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Application of population-based PKPD to improve anaesthetic drug titration in the individual van den Berg, Jop

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Application of population-based PKPD to improve anaesthetic drug titration in the individual

- JOHANNES PIETER VAN DEN BERG -

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CHAPTER 1

INTRODUCTION

Over the past decades the knowledge and technical possibilities in anesthetic pharmacology have expanded rapidly. These developments have enabled a better focus on patient specific factors to be incorporated into drug titration. This introduction provides some context to understand this thesis.

Pharmacokinetics

Pharmacokinetics (PK) describes the time course of the plasma concentration of the drug (“what the body does to the drug”). This is primarily determined by the rate of drug absorption, rate of distribution, metabolism and elimination. There is considerable variation across the population in these characteristics due to many factors including genotypic and phenotypic characteristics. In addition, the pharmacokinetics of one drug may be influenced due to interactions with other drugs. These are discussed in [chapter 2](#) where these key elements are further explained. Analyses for PK can be divided into two methods: 1) non-compartmental and 2) compartmental. The non-compartmental method is sometimes considered “conventional pharmacokinetics” and is commonly used in many textbooks and in drug descriptions. It is independent of drug models and tends to provide more consistent results between different analyses and researchers because it depends on standardized population-based mathematics and efficient study designs. These analyses are obligatory for authorization of a new product on the drug market and demanded by regulatory authorities. The second method, compartmental PK, is dependent on a chosen model structure which considers the body as a number of connected compartmental volumes (V’s, depicting the different body tissues and fluids) and rate constants (k’s) as a quantification of clearance (CL) as depicted in [figure 1-1](#). [Formulas 1-1 to 1-3](#) provide a mathematical example. The main benefit of the use of compartmental models is it provides the ability to explore PK variability across the population due to specific and non-specific individual factors called covariates. It can also be used to predict the time course of drug concentration. This can be further used to design optimal dosing schemes or to control drug administration. Models are quantified for their performance and ranked based on a chosen criterion whereafter the “optimal” model is used for further analysis. In these studies, multiple patients receive a bolus or infusion of a drug and the concentration is measured in blood samples acquired at various times. Non-linear mixed-effect modelling is often used to determine the best formulae to describe the observed data. Software packages such as NONMEM (ICON, Dublin, Ireland) are often used to analyze the data ([formula 1-4](#)).

$$Cl_{elimination} = V_1 * K_{10} \quad \text{Formula 1-1}$$

$$Cl_2 = V_2 * K_{21} \quad \text{Formula 1-2}$$

$$Cl_3 = V_3 * K_{31} \quad \text{Formula 1-3}$$

Formula 1-1 to 1-3 - Mathematical description of clearances. To describe the direction of the rate constant, subscript numbers are used (e.g. K_{12} describes the rate constant from volume 1 to volume 2). K’s can be interpreted as the fraction of the volume from which the drug distributes per time unit.

Figure 1-1 - Schematic descriptions of a three compartmental drug model. V = volume, CL = Clearance, K_{ij} = equilibration rate constants into the direction of volume i to j . Note that the PK and PD parts are coupled. The concept of pharmacodynamics and this coupling will be introduced in the paragraph 'PKPD coupling'.

Figure 1-2 - Visualization of a drug plasma concentration C_p using a three compartmental drug model over time (t). The graph can be distinguished into the sum (formula 1-4) of three different exponentials, reflecting three phases: 1) rapid distribution, slow distribution and terminal elimination. Some models are able to predict the time-concentration relationship with reasonable accuracy.⁷

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$$

Formula 1-4 - in which t is the time since bolus administration and C_p is the drug concentration at time t . α , β and γ are the exponents describing the curve shape per phase. It is the sum of PK first-order processes for each phase of the curve.

Covariates are measurable or observable patient or non-patient characteristics, such as gender, age, weight, time of day, and study group which can be inserted into the formula (**formula 1-5**).

The intention of adding covariate relationships to a model is usually to improve the accuracy of the predicted parameters and improve the model's ability to make accurate predictions.

Regression plots (**figure 1-3**) are used to determine the relationship between a model parameter and covariate, e.g. linearity (red line) or exponentiality (blue line). One may add any covariate that might be of interest. However, adding more covariates does not always lead to improvement. It might even harm model accuracy and clinical applicability. A careful selection of covariates is important to ensure that the model best describing the data is developed.

$$Cl_{elimination} = V_1 * K_{10} * Covariate \quad \text{Formula 1-5}$$

Formula 1-5 - An example of the mathematical description of the elimination clearance, incorporating a covariate. The covariate includes a certain mathematical weight that it has been given, based on the relation clearance and the specific covariate have (e.g. exponentially, linear etc.)

Figure 1-3 - Plot of V_1 calculations versus the age of the accompanying individual (example, not real data). The data can be used to assess the nature of the association between V_1 and age. As an illustration of this, two lines have been added to the scatter plot to serve as examples: a linear (red) and an exponential (blue) trend line. The relationship that best predicts the data can be determined by calculated and comparing goodness of fit metrics.

It should be emphasized that these values for volumes, clearances and covariate weights are all mathematical simplifications of an extremely complex physiological reality. The intention of compartmental PK is describe the pharmacology of a drug in relatively simple mathematical terms to obtain a the best possible description of the time course of the plasma drug concentrations.

Pharmacodynamics

Pharmacodynamics is the study of the time-independent relationship between the concentration of the drug at the site of drug effect and the drug effect ('what the drug does to the body'). Drug effects can be either desired or undesired, but need to be clearly defined for pharmacodynamic analyses to be performed. Effects can be either dichotomous (either present or absent, e.g. movement) or continuous (e.g. processed electroencephalographic indices, blood pressure, oxygen saturation, etc.). It is essential that the chosen effect is unambiguous, reproducible, measurable (as it needs to be represented in a mathematical model) and relevant.¹

Figure 1-4 - Plot of a Hill curve (blue line), the C_{50} line (blue dashed line) is drawn at the place where C achieves 50% of the maximum effect (E_{50} dotted line).

Curves of concentration-response relationships for continuous variables are commonly sigmoid-shaped. In this case, at 'low' drug concentrations, very little drug effect is provoked. On the other hand, at 'high' drug concentrations, increasing the concentration leads to smaller and eventually

no increase of effect above the maximum effect possible, the E_{max} . This sigmoid-shaped curve, the E_{max} -curve ([figure 1-4](#)) can be mathematically described by the *Hill equation* ([formula 1-6](#)).

$$Effect = E_0 + \frac{(E_{max} - E_0) * C^\gamma}{C_{50}^\gamma + C^\gamma} \quad \text{Formula 1-6}$$

Formula 1-6 - E_{max} -equation or Hill-equation. E_0 is the baseline, E_{max} is the maximum effect. C is the concentration of the drug and γ describes the slope of the Hill curve and is also called the “Hill coefficient”.

PKPD Coupling

Despite the fact that general pharmacology is commonly focussed on drug plasma concentrations, this is not the site at which the effect is provoked. Most relevant for anaesthesia are drugs acting on receptors in the brain (e.g. GABA, NMDA). Drug effects can be coupled to pharmacokinetic models. However, in vivo measurement of ‘brain’ drug concentrations is not possible without crossing ethical boundaries or compromising on safety. The concentration of this site of action (the ‘effect site’) has therefore to be estimated from the data. This is most commonly done by adding a mathematical volume-less compartment (the ‘effect-site’) which produces a hysteresis between plasma and effect and quantified by a time-constant (K_{e0}) ([figure 1-1](#)). The combination of a pharmacokinetic model with an effect is called a pharmacokinetic-pharmacodynamic (PKPD) model.

As the effect-site compartment is usually assumed to have a negligible volume, only the **rate** of drug transport is mathematically relevant. This enables a mathematical (not anatomical) description of the ‘time lag’ (or *hysteresis* or *biophase*) between an increase or decrease in plasma concentration and the corresponding increase or decrease of the resultant effect. The units of K_{e0} are usually 1/time and thus a higher value results in a faster equilibration of effect, whereas a lower value describes a slower equilibration. The concept of hysteresis and the meaning in clinical anaesthesia is further explained in [chapter 5](#) in which we calculated the monitor delay of two EEG monitors in relation to the estimated effect-site concentration in clinical practice.

Applying PKPD concepts to clinical drug titration

The knowledge regarding the time course of a plasma concentration can be applied to drug administration techniques in order to increase the accuracy of drug titration. An example of such an application is a *target-controlled infusion (TCI)* system. As mentioned earlier, a three compartmental model can be used to describe pharmacology mathematically. The sum of clearances and volumes and the amount of drug that is administered (i.e. the differential equations) leads to a prediction of the drug concentration in the plasma or at the effect-site. The other way around, if one knows how much drug has been administered and what the desired effect-site or plasma concentration is, one can calculate how much of the drug is required to maintain this concentration (i.e. to compensate for the elimination). In anaesthesia, different models have been developed for e.g. propofol (Marsh, Schnider, Eleveld)²⁻⁴, remifentanyl (Minto)⁵,

sufentanil (Gepts)^{5,6} and dexmedetomidine (Hannivoort)⁷ which enables us to perform these calculations. So far, the Marsh, Schnider, Gepts and Minto models are clinically available. Due to its complexity, performing these calculations requires computer technology.

In target-controlled infusion (TCI) systems, PKPD models are incorporated in micro-processor equipped infusion pumps (TCI-pumps). These pumps have the ability to continuously perform the necessarily complex mathematics to perform TCI. This allows clinicians to leave an era of simplified dosing regimens restricted to bolus doses and fixed infusion rates to being able to calculate the precise amount of drug required to maintain a certain plasma concentration. This is less likely lead to either over- or underdosing compared to weight-based dosing schemes, as they do not easily result in steady state therapeutic drug concentration. Incorporating the drugs' pharmacokinetic and –dynamic characteristics and patients characteristics in the calculation of infusion rates leads to more stable drug concentrations.

In daily clinical practice, after having entered the patient characteristics into the pump's micro-processor, the anaesthesiologist sets and confirms a desired target drug (effect- or plasma) concentration and initial infusion rate. For induction of anaesthesia, the clinician presses the 'start'-button and the pump administers a drug bolus that is sufficient for the desired plasma or effect-site concentration to be reached within the shortest possible time. This is followed by continuous a time-varying infusion to maintain this concentration. TCI pumps are commonly used in daily anaesthetic practice.

Bayesian statistics and adaptation: individualizing anaesthetic drug models

Bayesian statistics provide the opportunity to link prior information (e.g. the population model being used) to new information (e.g. measurements of drug concentration in the patient in whom the model is being used). This field of statistics differs from the more classical frequentist statistics in the way that the first type is concerned with the uncertainty of information, whereas the latter is, more rigidly, based on the idea that probability represents the frequency at which a certain event will happen.⁸ The key element of this statistical form is noted in [formula 1-7](#).

$$P(\text{belief}|\text{data}) = \frac{P(\text{data}|\text{belief})}{P(\text{data})}$$

Formula 1-7 - The key concepts of the Bayesian principle. Note that $P(\text{belief}|\text{data})$ describes the posterior probability, $P(\text{data}|\text{belief})$ describes the likelihood and $P(\text{belief})$ describes the prior probability.

Analysis of individual data generates a set of individual clearances and volumes, and can then be analysed together to achieve an understanding of the distribution within the population of each variable. This results in a normal population distribution curve for each model parameter, describing the model parameter through the population. When the frequency is converted to a density ratio, it is referred to as a *probability density function (PDF)* for that specific parameter.

The probability is commonly described by the Greek letter ‘phi’ (ϕ). For normal distribution curves, generally three important characteristics apply: it has a mean value (μ , [formula 1-8](#)), a standard deviation (σ , [formula 1-9](#)) and the area under the curve (AUC) adds up to 1.

$$\mu = \frac{(X_1 + \dots + X_n)}{n} \quad \text{Formula 1-8}$$

$$\sigma = \sqrt{\frac{1}{n} \times \sum_{i=1}^n (X_i - \mu)^2} \quad \text{Formula 1-9}$$

$$L(\mu, \sigma|x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{\frac{-(x-\mu)^2}{2\sigma^2}} \quad \text{Formula 1-10}$$

Formula 1-8 to 1-10 - Formulas for mean (μ) and standard deviation (σ) and likelihood (L) for μ and σ , given datapoints x_n .

It is unlikely that the real parameter estimate is *exactly* μ . The *probability* that our true value actually is equal or lower can be calculated as the integral (i.e. the area under the curve, *AUC*) from x to μ . The other way around, the integral from μ to 1 calculates the probability that the true value is equal or higher than μ . This is based on the fact that the total AUC for a PDF equals 1. Each individual relates to a certain degree to the population average. The likelihood that the population curve is actually the most optimal curve for the individual (given the data for this individual can be calculated using the *likelihood function* as is shown in [formula 1-10](#). This describes the mathematical likelihood for the data (x) given a population μ and σ . The point with the highest likelihood is the most likely value for the distribution curve given the data. To calculate the value with the highest likelihood, one approach is to use the mathematical derivative of the *likelihood function* (see [appendix chapter 4](#)). This calculation can be performed for each model parameter resulting in a more optimal value for the individual, while considering the population model. Using this method, one ‘shifts’ the distribution curve from the population value towards the individual observations. The intention is to improve the model’s population-based predictive ability in the particular individual. This concept is applied and further explained in [chapter 4](#), its [appendix](#) and [chapter 5](#).

Evaluation of PKPD-model performance

After the development of a PK or PD model the model’s performance in clinical practice must be evaluated. For this purpose, the criteria as described by Varvel and co-workers is commonly used. These are applied in [chapter 4](#). The basis of these criteria is the *prediction error*. Bias and precision are defined by calculating the median prediction error (MDPE) and median absolute performance error (MDAPE) as described by Varvel et al., respectively.⁹ As one may notice, all results of the Varvel criteria are based on the prediction error (PE). For PK precision (MDAPE) of 20-30% with a precision (MDPE) of 10-20% is generally denoted as being “acceptable”^{9,10}, although in reality there is no rigid threshold that defines clinically acceptable or useful performance.

$$PE(\%) = \frac{(C_m - C_p)}{C_p} \times 100$$

Formula 1-11

$$MDAPE = \text{Median} \{ |PE_{ij}|, j=1, \dots, N_j \}$$

Formula 1-12

$$MDPE = \text{Median} \{ PE_{ij}, j=1, \dots, N_j \}$$

Formula 1-13

$$\text{Divergence} = 60 \times \sum_{j=1}^{N_j} |PE_{ij}| \times t_{ij} -$$

Formula 1-14

$$\text{Wobble} = \text{median absolute deviation of } \{ PE_{ij}, j=1, \dots, N_j \} \text{ from MDPE}$$

Formula 1-15

Formula's 1-11 to 1-15 - formulas describing the Varvel criteria of model performance. **PE**: prediction error. C_m = measured concentration, C_p = predicted concentration. **MDAPE**: Median Absolute Prediction Error. $|PE_{ij}|$ = Absolute prediction error of the j th measurement in the i th patient. **MDPE**: Median Prediction error. In this formula the median value of the absolute PE at any time (j) until the total amount of measurements (N_j). **MDPE**: Median Prediction error. **Divergence**: linear slope (divergence per hour). N_j = number of measurements, T_j = time in minutes. **Wobble**: quantification of the ability to reach and maintain a stable plasma concentration.

The concepts of *bias* and *precision* can be illustrated by a dart board analogy. (**figure 1-5**) The intention is to aim for the bulls eye (i.e. the reference for the true value). A useless model is imprecise and unbiased (i.e. all arrows are scattered over the dart board without any relationship or coherence). *Divergence* provides information about the progression of size and scope of the deviation from the measured concentration in relation to the time (unit: divergence per hour). A negative value for divergence implies convergence, whereas a positive value implies divergence, i.e. predictions become more or less accurate over time, respectively. *Wobble* quantifies whether an infusion system is able to reach and maintain a stable plasma concentration. In this formula, the variability in PE (median absolute deviation of the PE's from the MDPE's at any given moment (j) of a total number of measurements (N_j)).

Formula 1-5 - The concept of bias and accuracy. Note that bias describes the distance from the reference value and precision the density of the cloud of measurements.

Drug interaction models

Patients are often administered several drugs at once and another important step in individualizing anaesthesia is the ability to apply interaction models to predict the effect of multiple administered drugs. The principle of drug interactions is explained in [chapter 3](#). In [chapter 6](#) the interaction model as described by Bouillon and co-workers is prospectively applied for induction of anaesthesia.¹¹

Aims of this thesis

This thesis aims to contribute to current knowledge in anaesthetic pharmacology by surveying aspects of optimizing and individualizing anaesthetic drug administration by applying state-of-the-art knowledge.

[Chapter 2](#) summarizes the current knowledge regarding drug interactions in anaesthesia and how this could be used in optimizing drug titration.

[Chapter 3](#) describes the effectiveness of optimizing individual PK parameters by using exhaled propofol concentration measurements.

[Chapter 4](#) describes the effectiveness of Bayesian adjustment of the PK model for propofol, using measured full blood propofol concentrations as input.

[Chapter 5](#) describes the hysteresis between propofol administration and electro-encephalographic measures of clinical effect, using two different EEG-monitor devices.

[Chapter 6](#) prospectively applies a well-established population-based propofol-remifentanyl interaction model in the individual, surveying the effects on hemodynamics and EEG along the PTOL90 isobole.

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CHAPTER 2

PHARMACOKINETIC AND PHARMACODYNAMIC
INTERACTIONS IN ANAESTHESIA. A REVIEW OF
CURRENT KNOWLEDGE AND HOW IT CAN BE USED TO
OPTMISE ANAESTHETIC DRUG ADMINISTRATION.

Modified from *Br. J. Anaesth.* 2017 Jan; 118(1):44-57

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J.K. Götz Wietasch, Anthony R. Absalom, Michel M.R.F. Struys

Summary

This review describes the basics of pharmacokinetic and pharmacodynamic drug interactions and methodological points of particular interest when designing drug interaction studies. It also provides an overview of the available literature concerning interactions, with emphasis on graphic representation of interactions using isoboles and response surface models. It gives examples on how to transform this knowledge into clinically and educationally applicable (bed-side) tools.

Introduction

Drug interactions can be described as the pharmacological influence of one drug on another drug (**figure 2-1**), when administered in combination.¹ Anaesthetists routinely combine drugs such as opioids and hypnotics in clinical practice. However, dosing is often based on building experience throughout years of training and local habits. It remains a challenge to teach clinicians how to combine these drugs in order to reach and maintain optimal anaesthetic conditions while minimising side effects such as haemodynamic alterations or prolonged recovery times. It has to be clear that not all drug combinations lead to similar and adequate anaesthetic conditions. A good understanding and knowledge of drug interactions may improve the ability to titrate multiple drugs more effectively.²

Figure 2-1 Schematically visualization of the pharmacokinetic and pharmacodynamic interaction between hypnotics and analgesics. Note that this visualization is also valid in case of any other combination of two drugs that interact. Modified (with permission) from Sahinovic et al.⁵²

While physicians are typically more interested in controlling the time course of drug effect than in controlling plasma concentrations, research on anaesthetic drug interactions is often focused on pharmacokinetic and pharmacodynamics as well. Pharmacodynamic drug interaction studies provide information about drug effect when two or more drugs are administered. This review provides an overview of the available literature concerning interactions, with emphasis on graphic representation of interactions using isoboles and response surface models. It closes with an overview of newly developed computer software to apply this knowledge in clinical practice.

Pharmacokinetic drug interactions

Drug interactions can occur on a pharmacokinetic (PK) and/or a pharmacodynamic (PD) level. PK drug interactions will generally also result in an altered PD effect. As most drug administration in the daily clinical practice of anaesthesia is titrated toward a desired clinical effect, PK interactions are often not considered separately from PD interactions for application. Nevertheless, clinicians should understand the mechanisms of PK interactions to be able to fully appreciate the consequences of some dosing scheme. Situations of particular importance are when one drug affects the quantity and/or time course of absorption, volume and rate of distribution and/or elimination of another drug.

Absorption

Absorption is the process of drug molecules crossing biological membranes from the site of administration into the plasma. When anaesthetic drugs are administered intravenously absorption problems are largely bypassed. In case of the use of volatile anaesthetics, the absorption might be influenced by ventilation-perfusion ratios, membrane pathology but also by ventilator settings, as this is mainly dependent on gradients between alveoli and pulmonary capillaries.³⁻⁶

Following anaesthesia with halothane and diazepam, peak plasma concentrations of paracetamol administered one hour post-operatively were significantly delayed and decreased, compared to conditions without anaesthesia, as a result of delay in gastric emptying and therefore slower absorption.⁷ Therefore, higher doses of orally administered drugs may be considered before anaesthesia to guarantee equivalent plasma concentrations.

Distribution

The volume of distribution is the apparent volume in which an administered dose would need to be dissolved in order to yield some particular plasma concentration. When a drug has a higher affinity for tissues other than plasma, the volume of distribution may be large, and can even be much larger than the dimensions of the human body. This is the case for propofol, which is characterized by considerable redistribution to adipose tissue, resulting in a large volume of distribution of about 300L.^{8,9}

Simultaneously administered drugs can affect the volume of distribution through several mechanisms. First, drugs may compete for binding sites on plasma proteins (e.g. on albumin and α 1-acid glycoprotein) thereby potentially increasing the unbound fraction and resulting in a lower volume of distribution.¹⁰⁻¹³ Second, drugs that decrease cardiac output may decrease the perfusion of tissues involved in redistribution of other drugs, thereby altering their volume of distribution.¹⁴ A decrease in propofol requirements has been found in the presence of esmolol, likely due to distribution alterations.¹⁵

Elimination

Drugs can be eliminated by excretion (e.g. renal elimination of sugammadex and renal and biliary excretion of rocuronium^{16 17}), biotransformation (e.g. hepatic metabolism of propofol¹⁸) or spontaneous degradation (e.g. Hofmann degradation of cisatracurium¹⁹). The elimination capacity of the body is quantified as clearance, which may be defined as the volume of plasma that is cleared of the active drug per unit of time, or as the rate of drug elimination divided by the plasma concentration.

Elimination of a drug is often influenced by the presence of other drugs.²⁰ Drugs that alter cardiac output alter liver blood flow also and may influence clearance as described in an animal model by Ludbrook and co-workers. Generally, in a sheep model cardiac output is found to be inversely related to arterial and brain propofol concentrations.²¹ Lange et al first described how propofol decreases liver perfusion and thereby decreases its own elimination.²² In a more recent study it was shown that a decreased cardiac output, induced by a remifentanyl infusion, lead to a higher propofol concentration as a result of decreased hepatic and renal blood flow.^{15 21 23-26}

Hepatic clearance is a complex process, dependent on several families of enzymes responsible for drug metabolism. The cytochrome P450 family (CYP450) is responsible for metabolizing many anaesthetic drugs. Some drugs cause CYP450 enzyme induction, resulting in an accelerated breakdown of drugs metabolised by this enzyme. For example, activation of liver enzymes by anti-epileptic drugs leads to decreased plasma concentrations of fentanyl, methadone, pethidine, paracetamol as well as some non-depolarizing neuromuscular blocking agents such as pancuronium, rocuronium and vecuronium.^{27 28} Conversely, CYP450 enzyme inhibition leads to reduced breakdown of some drugs. An example of this is decreased in vitro enzymatic degradation of alfentanil and sufentanil in hepatic microsomes due to the presence of propofol.²⁹

The clinical applicability of pharmacokinetic interaction studies

Research into PK interactions is relevant to promote safe practise and to investigate toxicity and side effects. Technical software is available to warn physicians and pharmacists of potential unintended PK interactions,³⁰ but these are not commonly used in daily anaesthetic practice. Current attempts to measure individual plasma drug concentrations at the bedside of the patient are promising but have still significant limitations.³¹⁻³⁷ To get an idea of the time course of the plasma concentration we are limited to pharmacokinetic predictions based at best on intermittent blood sample analysis or on estimations based on current knowledge of interactions. As a consequence, the effect of a drug on the plasma concentration of another drug is currently not directly known to or quantifiable by the clinician. As anaesthetists are generally more focussed on control of the time course of desired drug effect, rather than plasma concentrations, a mathematical description of the resultant combined effect of two drugs administered together may be of more clinical value compared to a detailed description of PK interactions in anaesthesia. Available tools and their development are described in the next paragraph.

