Study of the application of pharmacokinetic-pharmacodynamic modeling to optimize propofol administration during anaesthesia

Studie over het gebruik van farmacokinetische-farmacodynamische modellen om de toediening van propofol te optimaliseren tijdens anesthesie.

Thesis submitted to obtain the degree of Doctor in Medical Science

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Aan An, Lien en Sam

Volgend jaar ben ik 20 jaar actief in anesthesie. Wat mij vanaf de start boeide was het belang van basiswetenschappen als fysiologie en farmacologie. Gaandeweg liet ik mij echter graag opslorpen door het vele klinische werk en kwam wetenschappelijk werk op het tweede plan. Onder de auspiciën van Prof. dr. G. Rolly startte ik mijn specialisatie opleiding, het was samen met hem dat ik mijn eerste anesthesie voor keizersnede uitvoerde.

Prof. dr. Linda Versichelen deelde met mij haar enthousiasme voor het Chirurgisch Dagziekenhuis. Zij was het ook die de vele theorie- en praktijklessen EHBO van de vakgroep anesthesiologie met grote toewijding verzorgde en samen met haar gaf ik mijn eerste lessen anesthesie en reanimatie aan talrijke jonge studenten van onze faculteit geneeskunde.

Ondertussen ondernamen de professoren Eric Mortier en Patrick Wouters verwoede en intense pogingen om mij te overtuigen tot het schrijven van een doctoraat. Het woord 'doctoraat' bleef echter lang als een bedreiging klinken maar werd uiteindelijk een persoonlijke uitdaging.

Het zijn echter Prof. dr. Michel Struys en Prof. dr. Hugo Vereecke en met hen de coauteurs van de artikels, die het resultaat, zoals het vandaag hier voorligt, mogelijk hebben gemaakt. Prof. dr. Peter De Paepe heeft mee gewaakt over de kwaliteit van het manuscript en zorgde ervoor op zijn rustige manier dat het werk nooit stil viel. De leden van de leescommissie (de professoren Stefan De Hert en Koen Boussery), en de leden van de examenjury (de professoren Walter Buylaert, Luc Van Bortel, Karel Allegaert en Patrick Wouters) lazen het werk aandachtig door, hun aanmerkingen kwamen de thesis alleen ten goede.

Tandartsen bleven een rode draad doorheen het werk. Prof. dr. Luc Marks zorgde mee voor inclusie van patiënten. Prof. dr. Luc Martens leidde op bijna poëtische wijze de ceremonie. Maar mijn mooiste dankwoord is voor An, mijn echtgenote, die mij blijvend steunt en mij reeds 20 jaar deelt met het UZGent.

Een thesis schrijven is dus vooral teamwork !!! Mijn naaste collega's namen regelmatig het werk over in de kliniek want jonge moeders konden en wilden eenmaal niet wachten! Het CDC bleef perfect op koers dankzij Kristof Tassenoy en z'n team. Frieda en de medewerkers van het secretariaat anesthesie droegen hun steentje bij tot de layout van dit werk en waren door hun administratieve ondersteuning een fantastische hulp.

Thuis kon ik rekenen op dochter Lien: met enkele snelle maar efficiënte muisclicks hielp ze mij vaak uit de knoei. Zoon Sam nam heel wat taken thuis van mij over.

Bovenal geven ze mij dagelijks de ruimte om professioneel bezig te zijn.

Aan allen van harte bedankt !!!

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LIST of ABBREVIATIONS

AEP	auditory evoked potentials
BIS	bispectral index
Ce	effect-site concentration
Ce50	effect-site concentration for 50% effect
Cl	clearance
Cp	plasma concentration
EEG	electro encephalography
Emax	maximal possible drug effect
IQR	interquartile range
IV	intravenous
K_{e0}	effect-site concentration equilibration constant
LBM	lean body mass
LOC	loss of consciousness
LORNC	loss of respone to name calling
MDAPE	median of absolute values of performance errors
MDPE	median performance error
NONMEM	non linear mixed effects modeling
OBJFN	objective function
PD	pharmacodynamics
PE	performance/prediction error
PK	pharmacokinetics
PWT	population median weight
ROC	return of consciousness
SD	standard deviation
SE	standard error
TCI	target controlled infusion
TIVA	total intravenous anaesthesia
TTPE	time to peak effect
γ	steepness of the concentration-versus-response curve

CHAPTER 1

OUTLINE AND AIMS OF THE THESIS

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The goal of administering propofol as a hypnotic drug is to obtain and maintain a desired time course of clinical and therapeutic effect as accurately as possible: e.g. loss of response to name calling (LORNC) or predefined bispectral index values (BIS). The specific effect-site drug concentrations to evoke this effect, can be obtained through different dosing regimens. The key question remains which dosing regimen provides optimal control of the time course of the effect of propofol. Standard dosing guidelines ignore the large inter-individual variability in dose-response relationship. Pharmacokinetic-pharmacodynamic (PK-PD) models used in TCI (target controlled infusion) systems reduce this variability by incorporating different co-variates but still model inaccuracy limits universal application of a specified PK-PD model. This thesis discusses several sources of model inaccuracy.

The dose-response relationship can be divided into three parts. The first part involves the relationship between the administered dose and the plasma concentration (pharmacokinetics) and the second part the relationship between plasma or effect site concentration and clinical effect (pharmacodynamics). The final part is the coupling between PK and PD. Additionally, it is important to recognize that these relationships are subject to population variability. It has been proven that incorporating PK-PD information as an additional input to guide clinical anaesthesia can result in better patient care[1-8]. As such, it is important that anaesthetists learn and understand basic anaesthetic pharmacological principles and apply the available pharmacology-based technology into their daily clinical practice[9].

Optimized patient-individual dosing may be achieved by the application of pharmacokinetic and pharmacodynamic models with real-time estimation of the dose-response relationship online. For intravenous anesthetics such as propofol, target-controlled infusion (TCI) techniques based on compartmental models have been developed and are used frequently in daily clinical practice. A target controlled infusion (TCI) aims to achieve a user-defined drug concentration in a "body compartment" of interest, using a computer or microprocessor. These systems use multi-compartmental PK-PD models to calculate the infusion rates required to achieve the specific target concentration. A clinician using a TCI system to administer an intravenous hypnotic is thus able to set a desired ("target") drug concentration, and then adjust it based on clinical response or measurements of drug effect. A computer or microprocessor performs the complex calculations, and controls the infusion pump. Classically, plasma or effect-site concentrations are targeted[10] .

The development of target-controlled infusion (TCI) technology, has enabled clinicians to manage more precisely the complex relationship between dose, blood-concentration, effect-site concentration and clinical effect.

One of the most important components of TCI is an accurate PK-PD model describing the time course of drug plasma concentration and effect-site concentration. The search for the optimal PK-PD model has a long standing history and is continuously developing. Investigators are still searching for the optimal PK-PD model predicting the time course of propofol concentrations and hence hypnotic effect.

This thesis aims at guiding the clinician who makes use of target –controlled infusion (TCI) in daily clinical practice through different PK-PD models. The choice of the model is crucial as an inaccurate model choice can result in a lack of effect or too much effect. However, (possible known) various sources of modeling inaccuracies may bias the TCI concept and may therefore be relevant for clinical practice. As these are not well documented in the literature we aimed to investigate the impact of these inaccuracies.

1) We hypothesized that especially during the first minutes following bolus administration of propofol the prediction error using three compartmental PK models may be large. Due to failure to describe the very early drug distribution in the central compartment: the mixing within the vascular volume, blood flow and subsequently the distribution of the drug to both active and inactive tissues. We tested the hypothesis that different injection rates of propofol correspond with different k_{e0}'s. Initially estimated blood concentrations were used, in a second stage we performed frequent arterial blood sampling (and measure propofol concentrations) during the first minutes following propofol bolus administration.

2) We hypothesized that available PK-PD models for propofol would be able to accurately estimate the effect-site concentration of propofol at loss-of-consciousness and consequently that the effect would remain stable once this concentration is maintained. We tested this hypothesis comparing clinically applied compartmental PK-PD models for propofol.

3) We hypothesized that the estimation of the PD model, using published PK models, does not ensure accurate estimates for PK and PD parameters. An accurate estimation of k_{e0}, linking the kinetic and dynamic model, demands an integrated PK-PD study, combining measurement of blood concentrations and drug effect which are then used to construct a PK-PD model within the same specific population. This results in an overall model describing the dose-response behavior of the drug, with an accurate estimation of the k_{e0}. We tested this hypothesis by constructing a PK-PD model in a pediatric patient-population based on measured blood concentrations and BIS values. In a second step we used published PK models to re-estimate the PD model. We tested the hypothesis that these predicted PK parameters would be able to identify the best-performing PK model and to provide accurate estimations for the true PD parameters.

CHAPTER 2

BASIC PRINCIPLES AND REVIEW OF THE LITERATURE

CHAPTER 2 BASIC PRINCIPLES AND REVIEW OF THE LITERATURE

2.1. Controlling the dose-response relationship

The main drugs used to provide general anaesthesia are hypnotics, analgesics and muscle relaxants. These drugs induce unconsciousness, analgesia, suppression of the hemodynamic response and suppression of reflex movements[11]. This thesis will focus mainly on pharmacological properties of propofol as the hypnotic component of anaesthesia.

Controlling the time course and the degree of hypnotic drug effect is a very important goal in anaesthetic practice. The patient should loose consciousness rapidly during induction and the level of consciousness should be easily titrated to the level of surgical stimulation.

On the one hand, under dosing the hypnotic component of anaesthesia might result in 'awareness' or an accidental awakening[12-14] of the patient during surgery, which is a very distressing event for both the patient and anaesthetist and is to be absolutely avoided.

On the other hand, excessive doses of hypnotic will increase the incidence and the degree of side effects and possibly accounts for long-term morbidity and mortality[15].

Once the surgical procedure is finished the drug effect should dissipate so that the patient wakes up as rapidly as possible. From this moment on any residual hypnotic or sedative effect is deemed as 'adverse effect' that delays early recovery and transit times from high dependency to low care units. In ambulatory anaesthesia any residual sedation is unwanted as it negatively influences 'home-readiness'[16] (Table 1).

Optimal patient-individual dosing may be achieved by the application of pharmacokinetic-pharmacodynamic principles. Using the dose-response relationship, drug titration should be done as close as possible to the drug effect. Titrating a specific effect or, if not possible, a specific effect-site concentration offers advantages. As the effect-site or plasma concentrations are not continuously measurable on-line for most intravenous drugs used during anaesthesia (in contrast to inhaled anaesthetics[17-19]), it requires a pharmacokinetic and/or pharmacodynamic drug model and a computer continuously updating the administration rate to maintain an estimated drug effect or drug concentration. If a specific plasma or effect-site concentration is titrated, this technique is called target-controlled infusion (TCI). TCI is an infusion controlled in such a manner as to achieve a user-defined estimated drug concentration in a body compartment or tissue of interest. A clinician using a TCI system to administer an anaesthetic agent is thus able to set and adjust a desired drug concentration, usually referred to as the "target concentration", based on clinical observation of the patient or measurement of drug effect. Multicompartmental pharmacokinetic-dynamic models are used by TCI systems to calculate the infusion rates re-

quired to achieve the target concentration. A computer or microprocessor is required to perform the complex calculations, and to control the infusion pump. Classically, plasma or effect-site concentrations are targeted. When the effect-site is targeted, the classical multi-compartmental pharmacokinetic model has to be extended with an effect-site compartment.

In experimental conditions it is already possible to quantitate expiratory propofol concentrations. These techniques range from discontinuous techniques to fast and very fast analysing techniques. As these very fast techniques result in analytical times within seconds to milliseconds, on-line detection of expiratory propofol concentration will possibly become available in the future. Several authors have shown good correlation between propofol concentration in the brain, blood and exhaled breath.[20-23]

Advantages and disadvantages of Total Intravenous Anesthesia with propofol	
Advantages	*Disadvantages*
Induction is very rapid in onset	Pain during injection of propofol
Rapid onset of action independent from alveolar ventilation	Need sophisticated infusion pumps with algorithms for the TCI software
Improved quality of emergence from anesthesia	Greater pharmacokinetic and pharmacodynamic interindividual variability
Very smooth and peaceful recovery	Difficult to estimate blood concentration of propofol in real time at the moment
No risk of environmental pollution	Propofol infusion syndrome
Reduction in the incidence of postoperative nausea and vomiting	
Method of choice in patients at risk of malignant hyperthermia	
Method of choice in some patients with congenital myopathies	
Can be reliably administered to maintain anesthesia in patients undergoing airway procedures	

Table 1. Advantages and disadvantages of TIVA with propofol

2.2 Developing a compartmental kinetic model for TCI.

'Like paintings pharmacokinetic models range from the completely abstract to the naturalistic.'[24]

In order to target a specific plasma concentration of propofol one must know what happens when a specific amount of drug is administered to a patient in a specific time frame. For this, one needs pharmacokinetics describing the time course of the plasma concentration, or stated otherwise "what does the body with the drug ?" Typically a bolus or short-lasting infusion can be given and than blood samples are taken to describe the time course of the plasma concentration. With this information one can try to predict what will probably be the plasma concentration when a certain amount of propofol is injected.

If the human body was one single compartment, it would be easy to describe the time course of the concentration of a hypothetical drug. A basic assumption of the concept of a one-compartment representation of distribution is that equilibration of drug between tissues and blood occurs spontaneously and immediately. Knowing the volume of that compartment would enable us to know the concentration of a given amount (dose) of a specific drug (equation 1).

$$C_0 = \frac{x_0}{V} \qquad \text{equation 1}$$

Where C_0 is the concentration at time 0, x_0 is the initial dose of drug, V is the volume of the compartment.

The clearance of a drug is typically a first-order process. The rate of change for a first-order process is :

$$\frac{dx}{dt} = -k.x \qquad \text{equation 2}$$

x is the amount of drug, k is the rate constant for drug elimination, the unit of k is $time^{-1}$.

If a value of x at time t is needed, x(t), it can be found as:

$$x(t)=x_0.e^{-kt}$$ equation 3

x_0 is the amount of drug concentration at $t=t_0$ or the initial dose, x(t) is the amount of drug at time t,

by using equation 1 the plasma concentration can be found as:

$$C(t)= C_0 . e^{-kt}$$ equation 4

However in reality drug distributes from the plasma to different groups of tissues, a process that takes time. A multi-compartmental model is needed to describe this phenomenon. The time required for distribution depends on tissue perfusion, permeability characteristics of tissue membranes for the drug, lipid solubility and its partitioning between tissues and blood. The drug is also distributed to eliminating organs, so clearance starts immediately.

When the anaesthetist injects a given amount of drug, e.g. propofol, the drug will initially dilute in a certain volume, the central volume of distribution (V_1 or V_c) (fig1). This volume reflects the volume of the heart, great vessels and the venous volume of the upper arm. The drug passes through the lungs and eventually meets the arterial circulation. Immediately however propofol fades to peripheral tissues away from the plasma. Two groups of tissues, compartments, receive propofol from the central volume of distribution.

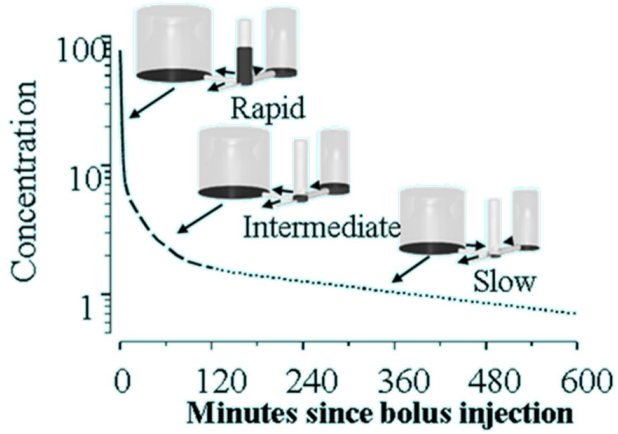

Fig 1 A three compartmental pharmacokinetic model. The drug is administered in the central compartment (small container in the middle), from which it is eliminated and distributed to a rapid equilibrating peripheral compartment (right hand container) and a slow equilibrating peripheral compartment (left hand, largest container). In the y axis the log (plasma concentration) is plotted against time in the x axis. Figure from S. Shafer[25]

One group of tissues, the 'vessel rich group', originally receives a lot of propofol from the central compartment and hence is called the second compartment (V_2) and rapidly equilibrates with the central volume.

The drug eventually moves to another group of tissues, the 'vessel poor' group, characterized by a slow equilibration with the central volume; the 'inflow' of propofol in this third compartment (V_3) is much slower.

The volumes and equilibration constants of a three-compartmental pharmacokinetic (PK) model can be estimated by administering an amount of propofol in a standardized population. Subsequently blood samples are drawn at specific time-points for measuring propofol plasma concentrations. The results are depicted in a log (plasma concentration) over time graph. Three distinct phases can be distinguished (fig1). The initial distribution phase following bolus injection describes distribution from plasma to the rapidly equilibrating tissues. A slower second distribution phase is explained by a movement of the drug into more slowly equilibrating tissues and a return of the drug from the most rapidly equilibrating tissue. The terminal phase is a straight line when plotted on a semi logarithmic graph and is often called the elimination phase because the primary mechanism for decreasing drug concentration during the terminal phase is elimination from the body.

The rates of drug metabolism and distribution can be interchangeably described by rate constants or clearances. A rate constant describes a proportion of drug in a compartment undergoing a process during a unit of time, and

is thus reported with the units min^{-1} or hr^{-1}. By convention k_{10} is used to denote the rate constant for metabolism or elimination. The symbols k_{12}, k_{21}, k_{13}, k_{31} are used to denote the rate constants for drug transfer from V_1 to V_2, from V_2 back to V_1, from V_1 to V_3, and from V_3 back to V_1 respectively.

Clearances describe a volume (of a compartment) that is 'cleared' from drug during a unit of time. The units are thus ml/min or ml/hr.

For a three-compartmental model it is more difficult to calculate the inter-compartmental rate constants. Analogous to equation 2 and 3 the equations for a three-compartmental model are:

$$\mathbf{dx_1/dt = I - dx_2/dt - dx_3/dt - x_1k_{10}} \qquad \text{equation 5}$$

$$\mathbf{dx_2/dt = x_1k_{12} - x_2k_{21}} \qquad \text{equation 6}$$

$$\mathbf{dx_3/dt = x_1k_{13} - x_3k_{31}} \qquad \text{equation 7}$$

Integration of equations 6 and 7 in equation 5 and rearrangement yields equation 8

$$\mathbf{dx_1/dt = I + x_2k_{21} + x_3k_{31} - x_1k_{10} - x_1k_{12} - x_1k_{13}} \qquad \text{equation 8}$$

Where I is the rate of drug input, x is the amount of drug for a specific compartment and k is a micro-rate constant

The dataset gives rise to a pharmacokinetic model, a mathematical fitting of measured concentrations. The model not only describes the time course of drug concentration in a studied population but subsequently it can be used to predict the blood concentration profile of a drug after a bolus dose or an infusion of varying duration in a subject that corresponds to the typical patient of the original study population.

