 (32%) (4.01–17.7)
$C50_{SEVO}$ (vol%)	1.99 (6%) (1.68–2.23)	1.82 (8%) (1.49–2.11)	1.88 (7%) (1.58–2.14)	1.09 (97%) (0.08–3.28)
γ	1.88 (10%) (1.53–2.27)	1.87 (9%) (1.54–2.26)	2.08 (8%) (1.76–2.40)	1.16 (29%) (0.77–2.15)
E_0	89.5 (4%) (83.5–99.1)	97.1 (5%) (84.3–110)	103 (4%) (95–113)	4.32 (57%) (2.35–19.9)
$IIV(C50_{REMI})$	20% (14%) (14–25%)	59% (19%) (33–86%)	67% (19%) (43–99%)	0*
$IIV(C50_{SEVO})$	20%†	22% (22%) (8–30%)	25% (19%) (13–34%)	18% (24%) (0–26%)
Residual SD	6.2‡ (9%) (5.0–7.2)	9.5‡ (10%) (7.5–11.1)	9.6‡ (10%) (7.5–11.2)	27%§ (11%) (22–33%)
$\Delta C50_{SEVO}$ (vol%)	0.30 (18%) (0.20–0.41)	0.31 (22%) (0.18–0.46)	0.36 (20%) (0.23–0.52)	II

Values are typical values, relative standard error (% of the typical value) and 95% CI obtained by bootstrapping.

* Not significantly different from zero; † Common value for remifentanil and sevoflurane; ‡ Additive error; § Proportional error; II Could not be estimated (for details, see text).

BIS = bispectral index; CVI = Composite Variability Index; $C50_{REMI}$ = effect-site concentration of remifentanil with 50% effect; $C50_{SEVO}$ = effect-site concentration of sevoflurane with 50% effect; $\Delta C50_{SEVO}$ = increase of $C50_{SEVO}$ after laryngoscopy, as obtained in a separate analysis (see text); E_0 = baseline value in the absence of drugs; γ = model parameter reflecting the steepness of the concentration–effect relationship; $IIV(C50_{REMI})$ and $IIV(C50_{SEVO})$ = interindividual variability for $C50_{REMI}$ and $C50_{SEVO}$, respectively (calculated as the square root of interindividual variance, multiplied by 100%); Residual SD = SD of the differences between the observed and predicted responses (calculated as the square root of the residual variance); RE = response entropy; SE = state entropy.

26 Model Development for CVI

In four patients, the CVI could not be calculated due to missing data. In 17 patients, the CVI could not be calculated from the available electroencephalogram registration in one or more periods. In total, 122 CVI values in 36 patients were available.

For CVI, the objective function value of the Reduced Greco model was lower than for the Greco model and Minto model. The proportional error model fitted better to the data than the additional error model, as concluded from the objective function value and diagnostic plots of residuals. Using the Hierarchical model, the slope factor γ for remifentanil (0.289) and $C50_{SEVO}$ (0.266 vol.%) was very low, E_0 (10.2) was much higher than the highest observed CVI value, and standard errors were high; therefore, this model was not accepted as a valid model.

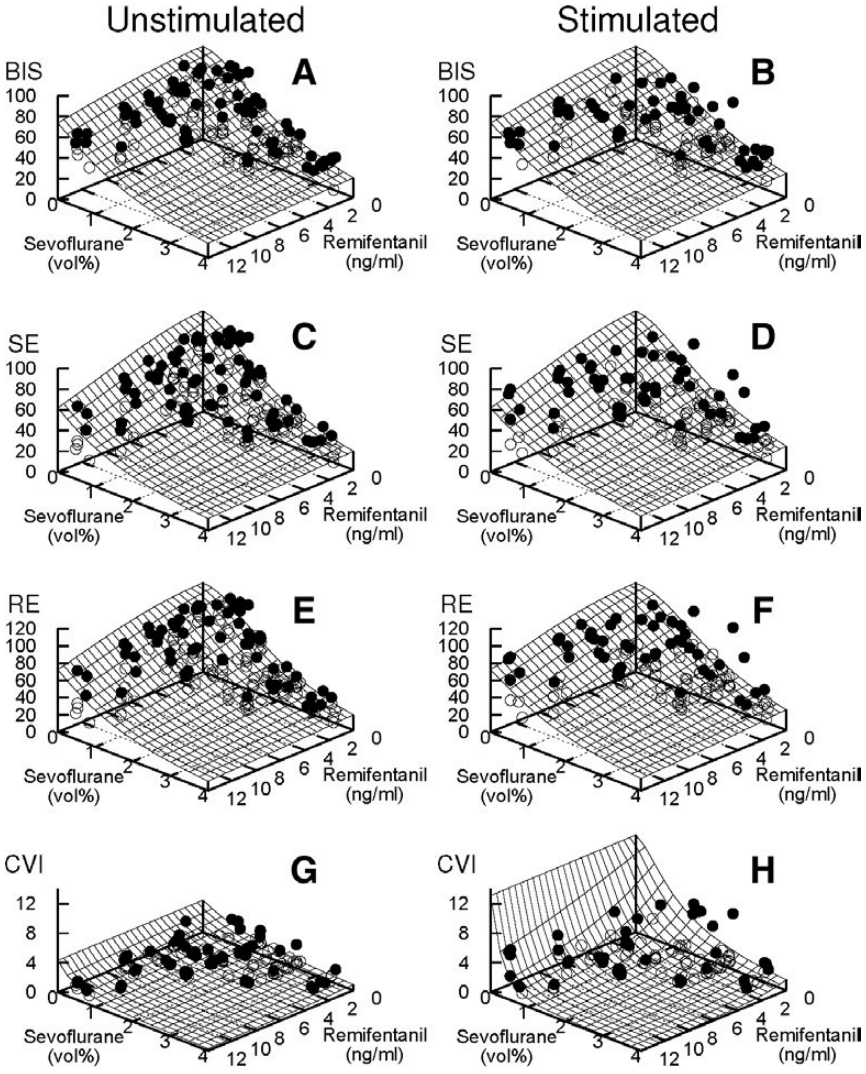


Fig. 1. Response surface for electroencephalographic endpoints before stimulation (*A*, *C*, *E*, *G*) and after stimulation (*B*, *D*, *F*, *H*) was applied: Bispectral index (BIS), state entropy (SE), response entropy (RE), and Composite Variability Index (CVI), as a function of the end-tidal steady-state sevoflurane concentration and the predicted remifentanil effect-site concentration, calculated from the data listed in table 1. Measured values above the surface are shown as *filled circles* and below the surface as *open circles*.

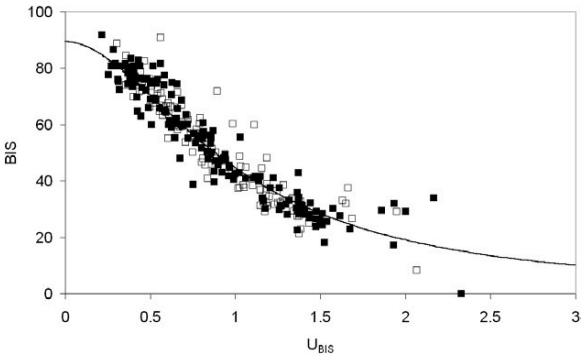


Fig. 2. Relationship between the normalized combined potency U_{BIS} according to the Greco model and the observed bispectral index (BIS) (*squares*, n = 159) and predicted BIS (*solid line*; calculated from the data listed in table 1) for unstimulated (*filled symbols*) and stimulated (*open symbols*).

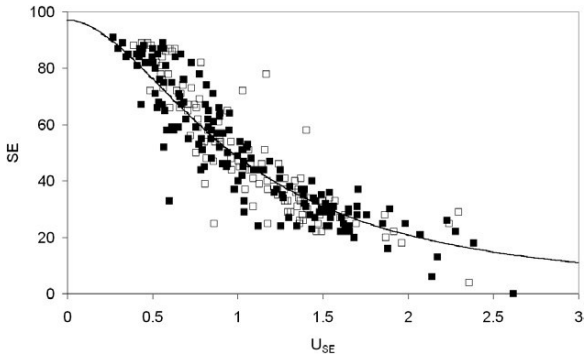


Fig. 3. Relationship between the normalized combined potency U_{SE} according to the Greco model and the observed state entropy (SE) (*squares*, n = 159) and predicted SE (*solid line*; calculated from the data listed in table 1) for unstimulated (*filled symbols*) and stimulated (*open symbols*).

27 Final Model for CVI

The results for the final Reduced Greco model are shown in table 1. The residual error of 27% is large and the CIs for the model parameters are wide, reflecting the poor fit.

The response surface of the final model for CVI is shown in figure 1. Figure 5 depicts the observed (filled symbols) and predicted CVI values (solid line) *versus* the normalized combined potency U_{CVI}. The CVI has a sigmoidal E_{max} relationship with U_{CVI}, which is comparable in behavior to BIS, SE, and RE.

28 Model Development for SPI

In two patients, the SPI could not be calculated due to missing data. In four patients, the SPI could not be calculated from the available plethysmography data in one or more periods. In total, SPI data from 145 periods in 38 patients were available.

Modeling of the SPI data did not result in reliable results. Plotting the SPI data against the sevoflurane or remifentanil concentration revealed that the SPI value is hardly affected by sevoflurane or remifentanil, in contrast to the BIS, SE, RE, and CVI (data not shown).

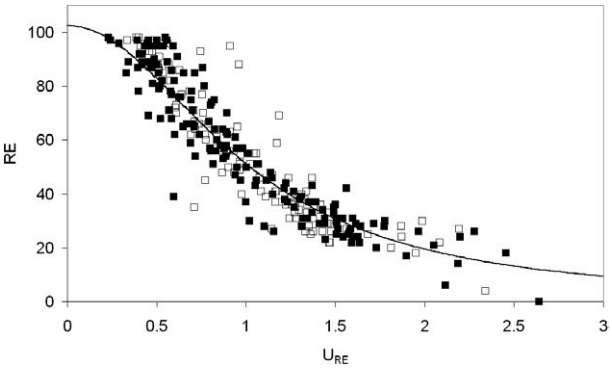


Fig. 4. Relationship between the normalized combined potency U_{RE} according to the Greco model and the observed response entropy (RE) (*squares*, n = 159) and predicted RE (*solid line*; calculated from the data listed in table 1) for unstimulated (*filled symbols*) and stimulated (*open symbols*).

29 Data after Stimulation

The data after stimulation were first analyzed using an identical modeling approach as applied on the unstimulated data. For BIS, SE, and RE, the number of data points was 114 (in 45 periods, laryngoscopy was not applied for ethical or other reasons). The optimal models were identical and the parameters were broadly comparable with the results before the assessment of OAA/S, except for $C50_{SEVO}$, which was consistently higher after the series of stimulation (data not shown).

Next, to investigate this effect of stimulation on the model parameters, we performed a simultaneous fitting of the data before OAA/S (= unstimulated anesthesia state) and after laryngoscopy in a model-building process (= stimulated anesthesia state), starting with fixed common parameters for both data sets, followed by adding parameters for the difference between before OAA/S and after laryngoscopy. This analysis revealed that C50SEVO was significantly higher after laryngoscopy for BIS, SE, and RE, with an average increase of 0.3 vol% sevoflurane (table 1), whereas the other parameters did not change. The response surfaces of the final models for BIS, SE, and RE are shown in figure 1. Figures 2–4 depict the observed values (open symbols) and predicted values (solid line) versus the normalized combined potency U for BIS, SE, and SE, respectively. Because the baseline values, maximal effect and steepness of the model are not affected by the stimulation, the relationship between U and predicted value is not affected, and the solid line is identical for unstimulated and stimulated conditions. For each combination of sevoflurane and remifentanil, the value UBIS (similar for USE and URE) after stimulation is lower compared with the unstimulated state as a result of the higher C50SEVO. Consequently, the predicted BIS after stimulation will be higher than in the unstimulated state, reflecting a reduction of the combined drug effect. In other words, stimulation moves U_{BIS} to the left, and the predicted BIS upwards along the solid lines of figures 2–4.

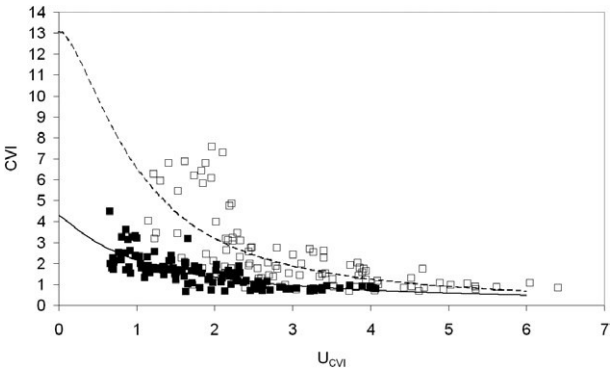


Fig. 5. Relationship between the normalized combined potency U_{CVI} according to the Reduced Greco model and the observed Composite Variability Index (CVI) (*squares*, n = 122) and predicted CVI (*lines*; calculated from the data listed in table 1) for unstimulated (*filled symbols*, *solid line*) and stimulated (*open symbols*, *dashed line*).

In contrast, simultaneous analysis of the CVI data before OAA/S and after laryngoscopy, with parameters fixed to the values from the analysis of the data before OAA/S alone (table 1), resulted in a lower value for $C50_{REMI}$ (3.09 ng/ml; CI, 1.78 to 4.68 ng/ml), a higher value for γ (1.62; CI, 1.28 to 1.79), and E_0 (13.1; CI, 9.4 to 17.2). Also, the residual SD (46%; CI, 37 to 53%) after stimulation was higher, indicating an even larger variability in the dose–response relationship of CVI compared with the unstimulated condition. Figure 5 depicts the observed values (open symbols) and predicted CVI (dashed line) *versus* the normalized combined potency U_{CVI}, respectively. Figure 5 also shows the shift in dose–response relationship of CVI *versus* U_{CVI} between the unstimulated (solid line) and stimulated

condition (dashed line). Because the baseline and steepness are affected by the stimulation, the relationship between U_{CVI} and predicted value is different for the unstimulated and stimulated data. The response surface for CVI after stimulation is shown in figure 1.

The SPI data after stimulation (104 valid SPI values) were analyzed using the same approaches. Similar to the unstimulated data, the SPI values after stimulation were hardly affected by sevoflurane or remifentanil, and modeling did not result in reliable results (data not shown).

210 Isoboles

In figure 6, the isoboles of BIS values from 10 to 80 are depicted for the unstimulated (solid lines) and stimulated (dashed lines) condition. The additive nature of the interaction results in linear isoboles for the complete range of BIS values. The isoboles are shifted upwards after stimulation, reflecting the increase in $C50_{SEVO}$.

In figure 7, the isoboles of CVI values from 0.5 to 3 are depicted for the unstimulated (solid lines) and stimulated (dashed lines) condition, showing a synergistic nature of the interaction, as reflected by the Reduced Greco model. For low CVI values, the isoboles of the stimulated condition intersect the isoboles of the unstimulated condition.

For SPI, no isoboles could be depicted, as we could not fit an appropriate response surface model to the data.

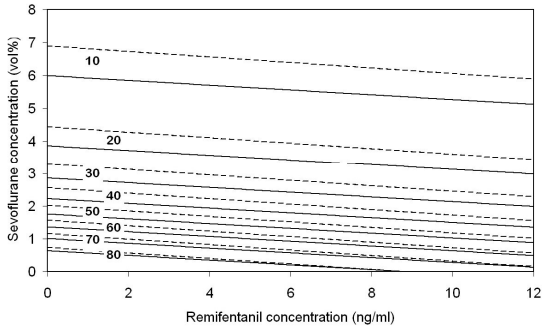


Fig. 6. Isoboles for bispectral index values of 10, 20, 30, 40, 50, 60, 70, and 80 for the unstimulated (*solid lines*) and stimu-lated (*dashed lines*) data, as a function of the end-tidal sevoflurane concentration and the predicted remifentanil effect-site concentration, calculated from the data listed in table 1.

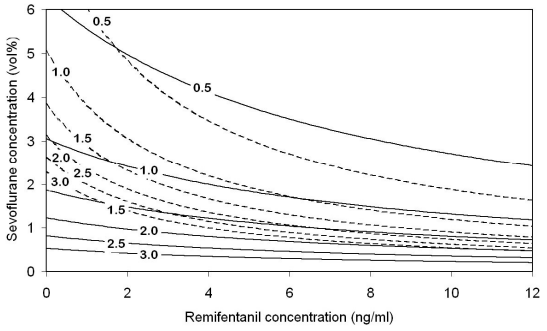


Fig. 7. Isoboles for Composite Variability Index values of 0.5, 1, 1.5, 2, 2.5, and 3 for the unstimulated (*solid lines*) and stimulated (*dashed lines*) data, as a function of the end-tidal sevoflurane concentration and the predicted remifentanil effect-site concentration, calculated from the data listed in table 1.

3 Discussion

We describe the interaction between sevoflurane and remifentanil on BIS, SE, RE, CVI, and SPI. Although opioids have a rather weak effect on the electroencephalogram, we found an additive effect of remifentanil on reduction of BIS, SE, and RE by sevoflurane. The effect on CVI was synergistic. The SPI was not affected by sevoflurane or remifentanil. The Greco model provided the best fit of the data for BIS, SE, and RE, whereas the reduced Greco

model best described CVI. Interestingly, the structural interaction model was not affected by noxious stimulation, but noxious stimulation did increase the $C50_{SEVO}$ for BIS, SE, and RE by 20%, whereas the $C50_{REMI}$ did not change. In contrast, for CVI all model parameters changed except $C50_{SEVO}$.

The findings on (unstimulated) BIS, SE, and RE are in agreement with that reported in previous literature. Nieuwenhuijs et al.[12] presented an interaction model during sevoflurane–alfentanil anesthesia, suggesting additivity for BIS. During propofol anesthesia, Vanluchene et al.[3] found that remifentanil evoked an increase in the threshold for loss of consciousness on BIS, SE, and RE in a dose-dependent way, but no conclusion was drawn on the nature of this interaction. Bouillon et al.[13] found additivity for BIS during propofol–remifentanil anesthesia. Schumacher et al.[10] found an additive interaction on BIS for combined propofol and sevoflurane. Conversely, the interaction of sevoflurane and remifentanil on clinical endpoints of effect, as published by Heyse et al.,[2] was not additive but synergistic. Also, $C50_{REMI}$ was 10-fold higher for BIS, SE, and RE compared with $C50_{REMI}$ for dichotomous endpoints.[2] Apparently, the opioid effect on the electroencephalogram is weak, despite a strong effect on patient responsiveness. This may explain why electroencephalographic variables are poor predictors of responsiveness to noxious stimuli.

According to the parameter estimates (table 1), BIS is least opioid sensitive, followed by SE, RE, and CVI, whereas BIS, SE, and RE are equally sensitive to sevoflurane, but less than CVI. The slope of the response surfaces is similar for BIS, SE, and RE, but steeper than the slope for CVI (fig. 5). The interaction model for BIS is characterized by the lowest interindividual (table 1: IIV [$C50_{REMI}$]) and residual variability.

Interaction models not only define combined effects of sevoflurane and remifentanil as a response surface but also allow expression of the potency of a combination of drugs as one dimensionless number. For this purpose, we introduced "U" being units of combined potency related to each of the investigated effects variables. For example, U_{BIS} is the sum of the sevoflurane and remifentanil concentration both normalized to the respective C50's of the BIS dose–response curve (equations 2 and 4). The potency $U_{BIS} = 1$ can be achieved by 1.99 vol% of sevoflurane (=$C50_{SEVO}$) or (e.g.) by 1.49 vol% of sevoflurane (=$0.75 \times C50_{SEVO}$) plus 6.8ng/ml of remifentanil (=$0.25 \times C50_{REMI}$). As C50 is specific for each electroencephalographic variable, one given sevoflurane and remifentanil concentration does not yield identical values of "U" for BIS, SE, RE, or CVI. According to the final models (table 1), 1.5 vol% of sevoflurane combined with 5ng/ml of remifentanil yields a U_{BIS}, U_{SE}, U_{RE}, and U_{CVI} of 0.94, 1.13, 1.07, and 2.29, respectively.

In concordance with Minto et al.,[11] we consider the combination of two drugs as a virtual new drug. "U" can be used as if it was a drug concentration of that virtual new drug on the x-axis of a two-dimensional concentration–response curve (figs. 2–5). With the selected interaction models, the combined potency "U" predicted the effect on BIS, SE, and RE with an error of approximately 10%, which is comparable to that reported in the previous studies.[13]

"U" as a number represents potency of a combination of sevoflurane and remifentanil to suppress the electroencephalographic variable and has similarities with the Noxious Stimulation Response Index.[14] The Noxious Stimulation Response Index is based on the suppression of a response to laryngoscopy, using the Hierarchical interaction model. The $C50_{REMI}$ (1.16ng/ml) in this model is much lower than the $C50_{REMI}$ in the current study (7.5 to 27.3ng/ml, depending on the type of electroencephalographic variable). This makes Noxious

Stimulation Response Index much more opioid sensitive compared with "U," which is in agreement with the fact that hypnotics have a stronger effect on electroencephalogram than the effects of opioids on electroencephalogram. The clinical utility of any of the "U"s or Noxious Stimulation Response Index to titrate opioids and hypnotics remains to be determined.

The CVI as a potential indicator of nociception behaved similar as dichotomous endpoints in the previous study[2]: the interaction was synergistic. The best fit was found with the reduced Greco model. As expected, the concentration–response curve of CVI was affected by noxious stimulation (figs. 5 and 7), especially due to a substantial increase in baseline effect (E0), probably due to an increase in electromyographic activity. The dose–response curve was rather flat, and a ceiling effect was observed at the level of a CVI of approximately 1 (fig. 5). This explains why a larger increase of the sevoflurane concentration is needed to lower CVI from 1 to 0.5 than that required to lower CVI from 3 to 2.5 (fig. 7). Although noxious stimulation and opioids evoke a greater effect on CVI than on BIS, SE, and RE, CVI may offer lower discriminating capacity compared with BIS, SE, and RE. Even in our best-fitted model, the differences between estimated and observed CVI were high, especially after noxious stimulation (figs. 1 and 5).

The poststimulation data set represents a population that is in a pharmacological pseudosteady state (at similar drug concentrations as before stimulation), where the applied stimuli may have disrupted the balance between drug concentrations and effect variables. Assuming that noxious stimulation might induce an arousal response on the electroencephalographic variables, we hypothesized that the parameter estimates from the poststimulation data could be different from those of the prestimulation data. We expected larger differences in model estimates for CVI and SPI compared with BIS, SE, and RE, as the arousal response in BIS is already suppressed by rather low remifentanil concentrations.[15]

For all poststimulation response surface models, the structural model with the lowest objective function was identical to the prestimulation model. For BIS, SE, and RE, the model parameters hardly changed, except for $C50_{SEVO}$ (consistently 0.3 vol% higher after laryngoscopy). This pharmacodynamic shift is consistent for BIS and entropy and it is only little smaller than the difference between $C50_{SEVO}$ for tolerance of shake and shout and laryngoscopy, found in the previous article (0.53 vol%).[2] Typical accuracy for measuring sevoflurane end-tidal concentrations is ±0.15 vol% + 5% of reading. The time between nonstimulation and poststimulation sampling did not exceed 6min and therefore was assumed to be constant. Therefore, we consider 0.3 vol% (or 14% of 1 minimal alveolar concentration) as clinically relevant. The sevoflurane and remifentanil concentrations mentioned above (1.5 vol% and 5 ng/ml) yield a poststimulation U for BIS, SE, and RE which is approximately 10% lower than the prestimulation U. Therefore, both single-model parameters (e.g., C50s) and combined potency U could be used as surrogate measures of stimulus intensity.

For CVI, the changes in the poststimulation model are complex. $C50_{REMI}$ decreased to 3.09 ng/ml. Gamma and the baseline effect (E0) increased. The increased steepness of the dose–response curve and the larger difference between baseline and maximal effect suggest an improved descriptive capacity for CVI in stimulated compared with unstimulated conditions. However, the residual SD and the standard errors of the parameters indicate a larger variability in the dose–response relationship compared with the unstimulated

condition. Our finding is in agreement with the notion that a noxious stimulus is mandatory to measure the balance between nociception and antinociception accurately.

For SPI, we were not able to extract plausible parameter estimates from our data, neither from prestimulation nor from poststimulation observations. Either SPI is hardly affected by sevoflurane and remifentanil or the inter- and intraindividual variability of SPI hides a minimal dose– response relationship. The sympathetic and parasympathetic nerve system may be affected by many confounding factors apart from noxious stimulation and anesthetic drug dosages. The inability to detect any dose–response relationship in steady-state conditions, both with or without noxious stimulation, lowers the expectations for SPI as a guide for titrating sevoflurane and remifentanil anesthesia.

In conclusion, sevoflurane and remifentanil are additive on BIS and entropy, but they act synergistic on CVI. SPI is not correlated to drug concentrations. Noxious stimulation did not change structural models but increased the C50 of sevoflurane related to BIS and entropy, whereas a more complex parameter shift was found for CVI.

3111 Acknowledgments

The authors thank Chandran Seshagiri, Ph.D. (Covidien, Boulder, Colorado), for the calculation of the Composite Variability Index values and Kimmo Uutela, Ph.D. (GE Healthcare, Helsinki, Finland), for the calculation of the Surgical Pleth Index values.
This work was supported by a nonrestrictive educational grant from Dräger Medical (Lübeck, Germany) and partially by departmental and institutional funding. Drs. Struys and Luginbühl have received unrestricted educational grants from Dräger Medical, Lübeck, Germany.

3112 Competing Interests

The authors declare no competing interests.