Pharmacodynamic drug interactions

Figure 2-2 Simulated induction of anaesthesia with a bolus of propofol and maintenance with sevoflurane combined with a remifentanil target controlled infusion in a 35 year old male subject (weight 70 kg, height 175 cm). Induction starts with a remifentanil infusion targeting effect-site concentrations of 1.5, 3 or 5 ng ml^{-1} , respectively. A propofol bolus of 1.5 mg kg^{-1} (panel A, C, E) or 2.5 mg kg^{-1} (panel B, D, F) is given 2 minutes after the start of the remifentanil infusion. To maintain a P_{TOL} of 90% (PD endpoint), sevoflurane has to be started 1, 3 and 4 minutes after the smaller propofol bolus (respectively panel A-C-E) or 3.3, 4.5 and 5.6 minutes after the larger propofol bolus (respectively panel B-D-F). Note the pharmacodynamic interaction as the P_{TOL} is maintained in steady state remifentanil infusion during changing plasma concentrations of two different hypnotics (i.e. propofol and sevoflurane). Used with permission from Hannivoort et al., previously published as web supplement.¹¹⁵

Pharmacodynamics describes the relationship between the drug concentration at its site of action, typically a receptor, and the corresponding effect of a drug. Administration of a combination of drugs may result in an alteration of this dose-response relationship. A clinically relevant example of such an interaction is given in [figure 2-2](#). The assumption in PD interaction studies is that the underlying PK interaction inevitably leads to a subsequent alteration in clinical effect. By studying the clinical effect directly, the underlying PK interaction is handled as one of the covariates that cause variability in the model. Ideally, PK and PD interactions should be studied simultaneously in a selected population to capture as much information as possible on the mechanisms underlying the observed effect. Many designs for drug interaction studies have been developed in the past, hereby taking into account that anaesthetists are not only interested in knowing 50% of a specific maximal drug effect, but rather in the entire spectrum and especially in the effect in the clinical range, usually occurring between 95% and 99% of the maximal drug effect. The criss-cross design appears to be the most efficient and effective way to study interactions.³⁶ With this approach a randomly selected group of participants receives a fixed concentration of drug A, and varying concentrations of drug B, whereas in a second subset of participants, a fixed target concentration of drug B is applied, while varying concentrations of drug A are administered.³⁸

Interaction studies reveal the nature of the PD interaction between two or more drugs. In general, three different types of interactions can occur^{39 40}: additivity, supra-additivity (i.e. synergism) and infra-additivity (i.e. antagonism), as visualized in [figure 2-3](#). Besides their direct clinical relevance, these models give an impression of the underlying pharmacokinetic pathways involved. Strict additivity implies that two drugs have a common site of action, whereas deviation from additivity implies different sites of action.¹

Figure 2-3 Description of additivity, supra-additivity and infra-additivity. Each line represents an equipotent effect resulting from different drug combinations ($a+b$). In case of additivity, the combined effect equals the expected effect by simple addition. This is usually the case when two drugs, acting via the same physiological pathways, are combined together. In case of supra- and infra additivity (usually drugs that work via different pathways), the combined effect is greater or smaller than expected by simple addition (usually when two drugs compete each other on the same receptor), respectively. Supra- and infra-additivity are also named as synergistic and antagonistic in literature, respectively.

The relationship between drug plasma (or target) concentrations and the resulting effect can be described using two types of figures: isoboles and response surface graphs ([figure 2-4](#)).⁴¹ Isoboles are two dimensional graphs showing drug combinations over a clinical range that evoke some predefined effect (e.g. the 50% probability of tolerance to surgical incision). Response surface models are more complex, but more informative.⁴² They predict the probability of clinical effect of the full clinical range of combinations of two drugs. This is often illustrated by a three-dimensional representation of the interaction over a spectrum of drug doses and drug effects. In this respect, a response surface model represents an infinite number of isoboles, representing numerous drug plasma concentration combinations.^{38 41}

Figure 2-4 Response surface model for probability of tolerance to laryngoscopy (right graph) and BIS (left graph) for sevoflurane and remifentanyl. This 3D-model describes the interaction effect of any drug combinations within the ranges. Please note that the sevoflurane concentration axis shows ascending concentrations from 0-4 in case of PTOL, and descending concentrations from 4-0 in the case of BIS. From the source data, black dots represent the patients tolerance to laryngoscopy, whereas blanc dots represent the responsive patients. The bold black line drawn through the 3D-model represents the 90% isobole to illustrate that the model represents an infinite amount of isoboles as well. For BIS, the dotted line represent all equipotent combinations to reach BIS=40, whereas the continuous black line represent combinations to reach BIS = 60.

A number of different response surface models have been developed in the literature to handle different types of drug interaction mechanisms. This implies that it would be useful to determine which theoretical type fits the new dataset the best. Heyse and co-workers compared the ability of 4 different response surface models to fit a single sevoflurane-remifentanyl interaction dataset and found that there was considerable difference between the response surface models in their ability to fit the observed data.⁴³ For response surface models to be useful in daily clinical practice, two methodological aspects for the study design are of great importance: reproducible drug titration and clinically relevant drug end-points (i.e. “effect”).

Reproducible drug titration

The effects observed after administration of drugs can only be clinically relevant if the methodology of dosing can be reproduced by others. For volatile agents this is not a major issue as the end-tidal alveolar concentration of the volatile agents is routinely monitored and is a reasonable surrogate representation of the plasma concentration in the individual. Once the end-tidal concentration is maintained at a desired target for a sufficiently long time (so that steady state conditions are reached), one can assume that the plasma and effect-site compartments are in equilibrium.^{44 45} Nevertheless, Frei and co-workers have put the accuracy of this surrogate into perspective by showing the existence of significant and persisting differences between end-tidal and measured arterial concentrations of isoflurane.⁴⁶

For intravenous drug delivery we lack this ability to continuously measure or accurately predict the plasma concentrations in the individual. In order to improve reproducible drug titration for intravenous drugs, a different approach of dosing guidelines was necessary.⁴⁷⁻⁴⁹ A fixed infusion

regimen based on volumetric infusion (ml h^{-1} or $\text{ml kg}^{-1} \text{h}^{-1}$) may lead to a large difference in plasma concentration between individuals due to the inevitable biological variability in pharmacokinetics within the population.⁵⁰⁻⁵² When compared to the fixed infusion pumps, target controlled infusion (TCI) pumps (i.e. with microprocessor equipped syringe pumps driven by calculations obtained from PK models), are able to reach and maintain a steady state plasma concentration more accurately in clinical practice and validation studies.^{50 53-55} However, one of the inevitable limitations of all population PK models is the residual prediction error – the discrepancy between the (population derived) prediction and the individual plasma (or effect-site) concentration. Experts have recommend that in terms of the Varvel criteria, median prediction error should not exceed more than 20% for plasma concentration estimations for a TCI system to be useful in clinical application.^{56 57} Strategies, such as Bayesian optimisation, are and will be studied to reduce population based errors.⁵⁸⁻⁶⁰ However, Coppens et al. showed that the strength of certain models does not lie in predicting effects in the individual patient, but rather in the ability to maintain this effect once it is reached.⁵⁴

Commonly used PK models for anaesthesia drugs in clinical practice are: the Schnider and Marsh model for propofol^{61 62} the Minto model for remifentanyl⁶³ and the Gepts model for sufentanil⁶⁴ An example of the ongoing search for improvement of PK models for individual drug titration is the work of Eleveld and coworkers, who recently presented a generalized model for propofol, based on data from a large population with a wide range of demographic characteristics.⁶⁵ This model was validated in obese patients and appeared to perform well in this group.⁶⁶ Prediction errors are also likely to exist in interaction models. In a recent study, Short et al., prospectively validated the Bouillon interaction model for propofol and remifentanyl on BIS and showed an overall performance as described by MDPE of 8% (SD 24%) and MDAPE of 25% (SD 13%).⁶⁷ Certain based model errors are most likely the result of population variability. Therefore, the exact drug dose combinations of interaction models must be read with caution in the individual. As such, individual adjustments are likely necessary. More prospective validation studies of interaction models are required for these models, with emphasis on group such as elderly, children and patients with specific illnesses.

Clinically relevant endpoints

In theory, any drug effect can serve as an endpoint to explore the nature of drug interaction. However, if it is the intention to apply the findings in clinical practice then chosen effect needs to be unambiguous and relevant for the clinical setting. Clinical endpoints of responsiveness to a stimulus are generally used to observe whether the patient is sufficiently anaesthetized.^{1 68} A variety of verbal, tactile or noxious stimuli have been proposed as precipitants of a subsequent motor, haemodynamic or EEG response. The first is more dichotomous (i.e. the patients responds or does not), whereas the latter two are continuous and allow observation of a gradual change over time within the individual patient. The (unwanted) side-effects of anaesthetic agents, such as respiratory depression, have also been studied as endpoints.^{69 70}

Monitors that measure the neuro-physiological changes evoked by anaesthetics have been proposed as a surrogate indicator of hypnotic drug effect. They provide continuous information on the patients' state, based on changes in cortical electrical activity. These measures allow quantification of a gradual change in individual patients, even in the case when clinically detectable responses may have dissipated. Some of these indices are widely used in clinical practice, such as the bispectral index (BIS)^{71 72}, spectral entropy^{73 74}, the index of consciousness⁷⁵, the patient state index⁷⁶ and the auditory evoked potential index.^{77 78} However, these methods lack the ability to evaluate the balance between nociception and antinociception.⁷⁹ For this purpose, some new variables have been developed. qNOX (Quantum Medical, Barcelona, Spain) has been shown to be able to predict this balance in the presence of a noxious stimulus, but further research is required to confirm these findings.⁸⁰ The composite variability index (CVI), which is derived from bispectral index variability and frontal EMG activity, appears to correlate with motor responses to shake and shout, according to a recent study by Sahinovic and coworkers.⁸¹ However, this index has been shown to be more dependent on the hypnotic than the analgesic drug component. The study also shows that heart rate and mean arterial pressure are poor predictors of movement on noxious stimulation. This stands in apparent contrast to the widespread routine clinical monitoring of these signals for the purposes of drug titration towards previously named balance.⁸¹ In a more recent study, the authors combined antinociception parameters (i.e. cortical input and CVI) and hypnotic parameters (i.e. composite cortical state and BIS), showing a potency to predict responsiveness of patients to tetanic stimuli more accurately.⁸² As such, the search for the ideal predictor of responsiveness to noxious stimuli remains work in progress.

From MAC to Isoholes to Response Surface Models

The first PD interaction studies in anaesthesia (“MAC reduction” studies) were mainly focused on inhaled anaesthetics in combination with opioids, due to the direct availability of end-tidal concentration measurements which, in steady state, are reasonably representative of plasma concentration. MAC₅₀ (or EC₅₀) is defined as the *minimal alveolar concentration* required to prevent 50% of subjects from moving in response to a noxious stimulus.⁸³ Later, the ability to standardize and predict plasma concentration arose and it became possible to study interactions in patients receiving total intravenous anaesthesia (TIVA). As such, one may state that the isoboles as discussed earlier for TIVA are analogous to the family of MAC reduction curves for inhalational anaesthesia.

Volatile anaesthetics – Opioid interactions

Volatile anaesthetics and opioids exhibit strong supra-additive interactions. Even small doses of opioids reduce the MAC of volatile anaesthetics. Synergy between volatile anaesthetics and opioids is found for skin incision, verbal response at emergence and for haemodynamic response on skin incision. In the presence of 0.5 ng ml⁻¹ of fentanyl, the MAC₅₀ of desflurane (for skin incision) is reduced by 50%.⁸⁴ For isoflurane, an equivalent MAC reduction has been shown with 1.67, 28.8, 1.37 and 0.15 ng ml⁻¹ of fentanyl⁸⁵, alfentanil⁸⁶, remifentanil⁸⁷ and sufentanil⁸⁸ respectively. Likewise, the MAC of sevoflurane is reduced by 50% by a plasma concentration of 1.8 ng ml⁻¹ fentanyl⁸⁹ or 1.69 ng ml⁻¹ remifentanil (with the latter reduction based on laryngoscopy as stimulus).⁴³

Response surface models are rarely available in the literature concerning volatile-opioid drug interactions. In the interaction between sevoflurane and alfentanil, a model developed for more continuous endpoints showed supra-additivity for heart rate and respiratory control, but independence of the BIS with respect to alfentanil concentration.⁹⁰ The effect on BIS (and state entropy and response entropy as well) was confirmed for sevoflurane-remifentanil anaesthesia.⁹¹ Manyam and co-workers developed a model showing supra-additivity in preventing movement to pain with sevoflurane and remifentanil, which was later enhanced by using a physiological model for sevoflurane pharmacokinetics instead of end-tidal concentrations.^{92,93} Bi and co-workers presented a model of sevoflurane and remifentanil showing that the supra-additive effect on prevention of haemodynamic responses to laryngoscopy is stronger than for the occurrence of circulatory depression.⁹⁴ Heyse and co-workers aimed to fit multiple interaction models to the data from a sevoflurane-remifentanil anaesthesia and multiple stimuli (verbal, tactile and painful). They found that the hierarchical model of Bouillon and co-workers fit the data best.⁴³ The addition of nitrous oxide showed an additive interaction.⁹⁵ Finally, using MAC equipotency and opioid equivalencies, it has been shown that previous findings can be extrapolated to other volatile-opioid combinations.⁴⁴ This is supported by a study revealing that 50% of the subjects undergoing fentanyl-isoflurane anaesthesia woke within two minutes of the time predicted by extrapolation from a sevoflurane-remifentanil model predicted wake up-time, on the basis of equivalence.⁹⁶ More recently, a study showed accurate predictions for wake-up time from a

sevoflurane-remifentanyl interaction model adapted to equipotent sufentanil-desflurane doses that were used.⁹⁷

Intravenous anaesthetics – Opioid interactions

The interaction between opioids and the intravenous anaesthetic agents is also supra-additive, although it is less strong for hypnotic endpoints such as sedation and unresponsiveness (Loss of consciousness (LOC)) than for anaesthetic endpoints (such as response to noxious stimuli). However, characterizing this interaction is different because the volatile anaesthetics possess some analgesic effects (or at least attenuate movement responses to noxious stimuli via peripheral/spinal effects), whereas this has not been shown for the intravenous anaesthetic agents.

The 50 and 95% probability of LOC isoboles for fentanyl and propofol show a supra-additive interaction. However, the effect of fentanyl is limited as the maximum reduction of 50% probability is reached at 3 ng ml⁻¹ fentanyl.⁹⁸ The haemodynamic effects (heart rate and systolic blood pressure) of propofol and fentanyl responses to skin incision and peritoneal wall retraction have also been studied.⁹⁹

The interaction between propofol and sufentanil has been described in a response surface model describing probability of loss of consciousness, and shows a more additive interaction.¹⁰⁰ The lesser influence of sufentanil on LOC was confirmed by a later study with fixed sufentanil concentrations whilst changing propofol to keep the BIS within a certain range.¹⁰¹ On the other hand, sufentanil is able to suppress motor and haemodynamic responses to noxious stimuli.¹⁰¹ Indeed a combination of 1.2 µg ml⁻¹ propofol and 0.456 ng ml⁻¹ sufentanil has been successfully used for conscious sedation during (very painful) burn wound dressing changes, without respiratory depression, and with good doctor and patient satisfaction scores in 95% of patients.¹⁰² Studies of the interaction between propofol and alfentanil on loss of response to eye lash reflex, laryngoscopy and various surgical stimuli in patients undergoing elective surgery, showed supra-additive interactions.^{103 104} However, it has also been shown that alfentanil amplifies the depressant effect of propofol on blood pressure and does therefore not contribute to haemodynamic stability during induction.¹⁰⁴ In an innovative study, Vuyk and colleagues used simulation of recovery times for various opioids to an isobole of 50% probability for return of consciousness.¹⁰⁵ Midazolam and alfentanil tend to act supra-additively with regard to responses to verbal command.¹⁰⁶

The interaction between propofol and remifentanyl has been studied extensively and is supra-additive for noxious stimuli as well as hypnotic endpoints. Shake and shout¹⁰⁷⁻¹⁰⁹, laryngoscopy¹⁰⁷⁻¹¹⁰, intubation¹¹⁰, intra-abdominal surgery¹¹⁰, tibial pressure algometry¹⁰⁸, electrical tetany¹⁰⁸, recovery times¹⁰⁹ and post-operative pain responses¹⁰⁹ have all been shown exhibit supra-additive interactions. For more continuous, electroencephalogram-derived parameters, the results for remifentanyl are contradictory, showing no synergism (with propofol) for BIS in one study¹¹¹,

additivity^{107 112} and supra-additivity in other studies.^{26 113 114} For propofol and remifentanyl, Nieuwenhuijs and coworkers described a supra-additive interaction on cardiorespiratory control.¹¹¹ More recently, a triple drug interaction (propofol, sevoflurane and remifentanyl) model was described by Hannivoort et al. for tolerance of laryngoscopy and its derivative, the newly developed NSRI. In this triple drug interaction study they described all drug combinations with regard to probability of tolerance to laryngoscopy (PTOL). They showed an additive interaction between sevoflurane and propofol when titrated towards PTOL50 doses. A synergistic effect was found for remifentanyl when combined with propofol and sevoflurane.¹¹⁵

Due to its ultra-short-acting pharmacokinetics and its pharmacodynamic profile, remifentanyl is suitable for use for sedation and this indication is becoming more frequently the responsibility for anaesthetists. Several studies have been performed to provide insight into the effects of propofol-remifentanyl drug combinations on endpoints relevant to sedation, such as prevention of gag-reflex on oesophageal instrumentation.¹¹⁶ Higher propofol-lower remifentanyl combinations have been found to obtund responses to oesophageal instrumentation while avoiding intolerable ventilatory depression.⁶⁹ A simulation study of various commonly used propofol-remifentanyl combinations for upper gastrointestinal endoscopy revealed that this combination is not only associated with better conditions for oesophageal instrumentation, but also with rapid return of responsiveness, compared to propofol-only regimens.¹¹⁷ Other investigators have produced models for the effect of different propofol-remifentanyl combinations on the BIS and index of consciousness (IOC) during endoscopic procedures.¹¹⁸

Overall, following an era during which many studies modelled the blunting of responses to noxious stimuli, the search for strategies to optimise the balance between reaching the preferred effect, while taking in account the unwanted (side) effects, continues. For this purpose, the “well-being” model was designed for propofol-remifentanyl, which describes not only the preferred effect, but balances between negative and positive effects of drug combinations.⁷⁰

Hypnotic– Hypnotic interactions

In common daily practice, hypnotics are often combined, most frequently in the contexts of benzodiazepine premedication, drugs used for sedation or the switch from bolus propofol administration for induction to volatile maintenance anaesthesia.

A few studies have addressed midazolam-propofol interactions and these have shown varying results of supra-additivity¹¹⁹⁻¹²¹ or additivity.^{122 123} Remarkably, adding alfentanil to these two sedatives lead to a weaker synergistic interaction than expected when compared with dual combinations.^{122 124} Most data was collected in a non-steady state and without accurate PK-models and so a high variability of effect site concentration could have confounding effects. A standardized, well-performed interaction study in steady state has not yet been performed. Although the nature of the interaction appears to be clear, a full quantification has not yet been revealed.

The combination of alpha-2-agonists such as clonidine and dexmedetomidine with other anaesthetics has been less well described. The addition of dexmedetomidine 0.66 ng ml^{-1} using TCI reduces the EC_{50} for motor response to electrical stimulation of propofol from 6.63 to $3.89 \text{ } \mu\text{g ml}^{-1}$. However, the type of interaction could not be clearly identified due to methodological reasons.¹²⁵ Another study showed that an loading infusion of $1 \text{ } \mu\text{g kg}^{-1}$ dexmedetomidine over 10 minutes, followed by a maintenance infusion dose of $0.5 \text{ } \mu\text{g kg}^{-1} \text{ h}^{-1}$ did not reduce the EC_{50} of propofol for responses to oesophagogastroduodenoscopy in children.¹²⁶ As for propofol and midazolam, well performed interaction studies are still absent. Ideally these studies should apply response surface models and newly developed PK(PD)-models, such as the three-compartmental dexmedetomidine produced by Hannivoort *et al.*¹²⁷ For clonidine, a response surface model has been developed, showing that $5.0 \text{ } \mu\text{g kg}^{-1}$ of oral clonidine 90 minutes prior to arrival at the operation room reduces the propofol EC_{50} for response to verbal command about 65% from 2.67 to $0.91 \text{ } \mu\text{g ml}^{-1}$ and that the interaction appears to be additive.¹²⁸ For laryngeal mask placement, oral clonidine premedication has been shown to reduce propofol requirements.¹²⁹ Whether the nature of this interaction is comparable needs to be confirmed.

Simple additivity was found for the propofol – sevoflurane interaction to response on shake and shout, tetanic stimulus, laryngeal mask insertion and laryngoscopy¹³⁰, LOC and movement to skin incision.¹³¹ The interaction on BIS, state entropy and response entropy was additive as well.^{130 132} When looking at the arousal response – i.e. the increase of BIS following a noxious stimulus – combining propofol with sevoflurane or desflurane does not seem to lead to a complete blunt of this response. However, in contrast to sevoflurane, desflurane seems to partially blunt this response.¹³³ The additivity was confirmed in an in-vitro study for stimulation of GABA-receptors, suggesting a single-receptor interaction.¹³⁴

The clinical applicability of pharmacodynamic drug interaction models

Despite the more clinically oriented and applicable end points, pharmacodynamic studies still have one major clinical limitation: it is impossible for the clinician to learn all the possible drug combinations and their accompanying pharmacodynamic results by heart. Nevertheless, well performed application of pharmacology may lead to better patient care and it appears to be also one of the most important parts.² In order to serve as a handle for teaching and training, many computer based tools or simulation programs have been developed¹³⁵ of which some will be discussed in the next paragraph.²

Teaching drug interaction by applying Simulated Drug Administration

Simulation of drug administration can help anaesthetists to improve the quality of anaesthetic care by assisting with selection of appropriate and optimal drug doses and combinations.¹³⁶ The quality of simulations and didactic techniques have improved over recent years. Simulators vary from basic excel-worksheets to advanced, realistic, attractive (virtual) reality simulators.² A distinction can be made in tools helpful for experimentation in a simulation setting, such as PKPD-tools, TIVA-trainer, Gasman, RUGLOOP II and virtual anesthesia machine with other kinds of (commercially available) tools that focus more on providing real-time information, such as SmartPilot® View and Navigator™ Application Suite at the bed-side. A brief overview of some available simulators and their options of applicability is given in [table 2-1](#).

Drug advisory displays are currently being commercialized as a new concept in anaesthetic drug administration and for facilitated education in anaesthetic pharmacology.⁶⁸ Through direct measurement (e.g. for the volatile agents) or prediction of effect-site concentration (e.g. for propofol and opioids), the device tracks the anaesthetic drug doses which are administered to the patient throughout the procedure. The drug doses and predicted concentrations are used as input for a response surface model to predict the combined anaesthetic effect.³⁸ [Figure 2-5](#) shows two advisory screens that have been commercialized: The Navigator™ Application Suite (GE Healthcare, Helsinki, Finland), which reflects the effects (i.e. tolerance of intubation and shake and shout) in a time-based plot, whereas the SmartPilot® View (Dräger Medical, Lübeck, Germany) adds a two-dimensional graph with multiple isoboles and a measure of general anaesthetic potency called the Noxious Stimulation Response Index (NSRI).¹³⁷ The probabilities of tolerance of several stimuli are visualized on screen either through isoboles (SmartPilot® View) in a two dimensional graph or as an indicator of combined effect versus time (Navigator™ Application Suite). Despite their common objectives, the predictions of the devices are slightly different due to the use of different interaction models and the fact that they are based on data from separate interaction studies, i.e. the Navigator™ Application Suite uses the Minto model¹³⁸ to predict propofol-opioid interaction and the Greco model¹³⁹ for inhaled anaesthetics-opioid interaction, whereas the SmartPilot® View uses the hierarchical model of Bouillon¹⁰⁷ for both intravenous and inhaled anaesthesia administration. SmartPilot® View also allows a continuous estimation of effect during the transition from intravenous to inhaled anaesthetics and vice versa. Whether these drug displays are beneficial in daily clinical practice and to what endpoints, has not been revealed yet. A recent small non-randomized controlled study by Cirillo and colleagues showed that there might be benefits in the use of these displays, as it appeared that the consumption of volatile anaesthetics was lower in the groups where anaesthetic drug displays were used.¹⁴⁰

Figure 2-5 Upper screen: SmartPilot® View (Dräger, Lubeck, Germany). This specific screenshot shows an anaesthesia based on sevoflurane, propofol, remifentanyl and pancuronium. The graph on the left provides retro- and prospective information about the drug interaction between hypnotic and analgesic drugs. It provides predictive information regarding the following minutes from 'now'. This screen introduces the NSRI (right) as a new parameter. It also provides past and predictive information of BIS over time. (Printed with permission, © Dräger Medical GmbH, Lübeck, Germany). Lower screen: The Navigator™ Application Suite (GE Healthcare, Helsinki, Finland). This display provides a visualization and modelling tool for common volatile and intravenous anaesthetic drugs (in this case propofol, sevoflurane, remifentanyl and rocuronium). It calculates effect-site concentrations and displays these in a time-based graphical format. The total effect line (black line) visualizes the combined effect of the analgesic and sedative drugs. The display calculates the models for up to 1 h into the future. (Printed with permission, © General Electric Company, Helsinki, Finland)

Table 2-1 – Brief overview of some available drug administration simulators.