We developed our own pharmacokinetic model for propofol in children[26]. In this example (table 2) V_1 is the central volume for propofol in a 20 kg child. V_2 and V_3 are the volumes of the second and third compartment. Cl is the elimination clearance, the amount of the central volume that is cleared from propofol per min. Q_2 is an intercompartmental clearance, the amount of V_2 that is cleared from propofol per min. Q_3 is the amount of V_3 that is cleared from propofol per min.

Parameter	Units	Typical value
V1	L	3,5
V2	L	4,7
V3	L	19
Cl	$l * min^{-1}$	0,79
Q2	$l * min^{-1}$	2
Q3	l * min-1	0,67

Table 2 The Coppens PK model for propofol as an example. Values are calculated for a 20 kg child

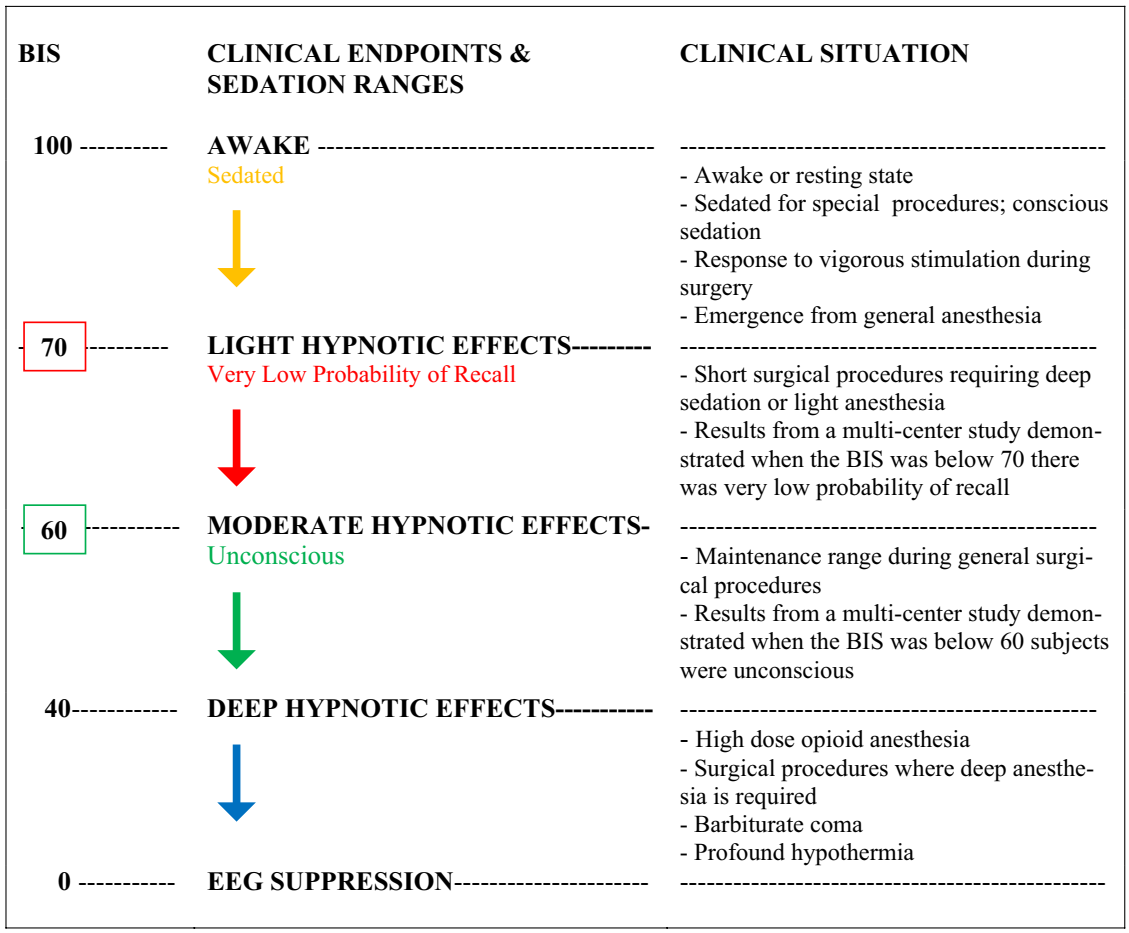

Fig 2 BIS Range guidelines. as included in the user guide of BIS XP® (Aspect Medical, MA, USA)

2.3 Measuring cerebral drug effect as a pharmacodynamic end-point

The hypnotic effect of propofol can be measured with bispectral index monitoring (BIS)[27,28]. BIS measures a selected part of a classical EEG signal that is highly associated with sedation/hypnosis, regardless of which type of agent is used to produce that clinical state. BIS index is a processed EEG parameter derived from multiple advanced signal processing techniques. The BIS algorithm provides a reliable processed EEG parameter of anaesthetic and sedative effect[29-31]. BIS generates a figure from 0 to 100. The awake patient typically has a

BIS value of 100. The value drops as the patient falls asleep. BIS values between 60 and 40 are associated with an appropriate anaesthetic level. Values lower than 40 are deemed as a too deep level of anaesthesia (fig 2).

Anesthetic depth is the result of hypnosis, amnesia, anti-nociception and reflex suppression. Soon after BIS monitoring was developed many studies appeared in the literature to validate the technique. Correlation studies try to link depth of anesthesia to specific BIS values. Sebel et al.[32] performed a multicenter trial where two groups of patients were included; in the control group patients were only monitored with BIS, in the treatment group anesthesia was titrated to a BIS value below 60. Primary endpoint of the study was the rate of patient movement as response to skin incision. In the control group, the mean BIS value was 66 (±19) and 43% of patients moved. In the treatment group the mean BIS value was 51 ±19 and only 13% of patients moved on skin incision. Movement on skin incision is a very rudimentary surrogate of depth of anesthesia. So other authors tried to correlate BIS values with levels of consciousness.

With increasing sedation[33] there was a progressive decrease in BIS during sedation with midazolam; Observer's assessment of alertness and sedation scores (OAAS/O) were correlated to BIS values. OAAS/O scores of 5 mean an awake state. OAAS/O of 1 means no response to tactile stimulation. OAAS/O scores of 5 correlated to BIS values of 95.4 ±2.3, scores of 4 to BIS values of 90.3 ±4.5, scores of 3 to BIS values of 86.6 ±4.6,scores of 2 to BIS values of 75.6 ±9.7 and an OAAS/O score of 1 corresponded with BIS values of 69.2 ±13. During recovery from midazolam sedation BIS values increased together with OAAS/O scores.

Leslie et al[34] compared measured propofol concentrations with BIS in volunteers. The mean propofol concentration to suppress learning by 50% was 0.66 µg/ml. BIS decreased linearly as propofol blood concentration increased. (r=0.69). Doi et al[35] also found a good correlation of BIS values with propofol blood concentrations.

Other studies used to validate 'Depth of Anesthesia' monitors look at recovery times. A multicenter randomized trial[36] (302 patients) studied patients under routine care versus patients guided under BIS monitoring. BIS monitoring led to a reduction in propofol requirements and earlier recovery. A meta-analysis of trials[37] (1383 day surgery patients) concluded that use of BIS monitoring significantly reduced anaesthetic consumption by 19%, reduced the incidence of nausea and vomiting by 23%, and reduced recovery time by 4 min.

A third kind of studies look at the ability of 'Depth of Anesthesia' monitors to prevent memory formation or awareness during anesthesia. For most anesthetists this remains a major objective. Ekman et al[38]. did a before and after comparison of the use of BIS monitoring (4945 patients undergoing general anesthesia with muscle relaxation, BIS monitored versus 7826 patients not BIS monitored). They found a 5-fold reduction in risk of awareness, 0.04% vs 0.18%. Myles et al[39]. found a reduced risk of awareness by 82% in a study of 2643 adult patients at high risk of awareness. However in an effectiveness study[40] (three hospitals, 21.601 patients) no significant difference in intraoperative awareness with explicit recall was detected between bispectral index and anesthetic concentration protocols. It concerned an unselected surgical population.

A Cochrane analysis[41] included 31 trials. In studies using clinical signs as control, the analysis demonstrates a significant effect of the BIS-guided anaesthesia: a risk reduction of intraoperative recall, a risk reduction of

awareness among surgical patients with high risk of awareness (2493 participants; OR 0.24). This effect was not demonstrated in studies using end tidal anaesthetic gas monitoring as standard practice (1981 participants; OR 1.01). BIS-guided anaesthesia reduced the requirement for propofol by 1.44 mg/kg/hr (662 participants), and for volatile anaesthetics (desflurane, sevoflurane, isoflurane) by 0.14 minimal alveolarconcentration equivalents (MAC) in 928 participants. Irrespective of the anaesthetics used, BIS reduced the following recovery times: time for eye opening (2446 participants; by 2.14 min), response to verbal command (777 participants; by 2.73 min), time to extubation (1488 participants; by 2.87 min) and orientation (316 participants; by 2.57 min). BIS shortened the duration of postanaesthesia care unit stay by 7.63 min in 1940 participants.

2.4 Linking kinetics and dynamics using the concept of the effect-site concentration :

The standard pharmacokinetic model assumes that after bolus injection there is a complete mixing within the central compartment resulting in the peak plasma concentration occurring at time 0. Following bolus administration it takes 30 to 45 seconds for the drug to pass from the venous circulation to the arterial site.

However a hypnotic drug like propofol does not exert its effect in the arterial circulation. Propofol exerts its effect in the brain and so additional time is required for the drug to reach the target organ, penetrate the tissue and induce an intracellular process which will lead to the onset of drug effect (i.e. unconsciousness). This delay between peak plasma concentration and peak concentration in the brain is called hysteresis (fig 3).
The concentration of propofol in the brain can not be measured in every day clinical practice. In experimental conditions microdialysis techniques can be used when brain tissue becomes or is made accessible. Microdialysis probes measure free drug concentrations, which from a pharmacodynamic point of view is the concentration surrounding receptors[42].
However we can measure the hypnotic effect of propofol, and hence the time course of drug effect can be characterized. Knowing the time course of drug effect, the apparent rate of drug inflow into and from the effect site can be characterized. The time course of drug effect is a reflection of the time course of the effect site concentration.

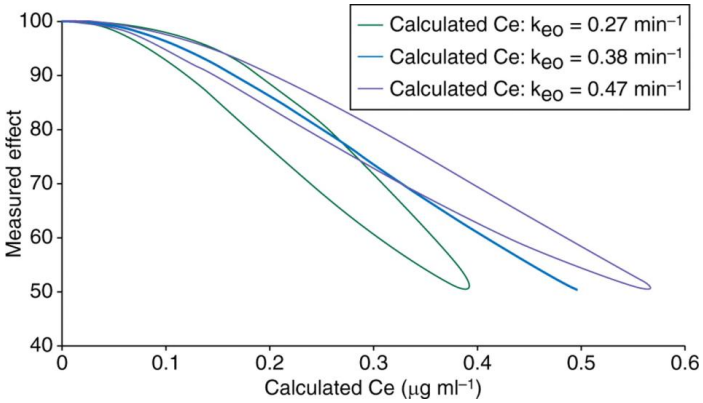

Fig 3 Hysteresis. The anaesthetic effect is measured continuously. Estimated effect-site concentration, C_e is calculated from the estimated plasma concentration and different k_{e0}'s With a k_{e0} of 0.38 min^{-1} there is a collapse of the hysteresis loop. Figure from Absalom et al[43]

The effect site[44,45] is the hypothetical compartment that mathematically links the time course of plasma drug concentration to the time course of drug effect and k_{e0} is the rate constant of drug elimination from the effect site (fig 4). The k_{e0} defines the proportional change in each unit of time of the concentration gradient between plasma and effect-site. The effect-site compartment is assumed to have negligible volume. Hence uptake of drug into the effect-site should have negligible influence on the plasma concentration of a drug, so that the calculated plasma concentration profile following an infusion of drug is identical for any value of k_{e0}.

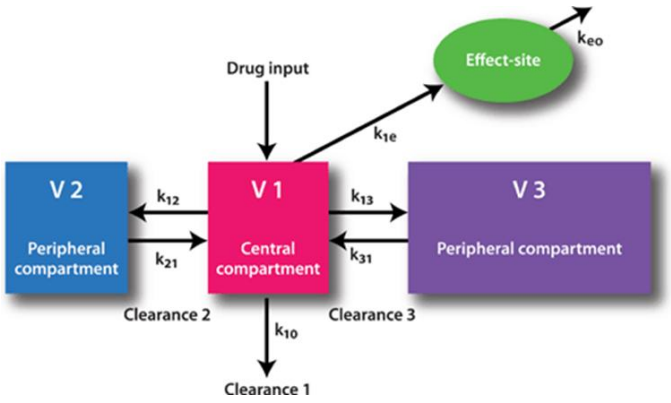

Fig 4. A three compartmental pharmacokinetic-pharmacodynamic model extended with an effect-site compartment. Figure from Mani[46]

An accurate estimation of k_{e0} demands an integrated pharmacokinetic-dynamic study combining blood sampling with frequent measurement of drug effect, resulting in an overall model for the dose response behavior of the drug.
Mathematically the effect-site concentration is the convolution of an input function (in this case, the plasma concentration over time) and the disposition function of the effect-site.

$$\mathbf{C_{effect\text{-}site}(t)=C_{plasma}(t) * D_{effect\text{-}site}(t)} \qquad \text{equation 9}$$

The disposition function of the biophase is typically modeled as a single exponential decay:

$$\mathbf{D_{effect\text{-}site}(t)=k_{e0}\, e^{-ke0t}} \qquad \text{equation 10}$$

The mono-exponential disposition function is simply an additional compartment that is connected to the central compartment.

We cannot measure directly the $C_{effect\text{-}site}$ or $D_{effect\text{-}site}$ but we can measure the drug effect. Knowing that the observed drug effect is a function of the drug concentration in the effect-site, it is possible to predict the drug effect as:

$$\mathbf{Effect=f_{PD}\,(C_{plasma}(t)*D_{effect\text{-}site}(t),\, P_{PD},\, k_{e0})} \qquad \text{equation 11}$$

Where f_{PD} is a pharmacodynamic model (typically sigmoidal in shape), P_{PD} represents the parameters of the pharmacodynamic (PD) model and k_{e0} is the rate constant for equilibration between plasma and the effect-site. Nonlinear regression programs are used to link values of P_{PD} and k_{e0} that best predicts the time course of drug effect. This method is called loop collapsing (fig 5).

If no integrated pharmacokinetic-dynamic model exists, the time to peak effect after a bolus injection can be used to recalculate k_{e0} using the pharmacokinetic model to yield the correct time to peak effect. After a propofol bolus there is a rapid increase in plasma concentration followed by a tri-exponential decline. As long as the plasma concentration of propofol is greater than the concentration in the effect-site, the effect-site concentration increases. After a bolus dose the maximum effect site concentrations occurs at the point where the plasma and effect-site concentration curves cross (fig 6). As the hypnotic effect of propofol is determined by the effect-site concentration, the time delay between a bolus dose injection and the time at which the plasma and effect-site concentrations intersects is referred to as 'the time to peak effect' (TTPE).

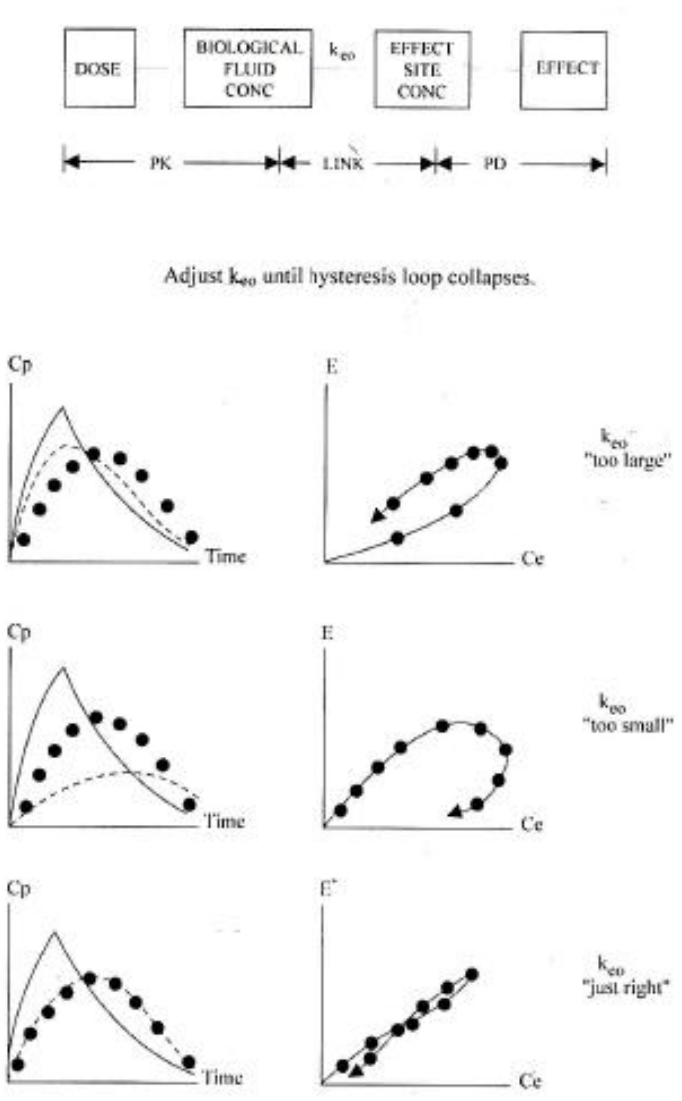

Fig 5 : Hysteresis loop collapsing: broken lines represent calculated effect-site concentrations, circles are observed measures of effect, full lines are plasma concentrations, an effect-site concentration vs effect hysteresis loop is generated by plotting each observed effect against the effect-site concentration predicted for the same time and connecting these points (by line segments) in time order; an effect versus effect –site concentration curve is obtained for the trial k_{e0}. The final k_{e0} estimate is the value that best collapses the hysteresis loop in the effect versus effect-site concentration curve with superimposition of both limbs of the curve. Figure from Bührer[47]

Constructing curves for estimated effect-site concentrations with different k_{e0} and comparing them with the curve for the measured effect allows to choose the k_{e0} value that best predicts the time course of effect.