4 References

1. Glass PS: Anesthetic drug interactions: An insight into general anesthesia—Its mechanism and dosing strategies. *Anesthesiology* 1998; 88:5–6
2. Heyse B, Proost JH, schumacher PM, Bouillon TW, Vereecke HE, Eleveld DJ, Luginbühl M, Struys MM: Sevoflurane remifentanil interaction: Comparison of different response surface models. ANesthesiology 2012; 116:311–23
3. Vanluchene Al, Struys MM, Heyse BE, Mortier EP: Spectral entropy measurement of patient responsiveness during propofol and remifentanil. A comparison with the bispectral index. Br J Anaesth 2004; 93:645–54
4. Huiku M, Uutela K, van Gils M, Korhonen I, Kymäläinen M, Meriläinen P, Paloheimo M, Rantanen M, takala P, Viertiö-Oja H, Yli-Hankala A: Assessment of surgical stress during general anaesthesia. Br J Anaesth 2007; 98:447–55
5. Mathews DM, Clark l, Johansen J, Matute E, Seshagiri CV: Increases in electroencephalogram and electromyogram variability are associated with an increased incidence of intraoperative somatic response. Anesth Analg 2012; 114:759–70
6. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifent¬anil. I. Model development. *Anesthesiology* 1997; 86:10–23
7. Minto CF, Schnider TW, Shafer SL: Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. *Anesthesiology* 1997; 86:24–33
8. Short TG, Ho TY, Minto CF, Schnider TW, Shafer SL: Efficient trial design for eliciting a pharmacokinetic-pharmacodynamic model-based response surface describing the interaction between two intravenous anesthetic drugs. *Anesthesiology* 2002; 96:400–8
9. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL: Validity and reliability of the observer's Assessment of Alertness/sedation scale: Study with intravenous midazolam. J Clin Psychopharmacol 1990; 10:244–51
10. Schumacher PM, Dossche J, Mortier EP, Luginbuehl M, Bouillon TW, Struys MM: Response surface modeling of the interaction between propofol and sevoflurane. *Anesthesiology* 2009; 111:790–804
11. Minto CF, Schnider TW, Short TG, Gregg KM, Gentilini A, Shafer SL: Response surface model for anesthetic drug interactions. *Anesthesiology* 2000; 92:1603–16
12. Nieuwenhuijs DJ, Olofsen E, Romberg RR, Sarton E, Ward D, Engbers F, Vuyk J, Mooren R, Teppema LJ, Dahan A: Response surface modeling of remifentanil-propofol interaction on cardiorespiratory control and bispectral index. *Anesthesiology* 2003; 98:312–22
13. Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, Shafer SL: Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. *Anesthesiology* 2004; 100:1353–72

14. Luginbühl M, Schumacher PM, Vuilleumier P, Vereecke H, Heyse B, Bouillon TW, Struys MM: Noxious stimulation response index: A novel anesthetic state index based on hypnotic-opioid interaction. *Anesthesiology* 2010; 112:872–80
15. Guignard B, Menigaux C, Dupont X, Fletcher D, Chauvin M: The effect of remifentanil on the bispectral index change and hemodynamic responses after orotracheal intubation. Anesth Analg 2000; 90:161–7

Chapter 5 Interaction between Nitrous Oxide, Sevoflurane, and Opioids

A Response Surface Approach

Hugo Ed. M. Vereecke, M.D., Ph.D.,* Johannes H. Proost, Pharm.D., Ph.D.,† Bjorn Heyse, M.D.,‡ Douglas J. Eleveld, Ph.D.,§ Takasumi Katoh, M.D.,‖ Martin Luginbühl, M.D., Ph.D.,# Michel M. R. F. Struys, M.D., Ph.D.**

Anesthesiology. 2013 Apr;118(4):894-902

ABSTRACT

Background: The interaction of sevoflurane and opioids can be described by response surface modeling using the hierarchical model. We expanded this for combined administration of sevoflurane, opioids, and 66 vol.% nitrous oxide (N_2O), using historical data on the motor and hemodynamic responsiveness to incision, the minimal alveolar concentration, and minimal alveolar concentration to block autonomic reflexes to nociceptive stimuli, respectively.

Methods: Four potential actions of 66 vol.% N_2O were postulated: (1) N_2O is equivalent to A ng/ml of fentanyl (additive); (2) N_2O reduces *C*50 of fentanyl by factor B; (3) N_2O is equivalent to X vol.% of sevoflurane (additive); (4) N_2O reduces *C*50 of sevoflurane by factor Y. These four actions, and all combinations, were fitted on the data using NONMEM (version VI, Icon Development Solutions, Ellicott City, MD), assuming identical interaction parameters (A, B, X, Y) for movement and sympathetic responses.

Results: Sixty-six volume percentage nitrous oxide evokes an additive effect corresponding to 0.27 ng/ml fentanyl (A) with an additive effect corresponding to 0.54 vol.% sevoflurane (X). Parameters B and Y did not improve the fit.

Conclusion: The effect of nitrous oxide can be incorporated into the hierarchical interaction model with a simple extension. The model can be used to predict the probability of movement and sympathetic responses during sevoflurane anesthesia taking into account interactions with opioids and 66 vol.% N_2O.

Katoh *et al*.[1] described the reduction of minimal alveolar concentration (MAC) and MAC to block autonomic reflexes to nociceptive stimuli (MAC-BAR) of sevoflurane by fentanyl. MAC and MAC-BAR are the minimal alveolar anesthetic concentrations that evoke respectively "immobility" or "hemodynamic stability" after surgical incision in 50% of subjects. Nitrous oxide (N_2O) is combined with inhaled anesthetics in anesthesia for its potentiating effects. For this reason, Katoh *et al*.[1] also tested the MAC reduction evoked by nitrous oxide.

The classical MAC reduction studies use a logistic regression approach.[2] The logistic regression approach as applied by Katoh *et al.* does not provide unique parameters describing the influence of nitrous oxide, independent of the type of response (movement or hemodynamic), thus not allowing to apply the results to other responses. Because the article of Katoh *et al*. does not provide the model parameters of the logistic regression analysis, it does not allow a flexible calculation of the probability of response at any drug level.

Currently, nonlinear mixed effect modeling is considered to be the definitive standard for modeling three dimensional response surfaces on interaction datasets.[3] One of the advantages of the response surface approach is that a single formula describes the full range of effect for any combination of drugs.[2,3] Recently, Heyse *et al*.[4] reviewed several equations that have been proposed as structural model for response surface modeling and found that the hierarchical model (with fixed *C*50 of opioids) performed best to predict the response to multiple noxious and non-noxious stimuli during a sevoflurane–remifentanil anesthesia. In contrast to the logistic regression approach, the hierarchical model is a mechanism-based model in which every parameter represents a pharmacologic endpoint, which has clinical meaning (*e.g.*, potency of the opioid, potency of the hypnotic, steepness of the dose–response relationship). The parameters of the logistic regression are mathematical constants that have no physiological or pharmacologic correlate.

A response surface model that describes the effects of nitrous oxide has not yet been described. We hypothesized that the hierarchical model could be expanded further to allow flexible inclusion of the effects of 66 vol.% N_2O in the interaction between opioids and sevoflurane.

The methodology for response surface modeling demands high numbers of observations in volunteers or patients, considerable costs, and manpower. Fortunately, we had the opportunity to reuse the historical dataset of Katoh *et al.*[1] Contemporary analyzing methods can extract more information from this data compared with the classical MAC reduction approach. The data from Katoh *et al.*[1] contain large numbers of observations with sufficient numbers of responders and nonresponders and a wide range of drug doses.

The purpose of the current study was to develop a response surface model for the combination of sevoflurane, nitrous oxide, and fentanyl using this dataset.

1 Materials and Methods

11 Data

The study by Katoh *et al.*[1] was performed after approval from the District Ethics Committee of Hamamatsu University Hospital (Hamamatsu, Japan), and individual informed consent had been obtained from all patients. We reanalyzed the raw data from Katoh *et al.*[1] on the sevoflurane MAC and MAC-BAR reduction by fentanyl in the presence (n = 86 patients) or absence (n = 96 patients) of 66 vol.% N_2O. Patients were randomly assigned to receive

nitrous oxide or not. Patients of both sexes, between 20 and 50 years, were classified as American Society of Anesthesiologists physical status I and were scheduled for elective surgery of the abdomen, extremities, or body surface.

12 Anesthetic Management

The anesthetic management and data collection were described in detail in the original article.[1] In short, all patients fasted for at least 8 h before anesthesia and received no premedication. A target-controlled infusion of fentanyl (using the pharmacokinetic model published by Shafer *et al*.[5]) was initiated in all patients, according to a randomization list. Fentanyl plasma concentration targets ranged between 0 and 8 ng/ml. Inhaled induction was performed with sevoflurane 8% in 100% oxygen (control group) or sevoflurane 8% in oxygen with 66 vol.% N_2O group. After loss of consciousness and precurarization with 0.02 mg/kg vecuronium, 1.5 mg/kg succinylcholine was administered and tracheal intubation was performed to secure the airway for the remainder of the study. Ventilation was adjusted to maintain normocapnia. An end-tidal concentration of sevoflurane was targeted according to a randomization list, between 0 and 4.5 vol.%. N_2O was administered at an end-tidal concentration of 66 vol.%. End-tidal concentrations of sevoflurane, nitrous oxide, and carbon dioxide were measured continuously using an infrared multigas anesthetic analyzer (Capnomac Ultima, Datex, Helsinki, Finland), which was calibrated before anesthesia for each patient using a standard gas mixture. Gas samples were collected *via* a catheter placed at the tracheal end of the endotracheal tube.

After intubation and setting the drug targets for maintenance, a 20-min delay was respected to allow equilibration between the effect-site concentration and the end-tidal vapor pressure of sevoflurane and the plasma concentration of fentanyl, respectively. As such, all observations of the responses were performed during a pharmacologic pseudo steady state. This was confirmed by analysis of venous blood samples taken 5 min before and within 30 s after incision. Patients with a difference in measured plasma fentanyl concentration of more than 35% between samples were excluded from further analysis. The delay of 20 min also allowed recovery from the neuromuscular blocking agents, which was confirmed by monitoring the recovery.

Twenty minutes after intubation, the surgeon made an abdominal incision and somatic or hemodynamic responses were observed. Positive response was defined as a somatic or hemodynamic change within 60 s after incision. Coughing, chewing, or swallowing was not considered a purposeful movement. Hemodynamic response was defined as an increase in heart rate or systolic blood pressure of more than 15% over the preincision baseline value.

13 Interaction Model

The probability of tolerance, *P*, to a certain stimulus (*e.g.* , incision) can be expressed as

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

where *U* represents the normalized potency of a single drug or a combination of drugs. *U* is a function of the drug effect-site concentrations and model parameters, reflecting the relative drug concentration, and γ is the slope parameter reflecting the steepness of the concentration–effect relationship.[4,6]

The hierarchical model (equation 2) can be incorporated in equation 1 for calculating all levels of probability of response.[6]

$$U = U_{SEVO} \cdot (1 + U_O{}^{\gamma_O}) \quad (2)$$

where

$$U_O = \frac{C_O}{C50_O} \quad (3)$$

and

$$U_{SEV} = \frac{C_{SEVO}}{C50_{SEVO}} \quad (4)$$

U_O and U_{SEVO} are the normalized opioid and sevoflurane effect-site concentrations, C_O is the effect-site concentration of the opioid, C_{SEVO} is the sevoflurane effect-site concentration, $C50_O$ is the effect-site concentration of the opioid that decreases $C50_{SEVO}$ by 50%, $C50_{SEVO}$ is the sevoflurane effect-site concentration that results in $P = 0.5$ in the absence of opioid, and γ_O is the slope parameter reflecting the steepness of the concentration-effect relationship of the opioid.

The hierarchical model resulted in the best fit during sevoflurane–remifentanil interactions.[4] We first used the same structural model to fit the interaction in the control group (sevoflurane, fentanyl, without N 2 O) of the study by Katoh *et al*.[1]

The data of the study by Katoh *et al*. did not allow a full response surface modeling of the three drugs (sevoflurane, fentanyl, N_2O) because N_2O was applied at a single concentration level (66 vol.%) only. Therefore, the influence of N_2O was treated as a covariate in the hierarchical model of sevoflurane and opioids. For this purpose, we postulated that N_2O interacts with sevoflurane and/or fentanyl as expressed below.

1. Fentanyl:
    a. N_2O is equivalent to a concentration of A ng/ml of fentanyl (additive interaction)

b. N_2O reduces the *C*50 of fentanyl by a factor B (potentiation, nonadditive interaction)

2. Sevoflurane:

a. N_2O is equivalent to a concentration of X vol.% of sevoflurane (additive interaction)

b. N_2O reduces the *C*50 of sevoflurane by a factor Y (potentiation, nonadditive interaction)

To incorporate these assumptions into the hierarchical model, parameter *A*, *B*, *X*, and *Y* were added to equations 3 and 4, as shown in equations 5 and 6:

$$U_O = \frac{C_O + A}{C50_O \cdot B} \tag{5}$$

$$U_{SEV} = \frac{C_{SEVO} + X}{C50_{SEVO} \cdot Y} \tag{6}$$

Using equations 5 and 6 as a structural model, each of the postulated actions of N_2O and any of the combinations of *A*, *B*, *X*, and *Y* were fitted simultaneously to all data for model parameter estimation.

14 Parameter Estimation

The model parameters were estimated using NONMEM VI version 2.0 (Icon Development Solutions, Ellicott City, MD), using FOCE LAPLACE and LIKELIHOOD options. Platform was Windows XP (Microsoft, Redmond, WA) and compiler was G95. For all parameters, the interindividual variability was either assumed to be absent or to have a lognormal distribution. Model building was performed starting with the simplest form of each model and expanding the model with interaction terms and interindividual variability, until the decrease of the objective function value (OFV) was no longer statistically significant using the chi-square test. For each added parameter, a difference of 3.84 units in OFV was considered statistical significant at $P < 0.05$.

The NONMEM analysis was performed with various values for initial estimates and boundary values. The results were accepted as valid only if both minimization and covariance step were successful, unless stated otherwise.

To evaluate the uncertainty in the parameters of the final model, nonparametric 95% CIs of the model parameters were obtained from a bootstrap analysis, based on 500 sets of 177 patients each, randomly selected from the available 177 patients, using a custom program written in C. Results were analyzed in Microsoft Excel version 2010. In addition, log-likelihood profiles were calculated for each population parameter, and the nonparametric 95% CIs were obtained assuming a chi-square distribution with one degree of freedom and $P = 0.025$, resulting in a critical difference of 5.02 in the OFV.

Several performance measures were calculated from the prediction errors, *i.e.*, the difference between the predicted probability of tolerance minus the observed response (0

for responsive, 1 for tolerant): Mean Prediction Error, Mean Absolute Prediction Error, and Root Mean Squared Error. In addition, the Prediction Error Score was calculated as the percentage of mispredicted responses, *i.e.* , if tolerant, the probability of tolerance was less than 0.5, or if responsive, the probability of tolerance was more than 0.5.

15 Statistical Analysis

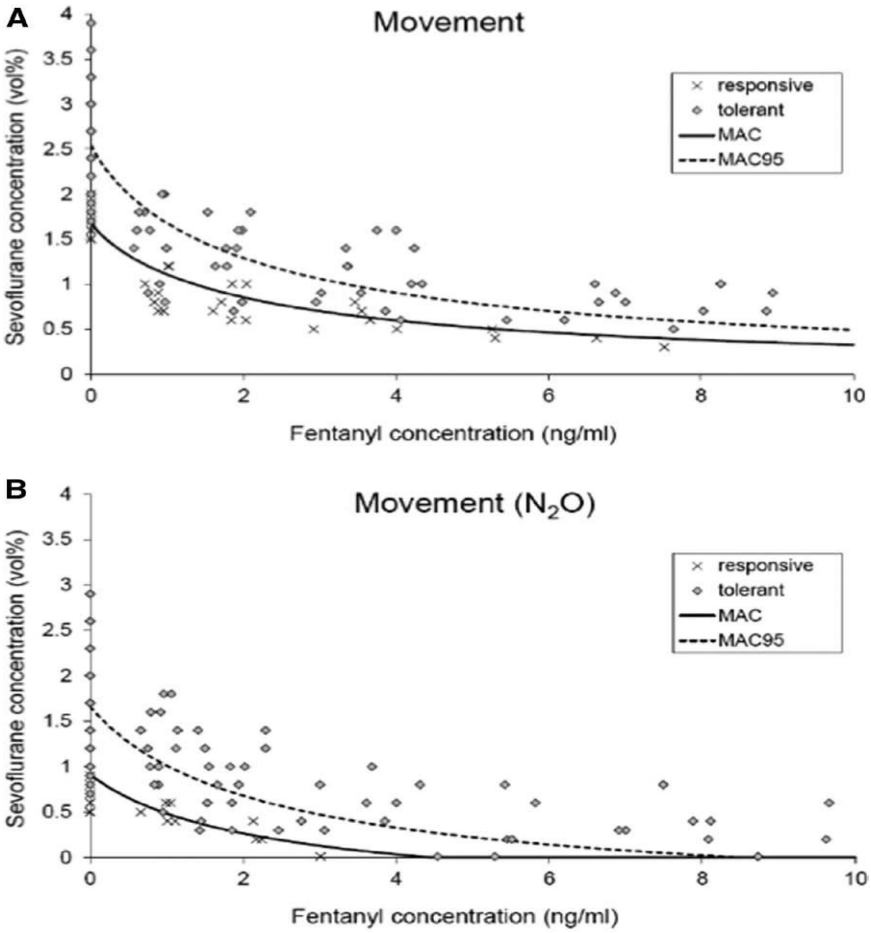
All model parameters are reported as typical values with standard errors (expressed in % of the typical value) within parentheses, and clinical data are given as mean and SD.

2 Results

Of the 96 patients not receiving nitrous oxide, two patients were excluded because of hypotension and the administration of ephedrine before the incision, and three patients were excluded because they were judged as being awake just before skin incision. Therefore, our analysis was performed on the remaining 177 patients of which 86 did receive nitrous oxide and 91 did not. Demographic data can be found in the original article.[1] The measured drug concentration of fentanyl before incision ranged between 0 and 10 ng/ml. The measured end-tidal partial pressure of sevoflurane at the time of observation ranged between 0 and 4 vol.%.

Table 1. The Objective Function Value (OFV), No. of Parameters, Parameter Estimations, and Measures of Performance for the Hierarchical Model Derived from the Control Group (without Nitrous Oxide) and for Three Competing Models (Sevoflurane-Additivity Model, Sevoflurane/Opioid-Additivity Model, and Sevoflurane-Additivity/Potentiation Model) Derived from the Total Dataset

	Units	Control Group (Without Nitrous Oxide)	Sevoflurane-Additivity Model (X)	Sevoflurane/Opioid-Additivity Model (XA)	Sevoflurane-Additivity/Potentiation Model (XY)
OFV	—	*	209.0	200.8	199.5
No. of parameters	—	6	7	8	8
Model parameters					
$C50_{O\text{-movement}}$	ng/ml	2.07 (22)	2.46 (16)	2.07 (19)	2.13 (16)
$C50_{O\text{-hemodynamic}}$	ng/ml	0.43 (41)	0.71 (19)	0.47 (33)	0.62 (20)
$C50_{SEVO\text{-movement}}$	vol.%	1.73 (8)	1.59 (6)	1.68 (7)	1.71 (6)
$C50_{SEVO\text{-hemodynamic}}$	vol.%	4.60 (18)	3.59 (8)	4.63 (17)	4.18 (11)
γ_O	—	0.931 (12)	0.941 (9)	0.907 (10)	0.982 (9)
γ	—	6.40 (17)	6.92 (12)	7.09 (12)	6.70 (13)
X	vol.%	—	0.64 (9)	0.54 (11)	0.35 (22)
Y	—	—	—	—	0.70 (11)
A	ng/ml	—	—	0.27 (43)	—
Model performance					
MPE (%)	—		0.0	0.0	0.0
MAPE (%)	—		19.1	18.2	18.1
RMSE (%)	—		31.2	30.4	30.3
Prediction error score (%)	—		14.7	12.1	12.4



Typical values (standard error, in % of the typical value).

* Obtained from data without nitrous oxide; therefore, OFV is not comparable to other models. γ = steepness of concentration–effect relationship of sevoflurane; γ_O = steepness of concentration–effect relationship of opioid; MAPE = mean absolute prediction error; MPE = mean prediction error; OFV = objective function value; RMSE = root mean squared error; *prediction error score* = *percentage of mispredicted responses; X, Y, A* = interaction parameters for nitrous oxide, identical for movement and hemodynamic responses,

Fig. 1. Observed somatic responses to incision in the control group (*A*) and in the nitrous oxide (N_2O) group (*B*). Minimal alveolar concentration (MAC) that evokes 50% tolerance to incision (MAC). MAC that evokes 95% tolerance to incision. (MAC95) MAC and MAC95 calculated with the sevoflurane/opioid-additivity model (XA).

To identify the model for the interaction of sevoflurane and fentanyl, the data from patients not receiving nitrous oxide (control group) were analyzed using the hierarchical model with separate, unconstrained values for $C50_O$ for movement and sympathetic responses.[4,6] Using the fixed $C50_O$ and the scaled $C50_O$ approach resulted in an increase of OFV by 29 and 37, respectively. Therefore, the model with separate values for $C50_O$ was considered the appropriate model for the interaction of sevoflurane and fentanyl for movement and sympathetic responses. Parameter estimations are listed in table 1.
For the simultaneous analysis of all data, the hierarchical model with different values of $C50_O$ and $C50_{SEVO}$ for movement and sympathetic responses was expanded by one of the factors *X*, *Y*, *A*, or *B*, resulting in a decrease of the OFV by 123, 54, 35, and 57, respectively, showing that factor *X* (called the sevoflurane-additivity model [*X*]) is the most influential factor in the model. Using different values of *X* for movement and for sympathetic responses in the sevoflurane-additivity model (*X*) did not result in a significant difference of OFV (–0.6).

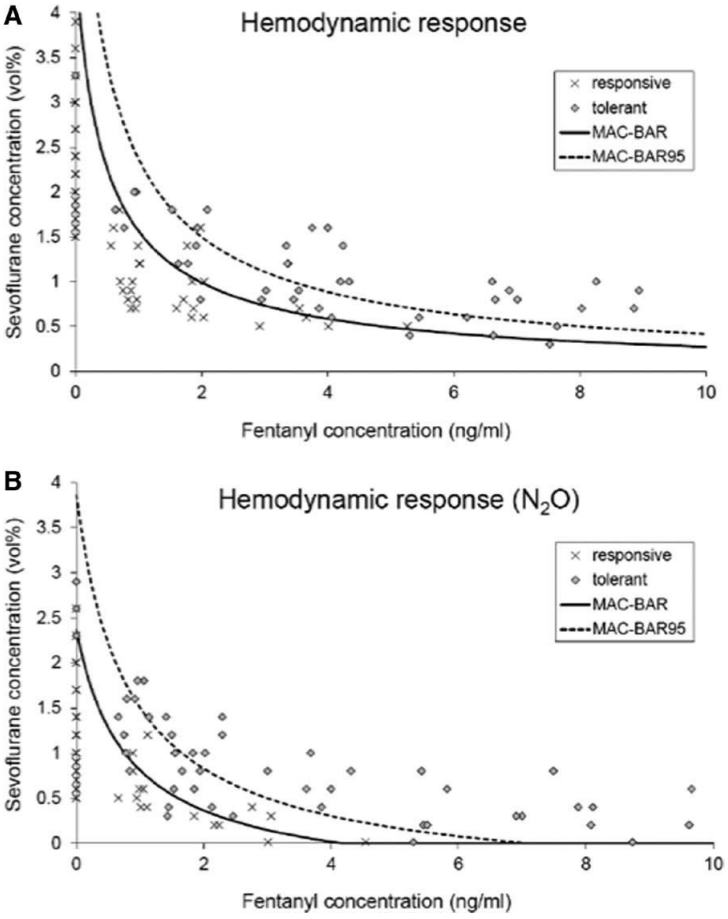


Fig. 2. Observed hemodynamic responses to incision in the control group (*A*) and in the nitrous oxide (N_2O) group (*B*). Minimal alveolar concentration to block autonomic reflexes to nociceptive stimuli in 50% of patients (MAC-BAR) and 95% of patients (MAC-BAR95) using the sevoflurane/opioid-additivity model (XA).

In a second step, we expanded the sevoflurane-additivity model (*X*) further by including factors *A* or *B* in the equation. Inclusion of factor *A* in combination with factor *X* (sevoflurane/opioid-additivity model [XA]) resulted in a significant decrease of the OFV by 8.2 units. Using separate values of *X* and *A* for movement and sympathetic responses did not result in a significant drop of the OFV. Combining factor *B* with factor *X* did not result in a significant decrease of OFV (–1.5).

In a third step, we combined factor *X* with factor *Y* (sevoflurane-additivity/potentiation model [XY]), which resulted in a decrease of the OFV of –9.5 units compared with the sevoflurane-additivity model (*X*). This model mathematically combines an additive (*X*) and nonadditive (*Y*) interaction of nitrous oxide with sevoflurane. This model does not support an independent interaction of nitrous oxide with fentanyl. The difference between the OFV of the sevoflurane/opioid-additivity (XA) and sevoflurane - additivity/potentiation (XY) models is not significant.

Finally, the combinations of three or four factors, including *X* (XYA, XYB, XAB, XYAB), did not result in lower OFV. In addition, the inclusion of intraindividual variability in any parameter did not result in a significant reduction of OFV for any model.

The final results of the parameter estimations for three adequately fitting models are listed in table 1. In all models, the values for *X*, *Y*, and *A* are identical for movement and sympathetic responses. Figures 1 and 2 show the observed somatic (fig. 1) and

hemodynamic (fig. 2) responses to incision in the control group (fig. 2A) and in the nitrous oxide group (fig. 2B), and MAC and MAC95 (fig. 1) and MAC-BAR and MAC-BAR95 (fig. 2) for the sevoflurane/opioid-additivity model (XA). Figure 3 shows the three-dimensional response surface as predicted by this model for movement (fig. 3, A and C) and hemodynamic responses (fig. 3, B and D) after incision in the control group (fig. 3, A and B) and in the nitrous oxide group (fig. 3, C and D). MAC, MAC-BAR, MAC95, and MAC-BAR95 estimations for sevoflurane in the absence and presence of nitrous oxide and fentanyl for the sevoflurane/opioid-additivity model (XA) are also listed in table 2. The values are within comparable range of the results of Katoh *et al*.[1] (table 3). The differences between the sevoflurane/opioid-additivity (XA) and sevoflurane-additivity/ potentiation (XY) models with respect to the measures of "goodness-of-prediction" were rather small (table 1).