Simulator	Developed by	Access	Application	Applicability
PKPD-tools	Minto, Schneider	www.pkpdtools.com	Add-in for Microsoft Excel.	Simulation/education, recalculation, ability to simulate TC _i , data handling in research.
CCIP	The Chinese University of Hong Kong, Prince of Wales Hospital, Dept. of Anaesthesia and Intensive Care, Hong Kong, China	www.cuhk.edu.hk/med/ans/softwares.htm	PC-based software	Computer Controlled Infusion Pump (CCIP) software, which can control the amount of drug inside the Plasma Site and Effect site compartments of the patient, with respect to the interaction of two different drugs (predicted combined effect).
TVAt-trainer	Engbers Leiden University, The Netherlands	www.eurosviva.org	PC-based software	Discovering interaction models, calculation of plasma and effect-site concentration of intravenous administered drugs.
TVAt-trainer X	Engbers, Leiden University, The Netherlands (and Guttabv ©)	www.eurosviva.org	Software for iPad or iPhone	Educational programme, developed to explain PK principles and show the PK properties of IV anaesthetics and other drugs
Anesthasist	Palma Healthcare Systems LLC, Madison, WI, USA	www.palmahhealthcare.com	Software for iPad, iPhone and iPod	Educational tool used for understanding and visualizing PK, PD and interactions of commonly used anaesthetic drugs.
GASMAN	Med Man Simulations®	www.gasmanweb.com	PC-based software	Educational simulation tool to teach pharmacokinetics and – economics.
Virtual Anesthesia Monitor	University of Florida, USA	www.vam.anest.ufl.edu	PC-based software	Visualizing PK models, pill dosage/compliance simulations, anesthesia machine simulation with inhaled anaesthetics and more.
RUGLOOP II	Ghent University and Demed Medical, Gent Belgium	www.demed.be	PC-based software	Visualisation of PK and PD models, online PK/PD monitoring, TC _i , closed-loop
Navigator™ Application Suite	GE Healthcare, Helsinki, Finland	http://www3.gehealthcare.co.uk/	Stand-alone device, coupled with used syringe pumps (either TC _i or volumetric)	Bed-side applicable tool intended to apply the available knowledge of PD-drug interaction into a clinical guidance tool for drug delivery.
SmartPilot® View	Dräger Medical, Lübeck, Germany	www.draeger.com	Stand-alone device, coupled with used syringe pumps (either TC _i or volumetric)	Idem

Conclusion

In conclusion, knowledge of pharmacokinetic and pharmacodynamic drug interactions in anaesthesia can contribute to the optimization of anaesthetic drug administration. Drug interaction studies aim to rationalize combined drug dosing by quantifying the nature of interaction between opioids, hypnotics and volatile agents. Reproducible drug titration and unambiguous endpoints are essential in such studies for them to be clinically applicable. Validation studies of many interaction models are still required. While many of these drug interaction studies have been performed, the information is not accessible and applicable at the bed side without computer assistance. Advisory screens and computer-based training tools can teach physicians and help them to apply this knowledge in clinical anaesthetic practice.

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CHAPTER 3

PROPOFOL BREATH MONITORING AS A POTENTIAL TOOL TO IMPROVE THE PREDICTION OF INTRAOPERATIVE PLASMA CONCENTRATIONS

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Abstract

Introduction

Monitoring of drug concentrations in breathing gas is routinely being used to individualize drug dosing for the inhalation anesthetics. For intravenous anesthetics however, no decisive evidence in favor of breath concentration monitoring has been presented up until now. At the same time, questions remain with respect to the performance of currently used plasma PK models, implemented in target-controlled-infusion (TCI) systems. In this study we set out to investigate whether breath monitoring of propofol could improve the predictive performance of currently applied TCI models.

Methods

Based on data from a healthy volunteer study, we developed an addition, to the current state-of-the-art PK model for propofol, to accommodate breath concentration measurements. The potential of using this PKPD model in a Bayesian forecasting setting was studied using a simulation study. Finally, by introducing BIS measurements and the accompanying BIS models into our PKPD model, we investigated the relationship between BIS and predicted breath concentrations.

Results and Discussion

We show that the current state-of-the-art pharmacokinetic model is easily extended to reliably describe propofol kinetics in exhaled breath. Furthermore, we show that the predictive performance of the *a-priori* model is improved by Bayesian adaptation based on the measured breath concentrations thereby allowing further treatment individualization and a more stringent control on the targeted plasma concentrations during general anesthesia. Finally, we demonstrated concordance between currently advocated BIS models, relying on predicted effect site concentrations, and our new approach in which BIS measurements are derived from predicted breath concentrations.

Introduction

In anesthesiology PK(PD) modeling is used extensively to develop target controlled infusion (TCI) systems. These systems use an established population PK model to estimate the required dosing regimen to be given to an individual patient to achieve and maintain a predefined target plasma (or effect-site) concentration. Although its use is becoming standard of care for the administration of intravenous anesthetics such as propofol, concerns remain with respect to the accuracy of these systems. Monitoring of drug concentrations in combination with a Bayesian adaptation of the *a-priori* model, could potentially address these concerns. Motamed et al. and Maitre et al. showed in a retrospective study that for rocuronium and alfentanil, respectively, Bayesian forecasting, based on timely plasma measurements, could improve the predictive performance of intraoperative plasma concentrations.^{1,2}

For propofol, clinical trials evaluating the predictive performance of currently used TCI models are ongoing.^{3,4} In addition to identifying the shortcomings of currently implemented propofol PK models (i.e. Marsh, Schnider and/or Eleveld)⁵⁻⁷, these studies could distinguish whether a Bayesian forecasting based on intermittent plasma sampling using conventional³ or bedside measurement systems⁴ could improve the predictive performance of current TCI systems. Recently, as step-up to these iterative blood sampling strategies, several groups focused on developing a measurement system that could detect propofol in exhaled breathing gas in real-time.

Although, not conventionally applied to intravenous anesthetics, monitoring of drug concentrations in breathing gas is not new. Moreover, it is routinely being used to individualize drug dosing for the inhalation anesthetics (isoflurane and sevoflurane). One of the advantages of following up on the exhaled drug concentration is that in this way the arterial concentration, which is proportional to the alveolar concentration, is controlled throughout the anesthetic procedure.

Unlike other intravenous anesthetics, propofol has a very high vapor pressure (3.1×10^{-3} mm Hg at 25°C). Fentanyl, for example, another intravenous agent, has a 100.000 fold lower vapor pressure (5.5×10^{-8} mm Hg at 25°C). This physico-chemical property makes that propofol readily distributes from the arterial (capillary) blood into the alveolar gas, thereby facilitating its possible detection in breathing gas. At the moment, research is ongoing to develop the necessary detection systems as well as the accompanying control systems/ PK models necessary to implement online breath analysis for propofol. Several groups^{8,9}, using a variety of detection systems going from ion mobility spectrometry (IMS) and ion molecule reaction mass spectrometry (IMR-MS), to electrochemical sensors, showed that it is possible to detect propofol in breathing gas during clinically relevant dosing regimens.

Up until today, to the best of our knowledge, three groups explored the possibility of applying compartmental modeling to describe propofol breath kinetics. Kreuer et al. and Ziaian et al. described propofol breath kinetics in human volunteers (n=1 and 17, respectively) using a compartmental pharmacokinetic model and a “PT1 model”, respectively.^{10 11} The latter is also known as a “low-pass filter” and is frequently used in acoustics engineering. Varadarajan et al.¹² used a compartmental modeling approach to describe propofol breath kinetics in pigs. In these studies, propofol breath concentrations were measured using IMR-MS, IMS and an electrochemical sensor, respectively.¹⁰⁻¹² In order to integrate the breath concentrations measurements with the plasma PK of propofol, two of these authors (Varadarajan et al. and Kreuer et al.)^{10 12} used predicted propofol plasma concentrations (Marsh model⁶), whereas Ziaian et al.^{6 11} used post hoc estimates of the Marsh model, tailored to measured propofol plasma concentrations, to serve as input for their breath models. None of the papers explored population PK modeling as a tool to simultaneously describe propofol plasma and breath kinetics, nor did these author’s investigate the potential clinical utility of monitoring propofol breath concentrations to predict plasma PK.

Therefore, using data from a healthy volunteer study, we set out to (i) develop an extension, to the current state-of-the-art propofol plasma PK model, capable of describing the exhalation kinetics of propofol and (ii) evaluate Bayesian forecasting based on measured propofol breath concentrations as a potential tool to improve the predictive performance of intraoperative propofol plasma concentrations. Furthermore, the usefulness of predicted breath concentrations as a predictor for propofol’s cerebral drug effects, as measured by BIS, was explored by comparing against frequently used BIS models.

Methods

Study design

The study was approved by the institutional review board and was carried out in concordance with ICH Guidelines for Good Clinical Practice (NCT01191021). After written informed consent, twenty healthy volunteers (ASA status I, age > 18) underwent general anesthesia with propofol (Diprivan® 1%, AstraZeneca). The volunteers received 0.4 mg.kg⁻¹.min⁻¹ propofol via a venous catheter for ten minutes followed by a 20 min recovery period. Afterwards, administration was resumed using a target-controlled infusion (TCI), based on Schnider et al.⁷ The TCI protocol consisted of 4 target plasma concentrations (2, 3, 4, and 5 µg.ml⁻¹), which were maintained for 15 min each. 90 Minutes after the start of the experiment the infusion was stopped and the study subjects were left to recover from anesthesia.

Propofol measurements in plasma (C_{plasma})

Arterial blood samples were centrifuged immediately after drawing. Blood plasma was then separated and frozen at -20°C temperature. The plasma samples were analyzed within 8 weeks after the experiments using an in-house developed method. Propofol plasma concentrations were determined with a liquid-chromatography tandem mass spectrometry assay. The lower limit of detection and quantification of the method were 60 and 100 ng * ml⁻¹, respectively.

Propofol breath measurements (C_{breath})

Breathing gas was sampled at 50 mL/min through a T-piece attached to the laryngeal mask of the study participants. An ion molecule reaction mass spectrometry system (IMR-MS, V&F medical development, Absam, Austria)¹³ was used to measure propofol in the sampled gas within 500ms. In order to distinguish between inspiratory and expiratory air a second mass spectrometry system based on electron impact determined carbon dioxide concentrations 10 times/second. Expiratory propofol data were extracted as the median expiratory breath signal of 30 s intervals from the recorded breath data as described previously.¹³

Determination of propofol cerebral drug effect (BIS)

The effect of propofol on the brain was determined with the bispectral index monitor (BIS, BIS Vista system, Covidien, Boulder, CO). The BIS monitor transforms the electroencephalogram into a dimensionless index ranging from 100 (fully awake individual) to 0 (deep anesthesia with isoelectric EEG activity). BIS smoothing time was set to 10s and BIS values were recorded every second.

Available Data

The final dataset included a median of 22 [range: 19 – 23] arterial plasma propofol concentrations, 208 [range: 118 – 272] propofol breath concentrations and 300 [range: 220

– 379] BIS measurements per subject. An overview of the characteristics of the healthy volunteers in our study is given in [Table 3-1](#).

Characteristic	mean [range]
Age (years)	27 [22.8 – 33.3]
Weight (kg)	74.1 [63.8 – 83.0]
Height (cm)	168.0 [162.2 – 178.5]
Sex (# males / # females)	9 / 11

Table 3-1 Characteristics of the study population. All included patients had ASA status I.

In order to reduce the computational burden during model development we reduced the number of propofol breath and BIS measurements per subject. At the same time we applied a median filter (span equal to 5 sec) to reduce the influence of outlying data during model development. In summary: the first out of every 10 consecutive, median-filtered, datapoints were retained in the dataset, resulting in a median of 22 and 30 measurements for the breath and BIS data, respectively.

For the prospective evaluation of the applicability of the Bayesian forecasting approach all of the available breath concentration measurements were used.

Model building of the PK model to describe propofol breath kinetics

We used the FOCE algorithm with interaction as implemented in NONMEM® (version 7.3; Icon Development Solutions, Hanover, MD, USA) to fit different breath models to our dataset. As a starting point for our model building, we used the individual PK parameters approach (IPP).¹⁴ For this approach, individual post-hoc PK parameters (CL, Q₂, Q₃, V₁, V₂ and V₃) were derived from the Eleveld model and were fixed for each individual during the subsequent evaluation of different breath models.⁵

Our choice for the Eleveld model as an *a-priori* model, rather than developing a PK model specific for this study population or using another published propofol PK model, was based on the model's documented general applicability and superior predictive performance in a wide variety of patient populations, making it, at the moment, state-of-the-art. Model building started with a structural model similar to the model proposed by Ziaian et al.¹¹ This model was implemented using an effect compartment (keO_{Lung}) and a scale parameter (K). The former was used to correct for the reported hysteresis between propofol plasma and breath concentrations whereas the latter was used to accommodate a.o. the unit conversion from µg/mL for the plasma measurements to parts per billion (ppb) for the measured breath concentrations.

Different modifications to this structural model were compared using the Akaike Information Criterion (AIC). Furthermore, as a safe-guard to over-parameterization, cross-validation was performed to compare the goodness-of-fit (GOF) of the different breath models. Once

population parameter estimates were obtained by fitting the breath models to the training cohort, the GOF of the post-hoc estimates of these model were evaluated in the validation cohorts. This process was repeated 4-fold, each time allocating $\frac{1}{4}$ and $\frac{3}{4}$ of the dataset to the validation and training cohort, respectively. Care was taken such that each subject in the dataset was allocated to a validation cohort once.

GOF, in terms of propofol breath concentrations in the validation cohort, was evaluated graphically in R® (R Foundation for Statistical Computing, Vienna, Austria) and numerically using the median prediction error (MdPE) and the root mean square error (RMSE).

Application of Bayesian forecasting to predict intraoperative propofol plasma concentrations

In order to evaluate the clinical utility of the final model (i.e. the potential to improve the predictive performance of the *a-priori* model) we conducted a simulation study. In this study, similar to the cross-validation described earlier, the final model was first fit to the training set. At this stage, the PPP&D approach¹⁴, which is known to produce less biased parameter estimates as compared to the IPP approach (at the expense of computing time), was used. In other words, during the estimation process the population parameters from the Eleveld model were fixed whilst allowing the parameters from the breath model to be estimated.

Next, using the parameter estimates for the breath model from the training set, the predictive performance was evaluated in a validation cohort in which the C_{plasma} were removed (i.e. the model was blinded for the measured propofol plasma concentrations to mimic the clinical situation where these concentrations are generally unknown). In order to study the change in predictive performance over time, this process was repeated for several datasets, differing from each other in the number of breath measurements that were used to predict propofol plasma concentrations (32 datasets in total, containing 1 min up until 100 min of breath concentration measurements). Predictive performance, during the propofol infusion regimens (i.e. the intraoperative timeframe), summarized in terms of MdPE and RMSE, was calculated by contrasting C_{plasma} with the predicted propofol concentrations.

PKPD model for propofol cerebral drug effects

As a final evaluation towards the usefulness of continuous monitoring of propofol breath concentrations we explored to what extent these breath concentrations could be used to explain/predict propofol's cerebral drug effects. To this end, as a reference PKPD model, a simplified version of the model proposed by Bjornsson et al. was added to our final model.¹⁵ The simplification consisted of using a single rather than a double effect compartment to model the hysteresis between C_{plasma} and BIS measurements. In line with

the model proposed by Bjornsson et al. the predicted effect side concentration (C_e) was used as a predictor in a sigmoid E_{max} model to describe changes in BIS ([Equation 3-1](#)).

$$BIS = BL_{BIS} - E_{max} \times \frac{C_e^\gamma}{EC_{50}^\gamma + C_e^\gamma} \quad (\text{Equation 3-1})$$

To evaluate the correlation between the individually predicted breath concentrations ($IPRED_{breath}$) and the BIS measurements, we fitted an additional model in which the $IPRED_{breath}$ from our final model were used in the sigmoid E_{max} model ([Equation 3-1](#)) instead of the C_e (this model required 1 parameter less, i.e. the $ke0_{BIS}$ associated with the C_e).

Results

Model building

As a starting point we decided to model propofol breath kinetics using a structural model similar to the model proposed by Ziaian et al.¹¹ Subsequently several modifications to this structural model were explored (Figure 3-1). Addition of a parameter describing inter-individual-variability (IIV) on K significantly improved the model's GOF (ΔAICc : -246.0).

Figure 3-1 Model building hierarchy.

Furthermore, in order to correct for a significant time-varying bias in the residual plots, 4 different modifications were explored. Model 4 assumed that K changes over time, an effect which could be expected from propofol effects on the ventilation-perfusion status of a patient. Initially, we implemented this using an indirect response model, linking the propofol blood concentrations to the stimulation/inhibition of a latent variable which, in turn, drives a change in K (an approach similar to the latent variable approach in Troconiz et al.)¹⁶. Nevertheless, based on the data, this was reduced to a simple linear time-dependent change in K over time.

Model 5 explored the possibility of a baseline-drift in the measurement system due to e.g. a gradual built-up of propofol, a compound which is known to have a high affinity for plastics

due to its high lipophilicity¹⁷. Model 6 explored the possibility of a time-varying ke_{0Lung} . This is in line with Bjornsson et al.¹⁵, who showed that propofol plasma kinetics were time-dependent. Finally, model 7 evaluated whether a non-linear detector response could be at the origin of this time-dependent bias in the residuals.

Figure 3-2 A plot of the conditionally weighted residuals (CWRES) versus time for the different models which were evaluated to correct for the observed time-dependent model-misspecification. Only model 4, which consists of a linearly increasing K over time is able to completely reduce the residual time-dependent bias.

Parameter	Model 8		BIS~f(C _e)		BIS~f(IPRED _{breath})	
	C _{plasma} (IPP) & C _{breath}		C _{plasma} (IPP) & C _{breath} & BIS		C _{plasma} (IPP) & C _{breath} & BIS	
	Estimate	RSE (%)	Estimate	RSE (%)	Estimate	RSE (%)
KeO _{Lung} (min ⁻¹)	0.152	5.7	0.152	5.7	0.146	9.0
KeO _{BIS} (min ⁻¹)			0.107	12.3		
K (ppb x mL x µg ⁻¹)	3.56	6.7	3.56	6.7	3.81	9.0
Slope (ppb x mL x (µg x min) ⁻¹)	0.022	8.8	0.022	8.8	0.017	20.7
BL _{BIS}			94.3	1.0	95.0	1.0
E _{max}			80.9	7.3	77.6	5.6
EC ₅₀			2.71 µg/mL	11.0	12.4 ppb	8.2
γ			2.43	20.0	2.49	18.6
IIV_K (%) ¹	23.7	37.6	23.7	37.6	25.8	37.4
IIV_Slope (%) ¹	40.9	38.2	40.9	38.2	50.8	50.0
IIV_E ₀ ⁴			0.716	30.0	0.656	29.1
IIV_EC ₅₀ (%) ¹			28.7	37.1	25.9	42.5
σ _{Plasma} , proportional (%) ³	21.6		21.6		21.6	
σ _{Breath} , proportional (%) ³	11.7		11.7		10.3	
σ _{Breath} , additive (ppb) ²	0.982		0.982		1.40	
σ _{BIS} , additive ²			0.47		0.45	

Table 3-2 Final parameter estimates and associated standard errors for our final model (model 8), which was obtained using an IPP approach where breath concentrations were modelled, keeping the plasma PK parameters fixed to the post-hoc estimates of the a-priori model. Furthermore parameter estimates are shown for 2 models evaluating propofol cerebral drug effects as a function of a modelled plasma effect-side concentration (C_e) and predicted breath concentrations (IPRED_{breath}), respectively. keO_{Lung}: rate constant for the lung effect compartment; keO_{BIS}: rate constant for the BIS effect compartment; K: scaling parameter for the lung compartment; Slope: time-dependency on K; BL_{BIS}: Typical value for the BIS at baseline; IIV: inter-individual variability; IIV_E₀: inter-individual variability in baseline BIS; σ: standard deviation of residual unexplained variability; RSE: relative standard error. Nb.: ¹ CV(%) is calculated according to: $\sqrt{e^{\omega} - 1} * 100\%$; ² Residual unexplained variability expressed as standard deviation or ³ as relative standard deviation; ⁴ IIV expressed as a variance in logit domain.

All four tested models significantly improved the model's GOF, leading to a decrease in AIC of 245.0, 163.0, 66.3 and 46.7, respectively. However, as shown in Figure 3-2, only model 4 successfully removed the residual bias across the entire observation period. Finally, to model 4, another random effect parameter was added to allow IIV on the time-dependency of K (denoted by a "slope" parameter), thereby further lowering the MdPE and RMSE to 0.2 % and 2.1 ppb, respectively. The GOF for the final model (i.e. model 8 in Figure 3-1) is shown in Figure 3-3, parameter estimates are given in Table 3-2.

Figure 3-3 Goodness-of-fit plot of the final model (model 8). Parameter estimates, obtained using the IPP approach, as described in the methods section, are given in Table 2. The top-left panel shows the apparent bias in the *a-priori* model which is passed on to the population predictions for the breath concentrations (C_{breath}) of the final model. The bottom panels show the absolute, individually weighted residuals (*iWRES*) versus individual predictions and the conditionally weighted residuals (*CWRES*) versus time.

Application of Bayesian forecasting to predict intraoperative propofol plasma concentrations

Figure 3-4 shows the C_{plasma} (for which the model was blinded) and the first 30 min of measured propofol breath concentrations for a representative individual from our study. From this figure it stands out that for this individual the predicted plasma concentrations from the *a-priori* model (solid line) are somewhat biased, thereby underestimating the C_{plasma} . After 30 min we used the measured C_{breath} up until that point to produce the post hoc predictions from our final model (dashed lines). When comparing the predicted plasma concentrations against the C_{plasma} for both approaches, it stands out that, for this individual, the post hoc predicted plasma concentrations from our final model are in closer

resemblance to the C_{plasma} then the *a-priori* predictions, thereby emphasizing the validity of our proposed approach.

Figure 3-4 Individual plot of a representative individual showing the measured plasma concentrations (C_{plasma}) (grey diamonds) and model predictions for the *a-priori* model (solid line) and the post-hoc prediction of our final model (dashed line). The Bayesian adaptation of the *a-priori* model was implemented 30 min into the treatment, using the first 30 min of breath concentration measurements only. Of note, during this process the model was blinded for the C_{plasma} . In order to give the reader an impression of the dosing regimen used throughout this study, we used grey shaded areas to show periods when no drug was infused.

Next, in order to fully explore the potential of this approach, this process was repeated using different time-frames of breath concentrations to predict the intraoperative propofol plasma concentrations, i.e. concentrations up until the last propofol infusion was stopped.

Figure 3-5 shows the change in predictive performance when including increasing amounts of breath concentrations

Figure 3-5 The change in predictive performance of our proposed approach as a function of the time-frame in which breath concentrations are monitored (as indicated in the x-axis). The median prediction error (MdPE) and root mean square error (RMSE) for the different individuals in our study are shown with a grey solid line. The solid red lines depict the overall change in predictive performance in our study population.

From this figure it is seen that the overall MdPE in the study population (red line in [Figure 3-5](#)) decreases from 42.8 %, when no breath concentrations are used (i.e. the *a-priori* MdPE), to an MdPE of -1.05 % when more than 35 minutes of breath concentrations are used. This indicates that, on a population level, our approach succeeds in reducing the apparent bias that is present in the *a-priori* model. On an individual level, for 11/20 of the volunteers in our study the initial bias is reduced (Mean reduction: 31.5 %, range: [1.3 %, 78.4 %]) and for the nine subjects the bias slightly increases (Mean increase: 11.8 %, range: [2.9 %, 31.0 %]).

When looking at the RMSE (bottom panel of [Figure 3-5](#)), a performance metric related to the precision of the predictions, we see that on a population level it reduces from 1.63 µg/mL, for the *a-priori* predictions, to 1.39 µg/mL, when using the full time course of the C_{breath} to

predict the intraoperative propofol plasma concentrations. On an individual level, the subjects whose bias was reduced benefit from an average decrease in RMSE of 0.8 µg/mL (range: [0.1 , 1.3]), whereas the other nine subjects show an average increase in RMSE of 0.6 µg/mL (range: [0.1 , 2.3]).

Predicted breath concentrations versus Ce as a predictor for propofol cerebral drug effects

In order to study whether $IPRED_{breath}$ could be a useful surrogate to the traditional predicted propofol effect site concentrations (C_e), as implemented in the model proposed by Bjornsson et al.¹⁵, we compared two different PKPD models for the BIS measurements (A graphical presentation of both models is given in [Figure 3-6](#)).

Figure 3-6 A graphical representation of both PKPD models that were fitted to the data in order to describe propofol's cerebral drug effects. The left model is the simplified version of the model proposed by Bjornsson et al.¹⁵ whereas the right model is our final model with a direct relationship between $IPRED_{breath}$ and BIS. $ke0_{Lung}$: rate constant for the lung effect compartment; $ke0_{BIS}$: rate constant for the BIS effect compartment; K_1 : individual scaling parameter for the lung compartment; BL_{BIS} : Typical value for the BIS at baseline; C_e : propofol concentration in the effect compartment.