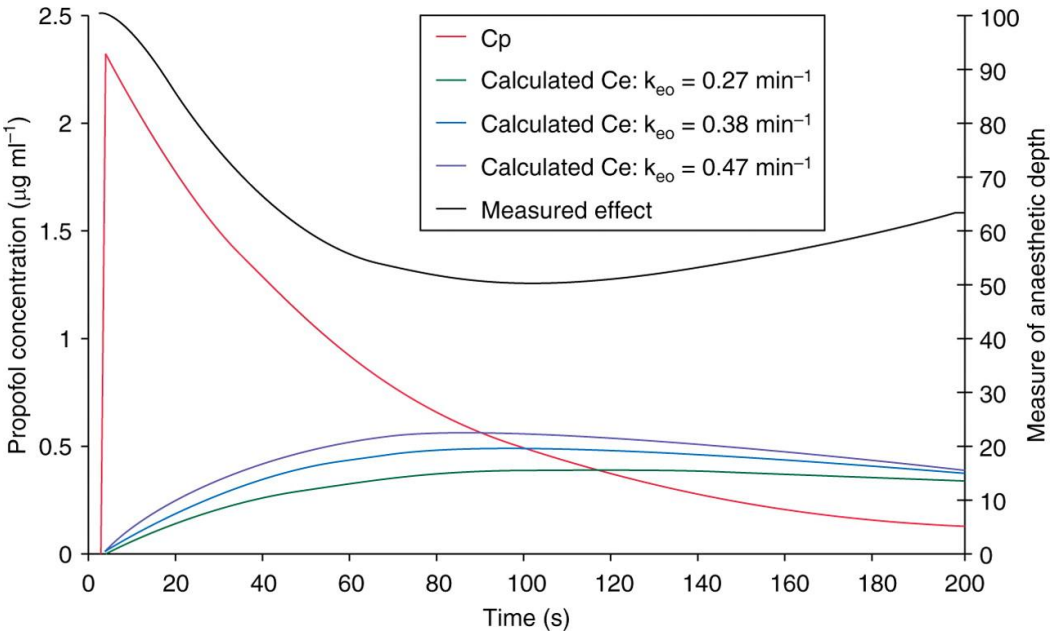

Fig 6 Estimation of k_{e0} using TTPE methodology. Estimated plasma concentrations and a measure of anaesthetic effect are plotted over time. The estimated effect-site concentrations resulting from different k_{e0} values are then calculated and plotted, to determine which k_{e0} value is associated with a peak effect-site concentration that matches the peak clinical effect. Figure from Absalom[43]

When targeting the effect site, the TCI system manipulates the plasma concentration to achieve the effect-site concentration as rapidly as possible, but without an overshoot at this effect-site level. The magnitude of the plasma concentration overshoot estimated by the system depends critically on the k_{e0} and also on the estimated rate of decline in the plasma concentration. If a slower k_{e0} is used, a greater overshoot in the peak plasma concentration will be required to produce a larger concentration gradient between the blood and effect-site and thereby to hasten plasma-effect-site equilibration.(Fig 7)

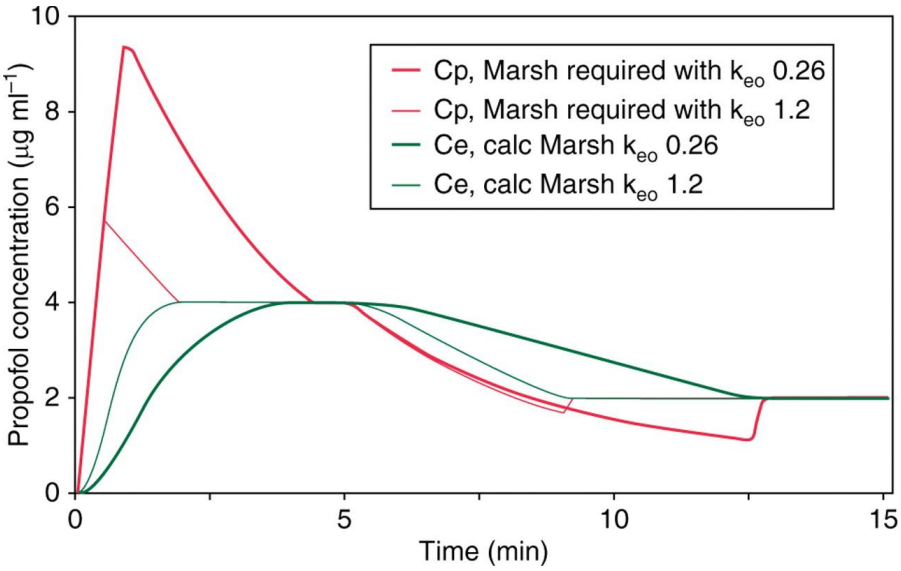

Fig 7 Effect-site targeted TCI for propofol (Marsh model), showing the effect of the choice of k_{e0}. If a slow k_{e0} is used, then a large overshoot in plasma concentration will result when the target concentration is increased. Figure from Absalom[43]

2.5 Non Linear Mixed Effects Modeling

Basically this thesis handles the time course of propofol concentrations in plasma or effect site in different study populations. Also the nature and magnitude of drug effect in relation to the concentration is being investigated.

Classical pharmacology tends to describe the dose-response relationship in a group of patients without taking into account the intra-individual and/or inter-individual physiological and pharmacological variation. Starting from measured plasma concentrations, data are pooled together as if all doses and all observations describe a single subject. This results in 'average' statistics with mean value and standard errors. Equal weight is assigned to every individual subject; sample values from significant outliers will have a significant effect on one or more of the average parameters in the final model. This approach suggests that many samples are taken in a large study population.

Population pharmacokinetics study the variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest. Certain patient demographics (e.g. body weight, gender, height, hair color[48] (!?)…), physiological functions (e.g. cardiac output, liver and kidney function…), therapeutic features and the presence of other therapies, can regularly alter dose-concentration relationships.

An advantage of population pharmacokinetic modeling is its ability to analyze sparse data sets (sometimes only one concentration measurement per patient is available). Basically, there are two approaches to population modeling, defined as the standard two stage approach and the non-linear mixed effect approach.

In the standard two stage approach, as a first step, the individual concentration-time profile is appreciated to generate parameters as volumes and clearances. In a second step, these parameters are summarized by calculating the mean, median and the variability between subjects (SE or IQR). A major drawback of this approach is that it requires a relatively high number of samples in each individual, while each patient has to contribute roughly the same number of samples. Moreover it is more difficult to distinguish between inter-individual (variability between subjects) and intra-individual or residual variability (variability within one subject, measurement error and model misspecification) and as a result inter-individual variability is often overestimated.

The population approach using non-linear mixed effects modeling to obtain pharmacokinetic parameters is the preferred approach, because the analysis is based on simultaneous analysis of all data of the entire population while still taking into account that different observations come from different patients[49]. Both the inter-individual and intra-individual variability are separately estimated in the dataset using this approach. The term 'mixed' in non-linear mixed effects modeling represents a mixture of fixed and random effects. For the fixed effects, a structural model describing the PK or PD is chosen (eg a three compartmental model for PK or an E_{max} model for PD). The random effects quantify the variability that is not explained by the fixed effects. These

random effects include inter-subject and intra-subject random variability, which are both simultaneously and separately estimated.

In general model building requires three different steps:

A structural model (fixed effects) has to be designed
A statistical sub-model (random effects) has to be developed
A covariate sub-model has to be identified

Fixed effects

The structural model contains descriptors of a process (disposition of propofol in the body, elimination, clearance, volume of distribution) (e.g. a three compartmental model for PK or an E_{max} model for PD) that vary among individuals. The population values for these parameters are called typical values and are expressed as θ's. The known, observable properties of individuals that cause these parameters to vary across the population are called 'fixed' effects or covariates. Covariates are specific predictors of PK and PD variability within the population. Covariates can be demographic (age, body weight, gender), pathophysiological (renal or hepatic function) and genetic/environmental. For example, if we know that clearance is proportional to weight, then we simply express clearance in the model as a scalar times weight. Weight has a fixed effect on clearance.

Random effects

After selecting the structural model, the statistical sub-model, which accounts for the inter-individual as well as the residual variability is chosen and tested. The random effects quantify the variability that is not explained by the fixed effects. These effects are called 'random' because they cannot be predicted in any way. There are two sources of random variability when dealing with biological data.
One kind of random effects is the unexplained differences between individuals. This is called inter-individual or between subject variability. It is often assumed that the variability between subjects follows a normal distribution with a mean of zero and variance ω2.

$$\theta_I = \theta_{TV} \cdot e^{\eta i} \qquad \text{equation 12}$$

Where θ_i is the parameter value in the ith patient, θ_{TV} is the typical value of the parameter in the population and η_i is a random variable in the ith patient with a mean of zero and a variance of ω^2.

The second source of variability is the residual error or 'noise'. This is the difference between the prediction of the model for the individual and the measured observation. This is called 'intra-individual' or within-subject variability. This is the result of noise in the dataset, error in the assay, errors in drug dose, etc (fig 8).

$$\mathbf{Y_{obs} = TY + \epsilon} \qquad \text{equation 13}$$

Where Y_{obs} is the observed value of Y, TY is the true value of Y and ϵ is the error, a normally distributed random variable with a mean of zero and a variance of σ^2.

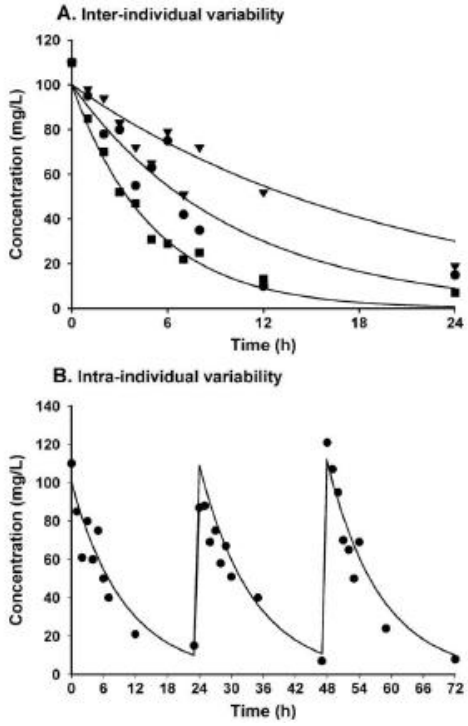

Fig 8 In a, the inter-individual variability among three individuals who received the same dose is shown. b presents the intra-individual or residual variability by showing the concentration–time profile after repeated administration. Figure from De Cock[49]

In this thesis NONMEM was used to explore the pharmacokinetic-dynamic relationship between BIS measurements (measures of cerebral hypnotic drug effect (=dependent variable)) and the calculated effect-site concentration of propofol (= independent variable). This relationship classically is described by a sigmoidal E_{max} model.

This model is determined by four variables: the baseline effect (E_0), the maximum effect (E_{max}), the effective dose compatible with 50% of the maximal effect (ED_{50}), and the slope of the sigmoidal curve (γ).

$$\textbf{Effect} = E_0 + (E_{max} - E_0)\frac{Ce^{\gamma}}{Ce^{\gamma} + Ce_{50}^{\gamma}} \qquad \text{equation 14}$$

Additionally we quantified the intra- and inter-individual variability, by estimating the respective variances for these random effects. Finally NONMEM provides a tool ('objective function') that allows to compare several estimated models on the same dataset, in order to determine the most optimal parameter estimation. Greatly simplified, the 'objective function' value should be decreased or minimized, as it reflects the mathematical process that aims to minimize the -2 log likelihood of the fit of the model to the observed dataset. We used this method in our studies to find the optimal set of parameters for describing a sigmoidal E_{max} model with our dataset.

2.6 Accuracy analysis of a TCI model

Acceptance of target-controlled drug delivery of propofol requires evaluation of both accuracy and outcome among patients in whom TCI has been used. Sources of inaccuracy with pharmacokinetic model-driven devices include software and hardware problems, and pharmacokinetic variability. Problems with software and hardware became rather exceptional. Biologic variability still is the major source of inaccuracy. Firstly, the pharmacokinetic model may be inaccurate, resulting in a difference between the predicted and the observed concentrations in an individual (residual error, noise). Individuals are far more complex than implied by simple compartmental models, and thus no such model can precisely predict the concentrations. Secondly the pharmacokinetic parameters of a patient may differ from the model, simply as a result of 'between-subject' variability, due to intrinsic biological inter-individual differences.

Accounting for as much as possible specific patients characteristics, i.e. covariates, is an attempt to compensate for biologic variability. The ultimate model still has to be developed[50].

The variability with TCI technology will always be less than the variability observed after a single manual bolus injection, or a continuous infusion at a fixed rate. The mechanism by which a TCI device decreases biologic variability is by incorporating patient covariates such as weight, height, sex, liver function, cardiac output,…The patient-specific model is subsequently used to control the drug administration according to the characteristics of the patient. Another mechanism by which TCI decreases variability is by accounting for drug accumulation in peripheral tissues. Targeting a specific concentration typically results in a steady concentra-

tion. The choice for a fixed infusion rate results in increasing plasma concentrations over time. Hu[51] et al. simulated a 10 mg bolus of propofol, a continuous infusion of 10 mg/min or a TCI regimen with a target of 1µg/ml. Plasma propofol concentrations were simulated with the Schnider model. Hu showed that the variability in estimated concentrations following bolus administration was twice the variability of concentration achieved with conventional infusion or TCI administration.
Performance of a pharmacokinetic model is the ability to estimate a specific drug plasma concentration. Numerically, the primary concern is how far the measured concentration deviates from the predicted concentration. A classical graphical representation of model performance is an XY plot depicting predicted versus measured plasma drug concentrations or the relationship measured/predicted drug concentration ratio versus time.

The most straightforward measure of good performance would be to simply estimate the size of the typical miss of the measured concentration from the targeted or predicted concentration. The smaller the size of the typical miss, the greater the accuracy of the TCI system, and the closer the predicted concentration is to the measured concentration.

The basis for quantification of performance is: the percentage performance error (PE):

$$\boldsymbol{PE_{ij} = \frac{Cm_{ij} - Cp_{ij}}{Cp_{ij}} \times 100} \qquad \text{equation 15}$$

Where Cp_{ij} is the jth prediction of the plasma drug concentration in the ith patient and Cm_{ij} the jth measurement of the plasma concentration in the ith patient.
Subsequently four measures are used to quantify the predictive performance of TCI systems and PK/PD models: median absolute performance error (MDAPE), median performance error (MDPE), divergence and wobble[52].

The first measure of TCI/model performance, reflecting the inaccuracy, is the median absolute performance error

$$\boldsymbol{MDAPE_i = median\left\{\left|PE_{ij}\right|, j = 1, \ldots, Ni\right\}} \qquad \text{equation 16}$$

Where N_i is the number of performance errors in the ith individual.
Another characteristic of TCI performance is whether the device produces measured drug concentrations that are systematically above or below the targeted concentrations, this is termed 'bias'. Bias is measured by the

median prediction error (MDPE). MDPE is a signed (positive or negative) value and thus represents the direction (over- or underprediction) of the performance error.

$$\boldsymbol{MDPE_i = median\left\{ PE_{ij}, j = 1, \dots, Ni \right\}} \qquad \text{equation 17}$$

Some individuals may differ from the general patient population and show a gradual worsening (or improvement) of TCI performance over time. This is 'divergence', the performance of the TCI deteriorates (or improves) systematically with time.

Divergence is calculated for each individual as the slope of the linear regression of that individual's absolute performance errors over time. A negative value indicates that the measured concentrations are converging with the predicted values over time. A positive value indicates the opposite.

Wobble is a measure of the variability of the PE_{ij} in ith individual. Wobble measures the total intra-individual variability in performance error.

$$\textbf{Wobble}_i = \textbf{median absolute deviation of } \left\{ PE_{ij}, j=1,\dots,N_i \right\} \textbf{ from MDPE}_i \qquad \text{equation 18}$$

As an example of how PK model performance is expressed an article by Sepulveda is discussed. Sepulveda[53] and colleagues investigated the performance of different currently available PK models for propofol in children. In a group of 41 children (3-26 months), they administered a bolus of 2,5 mg propofol, followed by an infusion of 8 mg/kg/h. Arterial blood samples were collected at regular intervals (fig.9 a.). For different PK models plasma concentrations were estimated by simulation using each individual weight and dose profile. For each measured plasma concentration the corresponding estimated plasma concentration was used to calculate the PE. For any individual this results in an MDPE and MDAPE. Overall for the whole group of patients this results in an MDPE and MDAPE for the model. One of the models investigated was the Coppens model. MDPE and MDAPE was calculated after bolus administration, during infusion and recovery. The Coppens model resulted in a MDPE of -13,-11,-32, and in a MDAPE of 23, 15 and 36, after bolus administration, during infusion and recovery respectively. MDPE and MDAPE during the test period for the model was -16,47 and 21,01 (fig 9). The negative value for MDPE reflects an overestimation of the model.

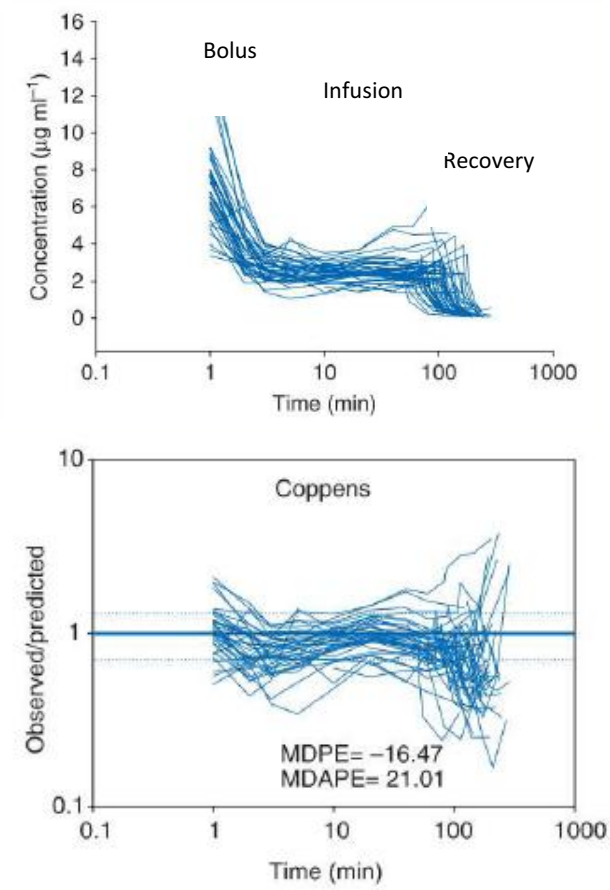

Fig. 9 a. Measured arterial propofol concentration versus time for each individual.

Fig 9 b. Time profile of the measured/predicted (with Coppens) propofol plasma concentrations for each individual. The dotted lines represent an acceptable range. The bold line indicates perfect prediction. MDPE = median performance error, MDAPE = median absolute performance error. Figure from Sepulveda[53]

2.7 Propofol: 'our study' drug: existing models

For propofol various multi-compartmental pharmacokinetic-dynamic models have been published. Coetzee et al.[54] compared the accuracy of some of the models published before 1995 and found that propofol TCI using the model published by Marsh resulted in acceptable performance (MDPE -7%; MDAPE18%).