The results of the final sevoflurane/opioid-additivity model (XA) were checked by performing a bootstrap analysis. The median parameters of the bootstrap analysis were in reasonable agreement with the NONMEM results. The 95% CI for the parameters *X* (0.54 vol.% sevoflurane) and *A* (0.27 ng/ ml fentanyl) were 0.41–0.67 vol.% and 0.07–0.62 ng/ml, respectively. The 95% CI obtained from the log-likelihood profiles was 0.42–0.68 vol.% for *X* and 0.05–0.58 ng/ml for *A*.

3 Discussion

In this reanalysis of previously published data, we present new information on the interaction between opioids, sevoflurane, and nitrous oxide compared with the original work.[1] We found that a simple extension of the hierarchical model (equations 2–6) integrates the additional effect of 66 vol.% N_2O to the interaction of fentanyl and sevoflurane using a response surface modeling approach.

Although the opioid used was fentanyl, we often do refer to it using the more general term "opioid." This is a deliberate choice because the model may be applicable for other opioids also, provided that equipotent doses of the other opioids are given.[7]

The major difference between our analysis (using the hierarchical model) and the original analysis by Katoh *et al*. (using logistic regression) is that our analysis was performed on all data simultaneously, *i.e.*, a single analysis with parameters common for the groups (movement and sympathetic response, without and with nitrous oxide) where appropriate, rather than on all four groups of data separately. In principle, both approaches are equally valid, and we confirmed that the MAC and MAC-BAR values for both approaches are comparable. However, the separate logistic analysis does not provide unique parameters describing the influence of nitrous oxide, in contrast to the simultaneous response surface approach providing these parameters (*A*, *B*, *X*, *Y*). The unique parameters allow to apply the results to other responses to noxious stimuli, *e.g.*, tolerance to laryngoscopy, taking into account the difference in intensity of the noxious stimuli. Once the interaction of sevoflurane and opioids has been adequately described by the hierarchical model, the interaction with nitrous oxide can be modeled by adding parameters *A*, *B*, *X*, and/or *Y* of the nitrous oxide interaction according to equations 5 and 6.

We used the hierarchical model in our analysis, because this model was found to describe the interaction between sevoflurane and remifentanil best.[4] For comparison, we also tested the Greco model, reduced Greco model, and the logistic model using the simultaneous approach. For each of the tested models, and for each model for the nitrous

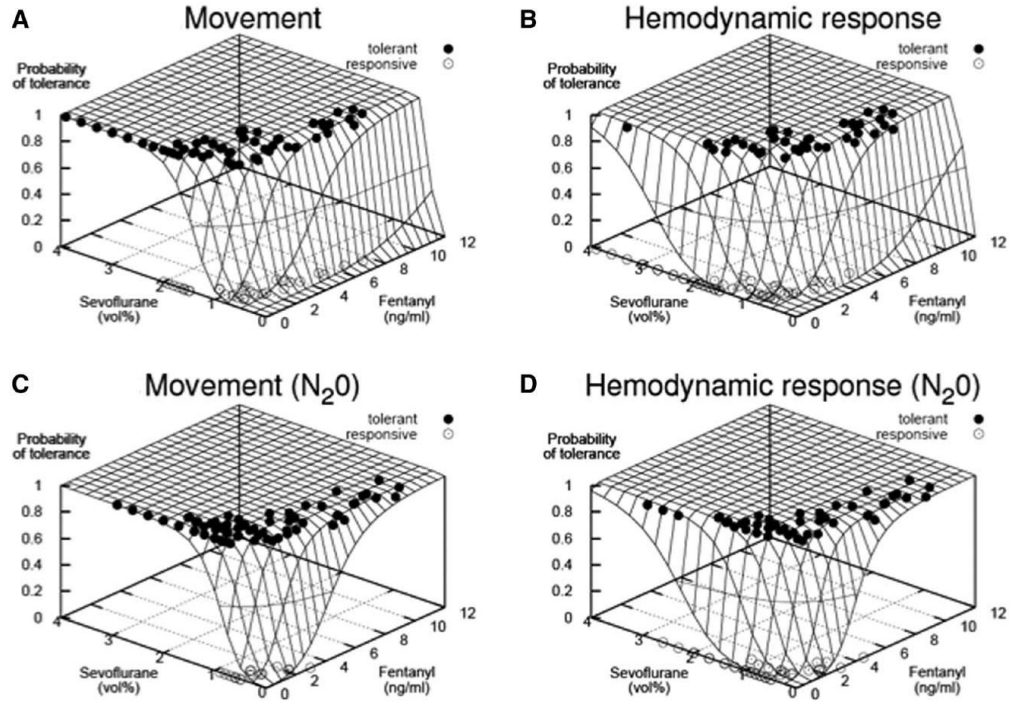


Fig. 3. Three-dimensional response surfaces as predicted by the sevoflurane/opioid-additivity model (XA). *A* and *B*, Response surface for, respectively, movement and hemodynamic responses after incision in the control group (fentanyl, sevoflurane, no nitrous oxide). *C* and *D*, Response surface for, respectively, movement and hemodynamic responses after incision in the nitrous oxide (N_2O) group (fentanyl, sevoflurane, 66 vol.% nitrous oxide).

oxide effect (*X*, XY, XA), the OFV values and model parameters were close to that of the hierarchical model. From a clinical point of view, the hierarchical model reflects the physiologic sequence of the opioid and hypnotic drug effect : Opioids reduce the afferent nociceptive transmission to medulla, thalamus, and cortex and thus the arousal response to the nociceptive stimulus and thus the hypnotic drug concentration to keep the patient asleep or unresponsive.

The process of minimizing the OFV is presented in separate stages because each stage represents a logical sequence where we tested a hypothesis on the interaction mechanisms that may explain the observed data.

In the first stage of modeling, the sevoflurane-additivity model (*X*) fitted the data best, supporting the hypothesis that an additive interaction of nitrous oxide with sevoflurane contributes strongly to the leftward shift of the isoboles. Model *Y* (potentiation of sevoflurane) was by far inferior to the sevoflurane-additivity model (*X*), which suggests that a reduction of $C50_{SEVO}$ by nitrous oxide is less likely than an additive effect. This finding is in concordance with the MAC additivity principle.

The second stage explored whether the fit on the data can be improved by modeling the analgesic potency of nitrous oxide. The flexibility of the structural model increases by assuming an additional interaction between nitrous oxide and fentanyl (in an additive (*A*) or nonadditive (*B*) way, respectively). We found that 66 vol.% N_2O corresponds simultaneously to 0.27 ng/ml of fentanyl (*A*) and 0.54 vol.% of sevoflurane (*X*).

Table 2. MAC, MAC-BAR, MAC95, and MAC-BAR95 Values for Sevoflurane (vol.%) Calculated for the Sevoflurane/Opioid-Additivity Model (XA) in the Absence and Presence of 66 vol.% Nitrous Oxide (N2O) and Fentanyl (1, 3, or 6 ng/ml)

	No Fentanyl	1 ng/ml Fentanyl	3 ng/ml Fentanyl	6 ng/ml Fentanyl
MAC	1.68	1.11	0.70	0.46
$+N_2O$	0.91	0.48	0.13	0*
Reduction by 66 vol.% N_2O	46%	56%	82%	100%
MAC-BAR	4.63	1.56	0.73	0.42
$+N_2O$	2.37	0.81	0.15	0 *
Reduction by 66 vol.% N_2O	49%	48%	80%	100%
MAC95	2.54	1.68	1.06	0.70
$+N_2O$	1.66	1.01	0.47	0.14
Reduction by 66 vol.% N_2O	35%	40%	55%	80%
MAC-BAR95	7.02	2.36	1.11	0.64
$+N_2O$	3.87	1.50	0.50	0.08
Reduction by 66 vol.% N_2O	45%	36%	55%	88%

* No response in more than 50% of patients in the absence of sevoflurane.

MAC = concentration of sevoflurane (vol.%) required to avoid moving in 50% of patients; MAC-BAR = concentration of sevoflurane (vol.%) required to avoid hemodynamic response in 50% of patients; MAC95 = concentration of sevoflurane (vol.%) required to avoid moving in 95% of patients; MAC-BAR95 = concentration of sevoflurane (vol.%) required to avoid hemodynamic response in 95% of patients

Table 3. MAC, MAC-BAR, MAC95, and MAC-BAR95 Values for Sevoflurane (vol.%) as Reported by Katoh *et al.*[1] in the Absence and Presence of 66 vol.% Nitrous Oxide (N_2O) and Fentanyl (1, 3, or 6 ng/ml)

	No Fentanyl	1 ng/ml Fentanyl	3 ng/ml Fentanyl	6 ng/ml Fentanyl
MAC	1.85	1.16	0.72	0.48
$+N_2O$	0.79	*	*	*
MAC-BAR	4.15	1.78	0.71	0.33
$+N_2O$	2.52	*	*	*
MAC95	2.28	*	*	*
$+N_2O$	1.10	*	*	*
MAC-BAR95	6.26	*	*	*
$+N_2O$	2.98	*	*	*

* Data not reported in the original publication.

MAC = concentration of sevoflurane (vol.%) required to avoid moving in 50% of patients; MAC-BAR = concentration of sevoflurane (vol.%) required to avoid hemodynamic response in 50% of patients; MAC95 = concentration of sevoflurane (vol.%) required to avoid moving in 95% of patients; MAC-BAR95 = concentration of sevoflurane (vol.%) required to avoid hemodynamic response in 95% of patients.

The parameter estimates of sevoflurane MAC and MAC-BAR presented in table 2 are consistent with the results of the original article for the sevoflurane/opioid-additivity model (table 3). The reduction of sevoflurane MAC by 66 vol.% N_2O in the absence of fentanyl is 54

and 57% in the current and original study, respectively. The *C*50 of fentanyl is 2.07 ng/ml in the current study and 1.8 ng/ml in the original study. The small differences are presumably related to the differences in method of analysis. Stevens *et al*.[8] reported a reduction of the isoflurane MAC in the presence of 70% N_2O by 68%. Fragen and Dunn[9] reported a reduction of the sevoflurane MAC in the presence of 65% N_2O by 50%, whereas Rampil *et al*.[10] reported a 50% reduction for desflurane in the presence of 60% N_2O.

In the final stage of modeling, we tested several—more complex—combinations of interactions. Only the combination of parameters *X* and *Y* resulted in a comparably low OFV (but without significant difference with the sevoflurane/opioid additivity model [XA]). The sevoflurane-additivity/potentiation model (XY) is less consistent with current pharmacologic concepts because it describes the interaction between nitrous oxide and sevoflurane as a combined additive and nonadditive interaction with sevoflurane. In addition, no independent analgesic effect of nitrous oxide is included in this model. In addition, the *C*50 values of the sevoflurane/opioid-additivity model (XA) are closer to the *C*50 values in conditions without nitrous oxide (control group) compared with that of the sevoflurane additivity/potentiation (XY) model (table 1). For these reasons, we consider the sevoflurane/opioid-additivity model (XA) to be a better suited structural model to estimate responsiveness during opioid, sevoflurane, and nitrous oxide interaction.

A potential limitation of this study is based on the fact that data were derived from only one particular population (Asian). Even though MAC has limited variability within a population, interpopulation (ethnic) differences exist.[11] Therefore, the validity of the proposed response surface model must be tested prospectively in a population with wider ethnic variation.

Our response surface model only applies to the clinical endpoint of a somatic or hemodynamic response to a noxious stimulus, MAC and MAC-BAR, respectively. For the response to stimuli that test the hypnotic state of the patient, such as "shake and shout," "MAC_{awake}," "name calling," "the observer's assessment of alertness and sedation score," and the "isolated forearm technique," we were not able to model a response surface because these endpoints were not included in our dataset. Moreover, the available literature suggests that the nature of the interaction for hypnotic endpoints of anesthesia might be different compared with somatic responsiveness to noxious stimuli. Data from Katoh *et al.* suggest the interaction between sevoflurane and nitrous oxide for MAC_{awake} to be infra-additive and so is the effect on learning.[12–14] This has also been confirmed with thiopental and ethanol.[15,16] This differential characteristic of the interaction for responses on noxious and non-noxious stimuli is probably evoked through differential balance of the *N*-methyl-D-aspartate and *γ*-aminobutyric acid receptor type A receptor inhibition in the neural networks, especially in the unstimulated patient.[12] In addition, several electroencephalographic-derived measures of cerebral hypnotic drug effect do not detect the addition of nitrous oxide both during intravenous and inhalational anesthesia in unstimulated patients.[17] In conclusion, our final model currently is only applicable for responses to a noxious stimulus and does not allow extrapolation to hypnotic endpoints of anesthesia.

Another important limitation of the dataset used in this analysis is that only one concentration of nitrous oxide has been tested and that data for other concentrations of nitrous oxide are currently lacking. However, if we assume that lower concentrations of nitrous oxide (< 66vol.%) reduce the two interaction parameters *X* and *A* in a proportional

way, the proposed the sevoflurane/opioid-additivity model (XA) can be generalized for different concentrations of nitrous oxide (C_{N2O}) according to equations 7 and 8:

$$\boldsymbol{X = 0.54 * C_{N_2O}/66} \quad (7)$$

$$\boldsymbol{A = 0.27 * C_{N_2O}/66} \quad (8)$$

Because equations 7 and 8 cannot be verified from our data, but are based on one assumption of linearity in the interaction between 0 and 66 vol.% N_2O, the clinical performance of this proposed solution needs to be prospectively validated.

The final response surface equation presented in this study can easily be applied in advisory systems that provide bedside pharmacokinetic – dynamic information based on the demographics of the patient and the administered drug doses. Such devices are currently being commercialized for clinical practice; however, prospective validation is still mandatory to evaluate the population-based reference as a tool for the clinician to target desired levels of responsiveness in an individual case.[11]

4 Conclusion

The influence of 66 vol.% N_2O was best described by a combination of an additive effect corresponding to 0.27ng/ ml fentanyl (*A*) and an additive effect corresponding to 0.54 vol.% sevoflurane (*X*). With a simple extension, the effect of 66 vol.% N_2O can be incorporated in the hierarchical interaction model of sevoflurane and opioids and allows to model the triple interaction in a response surface.

5 References

1. Katoh T, Kobayashi S, Suzuki A, Iwamoto T, Bito H, Ikeda K: The effect of fentanyl on sevoflurane requirements for somatic and sympathetic responses to surgical incision. *Anesthesiology* 1999; 90:398–405
2. Greco WR, Bravo G, Parsons JC: The search for synergy: A critical review from a response surface perspective. Pharmacol Rev 1995; 47:331–85
3. Struys MM, Sahinovic M, Lichtenbelt BJ, Vereecke HE, Absalom AR: Optimizing intravenous drug administration by applying pharmacokinetic/pharmacodynamic concepts. Br J Anaesth 2011; 107:38–47
4. Heyse B, Proost JH, Schumacher PM, Bouillon TW, Vereecke HE, Eleveld DJ, Luginbühl M, Struys MM: Sevoflurane remifentanil interaction: Comparison of different response surface models. *Anesthesiology* 2012; 116:311–23
5. Shafer SL, Varvel JR, Aziz N, Scott JC: Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. *Anesthesiology* 1990; 73:1091–102
6. Bouillon T: Hypnotic and opioid anesthetic drug interactions on the CNS, focus on response surface modeling, modern anesthetics. Handbook of Experimental Pharmacology. Edited by Schuttler J, Schwilden H. Berlin, Springer-Verlag, 2008, pp 471–85
7. Vuyk J, Mertens MJ, Olofsen E, Burm AG, Bovill JG: Propofol anesthesia and rational opioid selection: Determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. *Anesthesiology* 1997; 87:1549–62
8. Stevens WD, Dolan WM, Gibbons RT, White A, Eger EI, Miller RD, DeJong RH, Elashoff RM: Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; 42:197–200
9. Fragen RJ, Dunn KL: The minimum alveolar concentration (MAC) of sevoflurane with and without nitrous oxide in elderly *versus* young adults. J Clin Anesth 1996; 8:352–6
10. Rampil IJ, Lockhart SH, Zwass MS, Peterson N, Yasuda N, Eger EI 2nd, Weiskopf RB, Damask MC: Clinical characteristics of desflurane in surgical patients: Minimum alveolar concentration. *Anesthesiology* 1991; 74:429–33
11. Ezri T, Sessler D, Weisenberg M, Muzikant G, Protianov M, Mascha E, Evron S: Association of ethnicity with the minimum alveolar concentration of sevoflurane. *Anesthesiology* 2007; 107:9–14
12. Katoh T, Ikeda K, Bito H: Does nitrous oxide antagonize sevoflurane-induced hypnosis? Br J Anaesth 1997; 79:465–8
13. Dwyer R, Bennett HL, Eger EI 2nd, Heilbron D: Effects of isoflurane and nitrous oxide in subanesthetic concentrations on memory and responsiveness in volunteers. *Anesthesiology* 1992; 77:888–98
14. Chortkoff BS, Bennett HL, Eger EI 2nd: Does nitrous oxide antagonize isoflurane-induced suppression of learning? *Anesthesiology* 1993; 79:724–32
15. Katoh T, Ikeda K: Nitrous oxide produces a non-linear reduction in thiopentone requirements. Br J Anaesth 1996; 77:265–7
16. Eger EI 2nd, Tang M, Liao M, Laster MJ, Solt K, Flood P, Jenkins A, Raines D, Hendrickx JF, Shafer SL, Yasumasa T, Sonner JM: Inhaled anesthetics do not combine to produce synergistic effects regarding minimum alveolar anesthetic concentration in rats. Anesth Analg 2008; 107:479–85

17. Ozcan MS, Ozcan MD, Khan QS, Thompson DM, Chetty PK: Does nitrous oxide affect bispectral index and state entropy when added to a propofol *versus* sevoflurane anesthetic? J Neurosurg Anesthesiol 2010; 22:309–15

Chapter 6 Noxious Stimulation Response Index

A Novel Anesthetic State Index Based on Hypnotic–Opioid Interaction

Martin Luginbühl, PD Dr. med., Peter M. Schumacher, M.Sc., Ph.D., Pascal Vuilleumier, M.D., Hugo Vereecke, M.D., Ph.D., Björn Heyse, M.D., Thomas W. Bouillon, PD Dr. med., Michel M.R.F. Struys, M.D., Ph.D.

Anesthesiology 2010; 112:872–80

ABSTRACT

Background: The noxious stimulation response index (NSRI) is a novel anesthetic depth index ranging between 100 and 0, computed from hypnotic and opioid effect-site concentrations using a hierarchical interaction model. The authors validated the NSRI on previously published data.

Methods: The data encompassed 44 women, American Society of Anesthesiology class I, randomly allocated to three groups receiving remifentanil infusions targeting 0, 2, and 4 ng/ml Propofol was given at stepwise increasing effect-site target concentrations. At each concentration, the observer assessment of alertness and sedation score, the response to eyelash and tetanic stimulation of the forearm, the bispectral index (BIS), and the acoustic evoked potential index (AAI) were recorded. The authors computed the NSRI for each stimulation and calculated the prediction probabilities (P_Ks) using a bootstrap technique. The P_Ks of the different predictors were compared with multiple pairwise comparisons with Bonferroni correction.

Results: The median (95% CI) P_K of the NSRI, BIS, and AAI for loss of response to tetanic stimulation was 0.87 (0.75–0.96), 0.73 (0.58–0.85), and 0.70 (0.54–0.84), respectively. The P_K of effect-site propofol concentration, BIS, and AAI for observer assessment of alertness and sedation score and loss of eyelash reflex were between 0.86 (0.80–0.92) and 0.92 (0.83–0.99), whereas the P_Ks of NSRI were 0.77 (0.68–0.85) and 0.82 (0.68–0.92). The P_K of the NSRI for BIS and AAI was 0.66 (0.58–0.73) and 0.63 (0.55–0.70), respectively.

Conclusion: The NSRI conveys information that better predicts the analgesic component of anesthesia than AAI, BIS, or predicted propofol or remifentanil concentrations. Prospective validation studies in the clinical setting are needed.

Presented at the Best Abstracts of the Meeting Session of the American Society of Anesthesiologists Annual Meeting, October 19, 2009.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journals Web site (www.anesthesiology.org).

The cerebral effect of hypnotic drugs is frequently measured using processed electroencephalography with and without stimulation. During general anesthesia, opioids are administered according to response to clinical stimuli mostly in terms of arterial pressure or heart rate increase. Several indices measuring the balance between nociception and antinociception during general anesthesia are under investigation, but no "analgesic state index" is available predicting responsiveness to noxious stimulation during combined administration of an analgesic and a hypnotic.

In an attempt to develop an analgesic state monitor during anesthesia, we have investigated pulse wave and heart rate variation in response to a standardized electrical stimulus on the ulnar nerve as surrogate variable.[1–3] These variables were not related to predicted remifentanil effect-site concentrations. Conversely, the predicted remifentanil effect-site concentration combined with the bispectral index (BIS) was a significant predictor of a relevant hemodynamic response to tracheal intubation.[2] The prediction was not improved by adding the pulse wave response to electrical ulnar nerve stimulation.[2] Given the close correlation of the effect-site propofol concentration and the BIS,[4] we believe that the predicted effect-site propofol concentrations together with the predicted effect-site opioid concentrations and an appropriate interaction model provide sufficient information to predict the responsiveness of an anesthetized patient to noxious stimulation.

Bouillon *et al.*[5] have described a response surface model for propofol and remifentanil in 2004. The model is the basis for a two-dimensional concentration domain interaction display in which predicted hypnotic and opioid concentrations are related to interaction isoboles such as the 50 and 90% tolerance of laryngoscopy isobole. To present the same information in a time-domain display, Schumacher *et al*.[6] have defined the noxious stimulation response index (NSRI, see Methods section) based on the modified hierarchical interaction model by Bouillon.[7] Generally speaking, the NSRI is a univariate index calculated from the weighted propofol and remifentanil concentrations corrected for interaction and normalized to a range between 0 and 100, where 100 reflects 100% probability and values approaching 0 reflect close to 0% probability of responding to laryngoscopy.

The aim of this study was to compare the NSRI with predicted remifentanil and propofol effect-site concentrations, BIS, and A-Line autoregressive index (acoustic evoked potential index [AAI], A-Line AEP monitor, Danmeter A/S, Odense, Denmark) in terms of prediction probability (P_K) of the hypnotic state and the responsiveness to a noxious stimulus in anesthetized patients, using a previously published data set.[4]

1 Materials and Methods

11 Patients and Protocol of the Previous Study

In the previous study by Struys *et al*.,[4] 45 American Society of Anesthesiologists physical status 1 patients scheduled for ambulatory gynecologic surgery were enrolled and randomized to three treatment groups. Approval and written informed consent was granted for the original study by Institutional Ethics Committee of the Ghent University Hospital, Ghent, Belgium. The mean (SD) age in the three groups was 33 (5)–34 (4), and the mean weight and height were 63 (10)–66 (11) kg and 167 (6)–168 (6) cm, respectively. Propofol was infused in all groups according to a staircase protocol starting with effect-site target

concentrations of 1.5 g/ml in group 1 (no remifentanil) and 1.0 g/ml in groups 2 and 3, in which remifentanil was added at effect-site target concentrations of 2.0 or 4.0 ng/ml, respectively. The infusion pumps were controlled by Rugloop II software (Demed, Temse, Belgium) using the pharmacokinetic parameter sets and effect-site equilibration constant (ke0) reported by Schnider *et al*.[8,9] for propofol and Minto *et al*.[10,11] for remifentanil.

Propofol concentration was increased in steps of 0.5 g/ml every 4 min. After an effect-site equilibration time of 4 min, that is, immediately before the next increase of the propofol target concentration, the eyelash reflex, the observer assessment of alertness and sedation score (OAAS), the BIS (Version 3.4, calculated by the A-2000 BIS® monitor, Aspect Medical Systems, Newton, MA), the AAI, and the propofol effect-site concentration were recorded. Thereafter, the presence or absence of a motor response to a 2-s tetanic stimulus (100 Hz, 50 mA) applied on the volar forearm was recorded. In the raw data set, the predicted propofol and remifentanil effect-site concentrations and the related eyelash reflex (present or absent), OAAS score, BIS, AAI, and response to tetanic stimulation were available.

12 The Hierarchical Propofol–Remifentanil Interaction Model

The NSRI is based on the hierarchical interaction model by Bouillon *et al.*[5] in 2004. The originally reported model was modified to increase parsimony while retaining its essential features (appendix).[7] On the basis of this modified model, the combination of predicted propofol and remifentanil concentrations can be expressed as probability to tolerate a certain reference stimulus, for example, tolerance of "shaking and shouting", as indicator of deep hypnosis. The original and the modified model are illustrated in figure 1.

1. Reduction of the incoming stimulus intensity:

$$\boldsymbol{postopioid\_intensity = preopioid\_intensity}\left(\mathbf{1} - \frac{\boldsymbol{Ce_{opioid}}}{\boldsymbol{Ce50_{opioid} + Ce_{opioid}}}\right) \quad \textit{(1)}$$

where postopioid_intensity = stimulus intensity after attenuation by the opioid, preopioid_intensity = intensity of the incoming stimulus, Ce_{opioid} = effect-site opioid concentration, and $Ce50_{opioid}$ = effect-site opioid concentration associated with a 50% reduction of preopioid_intensity. Therefore, the $Ce50_{opioid}$ does not represent the opioid concentrations associated with half maximal effect on the probability of tolerating the stimulus but it is the ability to increase the effectiveness of the hypnotic by altering the respective Ce50 of the hypnotic ($Ce50_{hyp}$, see Eq. 2). For a single stimulus, preopioid_intensity must be set to 1 to identify the C50 of the hypnotic (see Eq. 2). In this case, the postopioid_intensity is always a dimensionless number between 0 and 1, depending on the opioid concentration.