As seen from [Table 3-2](#), judging from the similar residual error standard deviations (0.47 and 0.45 for C_e and $IPRED_{breath}$ model, respectively), both models describe the change in BIS measurements to a similar degree. Furthermore, from the concordance between all other estimated parameters (except for EC_{50} , which has different dimensions in both models) and the similarity in AIC (4401 and 4379, for C_e and $IPRED_{breath}$ model, respectively) it seems that both the C_e and $IPRED_{breath}$ from our final model could be used interchangeably to predict/describe propofol's effects on the BIS index.

Discussion

Using data from a healthy volunteer study we set out to develop an extension, to the current state-of-the-art propofol plasma PK model⁵, capable of describing the exhalation kinetics of propofol. The final parameter estimates for ke_{0Lung} and K (0.152 min^{-1} and $3.56 \text{ ppb} \times \text{mL} \times \mu\text{g}^{-1}$, respectively), respectively describing the hysteresis and the proportional difference between C_{plasma} and C_{breath} , are very similar to the work of Ziaian et al.¹¹ who reported a median ke_{0Lung} (in the paper referred to as k_{L10}) of 0.155 min^{-1} and median K of $2.71 \text{ ppb} \times \text{mL} \times \mu\text{g}^{-1}$.

Although the clinical conditions (i.e. the propofol infusion regimen) were fairly similar in their study, it inspires confidence that Ziaian et al.¹¹ reported similar parameter estimates based on detection of propofol breath concentrations using a chemical sensor rather than IMR-MS. On the contrary, Kreuer et al.¹⁰ reported different parameter estimates. Although their estimated ke_{0Lung} (referred to as k_{1L} in the publication) is slightly similar to ours (0.209 min^{-1}), their estimate for K is very different (K was calculated from their publication as k_{L1}/k_{1L} and was $0.66 \text{ ppb} \times \text{mL} \times \mu\text{g}^{-1}$). The latter difference is in line with the differences in measured propofol breath concentrations between their study (maximum in between 0.6 and 0.8 ppb) and ours (maximum equals 53 ppb). Although we cannot provide a clear explanation for this discrepancy, it seems that causes other than the propofol dosing regimen (at their $3 \mu\text{g}/\text{mL}$ TCI target, propofol breath concentrations are $> 10 \text{ ppb}$ in our study), such as intrinsic issues with the IMS detection system, the systems used for calibration or the fact that they only studied a single subject rather than a population, might explain the difference in the parameter estimates.

An important part of our model building was devoted to the exploration of potential mechanisms that could give rise to a time-dependent model misspecification. Models 5 and 7 showed that correcting for intrinsic detector-related issues, such as drift (model 5) and detector non-linearity, weren't sufficient to remove the apparent bias. Furthermore, a correction for the potential time-dependent kinetics of propofol, an approach earlier proposed by Bjornsson et al.¹⁵, only slightly improved the model's GOF without completely reducing the model misspecification. Model 4, which incorporates a linearly increasing K over time, was the only model which could completely remove the observed time-dependent bias in the residual plots.

To our opinion, there are several possible mechanisms that could explain this time dependency. Firstly, an instrument-related issue causing the sensitivity of the detector to increase over time, might explain this phenomenon. Secondly, the time-dependent bias might originate from the propagation of a model misspecification in the plasma PK part of the model, i.e. the Eleveld model. Indeed, when we look at the conditionally weighted residuals for the Eleveld post-hoc plasma concentration predictions for our subjects, a qualitatively similar pattern is observed (Figure not shown). However, when we fit a custom

3 compartmental PK model combined with our proposed breath model to the data, the CWRES plot for the plasma concentrations normalize but the time-dependent bias for the breath concentrations remains.

Finally, complex underlying physiological phenomena, such as e.g. venous-arterial mixing, which have been hypothesized in the past to play a role during the first few minutes of propofol dosing and which are currently not addressed in our compartmental PK models might cause this time-dependency.^{18,19} Physiologically based PK models, which have been used extensively in past to describe exhalation kinetics of environmental pollutants or organic solvents and have been applied in the context of propofol PK, might address these hurdles in the future.²⁰⁻²⁶ Although these models provide superior insights into the physiology behind pharmacokinetic processes in comparison to compartmental PK models, their level of complexity often hinders the clinical implementation.

One of our objectives was to evaluate whether a Bayesian forecasting based on measured propofol breath concentrations could improve the predictive performance of intraoperative plasma concentrations. **Figures 3-4** and **3-5** clearly show that our proposed approach outperforms the most recent state-of-the-art model available for propofol. Although not all subjects benefit equally from our proposed approach, we showed that the magnitude of the improvements in MdPE and RMSE in the subjects who improved quantitatively outweigh the negative corrections for those who do not benefit from this approach. Overall, on a population level the bias (MdPE decreased from 42.8 % to -1.05 %) as well as the prediction error (RMSE decreased from 1.63 µg/mL to 1.39 µg/mL, i.e. a 15 % reduction) decreased significantly, demonstrating the clinical usefulness of our proposed approach.

Judging from **Figure 3-5** no significant improvements are attained beyond 30 min. This effect is most likely explained by the propofol dosing regimen used throughout this study. The initial fast infusion, resulting in a well-defined breath concentration peak, appears to be sufficiently informative to individualize the *a-priori* model predictions. Therefore, a different clinical setting, in which this first informative phase is absent, might require a prolonged collection of breath concentrations to achieve the maximum improvement in predictive performance.

At this point we would like to acknowledge that the current study might overestimate the potential of our proposed approach. Although we used a cross-validation approach to build our model as well as to conduct our simulation study, some of the components, such as the linear time-correction in K, might be study specific and might not extrapolate well to other studies. A thorough validation of this approach under different clinical regimens (i.e. different dosing, shorter/longer procedures) as well as in different patient populations (as opposed to the healthy volunteers in this study) should inform on the general applicability of this approach.

Finally we wanted to validate the utility of predicted propofol breath concentrations by investigating the correlation with a measure of propofol pharmacodynamics, i.e. BIS, frequently used in the clinic. By comparing two PKPD models, one relating BIS to $IPRED_{breath}$ and one, more classical approach where BIS is linked to a C_e (both approaches shown in [Figure 3-6](#) and in [Table 3-2](#)) we showed that predicted propofol breath concentrations could serve as a surrogate to the predicted effect site concentrations which are frequently used in the clinic to predict propofol's cerebral drug effects. In this respect, the EC_{50} of 12.4 ppb might provide an alternative measurable target to the established hypothetical effect compartment EC_{50} of 2.71 $\mu\text{g/mL}$.

Conclusion

In this work we showed that the current state-of-the-art propofol plasma PK model is easily extended to allow prediction of exhaled propofol concentrations. Furthermore, for the first time, we showed that monitoring of propofol breath concentrations could significantly improve the predictive performance of intraoperative propofol concentrations, thereby allowing further treatment individualization and a more stringent control on the targeted plasma concentrations during general anesthesia. Finally, using two different versions of a PKPD model, we showed that the predicted breath concentrations are a suitable alternative, to the currently used predicted effect site concentrations to describe/predict propofol's cerebral drug effects.

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CHAPTER 4

INFLUENCE OF BAYESIAN OPTIMIZATION ON THE PERFORMANCE OF PROPOFOL TARGET-CONTROLLED INFUSION.

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Abstract

Introduction

Target controlled infusion (TCI) systems use population-based pharmacokinetic (PK) models which do not take into account inter-individual residual variation. This study compares the bias and inaccuracy of a population-based versus a personalized TCI propofol titration using Bayesian adaptation. Hemodynamic and hypnotic stability was studied, as well as the prediction accuracy of the alternative PK models.

Methods

Double-blinded, prospective randomized controlled trial of 120 patients scheduled for cardiac surgery. Blood samples were obtained at 10, 35, 50, 65, 75 and 120 minutes and analyzed using a point-of-care propofol blood analyzer. Bayesian adaptation of the PK model was applied at 60 minutes in the intervention group. Median (Absolute) Performance Error (Md(A)PE) was used to evaluate the difference between bias and inaccuracy of the models. Haemodynamic (blood pressure, heart rate) and hypnotic (bispectral index) stability was studied. The predictive performance of 4 alternative propofol PK models was studied.

Results

MdPE and MdAPE did not differ between groups during the pre-adjustment period (control group: 6.3% and 16.0%; intervention group: 5.4% and 17.7%). MdPE differed in the post-adjustment period (12.5% vs. -0.3%), but MdAPE did not (18.5% vs. 14.7%). No difference in heart rate, MAP or BIS was found. Compared to the other models, the Eleveld propofol PK model (patients) showed the best prediction performance.

Conclusion

When an accurate population-based PK model is used for propofol TCI in cardiac patients a reduction in bias is possible but reduced inaccuracy is not observed if Bayesian adaptation is applied.

Introduction

Target-controlled infusion (TCI) is a computer-controlled drug infusion technique that aims to achieve a user-defined target drug concentration in the plasma or at the effect-site. TCI systems use multi-compartment pharmacokinetic-dynamic models to estimate the infusion rates needed to reach and maintain the desired target concentration of the respective drug.^{1 2} In clinical practice, TCI technology is frequently used to administer propofol³ and the pharmacokinetics of propofol have been extensively described.⁴⁻⁶ Recently Eleveld and colleagues⁷ developed a general purpose 3-compartment pharmacokinetic model which has acceptable performance over a wide range of patients and volunteers and can be incorporated into TCI systems.^{8 9}

All current TCI systems use population-typical values for drug distribution and clearance as the basis for further estimation in the individual patient. While this approach of using population estimates to steer drug infusions in an individual can achieve clinically acceptable anaesthetic conditions, it does retain a source of error because it does not adjust for inter-individual variability. Individuals do not exactly match calculated population typical individuals due to non-modelled residual biological variability, even if covariates such as age, gender, weight and height are included in the typical values for drug distribution and clearance.^{1 10 11} Sources of intra-individual variability, such as chronopharmacokinetics, are not included in current propofol PK models.¹²

A fully patient-specific pharmacokinetic model has the potential to achieve a more precisely controlled time course of plasma concentration but this approach suffers from practical drawbacks, mostly the lack of sufficient samples in a wide range of plasma concentrations for this individual. The method of Bayesian forecasting provides a compromise by tailoring the starting (population) model to a more patient-individualized model on the basis of measured blood samples.¹³ Individualizing pharmacokinetic models using intermittent or continuous drug concentration measurements in a Bayesian approach has been demonstrated successfully in an offline setting.^{14 15} This approach has seldom been applied in clinical practice for propofol administration because a method of fast, bed-side measurement of propofol concentrations has not been available. Recently, point of care analysis of propofol has become available (Pelorus 1500, Sphere Medical, Cambridge, UK) enabling the clinician to obtain accurate propofol blood concentration information at the bed-side in less than 5 minutes.¹⁶

The question remains if individualization of the propofol model during TCI will result in a significantly better prediction of propofol plasma concentrations subsequently. In this study, our primary aim was to compare the bias and precision of classical population-based TCI propofol versus personalized TCI propofol administration. We used a Bayesian approach for adjustment and individualization of the propofol pharmacokinetic (PK) model using bedside measured propofol concentrations. Secondly, we compared hypnotic and haemodynamic

stability before and after the adaptation as measured by EEG and other vital signs registered during routine clinical monitoring. Additionally, we investigated the accuracy of the applied propofol pharmacokinetic model published by Eleveld and colleagues⁷ versus previously published PK models for propofol.

Methods

Study Management and Registration

This trial was conducted at the department of Anaesthesiology at the University Medical Center Groningen, University of Groningen, The Netherlands, in accordance with the Declaration of Helsinki, and in compliance with Good Clinical Practice and applicable regulatory requirements. Ethics committee approval was obtained (UMCG Ethics' Committee, Groningen, The Netherlands, METc 2013/374) and the study was registered in a public registry (Dutch Trial Register, NTR4518) prior to the start of the study. All patients provided written informed consent before participation.

Subjects

Patients between 18 and 75 years of age, with a Body Mass Index between 18 and 35 kg/m², American Society of Anesthesia Physical Status Classification (ASA score) of I-III, scheduled for elective off-pump coronary artery bypass surgery and receiving propofol per standard clinical practice were eligible for this study. Subjects were excluded in case of neurological disease (dementia, cerebral stroke, seizures), psychiatric diseases, regular intake of benzodiazepines, antidepressants, antipsychotics or anticonvulsants, regular intake of opioids, relevant hepatic disease (Child B or higher), pregnancy or currently nursing, overt sign of alcohol abuse, contra-indications or allergies to the drugs used in the study or expected blood loss during surgery higher than 2000 ml.

Study Execution

This study was designed as a double-blinded, prospective, randomized controlled trial. Due to the specific screen design of the computer software used, the anaesthetist responsible for the clinical care of the patient could be blinded to the arm in which the patient was enrolled during the whole operation. Patients were randomized to one of the two study groups using the sealed envelope technique (60 intervention vs. 60 control group).

All patients in both groups received standard clinical anaesthesia care and monitoring. On arrival in the OR, a peripheral intravenous line was inserted in the patients' non-dominant hand or forearm to deliver the required drugs and fluids. Routine vital signs monitors consisting of 5-leads ECG, pulse oximetry, non-invasive blood pressure (IntelliVue MX800, Philips, Eindhoven, The Netherlands) and frontal bispectral index (BIS, Covidien, Dublin, Ireland) were connected. Before induction of anaesthesia, a catheter was placed under topical anaesthesia in the radial artery of the patient's non-dominant hand and connected to a pressure transducer to measure continuous arterial blood pressure and to draw blood samples.

Anaesthesia was induced with a bolus dose of sufentanil and propofol TCI as part of routine clinical care. The initial plasma target concentration was set by the clinician at his/her own

discretion and TCI was started. At loss of consciousness, rocuronium was administered to facilitate tracheal intubation. Anaesthesia was maintained with sufentanil and propofol TCI. Specific propofol target concentrations were selected to ensure haemodynamic stability and hypnotic homeostasis (BIS values between 40 and 60). Additional drugs and therapy to ensure patients' homeostasis during anaesthesia were allowed as part of routine anaesthetic practice. All patients received a central venous catheter for additional fluid and drug administration and for measuring central venous pressure.

Sufentanil was also used during maintenance of anaesthesia. Propofol was administered via a validated PC-based TCI system (RUGLOOP II, Demed, Temse, Belgium) connected to an infusion pump (Carefusion GH, Basingstoke, UK). In order to calculate the time course of propofol infusion to reach and maintain a target plasma concentration, the pharmacokinetic model published by Eleveld and colleagues⁷ was used. We applied the patients' model, not the volunteer model. For sufentanil, the model published by Gepts et al. was used.¹⁷

In all patients, propofol blood concentrations were obtained from arterial blood samples drawn at baseline before the start of drug administration and at 10, 35 and 50 minutes after the start of propofol infusion. These measured propofol blood concentrations were entered into a computer program and for the intervention group a Bayesian adjustment algorithm to individualize the primary predicted volumes of distribution and clearances in the propofol pharmacokinetic model for the individual being studied. After 60 minutes of propofol infusion, the individualized pharmacokinetic model was used for further propofol concentration predictions and TCI infusion rate calculations. Details of the algorithm can be found in the technical [appendix](#). In the control group, no model adjustment was performed and the population typical parameters were used for TCI throughout the procedure. We hypothesized that the error between predicted and measured propofol concentrations would be smaller after model adjustment in the intervention group compared to the error in the control group. To evaluate this, the propofol blood concentration was determined from arterial blood samples drawn at 5 and 15 minutes after the adjustment of the pharmacokinetic model parameters, followed by an additional sample every 60 minutes until the end of the infusion in both groups. One last sample was obtained at the end of infusion.

In the control group, blood samples were measured at identical times, and were also entered into the computer software, similarly to the intervention group, but without execution of the Bayesian adjustment algorithm. As a result, patients in the control group received propofol during the entire case using an unadjusted TCI pharmacokinetic model. We refer to the first hour of drug infusion before the moment of adaptation as the "pre-adjustment period" and the remaining part of the case after adaptation was defined as the "post-adjustment period". For clarity, during comparisons between groups we also refer to the time period after 60 minutes of drug infusion in the control group as "post-adjustment

period” even though no adjustment of the propofol pharmacokinetic parameters was done in this group.

Blood samples were handled by an investigator not involved in the clinical management of the patient. The results of the propofol concentration measurements were not made available to the clinician responsible for the clinical care of the patient and were only known by the independent investigator operating the computer system. In contrast, the predicted plasma concentrations were available to the clinician (on the Rugloop II software screen) at all times in both groups. As clinicians were blinded to group allocation they did not know if their patients’ pharmacokinetics were (to be) adjusted or not. In order to maintain blinding in the post-adaption situation, the clinician only had access to the propofol concentrations estimated by the population model, whereas the researcher was aware of the new C_p values. After adaptation the clinician could ask the researcher for an incremental change in the target C_p (e.g. “increase C_p by 0.5” or “decrease C_p by 0.2” etc). The researcher applied the changes to the target C_p without informing the clinician of the calculated C_p of the adapted model.

The propofol concentration in all samples was measured on site using the Pelorus 1500 analyzer (Sphere Medical, Cambridge, UK). This small tabletop device is capable of analyzing propofol blood concentrations within 5 minutes (linearity up to $12 \mu\text{g}\cdot\text{ml}^{-1}$ ($R^2 = 0.9993$), lower limit of $0.25 \mu\text{g}\cdot\text{ml}^{-1}$. Device imprecision in control solutions: $0.11 \mu\text{g}\cdot\text{ml}^{-1}$ at $5.32 \mu\text{g}\cdot\text{ml}^{-1}$ and $0.17 \mu\text{g}\cdot\text{ml}^{-1}$ at $10.3 \mu\text{g}\cdot\text{ml}^{-1}$; within run precision $0.04 \mu\text{g}\cdot\text{ml}^{-1}$ at $2.84 \mu\text{g}\cdot\text{ml}^{-1}$ and $0.08 \mu\text{g}\cdot\text{ml}^{-1}$ at $6.68 \mu\text{g}\cdot\text{ml}^{-1}$; overall bias $0.15 \mu\text{g}\cdot\text{ml}^{-1}$ (95% confidence interval -0.11 - $0.51 \mu\text{g}\cdot\text{ml}^{-1}$)) using visible absorption spectrometry, as earlier described by Cowley and coworkers and Liu and coworkers.^{16 18}

Sample size calculation

The required sample size was determined by Monte-Carlo simulations of the experimental design. Posthoc estimated “true” individual pharmacokinetic models were taken from previously published propofol population pharmacokinetics⁷ and it was assumed that the studied population of cardiac patients has a 15% lower clearance due to reduced cardiac output and liver blood flow. We simulated 10000 experiment replicates and found that with a sample size of 50 patients per group 82.5% of replicates were successful ($p < 0.05$) in detecting improved predictive performance (lower *MdAPE*, defined in the next section) in the intervention group in the post-adjustment phase compared to the control group. Taking into account the possibility for blood sample and technical problems and a risk of shorter than expected surgical procedures we included 60 patients in each group.

Data analysis and applied statistics

Recorded heart rate and MAP were filtered with a combination of manual (4 samples from 1 individual) and automatic artefact detection ($>30\%$ change within 1 minute treated as

missing). To study the inter-group differences in the time course of the predicted propofol plasma concentrations, BIS, heart rate, and mean arterial blood pressure, the difference between the mean values is plotted versus time, as published previously.¹⁹ The closer the differences between the means are to zero, the less difference there exists between groups at that specific time. Significance is reached between groups at that specific time when zero is not included in the 95% confidence interval area. Between groups, continuous data were analyzed using the independent samples *t*-test or Mann-Whitney test, where appropriate. Significance was set as $p < 0.05$ unless otherwise stated.

To evaluate PK predictive performance, we used the performance error (*PE*) and absolute performance error (*APE*) as previously described by Varvel et al.²⁰, and defined as:

$$PE = (C_{observed} - C_{predicted}) / C_{predicted} \times 100\%$$

and

$$APE = |PE|$$

For these measures the median values are reported, being the MdPE which indicates bias and the median *APE* (*MdAPE*) which indicates precision. These measures will be compared between the control and intervention groups using a Mann-Whitney test (two-sided). Results will be considered significant for $p < 0.01$.

For comparison of predictive performance of PK models from the literature we also evaluated Divergence and Wobble.²⁰ For Divergence we calculated the linear regression slope of *APE* with time for all individuals and report the population median value in %/hr. For Wobble we calculated the median absolute deviation of *PE* from MdPE in the individual and we report the population median value.

Post-hoc simulations of the predictive performance of other PK models

In all patients, infused amounts of propofol were continuously recorded and logged by the RUGLOOPII system. This enables a post-hoc simulation to test the predictive performance of other PK models from the literature versus the observed concentrations. We considered the PK models published by Marsh et al.⁴, Schnider et al.^{5,6}, and Cortinez et al.²¹ in addition to the applied model for patients and volunteers as published by Eleveld et al.⁷

Each model under evaluation was applied to the entire dataset with no Bayesian adjustment to generate the predicted propofol plasma concentrations to compare to the observed concentrations.

Results

A total of 120 patients were included in the data analysis as required to obtain sufficient power ([Figure 4-1](#)). The ethics' committee agreed that excluded patients could be replaced by adding individuals to the randomization list.

Figure 4-1 CONSORT flowchart of screened, considered, included and excluded patients. CNS = Central Nervous Systems, BMI = Body Mass Index, HLM = Heart Lung Machine.

The distribution of patients' demographics was similar between groups as listed in [table 4-1](#). In total 870 propofol plasma concentration observations were obtained from 120

individuals. **Figure 4-2** shows the targeted, the actual predicted and the measured propofol plasma concentration in the control and the intervention group. It can be observed in the absolute mean difference plots that the time course of these concentrations was similar between groups for both targeted and actual predicted propofol plasma concentrations in the pre-adjustment period. As expected, a drift in the absolute mean difference in target and predicted propofol plasma concentration was observed trending towards significance at the end of the case between groups.

Figure 4-3 depicts the individualization of the individual PK parameters (volumes of distribution and clearances) pre- and post-adaptation in the intervention group. In general, model parameters Q3 and V1 showed the greatest differences between the pre- and post-adaptation phases. This is likely due to the limitations of the pre-adaptation sampling schedule (it cannot be too long) and that Q3 was unconstrained for adaptation.

Group	N=	Age (years)	Weight (kg)	Height (cm)	BMI	Gender (m/f)
Control	60	62.0 (7.4) [44, 75]	91.5 (13.8) [46, 114]	178 (9) [152,197]	27.6 (3.1) [19.9,35.0]	54/6
Intervention	60	62.5 (7.5) [44, 75]	81.5 (12.7) [57,111]	178 (8) [156,192]	26.3 (3.1) [20.7,34.0]	56/4
Mann-Whitney <i>p</i> -value		0.827	0.184	0.721	0.157	0.490

Table 4-1 Patient demographics from data analyzed. Data are presented as median (standard deviation, SD) and ranges as [min, max]. BMI = Body Mass Index (kg * m²)

Figure 4-2 Targeted, predicted and measured propofol concentrations (Cp = Plasma concentration) for the control (A, B, and C) and intervention (D, E, and F) groups. Red lines denote the pre-adjustment phase and blue lines the post-adjustment phase. Vertical grey lines indicate the moment of PK model adjustment (intervention group). Panel G and H shows the difference between the mean values (and confidence intervals) between groups versus time for targeted and predicted propofol concentrations, respectively. Abs. Mn diff. Cp target = Absolute Mean different plasma concentration target.

Figure 4-3 Changes in the individual volumes of distribution (V) and clearances (Cl) pre- and postadaptation in the intervention group.

The ratio of the measured to predicted propofol concentrations and the predictive performance of the TCI systems for the control and intervention groups is plotted in [figure 4-4](#). The groups do not differ significantly in the pre-adjustment phase (MdPE of 6.3% vs. 5.4% and MdAPE of 16.0% vs. 17.7% for the control and intervention groups, respectively) but bias (MdPE) in the post-adjustment phase is lower in the intervention group compared to the control group (-0.3% vs. 12.5%) and overall (1.4% vs. 10.9%). Thus, the intervention group is better balanced with respect to over- or under-prediction than the control group. Accuracy (MdAPE) did not differ between the control and intervention groups, and thus neither group is better with respect to how closely the target is achieved.

[Table 4-2](#) depicts the predictive performance of other published propofol PK models when simulating the predicted plasma concentrations using the recorded drug infusion rates and comparing these with the measured propofol plasma concentrations in each individual patient. Compared to the Eleveld model for patients, a worse performance is observed for the Eleveld model derived from volunteers and the Schnider model and a very poor performance is found for the Marsh and Cortinez model.

No differences were found in the depth of anaesthesia level as measured by BIS (except for short lasting difference at the induction) or haemodynamic stability (heart rate and mean arterial blood pressure) between both groups ([Figure 4-5](#)).