The Marsh[55] model for propofol was first published in 1991. Compartmental volumes (V_1 , V_2 and V_3) and clearances are proportional to body weight, whereas rate constants for redistribution are fixed. The Marsh model was adapted from the Gepts[56] three-compartmental model, developed from a study involving three groups of six patients who each received constant rate infusions of propofol at either 3,6 or 9 mg kg^{-1} h^{-1}.

The Marsh model was incorporated in the first commercially available TCI system. This device, the Diprifusor®, was originally developed for targeting plasma concentration of propofol. Early models only displayed the target and the estimated plasma concentration. The Diprifusor® microprocessor controlled a syringe recognition system that only allowed the use of glass pre-filled 50 ml syringes of 1% or 2% propofol (Diprivan® 1%TM or Diprivan® 2%TM, AstraZeneca). The major drawback of the Marsh model is the lack of effect compartmental information and the fact that weight is the only covariate.

A k_{e0} value of 0.26 min^{-1} was used with the Marsh model in first generation TCI pumps, to enable effect-site estimations to be made and displayed as additional information. The data on which this k_{e0} was based were never published in the literature, although it is quite similar to the value of 0.2 min^{-1} found by Billard et al.[57]

Struys and colleagues published evidence that a k_{e0} of 1.2 min^{-1} used in conjunction with the Marsh pharmacokinetic parameters more accurately predicted the time course of clinical effect (BIS) than the k_{e0} of 0.26 min^{-1} . A k_{e0} of 1.2 min^{-1} used with the Marsh model results in an estimated time to peak effect of approximately 1.6 min, which is consistent with the findings of other groups. This combination is used in the Base Primea TCI system[4] and results in more gentle manipulations of the plasma concentration when effect-site targeting mode is used. In the pump, it is defined as the 'modified Marsh model'.

Schnider[58] et al. evaluated age, height, weight and lean body mass (LBM) as covariates in a new combined pharmacokinetic-dynamic three-compartmental model. The large variability of the study population (18-81 years and 44-123 kg) provides a wide applicability of the model.

The Schnider model has fixed values for V_1,V_3,k_{13}, and k_{31}, adjusts V_2, k_{12}, k_{21}, for age and adjusts k_{10}, according to total body weight, lean body mass (LBM), and height. In plasma targeting mode, the small, fixed V_1 results in very small initial doses on starting the system. The Schnider model however also describes the dose-effect relationship for propofol and hence has a pharmacodynamic component.

Schnider used semi-linear canonical correlation to calculate the 'canonical univariate parameter' from EEG data recorded from the volunteers in his study, and used this to track the time course of the pharmacodynamic effect of propofol. The median TTPE of a propofol bolus, determined by this parameter, was 1.69 min. Based on visual inspection of the EEG the TTPE ranged from 1.0 to 2.4 min (median 1.6 min). When a TTPE of 1.6 min was used to calculate the k_{eo} for each of their volunteers, the median k_{eo} was 0.456 min^{-1}. The authors concluded that a k_{eo} of 0.456 min^{-1} used with the pharmacokinetic parameters determined in the same group of volunteers provided the best description of the time course of clinical effect of propofol.

Most pediatric anaesthetists still prefer inhalation anaesthetics for both the induction and maintenance of anaesthesia because of the ease of use and the rapid reversibility[59]. Although, propofol is infrequently used in children, propofol anaesthesia may present some clinical advantages: reduced incidence of postoperative nausea and vomiting[60,61], decrease in emergence agitation compared to volatile agents[62,63]. Total Intravenous Anaesthesia (TIVA) has demonstrated advantages in ambulatory surgery for short procedures but also for sedation and spontaneous breathing procedures. In some procedures where the airway is manipulated by the surgeon or pediatrician, the use of intravenous anaesthesia is obligatory as administration of inhalational anaesthetic is not possible such as in situations where jet ventilation is performed or intermittent manual ventilation by face mask[64].
In patients who are at risk of malignant hyperthermia propofol is the only safe option[65,66]. Environmental issues could convince the anesthesiologist to use intravenous anesthesia: inhalational anesthetics are detrimental for the ozon layer[67]. Nitrous oxide is partially responsible for the greenhouse effect[68].

Unfortunately intravenous induction of anesthesia with propofol causes pain, apnea and occasionally hypotension in children. Prolonged administration of propofol has resulted in severe life threatening side-effects and death associated with rhabdomyolysis, lactic acidosis, myocardial toxicity and malignant dysrythmias (propofol infusion syndrome)[69-75]. This unpredictable and potentially lethal complication of propofol resulted in some reluctance towards the use of propofol for long term sedation in children.

	Marsh		Schnider	
	General model	70 kg individual	General model	70 kg male 170 cm height
V_1	0.228 litre kg^{-1}	15.9 litre	4.27 litre	4.27 litre
V_2	0.463 litre kg^{-1}	32.4 litre	18.9−0.391×(age−53) litre	24.0 litre
V_3	2.893 litre kg^{-1}	202.0 litre	238 litre	238 litre
K_{10} min^{-1}	0.119	0.119 min^{-1}	0.443+0.0107×(weight−77)−0.0159×(LBM−59)+0.0062×(height−177)	0.384 min^{-1}
K_{12} min^{-1}	0.112	0.112	0.302−0.0056×(age−53)	0,375 min^{-1}
K_{13} min^{-1}	0.042	0.042	0.196	0.196
K_{21} min^{-1}	0.055	0.055	[1.29−0.024×(age−53)]/[18.9−0.391×(age−53)]	0.067
K_{31} min^{-1}	0.0033	0.0033	0.0035	0.004
K_{e0} min^{-1}	0.26	0.26	0.456	0.0456
TTPE min	4.5 min	4.5	1.69	1.69

Table 3 Pharmacokinetic models for propofol in adults: Marsh and Schnider

Two pharmacokinetic models for propofol in children are available in clinical TCI systems.

In 1999 Kataria[76] et al. published a three compartmental model in a healthy pediatric population between 3 and 11 years. 658 venous plasma samples were taken. In this model compartmental volumes are a linear function of body weight, while rate constants are fixed. They incorporated in their model various covariates (age, weight, gender and body surface area) to investigate the improvement of its accuracy. Weight adjusting the volumes and clearances significantly improved the accuracy of the pharmacokinetics. Age as an additional covariate for the volume of the rapid distribution compartment only slightly improved the model and therefore was ultimately left out the final model. The weight proportional model predicts that children will need infusion rates 50-100% higher than adults to maintain any desired propofol concentration during the first 30 minutes.

Murat[77] et al found that the pharmacokinetics of propofol in children aged 1-3 years of age differ from those reported in older children and adults. They reported poor prediction of the Kataria model in small children.

The larger central compartment together with the higher clearance explain the increased requirements for propofol for both induction and maintenance of anaesthesia in young children compared to older children; the latter will also require more propofol than adults. Age-related pharmacokinetic differences may explain why adult pharmacokinetic model-driven algorithms systematically overpredict the measured blood concentrations in children aged 2-10 years. Our group was the first to prospectively validate the Kataria model.

In 1991 Marsh et al. studied the accuracy of their adult pharmacokinetic model (as used in Diprifusor®) in 20 children[55]. They found a consistent overprediction of the blood concentrations; measured blood concentrations were significantly less than those predicted by the model. The Marsh model was then revised to produce a model specific for children: the size of the central volume was increased approximately by 50%, but remained a linear function of body weight. The clearance of propofol was found 25% higher compared to adults. The initial bolus should be increased by 50% compared to adults and maintenance infusion at equilibrium should also be increased by 25%. This new model performed better when tested prospectively in 10 children. Marsh and colleagues' findings were consistent with those of other groups of workers who found that the pharmacokinetics of propofol differ between children and adults.

	Marsh adult	Marsh pediatric
V_c ml kg^{-1}	228	343
K_{10} min^{-1}	0,119	0,1
K_{12} min^{-1}	0,112	0,0855
K_{13} min^{-1}	0,0419	0,021
K_{21} min^{-1}	0,055	0,033
K_{31} min^{-1}	0,0033	0,0033

Table 4 Marsh adult versus pediatric PK model for propofol

Short et al[78] evaluated prospectively the Marsh model in 10 Chinese children aged 4-10 yr and found a lower precision and a large negative bias. In their revised model (20 Chinese children) the volume of the central compartment is larger than that of Marsh et al.

Schüttler[79] analyzed 4112 propofol plasma concentrations of 270 individuals (age 2-88 years). The data came from 9 studies covering pediatric, adult and geriatric patients. Propofol was administered as a bolus or infusion, and venous or arterial blood samples were drawn. The effect of age, weight, type of administration and sampling site were investigated. The inclusion of age and weight as covariates improved their model.

Weight was found to be a significant covariate for elimination clearance (fig 10), the two inter-compartmental clearances and the volumes of the central compartment and the volume of V_2. Nearly all parameters were found to alter with bolus administration compared to infusion data. The model described more accurately the pharmacokinetics when sampling site was accounted for in the equation for Cl_2 . Also V_1, V_2, and Cl_2 were larger after bolus then after infusion. Cl_3 was decreased.

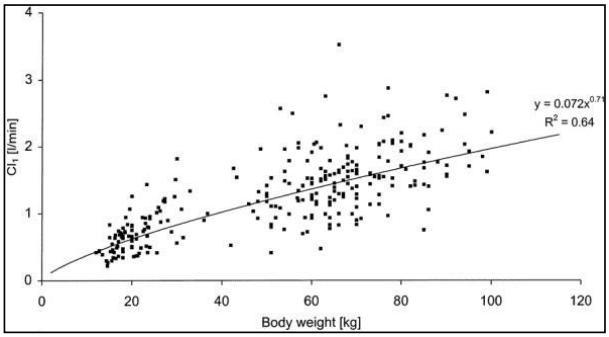

Fig 10 elimination clearance as a function of body weight Figure from Schüttler[79]

The final Schüttler model was able to describe the pharmacokinetics with sufficient precision for concentrations below 8 µg/ml. At higher concentrations the model underestimates the plasma concentration; the measured concentrations are systematically higher. This underestimation may indicate nonlinear pharmacokinetics of propofol, in the sense that the total body clearance decreases with increasing concentration. The authors suggest that this may be explained by the fact that propofol reduces liver blood flow, particularly at high concentrations such as shortly after bolus administration. This also reflects the problem of the assumption of instantaneous mixing of propofol in the initial distribution volume.

The Paedfusor is a prototype target-controlled infusion system developed by Absalom[80] et al in 1998 using a preliminary model developed by Schüttler before the publication of his final model. In the Paedfusor the central compartment volume and clearance have a nonlinear correlation with weight, and the size of the central compartment is quite larger compared to Marsh pediatric and Schüttler model. To validate the model 29 children aged 1-15 years were investigated. As the children were scheduled for cardiac surgery or cardiac catheterization, the researchers were able to obtain arterial samples (9 per patient). The predictive indices of median performance error (MDAPE) of the Paedfusor system, and median absolute performance error were found to be 4.1% and 9.7% respectively and the median value for wobble was 8.3%.

All the pediatric models listed in table 5 show distribution volumes two times greater than in adult models with a wide inter-individual variability and a moderate increase in the metabolic clearance with moderate inter-individual variability[81]

	Marsh	Kataria	Short	Schüttler	Paedfusor	Schnider
V_1 litre	6.8	7.6	8.6	7.6	9.2	4.27
V_2 litre	17.6	17.4	11.13	20	19	37.3
V_3 litre	40.68	122.34	68.8	266	117.1	238
Cl_1 l . min^{-1}	0.68	0.74	0.83	0.56	0.58	0.37
Cl_2 l . min^{-1}	0.58	1.26	1.22	1.04	1.05	2.42
Cl_3 l . min^{-1}	0.14	0.5	0.34	0.46	0.39	0.83
K_{10} min^{-1}	0.1	0.097	0.0967	0.073	0.063	0.086
K_{12} min^{-1}	0.0855	0.166	0.1413	0.135	0.114	0.565
K_{13} min^{-1}	0.021	0.066	0.0392	0.059	0.042	0.196
K_{21} min^{-1}	0.033	0.072	0.1092	0.052	0.055	0.065
K_{31} min^{-1}	0.00351	0.0041	0.0049	0.0017	0.0033	0.0035

Table 5 Comparison between the variables calculated with the different pediatric models and the Schnider model for a 6 year old child (20 kg)

The original analyses leading to the derivation of the Kataria and Paedfusor models were based on pharmacokinetic data only. However, values for k_{e0} and the blood-brain equilibration rate constant have been retrospectively generated for both models using the time to peak effect technique.

Traditionally target-controlled infusion in children was limited to plasma targeted infusion. Targeting the effect site concentration may offer advantages. In adults several studies have demonstrated that a TCI device controlling the concentration at the effect site, produces a desired time course of drug effect more efficiently than a device that only controls plasma concentration[2,4,82].

Muñoz[83] et al. determined the t_{peak} of propofol in children. As Schnider found that t_{peak} is higher with increasing age, Muñoz hypothesized a shorter tpeak in children. Additionally they calculated plasma effect site equilibration rate constant, k_{e0}, for propofol both in children and adults, using the time to peak effect method published by Minto[84] et al. The authors used auditory evoked potentials (AEP) as a measure of the hypnotic effect of

propofol. AEP's are electrical potentials recorded from the central nervous system (cerebral cortex). AEP's are generated as a response to an acoustic signal or sound through the ascending auditory pathway. This has been extensively investigated as another measure of anaesthetic effect of hypnotics.

The pharmacokinetic parameters were based on the Kataria and Paedfusor (Schüttler preliminary) model for the pediatric patients and the Schnider model for the adult patients.

They observed a t_{peak} of 80 s in adults and 132 s in children.Using the corresponding PK model they estimated a median k_{e0} of 0.56 min^{-1} in adults (Schnider) and a median k_{e0} of 0.41 min^{-1} (Kataria) or 0.91 min^{-1} (Paedfusor) in children. This results in a predicted peak effect of propofol occurring significantly later in children compared with adults: the mean t_{peak} after a submaximal dose of propofol in adults is 82 ± 2s versus 131 ± 25s (Kataria) or 128 ± 3s (Paedfusor) in children. There is a good correlation between observed and estimated t_{peak}'s.

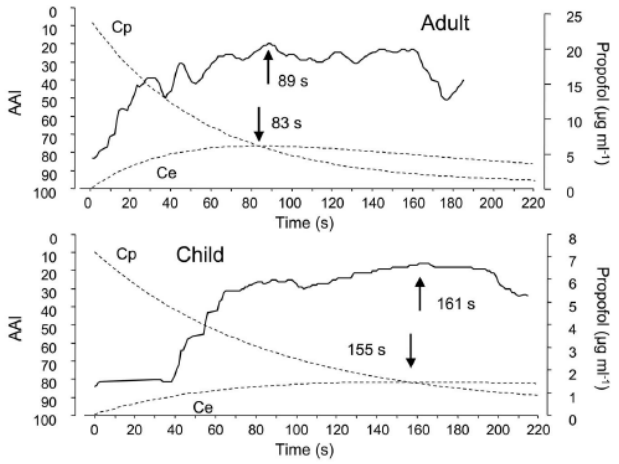

Fig 11. A-Line ARX index (AAI) values after propofol (thick line) of an adult (upper graph) and child (lower graph). AAI recordings have been turned upside-down to display graphically the "increase" in the effect. The thin, dashed lines represent the plasma (Cp) and effect site (Ce) concentration of propofol after 100-mg and 60-mg bolus doses in the adult and child, respectively. In the adult, Cp and Ce have been estimated with the parameters of Schnider and the individual plasma effect site equilibration rate constant (0.502 min^{-1}). In the child, Cp and Ce have been estimated with the parameters of Kataria and the individual plasma effect site equilibration rate constant (0.229 min^{-1}). Ce's peak 6 s earlier than time to peak effect measured from the AAI recording because we subtracted the 6-s delay in the signal of the monitor for calculation of Ce peak. Figure from Munoz [83]

Rigouzzo[85] et al. tried to identify the best model to describe pharmacokinetics and pharmacodynamics of propofol in children. Children were treated with plasma target controlled infusion based on the Kataria model, adults with the Schnider model. They also measured BIS values during induction. They simulated several

pharmacokinetic models in children: Kataria, pediatric Marsh, Schüttler and Schnider. The relationschip between BIS values and the predicted concentrations were analyzed as the basis for pharmacodynamic variables: the time to peak effect, T_{peak}, k_{e0}, C_{e50} .
They identified the Schnider model for adults as the model that best predicted concentration/effect relationships in prepubertal children. The Schnider model is unique in that both age and lean body mass are included as covariates, thus allowing a more precise tailoring of individual predicted propofol concentrations. In the same study, puberty as a covariate, further improved the model. The time to peak effect is shorter in children (0.71 min vs 1.73 min in adults).The k_{e0} is higher in children than in adults (1.17 vs 0.375). The C_{e50} is approximately 20% higher in children. This could reflect the fact that there is a lower sensitivity for propofol in children versus adults. Venous blood samples were drawn to analyse the pharmacokinetic performance. The pharmacokinetic predictive performances of Kataria and Schnider model in children were low.

Jeleazcov et al[86]. also found PD parameters to be age dependent: k_{e0} decreased with age, t_{peak} increased with age. Indeed growth and maturation are likely to induce changes on PK and PD characteristics. Also in adults it has been shown that the required propofol concentration decreases with increasing age[87]. However in the previous studies PD parameters were calculated, starting from estimated in stead of measured plasma concentrations with possible bias in resulting parameters.

We performed our own PK/PD model for propofol in children and compared its performance to the existing models[26]. We made use of blood samples and BIS to correlate propofol dose to effect and for that reason our PD parameters possibly may be more accurate. Results are shown in chapter 5.

Dataset	N		sampling	Age yr	Weight kg	ref
Coetzee Validation study	30	patients	arterial	21-58	42-38	54
Gepts	16	patients	arterial	25-65	48-84	56
Kataria	53	patients	venous	3-11	15-60	76
Schnider	24	volunteers	arterial	18-81	44-123	58
Coppens	28	patients	venous	3-11	15-54	26
Marsh	37	patients	venous	2-17	12-54	55
Billard	51	patients	venous	26-69	40-89	57
Struys	10	volunteers	arterial	22-48	51-86	102
Short	10	patients		4-10		78
Short revised	20	patients				78
Schüttler	270	pat/vol	art/venous	2-88	12-100	79
Absalom	29	patients	arterial	1-15	5-53	80

Table 6 PK models for propofol

2.8 Front-end kinetics and re-circulatory models

The drugs we use in anesthesia typically have a rapid onset of effect (e.g. hypnotics, opiates) and have a low margin of safety (depression of the cardiovascular and respiratory system !). Furthermore there is a large inter-individual variability both on a pharmacokinetic and pharmacodynamic base. The effects appear rapidly (seconds to minutes after injection) but in contrast traditional pharmacokinetic models are based on blood samples that are drawn after maximal or peak effect occurred. Understanding the pharmacokinetics of early drug distribution is essential for explaining the variability in response.