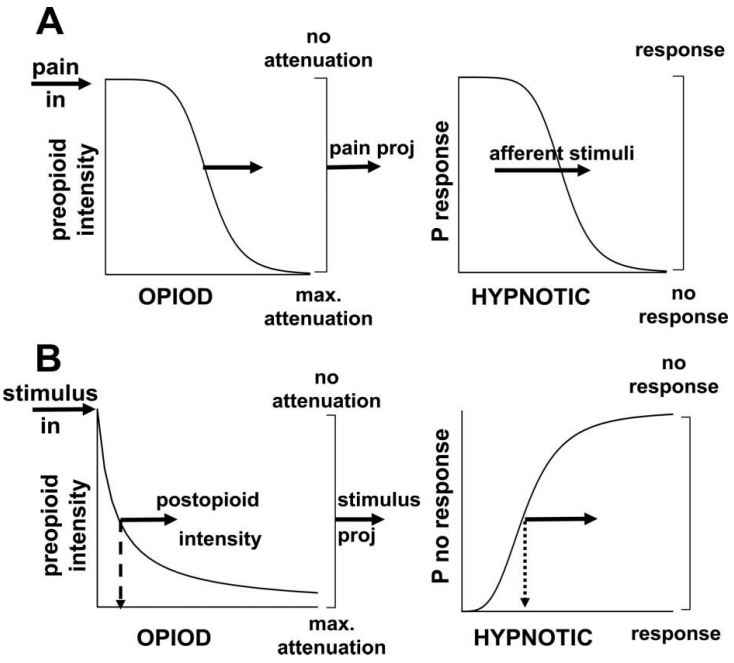


Fig. 1. Comparison of the original and the modified hierarchal opioid–hypnotic interaction model. The endpoint of the opioid–hypnotic interaction is the probability of response ($P_{response}$, original model, *A*) or nonresponse to a stimulus ($P_{nonresponse}$, modified model, *B*). The incoming stimulus is attenuated by the presence of an opioid. $P_{response}$ or $P_{nonresponse}$ is dependent on the strength of the attenuated stimulus, the hypnotic drug concentration, and the hypnotic drug concentration associated with a 50% probability of response/nonresponse ($C50_{hypnotic}$). In the original model (*A*), the incoming stimulus ("pain in") of a strength-labeled preopioid_intensity on the y-axis is attenuated by the opioid (on the x-axis) according to a negative E_{max} model resulting in an afferent stimulus with a strength that is a fraction of preopioid_intensity. The preopioid stimulus intensity and the slope parameter of this E_{max} model are estimated from the data. The projected pain ("pain proj") refers to the intensity of the attenuated stimulus transmitted to the central nervous system (also labeled as "afferent stimuli" in the original model). $P_{response}$ is estimated from a negative E_{max} model. In the modified model (*B*), the terms "pain in" and "pain proj" are replaced by "stimulus in" and "stimulus proj", respectively because unconscious anesthetized patients do not feel pain. Attenuation of preopioid_intensity follows a fractional E_{max} model with a fixed slope constant of 1. The $C50_{opioid}$ (dashed arrow) is the opioid concentration reducing the strength of preopioid_intensity by 50%. $P_{nonresponse}$ is estimated with a positive E_{max} model, including the parameters postopioid_intensity, current hypnotic drug concentration (x-axis), and the $C50_{hypnotic}$ (dotted arrow). Supplemental Digital Content 1 illustrates the behavior of the modified model, http://links.lww.com/ALN/A578 (for further information refer to the appendix).

2. Calculation of probability of tolerance to an incoming stimulus: the postopioid_intensity modifies the $Ce50_{hyp}$ representing the hypnotic concentration that corresponds to a 50% probability of tolerance of a stimulus with preopioid_intensity in the absence of opioid.

$$P_{no-response} = \frac{\left(\frac{Ce_{hyp}}{Ce_{hyp} \cdot postopioid\_intensity}\right)^{\phi}}{1 + \left(\frac{Ce_{hyp}}{Ce_{hyp} \cdot postopioid\_intensity}\right)^{\phi}} \quad (2)$$

where $P_{no\text{-}response}$ = probability of nonresponse to a stimulus, Ce_{hyp} = effect-site concentration of hypnotic, and ϕ = slope parameter.

In summary, the model expresses the probability of nonresponse to a stimulus as a function of the stimulus strength (as incorporated in postopioid_intensity) and the opioid and hypnotic drug concentrations. The modified model is depicted in figure 1B (for further details see the appendix). The mechanistic behavior of the model is further illustrated in Supplemental Digital Content 1, which contains an interactive excel worksheet for model simulation, http://links.lww.com/ALN/A578.

3. Extension to stimuli of differing intensity: Under the assumption that the opioid potency ($C50_{opioid}$) is identical for fractional suppression of stimuli of differing strength, only one parameter has to be added per additional stimulus, either "preopioid_intensity of $stimulus_n$" (n suffix for the nth stimulus) or, alternatively, the model can be parameterized with "$C50_{hyp\ n}$" (n suffix for the $C50_{hyp}$ related to the nth stimulus). If the second parameterization is chosen, the ratio of the respective C50s yields the relative strength of the stimuli. The second parameterization was chosen with "shake and shout" as reference stimulus with a preopioid_intensity of 1. The relative intensity of laryngoscopy then corresponds to the ratio of the propofol $Ce50_{TOSS}$ and the $Ce50_{TOL}$ (Eq. 3).

$$\boldsymbol{R_{lar} = \frac{Ce50_{hypTOL}}{Ce50_{hypTOSS}}} \qquad \textit{(3)}$$

Where R_{lar} = intensity ratio of laryngoscopy to the calibration stimulus shaking and shouting, $Ce50_{hypTOL}$ and $Ce50_{hypTOSS}$ = effect-site hypnotic concentrations associated with 50% probability of tolerating laryngoscopy and shake and shout, respectively. The parameter estimates (SE) for $Ce50_{hypTOL}$ and $Ce50_{hypTOSS}$ according to the modified model were 8.46 (1.98) and 2.99 (0.75) g/ml^{-1}, respectively.[5] Intensity ratios compared with shake and shout can be computed for any other stimulus, provided the respective Ce50hyp is known.

121 Transformation of Probabilities of Tolerance into NSRI Units.

1. The combined potency of an opioid and a hypnotic for suppression of a stimulus of defined strength (N) can be expressed as :

$$\boldsymbol{N = \frac{Ce_{hyp}}{Ce50_{hyp} \times postopioid\_intensity}} \qquad \textit{(4)}$$

Therefore, equation 2 can be generalized according to equation 5.

$$\boldsymbol{P_{no-response} = \frac{N^{\phi}}{1 + N^{\phi}}}$$

(5)

2. The probability of no-response to laryngoscopy (P_{TOL}) can be computed according to equations 3 and 5.

$$\boldsymbol{P_{TOL} = \frac{\left(N/R_{lar}\right)^{\phi}}{1 + \left(N/R_{lar}\right)^{\phi}}}$$

(6)

3. Normalization to a scale from 0 to 100 and calibration: for ergonomic reasons (conformity with standard electroencephalographic monitoring), the increasing probability of tolerating laryngoscopy (scale from 0 to 1) with increasing drug concentrations was transformed into a decreasing value from 100 (probability of no-response to laryngoscopy 0) to 0 (probability of no-response to laryngoscopy asymptotically approaching 1) by transformation and by modifying the slope parameter of equation 6. The NSRI value can therefore decrease near 0 but never be exactly 0. By using the same structural model as for the probability of no-response to laryngoscopy, the NSRI is defined as follows.

$$\boldsymbol{NSRI = 100 \times \left(1 - \frac{\left(N/R_{lar}\right)^{sl}}{1 + \left(N/R_{lar}\right)^{sl}}\right)}$$

(7)

where slope factor sl is an empirically calibrated scalar and not an estimated model parameter or a mathematical transformation of the slope parameter. Regardless of the value of sl, a P_{TOL} of 0.5 corresponds to a NSRI of 50. The slope factor sl was calibrated to transform a P_{TOL} of 0.9 to an NSRI of 20, yielding sl = 2.18. The NSRI has the same underlying structural model but is not a direct mathematical transformation of P_{TOL}. The relationship between the NSRI and the probability of tolerance of laryngoscopy is depicted in figure 2.

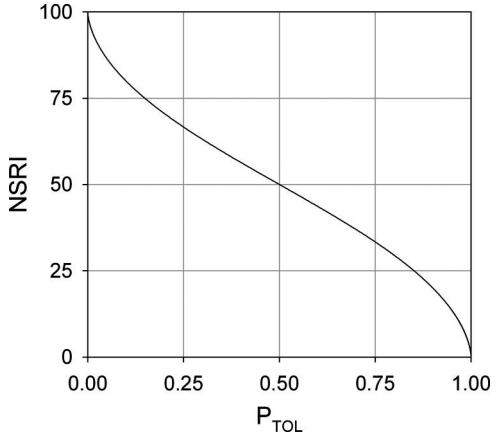


Fig. 2. The relation of the probability to tolerate laryngoscopy and noxious stimulation response index (NSRI). The NSRI is calculated using the same structural model as the probability to tolerate laryngoscopy (P_{TOL}) but with a modified slope constant. The figure related the P_{TOL} to corresponding NSRI values. An NSRI of 50 and 20 corresponds to 50% and 90% probability of tolerating laryngoscopy, respectively. The shape of the curve is dependent on the slope constant.

13 Data Evaluation and Statistics

The predicted propofol and remifentanil effect-site concentrations from the previous study[4] were used to compute the related NSRI according to equations 1, 4, and 7.

For comparison, P_{TOL} was calculated according to equations 1 and 2. Primary independent variables (predictors) were the NSRI and the predicted propofol and remifentanil effect-site concentrations. Primary dependent variables were the modified OAAS (full scale, table 1), the presence or absence of the eyelash reflex, and the presence or absence of a motor response to electrical tetanic stimulation of the forearm (dichotomous), BIS, and AAI values (continuous data). The BIS and the AAI were also used as predictors of OAAS and response to eyelash and tetanic stimulation. A similar analysis was performed for P_{TOL}.

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly an/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Table 1. Modified Observer Assessment of Alertness and Sedation Score as Applied by Struys *et al.*[4]

For all predictors, the P_Ks for all variables to be predicted were calculated. The prediction probability macro (PKMACRO; Excel spreadsheet) developed by Smith *et al.*,[12] which was used for data evaluation in the previous article,[4] is designed for analysis of independent data. Because the data were not independent, we applied a bootstrap technique with 1,000 random samples of the 263 data points for each dependent variable for P_K calculation using Matlab (The Mathworks Inc., Natick, MA). Each sample included one random data point per patient, that is, 44 data points. The P_K value was then calculated for each sample using the PKMACRO functionality within Matlab. With this modification, the

assumption of independence of the data was not violated. Because the P_K values were not normally distributed, they are presented in box plots. To avoid assumptions on the distribution of the bootstrap samples, the 2.5–97.5 percentile range of the 1,000 P_K was calculated to approximate the 95% CI of the resampled P_Ks. The differences between a median P_Ks of a given predictor (*e.g.*, NSRI) and another predictor (*e.g.*, BIS) in predicting the same variable (*e.g.*, OAAS) were considered statistically significant if the median P_K of the first was outside the 95% CI of the second predictor, corresponding to an [*alpha*] of 0.05. Because statistical testing with calculation of *P* values might be affected by the bootstrap distribution and the number of resamplings, we restrict our P_K comparison to this rather crude and conservative method and do not present the calculated *P* values.

To get a rough estimate of the intensity of the 2-s tetanic stimulation, the NSRI associated with a 50% probability of loss or response to tetanic stimulation was calculated using a simple logistic regression analysis in NONMEM (Version V, Globomax LLC, Hanover, MD). The naïve pooled data method was applied for parameter estimation. Patient identifier, NSRI, dependent variable (0 or 1),and missing dependent variable (0 or 1) were the input data. No further model building steps were performed, and no covariates were evaluated.

2 Results

The data of one patient were incomplete; hence, 263 data sets of 44 patients were available for our reanalysis.

The dependent variables loss of eyelash reflex, BIS, and AAI reflect the hypnotic state, whereas loss of response to tetanic stimulation reflects the analgesic state. The OAAS is mostly used as a clinical measure of the hypnotic state and dominated by hypnotic surrogate endpoints; however, the discrimination between levels 1 and 0 is based on the response to a painful stimulus (trapezius squeeze). The results of the P_K analysis are presented in figure 3.

The P_K values (95% CI) for prediction of OAAS by the effect-site propofol concentration, the BIS, the AAI, and the NSRI were 0.88 (0.81–0.93), 0.88 (0.82–0.93), 0.86 (0.80–0.92), and 0.77 (0.68–0.85), respectively.

The P_K values of NSRI, effect-site propofol concentration, BIS, and AAI for prediction of loss of response to tetanic stimulation were 0.87 (0.75–0.96), 0.68 (0.54–0.81), 0.73 (0.58–0.85), and 0.70(0.54–0.84), respectively, whereas the corresponding P_K of the remifentanil effect-site concentration was 0.66 (0.50–0.80). The reason for the median propofol P_K being slightly higher than the remifentanil P_K might be explained by the study design including only two remifentanil concentrations.

The P_Ks of the remifentanil effect-site concentration to predict OAAS, loss of eyelash reflex, BIS, and AAI were (0.32–0.54), 0.41 (0.26–0.59), 0.36 (0.29–0.45), and 0.38 (0.30–0.46), respectively, which indicates a slight reverse prediction, most likely caused by study design (in groups with remifentanil, the propofol concentrations were lower).[4]

The P_K for P_{TOL} was similar to NSRI (fig. 3B) because the NSRI is the transformed and rescaled P_{TOL}. The NSRI (SE of the estimate) associated with a 50% probability of loss of response to tetanic stimulation was 61 (SE, 3.8) (fig. 4).

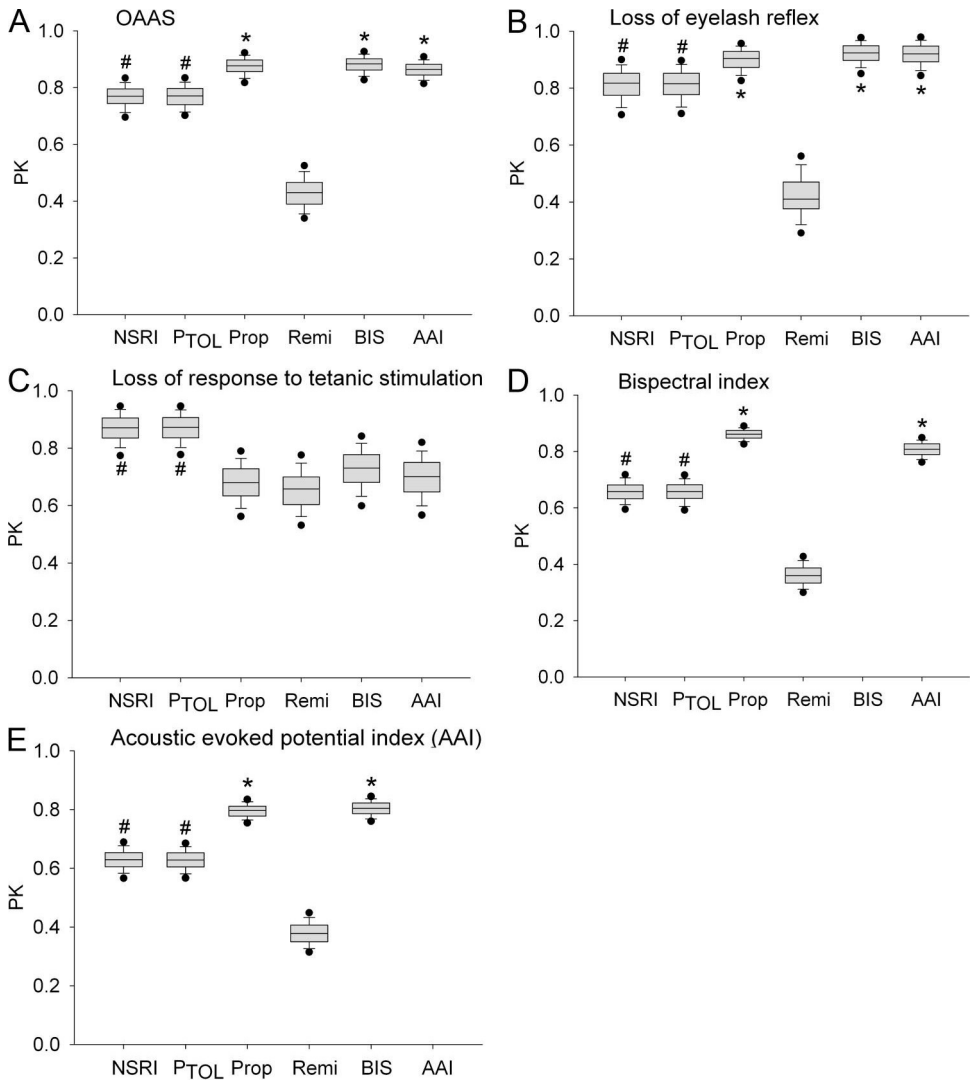


Fig. 3. Prediction probabilities (P_Ks) of different predictors and predicted variables. The P_K values according to Smith *et al.*[12] were estimated from 1,000 random samples of 263 data points from 44 patients, with 1 data point per patient in each sample. The data are presented as *box plots* with median values depicted as *horizontal lines* and the interquartile range (*lower* and *upper limits of the boxes*). The *error bars* represent the 10 and 90 percentiles, and the *black circles* the 5 and 95 percentiles. Pairwise comparison of the P_K values by comparing the median P_K of one predictor with the 2.5–97.5 percentile range of another predictor (corresponding to the 95% confidence interval). If the median P_K of the first is outside this percentile range, it is considered significantly different. *A*: observer assessment of alertness and sedation score (OAAS), *B*: loss of eyelash reflex, *C*: loss of motor response tetanic stimulation, *D*: bispectral index (BIS), and *E*: acoustic evoked potential index (AAI).* Significantly different compared with noxious stimulation response index (NSRI), probability to tolerate laryngoscopy (P_{TOL}), and effect-site remifentanil concentration (Remi); # Significantly different compared with effect-site propofol concentration (Prop), BIS, AAI, and Remi.

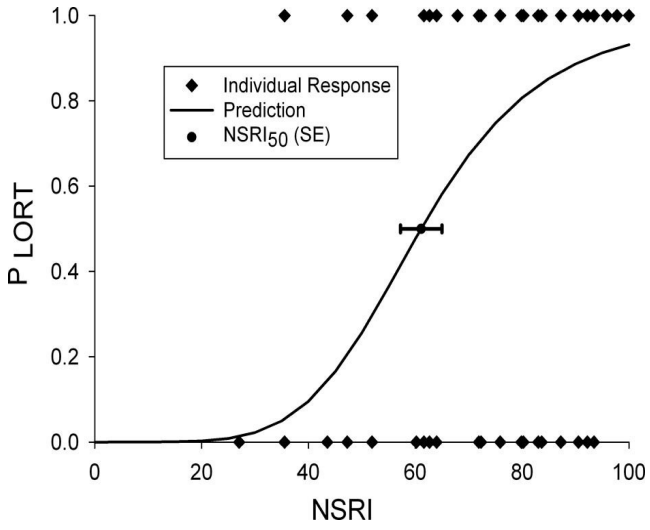


Fig. 4. The $NSRI_{50}$ for tolerance of 2-s tetanic stimulus: A logistic regression analysis with the naïve pooled data method (non-linear mixed effects modeling naïve pooled analysis) for dependent variables was performed to estimate the noxious stimulation response index (NSRI) value associated with a 50% probability to tolerate tetanic stimulation of the forearm ($NSRI_{50}$). P_{LORT} probability of tolerance of tetanic stimulation; *black diamonds* individual response to tetanic stimulation (1 response and 0 no response); prediction (*black line*) predicted probability of response according to the regression model; *black circle* NSRI associated with P_{LORT} 50%; error bars standard error of the estimate.

3 Discussion

The NSRI integrates the potency of a hypnotic and an opioid to synergistically suppress the response to a noxious stimulus. In this study, we have shown that the P_K of the NSRI and P_{TOL} to predict the probability of response to a 2-s, 50-mA, and 100-Hz tetanic stimulus is higher compared with all other investigated predictors. As expected, the P_K of the mainly hypnotic endpoints (loss of eyelash reflex and OAAS) was intermediate, and the P_K of electroencephalogram-based predictors (BIS and AAI) was low.

The predictive performance of propofol effect-site concentrations, BIS, and AAI to predict loss of consciousness in our study was as high as in a previous study in which P_Ks of 0.89–0.94 were reported.[13] The performance in predicting a response to noxious stimulation with these variables was 0.82–0.87 with pure propofol anesthesia[13] and 0.72–0.75 with coadministration of remifentanil.[4] These findings reflect the poor sensitivity of electroencephalogram-based measurements to the effect of opioids.

Surrogate endpoints potentially reflecting the analgesic state have been investigated. The surgical stress index uses the pulse plethysmography amplitude and the pulse rate derived from the pulse oximetry curve and discriminates strong *versus* light stimulation and low *versus* moderate remifentanil effect-site concentrations.[14] The skin conductance variation induced by several noxious and nonnoxious stimuli is a sensitive measure of stress[15,16] but discriminates only between the presence or absence of low remifentanil effect-site concentrations (2 ng/ml).[16] Whether it discriminates different opioid concentration levels or predicts the response to clinical stimuli is not known. Our investigations of the pulse plethysmography response to a 5-s 60-mA tetanic stimulus of the ulnar nerve as a surrogate variable to measure the analgesic state or the hemodynamic responsiveness of anesthetized patients were disappointing.[1,2] One reason was the large and probably random interindividual variation[1] of the signal (tetanic stimulation-induced variation of the pulse plethysmography trace). Therefore, we assume that baseline variability may reduce the predictive performance of any analgesic state index that is derived from physiologic signals related to the sympathoadrenergic stress response. Because the

NSRI takes into account predicted effect-site drug concentrations and their interaction only, these drawbacks do not apply. It seems that the prediction error of effect-site drug concentrations, which is greater or equal to 20%,[8,10] does not degrade the prediction performance of the NSRI. Because the NSRI accounts for the interaction of hypnotic and analgesic, it must be superior to single drug concentrations for prediction of any endpoint for which hypnotic/analgesic interactions have been demonstrated, that is, responsiveness to noxious stimuli during anesthesia.

In summary, the strengths of the NSRI are a predictive performance for noxious stimulation response in the clinically desirable range and its independence of physiologic signals as well as test stimuli. As with other anesthetic depth indicators or drug concentrations, the predictive performance expressed as P_K does not imply that a given NSRI value correctly predicts the response in an individual patient, but it means that the probability of response is highly correlated with the NSRI. The calibration of NSRI and P_{TOL} as anesthetic depth indicators was beyond the scope of this study and needs to be prospectively evaluated.

Because of the modification of the underlying hierarchical interaction model, the index is flexible for future development so that it can be extended to any combination of hypnotic and analgesic drugs. A discussion of the model modification is provided in the appendix. The interpretation of the NSRI numbers is straightforward. By definition, an NSRI of 50 means that the effect-site propofol and remifentanil concentrations are sufficient that the patient will tolerate laryngoscopy with a probability of 50%. An NSRI of 61 (3.9) means that the patient will tolerate a 2-s tetanic stimulus of the forearm with a probability of 50% and that this stimulus may be slightly weaker than laryngoscopy. Different probabilities for responses to different stimuli can be mapped on the curve with ease. Clinically desirable ranges of the NSRI during surgery can be inferred from the results of a future proof of concept study.

When the PKMACRO (calculating the P_K of a single predictor to one predicted variable) and the prediction probability difference macro (PKDMACRO) (comparing the P_Ks of different predictors) were used for validation of anesthetic depth indicators in the past, the assumption on independence of the data has been neglected. The reason for this is inherent in the study design with repeated measurements taken at several drug concentrations in the same subject. The resampling technique applied in this study is an attempt to solve this problem of the statistical analysis. Currently, it is not clear how far the resampling method affects the boundaries of our parameter estimates and to what extend a sampling bias could have been introduced. To clarify this, a formal evaluation of this technique under a range of circumstances in which the "true" bounds are known would be required, which is well beyond the scope of this study. Therefore, we have presented the 2.5–97.5 percentile ranges of the different P_Ks that approximate the 95% CIs and did not calculate any *P* values. To reject the null hypothesis that two P_Ks are similar, the median P_K of one predictor had to be outside the 95% CI of P_Ks of the other. Therefore, only large differences in the median P_Ks were accepted as significant, which are unlikely to be substantially affected by a potential sampling bias; for example, the difference between the P_Ks of NSRI and P_{TOL} and the P_Ks of all other predictors to predict response to a noxious stimulus (fig. 3). It is, therefore, unlikely that the main message of this study is affected by this yet unsolved statistical problem.

There are some other limitations of this study. First, it is a *post hoc* validation. Second, the selected propofol and remifentanil concentrations are not independent of each other. Third, the applied 2-s tetanic stimulus is substantially weaker than strong surgical

stimuli such as skin incision,[17] which is illustrated by the high $NSRI_{50}$ for loss of response to tetanic stimulation. Fourth, the data used for this validation were recorded only in a female patient population. Therefore, this study only attests to the usefulness of the NSRI as predictor of the response to medium-intensity stimuli during coadministration of propofol and remifentanil. Future studies have to validate the NSRI in the clinical setting for both total intravenous and balanced (volatile plus opioid) anesthesia and in both sexes.

We conclude that the NSRI is a promising anesthetic state index predicting response to noxious stimulation responsiveness and, to a lesser extent, the hypnotic state. Most probably, it will improve the dosing of hypnotics/volatiles and opioids. However, prospective validation studies in the clinical setting are needed to judge the use of the NSRI in everyday anesthetic practice.

The authors thank Anthony Absalom, M.D., Ph.D. (Professor, Department of Anesthesiology, University Medical Center, University of Groningen, Groningen, The Netherlands), for his helpful comments during the preparation of this manuscript.

4 Appendix : Modification of the Hierarchical Interaction Model

In this appendix, the steps of model modification as reported by Bouillon[7] are described. The original model[5] was modified to avoid overparameterization. The resulting modified model was found to be mathematically equivalent to a reduced Greco model, implying strong synergism. Its C50 for the opioid can be interpreted in analogy to a C50 for reduction of the minimal alveolar concentration of a volatile anesthetic.