	MdPE (%)	MdAPE (%)	Divergence (%/hr)	Wobble (%)
Eleveld (patients)	9.0[-74.8,255]	17.3[0.0,255]	0.8[-36.1, 43.2]	9.8[2.8, 31.7]
Eleveld (volunteers)	44.1[-68.6, 363]	44.6[0.15, 363]	2.9[-36.5, 59.6]	13.8 [1.9, 40.4]
Marsh	85.0[-55.2, 523]	85.0[0.4, 523]	-0.2[-84.9, 61.9]	17.6[4.2, 54.4]
Schnider	27.9[-73.5, 299]	30.5[0.1, 299]	4.6[-33.0, 60.9]	12.0[1.7, 39.9]
Cortinez	46.7[-68.0, 360]	47.9[0.0, 360]	6.2[-36.8, 70.0]	13.8[0.5, 47.4]

Table 4-2 Predictive performance of propofol PK models from the literature. Maximum and minimum values are represented as [min, max]. MdPE = Median Prediction Error, MdAPE = Median Absolute Prediction Error.

Figure 4-4 The ratio of measured to predicted propofol concentration for the control and intervention groups. Vertical grey lines indicate the moment of PK model adjustment (intervention group) or observations later than 60 min (Control group). Red lines denote the pre-adjustment phase and blue lines the post-adjustment phase. The * defines $p < 0,05$. MdPE = Mean different Prediction Error, MdAPE = Mean different Absolute Prediction Error.

Figure 4-5 Time course of heart rate and mean arterial blood pressure (INV MAP) and BIS for the control (A, B and C) and intervention (D, E and F) groups. Red lines denote the pre-adjustment phase and blue lines the post-adjustment phase. Vertical grey lines indicate the moment of PK model adjustment (intervention group). Panels G, H and I shows the difference between the mean values (and confidence intervals) between groups. Bpm = beat per minute, INV MAP = Invasive Mean Arterial Pressure in mmHg (obtained from an arterial line). Abs. Mn. Diff. Heart Rate / INV MAP / Bispectral Index = Absolute Mean different Heart Rate / Invasive Mean Arterial Pressure / Bispectral Index.

Discussion

TCI is traditionally applied using population PK models to predict drug concentrations and to calculate required infusion profiles. This approach focuses on a population typical individual and the drug administration profile necessary to achieve and maintain the desired target drug concentrations. However, in reality, TCI systems are applied to specific individuals and the predictions will not be perfect because randomly these individuals will not exactly match the population typical individual.¹⁰ While clever covariate correction methods (corrections for weight, age, etc.) can reduce this variability to some degree, some residual variability is unavoidable. The irreducible variability is expressed as unexplained population variability in the PK model parameters. Its' origin is the biological variability not captured by the simplistic (compared to biology at least) structure of the PK models, its' variability over time²², and the limitations of currently available data. Likely much of this variability is not understood by current pharmacological science and consequently cannot be captured properly in the composed models. While we may not be able to shed light on the unexplained biological variability, we can, to a degree, measure its influence in an individual. This can be achieved by making observations of drug concentrations and effects and comparing these to those predicted by the PK model. This information can be used to refine the PK model for a specific individual. If these actions can be performed within a clinical time frame it may enable on-line individualization of a PK model during the time course of a clinical procedure. Such individualized model may be expected to achieve less biased and inaccurate predictions for that individual compared to the unadjusted population model and consequently it might be more useful for guiding ongoing drug dosing during the clinical procedure. The value of the availability of an online method to minimize the bias and inaccuracy of the individual's propofol plasma-concentration predictions during TCI is not to be underestimated for clinical practice. It opens the road towards future medical possibilities to optimize propofol titration in pharmacologically challenging populations that already receive propofol without PK model adjustment. However, one should consider the ratio of benefits versus complexity and costs.

In this study, our primary aim was to compare the bias and precision of TCI propofol administration based on a classical population-based model, with that of TCI propofol administration based on an individualized model. We applied a Bayesian adjustment algorithm to individualize the propofol pharmacokinetic (PK) model parameters of distribution and clearance using bedside measured propofol concentrations.

As shown in [figure 4-2](#), propofol titration was performed similarly in both groups. In the pre-adjustment period, we logically observed similar propofol PK model bias and inaccuracy, as described by MdPE and MdAPE, respectively, in both groups. In the post-adjustment period, a significant reduction in bias was found, both intra-individually as well as between groups ([figure 4-4](#)), when using Bayesian adaptation to adjust propofol PK model parameters to individuals. This means that the individual reduction in bias resulted in less overall prediction bias. It should be noted that MdPE is a signed value and represents the direction of the over-

or under-prediction rather than the size of the possible bias, which is better represented by MdPE.²³ The beneficial results of MdPE did not result in a significant reduction of inaccuracy of the propofol PK model as described by MdAPE. Even though MdAPE does not reveal information on the direction of the possible bias, it quantifies its amplitude.

Previously, Glass et al. showed that for most clinically applicable and acceptable PK models, MdAPE lies between 20 and 30%.¹ To have a better understanding of the values of MdPE and MdAPE in our specific cardiac population, we compared the predictive performance of the Eleveld model (patients) to other published propofol PK models, such as the Marsh, Schnider and Cortinez model. Hereby, it should be noted that both the Marsh and the Schnider model are clinically available in various commercialized TCI pumps. With an MdAPE of less than 20%, predictive performance of the Eleveld PK model for patients is better than that of other PK models in the literature and better than the Eleveld model derived from data from volunteers who received propofol without any opioids. This analysis of performance error when using the patient version of the Eleveld model proves that this model is already accurately predicting the time course of propofol plasma concentration in the individual patient in our study, even without applying the Bayesian adjustments. This may have contributed to the lack of improvement in accuracy with Bayesian adaptation. It may be more difficult to improve an already well performing model compared to a poorly performing one, even if one only considers performance within a dosing occasion. Another obstacle is that adaptation cannot correct for structural model misspecification, an unavoidable source of error in models of biological processes. Although our results are obtained in a specific population with probable altered pharmacokinetics, our results may not necessarily reflect other patient groups. In more pharmacologically challenging populations, the unadjusted Eleveld PK model may perform more poorly. Bayesian adaptation might be more beneficial in those populations.

A Bayesian-based adjustment algorithm is influenced by the specific values of the applied PK model variances. For example, the variances in the applied Eleveld model⁷ are larger than the rather small variances described in the model published by Schnider et al.^{5,6} leading to a larger degree of adjustment. There are also complex performance tradeoffs with sampling and adaptation times. A longer pre-adaptation period with a greater number of samples might have enabled greater precision in estimating the individual effects. However, this may not be clinically beneficial because the improved estimates only become available closer to the end of the procedure. Even high-resolution individualization has been shown to not be beneficial for midazolam when applied across occasions.²⁴ However, this is a more difficult problem than we attempt here, individualization within a single occasion. This would imply that there is only limited value for increasing the number of samples. The possibility of erroneous observations leading to mal-adaptation of the PK model should also be considered as these can occur due to process or device errors or sample mishandling. Detecting and correcting these errors is not a straightforward process but would be

important for broader clinical use of PK adaptation schemes. In addition, on-line adaptation techniques require the correct functioning of the complex devices needed to intra-operatively estimate propofol concentrations. Periodic device failure was a reason for dropouts in this investigation and this is a drawback of the technique applied here. Reliability of the complete system will always be poorer than the least reliable essential component.

A similar range of propofol plasma concentrations was targeted in both groups. No differences were found in both hypnotic and haemodynamic conditions among groups. As such, the application of the model adjustment did not result in altered anaesthetic conditions. This might be due to the fact that the anaesthetist was able to alter the targeted propofol concentrations to maintain a specific hypnotic drug effect. Nevertheless, when comparing the target plasma concentrations in the post-adjustment period between the control and intervention group, a time-related drift towards significant differences in target concentration can be observed from the difference between the means and confidence intervals. This indicates the effect of the adjustment in the PK model in the required target concentration to maintain a specific hypnotic effect.

Conclusion

We conclude that when the Eleveld PK model (patients) is applied for TCI in cardiac patients a reduction in bias is possible while reduced inaccuracy is not observed if Bayesian adaptation is applied under the conditions of this investigation.

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APPENDIX TO CHAPTER 4

Bayesian adjustment for a three-compartment PK model concerns the individualization of the model parameters based on a population PK model structure and one or more concentration observations. Individualization is intended to improve prediction error in the particular individual from which the observations were obtained. This is achieved by moving the model parameter estimates away from the population estimates and towards values consistent with the observations. For K observations from an individual the posthoc Bayesian estimates for PK parameters can be estimated by minimizing the objective function which is twice the negative log-likelihood of the observations given population model:

$$-2\log(L_n) = \sum_{i=1}^K \frac{(Yobs_i - Ypred_i)^2}{\sigma^2} + \sum_{m=1}^M \frac{(P_m - Ppop_m)^2}{\sigma_m^2}$$

Where:

- $Yobs_i$ is the i^{th} concentration observed at time t
- $Ypred_i$ is the i^{th} concentration predicted by the PK model at time t
- σ^2 is the residual observation variance
- P is the estimated value for population parameters
- $Ppop$ are the PK model population parameter estimates
- σ_m^2 is the variance of the PK parameter across the population

For the Eleveld PK model for propofol the model parameter equations are:

$$\begin{aligned}
 f_{\text{sigmoid}}(x, E50, \lambda) &= x^\lambda / (x^\lambda + E50^\lambda) \\
 ADLT &= f_{\text{sigmoid}}(WGT, 16.6, 2.75) \\
 f_{\text{aging}}(x) &= e^{-0.001(\text{AGE}-35)x} \\
 CLAG &= 1 - f_{\text{sigmoid}}(PMA, 69.2, 8) \\
 PMAL &= \begin{cases} f_{\text{sigmoid}}(PMA, 22.2, 8), & \text{male} \\ 0, & \text{female} \end{cases} \\
 KGEN &= e^{0.225(CLAG(1-PMAL)+(1-CLAG)PMAL)ADLT} \\
 V1(l) &= \begin{cases} 5.74, & \text{healthy} \\ 9.77, & \text{patient} \end{cases} \cdot \frac{ADLT}{ADLT_{\text{ref}}} \cdot \begin{cases} 1, & \text{male} \\ 0.830, & \text{female} \end{cases} \cdot f_{\text{aging}}(3.55) \cdot e^{\begin{cases} \eta_1, & \text{healthy} \\ \eta_2, & \text{patient} \end{cases}} \\
 V2(l) &= \begin{cases} 11.8, & \text{healthy} \\ 29.0, & \text{patient} \end{cases} \cdot \left(\frac{WGT}{70} \right) \cdot f_{\text{aging}}(8.91) \cdot e^{\eta_3} \\
 V3(l) &= \begin{cases} 222, & \text{healthy} \\ 134, & \text{patient} \end{cases} \cdot \left(\frac{WGT}{70} \right)^{0.35} \cdot \frac{ADLT}{ADLT_{\text{ref}}} \cdot e^{\eta_4} \\
 CL(l/\text{min}) &= \begin{cases} 1.83, & \text{healthy} \\ 1.53, & \text{patient} \end{cases} \cdot \left(\frac{WGT}{70} \right)^{0.75} \cdot \frac{KGEN}{KGEN_{\text{ref}}} \cdot f_{\text{aging}}(3.55) \cdot e^{\eta_5} \\
 Q2(l/\text{min}) &= \begin{cases} 3.10, & \text{healthy} \\ 1.42, & \text{patient} \end{cases} \cdot \left(\frac{V2}{29.0} \right)^{0.75} \cdot f_{\text{aging}}((1-ADLT) \cdot 27.6 + ADLT \cdot 6.34) \cdot e^{\eta_6} \\
 Q3(l/\text{min}) &= \begin{cases} 1.08, & \text{healthy} \\ 0.608, & \text{patient} \end{cases} \cdot \left(\frac{V3}{134} \right)^{0.75} \cdot f_{\text{aging}}(6.34) \cdot e^{\begin{cases} \eta_7, & \text{healthy} \\ 0, & \text{patient} \end{cases}}
 \end{aligned}$$

Where:

- *WGT* is individual weight in kg
- *AGE* is individual age in years

The population variances in the model are:

	Variance	CV(%)
η_1	0.032	17.9
η_2	0.323	61.7
η_3	0.294	58.4
η_4	0.318	61.2
η_5	0.068	26.6
η_6	0.130	37.2
η_7	0.091	30.9

For the current investigation a residual error of 20% was assumed and thus the Bayesian adjustment procedure was performed by minimizing the following objective function:

$$\begin{aligned}
-2 \log(L_n) = & \sum_{i=1}^K \frac{\left(\frac{Cobs_i}{Cpred_i} - 1 \right)^2}{0.04} + \frac{(\ln(V1) - \ln(V1_{pop}))^2}{0.323} + \frac{(\ln(V2) - \ln(V2_{pop}))^2}{0.294} \\
& + \frac{(\ln(V3) - \ln(V3_{pop}))^2}{0.318} + \frac{(\ln(CL) - \ln(CL_{pop}))^2}{0.068} + \frac{(\ln(Q2) - \ln(Q2_{pop}))^2}{0.13}
\end{aligned}$$

Where:

- $Cobs_i$ and $Cpred_i$ are the observed and predicted propofol concentrations at time i for K time points.
- $V1, V2, V3, CL, Q2$ are the individual estimated volumes and clearances. The individual estimate of $Q3$ was not constrained.
- $V1_{pop}, V2_{pop}, V3_{pop}, CL_{pop}, Q2_{pop}$ are the population estimated volumes and clearances determined by the Eleveld PK model.

For the current investigation figure 3 in the main paper shows the differences in individual PK parameters pre- and post-adaptation.

CHAPTER 5

INFLUENCE OF AN “ELECTROENCEPHALOGRAPH (EEG) BASED” MONITOR CHOICE ON THE DELAY BETWEEN THE PREDICTED PROPOFOL EFFECT-SITE CONCENTRATION AND THE MEASURED DRUG EFFECT

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Abstract

Background

Clinicians can optimize propofol titration by using two sources of pharmacodynamic (PD) information: the predicted effect-site concentration ($C_{e_{prop}}$) and the electroencephalographically (EEG) measured drug effect. Relation between these sources should be time-independent, i.e., perfectly synchronized. In reality, various issues corrupt time-independency leading to asynchrony or in other words, hysteresis. This asynchrony can lead to conflicting information making effective drug dosing challenging. In this study, we tried to quantify and minimize the hysteresis between the $C_{e_{prop}}$ (calculated using the Schnider model for propofol) and EEG measured drug effect, using nonlinear mixed-effects modeling (NONMEM). Further, we measured the influence of EEG based monitor choice, namely Bispectral index (BIS) versus qCON monitor, on propofol PD hysteresis.

Methods

We analyzed the PD data from 165 patients undergoing propofol-remifentanyl anesthesia for outpatient surgery. Drugs were administered using target-controlled infusion pumps (TCI). Pumps were programmed with Schnider model for propofol and Minto model for remifentanyl. We constructed 2 PD models (direct models) relating the Schnider $C_{e_{prop}}$ to the measured BIS and qCON monitor values. We quantified the models' misspecification due to hysteresis, on an individual level, using the root mean square of errors (RMSE). Subsequently, we optimized the PD models' predictions by adding a lag term to both models (lag-time PD models) and quantified the optimization using the RMSE.

Results

There is a counter-clockwise hysteresis between $C_{e_{prop}}$ and BIS/qCON values. Not accounting for it resulted in a direct PD model with a $C_{e_{50}}$ of 6.24 $\mu\text{g/ml}$ and 8.62 $\mu\text{g/ml}$ and RSME (median and interquartile range (IQR)) of 9.38 (7.92-11.23) and 8.41(7.04-10.2) for BIS and qCON, respectively. Adding a modelled lag factor of 49 seconds to the BIS model and 53 seconds to the qCON model improved both models' prediction, resulting in similar $C_{e_{50}}$ (3.66 and 3.62 $\mu\text{g/ml}$ for BIS and qCON) and lower RMSE (median (IQR) of 7.87 (6.49-9.90) and 6.56 (5.28-8.57) for BIS and qCON.

Conclusion

There is a significant " $C_{e_{prop}}$ vs. EEG measured drug effect" hysteresis. Not accounting for it leads to conflicting PD information and false high $C_{e_{50}}$ for propofol in both monitors. Adding a lag term improved the PD model performance, improved the "pump-monitor" synchrony and made the estimates of $C_{e_{50}}$ for propofol more realistic and less monitor-dependent.

Introduction

Pharmacokinetics (PK) describes the time-course of the drug plasma concentration. Pharmacodynamics (PD) describes the time-independent relation between the achieved drug concentration at the drug-effect-site (C_e) and the resulting drug effect. The drug needs time to reach the effect-site. This action can be quantified by a first-order process defined as hysteresis and characterized by k_{e0} . During total intravenous anesthesia (TIVA), drug C_e can be predicted using target-controlled infusion (TCI) technology¹⁻³ or anesthesia drug displays⁴ while achieved drug effect can be measured by various processed electroencephalographic (EEG) measures.⁵ The concept of effect-site concentration takes into account this hysteresis and as such, the time course of the effect-site concentration should match the time course of the drug effect.

Both C_e and EEG information can be displayed to the anesthesiologist, thereby improving clinical decision making.^{6,7} Both sources of information can only be correlated at a specific moment if all biological and computational time-related issues are taken into account thereby ideally, resulting in perfect time synchronization. In reality, various time-related issues might corrupt the time-independency causing additional hysteresis in the dose-response relation.

The clinically applied PKPD models were developed using different effect measures than those presently used in the operating theatre. For propofol, Schnider and colleagues applied the propofol canonical univariate parameter (CUP_{prop}) to measure cerebral drug effect and generate the PD model.^{8,9} CUP_{prop} was developed without any processing delay because analyses were done offline.⁹ Clinically applicable processed EEG monitors require time to calculate an index value and display it on screen. This time delay varies between monitors and is influenced by non-steady-state conditions as present during clinical anesthesia. Pilge and colleagues found variable delay times for the Bispectral index (BIS[®], Medtronic, Dublin, Ireland) during transitions of consciousness.¹⁰ This delay can have an impact on monitor performance. Other monitors might have other delay characteristics.

Until today, no information is available on the influence of the monitor delay on the pharmacodynamics of propofol when using C_e targeted target controlled infusion (TCI) with the Schnider model.¹¹ As such, we studied the influence of these delays on the propofol PD parameters using two clinically available drug effect monitors namely, BIS and the qCON monitor (CONOX, Quantum Medical, Barcelona, Spain) during C_e targeted TCI for propofol during clinical anesthesia.

Material and Methods

Data collection

Data for this study was collected prospectively from September 2016 until July 2017 during clinical anesthesia for outpatient surgical procedures in the Ambulatory Surgery facility at Hospital CLINIC de Barcelona (Barcelona, Spain). Data collection was part of a larger project to construct a database containing observational PK and PD data on propofol and remifentanyl in clinical practice. We randomly extracted data of 165 patients from this database. The sample size was determined a priori to detect a qCON difference of 12 (assuming a standard deviation of 16) between awake and sedated patients with a power of 99% and a significance level of 0.01. Anonymized data collection was approved by the Ethics Committee of the Hospital CLINIC de Barcelona (Reg n°: 2013/ 8356). All patients gave written informed consent before inclusion. The manuscript was composed to adhere to the applicable CONSORT guidelines. Data from the TCI pumps and EEG monitors were collected in concordance with ICH Guidelines for Good Clinical Practice using dedicated recording software (RUGLOOP II, Demed, Temse, Belgium). Patients with an American Society of Anesthesiologists (ASA) Physical Status Classification Score of 1-3 were eligible for inclusion. Morbidly obese patients and patients affected by medical conditions or being treated with medications that could affect the electroencephalographic tracings were excluded.

General anesthesia

Patients received propofol and remifentanyl TIVA while undergoing gynecologic and abdominal surgery procedures, e.g., hysteroscopy, urinary incontinence repair, open or laparoscopic inguinal or umbilical hernia repair and laparoscopic cholecystectomy. Both drugs were infused using TCI pumps (Base Primea, FreseniusVial, Brezins, France). TCI was targeting the effect-site concentration (C_e) using the Schnider PKPD model^{8,9} for propofol and the Minto PKPD model for remifentanyl.¹² In their original publication, Schnider used the CUP_{Prop} to determine the drug effect of propofol while Minto used the spectral edge frequency (SEF) to determine the drug effect of remifentanyl.

The general anesthesia approach was that of a routine clinical case. In order to minimize the influence of the anesthesia care providers on the study outcome, only two anesthesiologists were involved in patient care during data collection. Each of them had more than ten years of experience in the use of TCI for TIVA.

A typical case started with a remifentanyl infusion of 1.5 ng/mL while the patient was fully monitored. Subsequently, a target C_{ePROP} was chosen by the clinician between 4.5 and 6 $\mu\text{g}\cdot\text{mL}^{-1}$ of propofol. Induction started until loss of response to a verbal command. Next, the target C_{eREMI} was raised to 4 $\text{ng}\cdot\text{mL}^{-1}$ when LMA was the chosen airway control method or to 6 $\text{ng}\cdot\text{mL}^{-1}$ remifentanyl if laryngoscopy and intubation was to be performed. In the latter case, a bolus of 30 mg of rocuronium was administered two minutes before attempting laryngoscopy in order to facilitate endotracheal intubation. Control of the TCI pumps was at

the full discretion of the attending anesthesia team. During surgery, target C_{ePROP} and C_{eREMI} were tailored to individual patients' needs. At the end of the surgery, TCI C_e targets were set to 0 and patients were left to recover from anesthesia spontaneously, i.e. without any external stimulation until opening of the eyes. After that they were prompted to breathe deeply. For a complete overview of propofol and remifentanyl C_e targets and BIS and qCON values during the study please see the supplemental material.

EEG based drug effect monitors

The clinical cerebral drug effect of propofol was measured using two processed EEG monitors, namely, BIS monitor and qCON monitor.

Bispectral Index

BIS is a processed frontal EEG parameter index.¹³ It uses a proprietary algorithm containing fixed, weighted ratio of several EEG based sub-parameters (including β -ratio, SynchFastSlow, QUAZI and burst suppression ratio) obtained by time spectral and bispectral analysis of the raw signal to generate its output.¹⁴ It produces a dimensionless number between a 99 and a 0 representing no drug effect noticeable and a maximal hypnotic drug effect, respectively.

qCON

qCON is also a processed frontal EEG parameter index. qCON's development has been previously described in detail by Jensen and colleagues.¹⁵ In short, qCON is calculated by feeding in frequency power ratios of 4 different EEG frequencies bands (4-8 Hz, 8-13 Hz, 11-22 Hz, 33-44 Hz) and the burst suppression ratio into a mathematical model called “Quadratic Equation.” It generates an output on a 0-99 scale where decreasing output numbers indicates increasing hypnotic drug effect. The frequency ratios are calculated and updated every second.

Pharmacodynamic modeling of the concentration-effect relation (direct PD model)

Non-linear mixed-effects modeling (NONMEM) was used to study the relation between predicted propofol and remifentanyl effect-site concentrations and BIS and qCON. All models were fitted to the data using the FOCE estimation routine in NONMEM® (version 7.3; Icon Development Solutions, Hanover, MD, USA).

Model building was guided by the objective function value (OFV). A decrease in the OFV of 3.84 points was considered significant at the 5% level of significance. Goodness-of-fit of the different candidate models was evaluated graphically in R® (R Foundation for Statistical Computing, Vienna, Austria).

A sigmoid E_{max} model, as shown in [equation 5-1](#), was used to describe the non-linear relation between BIS or qCON and the predicted effect-site concentrations for propofol (C_{ePROP}) and remifentanyl (C_{eREMI}).

$$PD = PD_0 \times \left(1 - \frac{E_{max} \times C_{e,Prop}^{\gamma}}{Ce_{50,INT}^{\gamma} + C_{e,Prop}^{\gamma}} \right) \quad \text{Equation 5-1.}$$

In this model, the pharmacodynamic endpoint, BIS or qCON, is related to the $C_{e,Prop}$ according to a non-linear function with γ defining the steepness of the concentration-effect relation. PD_0 is the baseline BIS or qCON when no drug is present, and E_{max} is the maximum drug effect. The $Ce_{50,INT}$ is the predicted propofol effect-site concentration which produces 50% of the maximal drug effect. To account for the interaction between remifentanyl and propofol, a hierarchical interaction model as shown in [equation 5-2](#) was used.

$$Ce_{50,INT} = Ce_{50} \times \left(1 - \frac{POT_{max} \times C_{e,Remi}^{\gamma_R}}{Ce_{50,Remi}^{\gamma_R} + C_{e,Remi}^{\gamma_R}} \right) \quad \text{Equation 5-2.}$$

In this interaction model, the predicted effect-site concentration producing 50% of maximal drug effect ($Ce_{50,INT}$) is composed of the predicted Ce producing 50% of maximal drug effect when propofol is administered alone (Ce_{50}) and an interaction term that describes the influence of remifentanyl on this Ce_{50} . The predicted effect-site concentration of remifentanyl (Ce_{Remi}) decreases the propofol Ce_{50} according to a non-linear function with γ_R defining the steepness of the curve, POT_{max} being the maximum influence of remifentanyl on the $Ce_{50,Prop}$ and $Ce_{50,Remi}$ being the predicted Ce producing half of this maximum potentiation. To reduce the number of estimable parameters in the models, we assumed a baseline BIS or qCON (PD_0) value of 100 and a maximum propofol drug effect (E_{max}) of 1.