Multi-compartmental PK models are based on the simplifying assumption that intravenously administered drugs mix instantaneously and completely within the initial distribution volume (central compartment, V_c) that includes, at a minimum, the intravascular space. Conventional PK models overestimate V_c because they ignore the complexity of intravascular mixing.[88] When PK models in which V_c is overestimated are used to design target-controlled infusions, drug concentrations not only greatly exceed the target concentrations in the first minutes after starting the infusion but also long thereafter. Conventional PK models estimate V_c by dividing the dose by the hypothetical concentration at time zero, which is determined by back extrapolation of the concentration-versus-time relation. (fig 12 and 13). When the first blood sample is taken very early, i.e. high on the decreasing part of the concentration curve, the back-extrapolated value at time zero is high. When the first blood sample is taken later, i.e. lower on the decreasing part of the curve, then the back-extrapolated concentration at time zero will be lower (fig 14). A lower concentration at time zero will result in a higher estimate of V_c. In vivo the concentration at time zero is not maximal, in contrast to the back-extrapolated value. In reality the first part of the concentration vs. time curve shows a rapid increase to the maximal value[25]. Back-extrapolation from the first blood sample to concentration at time zero ignores the information available from the first-pass concentration versus time relation, i.e. the real in vivo plasma concentration versus time curve during the first minutes. This first part should be a reflection of the fact that there is a temporal lag between the time of intravenous drug administration and the time drug appears at an arterial sampling site, furthermore there may be significant drug uptake by the lung and washout[89] from it, and the mixing of drug and blood, even within what might be considered the true V_c is not instantaneous.[90]

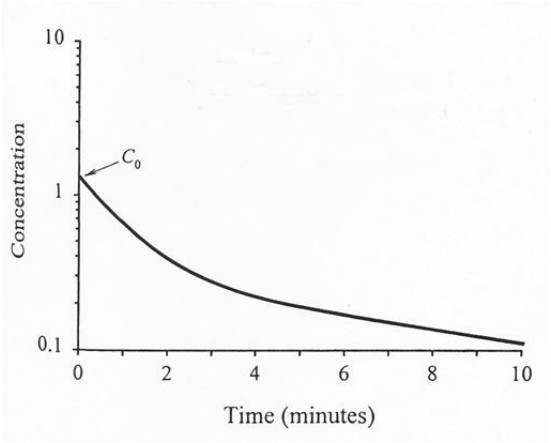

Fig 12 The central volume is based on the fundamentally flawed assumption that drug is instantaneously and completely mixed and hence that the concentration peaks at time 0. Figure from S Shafer[25]

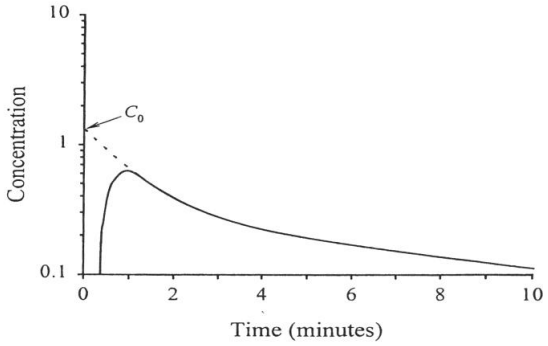

Fig 13 More realistic representation of the concentration vs time curve (solid line). The dashed line represents an estimation by back-extrapolation. Figure from S Shafer[25]

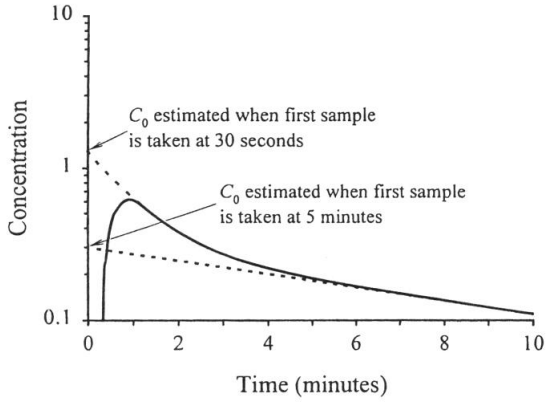

Fig 14 The influence of study design on the estimate of the concentration at time 0 and hence the estimate of V_1. Studies with rapid early sampling typically have smaller estimates of V_1 than studies in which the first samples are drawn many minutes after drug administration. Figure from S. Shafer[25]

Front-end kinetics were more accurately described by Masui et al[91]. He used a conventional two compartmental PK model extended with a LAG and TRANSIT model, describing the time required for the venously injected drug to reach the sampling site of arterial blood. He showed that propofol administration rate influences the early phase kinetics but not the dynamics, resulting in equal k_{eo}'s for the different rate of administration.

The mixing period may be better described with physiologic pharmacokinetic models that account for cardiac output, and hence drug distribution, among tissues with similar perfusion and drug solubility characteristics. Physiological PK models analyze volumes and clearances for each organ in the body, assuming that blood

flows throughout the system according to zero-order processes and that blood transfer between blood and tissues occurs according to first-order processes.

The recirculatory pharmacokinetic model also addresses concerns about traditional mammillary multicompartmental analysis. The model fits early arterial drug concentrations of samples frequently obtained soon after rapid intravenous input that resemble a drug concentration profile resulting from a zero-order infusion. In the fit of the model to the data, the concentration is 0 at time 0, and there is a delay between the time drug is administered and its appearance at the sampling site. Pulmonary drug uptake is an integral part of the model. Intravascular mixing is characterized, as is the role of cardiac output in drug distribution. Finally, the model accounts for arterial-mixed venous concentration differences.

The lungs are pharmacologically active organs and affect the blood concentrations of drugs given intravenously.[92] The lungs can take up, retain, metabolize and delay the release of many drugs. It has been shown that the first-pass pulmonary retention of a single dose of propofol is 28%.[93] There probably is no extra hepatic propofol metabolism in the human lung.

Upton and Lundbrook developed a physiologically based re-circulatory (fig 15) model of propofol kinetics in a sheep model[94], later extended to humans[95]. In the model particular attention was paid to representing those physiologic features that influence propofol bolus kinetics (vascular mixing during cardiac output) and propofol dynamics (cerebral kinetics, cerebral blood flow, cerebral concentration effect relationships). The incorporation of blood flow terms into the model was considered important because surgery and anesthetic management affects the state of the circulation, which may affect the disposition of propofol (Fig 16).

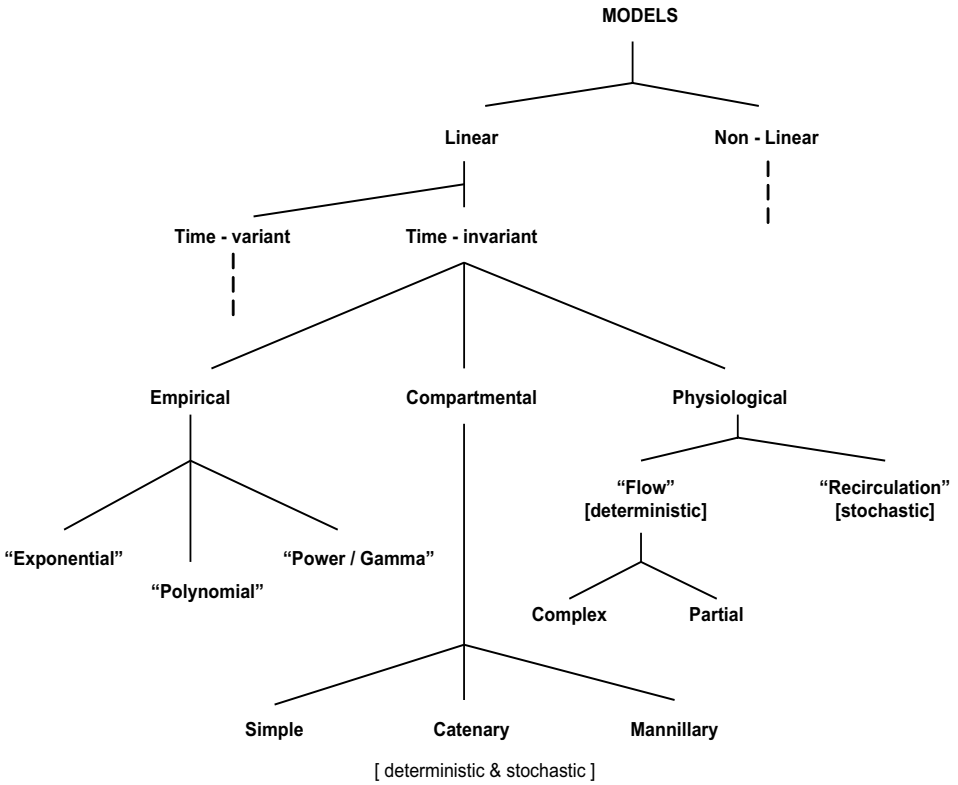

Fig 15 A taxonomy of pharmacokinetic models Compartmental mammillary models are just one approach; an over-simplification of a complex biological process. Other models account for more physiological phenomena but at the expense of more complicated mathematical descriptions and the requirement of large amount of data. Figure from Stoeckel[24]

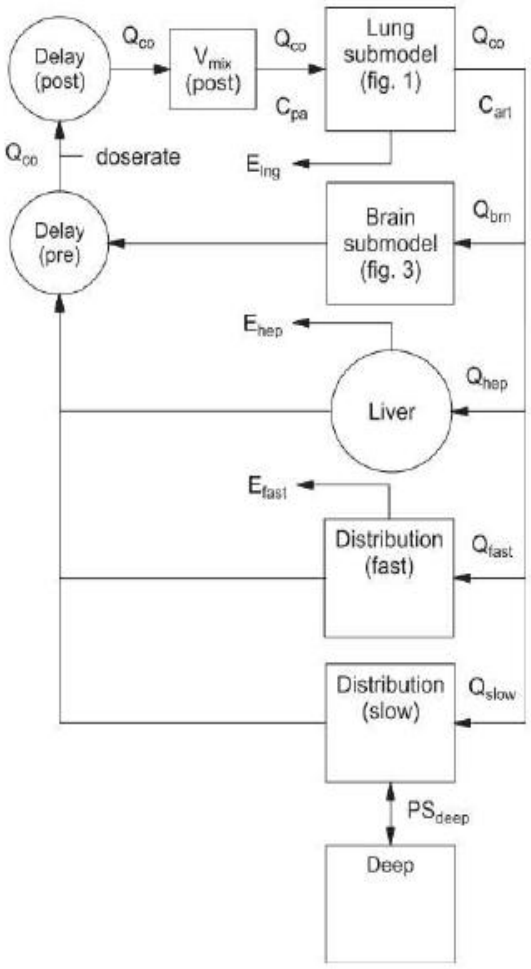

Fig 16 A schematic representation of the physiologically based recirculatory model (Upton model). The compartments of the model each have defined apparent distribution volumes (V) and associated blood flows (Q). The lungs were represented as a 3-compartment "tank in series" submodel, and the brain and "slow" tissues as membrane limited submodels. PS represents permeability terms for linking 2 compartments of these membrane-limited submodels. Delay(pre) and Delay(post) are delay terms accounting for intravascular transport. V_{mix} is a vascular mixing compartment. The symbols used are: C_{pa} = pulmonary artery drug concentration; C_{art} = arterial propofol concentration; C_{ven} = mixed venous propofol concentration; Q_{co} = cardiac output; Q_{brn} = brain blood flow; Q_{hep} = liver and gut blood flow; Q_{fast} = fast tissues blood flow; Q_{slow} = slow tissues blood flow; PS_{deep} = permeability term for slow tissues; E_{lng}=propofol extraction across the lungs; E_{hep}= propofol extraction across the liver and gut; E_{fast}=propofol extraction across the fast tissues (includes kidney). Figure from Upton[95]

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CHAPTER 3

Influence of Administration Rate on Propofol Plasma-Effect Site Equilibration

Anesthesiology 2007; 107:386-96

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Introduction

Classic multicompartmental mammillary models assume that drug added to the central compartment is instantaneously and completely mixed both at the venous and arterial site of the circulation. The biological phenomenon is more complex and classic models have difficulties to describe the time course of arterial drug concentrations in the very first minutes after intravenous drug administration.

When using estimated drug concentrations for a combined PK-PD model to describe the complete dose relationship, misspecification of the PK model over the first minutes could lead to misspecification of the pharmacodynamics and a less accurate interpretation of the plasma effect-site equilibration. PK-PD modeling without blood-sampling can be a source of error.

Influence of Administration Rate on Propofol Plasma–Effect Site Equilibration
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This article is accompanied by an Editorial View. Please see: Fisher DM: Take it to the limit (one more time). Anesthesiology 2007; 107:367–8.

ABSTRACT

Background: The authors hypothesized a difference in plasma–effect site equilibration, depicted by a first-order constant k_{e0}, depending on the injection rate of propofol.

Methods: Sixty-one patients received 2.5 mg/kg propofol given as a bolus or as a 1-, 2-, or 3-min infusion. The Bispectral Index was used to monitor drug effect. Propofol predicted plasma concentration was calculated using a three-compartment model and the effect site concentration over time as the convolution between the predicted plasma concentration and the disposition function of the effect site concentration. The authors evaluated the influence of the infusion rate on the k_{e0} by comparing the model with one k_{e0} for all groups with models estimating different k_{e0} values for each group. The authors also assessed the accuracy of two pharmacokinetic models after bolus injection.

Results: The best model based was a fixed (Bispectral Index ≥ 90) plus sigmoidal model (Bispectral Index < 90) with two values of k_{e0}, one for the bolus ($t_{½}$ k_{e0} = 1.2 min) and one for the infusions ($t_{½}$ k_{e0} = 2.2 min). However, the tested pharmacokinetic models poorly predicted the arterial concentrations in the first minutes after bolus injection. Simulations showed the requirement for two k_{e0} values for bolus and infusion was mostly a compensation for the inaccurate prediction of arterial concentrations after a bolus.

Conclusion: Propofol plasma–effect site equilibration occurs more rapidly after a bolus than after rapid infusion, based on the electroencephalogram as a drug effect measure, mostly because of misspecification of the pharmacokinetic model in the first minutes after bolus.

PROPOFOL transfer between the plasma and effect site can be modeled as a first-order process characterized by k_{e0}.[1,2] The standard model of k_{e0} assumes that the rate of equilibration between the plasma and the site of drug effect is independent of the rate of drug administration. However, there are conflicting data on the rate of equilibration between the plasma and the site of propofol drug effect. In a study involving both bolus injections and intravenous infusions, Schnider et al.[3] found that the rate of equilibration was rapid, with a half-time of equilibration, $t_{½}$ k_{e0}, of 1.5 min, and a peak effect, t_{peak}, of 1.7 min. Schnider's finding of rapid equilibration was subsequently validated by Struys et al.[4] However, using continuous infusions of propofol, Doufas et al.[5] found a much slower rate of plasma–effect site equilibration, with a $t_{½}$ k_{e0} of 4.1 min, and a t_{peak} of 2.7 min. They also found that infusion rate had no influence on k_{e0}.[5]

The maximum propofol infusion rate in the study of Doufas et al.[5] was 60 mg/min, far lower than the maximum rate of approximately 500 mg/min required for Schnider et al. to give a 2.5-mg bolus over 20 s. Doufas et al.[5] proposed that there could be a fundamental difference in plasma–effect site equilibration depending on whether propofol was given as a bolus or continuous infusion. We investigated this hypothesis.

Materials and Methods

Clinical Protocol

After institutional ethics committee approval, written informed consent was obtained from 61 female patients with American Society of Anesthesiologists physical status I, aged 18–45 yr, scheduled to undergo ambulatory gynecologic surgery. Exclusion criteria included weight less than 70% or more than 130% of ideal body weight, neurologic disorder, and recent use of psychoactive medication, including alcohol.

All patients were randomly assigned to one of four groups to receive 2.5 mg/kg propofol (Diprivan 1%; AstraZeneca, London, United Kingdom) given as a bolus (within 10 s) (group 1) or given as a continuous infusion over 1, 2, or 3 min (groups 2, 3, and 4, respectively). Bolus administration was performed manually. The continuous infusions were administered using a Fresenius Modular DPS Infusion Pump connected to a Fresenius Base A (Fresenius Vial Infusion Systems, Brézins, France). To ensure synchronized data recording, all monitor and infusion data were continuously captured by a computer running RUGLOOP II (Demed, Temse, Belgium) via multiple RS 232 interfaces. By tracking the infused propofol volume continuously in groups 2, 3, and 4, RUGLOOP II calculated the corresponding plasma concentration using the three-compartment model previously published by Schnider et al.[6] This model was selected because of its optimal performance in previous studies.[5] For group 1, the plasma concentration was calculated post hoc using RUGLOOP II simulation mode and the Schnider propofol pharmacokinetic model.[6]

Propofol was infused via a large left forearm vein. Every patient received approximately 100 ml crystalloid fluid during the study period. No fluid load was given before induction. No patient received preanesthetic medication. No other drugs were given. All patients maintained spontaneous ventilation via a facemask delivering 100% O_2. Before starting the drug administration, all patients were asked to close their eyes and relax for 2 min. Thereafter, baseline measures were taken. The operating room was kept silent to avoid noise-related stimulation and artifact.

Propofol drug effect was continuously monitored using the Bispectral Index (BIS; version 4.0; Aspect Medical Systems, Inc., Newton, MA). The BIS was derived from the frontal electroencephalogram and calculated by the A-2000 BIS® monitor using the four BIS®-Sensor electrodes. Electrode impedance was less than 5 kω. The smoothening time of the BIS® monitor was set at 15 s. The BIS data were captured in real time on a laptop computer using RUGLOOP II. Heart rate, noninvasive blood pressure, oxygen saturation measured by pulse oximetry, and capnography were recorded at 1-min time intervals using an S-5 monitor (Datex-Ohmeda, Helsinki, Finland) and were also captured electronically using RUGLOOP II. Averaging of the data was performed using 10-s intervals. All patients were monitored until return of consciousness after propofol administration, defined as spontaneous eye opening (without a stimulus).

Pharmacodynamic Modeling and Estimation of k_{e0}.

In our initial approach, the effect site was assumed to be linked to the plasma by a compartment of trivial volume with a first-order equilibrium constant of k_{e0}. The relation between propofol effect site concentration (Ce) and the electroencephalographic measures of anesthetic drug effect was described using a classic sigmoid E_{max} model:

$$\text{Effect} = E_0 + (E_{max} - E_0)\frac{Ce^{\gamma}}{Ce^{\gamma} + Ce_{50}^{\gamma}}$$

where Effect is the electroencephalographic effect (e.g., the measured BIS), E_0 is the baseline measurement when no drug is present, E_{max} is the maximum possible drug effect, Ce is the calculated effect site concentration of propofol, Ce_{50} is the Ce associated with 50% maximal drug effect, and γ is the steepness of the concentration-versus-response relation. The model parameters were estimated using NONMEM V (GloboMax LLC, Hanover, MD). For Ce_{50} and k_{e0}, interindividual variability was permitted using a log-normal distribution:

$$P_i = P_{TV}\, e^{-\eta i}$$

where P_i is the parameter value in the i^{th} patient, P_{TV} is the typical value of the parameter in the population, and η is a random variable with a mean of 0 and a variance of ω^2. Individual variability is reported as ω, the SD of η in the log domain, which is approximately the coefficient of variation in the standard domain. Residual intraindividual variability was modeled using a standard additive error model.