41 Model Modifications

The probability of response to a stimulus is a function of stimulus strength after attenuation by the opioid (postopioid_intensity), the $C50_{hypnotic}$, the slope factor, and the concentration of the hypnotic. As is evident from equation A,[5] only the product of $Ce50_{hypnotic}$ and postopioid_intensity, but not its individual components, is identifiable (Eq. A).

$$\boldsymbol{P_{responsiveness} = 1 - \frac{{Ce_{hypnotic}}^{\phi}}{{Ce_{hypnotic}}^{\phi} + \left(Ce50_{hypnotic} \times postopioid\_intensity\right)^{\phi}}} \qquad \textit{(A)}$$

where $P_{responsiveness}$ = probability that the patient responds to the incoming stimulus, $Ce_{hypnotic}$ = effect-site hypnotic drug concentration, $Ce50_{hypnotic}$ = effect-site hypnotic drug concentration associated with a 50% probability of nonresponsiveness, and ϕ = slope parameter.

In the absence of opioid, postopioid_intensity equals preopioid_intensity, as shown in equation B.

$$\boldsymbol{postopioid\_intensity = preopioid\_intensity\left(1 - \frac{{Ce_{opioid}}^{\gamma}}{\left(Ce50_{opioid} * preopioid\_intensity\right)^{\gamma} + {Ce_{opioid}}^{\gamma}}\right)} \qquad \textit{(B)}$$

where preopioid_intensity = intensity of the incoming stimulus, Ce_{opioid} = effect-site opioid concentration, $Ce50_{opioid}$ = the common opioid concentration reducing the intensity of an incoming stimulus by 50%, and gamma (γ) slope parameter.

From this, it follows that stimulus strength cannot be estimated *per se*, if only one stimulus is investigated and preopioid_intensity must be fixed to 1 to obtain the C50 of the hypnotic. For n stimulus strengths, the number of parameters describing stimulus strength equals n - 1. These parameters describe relative strength of stimulus compared with the reference stimulus with the intensity of 1. Alternatively, the model can be parameterized in terms of one C50 for the hypnotic per stimulus applied.

The model describing postopioid_intensity was also simplified. Because the original estimate of the slope factor almost equaled 1, the model was collapsed to a fractional E_{max} model. In the original model, the multiplication of the C50 of the opioid with the preopioid pain intensity was believed to be necessary to account for the fact that higher opioid

concentrations are needed to attenuate more severe pain. Although not obvious, this behavior is also displayed by the modified model (Eq. C).

$$\boldsymbol{postopioid\_intensity} = \boldsymbol{preopioid\_intensity}\left(1 - \frac{\boldsymbol{Ce_{opioid}}}{\boldsymbol{Ce50_{opioid}} + \boldsymbol{Ce_{opioid}}}\right) \quad (C)$$

It is therefore the absolute value of postopioid_intensity and the C50 hypnotic that determine the concentration of hypnotic needed to achieve a certain probability of nonresponsiveness for a certain preopioid stimulus strength.

We would like to further illustrate this with a straightforward example.

i. Simplest case: preopioid stimulus intensity = 1, Ce_{opioid} = 0, and $P_{nonresponsiveness}$ = 0.5. The Ce_{hyp} equals the C50 of the hypnotic.

ii. Add opioid to decrease Ce_{hyp} for $P_{nonresponsiveness}$ = 0.5 by 50%. The Ce_{opioid} that lowers the preopioid_intensity from 1 to a postopioid_intensity of 0.5 equals the $Ce50_{opioid}$ (Eqs. B and C).

iii. Add opioid to decrease Ce_{hyp} for $P_{nonresponsiveness}$ = 0.5 by 50%, for another stimulus with preopioid_intensity of 2. According to equation B (original model), the Ce_{opioid} = 6 x $Ce50_{opioid}$, whereas according to equation C (modified model), the Ce_{opioid} = 3 x $Ce50_{opioid}$.

Therefore, the most simplified equation C already predicts a profound increase of the opioid concentration needed to attenuate stimulus intensities higher than 1. A simulation spreadsheet is provided in Supplemental Digital Content 1, http://links.lww.com/ALN/A578.

The following parameter estimates (SE) were obtained in a reanalysis of the data from the previous study[5]: $Ce50_{propofol,\ TOSS}$ = 2.99 (0.75) g/ml, $Ce50_{propofol,\ TOL}$ = 8.46 (1.98) g/ml, and $Ce50_{remifentanil,\ TOSS}$ = 1.16 (0.48) ng/ml, whereas the $Ce50_{remifentanil,\ TOL}$ is implicitly modeled and not estimated from the data. The non-linear mixed effects modeling objective function was 80.2.

42 Discussion

When we reanalyzed the data from the original study,[7] the non-linear mixed effects modeling objective function value of the modified hierarchical model and the Greco model was equal, whereas it was 69 in the original model.[5] However, the small SEs of the parameter estimates in the original model are indicators of overparameterization.

Furthermore, the rather high Ce50 of propofol for hypnosis (4.82 g/ml) does not compare well with results from other studies[18,19] and clinical experience. In contrast, the $C_{50,\ propofol}$ for tolerance of shaking and shouting (corresponding to the $C_{50,\ propofol}$ for loss of consciousness) estimated with the modified model was 2.99 g/ml, which is well within the range of publisheddata.[13,19,20]

A structural benefit of the model is the ability to convert it into a reduced Greco model,[7] simplifying comparisons with existing studies. The $C_{50,\ opioid}$ in our model equals the reciprocal of that model according to equation D.

$$C_{50,opioid} = \frac{1}{\epsilon'} \qquad (D)$$

where $C_{50,\ opioid}$ = opioid concentration associated with half maximal attenuation of a stimulus in our model and ϵ' = the modified Greco interaction parameter for constellations in which the opioid effect in the absence of hypnotic is too weak to be identified but profoundly changes the potency of a coadministered hypnotic. This situation was encountered in the interaction study by Mertens *et al*.[19] The proof of interconvertability of the two models has been described elsewhere.[7] Interestingly, the $Ce_{50,\ remifentanil}$ estimated with the simplified Greco model from the propofol–remifentanil interaction data is 1.39 and 1.45 ng/ml for return of consciousness and for tolerating laryngoscopy, respectively, which is almost identical despite completely different stimulation strength and approximates the $C_{50,remifentanil}$ estimated with our modified hierarchical model (1.16 ng/ml).

The model for the probability of nonresponse in this study was, therefore, parametrized according to equation E.

$$P_{non-respons} = \frac{\left(\frac{Ce_{hypnotic}}{Ce50_{hypnotic} \cdot preopioi_{intensity}\left(1 - \frac{Ce_{opioid}}{(Ce50_{opioid} * preopioid_{intensity}) + Ce_{opioid}}\right)} \right)^{\phi}}{1 + \left(\frac{Ce_{hypnotic}}{Ce50_{hypnotic} \cdot preopioi_{intensity}\left(1 - \frac{Ce_{opioid}}{(Ce50_{opioid} * preopioid_{intensity}) + Ce_{opioid}}\right)} \right)^{\phi}} \qquad (E)$$

where $P_{nonresponse}$ = probability of tolerance of a given stimulus, $Ce_{hypnotic}$ = effect-site hypnotic drug concentration, $Ce50_{hypnotic}$ = effect-site hypnotic drug concentration associated with a 50% probability of nonresponse, preopioid_intensity = intensity of the stimulus without opioid attenuation, $Ce50_{opioid}$ = effect-site opioid drug concentration reducing the preopioid_intensity by 50%, and Ce_{opioid} = effect-site opioid concentration.

5 References

1. Luginbuhl M, Reichlin F, Sigurdsson GH, Zbinden AM, Petersen-Felix S: Prediction of the haemodynamic response to tracheal intubation: Comparison of laser-Doppler skin vasomotor reflex and pulse wave reflex. Br J Anaesth 2002; 89:389–97
2. Luginbuhl M, Rufenacht M, Korhonen I, Gils M, Jakob S, Petersen-Felix S: Stimulation induced variability of pulse plethysmography does not discriminate responsiveness to intubation. Br J Anaesth 2006; 93:323–9
3. Luginbuhl M, Ypparila-Wolters H, Rufenacht M, Petersen Felix S, Korhonen I: Heart rate variability does not discriminate between different levels of haemodynamic responsiveness during surgical anaesthesia. Br J Anaesth 2007; 98:728–36
4. Struys MM, Vereecke H, Moerman A, Jensen EW, Verhaeghen D, De NN, Dumortier FJ, Mortier EP: Ability of the bispectral index, autoregressive modelling with exogenous input-derived auditory evoked potentials, and predicted propofol concentrations to measure patient responsiveness during anesthesia with propofol and remifentanil. *Anesthesiology* 2003; 99:802–12
5. Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, Shafer SL: Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. *Anesthesiology* 2004; 100:1353–72
6. Schumacher PM, Bouillon TW, Leibundgut D, Hartwich V, Luginbuhl M: Time-based online display of a noxious stimulus response index based on pharmacological data. *Anesthesiology* 2007; 107:A17
7. Bouillon TW: Hypnotic and opioid anesthetic drug interactions on the CNS, focus on response surface modeling, Modern Anesthetics. Handbook of Experimental Pharmacology. Edited by Schuttler J, Schwilden H. Berlin, Springer, 2008, pp 471–87
8. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998; 88: 1170–82
9. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999; 90:1502–16
10. Minto CF, Schnider TW, Egan TD, Youngs EJ, Muir KT, Hoke F, Mandema JW, Shafer SL, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ: The influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil I. Model development. *Anesthesiology* 1997; 86:10–23
11. Minto CF, Schnider TW, Shafer SL: The pharmacokinetics and pharmacodynamics of remifentanil II. Model application *Anesthesiology* 1997; 86:24–33
12. Smith WD, Dutton RC, Smith NT: Measuring the performance of anesthetic depth indicators. *Anesthesiology* 1996; 84:38–51
13. Struys MM, Jensen EW, Smith W, Smith NT, Rampil I, Dumortier FJ, Mestach C, Mortier EP: Performance of the ARX derived auditory evoked potential index as an indicator of anesthetic depth: A comparison with bispectral index and hemodynamic measures during propofol administration. *Anesthesiology* 2002; 96:803–16
14. Huiku M, Uutela K, Van Gils M, Korhonen I, Kymalainen M, Merilainen P, Paloheimo M, Rantanen M, Takala P, Viertio-Oja H, Yli-Hankala A: Assessment of surgical stress during general anaesthesia. Br J Anaesth 2007; 98:447–55

15. Gjerstad AC, Storm H, Hagen R, Huiku M, Qvigstad E, Raeder J: Skin conductance or entropy for detection of non-noxious stimulation during different clinical levels of sedation. Acta Anaesthesiol Scand 2007; 51:1–7
16. Gjerstad AC, Storm H, Hagen R, Huiku M, Qvigstad E, RaederJ: Comparison of skin conductance with entropy during intubation, tetanic stimulation and emergence from general anaesthesia. Acta Anaesthesiol Scand 2007; 51: 8–15
17. Rantanen M, Ypparila-Wolters H, van GM, Yli-Hankala A, Huiku M, Kymalainen M, Korhonen I: Tetanic stimulus of ulnar nerve as a predictor of heart rate response to skin incision in propofol remifentanil anaesthesia. Br J Anaesth 2007; 99:509–13
18. Kern SE, Xie G, White JL, Egan TD: A response surface analysis of propofol-remifentanil pharmacodynamic interaction in volunteers. *Anesthesiology* 2004; 100:1373–81
19. Mertens MJ, Olofsen E, Engbers FH, Burm AG, Bovill JG, Vuyk J: Propofol reduces perioperative remifentanil requirements in a synergistic manner: Response surface modeling of perioperative remifentanil-propofol interactions. *Anesthesiology* 2003; 99:347–59
20. Smith C, McEwan AI, Jhaveri R, Wilkinson M, Goodman D, Smith LR, Canada AT, Glass PS: The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision. *Anesthesiology* 1994; 81:820–8

Chapter 7 Probability to tolerate laryngoscopy and noxious stimulation response index as general indicators of the anaesthetic potency of sevoflurane, propofol, and remifentanil

L. N. Hannivoort[1],†, H. E. M. Vereecke[1],†,*, J. H. Proost[1], B. E. K. Heyse[2],D. J. Eleveld[1], T. W. Bouillon[3], M. M. R. F. Struys[1,2] and M. Luginbühl[4]

[1]Department of Anaesthesiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands, [2]Department of Anaesthesia, Ghent University, Gent, Belgium, [3]Consulting Scientist, Arlesheim, Switzerland, and [4]Department of Anaesthesiology, Spital Tiefenau, University of Bern, Bern, Switzerland. *Corresponding author. E-mail: h.e.m.vereecke@umcg.nl

British Journal of Anaesthesia, 116 (5): 624–31 (2016)

Abstract

Background : The probability to tolerate laryngoscopy (P_{TOL}) and its derivative, the noxious stimulation response index (NSRI), have been proposed as measures of potency of a propofol–remifentanil drug combination. This study aims at developing a triple drug interaction model to estimate the combined potency of sevoflurane, propofol, and remifentanil in terms of P_{TOL}. We compare the predictive performance of PTOL and the NSRI with various anaesthetic depth monitors.

Methods : Data from three previous studies (n=120) were pooled and reanalysed. Movement response after laryngoscopy was observed with different combinations of propofol–remifentanil, sevoflurane–propofol, and sevoflurane–remifentanil. A triple interaction model to estimate P_{TOL} was developed. The NSRI was derived from P_{TOL}. The ability of P_{TOL} and the NSRI to predict observed tolerance of laryngoscopy (TOL) was compared with the following other measures : (i) effect-site concentrations of sevoflurane, propofol, and remifentanil (Ce_{SEVO}, Ce_{PROP}, and Ce_{REMI}); (ii) bispectral index; (iii) two measures of spectral entropy; (iv) composite variability index; and (v) surgical pleth index.

Results : Sevoflurane and propofol interact additively, whereas remifentanil interacts in a strongly synergistic manner. The effect-site concentrations of sevoflurane and propofol at a P_{TOL} of 50% (Ce50; SE) were 2.59 (0.13) vol % and 7.58 (0.49) μg ml^{-1}. A Ce_{REMI} of 1.36 (0.15) ng ml^{-1} reduced the Ce50 of sevoflurane and propofol by 50%. The common slope factor was 5.22 (0.52). The P_{TOL} and NSRI predict the movement response to laryngoscopy best.

Conclusions : The triple interaction model estimates the potency of any combination of sevoflurane, propofol, and remifentanil expressed as either P_{TOL} or NSRI.

Key words : drug interactions; laryngoscopy; propofol; remifentanil; sevoflurane

† Both authors contributed equally to this study and should both be regarded as first author. Accepted: February 25, 2016

Editor's key points

• The probability to tolerate laryngoscopy (P_{TOL}) and its derivative, noxious stimulation response index (NSRI), may be useful to quantify and compare the potency of volatile and i.v. anaesthetics, but it is not clear whether or not there are differences in the interactions of an opioid with a volatile anaesthetic and with an i.v. anaesthetic.

• A triple interaction model, which was developed using data from previous studies, indicated that sevoflurane and propofol interact additively, whereas remifentanil interacts in a strongly synergistic manner.

• The triple interaction model can estimate the potency of any combination of sevoflurane, propofol, and remifentanil.

Adequate anaesthesia can be defined as the combination of an accurate level of hypnosis with sufficient analgesia to avoid response to a noxious stimulation, where 'response' includes a variety of modalities, such as movement, haemodynamic response, or arousal. Most contemporary anaesthetic depth monitors are based on the processed EEG and correlate mainly with hypnotic drug effect; however, they do not reliably predict a response to noxious stimulation.[1 2] Recent attempts to measure analgesia, based on the variability of the processed EEG signal[3] or on changes in the autonomic nervous system as measured by pulse plethysmography,[4 5] were only partly successful. Similar decreasing accuracy was found for the propofol effect-site concentration (Ce_{PROP}) as a measure of drug effect in the presence of opioids.[1 2]

For decades, the probability of response to skin incision, defined as the minimal alveolar concentration (MAC), has been used to quantify and compare the potency of volatile agents.[6–9] More recently, Bouillon and colleagues[10] defined tolerance of laryngoscopy (TOL) as an absence of movement response to laryngoscopy, and they proposed the probability to tolerate laryngoscopy (P_{TOL}) as an alternative to MAC when using propofol instead of volatile agents. For ergonomic reasons and in order to cope with the clinical conformity of standard depth of anaesthesia monitoring, Luginbühl and colleagues[11] normalized and calibrated P_{TOL} towards a new index called the noxious stimulation response index (NSRI). The NSRI is a numerical depth of anaesthesia indicator that is directly derived from P_{TOL} and was first described for propofol and remifentanil anaesthesia. The NSRI and P_{TOL} are therefore interchangeable; they merely differ in scale. The NSRI is scaled between 100 (when no anaesthetic drugs are administered) and zero (indicating extensive combined drug effects), whereas P_{TOL} scales from zero to one.

Until now, specific P_{TOL} results have been found in three different drug interaction studies, resulting in separate response surface models for propofol–remifentanil,[10] sevoflurane–propofol,[12] and sevoflurane–remifentanil.[13] In order to use P_{TOL} (and NSRI) as general probabilistic parameters to represent the lack of responsiveness to a noxious stimulation in both i.v. and volatile anaesthesia conditions, supplemented with opioids, one needs to solve the problems of whether synergy of remifentanil with propofol is stronger than synergy with sevoflurane and whether the slope of the propofol–remifentanil and the sevoflurane–remifentanil response surfaces are different. This may be clarified by developing a triple interaction surface model, merging the information from the previously published dual drug models,[10 12 13] hereby also rescaling and expanding previously published P_{TOL} and NSRI scales.

For clinicians, a general P_{TOL} and its derivative, NSRI, would enable estimation of the concentration of sevoflurane that is equipotent to a given propofol concentration when used in combination with remifentanil. The primary purpose of the present study was to define a triple interaction response surface model to express the potency of any combination of sevoflurane, propofol, and remifentanil in terms of P_{TOL} and NSRI by merging the raw data from three previously published studies.[10 12 13] The secondary purposewas to test the ability of P_{TOL} and NSRI, calculated with the new triple interaction model parameters, to predict the observed TOL. We compared the performance of P_{TOL} and NSRI with other measures, such as single drug effect-site concentrations of sevoflurane, propofol, and remifentanil (Ce_{SEVO}, Ce_{PROP}, and Ce_{REMI}), current hypnotic effect monitors, such as the EEG-derived bispectral index (BIS; Covidien, Boulder, CO, USA)[14] and two measures of the EEG-derived spectral entropy, state entropy and response entropy (SE and RE; GE Healthcare, Helsinki, Finland),[15] and newer analgesic effect monitors, such as the BIS-derived composite variability index (CVI; Covidien)[3 16] and pulse plethysmograph derived surgical pleth index (SPI; GE Healthcare).[5]

1 Methods

We performed a response surface analysis of the pooled raw data from three previously published studies on interactions between sevoflurane, propofol, and remifentanil.[10 12 13 17] The Ethics' Committees from these original studies (Ghent University Hospital, Gent, Belgium and Stanford University, Stanford, CA, USA) both agreed that the anonymized original databases could be re-used for this analysis. As the original studies were executed and published long before the introduction of the public registration requirements, no registration of the original studies was possible.

The characteristics of the study populations are summarized in Supplementary File 1 and in the Results section. The study design and drug administration protocol have been described in detail in each of the studies. Briefly, combinations of propofol–remifentanil,[10] sevoflurane–propofol,[12] and sevoflurane–remifentanil[13 17] were administered using a modified crisscross design according to Short and colleagues.[18] Propofol and remifentanil were administered as computer-controlled infusions targeting effect-site or plasma concentrations using the pharmacokinetic and pharmacodynamic models by Schnider[19 20] and Minto,[21 22] respectively. While Bouillon and colleagues[10] used targeted plasma concentrations and observed an equilibration time of 15 min, Schumacher and colleagues[12] and Heyse and colleagues[13 17] applied target effect-site concentrations with an equilibration time of 12 min. Sevoflurane was titrated to achieve predetermined end-tidal concentrations using an ADU ventilator with an integrated AS3 monitor (GE Healthcare). These equilibration times are considered sufficient for all drugs to allow equilibration between the plasma and effect-site concentration. Acceptable prediction errors of the Schnider and Minto models were confirmed in the propofol–remifentanil study by means of repetitive blood sample analysis for propofol and remifentanil published previously.[23] A steady state for sevoflurane was confirmed through end-tidal measurements of sevoflurane concentrations. In all three studies, after equilibration of plasma and effect-site concentrations, a series of stimuli was applied and the presence or absence of movement response recorded. However, only TOL was used in our final analysis after initial model validation (see Results section).

The following drug effect monitors were used : BIS (BIS Version 3.22, A1000; Covidien) by Bouillon and colleagues;[10] BIS (Version 4.0, A-2000; Covidien); and SE and RE (M-Entropy; GE Healthcare) by Schumacher and colleagues[12] and Heyse and colleagues.[17] Additionally, Heyse and colleagues[17] computed the composite variability index (CVI; Covidien) and the surgical pleth index (SPI; GE Healthcare) off-line from the recorded raw EEG and pulse plethysmography data, respectively. Detailed information can be found in the original publications.

11 Pharmacodynamic model

The synergistic interactions between propofol and remifentanil and between sevoflurane and remifentanil were best described by the modified hierarchical model,[13 11 23] whereas the additive interaction between sevoflurane and propofolwas best described by the Greco model.[12] We therefore postulated that the interaction of the three compounds could be described by considering any combination of the three drugs as a virtual newdrug with the potency 'U'.[13 24]

Equation (1) is the sigmoidal response function for a dichotomous effect :

$$\boldsymbol{P_{TOL} = \frac{U^{\gamma}}{1 + U^{\gamma}}}$$

Equation (1)

where P_{TOL} is the probability of tolerance of laryngoscopy γ is the slope parameter that represents the steepness of the concentration – effect relationship, and U is the combined potency of the drugs according to Equation (2) :

$$\boldsymbol{U = \left(\frac{C_{SEVO}}{C50_{SEVO}} + \frac{C_{PROP}}{C50_{PROP}}\right) \cdot \left(1 + \left(\frac{C_{REMI}}{C50_{REMI}}\right)^{\gamma_O}\right)}$$

Equation (2)

where Ce_{SEVO}, Ce_{PROP} and Ce_{REMI} are the effect-site concentrations of sevoflurane, propofol and remifentanil, respectively, $Ce50_{SEVO}$ and $Ce50_{PROP}$ are the effect-site concentrations of sevoflurane and propofol, respectively, resulting in P_{TOL} = 0.5 if given alone, and $Ce50_{REMI}$ is the effect-site concentration of remifentanil that results in an increase of U by a factor 2 or an apparent decrease of the $Ce50_{SEVO}$ and $Ce50_{PROP}$ by 50%, and γ_o represents the steepness of the concentration-effect relationship of the opioid.

According to the parameter estimates of the original studies (Table 1), our hypothesis was that Ce50REMI, γ_o and γ were different for sevoflurane and propofol and we assumed a linear interpolation. The null hypothesis was that these parameters were similar. Linear interpolation was performed according to equations (3)-(5):

$$\boldsymbol{Ce50_{REMI} = Ce50_{REMI(SEVO)} * SF + Ce50_{REMI(PROP)} * (1 - SF)}$$

Equation (3)

$$\gamma_O = \gamma_{O(SEVO)} * SF + \gamma_{O(PROP)} * (1 - SF)$$

Equation (4)

$$\gamma = \gamma_{(SEVO)} * SF + \gamma_{(PROP)} * (1 - SF)$$

Equation (5)

where SF is the sevoflurane fraction defined in Equation (6):

$$SF = \frac{\frac{C_{SEVO}}{C50_{SEVO}}}{\left(\frac{C_{SEVO}}{C50_{SEVO}} + \frac{C_{PROP}}{C50_{PROP}}\right)}$$

Equation (6)

Thus, SF=0 if Ce_{SEVO}=0, and SF=1 if Ce_{PROP}=0, and SF is between zero and one for mixtures of sevoflurane and propofol. Note that the final models in the three original studies[10–12 23] are equivalent to equations (1)–(6), with the following specific constraints : γ_o =1 in the study by Bouillon and colleagues,[10] and $\gamma_{(SEVO)}$= $\gamma_{(PROP)}$ in Schumacher's study.[11]

The purpose of the model developed from the data is to predict P_{TOL} of random individuals in a population. Similar to the MAC, a P_{TOL} of 50% is the concentration where 50% of a population tolerates laryngoscopy without movement response (TOL). The individual concentration–response of the 'typical subject' was therefore not the focus of the study, and inter-individual variability was not included in the parameter estimation (naive pooling approach).

12 Selection of the final model and parameter estimation

In the first step, the data fromeach studywere separately fitted to the model [equations (1)–(6)] in order to determine the effect of considering only TOL instead of the whole series of stimuli as previously published. In the second step, a fit of the pooled TOL data was performed. In the pooled fit, the parameters $Ce50_{SEVO}$, $Ce50_{PROP}$, $Ce50_{REMI}$, γ_1, and γ_o were estimated assuming that the parameters $Ce50_{REMI}$, γ_o, and γ were identical for te two hypnotics sevoflurane and propofol. Then we tested whether different values for $Ce50_{REMI}$, γ_o, or γ for sevoflurane and propofol significantly improved the fit. In addition, we tested whether γowas significantly different from one. The results were accepted as valid only if both minimization and covariance steps were successful, unless stated otherwise.

The model parameters were estimated using NONMEM 7.2.0 (Icon Development Solutions, Hanover, MD, USA), using the Laplace method. The software was installed on a GNU Fortran 95 compiler (http://gcc.gnu.org) with Windows XP operating system (Microsoft, Redmond, WA, USA). PLT Tools (PLTsoft, San Francisco, CA, USA) was used as graphical user interface.