Inter-individual variability (IIV) around the population typical parameters was assumed according to a multivariate lognormal distribution with mean 0 and variances ω^2 . Residual unexplained variability (RUV) was described using additive error models.

Quantification of the model fit

To quantify the extent of model misspecification on an individual level we calculated the root mean squared error (RMSE) for every patient in the dataset according to equation 3.

$$RMSE_k = \sqrt{\frac{\sum_{i=0}^n (PD_{k,i} - IPRED_{k,i})^2}{n}} \quad \text{Equation 3}$$

In this equation, the RMSE for patient k is calculated from all measured PD variables (n) at times i (qCON or BIS) and the individually (post hoc) predicted response according to the model ($IPRED_{k,i}$).

Developing a PD model to accommodate for the hysteresis (lag-time PD model)

Based on the model described previously, we explored strategies to accommodate hysteresis between the predicted propofol and remifentanil effect-site concentrations and the measured BIS or qCON.

The approach consisted of applying a lag-time to the predicted C_{ePROP} and C_{eREMI} from the Schnider and Minto model, respectively. For this, we manually fitted the model to different shifted versions of the original dataset, as used before.¹⁶ The time-shift implies that observed qCON and BIS values were matched with a propofol and remifentanil C_e observed earlier. In other words, a BIS value which was originally observed at time x with a corresponding propofol C_e of y_x and remifentanil C_e of z_x is matched in the “new” dataset with C_e ’s of $y_{x-\Delta t}$ and $z_{x-\Delta t}$ which were observed at time $x - \Delta t$, with Δt denoting the lag-time. It is noteworthy to appreciate that across the different shifted datasets the vector of observed qCON or BIS values were identical, i.e., nothing changed to the dependent variable. The objective function value (OFV) was used to construct the discrete 3D likelihood surface and derive the (approximate) likelihood profiles for both estimated lag-times.

Results

Patients characteristics

Records from 165 patients were included in the study. Patient demographic data and drug dosing ranges are shown in [table 5-1](#). Nine out of 165 patients were male. Mean (SD) age was 53.1(15.4), mean weight was 66.8 kg (12.5) and mean height was 159 cm (0.07).

	MIN	q25	MEDIAN	q75	MAX	MEAN	SD
AGE (YR)	16	39	54	67	82	53.1	15.4
WEIGHT (KG)	42	58	65	76	119	66.8	12.5
HEIGHT (CM)	140	155	159	164	176	159	0.07
LBM (KG)	32.4	41.7	44.5	47.7	65.4	44.9	4.95
BSA (KG/M2)	1.29	1.58	1.67	1.80	2.19	1.68	0.15
CEPROP (μG.ML-1)	1	2.50	2.8	3.02	4.5	2.81	0.53
CEREMI (NG.ML-1)	1	2.09	2.6	3.01	4.47	2.66	0.65
LENGTH OF SESSION (MIN)	22.4	52.6	68.3	89	147	71.7	25.2

Table 5-1 Patient/surgical procedure characteristics and drug dosing ranges. $C_{e_{prop}}$ and $C_{e_{remi}}$ denote the median predicted C_e for each session.

Available data

For each patient, a median of 2146 [range: 719 – 4361] predicted $C_{e_{prop}}$ concentrations and 2144 [range: 711 – 4625] predicted $C_{e_{remi}}$ were recorded. Also, a median of 3983 [range: 1162 – 8413] BIS measurements and a median of 3905 [range: 1302 – 8428] qCON measurements were available. For an overview of the raw $C_{e_{prop}}$, $C_{e_{remi}}$ concentrations and BIS and qCON values collected during the study see [figure 5-1](#). Data from 6 subjects (3.6%) were excluded from the analysis due to errors in the predicted C_e records or the absence of BIS and/or qCON signal. In order to reduce the computational burden during model development, we reduced the number of BIS and qCON measurements per subject. For this, a random sample was drawn, thereby only retaining 1/10th of the observations. All data were analyzed using R® (R foundation for statistical computing, Vienna, Austria) using the “tidyverse” package.

Predicted $C_{e_{prop}}$ using the Schnider model versus qCON and BIS

As shown in the left panel of [Figure 5-2](#), there is a considerable clockwise hysteresis in the predicted $C_{e_{prop}}$ versus the BIS and the qCON index. Three patients shown are those with the lowest (top panel), median (middle panel) and highest (bottom panel) RMSE for qCON index. The overall median (IQR) for root mean squared error (RMSE) for BIS was 9.38 (7.92; 11.23) and for qCON was 8.41 (7.04; 10.2). [Table 5-2](#) shows the PD variable estimates for the direct PD model. C_{e50} was 6.24 (8.4) μg.mL⁻¹ for BIS and 8.62 (13.9) μg.mL⁻¹ for qCON. γ was 0.75 for BIS and 0.59 for qCON.

Figure 5-1 The figure shows raw Ce_{Prop} , Ce_{Remi} concentrations and BIS and qCON values collected during the study. (also known as the “spaghetti plots”). Each gray line denotes a single patient while average value is marked in red.

Collapsing the hysteresis loop with a lag-time PD model

The objective function value is lower for the lag time-PD models compared to the direct PD model, suggesting significant hysteresis between the BIS/qCON and the predicted propofol and remifentanyl effect-site concentrations according to the Schnider model and Minto model respectively. Based on the data, we decided to evaluate lag-times between 10 and 70 seconds for propofol and between 0 and 300 seconds for remifentanyl. All possible combinations of propofol and remifentanyl lag-times were explored (i.e., the entire discrete 3D surface was sampled). For qCON we found a lag-time of 53 seconds and 245 seconds for propofol and remifentanyl. For BIS the lag time was 49 seconds for propofol and 97 seconds for remifentanyl.

Figure 5-2 Hysteresis plots showing the trajectories for BIS (solid black lines) and qCON (solid grey lines) as a function of the predicted effect-site concentration for propofol (C_e). The left plot shows the raw data, whereas the right plot shows the predicted effect-site concentration offset with a lag time of 53 s (the optimal lag-time as defined by the Lag-time PD model for qCON). Patients shown are those with the lowest (top panel), median (middle panel) and highest (bottom panel) RMSE for qCON. Accounting for hysteresis by introducing a lag-time in the model reduces the RMSE for these patients from 17.3, 8.40 and 4.19 to 11.1, 7.1 and 2.87, respectively. The post hoc predicted qCON in the absence of remifentanyl is shown with a solid red line for illustrative purposes. **C_e** : Effect site concentration.

Chapter 5: Influence of an “electroencephalogram (EEG) based” monitor choice on the delay between the predicted propofol effect-site concentration and the measured drug effect

Parameter	PD models for BIS				PD models for qCON			
	Direct model		Lag-time model		Direct model		Lag-time model	
	Estimate	IIV	Estimate	IIV	Estimate	IIV	Estimate	IIV
LAG _{Prop} (s)	X	X	49		X	X	53	
LAG _{Remi} (s)	X	X	97		X	X	245	
C _{ES0,Prop} (µg.mL ⁻¹)	6.24 (8.4) [5.21; 7.27]	72% (17.9) [47; 97]	3.66 (5.2) [3.29; 4.03]	60% (14.8) [42; 77]	8.62 (13.9) [6.27; 11.0]	96 % (28.3) [43; 150]	3.62 (4.8) [3.28; 3.96]	56 % (18.3) [0.36; 0.76]
γ _{Prop}	0.75 (5.4) [0.67; 0.83]	41% (20.1) [25; 57]	0.90 (4.0) [0.83; 0.97]	44% (18.2) [28; 59]	0.59 (6.7) [0.51; 0.67]	44 % (18.3) [28; 60]	0.93 (4.0) [0.86; 1.00]	48 % (13.8) [35; 61]
C _{ES0,Remi} (ng.mL ⁻¹)	0.67 (8.5) [0.54; 0.79]		1.07 (7.9) [0.90; 1.23]		0.56 (13.7) [0.41; 0.71]		0.89 (15.8) [0.61; 1.16]	
γ _{Remi}	3.28 (13.0) [2.44; 4.11]		4.16 (20.4) [2.60; 5.82]		2.83 (18.7) [1.79; 3.87]		2.39 (46.0) [0.23; 4.54]	
POT _{max}	0.79 (3.1) [0.74; 0.84]		0.60 (4.3) [0.55; 0.65]		0.85 (3.5) [0.79; 0.91]		0.57 (7.7) [0.48; 0.66]	
σ _{Additive}	9.90 (4.5) [9.02; 10.7]		8.8 (5.7) [7.81; 9.78]		9.1 (5.0) [8.2; 10]		7.7 (7.2) [6.6; 8.8]	
OFV	372,870		356,996		365,879		342,808	

Tabel 5-2 Estimated parameters for the pharmacodynamic models for BIS and qCON. Numbers between parentheses indicate relative standard errors (%); 95% confidence intervals are shown in square brackets [] IIV: Inter-individual variability modeled using a lognormal distribution with variance w , expressed as percentage according to: $\sqrt{e^w} - 1 * 100\%$; LAG: Lag-time term added to the model (s); C_{ES0}: Effect site concentration necessary to achieve 50% of the drug effect; γ: The Hill coefficient representing the steepness of the concentration-response relationship; POT_{max}: The maximum influence (potentiation) of remifentanyl on the propofol C_{ES0}; σ_{Additive}: Standard deviation of the residual unexplained variability according to the additive error model; OFV: Objective function value.

Table 5-2 shows the estimated PD parameters for the BIS and the qCON direct PD vs. lag-time PD model. Compared to the estimates for the direct PD model, we found that estimated Ce_{50} is lower ($3.66 \mu\text{g.mL}^{-1}$ vs $6.24 \mu\text{g.mL}^{-1}$) and the estimated γ is higher (0.90 vs 0.75) in the lag-time model for BIS. Similarly, compared to the estimates for the direct model, we found in the lag-time qCON model that Ce_{50} was lower ($3.62 \mu\text{g.mL}^{-1}$ vs $8.62 \mu\text{g.mL}^{-1}$) and the estimated γ was also higher (0.93 vs 0.59). The estimates for the remifentanyl interaction with propofol ($POT_{\max}$, γ_R and $Ce_{50\text{Remi}}$) are also significantly influenced by the addition of the lag-time in the model. $POT_{\max}$ decreases both for BIS from 0.79 to 0.59 and qCON from 0.85 to 0.56 in the lag-time model.

Figure 5-3 Likelihood ratio profiles for the estimated delays in the lag time PD models for BIS (solid black line, left y-axis) and qCON (solid grey line, right y-axis). **OFV:** Objective function value.

Likelihood profiles, shown in **figure 5-3**, demonstrate good precision in the estimates for the lag-time. Confidence bounds derived from these profiles would be within ± 1 sec of the final estimate (as a 1-second change in the estimate increases the OFV with > 3.84 points). Implementing the lag-time PD model decreases Ce versus measured drug effect hysteresis. The right part of Figure 1 shows the reduction in the degree of hysteresis for three patients, whereas supplemental **figures 5-4** and **5-5** show a boxplot of paired RMSE estimates for all patients in the dataset for qCON and BIS, respectively. The median decrease in RMSE across patients is 20.3% with an interquartile range of 7.90% to 31.0% for qCON and 11.9% with an interquartile range of 4.58% to 19.4% for BIS index.

Figure 5-4 The figure shows the decrease in model misspecification for all patients in our study between both PD models for *qCON*. The median decrease in RMSE across patients is 20.3% with an interquartile range of 7.90% to 31.0%. **RMSE:** Root mean squared error

Figure 5-5 Figure showing the decrease in model misspecification for all patients in our study between both PD models for BIS. The median decrease in RMSE across patients is 11.9%, with an interquartile range of 4.58% to 19.4%. **RMSE:** Root mean squared error.

Figure 5-6 shows the predicted concentration-response curves according to the final lag-time model for the BIS index and the qCON. The predicted dose-response lag-time model curves for both indices have nearly identical trajectories.

Finally, **figure 5-7** shows a simulated course of propofol effect-site concentrations (Schnider PK model), qCON and BIS (lag-time model) values during a typical anesthesia session.

Figure 5-6 The figure shows the predicted BIS and qCON as a function of propofol effect-site concentration (C_e) according to the evaluated PD models. Solid lines represent the direct pharmacodynamic models while dotted lines represent the lag-time models. In order to keep the trajectories comparable lag-time model curves were calculated with C_e remifentanyl set to 0 (i.e. no potentiation of propofol effect by remifentanyl). Predicted BIS is shown with black lines whereas grey lines denote predictions for qCON. **C_e** : Effect site concentration.

Figure 5-7 The figure shows simulated propofol Schnider effect-site concentrations (Ce) and corresponding qCON and BIS values during a fictitious course of anesthesia. Three distinct anesthesia stages are marked. These are: 1) The induction of anesthesia (pump effect-site target set at 4 $\mu\text{g.ml}^{-1}$); 2) The reduction of effect-site target nearing the end of a case (pump effect-site target concentration decreased from 4 $\mu\text{g.ml}^{-1}$ to 2 $\mu\text{g.ml}^{-1}$); 3) The end of anesthesia. (pump effect-site target set at 0 $\mu\text{g.ml}^{-1}$).

Ce values were calculated using the Schnider pharmacokinetic model and K_{eo} of 0.456 min^{-1} . qCON and BIS values were calculated using the direct and lag-time pharmacodynamic models presented in this manuscript. The remifentanyl drug target Ce was set to 0. Simulations were conducted using PKPD tools for an average individual who participated in our study (54 years old, weight 65 kg, height 159 cm). Vertical solid lines and vertical dashed lines mark the moment when a steady state is reached for the Ce and for the direct versus lag-time PD model, respectively.

Discussion

This study demonstrates that significant hysteresis exists between the Schnider predicted effect-site concentrations and measured qCON and BIS. The implementation of an additional lag-time of 53s and 49s for qCON and BIS substantially corrects for this hysteresis. Once hysteresis is accounted for, propofol PDs for BIS and qCON are nearly identical. This finding has important implications in pharmacological research and daily clinical practice.

When constructing a pharmacodynamic model, it is essential to take the monitor related delay into account. Not accounting for this delay results in unrealistic and monitor dependent estimates of pharmacodynamic parameters. A PD model, which does not account for the time delay, produced in our study Ce_{50prop} estimates of $6.24 \mu\text{g}\cdot\text{ml}^{-1}$ for BIS and $8.62 \mu\text{g}\cdot\text{ml}^{-1}$ for qCON. These estimate are very divergent, monitor dependent and much higher than previously reported.¹⁷ Lag time PD model on the other hand, a model that incorporates the time delay term in the estimation, produced similar and monitor independent estimates, which are more in line with previously published values. These are $3.66 \mu\text{g}\cdot\text{ml}^{-1}$ and $3.62 \mu\text{g}\cdot\text{ml}^{-1}$ for BIS and qCON respectfully.

Not accounting for monitor related delay, limits the monitor's usefulness to detect responsiveness and to optimize drug dose in daily clinical practice. Schneider and colleagues investigated the ability of 2 different EEG based monitors (BIS and PSI) to distinguish responsive from unresponsive patients during the induction and the end of anesthesia, i.e., during non-steady state pharmacological conditions.¹⁸ They concluded that despite significant differences in mean values, monitors were unable to reliably differentiate these two patient categories, due to high degree of variability. This result can, at least partially, be explained by monitor related latencies. In this study we have demonstrated that different monitors cause different latencies and that these latencies are not only monitor but also patient dependent. Pilge et al. have further demonstrated that monitor related latencies are also different during increasing and decreasing drug effect.¹⁰ All these factors combined, increase the measured drug effect variability at transitions of responsiveness and decrease their value in drug dose optimization.

Several mechanisms could be responsible for the observed monitor related latencies. First, currently available monitors need varying amounts of time to calculate and signal changing levels of drug effect. EEG signal needs to be acquired and pre-processed before it is ready for processing by an often proprietary algorithm.^{19 20} All these steps take anywhere from 14 to 155 seconds.^{10 21} Since the index algorithms are not publicly accessible, it remains unclear which part of the process is most responsible for the delay.

Age could also contribute to the monitor related latency. Due to study design constraints and the method of analysis (i.e. the estimation of a single population lag-time) this was not

explored in this study. Nevertheless, a possible dependency between patient age and the monitor latency might be an interesting topic for future studies.

Further, it is still unknown how to best define the hypnotic drug effect (the target PD variable). Thus different monitors and propofol PD models use divergent target PD variables to generate results. This inherently leads to poor EEG monitor/PD model synchrony and thus hysteresis. Schnider and colleagues used a canonical univariate parameter (CUP) for propofol to create a propofol PD model. However, this variable has not found an application in current generation of monitors. Since every PD variable has a unique temporal characteristic of drug action, a PD model optimized using a particular variable will have less than optimal prediction accuracy for different PD variables. This prediction inaccuracy manifests itself as hysteresis.

This study may be criticized because we did not develop a new kinetic-pharmacodynamic model of propofol for these two monitors.²² However, our primary goal was to devise a clinically applicable method of dealing with hysteresis using commercially available TCI and EEG technology. By devising a method to correct the existing PD model of propofol, we developed a method to improve the monitor/TCI pump synchrony without the need to reprogram or replace the existing TCI pumps. Other methods using multiple serial effect-site compartments might have offered other mathematical solutions for the additional monitor-generated hysteresis. However, these methods are mathematically and computationally elaborate, limiting their applicability in TCI systems and drug advisory displays, and therefore, were not further explored. Further limitation of this study is that the M: F gender ratio is skewed in our dataset. Even though the mixed-effects approach allows for M: F ratio difference, population estimates for Ce50 is conditional on this and should thus be interpreted in the light of this M:F ratio.

Conclusion

In conclusion, there is a significant hysteresis between the Schnider predicted propofol effect-site concentrations and the achieved drug effect measured by the qCON and the BIS monitors. This hysteresis is caused by the monitor but is independent of the monitor type used. Adding a lag-time of 53 seconds and 49 seconds for qCON and BIS respectively, corrects for this hysteresis, improving the PD model performance, increasing the “pump-monitor” synchrony and making the estimates of C_{e50} for propofol more realistic and more monitor-independent.

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CHAPTER 6

COMPARISON OF HAEMODYNAMIC- AND ELECTROENCEPHALOGRAPHIC-MONITORED EFFECTS EVOKED BY FOUR COMBINATIONS OF EFFECT-SITE CONCENTRATIONS OF PROPOFOL AND REMIFENTANIL, YIELDING A PREDICTED TOLERANCE TO LARYNGOSCOPY OF 90%.

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Abstract

Purpose

This prospective study evaluates haemodynamic and electroencephalographic effects observed when administering four combinations of effect-site concentrations of propofol (C_{EPROP}) and remifentanyl (C_{EREMI}), all yielding a single predicted probability of tolerance of laryngoscopy of 90% ($P_{TOL}=90\%$) according to the Bouillon interaction model. We aimed to identify combinations of C_{EPROP} and C_{EREMI} along a single isobole of P_{TOL} that result in favourable hypnotic and haemodynamic conditions. This knowledge could be of advantage in the development of drug advisory monitoring technology.

Methods

80 patients (18-90 years of age, ASA I–III) were randomized into four groups and titrated towards C_{EPROP} (Schnider model, $\mu\text{g}\cdot\text{ml}^{-1}$) and C_{EREMI} (Minto model, $\text{ng}\cdot\text{ml}^{-1}$) of respectively 8.6 and 1, 5.9 and 2, 3.6 and 4 and 2.0 and 8. After eleven minutes of equilibration, baseline measurements of haemodynamic endpoints and bispectral index were compared with three minutes of responsiveness measurements after laryngoscopy.

Results

Before Laryngoscopy, bispectral index differed significantly ($p < 0,000$) between groups in concordance with C_{EPROP} . Heart rate decreased with increasing C_{EREMI} ($p = 0,001$). The haemodynamic and arousal responses evoked by laryngoscopy were not significantly different between groups, but $C_{EPROP} = 3,6 \mu\text{g}\cdot\text{ml}^{-1}$ and $C_{EREMI} = 4 \text{ ng}\cdot\text{ml}^{-1}$ evoked the lowest median value for ΔHR and ΔSAP after laryngoscopy.

Conclusions

This study provides clinical insight on the hemodynamic and hypnotic consequences, when a model based predicted P_{TOL} is used as a target for combined effect-site controlled infusion of propofol and remifentanyl. Heart rate and bispectral index were significantly different between groups despite a theoretical equipotency for P_{TOL} , suggesting that each component of the anesthetic state (immobility, analgesia and hypnotic drug effect) should be considered as independent neurophysiological and pharmacological phenomena. However, claims of (in)accuracy of the predicted P_{TOL} must be considered preliminary because larger numbers of observations are required for that goal.

Introduction

Pharmacodynamic drug interactions are classically described using isoboles, which are iso-effect lines that connect all combinations of drug concentrations resulting in an equal clinical drug effect.¹ Combining several isoboles in a three dimensional response surface model allows to depict the total spectrum of the interaction between two drugs in relation to a specific effect of interest (figure 6-1). For example, the probability of tolerance to laryngoscopy (P_{TOL}) can be predicted using response surface drug interaction models, for every combinations of effect-site concentration of propofol (C_{EPROP}) and remifentanyl (C_{EREMI})^{2,3}, and it has been incorporated into commercially-available anaesthesia monitors, called advisory displays.^{1,3} The bedside availability of P_{TOL} creates opportunities for the clinician to improve the control over one of the main components of anaesthetic drug effect: the immobility in response to a noxious stimulus.^{1,3,4} It now is clinically feasible to titrate different combinations of C_{EPROP} and C_{EREMI} while maintaining a constant effect estimated by P_{TOL} . However, there is limited information whether titration towards various combinations of C_{EPROP} and C_{EREMI} , that yield a similar P_{TOL} , will be equally beneficial for the patient in view of electroencephalographic and haemodynamic effects, respectively representing the hypnotic and analgetic component of anaesthesia.⁴⁻¹¹

Figure 6-1 The left panel shows the three-dimensional response surface model of propofol and remifentanyl based on the data of Bouillon et al. A response surface model is a mathematical description, visualized in a 3-dimensional graph depicting the effect (in this case, the probability of tolerance of laryngoscopy (P_{TOL})) (z-axis) evoked by combining two different drugs (respectively the effect-site concentration of propofol and remifentanyl in the x and y axis). The thick line represents the $P_{TOL}=90\%$ isobole, which is also depicted in the two-dimensional cross-sectional graph (right panel), representing the isoboles that connect all combinations of drugs that evoke identical effect. The bullets on the isobole represent the four drug combinations used in this study (A-D from left to right, respectively).

For electroencephalographically-derived indices monitoring hypnotic drug effect, such as the bispectral index (BIS)(Medtronic, Minneapolis, Minnesota, USA) Bouillon and coworkers predict that BIS will decrease in concordance with increases in C_{EPROP} , however this

observation merits prospective confirmation.⁵ In contrast, for commonly monitored hemodynamic endpoints, such as heart rate (HR), systolic arterial blood pressure (SAP), stroke volume (SV) cardiac index (CI), systemic vascular resistance (SVR) and the systemic vascular resistance index (SVRI), it is striking that the interaction between C_{ePROP} and C_{eREMI} has not been described equally thorough using isoboles or response surface interaction models.

Therefore, this study explores the clinical consequences of a P_{TOL} guided titration using effect-site controlled target-controlled infusion of propofol and remifentanyl, in order to provide helpful insight on the haemodynamic and hypnotic consequences of this titration concept, using clinical advisory display monitors. The primary purpose was to compare the haemodynamic and electroencephalographic effects observed between four different combinations of C_{ePROP} and C_{eREMI} , all yielding a P_{TOL} of 90% as estimated by Bouillon et al³, both during steady-state conditions (before laryngoscopy), as well as in response to a laryngoscopy. For all measured endpoints, we hypothesize that no significant difference would be found between groups because the clinical condition is estimated to be equipotent for P_{TOL} .

As commercially advisory monitors become available as a monitoring tool to guide titration of combinations of drugs towards equipotency for P_{TOL} , this study is a first attempt to explore the subsequent hemodynamic consequences of such actions in a prospective study.¹ It must be demonstrated in a standardised and reproducible way that it is clinically safe to adjust drug administration according to the advice provided by these new advisory monitors.

Materials and Methods

Following Ethics Committee approval (University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, METc 2013/267) and clinical trial registration (ClinicalTrials.gov, #NCT02067936, principal investigator: H.E.M. Vereecke, Date of Registration: February 20th 2014, <http://goo.gl/z23qJG>) prior to patient enrolment, written informed consent was obtained from 80 patients (18-90 years of age, ASA I–III) scheduled for general anaesthesia for elective neurosurgical or maxillofacial surgical procedures. Exclusion criteria were BMI exceeding 35 kg·m⁻², allergies for either propofol and/or remifentanyl, overt signs of alcohol or drug abuse, diseases of the central nervous, hepatic disease (i.e. Child B or higher), the use of drugs acting on the central nervous system and the use of α - or β -receptor agonists or antagonists. Patients suspected for having a difficult airway were excluded to ensure a safe mask ventilation throughout the measurements.