After visual inspection of the BIS data above 90, and initial attempts to find a value of k_{e0} that fit all of the observations to a single pharmacodynamic model, we concluded that no model could be fit to the data. The raw BIS data showed an abrupt (< 15 s) transition from a BIS greater than 90 to a very low BIS, suggesting a nearly instantaneous state change. Therefore, we investigated the relation between propofol Ce and BIS using separate models for periods before and after the state change. The combined

model described all BIS data above 90 by a single value model ("one size fits all") and all data of 90 or less using the classic sigmoid E_{max} model.

For both model approaches (classic sigmoidal model or the combined fixed plus sigmoidal model), we assumed that the underlying sigmoidal model which describes the relation between the effect site concentration and the drug effect is not influenced by the method of drug administration. Indeed, this is a fundamental assumption underlying the standard model of the effect site. Therefore, we concurrently estimated the model parameters for all four groups, only permitting the value of k_{e0} to differ between groups. We evaluated the influence of the administration rate on the k_{e0} by comparing the log likelihood between a model with one k_{e0} for all administration rates with models estimating different k_{e0} values for each group. The addition of infusion rate specific values of k_{e0} was considered statistically significant when the log likelihood decreased by at least 6.63 ($P < 0.01$, chi-square test with 1 degree of freedom).[7]

NONMEM had difficulty simultaneously estimating the parameters of the structural model (e.g., the θ parameters) and the variance model (the ω parameters). Specifically, estimating both the structural and variance models simultaneously produced highly biased estimates of the parameters, as demonstrated by the observation that the post hoc estimates of the η parameter were uniformly either positive or negative. Therefore, we chose the best model using the naive pooled data method as described by Kataria et al.[8] After identifying the best structural model, we fixed the parameters of the structural model at the naive pooled data estimates and estimated the parameters of the intersubject and intrasubject variability models. This approach comes very close to the generalized least-squares method. The generalized least-squares approach involves three steps. In the first step, the intersubject variability (i.e., ω) is fixed at zero, and the typical values of the structural model (i.e., θ) are estimated. In the second step, the typical values of the structural model (i.e., θ) are fixed at the estimates from the first step, and the intersubject variability (i.e., ω]) is estimated. In the third step, the intersubject variability (i.e., ω) is fixed at the value from step 2, and the typical values of the structural model (i.e., η) are estimated for the last time. Our approach was to implement the first two steps of the generalized least-squares method.

The effect site concentrations over time were calculated as the convolution of the predicted plasma concentrations over time with the disposition function of the effect site, $k_{e0}\, e^{-ke0t}$. The convolution was based on a "connect-the-dots" approach previously used by Schnider et al.[3] In brief, increasing plasma concen-

trations were modeled using a linear interpretation between adjacent plasma concentrations. As such, when concentrations are increasing, the slope in the concentration from time t_1 to time t_2 can be modeled as

$$\text{slope} = \frac{Cp(t_2) - Cp(t_1)}{t_2 - t_1}$$

where Cp is the plasma concentration, and thus the plasma concentrations from time t_1 to time t_2 are described by the formula

$$C(t) = C(t_1) + slope \times (t - t_1)$$

The convolution of this with $k_{e0}\, e^{-ke0t}$ calculates the effect site concentration at time t_2 as a function of the effect site concentration at time t_1 and the plasma concentrations over the interval

$$Ce(t_2) = Ce(t_1)e^{-k_{e0}(t_2-t_1)} + (t_2 - t_1)slope + \frac{(k_{e0}C(t_1) - slope)(1 - e^{-k_{e0}(t_2-t_1)})}{k_{e0}}$$

Similarly, when concentrations are decreasing, the slope of the log of the concentrations from time t_1 to time t_2 can be modeled as

$$slope = \frac{Log\left(Cp(t_2)\right) - Log\,(Cp(t_1))}{t_2 - t_1}$$

and thus the plasma concentrations from time t_1 to time t_2 are described by the formula

$$C(t) = C(t_1)e^{slope\times(t-t_1)}$$

The convolution of this with $k_{e0}\, e^{-ke0t}$ calculates the effect site concentration at time t_2 as a function of the

effect site concentration at time t_1 and the plasma concentrations over the interval

$$Ce(t_2) = Ce(t_1)e^{-k_{e0}(t_2-t_1)} + \frac{C(t_1)k_{e0}(e^{slope\times(t_2-t_1)} - e^{-k_{e0}(t_2-t_1)})}{k_{e0} + slope}$$

The observed BIS value has a time delay for the measurement, which we fixed at 10 s and defined as lag time. This lag time is approximately the sum of half of the smoothing interval within the BIS® monitor and the time for the automated data collection.

We assessed the model performance by calculating the prediction error (PE) between measured (BIS_{meas}) and post hoc Bayesian predicted BIS (BIS_{pred}) values, as

$$PE = (BIS_{meas} - BIS_{pred}) \div BIS_{pred}$$

We also calculated median prediction error (MDPE) and absolute median prediction error, (MDAPE), for each patient.[9] Differences among groups for MDPE and MDAPE were tested using a Student t test with Bonferroni correction for multiple testing.

To observe whether the model reflects reality, we compared the observed time of maximum BIS response ($t_{max,BIS}$) with the time to reach maximum Ce ($t_{max,Ce}$) after the specific administration of propofol in each group.

Bolus Validation Study

The three-compartment pharmacokinetic model published by Schnider et al.[6] was used to predict the time course of the propofol plasma concentration in our study. For slowly administered continuous infusion of propofol, Doufas et al.[5] found that the pharmacokinetic model published by Schnider et al.[6] accurately predicted the propofol plasma concentrations in arterial blood. However, the accuracy of this model in the first 3 min after bolus injection is not described in the literature.

We therefore performed a study to validate the pharmacokinetics after bolus injection. In this study, we collected propofol arterial blood samples from 10 additional patients to evaluate the accuracy of the pharmacokinetic models published by Schnider et al.[6] and by Marsh et al.[10] in the first 5 min after intravenous propofol bolus. After additional ethics committee approval and written informed consent, 10 patients received a bolus dose of propofol (2.5 mg/kg) within 10 s in a large forearm vein. Propofol arterial blood samples were collected (contralateral from the injection of propofol) at 0, 30, 60, 120, 180, 240, and 300 s after injection. Propofol (bound and free) plasma concentrations were analyzed using a validated gas chromatographic–mass spectrometric method with solid-phase micro extraction. The time course of the propofol plasma concentration as predicted by both pharmacokinetic models (Schnider and Marsh) was simulated using RUGLOOP II. We calculated the PE of the predicted concentration and the MDAPE for both models for the first 5 min after injection.

The arterial concentrations in the first 5 min after bolus injection were compared with the predictions based on the pharmacokinetics reported by Schnider et al.[6] and by Marsh et al.[10] As described in the Results, neither pharmacokinetic parameter set accurately predicted the concentrations in the first 5 min after bolus injection. To see whether this misspecification might affect the estimation of k_{e0}, we calculated the effect site concentrations over time after bolus injection as a convolution of the median concentrations in these 10 individuals with $k_{e0}\ e^{-ke0t}$, the disposition function of the effect site. We then calculated the value of k_{e0} that predicted the observed time of peak BIS response.

Validation of the Applied Lag Time in the BIS Measurement

We fixed the lag time of the BIS at 10 s. Based on literature reports,[11] a longer lag time might be more appropriate. Therefore, we applied a post hoc analysis on our final selected model in an attempt to explore whether longer lag times would result in a better model for both the sigmoidal model and the fixed BIS plus sigmoidal model. Lag times between 10 and 25 s were evaluated, and the NONMEM objective functions were compared.

Validation of the Modeling Methods Using Another Data Set

We validated our final model results against the data previously published by Doufas et al.[5] In brief,

Doufas et al. analyzed the pharmacokinetics and pharmacodynamics of propofol in 18 healthy volunteers receiving five consecutive target-controlled propofol infusions. During each infusion, predicted Ce increased linearly at a rate of 0.1, 0.3, 0.5, 0.7, or 0.9 $\mu g \cdot ml^{-1} \cdot min^{-1}$ based on the Schnider pharmacokinetic–pharmacodynamic model. BIS was collected continuously during the infusions. Doufas et al.[5] fit a combined pharmacokinetic–dynamic model to their data. To describe the pharmacodynamics of propofol, a classic sigmoid E_{max} model was used. No lag time in the BIS was included in the model. The study results can be seen in the original publication.[5]

We validated four models: (1) a sigmoid E_{max} model without a lag time (same as the model used in the Doufas article; (2) a sigmoidal E_{max} model with a 10-s lag time (equivalent to our sigmoidal E_{max} model); (3) a model consisting of a fixed estimate of BIS values of 90 or greater and a sigmoidal E_{max} model for BIS values less than 90, with no lag time; and (4) a model consisting of a fixed estimate of BIS values of 90 or greater and a sigmoidal E_{max} model for BIS values less than 90, with a 10-s lag time (equivalent to our best model). We encountered identical problems with concurrent identification of the structural and variance models that we described when fitting our own data, and so we used the naive pooled data approach to identify the best model among the four structural models considered. After identification of the best structural model, we fixed the structural parameters and estimated the interindividual variability.

We assessed the performance of the optimal model by calculating the PE between BIS_{meas} and BIS_{pred} values, as well as the MDPE and MDAPE for each patient.[9]

Table 1. Demographic Data (Mean ± SD)

	Group 1 (n = 14)	Group 2 (n = 16)	Group 3 (n = 16)	Group 4 (n = 15)
Age, yr	34 ± 5	34 ± 4	33 ± 6	34 ± 6
Weight, kg	65 ± 11	65 ± 10	62 ± 8	66 ± 11
Height, cm	169 ± 7	169 ± 7	169 ± 4	167 ± 11

Table 2. Administration Characteristics for Propofol (Mean ± SD)

	Group 1 (n = 14)	Group 2 (n = 16)	Group 3 (n = 16)	Group 4 (n = 15)
Propofol dose, mg	162 ± 29	162 ± 24	154 ± 19	163 ± 28
Administration time, s	6.3 ± 3.3	60 ± 0	120 ± 0	180 ± 0
Administration rate, ml/h	10,979 ± 4,310	976 ± 147	462 ± 58	327 ± 57

Results

Model Estimation and Validation

All recorded data were used. No patients experienced hemodynamic or respiratory instability during the study. The demographics for patient in the four groups are shown in table 1. The amount of propofol given and the infusion rates are shown in table 2.

Figures 1A–D show the relation between the measured BIS and calculated plasma concentrations, Cp, versus time for the four groups, respectively. The dashed line shows the cutoff value of 90 used in the combined fixed plus sigmoidal model approach. Figures 1E–H show the relation between BIS and plasma concentration, revealing the hysteresis in the plasma concentration–versus–response relation.

Table 3. The NONMEM Objective Function (−2 Log Likelihood) for the Different Pharmacodynamic Models Investigated

Structural Model	Sigmoidal	Fixed ≥ 90, Sigmoidal < 90
One k_{e0} estimation for all groups	18,990	19,013
Separate k_{e0} estimations for bolus injection and the three infusion groups	18,944	18,773
Separate k_{e0} estimations for bolus, 1 min infusion, and 2 + 3 min infusion	18,942	18,768
Separate k_{e0} estimations for all four groups	18,942	18,767

Table 3 shows the NONMEM objective function (-2 log likelihood) for all investigated models. The NONMEM objective function improved by 46 points ($P << 0.001$) when the bolus group (group 1) was

given a k_{e0} distinct from the k_{e0} used for the three infusion groups (groups 2, 3, and 4). There was no significant benefit to adding distinct values of k_{e0} for the three infusion groups. Therefore, we selected the model with two values of k_{e0}, one for the bolus ($t_{½}$ k_{e0} = 1.2 min) and one for the infusions ($t_{½}$ k_{e0} = 2.2 min).

Our final model included estimates of interindividual variability on k_{e0} and Ce_{50}. In our final model, BIS values of 90 or greater were typically 95.6. BIS values less than 90 were described by a sigmoidal curve with ranging from a maximum value of 74 to a minimum of 25. The Ce_{50} for the sigmoidal portion was 5.1 μg/ml, with a γ of 3.4. The SDs in the log domain of Ce_{50} and k_{e0} were 0.27 and 0.83, respectively, which approximately correspond to the coefficient of variation in the standard domain. Additive residual intraindividual error was 7.2.

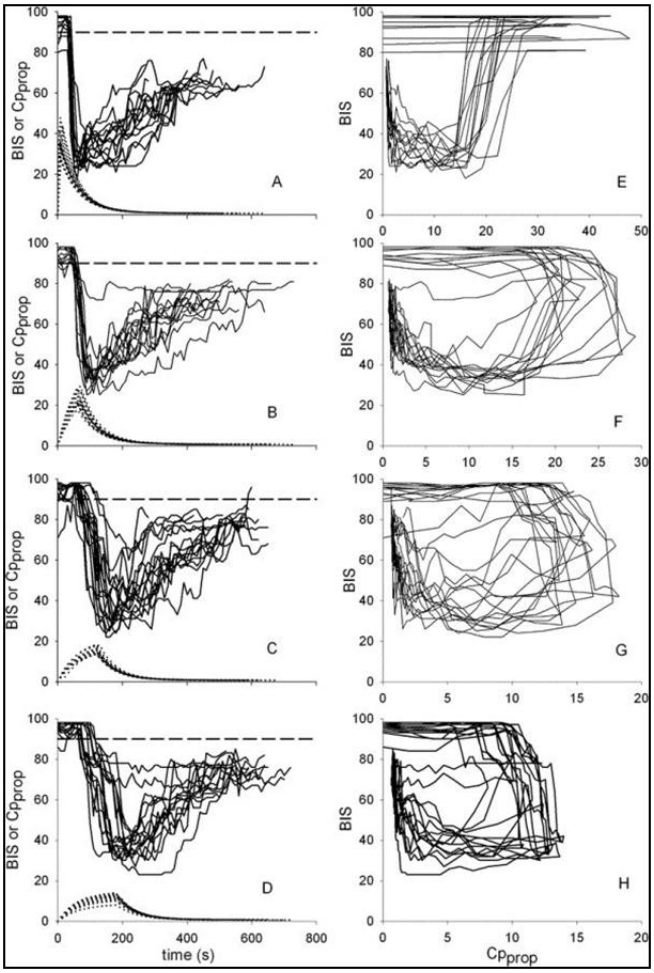

Fig. 1 Relation between the measured Bispectral Index (BIS) and propofol plasma concentration (Cpprop) versus time (s) for the four groups, in A-D. The dashed line shows the cutoff value for modeling when the two consecutive model approach was used (fixed ≥ 90, sigmoidal < 90), fixed at a BIS of 90. E-H show the relation between BIS and Cp, thereby revealing the hysteresis in the relation.

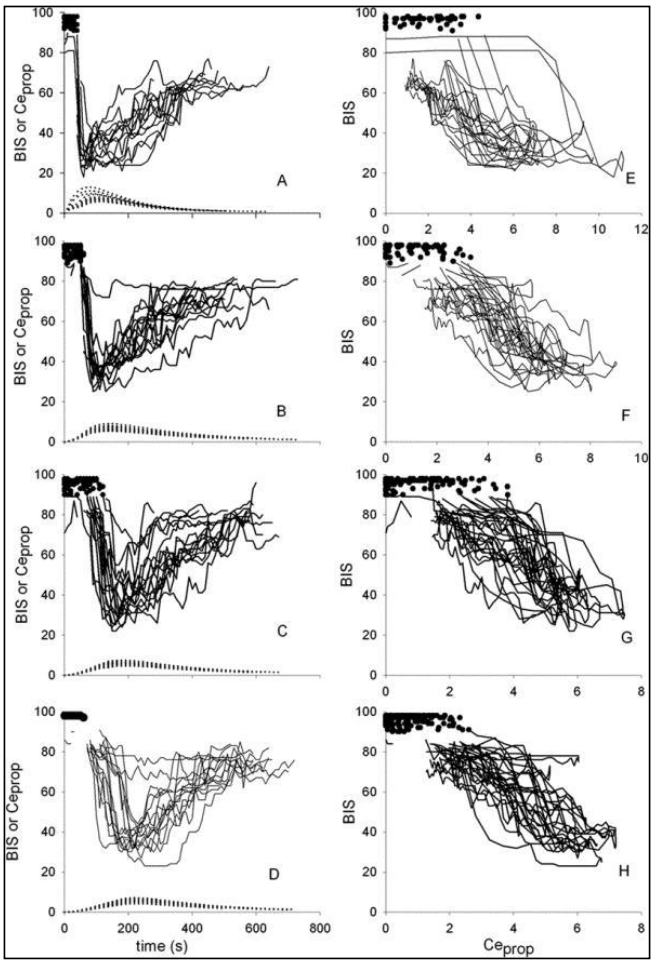

Fig. 2 Results from the best-fitting model (including estimates of interindividual variability on ke0 and effect site concentration associated with 50% maximal drug effect (Ce50). Individual measured Bispectral Index (BIS) values and the calculated Ce versus time for the four groups, in A-D. E-H show the BIS versus Ce, based on the ke0 estimate by NONMEM. To visualize the source data and results for the fixed number model, we showed the measured BIS data ≥ 90 as black circles. The second part (the sigmoid Emax model using BIS < 90) data are shown as straight lines.

Figures 2A–D show the raw BIS values and the calculated effect site concentration, Ce, versus time, showing the parallel between the time course of BIS and Ce. Figures 2E–H show the BIS versus Ce. BIS values of 90 or greater are depicted as black circles. BIS values less than 90 are shown as connected lines. Two individuals receiving the bolus injection had baseline BIS values below 90 (fig. 2E),

which escaped our efforts to censor the initial unresponsive portion of the BIS response. We did not decrease our censoring value (90) to censor these data because we did not wish to lose informative BIS values in other subjects.

Table 4 shows the median (range) results for the post hoc Bayesian estimates of Ce_{50} and $t_{½}$ k_{e0} for each individual in the four groups. Table 4 also shows the time of maximum BIS change ($t_{max,BIS}$), the time of maximum Ce ($t_{max,Ce}$) after the specific propofol infusion, and the absolute value of the difference between these times (t_{error}). The difference in the time of maximum BIS change and the time of the highest Ce can be used to assess the performance of the model. The median t_{error} was 0.6 min or less for all groups. For all patients, the individual results for the post hoc Bayesian estimates of Ce_{50} and $t_{½}$ k_{e0} in the four groups, $t_{max,BIS}$ and $t_{max,Ce}$ after the specific propofol infusion, and the absolute value of the difference between these times ($t_{abs,error}$) can be found in a supplement on the Anesthesiology Web site (http://www.anesthesiology.org).