Table 1 Comparison of model parameters of tolerance of laryngoscopy from three studies. IIV, inter-individual variability; P+R, propofol+remifentanil; S+P, sevoflurane+propofol; S+R, sevoflurane +remifentanil. Pooled data are observations from all three studies. SEVO/PROP ratio (vol% ml μg^{-1}) = $Ce50_{SEVO}/Ce50_{PROP}$. Typical values (standard error) [95% confidence interval] as published, from reanalysis using laryngoscopy data only, and from reanalysis of the pooled laryngoscopy data. *Calculated from $Ce50_{SEVO}/Ce50_{PROP}$, †Assumed to be equal for sevoflurane and propofol. ‡Not significantly different for sevoflurane and propofol. Not significantly different from one. §Not significantly different from zero. ||Inter-individual variability was not included in the analysis. $Ce50_{SEVO}$ and $Ce50_{PROP}$ are the effect-site concentrations of sevoflurane and propofol, respectively, resulting in PTOL = 0.5 if given alone; $Ce50_{REMI}$ is the effect-site concentration of remifentanil, resulting in an apparent decrease of the $Ce50_{SEVO}$ and $Ce50_{PROP}$ by 50%; g is the slope parameter of the concentration-effect relationship of sevoflurane and propofol; go is the slope parameter of the concentration-effect relationship of the opioid

	P + R		**S + P**		**S + R**		**Pooled data**
	(Bouillon 2004 and colleagues)[10]		**(Schumacher and colleagues)[12]**		**(Heyse and colleagues) [13]**		
number of patients	20		60		40		120
number of observations	95		274		152		521
	Published	Reanalysis	Published	Reanalysis	Published	Reanalysis	Reanalysis
$Ce50_{SEVO}$ (vol%)	-	-	2.83 (0.19)	2.76 (0.19)	2.00 (0.15)	2.11 (0.20)	2.59 (0.13) [2.36 – 2.91]
$Ce50_{PROP}$ (μg ml^{-1})	8.48 (1.98)	7.81 (1.76)	6.55 (0.51)	7.24 (0.60)	-	-	7.58 (0.49) [6.71 – 8.84]
$Ce50_{REMI}$ (ng ml^{-1})	1.16 (0.48)	1.31 (0.57)	-	-	1.69 (0.35)	1.91 (0.32)	1.36 (0.15) [1.06 – 1.67]
SEVO/PROP ratio	-	-	0.43*	0.381*	-	-	0.342*
γ	3.46 (0.83)	3.85 (1.10) [2.54-9.45]	17.6 (2.69)†	5.70 (0.69)‡ [4.56-7.51]	7.41 (0.86)	5.82 (0.97) [4.46-9.39]	5.22 (0.52)‡ [4.22 – 6.51]
γ_O	1 ¶	1 ¶	-	-	0.718 (0.085)	1 ¶	1 ¶
IIV($Ce50_{SEVO}$)	-	-	32%	||	20%	||	||
IIV($Ce50_{PROP}$)	§	||	31%	||	-	-	||
IIV($Ce50_{REMI}$)	§	||	-	-	§	||	||

To determine the final model, non-parametric 95% confidence intervals (CIs) were calculated, using a bootstrap analysis based on 2000 sets, stratified according to the original studies. Assuming a χ^2 distribution with one degree of freedom, an improvement of the objective function value of 3.84, corresponding to a value of $P<0.05$, was considered significant.

The P_{TOL} was calculated from equation (1) and NSRI from equation (7):

$$NSRI = \frac{100}{1 + \left(\frac{P_{TOL}}{1 - P_{TOL}}\right)^{s}}$$

Equation (7)

where s is a constant (s = 0.63093).

For further information on the transformation of P_{TOL} to NSRI, see Supplementary File 2.

13 Model evaluation

The data of responders and non-responders were plotted together with the 50 and 90% isoboles, derived from the original models,[10 12 13 23] and the final model for visual inspection of the goodness of fit. Additionally, we plotted the observed P_{TOL} against the P_{TOL} predicted by all models to compare the ability of the final model for P_{TOL} with the previously published models. The observed P_{TOL} was obtained from the raw data according to the following procedure. For each observation (response or no response to laryngoscopy), the predicted P_{TOL} was calculated from the effect-site concentrations and model parameters (Table 1) using equations (1) and (2). Then the predicted P_{TOL} of each observation and the related true response (0 or 1) were sorted with increasing value of predicted P_{TOL}. The observed P_{TOL} was defined as the average of the response of the index observation and the next 10 observations with a lower and a higher predicted P_{TOL}. The observed P_{TOL} is thus a moving average over 21 observations, where the missing values at the lower and upper end were omitted. The resulting plots allow a visual inspection of the goodness of fit, as shown in Supplementary File 3. The mean absolute prediction error (MAPE) was calculated as the mean of the absolute value of the difference between the observed and predicted P_{TOL}. For clarification to the reader, the 'observed P_{TOL}' is used only for this specific model validation. Otherwise in this work, 'P_{TOL}' always refers to the 'predicted P_{TOL}'.

In a second validation, we used the raw data of two original studies for parameter estimation and the raw data of the third study for model validation, as shownin the Supplementary File 4.

14 Assessment of prediction probability

The prediction probability (P_K) is based on multiple comparisons of two data points from the total data set, to investigate the degree of association between each predictor and the observed tolerance. A P_K value of 0.5 implies no association, thus a poor prediction

probability; a value of one implies complete association, thus an excellent prediction probability.[25 26]

We used P_K to assess the performance of predicted P_{TOL}, its derivative, NSRI, and the observed BIS, SE, RE, CVI, and SPI to predict TOL. For comparison, the P_K values of the single drug concentrations (Ce_{SEVO}, Ce_{PROP}, and Ce_{REMI}) were also determined. Using single drug concentrations as estimates of the likelihood of tolerance does not take into account the effect of simultaneously administered drugs; therefore, we hypothesized that they are less accurate than the predicted P_{TOL} as a result of this limitation.

The drug concentrations, their related variables, and the monitor records immediately before the stimulus series were used as independent variables to predict the response.

To ensure that the predicted P_{TOL} and its derivative, NSRI, are independent of the observed P_{TOL}, the calculation of P_K for P_{TOL} and NSRI was performed by a two-fold cross-validation procedure. The total data set was divided into two subsets, each containing 60 patients, randomly drawn from the propofol–remifentanil[10] (10 patients), sevoflurane–propofol[12] (30 patients), and sevoflurane–remifentanil[13] (20 patients) studies. In each subset, a population interaction model was modelled and used for calculating P_{TOL} and NSRI in the other subgroup. The parameter estimates for calculating P_{TOL} and NSRI from one subgroup were thus used to validate the prediction in the other subgroup.

Bootstrapping (1000 replicates) was used to determine 95% CIs of the P_K values for each predictor and also the difference between the P_K values of each combination of two predictors. Significance was achieved if the 95% CI of the difference did not include zero ($P<0.05$).

All P_K calculations were performed in Excel 2003 (Microsoft) using VBA macros.

15 Statistical analysis

In all patients, we were able to compare the predictive performance of predicted P_{TOL}, NSRI, Ce_{SEVO}, Ce_{PROP}, Ce_{REMI}, and BIS to predict TOL (P_K performance comparison 1). In data obtained from the sevoflurane–propofol and the sevoflurane–remifentanil studies, SE and RE were additionally available as predictors (P_K performance comparison 2). In the data obtained from the sevoflurane–remifentanil study, SPI and CVI were also evaluated, as predictors of TOL (P_K performance comparison 3). Results of each performance comparison should be seen as a separate test of performance because the data sets are different.

Statistical significance is set to $P<0.05$ unless stated otherwise. All model parameters are reported as typical values with SE within parentheses. Clinical data are given as mean and SD or as median and range, when appropriate.

2 Results

21 Study population

The characteristics of the populations of the three studies were comparable. The mean (range) weight was 69 (50–120), 66 (50–102), and 64 (50–103) kg in the propofol–remifentanil,[10] the sevoflurane–propofol,[12] and the sevoflurane–remifentranil[13] trial,

respectively. The mean height was 169 (155–184), 172 (150–190), and 172 (157–186) cm, the mean age 34 (20–43), 30 (18–58), and 26 (18–54) yr, and the gender ratio (female/male) 10/10, 33/27, and 26/14, respectively.

22 Common response surface of sevoflurane, propofol, and remifentanil

The results of the reanalysis of the three studies by separate and pooled analysis of the laryngoscopy data are summarized in Table 1, together with the results reported in the original papers. The separate reanalysis of each study gave slightly different results from those reported in the original paper, because only the laryngoscopy data were included and because inter-individual variation of the parameter estimates was not included in our analysis.

In the pooled analysis of the laryngoscopy data fromthe three studies, we could not confirm the hypothesis that $Ce50_{REMI}$ and γ are different for sevoflurane and propofol. In addition, γ_o was not significantly different from one. When the $Ce50_{REMI}$ was allowed to vary between sevoflurane and propofol, the parameter estimates were 1.37 and 1.33 ng ml^{-1}, respectively, with an 'improvement' of the NONMEM objective function of 0.018. When γ was allowed to vary between sevoflurane and propofol, the parameter estimates (SE) were 5.55 (0.74) and 4.71 (0.87), respectively, with an improvement of the NONMEM objective function of 0.420. As a result, the data of the three studies can be well described with only four model parameters ($Ce50_{SEVO}$, $Ce50_{PROP}$, $Ce50_{REMI}$, and γ), with good precision (i.e. the SE values were smaller than in the original papers and in the separate analysis; Table 1). Equation (2) may therefore be simplified to :

$$\boldsymbol{U = \left(\frac{C_{SEVO}}{C50_{SEVO}} + \frac{C_{PROP}}{C50_{PROP}}\right) \cdot \left(1 + \frac{C_{REMI}}{C50_{REMI}}\right)}$$

Equation (8)

also known as the reduced Greco model.[7 17] Equation (8) is thus the final model of the combined effect of sevoflurane, propofol and remifentanil.

The CIs calculated from the bootstrap analysis are presented in Table 1. In order to calculate P_{TOL} using equation (1), U was calculated using equation (8) by entering the parameter estimates of the pooled analysis in the formula (Table 1). Figure 1 shows the presence or absence of TOL as a function of U.

23 Model evaluation

The 50 and 90% TOL isoboles and the raw data of responders and non-responders are shown in Figure $2_{A\text{-}C}$. The MAPE was calculated for the following three models: (i) a model as published (i.e. computed from the raw data of each single study including the response to all applied stimuli); (ii) a model reanalysed from the data of each single study including the response to laryngoscopy only; and (iii) the final model computed from the pooled data of all three studies including response to laryngoscopy only. For propofol–remifentanil, the MAPEs of the predicted P_{TOL} of the resulting models were 1.8, 2.3, and 3.9%, respectively. For sevoflurane–propofol, the MAPEs were 14.6, 6.8, and 6.9%, and for sevoflurane–

remifentanil, the MAPEs were 5.3, 3.0, and 4.1%, respectively. Thus, the MAPE values of the triple interaction model are close to those of the separate reanalysis of each study and are lower than those obtained from the published models, except for propofol–remifentanil, where MAPE is low for all models. The reason for the rather large MAPE for the sevoflurane–propofol data is visible in Figure 1. In the absence of remifentanil, the maximal U was only 1.56, which was only little above the range of U where responders and non-responders were observed. A plot of observed vs predicted P_{TOL} allowing for a visual inspection of the goodness of fit is presented in Supplementary File 3. The result of the cross-validation based on parameter estimation from the raw data of two studies and validation with the raw data of the third study is presented in Supplementary File 4.

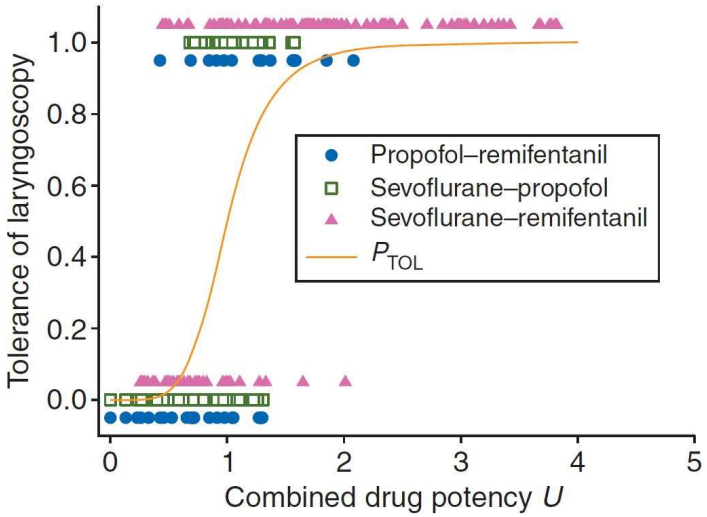


Fig 1 The observed movement response and non-response to laryngoscopy is presented as a function of the total potency of the drug combination expressed as 'U' [equation (8)]. A value of one denotes tolerance of laryngoscopy (no movement); a value of zero denotes movement response. Data are from the propofol–remifentanil study,[10] sevoflurane–propofol study,[12] and sevoflurane–remifentanil study.[13] The sigmoid concentration–response curve represents equation (1) with the final model.

24 Prediction probability

Table 2 shows the results for P_K to assess the performance of P_{TOL}, its derivative, NSRI, and the observed BIS, SE, RE, CVI, and SPI to predict TOL. For comparison, the P_K values of the single drug concentrations (Ce_{SEVO}, Ce_{PROP}, and Ce_{REMI}) were also determined and are shown in Table 2.

3 Discussion

With a pooled analysis of data from three previously published studies of similar design on dual drug interactions, a triple interaction model was developed to describe the anaesthetic potency of combinations of sevoflurane, propofol, and remifentanil in terms of P_{TOL} and its derivative, the NSRI. The model that fits the data best can be interpreted as an extension of the hierarchical hypnotic–opioid interaction model published previously.[10 11 13 23]

We found that the interaction between sevoflurane and propofol is additive when their concentrations are normalized to their respective effect-site concentration inducing TOL in 50% of the population. This is a confirmation of earlier work.[12 27 28] Remifentanil has a strong but equally synergistic effect on sevoflurane and propofol. In contrast to original

publications,[10 12 13] the pooled analysis did not support different Ce50 values for remifentanil nor different slope factors for sevoflurane and propofol. This is not surprising, because the SE values of both parameters were ~20% in the study by Heyse and colleagues[13] and ~40% in the study by Bouillon and colleagues[10] for Ce50, and the 95% CIs for the slopes were overlapping in all three studies. As such, our common $Ce50_{REMI}$ and slope are within the SE of the values published previously (Table 1).

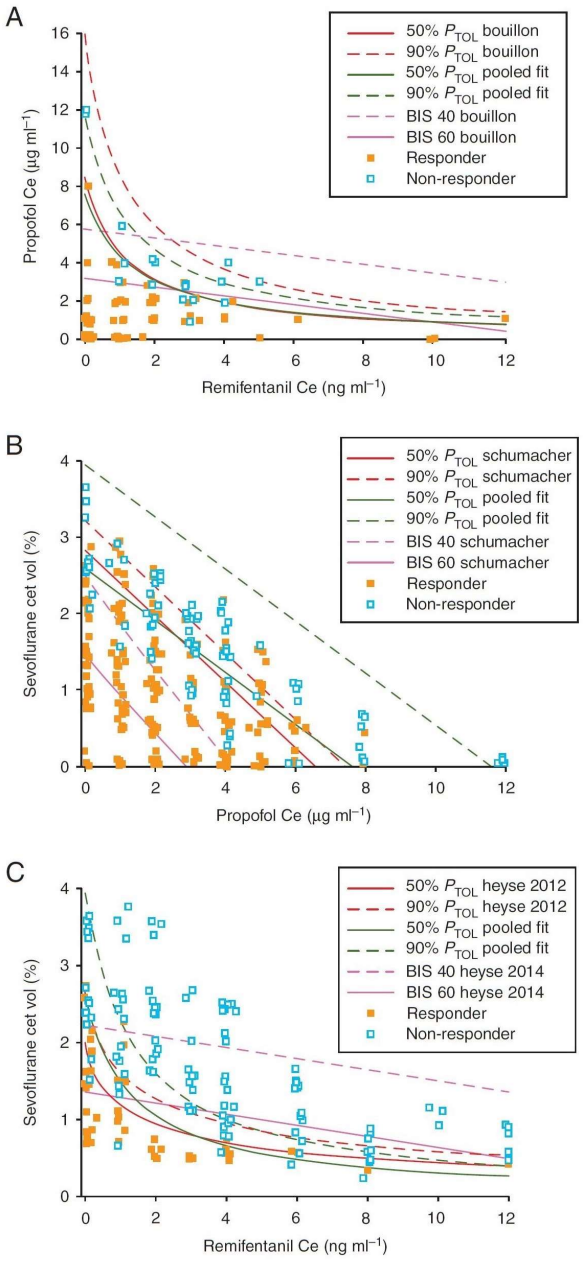


Fig 2 Goodness-of-fit plot of the tolerance of laryngoscopy isoboles (P_{TOL}) for propofol–remifentanil (P+R; A), sevoflurane–propofol (S+P; B), and sevoflurane–remifentanil (S+R; C) combinations. Non-responders and responders to laryngoscopy are indicated. To avoid superposition of multiple responses at the same point, concentration values were slightly modified by adding a random value with mean zero and SD 0.1. The 50% (continuous lines) and 90% (dashed lines) isoboles calculated with the original models (blue (A), blue (B), and blue (C))[10 12 13] and the new interaction model (green; Table 1) are plotted with the BIS 40 (pink dashed line) and BIS 60 (pink continous line) isoboles according to the original response surface model.[10 12 17] For remifentanil concentrations >2 ng ml^{-1}, the 90% P_{TOL} isobole is between the BIS 40 and BIS 60 isobole, which corresponds to clinical dosing practice. The additive isobole for the sevoflurane and propofol interaction (straight lines) are well above the BIS 40 isobole, which reflects the fact that the EEG-suppressing effect of the two hypnotic drugs is much stronger than the potency to suppress the response to laryngoscopy. Ce, effect-site concentration; Cet, end-tidal concentration; BIS, Bispectral Index.

Various model validation methods were applied and proved that our final model describes the data accurately and represents clinical reality. In Figure 2, the 50 and 90%P_{TOL} isoboles calculated with the triple interaction model and with the previous two-drug interaction models[10 12 13] are plotted together with the raw data from the three studies to

Table 2 Prediction probabilities (P_K) of all studied measures to detect tolerance of laryngoscopy. Numbers are prediction probabilities according to Smith and colleagues[25] estimated from the data (95% confidence intervals estimated from a bootstrap analysis). The best predictor for each stimulus is highlighted (bold). *P<0.05 compared with Ce_{PROP}. †P<0.05 compared with Ce_{SEVO}, Ce_{PROP}, Ce_{REMI}, and BIS. ‡P<0.05 compared with Ce_{SEVO}, Ce_{PROP}, Ce_{REMI}, BIS, SE, and RE. P<0.05 compared with SPI. §P<0.05 compared with Ce_{SEVO}, Ce_{REMI}, BIS, SE, RE, CVI, and SPI. P_{TOL} is the 'predicted P_{TOL}' calculated from the effect-site concentrations and model parameters. Ce_{SEVO}, Ce_{PROP} and Ce_{REMI} are the effect-site concentrations of sevoflurane, propofol and remifentanil, respectively; BIS, Bispectral Index; SE, State Entropy; RE, Response Entropy; CVI, Composite Variability Index; SPI, Surgical Pleth Index

Ce_{SEVO}	Ce_{PROP}	Ce_{REMI}	BIS	SE	RE	CVI	SPI	NSRI
Whole population (n=120)								
0.73*	0.46	0.67*	0.71*	-	-	-	-	**0.92**†
(0.68-0.77)	(0.41-0.51)	(0.61-0.72)	(0.66-0.77)					(0.90-0.94)
Subgroups sevoflurane-propofol and sevoflurane-remifentanil (n=100)								
0.71*	0.41	0.70*	0.65*	0.69*	0.69*	-	-	**0.92** ‡
(0.66-0.76)	(0.35-0.47)	(0.65-0.74)	(0.59-0.71)	(0.63-0.75)	(0.63-0.75)			(0.89-0.94)
Subgroup sevoflurane – remifentanil (n=40)								
0.76¶	-	0.72	0.78¶	0.78¶	0.77¶	0.74	0.57	**0.95** §
(0.68-0.84)		(0.64-0.80)	(0.69-0.86)	(0.68-0.86)	(0.67-0.86)	(0.62-0.84)	(0.48-0.69)	(0.91-0.98)

demonstrate the goodness of fit. Additionally, the clinically used BIS 40 and BIS 60 isoboles as predicted from previous studies are shown.[10 17] The difference in the shape of the isoboles is related to the difference in Ce50 values and the different slopes between current and previously published models (Table 1). For remifentanil concentrations >2 ng ml^{-1}, the 90% P_{TOL} isobole is between the BIS 40 and BIS 60 isobole, which corresponds to clinical dosing practice. This is consistent with previous data on the sevoflurane–remifentanil interaction by Manyam and colleagues,[29] who demonstrated that the 95% isobole for suppressing response to tetanic stimulationwas between the BIS 60 and 70 isobole at remifentanil concentrations greater than ~3 ng ml^{-1}. The additive 50 and 90% isoboles for the sevoflurane and propofol interaction (straight lines) are well above the BIS 40 isobole, which reflects the fact that the EEG-suppressing effect of the two hypnotic drugs is much stronger than the potency to suppress the response to laryngoscopy.

In a general sense, P_{TOL} can be considered an extension of the clinically applied MAC concept.[6] For the first time, the potency of inhaled and i.v. hypnotic drugs can be compared uniformly. Using our triple interaction model, the potency of any combination of sevoflurane, propofol, and remifentanil can be expressed as P_{TOL} or its derivative, NSRI. For example, a Ce_{REMI} of 3 ng ml^{-1} combined with either a Ce_{PROP} of 3 μg ml^{-1} or a Ce_{SEVO} of 1.03 vol% will yield a P_{TOL} of 0.7 or an NSRI of 31 and are thus considered equipotent. A more detailed clinical application is shown in Supplementary File 5. In a simulated anaesthesia induction with a bolus of propofol and a remifentanil target-controlled infusion, the time when sevoflurane needs to be administered depends on the size of the propofol bolus and the remifentanil concentration. The interaction model allows compensation for the decay of the propofol effect-site concentration by increasing the effectsite concentration of sevoflurane, in order to maintain a predefined total potency of the drugs in terms of P_{TOL}.

In the population, TOL was best predicted by P_{TOL} and NSRI (Table 2), whereas Ce_{SEVO}, Ce_{PROP}, Ce_{REMI}, and BIS were intermediate (0.7) and Ce_{PROP} was a poor predictor of TOL. In data obtained from the sevoflurane–propofol and the sevoflurane–remifentanil studies, SE and RE were also available and showed a moderate predictive accuracy, similar to BIS. In the data obtained from the sevoflurane–remifentanil study, CVI was found to be a moderately accurate predictor of TOL. The SPI was not able to predict TOL. Both P_{TOL} and NSRI outperformed the other measures in both sub-analyses.

A limitation of our study is that our triple interaction model is based on pooled data from three independently performed two-drug interaction studies, so no patient was given a combination of all three drugs. As a result, our model neither detects nor excludes a superimposed triple interaction in patients who receive all three drugs simultaneously. In a large triple interaction study on midazolam, propofol, and alfentanil, Minto and colleagues[24] found significant synergistic interactions of each pair of these compounds but no additional triple interaction when three drugs were combined. A significant and relevant triple interaction does not therefore seem likely, considering the additive interaction between sevoflurane and propofol, and the strong and similar synergistic interaction of remifentanil with both hypnotic drugs. Our model does produce predictions about PTOL when all three drugs are administered simultaneously, and these predictions are open to hypothesis testing. Outside of our model, these predictions are not available because no other triple interaction model exists for these drugs in current literature.

In conclusion, our response surface interaction model allows estimation of the potency of any combination of sevoflurane, propofol, and remifentanil as the probability to tolerate laryngoscopy. The P_{TOL} and its derivative, the NSRI, are good predictors of TOL. Clinical applicability needs further validation in a prospective study, with surgical and other standardized stimuli.

4 Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.

5 Authors' contributions

Study conception and design: L.N.H., H.E.M.V., J.H.P., D.J.E., M.M.R.F.S., M.L.
Acquisition of data: B.H., T.B., M.L., M.M.R.F.S.
Data analysis: J.H.P., D.J.E.
Interpretation of data: L.N.H., H.E.M.V., J.H.P., D.J.E.,T.B., M.M.R.F.S.,M.L.
Manuscript preparation: L.N.H., H.E.M.V., J.H.P., T.B., M.M.R.F.S., M.L.

6 Declaration of interest

M.M.R.F.S. and M.L. have received unrestricted educational grants from Dräger Medical, Lübeck, Germany. M.M.R.F.S. is an editor and editorial board member for the British Journal of Anaesthesia but was not involved in the editorial process of this work. The other authors declare no conflicts of interest.

7 Funding

Departmental and institutional funding. Two of the underlying studies[12 13] were supported by a non-restrictive educational grant from Dräger Medical (Lübeck, Germany).