Study Design

The study was designed as a prospective double-blind, randomized, interventional trial. All measurements and study interventions were performed in a quiet operating room, before surgery commenced. After screening for eligibility and informed consent, 80 patients were randomized into four groups of 20 participants each, using sealed envelopes drawn at random. Patients received 1000 mg paracetamol as premedication. No benzodiazepine or other sedative drug was administered to the patient prior to the procedure.

The anaesthesiologist who performed mask ventilation, laryngoscopy and the observation of motor response was blinded to group allocation. If any airway problem occurred at any time during the study, the anaesthesiologist could decide to un-blind the randomization and take all necessary measures. Such patients were excluded from further data analysis and replaced. Administration of the drugs and data collection was performed by an (unblinded) researcher who operated a laptop running RUGLOOP II software (Demed Engineering, Temse, Belgium), a data collection program which also controls the target-controlled infusion pumps.

An intravenous line was inserted in a large forearm vein. Electrocardiography (ECG), pulse-oximetry (SpO₂) and intermittent non-invasive blood pressure (NIBP) monitoring was measured using the Philips Intellivue MP70 patient monitor (Philips Healthcare, Eindhoven, The Netherlands). CI, SV, SVI and SVRI were measured continuously by the ccNexfin Monitor (BMEYE, Amsterdam, Netherlands; now Edwards Lifesciences, Irvine, CA, USA). Measurements were performed using a non-invasive ccNexfin finger cuff attached to the third digit of the contralateral hand of the NIBP measurements. The heart reference system (HRS™) of Nexfin® was positioned at mid-axillary level in the supine positioned patient to calibrate for hydrostatic pressure differences between the position of the finger and the level of the heart. Bispectral index was measured using a unilateral BIS Quatro Sensor (and a BIS Vista monitor (all: Medtronic, Dublin, Ireland), smoothing delay time was set at 15

seconds with data storage every second. BIS and suppression ratio were compared between groups.

Study Drug administration

Propofol 2% (Braun, Melsungen, Germany) and remifentanyl 50 µg·ml⁻¹ (GlaxoSmithKline BV, Zeist, The Netherlands) were both administered by means of RUGLOOP II, a data collection and drug delivery software that runs on a PC (Penta Hercules Medical ETX, Penta GmbH, Munchengladbach, Germany) connected to infusion pumps (Asena GH, Becton Dickinson, San Diego, California, USA) and monitoring devices through USB ports, RS-232 interface and LAN connectivity. The software collects all data in a time-synchronized way. The pumps administer propofol and remifentanyl using an effect-site controlled target-controlled infusion with maximum infusion rates of 600 and 1200 ml·h⁻¹ respectively. For calculating Ce_{PROP} and Ce_{REMI} the pharmacokinetic-dynamic models of Schnider and Minto respectively were applied^{7,12}. For the Schnider model, the elimination equilibration constant of the effect-site (ke₀) was fixed to 0.456 min⁻¹. These models are identical to those used by Bouillon and coworkers for the interaction model development.⁶

Study procedure

After checking signal quality of all measurements, and before any drug was administered, patients were asked to close their eyes for 2 minutes for registration of awake measurements while breathing 100% oxygen through a gently applied face mask. Next, propofol and remifentanyl infusions were started simultaneously, targeted to one out of four equipotent drug combinations of Ce_{REMI} and Ce_{PROP} (see figure 6-1). These combinations were determined as follows: First, four values of Ce_{REMI} were chosen over a wide clinically relevant range, i.e. 1, 2, 4 and 8 ng·ml⁻¹ for groups A, B, C and D, respectively. The corresponding Ce_{PROP} resulting in P_{TOL}=90% was obtained from the sigmoidal response function for a dichotomous effect.^{5,9,13}

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

(1)

where γ is the slope parameter, representing the steepness of the concentration-effect relationship, and U is the combined potency of the drugs according to

$$U = \frac{Ce_{PROP}}{Ce_{50PROP}} * \left[1 + \frac{Ce_{REMI}}{Ce_{50REMI}} \right]$$

(2)

where Ce_{50PROP} is the effect-site concentration of propofol resulting in P_{TOL}=0.5 if given alone, and Ce_{50REMI} is the Ce_{REMI} that results in an increase of U by a factor 2 or an apparent decrease of Ce_{50PROP} by 50%. The model parameters of the Bouillon study were taken from table 1 of the article by Hannivoort et al.: Ce_{50PROP}=8.48 µg·ml⁻¹, Ce_{50REMI} = 1.16 ng·ml⁻¹ and

$\gamma=3.46$.¹⁰ It follows from equation 1 that $U=1.887$ for $P_{TOL}=90\%$. For each of the four remifentanyl concentrations, the corresponding propofol concentration was calculated from equation 2, resulting in the previously mentioned drug dose combinations.

Once C_{EPROP} and C_{EREMI} reached the desired target, eleven minutes of equilibration time ensures minimal prediction errors of the applied models during the observations.¹¹ Subsequently, one minute of baseline measurement was performed followed by a laryngoscopy, with an aim to visualize the larynx and thereby exert a standardized noxious stimulus, for a duration of 10 seconds. The time point of 'laryngoscopy' originally was registered as the moment of full traction on the laryngoscope. We noticed during the conduct of the study that the manipulations to start laryngoscopy (such as removal of the face mask and oral introduction of the laryngoscope) may already have triggered hemodynamic, motor or electroencephalographic responses in some cases, several seconds before maximum traction was reached. For the analysis of data, we pragmatically defined the "start of laryngoscopy" as a time point 30 seconds before full traction was applied. After laryngoscopy, another three minutes of data registration were maintained to observe the presence or absence of movement and haemodynamic or electroencephalographic measurements. Motor response was defined as movement of extremities, opening of eyes, gag reflex or coughing within three minutes after the initial manipulations for starting laryngoscopy. After the three minutes observation of response, the study ended, and regular care was resumed.

Safety precautions

In case of unsustainable respiratory inhibition or apnea during induction or during the equilibration time, gentle airway manoeuvres (e.g. adjustment of the face mask, chin lift, hyperextension or pillow adjustments) were performed to facilitate mask-bag ventilation. In case of difficulties to obtain an open airway, or haemoglobin oxygen desaturation, an oropharyngeal airway was introduced. If respiratory escape manoeuvres caused a motor, haemodynamic or arousal response during the measurements of the pre-stimulation baseline minute (minute 10 to 11) the patient was excluded from analysis, due to the lack of steady state conditions. In case of bradycardia below $40 \cdot \text{min}^{-1}$ or a decrease in mean arterial pressure below 50 mmHg, respectively 0.5mg of atropine or 5mg of ephedrine, was administered as rescue medication. The number of rescue interventions and the total dose of atropine and ephedrine were also registered for comparison between groups.

Statistics and data analysis

For the primary haemodynamic and electroencephalographic endpoints, no previous data was available to make reasonable assumptions for an a-priori power calculation of the sample size required. We thus pragmatically chose to include 20 patients per group, based on our previous experiences in pharmacodynamic studies. In this clinical evaluation study, we accepted the validity and accuracy of the published values for P_{TOL} .³

All collected data from different storage systems was synchronized using an algorithm in R (R, The R foundation for statistical computing, Vienna, Austria), after rejecting obvious false values (e.g. negative blood pressure). The algorithm defined a short-lasting ($< 1\text{sec}$) difference of 30% between two subsequent time points (1 sec. interval) as an artefact. BIS-measurements with a signal quality index < 50 were removed. All raw data (after artefact rejection) of the haemodynamic and BIS-measurements are plotted from the baseline minute to three minutes after laryngoscopy. We also plot SR as measured by BIS.

Significant difference was defined when $p < 0.05$. Baseline characteristics were compared using ANOVA tests or a non-parametric Kruskal Wallis test with Nemenyi post hoc test, depending on normality of the distribution, which was tested using the Shapiro-Wilk test. After testing for normality, haemodynamic variables, (HR, SAP, CI, SVI, SVRI) and BIS were compared between groups, both at baseline and in response to laryngoscopy. The median and range of the baseline data were compared using a Kruskal-Wallis test.

To allow a comparison of the magnitude of haemodynamic (ΔHR , ΔSAP , ΔCI , ΔSVI , ΔSVRI) and arousal responses (ΔBIS) evoked by laryngoscopy between groups, the difference between the median of the baseline values and the maximum value observed during the response period was calculated for all endpoints and for each subject, and then averaged (median $\pm$ standard deviation) for the population. A Kruskal-Wallis test was used to test for significant differences between groups.

Whenever the individual ΔHR , ΔSAP , ΔCI , ΔSVI , ΔSVRI exceeds 20% of the baseline value, we defined that case as a “haemodynamic responder” and compared the number of responders between groups. A threshold of 20% was chosen as it is a commonly used definition of perioperative hypotension in current literature.¹³⁻¹⁵ For ΔBIS , we also counted the number of arousal responses in a similar fashion but used a 30% threshold instead. Changes in BIS $< 20\%$ rarely trigger a therapeutic intervention because fluctuations of that magnitude over time are common for BIS.¹⁶

Results

An overview of the screenings/inclusion/exclusions can be found in the CONSORT diagram (figure 6-2). Patient characteristics are described in Table 1. No serious adverse events occurred during the conduct of the study. 87 patients were randomized to the four groups. In groups C and D, 3 and 4 patients were replaced, respectively. The remaining 80 patients were included in the data analysis. The patient characteristics were comparable between groups (Table 6-1, panel A).

Figure 6-2 CONSORT diagram

Table 6-1 Patient characteristics and comparison between hemodynamic- and electroencephalographic baseline measurements. Baseline heart rate was different between groups ($p < 0.000$), as was BIS between groups ($p < 0.00$). # $p = 0.004$; \$ $p = 0.045$; % @, ^, +, \$ and £ $p < 0.000$.

A		Group A Remifentanyl 1 ng·ml ⁻¹ ; propofol 8.6 ug·ml ⁻¹	Group B Remifentanyl 2 ng·ml ⁻¹ ; propofol 5.9 ug·ml ⁻¹	Group C Remifentanyl 4 ng·ml ⁻¹ ; propofol 3.6 ug·ml ⁻¹	Group D Remifentanyl 8 ng·ml ⁻¹ ; propofol 2.0 ug·ml ⁻¹	
Patient characteristics	Age (years); Mean (SD) Range []	50 (±13.7) [46]	52 (±13.1) [50]	51 (±17.5) [56]	58 (±10.7) [33]	
	Gender (m/f)	10/10	10/10	10/10	12/8	
	BMI (kg·m ⁻²); Median [range]	26 [23-29]	26 [24-28]	26 [24-26]	26.5 [23-28]	
B						p
Median baseline values Range [P25-P75]	Heart Rate (beats · min ⁻¹)	71# [60-73]	68\$ % [63-72]	60\$ [56-63]	60# % [56-62]	0,003
	Systolic Blood Pressure (mmHg)	94 [84-101]	90 [79-105]	97 [87-101]	104 [80-108]	0,629
	Stroke Volume Index (ml · m ⁻²)	44 [36-45]	39 [35-46]	42 [34-46]	40 [34-48]	0,947
	Systemic Vascular Resistance Index (dyn · s · cm ⁻⁵)	2104 [1804-2337]	2151 [1902-2544]	2226 [2063-2556]	2665 [2021-3095]	0,333
	Cardiac Index (L · min · m ⁻²)	2.60 [2.38-3.23]	2.55 [2.30-3.20]	2.35 [2.19-2.62]	2.25 [1.98-2.80]	0,162
	BIS	25 @ ^ [23-27]	30 + \$ [25-40]	44 @ + £ [41-55]	64 ^ \$ £ [59-72]	< 0,001

In figures 6-3 and 6-4, the haemodynamic and electroencephalographic endpoints, respectively, are plotted over time from the baseline measurements till the end of the response observation time. These figures give an impression of the population variability at baseline for each studied measurement, and the magnitude of the respective responses to laryngoscopy.

Figure 6-3 The evolution of the observed haemodynamic variables between -60 to +180 seconds from the start of laryngoscopy (Time = 0). The grey lines represent the results for each individual patient. The black line is the population median value. Group A (remifentanyl $1 \text{ ng} \cdot \text{ml}^{-1}$ and propofol $8.6 \text{ µg} \cdot \text{ml}^{-1}$), Group B (remifentanyl $2 \text{ ng} \cdot \text{ml}^{-1}$ and propofol $5.9 \text{ µg} \cdot \text{ml}^{-1}$), Group C (remifentanyl $4 \text{ ng} \cdot \text{ml}^{-1}$ and propofol $3.6 \text{ µg} \cdot \text{ml}^{-1}$) and Group D (remifentanyl $8 \text{ ng} \cdot \text{ml}^{-1}$ and propofol $2.0 \text{ µg} \cdot \text{ml}^{-1}$).

Figure 6-4 The evolution of the observed electroencephalographic variables between -60 to +120 seconds from the start of laryngoscopy (Time =0). The grey lines represent the results for each individual patient. The black line is the population median value. Group A (remifentanyl 1 ng · ml⁻¹ and propofol 8.6 µg · ml⁻¹), Group B (remifentanyl 2 ng · ml⁻¹ and propofol 5.9 µg · ml⁻¹), Group C (remifentanyl 4 ng · ml⁻¹ and propofol 3.6 µg · ml⁻¹) and Group D (remifentanyl 8 ng · ml⁻¹ and propofol 2.0 µg · ml⁻¹). BIS SR = suppression ratio as measured by the bispectral index monitor.

We observed 2, 1, 4 and 8 motor responders after laryngoscopy in group A, B, C and D, respectively. The higher number of responders in group D may be related to several patients who did not reach a sufficient level of hypnotic drug effect before laryngoscopy, as also reflected in the high BIS values. Even the removal of the face mask resulted in return of responsiveness for some patients of group D.

Table 6-1 panel B shows the statistical result for the comparison of the baseline measurements between groups. HR at baseline was significantly higher in groups A and B versus C and D ($p < 0,000$): median HR (25-75% range) for groups A, B, C and D were 71 (59-

73), 68 (63-72), 60 (56-63) and 60 (56-62) beats·min⁻¹, respectively. Median CI was 0.3 L·min⁻¹ higher in groups A and B compared to C and D (not statistically significant, $p = 0,162$). Median SAP, CI, SVI and SVRI were not significantly different at baseline between groups.

Table 6-2 shows the results of the magnitude of the haemodynamic and arousal responses after laryngoscopy (Δ HR, Δ SAP, Δ CI, Δ SVI, Δ SVRI, Δ BIS). The median haemodynamic responses evoked by laryngoscopy were moderate and not significantly different between groups for all measured variables. Group C had the lowest median value for Δ HR and Δ SAP.

We identified 5 (25%), 6 (30%), 7 (35%) and 9 (45%) HR responders in groups A, B, C and D, respectively who had a 20% increase of HR evoked by laryngoscopy.

For Δ SAP, groups A and B contained almost double the number of responders of groups C and D (16, 17, 8 and 9 for groups A, B, C and D, respectively).

After induction and during the equilibration phase, respectively 7, 4, 10 and 5 out of 20 patients in group A, B, C and D needed rescue medication for hypotension being one or two administrations of ephedrine 5 mg, before baseline measurements were performed. No administration of ephedrine was needed during the steady state measurements. No atropine was administered as a rescue for bradycardia.

For BIS at baseline, groups A and B showed significantly lower BIS ($p < 0,000$) at baseline compared to groups C and D (Table 1, Panel B), which is consistent with the higher C_{ePROP} in groups A and B. Also, groups A and B contained the highest number of cases with SR levels $>5\%$ (figure 4). In group C, we observed the highest number of patients with continuous BIS values that remained within the desired range (between 40 and 60). (Figure 4). Only 3 out of 20 patients showed minimal burst suppression patterns (SR $<5\%$) at baseline in group C.

Table 6-2 Comparison of difference between the median value before versus the maximum value after laryngoscopy for each parameter. BIS was different between groups ($p = 0,006$), as was systolic blood pressure ($p = 0,03$). # $p < 0,005$.

Δ pre-post stimulation (MD [P25-P75])	Group A	Group B	Group C	Group D	P
	Remifentanyl 1 ng·ml ⁻¹ ; propofol 8.6 ug·ml ⁻¹	Remifentanyl 2 ng·ml ⁻¹ ; propofol 5.9 ug·ml ⁻¹	Remifentanyl 4 ng·ml ⁻¹ ; propofol 3.6 ug·ml ⁻¹	Remifentanyl 8 ng·ml ⁻¹ ; propofol 2.0 ug·ml ⁻¹	
	10 [7 - 14]	10 [4 - 15]	6 [3 - 16]	8 [4 - 30]	0,498
	Δ Heart Rate (beats · min ⁻¹)				
	Δ Systolic Blood Pressure (mmHg)	32 [21 - 40]	30 [18 - 45]	21 [11 - 40]	0,153
	Δ Stroke Volume Index (ml · b · m ⁻²)	7 [5 - 9]	8 [5 - 9]	5 [4 - 8]	0,750
	Δ Systemic Vascular Resistance Index (dyn · s · cm ⁻⁵)	485 [269 - 1143]	849 [455 - 1313]	800 [329 - 3726]	0,558
	Δ Cardiac Index (L · min · m ⁻²)	0.55 [0.38 - 0.72]	0.40 [0.38 - 0.70]	0.40 [0.3 - 1.1]	0,799
	Δ BIS	3 # [2 - 7]	7 [3 - 11]	11 # [7 - 17]	8 [4 - 12]
					0,011

For the BIS response to laryngoscopy, only group A showed a statistically significant lower Δ BIS compared to group C ($p = 0.011$) which may be related to the high incidence of SR>5% at baseline, indicating excessive hypnotic drug effect in group A. For all other groups Δ BIS was indistinguishable between groups. The number of BIS arousal responses (>30% increase after laryngoscopy) was respectively 25, 40, 40 and 10% for groups A to D. The low incidence of arousal in group A and D are probably both biased due to respectively the high incidence of SR>5% in group A and the high baseline BIS values in group D that cannot rise another 30%.

Discussion

This study explores the haemodynamic and hypnotic effects evoked by four different combinations of C_{ePROP} and C_{eREMI} , all yielding an identical predicted P_{TOL} according to the Bouillon interaction model. P_{TOL} is a theoretical -population derived- metric for immobility in response to a noxious stimulus and has been integrated in clinically-available advisory monitors for drug titration during anesthesia, however the clinical usefulness still needs further prospective validation. In this clinical evaluation study, we accepted the validity and accuracy of the published values for P_{TOL} . As such, any claim of (in)accuracy of the predicted P_{TOL} must be considered preliminary because larger numbers of observations are required for that goal. However, as commercialized advisory screens are already clinically available to allow titration towards this population derived prediction of P_{TOL} , our current dataset does provide valuable information on the hemodynamic and hypnotic consequences of such deliberately combined drug titration using effect-site controlled target-controlled infusion.^{5 17}

We did find that titration towards the four theoretically equipotent combinations of C_{ePROP} and C_{eREMI} (for predicted $P_{TOL}=90\%$) does result in moderate -but clinically relevant- differences of haemodynamic and hypnotic drug effects between groups.

Before laryngoscopy, similar SAP, CI, SVI and SVRI was found in all groups except for heart rate, which is moderately (but statistically significant) lower in groups with higher C_{eREMI} concentrations. This is in concordance with a study of Hayashi and coworkers showing a cut-off point for heart rate reduction at remifentanyl concentrations around $3.5 \text{ ng}\cdot\text{ml}^{-1}$.¹⁸

The apparent similar haemodynamic state between groups before laryngoscopy could only be achieved after a variable number of patients reached a safety threshold during the non-steady state induction of anaesthesia. They needed rescue treatment with ephedrine at variable timepoints. We were not able to identify any causal relationship between the occurrence of such events and group randomization, neither for the number of rescue treatments nor for the total dose of ephedrine administered. This observation may challenge the commonly accepted notion that high levels of opioids during balanced anaesthesia result in more stable hemodynamic conditions. It merits further research towards the immediate haemodynamic effects evoked by the non-steady state induction of anaesthesia, using effect-site controlled target-controlled infusion. For this study pharmacological steady-state conditions were required, which was only reached after an equilibration period of 11 minutes. As such, we cannot report on observations during non-steady state conditions.

After laryngoscopy, one would expect the lowest haemodynamic response in groups with higher C_{eREMI} , however, the median haemodynamic responses (ΔHR , ΔSAP , ΔCI , ΔSVI , $\Delta SVRI$) were moderate in severity and not significantly different between groups (Table 2). The number of patients that showed a $>20\%$ difference in baseline HR was similar for groups A, B

and C. Group D had the highest incidence (45%) of HR responses. This finding may be a biased by the substantial number of patients with high BIS (>60) in group D, suggesting an insufficient hypnotic drug effect. Indeed, several patients immediately opened their eyes once the face mask was removed and before laryngoscopy could be initiated. For Δ SAP, groups A and B contained almost double the number of responders of groups C and D, which is concordant with the higher C_{eREM} in groups C and D.

BIS showed significant differences in baseline measurements with several cases of high $SR > 5\%$, indicating an excessive hypnotic drug effect in groups A and B (Figure 4). In contrast, group D included many cases of BIS above the upper limit threshold of 60 (increasing the risk for conscious perception). Therefore, BIS appears to be inversely related to C_{ePROP} , which agrees with earlier studies.^{10 19} An arousal response of BIS evoked by laryngoscopy may be a sign of inadequate analgesic effect and is associated with increased risks for unintentional conscious perception.¹⁸ The magnitude of arousal, measured by BIS was small in our study and not significantly different between groups (Table 2).

Our data allows to identify whether some combinations of C_{ePROP} and C_{eREM} evoke more favourable conditions, when evaluating all effects together. We found that in group C, during baseline measurements, only a moderate decrease in HR and no significant difference in SAP can be observed compared to other groups. Group C also contained the highest number of patients with an adequate BIS range before laryngoscopy while the absence of high SR suggests absence of overdosing of hypnotic drug effect. Group C also had the lowest median value for Δ HR and Δ SAP evoked by laryngoscopy. We observed 4 motoric responders out of 20 in group C which is an acceptable clinical result, considering the predicted $P_{TOL} = 90\%$ and its corresponding confidence interval (not published post-hoc analysis). However, the latter conclusion must be interpreted cautiously due to the insufficient power of our study to validate the accuracy of P_{TOL} as a metric of drug effect.

Conclusion

In conclusion, this study provides clinical insight on the haemodynamic and hypnotic consequences, when a model based predicted P_{TOL} is used as a target for combined intravenous administration of propofol and remifentanyl, using effect-site controlled target-controlled infusion pumps. Heart rate and bispectral index were significantly different between groups despite a theoretical equipotency for P_{TOL} , suggesting that each component of the anaesthetic state (immobility, analgesia and hypnotic drug effect) should be considered as independent neurophysiological and pharmacological phenomena.

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CHAPTER 7

SUMMARY, DISCUSSION AND FUTURE PERSPECTIVES.

Over the past decades possibilities to individualize drug titration have expanded rapidly. This development follows an era of increasing knowledge of anesthetic pharmacology. Advanced computer technology has helped to improvement drug administration techniques by providing the computing power necessary for controlling target-controlled infusion systems. However, as mentioned in [chapter 1](#), these systems are commonly based on population-based models, which subsequently have a certain degree of error when applied to the individual. A major goal for an anaesthetist is to titrate drugs accurately. As over- and under-dosing are highly undesirable, as they result in increased side effects or insufficient anaesthesia, respectively, reduction of this error seems favorable.¹

This thesis expands our current knowledge by surveying the possibilities to optimize population-based drug titration in the individual and prospectively apply knowledge into clinical practice. As each chapter is accompanied by a chapter-specific discussion, we will focus here on summarizing the main findings of this thesis and debates the essential issues of discussion and future perspectives.

Summary

[Chapter 1](#) provides an overview of current knowledge regarding anesthetic pharmacology. It describes the concepts of pharmacokinetics, pharmacodynamics and the coupling between PK and PD. As topic of interest in this thesis ([chapter 5](#)), the concept of *hysteresis* was introduced. We also introduced PKPD models and their evaluation and the clinical use of target-controlled infusion. As most models are *population-based*, the concept of Bayesian *individualization* was introduced, and is applied in [chapters 3 and 4](#). Using Bayesian statistics, input from a specific patient is used to adapt and individualize a population model in the direction of our specific patient. Lastly in this chapter, we introduced the concept of drug interactions, as general anaesthesia is commonly applied using multiple drugs acting together, which was the topic of interest in [chapter 6](#).

[Chapter 2](#) describes the concept of drug interactions in anesthetic pharmacology. The review summarizes the current knowledge of PK and PD interactions and their relevance in anesthetic practice from an educational point of view. Thereby, it provides backgrounds of how drug interactions studies could be designed, interpreted and visualized. This introduces the reader in the concepts of isoboles and response surface models to do so. Lastly, it previews how this knowledge can be applied to clinically applicable (bed-side) tools, such as SmartPilot View or Navigator Suite.