Table 4. Median (Range) for the Individual Ce_{50}, $t_{½}$ k_{e0}, $t_{max,BIS}$, and $t_{max,Ce}$ in Each Group

	Ce_{50}	$t_{½}$ k_{e0}	$t_{max,BIS}$	$t_{max,Ce}$	$t_{abs,error}$	MDPE	MDAPE
Group 1	3.7 (5.1)	1.6 (3)	1.9 (1.2)	1.7 (0.5)	0.2 (0.9)	−0.15 (0.31)	0.18 (21)
Group 2	5.7 (9.1)	2.9 (4.5)	1.7 (0.9)	2.3 (0.3)	0.6 (1)	0.08 (0.36)	0.11 (0.18)
Group 3	5.1 (6.3)	2.2 (2.3)	2.7 (1.6)	3 (0.2)	0.4 (0.9)	0.02 (0.49)	0.1 (0.25)
Group 4	5.4 (10)	2.5 (1.9)	3.7 (1.4)	3.7 (0.1)	02 (0.7)	0.05 (0.36)	0.09 (0.17)

BIS = Bispectral Index; Ce = effect site concentration; Ce_{50} = effect site concentration associated with 50% maximal drug effect; MDAPE = median absolute prediction error; MDPE = median prediction error.

The performance accuracy for the final model was assessed by calculating the PE. Figures 3A–D show the individual PE versus time for the four groups, respectively. Median (range) MDPE and MDAPE for each group was calculated as shown in table 4. The MDAPE was 18% or less for all groups. No group showed significant bias (MDPE). All individual MDPE and MDAPE calculations can be found on the Anesthesiology Web site (http://www.anesthesiology.org).

Bolus Validation Study

Ten female patients were included, and all blood samples were analyzed. Demographics were similar

in study groups 1 through 4 (age, 34 ± 8 yr; weight, 63 ± 10 kg; height, 163 ± 7 cm). For both models, measured versus predicted propofol plasma concentrations and individual PE% versus time are plotted in figure 4. The mean (SD) PEs were -40.50 (53.08) and -25.90 (36.80)% for the Marsh and Schnider models, respectively. The mean MDAPEs were 60.22 (28.24) and 39.45 (21.38)% for the Marsh and Schnider models, respectively.

Figure 5 shows the median arterial concentrations from the bolus. The effect site concentrations were computed based on a $t_{½}$ k_{e0} of 2.0 min and predict a peak effect site concentration of 1.9 min, consistent with the time of peak BIS effect in our bolus study (table 4, group 1). All data can be found on the Anesthesiology Web site (http://www.anesthesiology.org).

Validation of the Applied Lag Time in the BIS Measurement

Table 5 shows the -2 log likelihood values (the NONMEM objective function) when applying different lag times. The best result is obtained when implementing a 10-s lag time in the combined fixed plus sigmoidal model approach.

Table 5. The NONMEM Objective Function (−2 Log Likelihood) When Implementing Different Lag Times in the Final Sigmoidal and Fixed plus Sigmoidal Model

Lag Time, s	Sigmoidal Model	Fixed + Sigmoidal Model
10	18,994	18,774
15	18,947	18,824
20	18,963	18,876
25	19,006	18,920

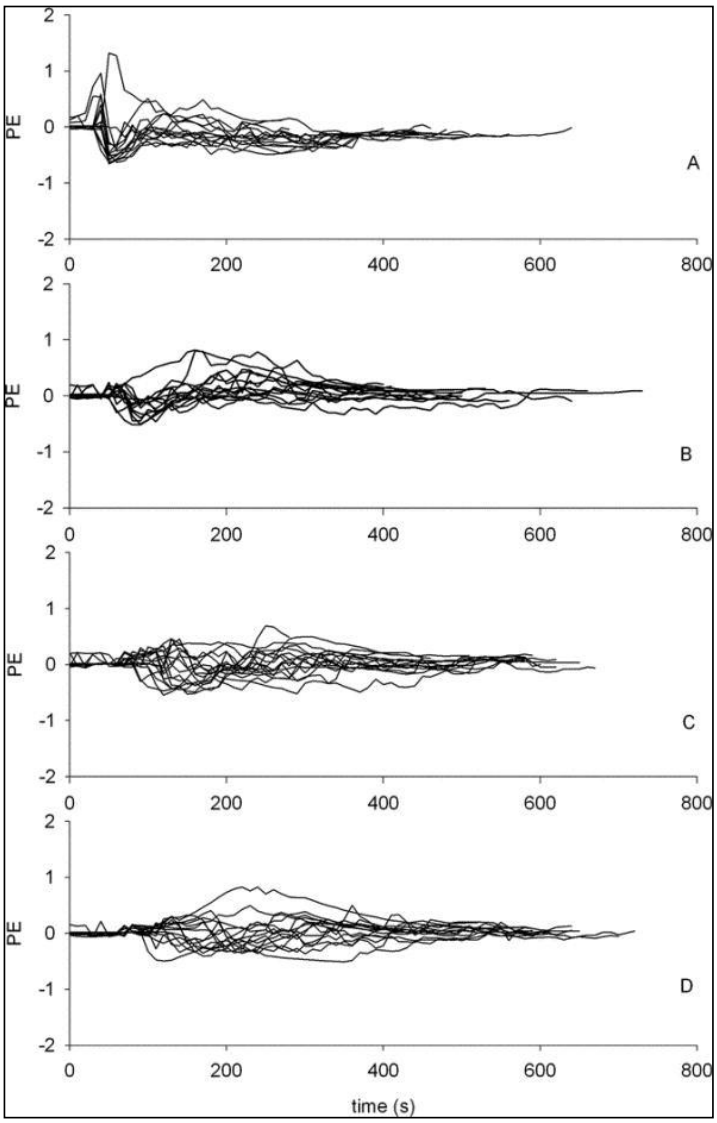

Fig. 3 Individual prediction errors (PEs) versus time for the four groups, in A-D.

Method Validation

All data from the 18 volunteers in the original publication by Doufas et al. were included in the model validation. Figure 6A shows the relation between BIS and Cp for the Doufas validation data set. Table

6 shows the -2 log likelihood values (the NONMEM objective function) and the typical values for all investigated models. Doufas' data were best described by a single estimate for those BIS observations of 90 or greater, and a sigmoidal E_{max} model for BIS values less than 90, with a 10-s delay, exactly as was the case for our data. Most critically, this model estimated a $t_{½}$ k_{e0} of 2.1 min, very close to our estimate of 2.2 min for infusions. The SDs in the log domain of Ce_{50} and k_{e0} were 0.31 and 1.29, respectively. Additive residual intraindividual error was 9 (i.e., residual variance = 81).

Figure 6B shows the relation between BIS and Ce for each individual, based on the best model and the post hoc Bayesian estimates of Ce_{50} and k_{e0}. The individual PEs are shown in figure 6C.

The median (range) post hoc Bayesian parameter estimates for all subjects in the validation data set are shown in table 7, as well as the individual MDPE and MDAPE. The model performed well, with an MDAPE less than 9% and minimal bias (5%). The Ce_{50} in the validation set is less than in our data set (3.6 vs. 5.1 µg/ml) but is similar to that seen in our bolus group (3.7 µg/ml; table 4).

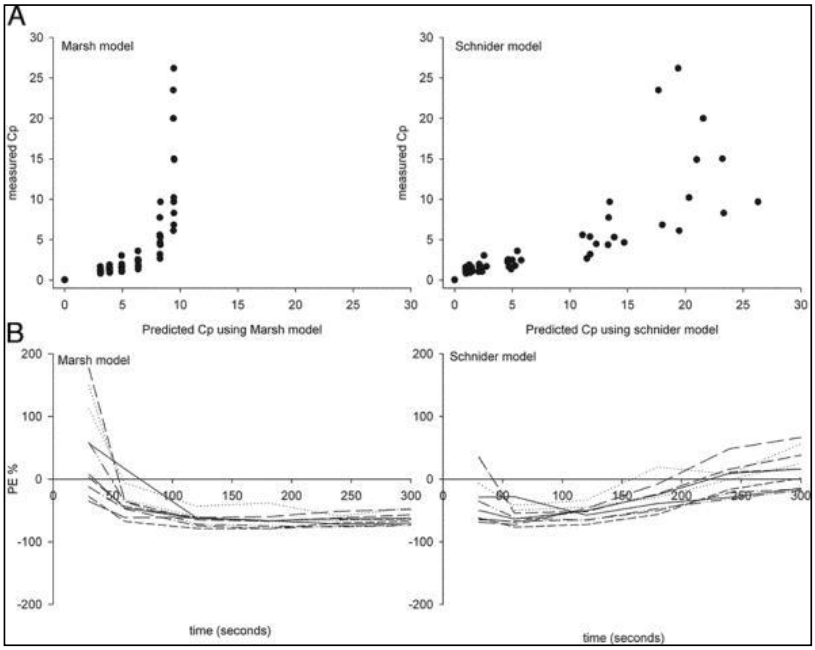

Fig. 4 The bolus injection validation set. The relation between the individual measured propofol plasma concentration (Cp) and the plasma concentration predicted by the Marsh and Schnider pharmacokinetic models (A). The time course of the prediction error (PE%) for both applied models (B).

The estimate of γ in the validation set is less than in our data set (1.3 vs. 3.4). For all patients, individual data can be found on the Anesthesiology Web site (http://www.anesthesiology.org).

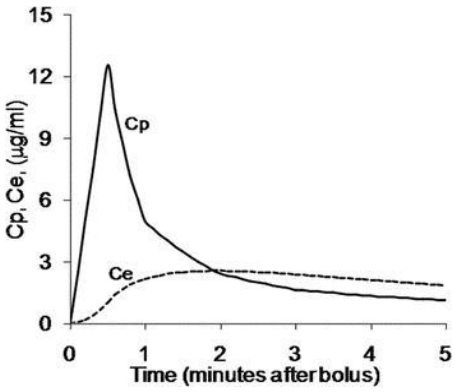

Fig. 5 The median plasma concentrations (Cp) from the 10 patients in the bolus validation study, and the effect site concentrations (Ce) predicted by a t1/2 ke0 of 2.0. The time of peak effect, 1.9 min, matches the median time of peak Bispectral Index in the bolus study (table 4).

Discussion

Our goal was to determine whether the equilibration rate between plasma and effect site was influenced by rate of propofol administration. If so, this must be considered when designing drug infusions, and is particularly relevant for target-controlled infusion systems. We tested this by examining the time course of electroencephalographic (BIS) response to a bolus and three infusion rates. The apparent plasma–effect site equilibration for bolus injections is faster than for infusions. This is consistent with the hypothesis of Doufas et al.[5] who speculated that this might be the explanation for the difference between plasma–effect site equilibration in their study versus the study by Schnider et al.[3] The accuracy of the pharmacodynamic models is demonstrated by the reasonable values of MDAPE and the agreement between the observed time to maximum BIS changes and the calculated time to the highest effect site concentration after a specific propofol administration (depending on the group).

Because this study aimed at answering the question of why different k_{e0}s are found in the literature, even when using the same pharmacokinetic model, we wanted to explore bolus injections (as used by Schnider et al.[3]) and various infusion rates covering published work and clinical practice. Our bolus was 2.5 mg/kg given over 10 s. Our slowest administration was an infusion of 2.5 mg/kg given over 3 min, which is 50 mg kg^{-1} h^{-1}. This is lower than the critical infusion rate of 80 mg kg^{-1} h^{-1} that Kazama et al.[12] postulate causes incomplete mixing in the central compartment.

Classically, the sigmoid E_{max} model has been applied successfully for pharmacodynamic modeling of propofol. However, when observing our raw BIS data, we found that the BIS values showed no change during the initial increase in effect site propofol concentration, until there was an abrupt decrease. This may reflect an acute change in BIS with loss of consciousness, although the article by Doufas et al. examined BIS at loss of consciousness and did not detect any abrupt state change. This might be due to the fact that they used an Observers' Assessment of Anesthesia/Sedation score of less than 2 (= loss of responsiveness to shaking and shouting) as their endpoint.[5] Alternatively, this delay may reflect the combination of the averaging algorithm to calculate BIS (i.e., smoothing rate) and the delay in adaptation of one of the artifact rejection preprocessing steps, that rejects large changes in the electroencephalogram as artifact until those changes persist for approximately 5 s (Scott Greenwald, Ph.D., Vice President of Research, Aspect Medical Systems, Newton, MA, verbal personal communication, April 2005). We found that the inclusion of a lag time of 10 s into our model resulted in the best fit. Longer lag times resulted in worse fits of the model to the data. Regardless, the initial observations when the BIS was unambiguously unresponsive to changing propofol concentrations (figs. 1E–H) were censored from the sigmoidal model by introducing a separate model for BIS values of 90 or greater and BIS values less than 90. This model significantly improved the quality of the fit with our data ($P << 0.001$ for the 2 k_{e0} model; table 3) and with the validation data set from Doufas et al.[5] ($P << 0.001$ for the models with 10-s delays; table 6).

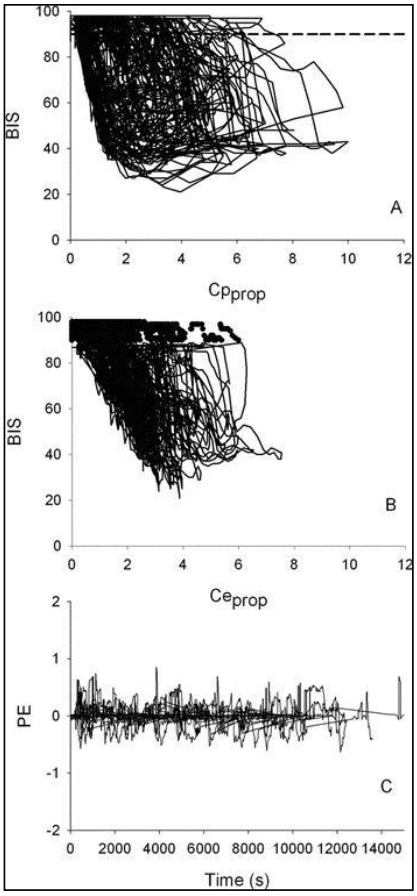

Fig. 6 The validation data set. A shows the relation between the measured Bispectral Index (BIS) and propofol plasma concentration (Cpprop). B shows BIS versus effect site concentration (Ceprop), based on ke0 estimate by NONMEM. To visualize the source data and results for the fixed number model, we showed the measured BIS data ≥ 90 as black circles. The second part (the sigmoid Emax model using BIS<90) data are shown as straight lines. C shows the individual prediction error (PE) from the best fitting model (fixed ≥ 90, sigmoidal <90, 10 s delay; including estimates of interindividual variabililty on ke0 and Ce_{50}).

If propofol administration rate is influencing the time course of drug effect, a model incorporating different estimates of k_{e0} for different infusion rates would yield a better model fit than a model whereby one k_{e0} was used to describe the time course of effect site concentration independent of drug

administration rate. We found that the model discriminating the bolus injection group from the three continuous infusion groups yielded a significantly better fit than a model with a single k_{e0} for all four groups. In our bolus group, the value of $t_{½}$ k_{e0} was 1.2 min, very close to the value of 1.5 min reported by Schnider et al.[3] whose value of k_{e0} was primarily based on bolus propofol administration. In the Schnider study, the bolus was administered in a mean time of 18 s (range, 13–24 s), which is somewhat slower than in our study (table 2). In addition, our calculated time of maximum BIS effect in the bolus group was 1.7 min (table 4), exactly the same as reported by Schnider et al.[3] Our $t_{½}$ k_{e0} of 2.2 min for propofol administration by infusion is in agreement with the value computed from the validation data set of Doufas et al.[5] of 2.1 min, both of which reflect fast infusions, but obviously less rapid than bolus injections.

Table 6. Validation Modeling Using the Data Set Previously Published by Doufas *et al.*[5]

	Sigmoid Model, No Delay	Sigmoid Model, 10-s Delay	Fixed ≥ 90, Sigmoidal < 90, No Delay	Fixed ≥ 90, Sigmoidal < 90, 10-s Delay
−2 Log likelihood	37,498	37,379	35,087	34,952
Average BIS for values ≥ 90	NR	NR	95.5	95.5
Ce_{50}	2.8	2.8	3.6	3.6
γ	1.4	1.4	1.2	1.3
E_0	100	100	90	90
E_{max}	25	25	25	25
$t_{½}$ k_{e0}, min	3.4	3.1	2.2	2.1
k_{e0}, min^{-1}	0.20	0.22	0.32	0.34

BIS = Bispectral Index; Ce_{50} = effect site concentration associated with 50% maximal drug effect; E_0 = baseline measurement when no drug is present; E_{max} = maximum possible drug effect; γ = steepness of the concentration-*versus*-response relation; NR = not relevant.

Our findings are consistent with propofol modeling studies using a conventional continuous infusion, which have reported propofol $t_{½}$ k_{e0}s between 2.3 and 3.5 min. In the first commercial target-controlled infusion device (Diprifusor; AstraZeneca), the kinetic model described by Marsh et al.[10] was linked to a $t_{½}$ k_{e0} of 2.65 min as described by Schwilden et al.[13] and based on slow continuous infusion data. Billard et al.[14] administered propofol (continuous infusion of 0.5 mg · kg^{-1} · min^{-1} until burst suppression) and measured the electroencephalographic effect using three different electroencephalographic measures. The estimates of $t_{½}$ k_{e0} were significantly higher (mean, 2.6 min) for delta power than those for spectral edge 95% (mean, 3.5 min) and Bispectral Index version 1.1 (mean, 3.5 min). White et al.[15] used midlatency auditory evoked potentials to measure propofol drug effect, when administered as a continuous infusion (0.5 mg · kg^{-1} · min^{-1}), and calculated a k_{e0} of 3.5 min (mean value). All of these effect measures were modeled without including any delay in the electroencephalographic measure.

Table 7. Median (Range) Individual Ce_{50}, $t_{½}$ k_{e0}, MDPE, and MDAPE for Each Individual Subject, TV with CV in the Doufas Validation Data Set, Using the *Post Hoc* Bayesian Estimates of the Best Model*

	Ce_{50}	$t_{½}$ k_{e0}	MDPE	MDAPE
Median (range)	3.68 (8.28)	1.51 (1.5)	0.007 (0.171)	0.060 (0.129)
TV	3.63	2.06	NA	NA
CV, %	31	129	NA	NA

* Fixed ≥ 90, sigmoidal < 90, 10-s delay.

Ce_{50} = effect site concentration associated with 50% maximal drug effect; CV = coefficient of variation; MDAPE = median absolute prediction error; MDPE = median prediction error; NA = not applicable; TV = typical population value.