8 References

1. Vanluchene ALG, Struys MMRF, Heyse BEK, Mortier EP. Spectral entropy measurement of patient responsiveness during propofol and remifentanil. A comparison with the bispectral index. Br J Anaesth 2004; 93: 645–54
2. Vanluchene ALG, Vereecke H, Thas O, Mortier EP, Shafer SL,Struys MMRF. Spectral entropy as an electroencephalographicmeasure of anesthetic drug effect: a comparison with bispectral index and processed midlatency auditory evoked response. Anesthesiology 2004; 101: 34–42
3. Sahinovic MM, Eleveld DJ, Kalmar AF, et al. Accuracy of the Composite Variability Index as a measure of the balance between nociception and antinociception during anesthesia. Anesth Analg 2014; 119: 288–301
4. Huiku M, Uutela K, van Gils M, et al. Assessment of surgical stress during general anaesthesia. Br J Anaesth 2007; 98: 447–55
5. Rantanen M, Yli-Hankala A, van Gils M, et al. Novel multiparameter approach for measurement of nociception at skin incision during general anaesthesia. Br J Anaesth 2006; 96: 367–76
6. Eger EId, Saidman LJ, Brandstater B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. Anesthesiology 1965; 26: 756–63
7. de Jong RH, Eger EI 2nd.MAC expanded:AD50 andAD95 values of common inhalation anesthetics in man. Anesthesiology 1975;42: 384–9
8. Zbinden AM, Maggiorini M, Petersen-Felix S, Lauber R, Thomson DA, Minder CE. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. I. Motor reactions. Anesthesiology 1994; 80: 253–60
9. Zbinden AM, Petersen-Felix S, Thomson DA. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. II. Hemodynamic responses. Anesthesiology 1994; 80: 261–7
10. Bouillon TW, Bruhn J, Radulescu L, et al. Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. Anesthesiology 2004; 100: 1353–72
11. Luginbühl M, Schumacher PM, Vuilleumier P, et al. Noxious stimulation response index: a novel anesthetic state index based on hypnotic–opioid interaction. Anesthesiology 2010; 112: 872–80
12. Schumacher PM, Dossche J, Mortier EP, Luginbuehl M, Bouillon TW, Struys MM. Response surface modeling of the interaction between propofol and sevoflurane. Anesthesiology 2009; 111: 790–804
13. Heyse BEK, Proost JH, Schumacher PM, et al. Sevoflurane remifentanil interaction : comparison of different response surface models. Anesthesiology 2012; 116: 311–23
14. Rampil IJ. A primer for EEG signal processing in anesthesia. Anesthesiology 1998; 89: 980–1002
15. Viertiö-Oja H, Maja V, Särkelä M, et al. Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. Acta Anaesthesiol Scand 2004; 48: 154–61
16. Mathews DM, Clark L, Johansen J, Matute E, Seshagiri CV. Increases in electroencephalogram and electromyogram variability are associated with an

increased incidence of intraoperative somatic response. Anesth Analg 2012; 114: 759–70
17. Heyse BEK, Proost JH, Hannivoort LN, et al. A response surface model approach for continuous measures of hypnotic and analgesic effect during sevoflurane–remifentanil interaction : quantifying the pharmacodynamic shift evoked by stimulation. Anesthesiology 2014; 120: 1390–9
18. Short TG, Ho TY, Minto CF, Schnider TW, Shafer SL. Efficient trial design for eliciting a pharmacokinetic–pharmacodynamics model-based response surface describing the interaction between two intravenous anesthetic drugs. Anesthesiology 2002; 96: 400–8
19. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology 1998; 88: 1170–82
20. Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. Anesthesiology 1999; 90: 1502–16
21. Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 1997; 86: 10–23
22. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. Anesthesiology 1997; 86: 24–33
23. Bouillon TW. Hypnotic and opioid anesthetic drug interactions on the CNS, focus on response surface modelling. In: Schuttler J, Schwilden H, eds. Modern Anesthetics, Handbook of Experimental Pharmacology 182. Berlin, Heidelberg: Springer-Verlag, 2008; 471–8
24. Minto CF, Schnider TW, Short TG, Gregg KM, Gentilini A, Shafer SL. Response surface model for anesthetic drug interactions. Anesthesiology 2000; 92: 1603–16
25. Smith WD, Dutton RC, Smith NT. Measuring the performance of anesthetic depth indicators. Anesthesiology 1996; 84: 38–51
26. Smith WD, Dutton RC, Smith NT. Ameasure of association for assessing prediction accuracy that is a generalization of nonparametric ROC area. Stat Med 1996; 15: 1199–215
27. Sebel LE, Richardson JE, Singh SP, Bell SV, Jenkins A. Additive effects of sevoflurane and propofol on γ-aminobutyric acid receptor function. Anesthesiology 2006; 104: 1176–83
28. Harris RS, Lazar O, Johansen JW, Sebel PS. Interaction of propofol and sevoflurane on loss of consciousness and movement to skin incision during general anesthesia. Anesthesiology 2006; 104: 1170–5
29. Manyam SC, Gupta DK, Johnson KB, et al. When is a bispectral index of 60 too low? Rational processed electroencephalographic targets are dependent on the sedative–opioid ratio. Anesthesiology 2007; 106: 472–83

Chapter 8 Discussion

In daily practice, the primary objective of anesthesiologists is to balance the administration of anesthetic drugs during general anesthesia in such a manner as to achieve crucial objectives like hypnosis, analgesia, immobility and control over the autonomous nervous system. Currently, anesthesiologists have to rely on clinical experience, a partial knowledge of interactions, and intuition to guide the patient in a safe drug-dosing practice to achieve these objectives. Synergistically acting agents are meticulously combined, trying to avoid side effects and to minimize the administered dose without the use of tools that provide practical recommendations how to combine our anesthetic drugs. Improving the knowledge of the interactions involved by means of measuring the desired objectives and linking these measurements to pharmacokinetic and dynamic modeling of multiple drugs could optimize the process to reach the appointed goals in a more predictable way.

During most anesthetic procedures, multiple drug combinations are used. However, analgesics and hypnotics are combined routinely to realize some fundamental endpoints of anesthesia. Regarding hypnotic-opioid interactions, others described interactions between propofol-fentanyl,[12–14] propofol-midazolam-alfentanil,[11,15] propofol-alfentanil-nitrous oxide,[16] propofol-alfentanil[17–19], propofol-opioids,[20,21] propofol-remifentanil,[22–27] desflurane-fentanyl,[28] desflurane-remifentanil,[29] sevoflurane-fentanyl,[30–32] sevoflurane-remifentanil,[33,34] isoflurane-fentanyl[35–37], isoflurane-alfentanyl,[36] isoflurane-sufentanyl,[38] isoflurane-remifentanil,[39]... previously. Some of them hereby also described various strategies for modeling pharmacodynamic interactions using response surface techniques.

As during anesthesia, volatile anesthetics such as sevoflurane (with or without nitrous oxide) are frequently combined with opioids such as remifentanil, we aimed at describing the relationship between those two (or three) drugs. The published knowledge on these drug interactions can be considered incomplete. Previously, Manyam and colleagues developed a response surface for various pharmacodynamic responses using a Logit model approach and found synergy between sevoflurane and remifentanil for all responses.[40] Unfortunately, as this study suffered from non-steady-state conditions at the moment of the observations. These researchers improved their data using calculated effect-site sevoflurane concentrations and a specific surface model instead of a Logit approach.[41] Accounting for the lag time between sevoflurane effect-site concentration and end-tidal concentration improved the predictions of responsiveness during anesthesia but had no effect on the accuracy of prediction of a response to a noxious stimulus in recovery. They concluded that models may be useful in predicting events of clinical interest, but large-scale evaluations with numerous patients are needed to better characterize the interaction. Furthermore, the interaction between sevoflurane and remifentanil on continuous measures, like BIS, SE, RE, CVI, and SPI, has not yet been described.

As a result, we aimed in this thesis to enlarge the knowledge on the interaction between sevoflurane, nitrous oxide and opioids using both dichotomous and continuous measures of drug effect and with and without noxious stimulation. Secondly, we hypothesized that the applied surface model approach might influence the resulting interaction and has to be

explored during the model development. Thirdly, we aimed at using surface interaction models to develop a new predictive anesthetic state index. Last but not least we hoped to develop a triple interaction model, describing the interaction between sevoflurane, propofol and remifentanil.

We first studied the pharmacodynamic interaction between sevoflurane and remifentanil using dichotomous measures of drug effect. A number of response surface models have been developed to describe the relationship between the concentrations of two drugs and their combined clinical effects. In Chapter 3 we examined the interaction of remifentanil and sevoflurane on the probability of tolerance to shake and shout, tetanic stimulation, laryngeal mask airway insertion, and laryngoscopy in patients. Additionally, we investigated the performance of five different response surface models to predict the likelihood of response.

As expected, the pharmacodynamic interaction between sevoflurane and remifentanil was strongly synergistic for both the hypnotic and the analgesic components of anesthesia, as illustrated by tolerance to shake and shout, tetanic stimulation, LMA insertion, and laryngoscopy. The main finding of this study is the validity of the modified hierarchical model (or Fixed $C50_O$ Hierarchical model), assuming an identical C_{e50} of the opioid for different stimuli. The slope parameter of the hypnotic as well as the opioid are also identical for different stimuli. Consequently, these three assumptions will result in different C_{e50}'s of the hypnotic for different stimuli.

The Hierarchical models are semi-mechanistic models that have been developed to detect synergism for the combination of an analgesic and a hypnotic drug using a simple mathematical reconstruction of neuropathic pathways, as opposed to other more generalistic models. These Hierarchical models, as well as the Reduced Greco model, assume no relevant opioid effect if given alone, and therefore these models fitted better to the data than the Greco and Minto models. The differences between the Reduced Greco model, Scaled $C50_O$ Hierarchical model, and Fixed $C50_O$ Hierarchical model were rather small, and each of these three models fitted reasonably well to the data. However, the OFV and Akaike Information Criterion unequivocally showed that the Fixed $C50_O$ Hierarchical model resulted in the best fit to our data. Furthermore, we illustrated the importance of exploring the various surface modeling approaches when studying pharmacodynamic drug interactions as model selection might influence the results.

In Chapter 4, we studied the interaction between sevoflurane and remifentanil on bispectral index (BIS), state entropy (SE), response entropy (RE), Composite Variability Index (CVI), and Surgical Pleth Index (SPI), by using a response surface methodology. Overall, we hypothesized that the nature of the various interactions should be synergistic for the continuous measures as this is in concordance with the interaction on dichotomous clinical endpoints as we described. The secondary goal of the study was to investigate whether noxious stimulation significantly affects the model structure or the model parameters. The influence of stimulation on this interaction was examined by comparing the data before OAA/S score (unstimulated state) with data after laryngoscopy (stimulated state).

Although opioids have a rather weak effect on the electroencephalogram, we found an additive effect of remifentanil on reduction of BIS, SE, and RE by sevoflurane. The effect on CVI was synergistic. The SPI was not affected by sevoflurane or remifentanil. The Greco model provided the best fit of the data for BIS and Entropy (SE and RE), whereas the reduced Greco model best described CVI. The findings on (unstimulated) BIS, SE, and RE are in agreement with that reported in previous literature. Nieuwenhuijs et al.[114] presented an interaction model during sevoflurane–alfentanil anesthesia, suggesting additivity for BIS. Bouillon et al.[26] found additivity for BIS during propofol–remifentanil anesthesia. Schumacher et al.[76] found an additive interaction on BIS for combined propofol and sevoflurane.

Conversely, the interaction of sevoflurane and remifentanil on clinical endpoints of effect (cfr. supra) was not additive but synergistic. Also, $C50_{remi}$ was 10-fold higher for BIS, SE, and RE compared with $C50_{remi}$ for dichotomous endpoints. Apparently, the opioid effect on the electroencephalogram is weak, despite a strong effect on patient responsiveness. This may explain why electroencephalographic variables are poor predictors of responsiveness to noxious stimuli.

Interestingly, the structural interaction model was not affected by noxious stimulation, but noxious stimulation did increase the $C50_{sevo}$ for BIS, SE, and RE by 20%, whereas the $C50_{remi}$ did not change. In contrast, for CVI all model parameters changed except $C50_{sevo}$.

For all poststimulation response surface models, the structural model with the lowest objective function was identical to the prestimulation model. For BIS, SE, and RE, the model parameters hardly changed, except for $C50_{SEVO}$ (consistently 0.3 vol% higher after laryngoscopy). This pharmacodynamic shift is consistent for BIS and entropy and it is only a fragment smaller than the difference between $C50_{SEVO}$ for tolerance of shake and shout and laryngoscopy, found in the previous article (0.53 vol%). For CVI, the changes in the poststimulation model are complex. $C50_{REMI}$ decreased to 3.09 ng/ml. Gamma and the baseline effect (E_0) increased. The increased steepness of the dose–response curve and the larger difference between baseline and maximal effect suggest an improved descriptive capacity for CVI in stimulated compared with unstimulated conditions. However, the residual SD and the standard errors of the parameters indicate a larger variability in the dose–response relationship compared with the unstimulated condition. For SPI, we were not able to extract plausible parameter estimates from our data, neither from prestimulation nor from poststimulation observations. The inability to detect any dose–response relationship in steady-state conditions, both with or without noxious stimulation, lowers the expectations for SPI as a guide for titrating sevoflurane and remifentanil anesthesia.

After generating the data from the sevoflurane - remifentanil interaction studies, we initiated a study with similar study design and with the objective to enlarge our knowledge regarding the interaction between sevoflurane, remifentanil and nitrous oxide. To achieve our goal we had to administer combinations of nitrous oxide, sevoflurane and remifentanil

for a longer period of time, aiming for steady state concentrations. Especially in the low dose range of the applied products, this yielded to “semi-conscious”, uncooperative patients with sometimes episodes of aggressive behavior. Sometimes they didn’t allow mask ventilation but simultaneously suffered from hypoventilation resulting in hypoxemia. After examining a few cases we aborted the study to avoid adverse events. Being persistent, we incorporated a period of reflection, and subsequently started a search for available historical data with the intention to reanalyze existing data to expand the interaction model that way. The results from our quest can be found in Chapter 5.

Katoh described the reduction of minimal alveolar concentration (MAC) and MAC to block autonomic reflexes to nociceptive stimuli (MAC-BAR) of sevoflurane by fentanyl. They also tested the MAC reduction evoked by nitrous oxide.[31] Because the article of Katoh does not provide the model parameters of the logistic regression analysis, it does not allow a flexible calculation of the probability of response at any drug level. Currently, nonlinear mixed effect modeling is considered to be the definitive standard for modeling three-dimensional response surfaces on interaction datasets.[115] A response surface model that describes the effects of nitrous oxide has not yet been described. We hypothesized that the hierarchical model could be expanded further to allow flexible inclusion of the effects of 66 vol.% N_2O in the interaction between opioids and sevoflurane. Because, in the original dataset, N_2O was applied at a single concentration level only, the data did not allow a full response surface modelling of the three drugs. Therefore, the influence of N_2O was treated as a covariate in the hierarchical model of sevoflurane and opioids.

The influence of 66 vol.% N_2O was best described by a combination of an additive effect corresponding to 0.27 ng/ ml fentanyl and an additive effect corresponding to 0.54 vol.% sevoflurane. With a simple extension, the effect of 66 vol.% N_2O can be incorporated in the hierarchical interaction model of sevoflurane and opioids and allows to model the triple interaction in a response surface. Although the opioid used was fentanyl, the model may be applicable for other opioids also, provided that equipotent doses of the other opioids are given.[20]

As already mentioned, the third aim of this thesis was to use surface interaction models to develop a predictive anesthetic state index. This resulted in the Noxious Stimulation Response Index. The NSRI is proposed to *predict*, based on the effect-site concentrations of an opioid and an anesthetic, the likelihood of response to a noxious stimulus during anesthesia.[116] Generally speaking, the NSRI is an index calculated from the weighted propofol and remifentanil concentrations, corrected for interaction and normalized to a range between 0 and 100, where 100 reflects 100% probability and values approaching 0 reflect close to 0% probability of responding to laryngoscopy. By definition, an NSRI of 50 means that the effect-site propofol and remifentanil concentrations are sufficient that the patient will tolerate laryngoscopy with a probability of 50%.

The strength of the NSRI lies in the fact that is has a predictive performance for noxious stimulation response in the clinically desirable range and its independence of physiologic signals as well as test stimuli. As with other anesthetic depth indicators or drug

concentrations, the predictive performance expressed as P_K does not imply that a given NSRI value correctly predicts the response in an individual patient, but it means that the probability of response is highly correlated with the NSRI.

We conclude that the NSRI is a promising anesthetic state index predicting response to noxious stimulation responsiveness and, to a lesser extent, the hypnotic state. Most probably, it will improve the dosing of hypnotics/volatiles and opioids. However, prospective validation studies in the clinical setting are needed to judge the use of the NSRI in everyday anesthetic practice.

Our group studied the interaction between sevoflurane and propofol[76], sevoflurane and remifentanil[117,118] extensively. Furthermore, data describing the interaction between propofol and remifentanil, from a similarly designed study, are available.[26] In several countries, the combination of sevoflurane, propofol and opioids is used on a daily basis, making the rationale for a triple interaction study self-evident. So we performed a response surface analysis of the pooled raw data from three published studies on interactions between sevoflurane, propofol and remifentanil. A triple interaction model was developed to describe the anaesthetic potency of combinations of sevoflurane, propofol and remifentanil in terms of a generalized P_{TOL} and NSRI. With the new interaction model the potency of any combination of sevoflurane propofol and remifentanil can be expressed as P_{TOL} or as NSRI.

The model that fits the data best is an extension of the hierarchical hypnotic-opioid interaction model published previously.[26,97,117,119] We found that the interaction between sevoflurane and propofol is additive when their concentrations are normalized to their respective effect-site concentration inducing TOL in 50% of the population.

In contrast, remifentanil has a strong but equally synergistic interaction with both hypnotics. According to the hierarchical interaction model,[97] the $Ce50_{REMI}$ is the remifentanil effect-site concentration reducing the Ce50 of sevoflurane and/or propofol by 50%. In contrast to previous publications[26,117] the pooled analysis did not support different Ce50s for remifentanil or different slope factors for propofol and sevoflurane. As a consequence, the response surface defined by the final model has a similar shape for propofol and sevoflurane. This is not surprising, because the SE values of both parameters were ~20% in the sevoflurane-remifentanil study[120] and ~40% in the propofol-remifentanil study[26] for Ce50, and the 95% CIs for the slopes were overlapping in all three studies. As such, our common $Ce50_{REMI}$ and slope are within the SE of the values published previously (cf Chapter 7, Table 1).
In a general sense, P_{TOL} can be considered an extension of the clinically applied MAC concept.[88] For the first time, the potency of inhaled and i.v. hypnotic drugs can be compared uniformly. Using our triple interaction model, the potency of any combination of sevoflurane, propofol, and remifentanil can be expressed as P_{TOL} or its derivative, NSRI. For example, a Ce_{REMI} of 3 ng ml^{-1} combined with either a Ce_{PROP} of 3 µg ml^{-1} or a Ce_{SEVO} of 1.03 vol% will yield a P_{TOL} of 0.7 or an NSRI of 31 and are thus considered equipotent. In a simulated anaesthesia induction with a bolus of propofol and a remifentanil target-

controlled infusion, the time when sevoflurane needs to be administered depends on the size of the propofol bolus and the remifentanil concentration. The interaction model allows compensation for the decay of the propofol effect-site concentration by increasing the effect-site concentration of sevoflurane, in order to maintain a predefined total potency of the drugs in terms of P_{TOL}.

In our study NSRI predicted tolerance to laryngoscopy substantially better than single drug effect-site concentrations or electro-encephalographic depth of anaesthesia monitors (BIS, SE, RE, CVI). However, the latter predicted response to non-noxious stimulation (shake and shout) slightly but significantly better than the NSRI. In data obtained from the sevoflurane–propofol and the sevoflurane–remifentanil studies, SE and RE were also available and showed a moderate predictive accuracy, similar to BIS. In the data obtained from the sevoflurane–remifentanil study, CVI was found to be a moderately accurate predictor of TOL. The SPI was not able to predict TOL. Both P_{TOL} and NSRI outperformed the other measures in both sub-analyses (cf Chapter 7, Table 2). The reason why pharmacologic depth of anaesthesia indicators, such as NSRI or P_{TOL} are potentially superior to electro-encephalographic depth of anaesthesia monitors in predicting responsiveness, is the fact that NSRI is affected by each of the drugs (propofol, volatile anaesthetics and opioids). Conversely, BIS, SE and RE mainly reflect changes of propofol and/or volatile anaesthetics and are far less affected by opioids. Additionally, at moderate drug concentrations the effect of propofol or volatile anaesthetics on BIS or other EEG monitors shows a plateau, where an increase in drug-concentration does not change the monitor readings much.[121–123] Therefore, NSRI may be more descriptive for a change in anaesthetic condition compared to EEG derived monitors.

There are certainly limitations to our study. Our triple interaction model is based on pooled data of three independently performed two-drug interaction studies, so no patient was given a combination of all three drugs. As a result, a triple interaction of the three drugs could not be detected, nor excluded. However, a significant and relevant triple interaction does not seem likely, taking into account the additive interaction of sevoflurane and propofol, and the similar synergistic interaction of remifentanil with both hypnotic drugs. This assumption is supported by the large triple interaction study on midazolam, propofol and alfentanil by Minto *et al.*, who found significant synergistic interactions of each pair of these compounds but no triple interaction.[11] A reanalysis of their raw data from 400 patients revealed that the parameter estimates did not change if the 50 patients receiving all three drugs were included or not.

This thesis generates some perspectives for further research. The data and equations presented in this thesis can easily be applied in advisory systems that provide bedside pharmacokinetic-dynamic information based on the demographics of the patient and the administered drug doses. Such devices are currently being commercialized for clinical practice. However, prospective validation is still mandatory to evaluate the population-based reference as a tool for the clinician to target desired levels of responsiveness in an individual case. Optimizing the pharmacokinetic/pharmacodynamic model to the individual

patient with feedback mechanisms shifting the response surface to the optimum for each particular patient is a potential line of approach in the long term future.
Furthermore, these systems use fixed potency ratios between different opioids to extrapolate the interaction surfaces between hypnotics and various opioids. Other hypnotics, like midazolam or diazepam are also routinely used in daily practice. At this moment, the influence of midazolam (or diazepam) on the continuous measurements of hypnotic effects of the interaction between sevoflurane, propofol and opioids remains to be clarified. Additional, prospective, clinical studies are needed to confirm or develop these response surfaces.

Today, several commercially available monitors measure the hypnotic effect in a continuous way. In contrast, measuring the balance between nociception and anti-nociception remains a challenge. By normalizing the nociceptive stimulus (eg. laryngoscopy) and using pharmacological data, the NSRI bypasses the need for measuring this balance and predicts the response to noxious stimulation and, to a lesser extent, the hypnotic state. Most probably, it will improve the dosing of hypnotics/volatiles and opioids. However, prospective validation studies in the clinical setting are needed to judge the use of the NSRI in everyday anesthetic practice.

1 References

1. Franks, N. P. General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. *Nat. Rev. Neurosci.* **9,** 370–386 (2008).
2. Cantor, R. S. Breaking the Meyer-Overton rule: predicted effects of varying stiffness and interfacial activity on the intrinsic potency of anesthetics. *Biophys. J.* **80,** 2284–2297 (2001).
3. Woodbridge, P. D. CHANGING CONCEPTS CONCERNING DEPTH OF ANESTHESIA. *Anesthesiology* **18,** (1957).
4. Glass, P. S. A. Anesthetic Drug Interactions: An Insight into General Anesthesia - Its Mechanism and Dosing Strategies. *Anesthesiology* **88,** (1998).
5. Chernik, D. A. *et al.* Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J. Clin. Psychopharmacol.* **10,** 244–51 (1990).
6. Liu, J., Singh, H. & White, P. F. Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. *Anesth. Analg.* **84,** 185–9 (1997).
7. Vanluchene, a L. G., Struys, M. M. R. F., Heyse, B. E. K. & Mortier, E. P. Spectral entropy measurement of patient responsiveness during propofol and remifentanil. A comparison with the bispectral index. *Br. J. Anaesth.* **93,** 645–54 (2004).
8. Heyse, B. *et al.* Comparison of contemporary EEG derived depth of anesthesia monitors with a 5 step validation process. *Acta Anaesthesiol. Belg.* **60,** 19–33 (2009).
9. Sahinovic, M. M. *et al.* Accuracy of the composite variability index as a measure of the balance between nociception and antinociception during anesthesia. *Anesth. Analg.* **119,** 288–301 (2014).
10. Greco, W. R., Park, H. S. & Rustum, Y. M. Application of a new approach for the quantitation of drug synergism to the combination of cis-diamminedichloroplatinum and 1-beta-D-arabinofuranosylcytosine. *Cancer Res.* **50,** 5318–27 (1990).
11. Minto, C. F. *et al.* Response surface model for anesthetic drug interactions. *Anesthesiology* **92,** 1603–16 (2000).
12. Smith, C. *et al. The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision. Anesthesiology* **81,** (1994).
13. Billard, V., Moulla, F., Bourgain, J. L., Megnigbeto, A. & Stanski, D. R. *Hemodynamic response to induction and intubation. Propofol/fentanyl interaction. Anesthesiology* **81,** (1994).
14. Kazama, T., Ikeda, K. & Morita, K. *The pharmacodynamic interaction between propofol and fentanyl with respect to the suppression of somatic or hemodynamic responses to skin incision, peritoneum incision, and abdominal wall retraction. Anesthesiology* **89,** (1998).
15. Vuyk, J., Hennis, P. J., Burm, A. G., de Voogt, J. W. & Spierdijk, J. *Comparison of*

midazolam and propofol in combination with alfentanil for total intravenous anesthesia. Anesthesia and analgesia **71,** (1990).

16. Vuyk, J. *et al.* Pharmacodynamics of alfentanil as a supplement to propofol or nitrous oxide for lower abdominal surgery in female patients. *Anesthesiology* **78,** 1036–1045; discussion 23A (1993).
17. Vuyk, J. *et al. The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. Anesthesiology* **83,** (1995).
18. Vuyk, J. *et al.* Pharmacodynamic interaction between propofol and alfentanil when given for induction of anesthesia. *Anesthesiology* **84,** 288–299 (1996).
19. Schwilden, H. *et al. Testing and modelling the interaction of alfentanil and propofol on the EEG. European journal of anaesthesiology* **20,** (2003).
20. Vuyk, J., Mertens, M. J., Olofsen, E., Burm, A. G. & Bovill, J. G. Propofol anesthesia and rational opioid selection: determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. *Anesthesiology* **87,** 1549–1562 (1997).
21. Vuyk, J. Pharmacokinetic and pharmacodynamic interactions between opioids and propofol. in *Journal of Clinical Anesthesia* **9,** (1997).
22. Bruhn, J. *et al.* Correlation of approximate entropy, bispectral index, and spectral edge frequency 95 (SEF95) with clinical signs of 'anesthetic depth' during coadministration of propofol and remifentanil. *Anesthesiology* **98,** 621–7 (2003).
23. Röpcke, H., Könen-Bergmann, M., Cuhls, M., Bouillon, T. & Hoeft, A. Propofol and remifentanil pharmacodynamic interaction during orthopedic surgical procedures as measured by effects on bispectral index. *J. Clin. Anesth.* **13,** 198–207 (2001).
24. Vanluchene, A. L. G. *et al.* Spectral Entropy as an Electroencephalographic Measure of Anesthetic Drug Effect. *Anesthesiology* **101,** 34–42 (2004).
25. Bouillon, T. *et al.* Non-steady state analysis of the pharmacokinetic interaction between propofol and remifentanil. *Anesthesiology* **97,** 1350–62 (2002).
26. Bouillon, T. W. *et al.* Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. *Anesthesiology* **100,** 1353–72 (2004).
27. Luginbühl, M. *et al.* Noxious stimulation response index: a novel anesthetic state index based on hypnotic-opioid interaction. *Anesthesiology* **112,** 872–80 (2010).
28. Sebel, P. S. *et al.* Reduction of the MAC of desflurane with fentanyl. *Anesthesiology* **76,** 52–9 (1992).
29. Albertin, A. *et al.* The effect of adding two target-controlled concentrations (1-3 ng mL -1) of remifentanil on MAC BAR of desflurane. *Eur. J. Anaesthesiol.* **23,** 510–516 (2006).
30. Katoh, T. & Ikeda, K. The effects of fentanyl on sevoflurane requirements for loss of consciousness and skin incision. *Anesthesiology* **88,** 18–24 (1998).