[Chapter 3](#) describes the use of exhaled propofol concentration measurements to optimize propofol PK models. In this study, 1) an extension was added to an existing propofol PK model, 2) a Bayesian algorithm was used, intended to optimize the predictive performance of intraoperative propofol plasma concentrations, based on propofol breath concentrations and 3) The effect of BIS was coupled to this breath concentration aiming to use this breath

concentration as a predictive tool of clinical effect. The study showed that it was possible to extend the existing model and as such, to use exhaled propofol concentrations to predict the accompanying plasma (and effect-site) concentration of the drug. A Bayesian update was applied in order to increase the model's predictive performance. Availability of measured exhaled propofol concentrations could be beneficial, as they could facilitate a more stringent control of the targeted plasma concentration.

Chapter 4 describes the use of bed-side measurements of whole blood propofol concentrations as input for a Bayesian optimization algorithm for the Eleveld PK model for propofol. This prospective, randomized controlled trial concludes that this optimization strategy improves bias, but not precision. This means that the direction of measured vs. predicted concentration improved, but not the magnitude of this difference. Besides this information, we compared the relatively new Eleveld model to some of the preceding PK-models for propofol. We showed that this model performed better than its predecessors and even better than this model when studied in a population without the use of opioids. The latter is hard to explain. Despite the inability to improve the model's accuracy, this study has contributed to current pharmacological science in multiple ways. First, Bayesian optimization would only be useful when there is only limited fit of the patient into the population-based model. When the right model is chosen, as we did with the promising Eleveld model, further improvement is hard to achieve. Second, we demonstrated the possibility to integrate i.v. drug concentration monitoring into drug administration. Last, this study contributed to the insight of posology of anesthesia, as introduced by Kuck and Egan in their editorial which accompanied our publication.² This describes the optimal balance between safety, effectiveness and efficiency in drug titration.

Chapter 5 describes and compares the time-delay of two EEG monitors and the effect as predicted by the effect-site concentration. We compared the bispectral index (BIS) and qCON index as measurement of clinical effect. Our primary conclusion was that there was a lag-time (or delay) of 53 and 49 seconds for qCON and BIS, respectively. We found that when we accounted for this 'lag time', the behavior of both EEG devices are comparable, which is important as this was still a point of debate when a study was performed using qCON. Thereby, this study provided insight in the relationship between propofol effect-site concentrations and qCON, which enables us to provide a sigmoidal e-max model, which might be useful for drug dose advices in clinical practice. Explanations of the lag time are difficult to provide, as the lag might be due to algorithms (which are commonly proprietary information) or as a result of differences in the population studied (M:F ratio or age).

In **chapter 6** the interaction model of Bouillon was prospectively surveyed. This model describes the interaction of propofol and remifentanyl. In this study, the PTOL90 isobole (i.e. the line joining drug concentration combinations that are 90% likely to cause tolerance of laryngoscopy) was used to calculate equipotent drug concentrations and to see if this

equipotency could also be derived from hemodynamic and electro-encephalographic measurements. Hemodynamic variables were measured using the Nexfin monitor, which is a non-invasive advanced hemodynamic monitor. Although the interchangeability between invasive hemodynamic monitoring (such as pulmonary artery thermodilution techniques) and Nexfin is still point of debate, especially for cardiac output measurement, it has shown good within-subject precision for blood pressure measurements.³⁻⁵ The electro-encephalogram was recorded and analysed by a BIS monitor, which calculates the bispectral index which is currently the gold standard in daily clinical practice. In this study we found that heart rate and bispectral index were not comparable between groups, implying that hemodynamics and electro-encephalographic variables should be considered as independent neurophysiological and pharmacological phenomena.

This study answers a very practical question: is there any difference in hemodynamics and EEG when titrating propofol-remifentanyl? This might be relevant in certain patient populations where hemodynamic shifts might be harmful, such as the critically-ill. We found that hemodynamic status was statistically comparable between groups. Commonly used arguments in favor of e.g. opioid-based induction of anesthesia are not supported by our data, which was collected in a wider population range than the original Bouillon study upon which the model was built.⁶ Further research is necessary to survey the first minutes of these inductions, as no clinician will wait for the eleven minutes of equilibration time to perform laryngoscopy as we did in our study.

General discussion and future perspectives

The main contribution of this thesis is that it confirms that well performing population-based PK and PD models perform accurately in clinical practice and in pharmacological simulations. As such, this thesis can be used as a plea for the use of these models. Bayesian optimization provides only limited improvement on that matter. It must be emphasized that in an already well performing model, clinically significant improvements are not likely to be expected in the individual patient. The residual error might be caused by biological variability, which is hard to include in a mathematical model, even in the presence of covariates. Extensions of the propofol model can be used to predict exhaled concentrations based on estimated plasma concentrations, and also the converse – i.e. exhaled concentrations can be used to estimate plasma concentrations. Extension of the propofol model to include exhaled propofol kinetic parameters would however require significant investments, which are unlikely to provide more clinically relevant improvements in drug concentration predictions, in relation to a well performing population model.

As mentioned in the first chapter, despite the need for accurate PK models to provide accurate target-controlled infusions, PK parameters are not generally the relevant target for clinicians. As it is not the plasma concentration that a clinician is aiming for, it seems more relevant for clinicians to titrate drug titration to achieve pharmacodynamic endpoints. As

such, it appears to be relevant to focus with drug advisory systems on PD endpoints. Feedback systems that use measurements as input parameters, such as (semi) closed loop systems, could be helpful in optimizing drug titration.⁷⁻⁹ Accurate drug administration models applied in TCI can be very helpful for the reproducibility of accurate drug titration. Adaptation of a population-based E-max model of the relationship between predicted plasma concentration and effect (e.g. electro-encephalographic monitoring) towards an individualized model, most likely with the application of a Bayesian algorithm, might provide useful drug dosing advices. This requires further study.

On the other hand, advisory screens equipped with the previously mentioned population-based models, could be helpful to help titrating drugs in the individual. This might be useful from a clinical and from an educational view. Current screen software is based on theoretical data on the interactions between drugs. In the case of propofol and remifentanyl estimated concentrations are used for the predictions, and furthermore the predictions are not influenced by the actual clinical effects in a specific patient. As such, prospective validation of advisory screens is required to show the clinical benefit. Although promising, little information has been published so far.^{10 11} The results are promising as changes have been shown in the clinician's behavior when these tools are applied in clinical practice.

Lastly, we showed that interaction models are a useful basis for drug dosing regimens. During the conduct of every general anaesthetic the clinician chooses from an infinite number of possibilities of drug combinations. It remains the question whether different propofol and remifentanyl concentrations lead to different haemodynamic or EEG patterns of change. Information on this matter, derived from population-based interaction models, could be very useful for titration in the individual. In [chapter 6](#) we showed that theoretical equipotency for one endpoint does not automatically lead to equipotency for other endpoints.

Conclusion

This series of studies contributes to the aim to improve anaesthetic drug titration in the individual from different perspectives and using advanced state-of-the-art technology. PK and PD models seem to be valuable tools to serve as basis for further enhancements, such as drug advisory tools.

CHAPTER 8

NEDERLANDSE SAMENVATTING

In de afgelopen decennia zijn de mogelijkheden om de toediening van medicatie te individualiseren enorm gegroeid. Dit volgt op een tijdperk waarin de kennis over anesthesiologische medicatietoediening is toegenomen. Geavanceerde computertechnologie biedt ons de mogelijkheid om complexe berekeningen te doen die nodig zijn voor zogenaamde target-controlled infusie (TCI) systemen. Dit zijn systemen die op basis van populatie-modellen berekeningen kunnen doen welke dosering past bij het nastreven van een bepaalde concentratie in het bloed of de 'effect-site'. Echter zijn deze systemen, zoals beschreven in [hoofdstuk 1](#) veelal populatie-gebaseerd wat leidt tot een zekere foutmarge wanneer men deze toepast in een individu. Een belangrijk doel voor de anesthesioloog is om medicatie adequaat te titreren. Aangezien over- en onderdosering hoogst onwenselijk zijn, daar deze leiden tot respectievelijk een toegenomen hoeveelheid bijwerkingen of onvoldoende anesthesie, lijkt het wenselijk om deze foutmarge verder terug te dringen.¹

Dit proefschrift vult een kennislacune door de mogelijkheden van het optimaliseren van deze populatie-gebaseerde medicatietoediening binnen het individu te verkennen. Bovendien brengt het deze kennis in de klinische praktijk. Aangezien ieder hoofdstuk reeds is voorzien van een hoofdstuk-specifieke discussie, focussen we in dit hoofdstuk op de hoofdlijnen van de bevindingen en worden enkel de essentiële discussiepunten besproken en blikken we vooruit naar de toekomst.

Samenvatting

[Hoofdstuk 1](#) geeft een samenvatting van de huidige kennis met betrekking tot anesthesiologische farmacologie. Het beschrijft concepten als farmacokinetiek, pharmacodynamiek en de koppeling tussen deze beiden. Aangezien in hoofdstuk 5 het concept 'hysteresis' van belang is, wordt dit hier ook besproken. We introduceren PKPD modellen, hun ontwikkeling en de klinische toepassing van TCI. Aangezien de meeste modellen *populatie-gebaseerd* zijn, introduceren we het concept van Bayesiaanse *individualisatie*, welke werden toegepast in [hoofdstuk 3 en 4](#). Met behulp van Bayesiaanse statistiek wordt het populatiemodel geindividualiseerd, gebaseerd op input van een specifieke patient. Tenslotte wordt in dit hoofdstuk het concept van geneesmiddeleninteracties geïntroduceerd, aangezien anesthesie vrijwel altijd wordt toegepast door meerdere medicamenten simultaan toe te dienen. Deze kennis wordt toegepast in [hoofdstuk 6](#).

[Hoofdstuk 2](#) beschrijft het concept van geneesmiddeleninteracties in meer detail, specifiek binnen de kaders van anesthesiologische farmacologie. Dit overzichtsartikel beschrijft de huidige kennis van PK en PD interacties en hun relevantie in de klinische praktijk vanuit een educatief oogpunt. Het biedt achtergronden over hoe studies kunnen worden ontworpen, geïnterpreteerd en gevisualiseerd die deze interacties beschrijven. Het introduceert de lezer in concepten van isobolen en 'response surface' modellen. Ten slotte beschrijft het hoe de

huidige kennis kan worden toegepast in klinisch toepasbare adviessystemen, die ‘aan het bed’ van de patient kunnen worden toegepast, zoals de SmartPilot View en Navigator Suite.

Hoofdstuk 3 beschrijft de toepassing van metingen van uitgedemde propofolconcentraties om propofol PK modellen te optimaliseren. In deze studie 1) werd een bestaand PK model uitgebreid voor deze optimalisatie; 2) werd een Bayesiaans algoritme gebruikt om het voorspellend vermogen van het model te verbeteren, gebruikmakend van deze uitademingsconcentraties; 3) werd het effect van BIS gekoppeld aan de uitgedemde concentraties teneinde deze concentraties voorspellend te maken voor klinisch effect. De studie toonde dat het mogelijk was om een bestaand model te verlengen en als zodanig, de uitgedemde propofolconcentraties te gebruiken om plasma- en effect-site concentraties van het medicament te voorspellen. Een Bayesiaanse update is toegepast om het model's voorspellend vermogen te verbeteren. Uitgedemde propofolconcentraties kunnen van meerwaarde zijn voor de clinicus, aangezien dit een meer nauwkeurige controle kan bieden op de doelconcentraties van propofol.

Hoofdstuk 4 beschrijft de toepassing van een ‘bed-side’ gemeten propofol volbloed concentratie als input voor een Bayesiaanse optimalisatie van het Eleveld PK model voor propofol. Deze prospectieve, gerandomiseerde, gecontroleerde trial concludeert dat deze optimalisatiestrategie de bias, maar niet de precisie verbeterd. Dit betekent dat de richting van gemeten vs. Voorspelde concentratie werd verbeterd, maar niet de grootte van dit verschil. Behoudens deze informatie werd ook het relatief nieuwe Eleveld-model vergeleken met diens voorgangers. We toonden dat dit model beter voorspelt dan de anderen, waarbij deze bovendien beter presteert dan het model zonder toepassing van opioïden. Dit laatste is moeilijk te verklaren. Ondanks het onvermogen om de accuraatheid van het model te verbeteren, heeft deze studie bijgedragen aan de farmacologische wetenschap op een aantal manieren. Ten eerste, Bayesiaanse adaptatie is zinvol wanneer het initiele model de huidige patient slechts beperkt beschrijft. Wanneer het juiste model is gekozen, zoals we hier deden met behulp van het veelbelovende Eleveld-model, verdere optimalisatie is moeilijk te bereiken. Ten tweede toonden we de mogelijkheid om real-time metingen te vatten in medicatie-titratie. Ten slotte droeg deze studie bij aan het inzicht in de ‘posologie’ van anesthesie, zoals Kuck en Egan introduceerden in hun editorial bij deze publicatie.² Dit beschrijft de balans tussen veiligheid, effectiviteit en efficiëntie in geneesmiddeltoediening.

Hoofdstuk 5 beschrijft en vergelijkt de tijdsvertraging tussen twee monitoren die hersenactiviteit meten en het effect zoals voorspeld met behulp van de effect-site concentratie. We vergeleken de ‘bispectral index’ (BIS) en de qCON index als klinisch effect. Onze conclusie was dat een tijdsvertraging van respectievelijk 53 en 49 seconden werd gevonden. Wanneer men corrigeert voor deze vertraging, het ‘gedrag’ van deze monitoren is vergelijkbaar, wat een belangrijke bevinding is aangezien dit nog altijd ter discussie stond bij de uitvoer van studies met de relatief nieuwe qCON. Daarbij gaf deze studie inzicht in de

relatie tussen propofol effect-site concentraties en qCON, wat de mogelijkheid biedt een e-maxcurve te construeren, welke van nut kan zijn voor doseringsadviezen voor medicatie in de klinische praktijk. Verklaringen voor de tijdsvertraging zijn moeilijk te geven, aangezien dit waarschijnlijk berust op de algorithmen (die geheim worden gehouden door de fabrikanten) of als een resultaat van de populatie (man/vrouw-ratio of leeftijd).

In **hoofdstuk 6** wordt het interactiemodel van Bouillon prospectief verkend in de klinische omgeving. Dit model beschrijft de interactie tussen propofol en remifentanyl. In deze studie werd de PTOL90 isobool (oftewel de lijn die de combinatie van geneesmiddelendoseringen beschrijft die leiden tot een gelijk effect) gebruikt om equipotentie (gelijke effectiviteit) geneesmiddelenconcentraties te berekenen en om te zien of deze equipotentie ook voor hemodynamische en electro-encephalographische metingen kan worden bereikt. In deze studie werd gebruik gemaakt van de Nexfin monitor; een niet-invasieve hemodynamische monitor. Hoewel de uitwisselbaarheid tussen invasieve hemodynamische monitoring (zoals bijvoorbeeld a. Pulmonalis thermodilutie technieken) en non-invasieve alternatieven nog altijd ter discussie staat, met name voor cardiac output metingen, is een goede precisie voor bloeddrukmetingen binnen het individu aangetoond.³⁻⁵ De hersenactiviteit werd gemeten en genalyseerd door een BIS-monitor, welke de bispectral index berekent, dat tot op heden gezien wordt als de goud standaard in de dagelijkse klinische praktijk. In deze studie vonden we dat hartslag en BIS niet vergelijkbaar waren per groep. Dit impliceert dat hemodynamica en hersenactiviteit beschouwd moeten worden als onafhankelijke neurofysiologische en farmacologische fenomenen.

Deze studie beantwoordt een zeer praktische vraag: is er een verschil in hemodynamiek en hersenactiviteit wanneer propofol-remifentanyl wordt toegediend? Dit kan van grote relevantie zijn in populaties waarin hemodynamische veranderingen schadelijk kunnen zijn, zoals de kritisch zieke patient. We vonden dat de hemodynamische status statistisch vergelijkbaar was tussen de groepen. Regelmatig geopperde argumenten in het voordeel van opioïd-gebaseerde anesthesie-inductie worden door deze data niet ondersteund. De data was verzameld in een populatie met een weidere spreiding dan die waarop het gebruikte model van Bouillon werd gebouwd.⁶ Verder onderzoek is nodig om de eerste minuten van deze inleidingen te verkennen, aangezien geen clinicus de elf minuten van equilibratie zal afwachten alvorens laryngoscopie uit te voeren, zoals wij deden in deze studie.

Algemene discussie en vooruitblik naar de toekomst

Dit proefschrift bevestigt dat goed presterende populatie-gebaseerde PK en PD modellen accuraat presteren in de klinische praktijk en in farmacologische simulaties, ook wanneer toegepast in een individu. Als zodanig kan dit proefschrift dan ook als pleidooi gelden voor het gebruik van deze modellen. Optimalisatie met behulp van Bayesiaanse statistiek verbetert de accuraatheid zeer beperkt. Belangrijk is te benoemen dat wanneer een model

de werkelijkheid al goed beschrijft, klinisch relevante verbetering moeilijk is te verkrijgen. De overgebleven foutmarge wordt waarschijnlijk veroorzaakt door biologische variabiliteit tussen mensen, hetgeen erg lastig is te omvatten in een wiskundig model, zelfs wanneer men meer covariaten toevoegt. Het model uitbreiden met uitgedemde propofolconcentraties kan hierin een uitkomst bieden. Op deze manier kan op basis van deze concentraties een schatting gemaakt worden van de plasma concentratie van het middel. Dit vereist echter een grote investering, terwijl dit hoogstwaarschijnlijk nauwelijks bijdraagt aan een klinisch relevante verbetering.

In het eerste hoofdstuk werd al genoemd dat, ondanks de noodzaak voor accurate PK modellen, de plasma concentratie niet het meest relevante doel is voor de clinicus. Het lijkt interessanter om een farmacodynamisch eindpunt te gebruiken om op te doseren. Het lijkt daarom interessanter om met systemen, zoals bijvoorbeeld medicatie-advies systemen, hierop te richten. Men zou dit bijvoorbeeld kunnen toepassen in (semi) closed-loop systemen die het daadwerkelijke effect koppelen aan modelmatige voorspellingen.⁷⁻⁹ Dit kan bijvoorbeeld door populatie-gebaseerde E-max modellen, met als effect bijvoorbeeld electro-encephalographische monitoren, meer naar het individu te verschuiven. Accurate TCI-modellen kunnen daarin bijdragen in de reproducibiliteit van medicatie toediening.

Aan de andere kant kunnen adviessystemen, uitgerust met de reeds veelbesproken populatie-gebaseerde modellen helpen om medicatie-adviezen te geven voor een individu. Dit kan van nut zijn voor enerzijds klinische toepassing en anderzijds voor educatieve doeleinden. Immers, met deze schermen kan je inzichtelijk maken hoe farmacologische principes werken en je klinische doelen inzichtelijk maken. Deze schermen zijn tot op heden uitgerust met theoretische informatie met betrekking tot interacties (dat wil zeggen: het combineren van meerdere medicamenten op hetzelfde moment). Propofol en remifentanyl bijvoorbeeld worden in de dagelijkse praktijk veelvuldig gecombineerd. De adviesschermen maken enkel gebruik van voorspelde concentraties om een uitspraak te doen over het resulterende effect. Het wordt niet beïnvloed door het daadwerkelijke effect. Derhalve lijkt prospectieve validatie van deze schermen noodzakelijk. Op dit vlak is echter nog weinig gepubliceerd, maar de eerste resultaten van studies hieromtrent zijn veelbelovend.^{10 11} In de praktijk lijken deze schermen daadwerkelijk het gedrag van de clinicus te veranderen wanneer ze worden toegepast in de praktijk.

Tenslotte toonden we in dit proefschrift dat interactiemodellen richtinggevend kunnen zijn voor de keuze van dosis combinaties. In de dagelijkse praktijk heeft de clinicus namelijk de keuze uit een oneindige hoeveelheid mogelijkheden van combinaties. De vraag blijft immers telkens of er relevante verschillen zitten tussen de verschillende combinaties op het gebied van bijvoorbeeld hemodynamiek of hersenactiviteit. De interactiemodellen kunnen hierover zinvolle uitspraken doen. In [hoofdstuk 6](#) toonden we dat theoretische gelijkeffectiviteit

(equipotentie) niet automatisch betekent dat er ook equipotentie is voor andere eindpunten.

Conclusie

Dit proefschrift draagt bij in het doel om anesthesiologische medicatietoediening te verbeteren in het individu vanuit verschillende perspectieven en daarbij gebruikmakend van geavanceerde state-of-the-art technologie. PK en PD models zijn daarin waardevolle middelen en dienen als een basis voor verdere verbeteringen, zoals farmacologische adviesystemen.

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List of abbreviations

AUC	Area under the curve	MAC	Minimum Alveolar Concentration
BIS	Bispectral Index	MAP	Mean Arterial Pressure
BMI	Body Mass Index	MDAPE	Median absolute prediction error
BPM	Beats per Minute	MDPE	Median prediction error
BSA	Body Surface Area	METC	Medical Ethics Board (Dutch acronym)
Cbreath	Breath concentration of a drug	NSRI	Noxious Stimulation Response Index
Ce	Effect-site concentration	OFV	Objective Function Value
CI	Cardiac Index	PD	Pharmacodynamics
Cl	Clearance	PDF	Probability Density Function
Cp	Plasma concentration	PE	Prediction Error
CUP	Canonical Univariate Parameter	PK	Pharmacokinetics
CWRES	Conditionally Weighted Residuals	POTmax	Maximum influence (potency) of remifentanyl on Ce50Prop
DAP	Diastolic Arterial Pressure	PTOL	Probability of Tolerance to Laryngoscopy
EEG	Electro-encephalogram	RMSE	Root Mean Square of Errors
Emax	max effect evoked by a drug	SAP	Systolic Arterial Pressure
EMG	Electro-myography	SEF	Spectral Edge Frequency
HLM	Heart-Lung Machine	SVI	Stroke Volume Index
IQR	Inter quartile Range	SVRI	Systemic Vascular Resistance Index
IWRES	Individually Weighted Residuals	TCI	Target-controlled infusion
k	Rate constant between compartments	TIVA	Total Intravenous Anesthesia
LBM	Lean Body Mass	V	Volume of a compartment
LOC	Loss of consciousness		

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Curriculum Vitae

Johannes Pieter (Jop) van den Berg werd in 1988 geboren in toenmalige Academisch Ziekenhuis Groningen, waar hij naar terugkeerde na het behalen van zijn VWO-diploma als student Geneeskunde in 2007. Het heette toen inmiddels het Universitair Medisch Centrum Groningen (UMCG).

Gebiologeerd door het vak van de anesthesioloog rondde hij zijn studie in 2013 af met een semi-artsstage en stage wetenschap op de afdeling anesthesiologie van het UMCG. Hij vervolgde zijn carrière als PhD-student in de onderzoekslijn van de anesthesiologische farmacologie onder de enthousiasmerende leiding van Prof. Dr. Michel M.R.F. Struys, Prof. Dr. Anthony (Tony) R. Absalom, Dr. Hugo E.M. Vereecke en later Dr. Pieter Colin, waarvan dit proefschrift de afronding is. Gedurende dit traject startte hij met zijn opleiding tot anesthesioloog met Prof. Dr. J.K. Götz Wietasch als opleider en urgentiegeneskunde als differentiatie. Zijn perifere opleidingsjaar genoot hij o.l.v. Dr. Jan Petersen in Heerenveen.

Naast zijn opleiding verwierf hij een basiskwalificatie onderwijs (BKO) vanuit zijn liefde en interesse voor onderwijs en opleiding. Hij ontwierp hiervoor het nieuwe junior co-assistentenschap anesthesiologie waarin nu veel meer studenten kennis kunnen maken met het vak.

In zijn vrije tijd is hij maatschappelijk actief als arts bij diverse publieksevenementen (o.a. festivals, sportevenementen) vanuit het Rode Kruis en als medisch manager evenementenzorg van deze organisatie. Hij is sinds 2013 medisch manager vanuit deze organisatie voor de Vierdaagse van Nijmegen waar hij leiding geeft over de medische dienst (ca. 60 artsen en verpleegkundigen) en samenwerkt met ketenpartners en inspectie voor gezondheidszorg en jeugd. Hij houdt van fietsen, zeilen, golf (met zijn vader), varen en zwemmen.

Sinds december 2020 werkt hij als anesthesioloog in het UMCG.

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Promoveren, de 'opleiding tot wetenschapper', is teamwork. Dit teamwork is van vitaal belang. Niet alleen om de wetenschappelijke output naar een hoger niveau te tillen, maar ook om als individu te groeien in de competenties die bij het onderzoekerschap horen. En dat heb ik gedaan in de afgelopen zeven jaar, waarvoor ik mijn dank wil uitspreken aan **iedereen** die op wat voor manier dan ook een bijdrage heeft geleverd aan dit proefschrift: jullie maakten mij een betere wetenschapper en hielpen mij dit proefschrift een te maken om trots op te zijn. In het bijzonder wil ik een aantal mensen bedanken.

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