31. Katoh, T. *et al.* The effect of fentanyl on sevoflurane requirements for somatic and sympathetic responses to surgical incision. *Anesthesiology* **90,** 398–405 (1999).

32. Katoh, T. *et al.* Fentanyl augments block of sympathetic responses to skin incision during sevoflurane anaesthesia in children. *Br. J. Anaesth.* **84,** 63–6 (2000).

33. Albertin, A., Casati, A., Bergonzi, P., Fano, G. & Torri, G. *Effects of two target-controlled concentrations (1 and 3 ng/ml) of remifentanil on MAC(BAR) of sevoflurane. Anesthesiology* **100,** (2004).

34. Olofsen, E., Sleigh, J. W. & Dahan, A. *The influence of remifentanil on the dynamic relationship between sevoflurane and surrogate anesthetic effect measures derived from the EEG. Anesthesiology* **96,** (2002).

35. McEwan, A. I. *et al.* Isoflurane minimum alveolar concentration reduction by fentanyl. *Anesthesiology* **78,** 864–9 (1993).

36. Westmoreland, C. L., Sebel, P. S. & Gropper, A. *Fentanyl or alfentanil decreases the minimum alveolar anesthetic concentration of isoflurane in surgical patients. Anesthesia and analgesia* **78,** (1994).

37. Syroid, N. D. *et al.* Response surface model predictions of emergence and response to pain in the recovery room: An evaluation of patients emerging from an isoflurane and fentanyl anesthetic. *Anesth. Analg.* **111,** 380–386 (2010).

38. Brunner, M. D. *et al. MAC reduction of isoflurane by sufentanil. British journal of anaesthesia* **72,** (1994).

39. Lang, E. *et al. Reduction of isoflurane minimal alveolar concentration by remifentanil. Anesthesiology* **85,** (1996).

40. Manyam, S. C. *et al.* Opioid-volatile anesthetic synergy: a response surface model with remifentanil and sevoflurane as prototypes. *Anesthesiology* **105,** 267–78 (2006).

41. Johnson, K. B. *et al.* An evaluation of remifentanil-sevoflurane response surface models in patients emerging from anesthesia: model improvement using effect-site sevoflurane concentrations. *Anesth. Analg.* **111,** 387–94 (2010).

42. Brown, E. N., Lydic, R. & Schiff, N. D. General anesthesia, sleep, and coma. *N. Engl. J. Med.* **363,** 2638–50 (2010).

43. Dahaba, A. a. Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. *Anesth. Analg.* **101,** 765–73 (2005).

44. Bruhn, J., Myles, P. S., Sneyd, R. & Struys, M. M. R. F. Depth of anaesthesia monitoring: what's available, what's validated and what's next? *Br. J. Anaesth.* **97,** 85–94 (2006).

45. Bard, J. W. The BIS monitor: a review and technology assessment. *AANA J.* **69,** 477–83 (2001).

46. Glass, P. S. *et al.* Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* **86,** 836–47 (1997).

47. Katoh, T., Suzuki, A. & Ikeda, K. Electroencephalographic derivatives as a tool for predicting the depth of sedation and anesthesia induced by sevoflurane. *Anesthesiology* **88,** 642–50 (1998).

48. Struys, M. M. R. F. *et al.* Ability of the bispectral index, autoregressive modelling with exogenous input-derived auditory evoked potentials, and predicted propofol concentrations to measure patient responsiveness during anesthesia with propofol and remifentanil. *Anesthesiology* **99,** 802–12 (2003).

49. Schmidt, G. N. *et al.* Comparative evaluation of the Datex-Ohmeda S/5 Entropy Module and the Bispectral Index monitor during propofol-remifentanil anesthesia. *Anesthesiology* **101,** 1283–90 (2004).

50. Bruhn, J., Röpcke, H. & Hoeft, A. Approximate entropy as an electroencephalographic measure of anesthetic drug effect during desflurane anesthesia. *Anesthesiology* **92,** 715–26 (2000).

51. Bruhn, J., Lehmann, L. E., Röpcke, H., Bouillon, T. W. & Hoeft, A. Shannon Entropy Applied to the Measurement of the Electroencephalographic Effects of Desflurane. *Anesthesiology* **95,** 30–35 (2001).

52. Viertiö-Oja, H. *et al.* Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. *Acta Anaesthesiol. Scand.* **48,** 154–61 (2004).

53. Hans, P., Giwer, J., Brichant, J. F., Dewandre, P.-Y. & Bonhomme, V. Effect of an intubation dose of rocuronium on Spectral Entropy and Bispectral Index responses to laryngoscopy during propofol anaesthesia. *Br. J. Anaesth.* **97,** 842–7 (2006).

54. Vereecke, H. E. M., Vanluchene, A. L., Mortier, E. P., Everaert, K. & Struys, M. M. R. F. The effects of ketamine and rocuronium on the A-Line auditory evoked potential index, Bispectral Index, and spectral entropy monitor during steady state propofol and remifentanil anesthesia. *Anesthesiology* **105,** 1122–34 (2006).

55. Aho, A. J., Lyytikäinen, L.-P., Yli-Hankala, A., Kamata, K. & Jäntti, V. Explaining Entropy responses after a noxious stimulus, with or without neuromuscular blocking agents, by means of the raw electroencephalographic and electromyographic characteristics. *Br. J. Anaesth.* **106,** 69–76 (2011).

56. Struys, M. M. R. F. *et al.* Performance of the ARX-derived auditory evoked potential index as an indicator of anesthetic depth: a comparison with bispectral index and hemodynamic measures during propofol administration. *Anesthesiology* **96,** 803–16 (2002).

57. Guignard, B., Menigaux, C., Dupont, X., Fletcher, D. & Chauvin, M. *The effect of remifentanil on the bispectral index change and hemodynamic responses after orotracheal intubation. Anesthesia and analgesia* **90,** (2000).

58. Huiku, M. *et al.* Assessment of surgical stress during general anaesthesia. *Br. J. Anaesth.* **98,** 447–55 (2007).

59. Chen, X. *et al.* Comparison of surgical stress index-guided analgesia with standard clinical practice during routine general anesthesia: a pilot study. *Anesthesiology* **112,** 1175–83 (2010).

60. Gonzalez, R. & Woods, R. *Digital image processing*. (2002).

61. Gruenewald, M. *et al.* Influence of different remifentanil concentrations on the performance of the surgical stress index to detect a standardized painful stimulus during sevoflurane anaesthesia. *Br. J. Anaesth.* **103,** 586–93 (2009).

62. Wennervirta, J. *et al.* Surgical stress index as a measure of nociception/antinociception balance during general anesthesia. *Acta Anaesthesiol. Scand.* **52,** 1038–45 (2008).

63. Chen, X. *et al.* Correlation of surgical pleth index with stress hormones during propofol-remifentanil anaesthesia. *ScientificWorldJournal.* **2012,** 879158 (2012).

64. Struys, M. M. R. F. *et al.* Changes in a surgical stress index in response to standardized pain stimuli during propofol-remifentanil infusion. *Br. J. Anaesth.* **99,** 359–67 (2007).

65. Ahonen, J., Jokela, R., Uutela, K. & Huiku, M. Surgical stress index reflects surgical stress in gynaecological laparoscopic day-case surgery. *Br. J. Anaesth.* **98,** 456–61 (2007).

66. Höcker, J. *et al.* Surgical stress index in response to pacemaker stimulation or atropine. *Br. J. Anaesth.* **105,** 150–4 (2010).

67. Bonhomme, V. *et al.* Comparison of the surgical Pleth Index™ with haemodynamic variables to assess nociception-anti-nociception balance during general anaesthesia. *Br. J. Anaesth.* **106,** 101–11 (2011).

68. Hans, P., Verscheure, S., Uutela, K., Hans, G. & Bonhomme, V. Effect of a fluid challenge on the Surgical Pleth Index during stable propofol-remifentanil anaesthesia. *Acta Anaesthesiol. Scand.* **56,** 787–96 (2012).

69. Ilies, C. *et al.* The effect of posture and anaesthetic technique on the surgical pleth index. *Anaesthesia* **67,** 508–13 (2012).

70. Röpcke, H. *et al.* Surgical stimulation shifts EEG concentration-response relationship of desflurane. *Anesthesiology* **94,** 390–9; discussion 5A (2001).

71. Menigaux, C. *et al.* Esmolol prevents movement and attenuates the BIS response to orotracheal intubation. *Br. J. Anaesth.* **89,** 857–62 (2002).

72. Mathews, D. M., Clark, L., Johansen, J., Matute, E. & Seshagiri, C. V. Increases in electroencephalogram and electromyogram variability are associated with an increased incidence of intraoperative somatic response. *Anesth. Analg.* **114,** 759–70 (2012).

73. Jensen, E. W., Litvan, H., Struys, M. & Martinez Vazquez, P. Pitfalls and challenges when assessing the depth of hypnosis during general anaesthesia by clinical signs and electronic indices. *Acta Anaesthesiol. Scand.* **48,** 1260–7 (2004).

74. Litvan, H. *et al.* Comparison of auditory evoked potentials and the A-line ARX Index for monitoring the hypnotic level during sevoflurane and propofol induction. *Acta Anaesthesiol. Scand.* **46,** 245–51 (2002).

75. Struys, M. *et al.* Clinical usefulness of the bispectral index for titrating propofol target effect-site concentration. *Anaesthesia* **53,** 4–12 (1998).

76. Schumacher, P. M. *et al.* Response Surface Modeling of the Interaction between Propofol and Sevoflurane. *Anesthesiology* **111,** (2009).

77. Absalom, A. R. & Struys, M. M. R. F. *Overview of Target Controlled Infusions and Total Intravenous Anesthesia*. (Academia Press, 2007).

78. Minto, C. F. *et al.* Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* **86,** 10–23 (1997).

79. Schnider, T. W. *et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology* **88,** (1998).

80. Gepts, E. *et al.* Linearity of pharmacokinetics and model estimation of sufentanil. *Anesthesiology* **83,** 1194–1204 (1995).

81. Marsh, B., White, M., Morton, N. & Kenny, G. N. Pharmacokinetic model driven infusion of propofol in children. *Br. J. Anaesth.* **67,** 41–48 (1991).

82. Evers, A. S. & Maze, M. *Anesthetic Pharmacology Physiologic Principles and Clinical Practice*. (Churchill Livingstone, 2004).

83. Hughes, M. A., Glass, P. S. & Jacobs, J. R. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology* **76,** 334–41 (1992).

84. Hull, C. J., Van Beem, H. B., McLeod, K., Sibbald, A. & Watson, M. J. A pharmacodynamic model for pancuronium. *Br. J. Anaesth.* **50,** 1113–23 (1978).

85. Sheiner, L. B., Stanski, D. R., Vozeh, S., Miller, R. D. & Ham, J. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. *Clin. Pharmacol. Ther.* **25,** 358–71 (1979).

86. Wakeling, H. G., Zimmerman, J. B., Howell, S. & Glass, P. S. Targeting effect compartment or central compartment concentration of propofol: what predicts loss of consciousness? *Anesthesiology* **90,** 92–7 (1999).

87. Goutelle, S. *et al.* The Hill equation: a review of its capabilities in pharmacological modelling. *Fundam. Clin. Pharmacol.* **22,** 633–48 (2008).

88. Eger, E. I., Saidman, L. J. & Brandstater, B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. *Anesthesiology* **26,** 756–63 (1965).

89. Greco, W. R., Bravo, G. & Parsons, J. C. The search for synergy: a critical review from a response surface perspective. *Pharmacol. Rev.* **47,** 331–85 (1995).

90. Vuyk, J., Lichtenbelt, B. J., Olofsen, E., van Kleef, J. W. & Dahan, A. Mixed-effects modeling of the influence of midazolam on propofol pharmacokinetics. *Anesth. Analg.* **108,** 1522–30 (2009).

91. Lichtenbelt, B. J. *et al.* Propofol reduces the distribution and clearance of midazolam. *Anesth. Analg.* **110,** 1597–606 (2010).

92. Short, T. G., Ho, T. Y., Minto, C. F., Schnider, T. W. & Shafer, S. L. Efficient Trial Design for Eliciting a Pharmacokinetic– Pharmacodynamic Model–based Response Surface

Describing the Interaction between Two Intravenous Anesthetic Drugs. *Anesthesiology* **96,** 400–408 (2002).

93. Loewe, S. Antagonisms and antagonists. *Pharmacol. Rev.* **9,** 237–42 (1957).

94. Berenbaum, M. Isobolographic, Algebraic, and Search Methods in the Analysis of Multiagent Synergy. *Int. J. Toxicol.* **7,** 927–938 (1988).

95. Fraser, T. R. Lecture on the Antagonism between the Actions of Active Substances. *Br. Med. J.* **2,** 485–7 (1872).

96. Prichard, M. N. & Shipman, C. A three-dimensional model to analyze drug-drug interactions. *Antiviral Res.* **14,** 181–205 (1990).

97. Bouillon, T. W. Hypnotic and opioid anesthetic drug interactions on the CNS, focus on response surface modeling. *Handb. Exp. Pharmacol.* 471–87 (2008). doi:10.1007/978-3-540-74806-9_22

98. Gessner, P. K. Isobolographic analysis of interactions: an update on applications and utility. *Toxicology* **105,** 161–79 (1995).

99. Fraser, T. R. Lecture on the Antagonism between the Actions of Active Substances. *Br. Med. J.* **2,** 457–9 (1872).

100. Lee, S.-I. Drug interaction: focusing on response surface models. *Korean J. Anesthesiol.* **58,** 421–434 (2010).

101. Fitzgerald, J. B., Schoeberl, B., Nielsen, U. B. & Sorger, P. K. Systems biology and combination therapy in the quest for clinical efficacy. *Nat. Chem. Biol.* **2,** 458–466 (2006).

102. Jonker, D. M., Visser, S. A. G., van der Graaf, P. H., Voskuyl, R. A. & Danhof, M. Towards a mechanism-based analysis of pharmacodynamic drug-drug interactions in vivo. *Pharmacol. Ther.* **106,** 1–18 (2005).

103. Alex S. Evers, Maze, M. & Kharasch, E. D. *Anesthetic Pharmacology: Basic Principles and Clinical Practice*. (Cambridge University Press, 2011).

104. Goldoni, M. & Johansson, C. A mathematical approach to study combined effects of toxicants in vitro: Evaluation of the Bliss independence criterion and the Loewe additivity model. *Toxicology in Vitro* **21,** 759–769 (2007).

105. Berenbaum, M. C. Criteria for analyzing interactions between biologically active agents. *Adv. Cancer Res.* **35,** 269–335 (1981).

106. Zhao, W. *et al.* A New Bliss Independence Model to Analyze Drug Combination Data. *J. Biomol. Screen.* **19,** 817–821 (2014).

107. Tallarida, R. J. Revisiting the isobole and related quantitative methods for assessing drug synergism. *J. Pharmacol. Exp. Ther.* **342,** 2–8 (2012).

108. Wong, K. C. Narcotics are not expected to produce unconsciousness and amnesia. *Anesth. Analg.* **62,** 625–6 (1983).

109. Hug, C. C. Does opioid 'anesthesia' exist? *Anesthesiology* **73,** 1–4 (1990).

110. Ausems, M. E., Hug, C. C., Stanski, D. R. & Burm, A. G. Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. *Anesthesiology* **65,** 362–73 (1986).

111. Scott, J. C. & Stanski, D. R. Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamic evaluation. *J. Pharmacol. Exp. Ther.* **240,** 159–166 (1987).

112. Bührer, M., Maitre, P. O., Hung, O. & Stanski, D. R. Electroencephalographic effects of benzodiazepines. I. Choosing an electroencephalographic parameter to measure the effect of midazolam on the central nervous system. *Clin. Pharmacol. Ther.* **48,** 544–554 (1990).

113. Short, T. G., Plummer, J. L. & Chui, P. T. Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil. *Br. J. Anaesth.* **69,** 162–7 (1992).

114. Nieuwenhuijs, D. J. F. *et al.* Response surface modeling of remifentanil-propofol interaction on cardiorespiratory control and bispectral index. *Anesthesiology* **98,** 312–322 (2003).

115. Struys, M. M. R. F., Sahinovic, M., Lichtenbelt, B. J., Vereecke, H. E. M. & Absalom, A. R. Optimizing intravenous drug administration by applying pharmacokinetic/pharmacodynamic concepts. *Br. J. Anaesth.* **107,** 38–47 (2011).

116. Schumacher, P. M. *et al.* Time-Based Online Display of a Noxious Stimulus Response Index Based on Pharmacological Data. **107,** A17 (2007).

117. Heyse, B. *et al.* Sevoflurane remifentanil interaction: comparison of different response surface models. *Anesthesiology* **116,** 311–23 (2012).

118. Heyse, B. *et al.* A response surface model approach for continuous measures of hypnotic and analgesic effect during sevoflurane-remifentanil interaction: quantifying the pharmacodynamic shift evoked by stimulation. *Anesthesiology* **120,** 1390–9 (2014).

119. Luginbuehl, M. *et al.* Noxious Stimulation Response Index. *Anesthesiology* **112,** 872–880 (2010).

120. Heyse, B. *et al.* Sevoflurane Remifentanil Interaction. *Anesthesiology* **116,** 311–323 (2012).

121. Kreuer, S. *et al.* Application of Bispectral Index and Narcotrend index to the measurement of the electroencephalographic effects of isoflurane with and without burst suppression. *Anesthesiology* **101,** 847–54 (2004).

122. Kreuer, S., Bruhn, J., Larsen, R., Bialas, P. & Wilhelm, W. Comparability of Narcotrend index and bispectral index during propofol anaesthesia. *Br. J. Anaesth.* **93,** 235–40 (2004).

123. Kreuer, S. *et al.* Comparative pharmacodynamic modeling using bispectral and narcotrend-index with and without a pharmacodynamic plateau during sevoflurane anesthesia. *Anesth. Analg.* **106,** 1171–81, table of contents (2008).

Chapter 9 Summary - Samenvatting

We aimed in this thesis to enlarge the knowledge on the pharmacodynamic interaction between sevoflurane, nitrous oxide and opioids using both dichotomous and continuous measures of drug effect. Secondly, we hypothesized that the applied response surface model approach might influence the resulting interaction and has to be explored during the model development. Thirdly, we aimed at using a response surface interaction model to develop a new predictive anesthetic state index.

First, we studied the interaction between sevoflurane and remifentanil using tolerance to shake and shout, tolerance to a tetanic stimulus, tolerance to the insertion of a laryngeal mask and tolerance to laryngoscopy as clinical measures. Additionally, we studied the influence of the various surface modeling approaches on the interaction model using these data. We also studied the response surface model approach during sevoflurane-remifentanil interaction using various EEG and autonomic nervous system derived continuous measures with or without noxious stimulus ("the pharmacodynamic shift"). As nitrous oxide is still used to supplement inhaled anesthetics such as sevoflurane, we reanalyzed existing data and we hypothesized that the hierarchical model could be expanded further to allow flexible inclusion of the effects of 66 vol.% N2O in the interaction between opioids and sevoflurane.

In an attempt to use drug interaction models as the input of a predictive anesthetic state index, we developed the NSRI (noxious stimulation response index). The NSRI is proposed to predict, based on the effect-site concentrations of an opioid and a hypnotic, the likelihood of response to a noxious stimulus, being the tolerance to laryngoscopy. More recently, we enlarged and adapted the original NSRI to deal with triple interaction models estimating the potency of any combination of sevoflurane, propofol and remifentanil in terms of the probability to tolerate laryngoscopy.

Het objectief van dit proefschrift was het vergroten van de kennis van farmacodynamische interacties tussen sevoflurane, lachgas en opiaten, dit zowel voor dichotome als voor continue parameters van drugeffect. Daarnaast onderzochten we de hypothese dat de toegepaste techniek om de response surface te bepalen de resultaten van de interactie zou kunnen beïnvloeden en derhalve dient te worden onderzocht tijdens het investigeren van een interactie. Tot slot hebben we getracht om via een interactiemodel, een index te ontwikkelen die invloed van anesthetica op ons brein tracht te voorspellen.

In eerste instantie hebben we de interactie tussen sevoflurane en remifentanil onderzocht voor vier verschillende dichotome parameters : score op de “Observer's Assessment of Alertness Sedation (OAA/S) schaal, tolerantie van een tetanische stimulus, tolerantie voor de plaatsing van een laryngeaal masker en de tolerantie voor laryngoscopie. Daarnaast onderzochten we of het toepassen van verschillende interactiemodellen een invloed had op de resultaten van deze data. We bestudeerden eveneens de invloed van de aan- of afwezigheid van een pijnlijke stimulus op de interactie tussen sevoflurane en remifentanil op meerdere afgeleide parameters. Deze parameters zijn afgeleid van het EEG signaal ofwel worden deze beïnvloed door autonoom zenuwstelsel. Ten einde het hiërarchisch interactiemodel voor sevoflurane - remifentanil ook toepasbaar te maken voor gebruik samen met lachgas, werd een historische dataset opnieuw geanalyseerd.

Om aan het derde objectief van dit proefschrift te voldoen werd de NSRI (Noxious Stimulation Response Index) ontwikkeld. Deze index heeft als doel om, op basis van de effect-site concentaties van een opiaat en een hypnoticum, de kans op een respons bij laryngosopie, of bij uitbreiding een pijnlijke stimulus, te voorspellen. In de laatste publicatie van dit werk hebben we de originele NSRI aangepast zodat deze voor elke combinatie van sevoflurane, propofol en remifentanil de kans op respons bij laryngoscopie kan inschatten.

Appendix 1

Describing $U_{50}(\theta)$ from Minto's model, using a quadratic function :

Suppose that only drug A is present, evoking an effect equal to 50% of maximal effect, then $\theta = 0$ and $U_{50}(0) = U_{50,A}$. Since only drug A is present $U_A = 1$ and $U_B = 0$. Applying this in Equation 14 $U_{50,A}$ must be equal to 1.
Applying this in Equation 16 reveals

Equation 24

$$\boldsymbol{U_{50}(0) = U_{50,A} = \beta_0 = 1}$$

Suppose that only drug B is present, evoking an effect equal to 50% of maximal effect, then $\theta = 1$ and $U_{50}(1) = U_{50,B}$. Since only drug A is present $U_A = 0$ and $U_B = 1$. Applying this in Equation 14 $U_{50,B}$ must be equal to 1.
Applying this in Equation 16 reveals

Equation 25

$$\boldsymbol{U_{50}(1) = U_{50,B} = \beta_0 + \beta_1 + \beta_2 = 1}$$

Combining and simplifying Equation 24 and Equation 25 yields :

Equation 26

$$\boldsymbol{\beta_1 = -\beta_2}$$

Applying the former equations in Equation 16 results in Equation 17 :

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

Appendix 2

Equation 21 can be rewritten in the following from :

Equation 27

$$P_{NR} = \frac{H^{\varphi}}{H^{\varphi} + (H_{50} \times PostOI)^{\varphi}}$$

Equation 28

$$P_{NR} = \frac{\frac{H^{\varphi}}{{H_{50}}^{\varphi}}}{\frac{H^{\varphi}}{{H_{50}}^{\varphi}} + \frac{{H_{50}}^{\varphi} \times PostOI^{\varphi}}{{H_{50}}^{\varphi}}}$$

Equation 29

$$P_{NR} = \frac{{U_H}^{\varphi}}{{U_H}^{\varphi} + Post0I^{\varphi}}$$

Equation 30

$$P_{NR} = \frac{\frac{{U_H}^{\varphi}}{PostOI^{\varphi}}}{\frac{{U_H}^{\varphi}}{PostOI^{\varphi}} + 1}$$

Equation 30 now resembles Equation 7. Combining those two equations U can be easily deducted :

Equation 31

$$U = \frac{U_H}{PostOI}$$

Combining Equation 31 with Equation 20 results in :

Equation 32

$$U = \frac{U_H}{PreOI\left(1 - \frac{O^{\gamma}}{(PreOI \times O_{50})^{\gamma} + O^{\gamma}}\right)}$$

Equation 33

$$U = \frac{U_H}{PreOI\left(1 - \frac{\frac{O^\gamma}{{O_{50}}^\gamma}}{\frac{PreOI^\gamma \times {O_{50}}^\gamma}{{O_{50}}^\gamma} + \frac{O^\gamma}{{O_{50}}^\gamma}}\right)}$$

Equation 34

$$U = \frac{U_H}{PreOI\left(1 - \frac{{U_O}^\gamma}{PreOI^\gamma + {U_O}^\gamma}\right)}$$

Equation 35

$$U = \frac{U_H}{\frac{PreOI}{PreOI^\gamma + {U_O}^\gamma} - \frac{{U_O}^\gamma}{PreOI^\gamma + {U_O}^\gamma}}$$

Equation 36

$$U = \frac{U_H}{\frac{PreOI \times PreOI^\gamma}{PreOI^\gamma + {U_O}^\gamma}}$$

Equation 22

$$U = \frac{U_H}{PreOI}\left(1 + \frac{{U_O}^\gamma}{PreOI^\gamma}\right)$$

List of abbreviations

AAI	A-Line autoregressive index
BIS	Bispectral index
C_e	effectsite concentration
CVI	Composite Variability Index
E_0	baseline effect
E_{max}	maximal effect
EEG	electroencephalogram
MAC	minimal alveolar concentration
MAC-BAR	minimal alveolar contentration to block autonomic reflexes
NONMEM	Non Linear Mixed Effect Modeling
NSRI	Noxious Stimulation Response Index
OAAS	Observers Assessment of Alerteness Sedation scale
OVF	Objective Function Value
P_x	probability of event x
P_K	prediction probability
RE	Response Entropy
SE	State Entropy
SPI	Surgical Pleth Index
TOL	tolerance of laryngoscopy
U_x	normalized concentration of drug x