K_{e0} is dependent on the accuracy of the underlying pharmacokinetic model, and if the pharmacokinetic model is biased, the estimate of k_{e0} will be biased by that error. One limitation of our study is that we did not include measurement of propofol plasma concentrations over time in our four groups. Similar to previously published work,[5,16–18] we applied the three-compartment model published by Schnider et al.[6] to predict the time course of the propofol plasma concentration. In the study by Doufas et al.,[5] the pharmacokinetic performance of the propofol pharmacokinetics reported by Schnider et al.[3] was validated with rapid arterial samples and found to be accurate. Because our study was designed specifically to test the hypothesis in the Doufas article that the difference in values of k_{e0} might depend on the difference between a bolus and a continuous infusion of propofol, we did not believe it was necessary to collect arterial blood samples in all patients during the bolus (similar to the infusion scheme used by Schnider in deriving the pharmacokinetics [6]) or the infusions (where the pharmacokinetics have been validated by both Doufas and Schnider).

However, the literature has not documented the accuracy of the Schnider pharmacokinetic model in the first minutes after bolus injection. Therefore, we added the bolus validation study and documented that neither model performed well in the first 3 min (fig. 4). The failure of both models in the first 3 min is an expected consequence of a flawed fundamental assumption with mammillary compartment

models: instantaneous mixing in the central compartment. Conventional two- and three-compartment mammillary compartment models assume that drug added to the central compartment is instantaneously completely mixed, and that this mixed plasma instantaneously appears in the arterial circulation. This is not the case, as extensively reported by Henthorn et al.[19–21] and others.[22,23] The reason that more complex models have not been integrated into target-controlled infusion systems is that incorporating this into target-controlled infusion algorithms introduces considerable mathematical complexity. Because the problem with model misspecification is limited to the first few minutes after bolus injection, there is limited incentive to develop hybrid models to correct the fundamentally flawed assumption of instantaneous mixing.

The initial error in the pharmacokinetic models is evident for the full 5 min with the Marsh model but seems to be resolving by 3 min with the Schnider model. Therefore, the Schnider model comes closest to fitting the bolus validation data and would be the better of the two models to use for this purpose.

The simulation results from the bolus validation study (fig. 5) show that a $t_{½}$ k_{e0} of 2.0 min, coupled to a more accurate pharmacokinetic model, predicts a peak effect site concentration of 1.9 min, as observed with our bolus data (table 4). This is fairly close to the $t_{½}$ k_{e0} of 2.2 min that we estimated for the three infusion groups, and demonstrates that most of the difference in k_{e0} between bolus and infusion administration is an artifact caused by the inability of mammillary models to accurately describe the concentrations in the first few minutes after bolus injection. The actual rate of blood–brain equilibration may not differ between bolus and infusion methods of administration.

This does not preclude the possibility that there are physiologic reasons the rate of plasma–effect site equilibration might change with infusion rate. Upton and Ludbrook [24,25] demonstrated that propofol decreases cerebral blood flow in a dose-dependent manner. This might explain why the plasma–effect site equilibration time of propofol could change between a bolus, whose high early concentrations acutely decrease cerebral blood flow, and an infusion, where the changes in cerebral blood flow would be small.

The rate of propofol administration influences the apparent rate of plasma–effect site equilibration. This is partly, and perhaps mostly, a result of the inability of conventional pharmacokinetic models to accurately describe the first few minutes after bolus injection. Target-controlled infusion devices need

to select the value of k_{e0} that will most accurately represent the effect site concentrations over time. The error in the pharmacokinetic model with rapid administration can be partly compensated for by the selection of k_{e0}. If the maximum infusion rate is between 300 and 900 ml/h, this corresponds to the infusion rates in our three infusion groups, and the $t_{½}$ k_{e0} should be approximately 2.2 min (k_{e0} = 0.32). However, if the infusion is closer to our bolus rate (2.5 mg/kg over 10 s almost equal to 6,300 ml/h), the faster $t_{½}$ k_{e0} of 1.2 min will better approximate the time course of drug effect. These values of k_{e0} are for use with the Schnider pharmacokinetics. If these data are to be implemented with other pharmacokinetics, then they should be implemented to achieve the predicted time of peak effect of 1.5 min if the device delivers an induction dose of propofol over a minute or less. If the pump is unable to infuse propofol that quickly, selecting k_{e0} based on a peak effect of 1.8 min is appropriate.[2]

We conclude that the observation of Doufas et al. is correct, although the explanation is surprising. There is a difference in the apparent rate of plasma–effect site equilibration between propofol boluses and propofol infusions. The difference is mostly caused by misspecification in the pharmacokinetic model over the first few minutes after bolus injection. A pharmacokinetic model that accurately predicted propofol concentration in the first few minutes after bolus injection, and for many hours after infusion, might improve the accuracy of target-controlled infusion administration when targeting the site of drug effect. If propofol infusion rate affects the apparent k_{e0} even when the pharmacokinetic model is unbiased, there may also be a physiologic basis for dependence of k_{e0} on propofol infusion rate.

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CHAPTER 4

Study of the time course of the clinical effect of propofol compared with the time course of the predicted effect-site concentration: performance of three pharmacokinetic – dynamic models

British Journal of Anaesthesia 104 (4): 452–8 (2010)

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Introduction

In this study we investigated the performance of 3 effect-site controlled drug titration algorithms in an ASA 1 and 2 population. One would expect that in such a population the estimated effect-site concentration has a constant function with the desired clinical effect. We studied whether the respective effect-site controlled titration algorithms allow to maintain this desired clinical effect over time, once the corresponding effect-site concentration in the individual patient is known and targeted. We therefore expected the BIS to stay at a constant level corresponding with loss of response to name calling in every patient. Nevertheless this was not the case. Patients woke up (Marsh) or BIS decreased (Schnider). The models are developed in different ways, have different parameters and hence generate different infusion rates when used in effect-site controlled TCI.

PK and PD estimates are closely linked to one another, they contribute to the (in-) accuracy of the estimated effect-site concentration to correlate with a clinical effect. Therefore optimal PK-PD model building should always be estimated simultaneously within one study population.

Study of the Time Course of the Clinical Effect of Propofol versus the Time Course of the Predicted Effect-site Concentration of Propofol. Performance of Three Pharmacokinetic-dynamic Models in Steady-State Conditions.

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Abstract

Background: In the ideal pharmacokinetic-dynamic (PK-PD) model for calculating the predicted effect-site concentration of propofol (Ce_{PROP}), for any Ce_{PROP} the corresponding hypnotic effect should be constant. We compared three PKPD models (Marsh PK with Shüttler PD, Schnider PK with fixed k_{e0}, and Schnider PK with Minto PD) in their ability to maintain a constant bispectral index (BIS), while using the respective effect-site controlled target controlled infusion (TCI) algorithms.

Methods: We randomized 60 patients to group M (Marsh's model with k_{e0}= 0.26 min^{-1}), Group S1 or group S2 (Schnider's model with a fixed k_{e0} = 0.456 min^{-1} or a k_{e0} adapted to a fixed time to peak effect = 1.6 min, respectively). All patients received propofol at constant rate until loss of consciousness. The corresponding Ce_{PROP}, as calculated by the respective models, was set as target for effect-site controlled TCI. We observed BIS for 20min. We hypothesized that BIS remains constant if Ce_{PROP} remains constant over time.

Results: All patients in group M woke up, one in group S1 and none in group S2. In groups S1 and S2, BIS remained constant after 11 minutes of constant Ce_{PROP}, at a more pronounced level of hypnotic drug effect than intended.

Conclusions: Targeting Ce_{PROP} at which patients lose consciousness with effect-site controlled TCI does not translate into an immediate constant effect.

Introduction

Three compartmental pharmacokinetic (PK) models are used in target controlled infusion (TCI) pumps to predict plasma-concentrations of propofol (Cp_{PROP}), based on drug input[1-4]. As the plasma is not the site of drug effect, hysteresis exists between Cp_{PROP} and clinical effect. Extending the PK model with an effect compartment enables modeling of the effect-site concentration of propofol (Ce_{PROP}) (called "link model" or "pharmacodynamic (PD) model")[5]. The extension of the PK model with a PD model requires one additional transfer constant, called k_{e0}. The relationship between Ce_{PROP} and effect is governed by a static (time independent) non-linear (sigmoidal) relationship. Therefore, a change in Ce_{PROP} should directly translate into a change of effect without time delay.

In TCI pumps, concentrations at the effect site are calculated with different pharmacokinetic models and different k_{e0}. In this study, we investigate differences in time course between Ce_{PROP} and clinical effect between models. We compare three PK-PD models to predict Ce_{PROP} corresponding with loss of response to name calling (LORNC). Subsequently, we use the respective effect-site controlled TCI algorithms to maintain a constant Ce_{PROP}. We hypothesized that by targeting Ce_{PROP} compatible with LORNC, the clinical signs of consciousness and bispectral index (BIS) should remain constant.

Materials and Methods

After institutional Ethics Committee approval (University Hospital, Ghent, Belgium), informed consent was obtained from 60 American Society of Anesthesiologists I patients, aged between 18 and 65 years, scheduled for minor ambulatory surgery. Exclusion criteria were weight less than 70% or more than 130% of ideal body weight, neurological disorder, and recent use of psychoactive medication, including alcohol. All measurements for this study were performed before surgery.

An 18 gauge intravenous line was positioned at a large forearm vein. Every patient received about 300ml of crystalloid fluid during the study period. No fluid load was given before induction of anesthesia. No patient received preoperative medication. No other drugs, including opioids, were given during the study period. All patients maintained spontaneous breathing with the use of a face mask delivering 100% of oxygen at 6 L/min.

Heart rate and non-invasive blood pressure, arterial oxygen saturation and capnography were recorded at 1-min time intervals using an S-5 monitor (GE Healthcare, Helsinki, Finland). Capnography was monitored by putting the side stream sample line in the face mask of the patient. This implies an error for quantification of the partial pressure of carbon dioxide, but it enabled monitoring of respiratory rate and free airway.

During the study period, bispectral Index (BIS) was derived from the frontal electroencephalogram (At-Fpzt) and calculated by a BIS® XP Monitor(version 4.0) (Aspect Medical Systems, Norwood, MA, USA) using a BIS-Sensor electrode (Aspect Medical Systems, Inc., Norwood, MA, USA). The smoothening time of the BIS monitor was set at 15 seconds.

All data was captured using RUGLOOPII (Demed, Temse, Belgium), a computer-assisted data management device, that simultaneously drives and controls an Asena GH Infusion Pump (Carefusion, Basingstoke, UK) for the administration of propofol. At the start of the study, propofol 1% is administered at 300 ml/h. Meanwhile, the corresponding effect-site concentration of propofol (Ce_{PROP}) is calculated in a time synchronized way by RUGLOOPII using one of the studied PK-PD models, defined by randomization. At any given time, the researcher was able to switch this regular propofol administration to an effect-site controlled target controlled infusion (TCI) setting, using the same PK-PD parameters.

Before starting the drug administration, all patients were asked to close their eyes and relax for two minutes. During that time, signal quality, impedance of the electrodes and the adequate capturing of all parameters by RUGLOOPII was verified. Propofol 1% was started at 300 ml/h. The propofol infusion was maintained until we observed loss of response to name calling (LORNC). At LORNC, the corresponding Ce_{PROP}, as calculated by one of the three studied PK-PD models, was set as a target for effect-site controlled TCI administration, using the same PK-PD model as defined by the randomization process. This effect-site controlled TCI of propofol was maintained for an additional 20 minutes if feasible. During that time the clinical level of consciousness was verified by repeated name calling every 15 seconds. BIS was also observed during the entire study period as an objective quantification of cerebral hypnotic effect.[6] The study period ended after 20 minutes of measurements or when a patient regained consciousness (ROC) defined as a return of responsiveness on name calling.

LORNC was defined as a transition from level 3 to 2 on the modified Observers Assessment of Alertness and Sedation (OAA/S) scale.[6-7] To avoid inter-observer differences for defining LORNC, the methodology was standardized according to a predefined sequence of actions. Before induction, the patients were asked

to reply with "yes" every time their name was called. Name calling was repeated every 15 seconds (based on the RUGLOOPII case time) until no response was observed. If the patient did not respond within 5 seconds after name calling, the name was repeated twice. When the patient did not respond to the second name calling, the OAA/S was set at 2. A positive response to the second name calling was classified as OAA/S = 3. In that case, an additional 15 seconds delay was respected before repeating the name calling.

We randomized all patients to one of three study groups. For Group M, the effect-site concentration was calculated by the PK model of Marsh extended with a ke0 = 0.26 min^{-1}.[3,4,8,9] This model has been commercialized for plasma controlled TCI in the Diprifusor® Infusion module. (AstraZeneca, Brussels, Belgium). In this commercialized device the calculated Ce_{PROP} is only available as background information. The Marsh PK-PD parameters are currently not commercially available for effect-site controlled TCI, but RUGLOOPII overruled this limitation, and was set to allow effect-site controlled TCI with this parameter set.

For Group S1 and S2, the pharmacokinetic parameters as described by Schnider were used. In group S1, the original PK-PD model of Schnider was used. In this model k_{e0} is constant for all individuals (0.456 min^{-1})[2]. This model is commercially available in the Fresenius Base Primea (Fresenius Vial Infusion Systems, Brézins, France).

For Group S2, the pharmacokinetic parameters are identical to group S1, but Ce_{PROP} was computed using the time-to-peak effect (TTPE) method as described by Minto et al.[10] Ce_{PROP} is calculated to yield a constant TTPE between individuals of 1.6 min (=101sec) after bolus injection, resulting in a individually variable k_{e0}.[10] This model is commercially available in the Asena PK pump for effect-site controlled TCI. (Carefusion, Basingstoke, UK)

All parameters of the PK-PD models can be found in detail in table 1.

Table 1: The three studied PKPD models. LBM = Lean body mass

Table 1: PKPD Model parameters	V1 (L/kg)			k10 (min^{-1})	k12 (min^{-1})	k21 (min^{-1})	k13 (min^{-1})	k31 (min-1)	ke0 (min^{-1})	TTPE (sec)
Marsh/ Shüttler	0.228			0.119	0.112	0.055	0.042	0.0033	0.26	270
	V1 (L)	**V2 (L)**	**V3 (L)**	**Clearance 1**	**Clearance 2**		**Clearance 3**		**ke0 (min^{-1})**	**TTPE (sec)**
Schnider PKPD	4.27	18.9 - [0.39 x(age -53)]	238	1.89+[(height - 177) x0.0264]+ [(weight-77) x0.0456] + [(LBM-59) x (-0.0681)]	0.302 - 0.0056 x (age-53)		[1.29 - 0.024x (age - 53)] / [18.9 - 0.39 x (age-53)]		0.456	92 (+/- 4)
	V1 (L)	**V2 (L)**	**V3 (L)**	**Clearance 1**	**Clearance 2**		**Clearance 3**		**ke0 (min^{-1})**	**TTPE (sec)**
Schnider PK/ Min-to PD	4.27	18.9 - [0.39 x(age -53)]	238	1.89+[(height - 177) x0.0264]+ [(weight-77) x0.0456] + [(LBM-59) x (-0.0681)]	0.302 - 0.0056 x (age-53)		[1.29 - 0.024x (age - 53)] / [18.9 - 0.39 x (age-53)]		0.362 (+/- 0.04)	101

Statistical analysis

Statistical significance was set at $p<0.05$ except mentioned otherwise. Differences in demographics between groups are tested using Anova except mentioned otherwise. All haemodynamic and electro-encephalographic data are extracted from RUGLOOPII using LABGRAB software (Demed, Temse, Belgium) in 5 seconds intervals. We compared the Ce_{PROP} compatible with LORNC in all groups, using Anova.

For BIS, we averaged all individual BIS values per minute and calculated the mean population BIS and standard deviation per minute for the duration of the study. Steady-state in BIS was defined as a non significant difference between the respective mean BIS over consecutive minutes, as found by a repeated measures ANOVA with Tukey-Kramer post hoc test.

Results

Demographics are shown in table 2. Groups are not significantly different for age, weight, length and LBM. Group S2 contains a higher number of male participants compared to group M and S1. The time to LORNC and the BIS compatible with LORNC were also not significantly different between groups. (Table 2)
Figure 1 (A, B and C) shows the individual Cp_{PROP} and Ce_{PROP} versus time for group M, S1 and S2 respectively. The mean Ce_{PROP} compatible with LORNC was significantly different between groups ($p<0.0001$), being 1.96 (+/-0.55), 5.54 (+/-0.75) and 5.08 (+/-1.20) µg/ml for group M, S1 and S2 respectively. The mean Ce_{PROP} at LORNC was not significantly different between groups S1 and S2.

In group M, we found that all patients regained consciousness after a mean duration of 401 (+/-102) sec. In contrast, in Group S1, only one patient regained consciousness after 505 seconds of propofol titration and all patients remained unconscious in group S2 throughout the entire study period.

Figure 2 shows the individual BIS measurements over time (figure 2A,C,E) and the corresponding mean BIS values for every minute of measurement (figure 2 B,D,F). Steady state in BIS values was found after respectively 6 minutes in group M, and 11 minutes in both S1 and S2. (Indicated by stars in figure 2B, 2D and 2E) For group M, this steady-state in BIS was only found after return of consciousness occurred in all patients, at a clinically relevant lighter level of hypnotic drug effect than intended. For group S1 and S2,

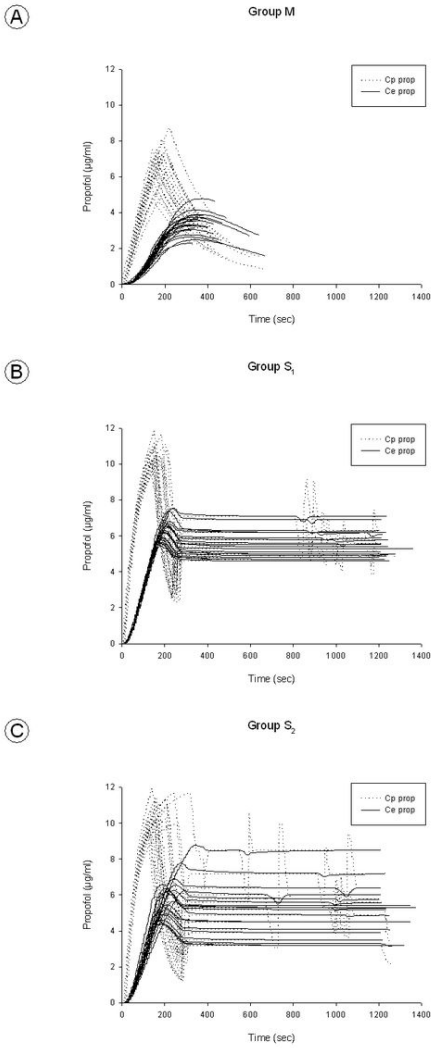

Fig 1 The individual plasma-(dotted line) and effect-site concentration (full line) versus time in Group M (Marsh's model) (A), Group S1 (Schnider's model with a fixed k_{e0}) (B), and Group S2 (Schnider's model with a fixed TTPE) (C)

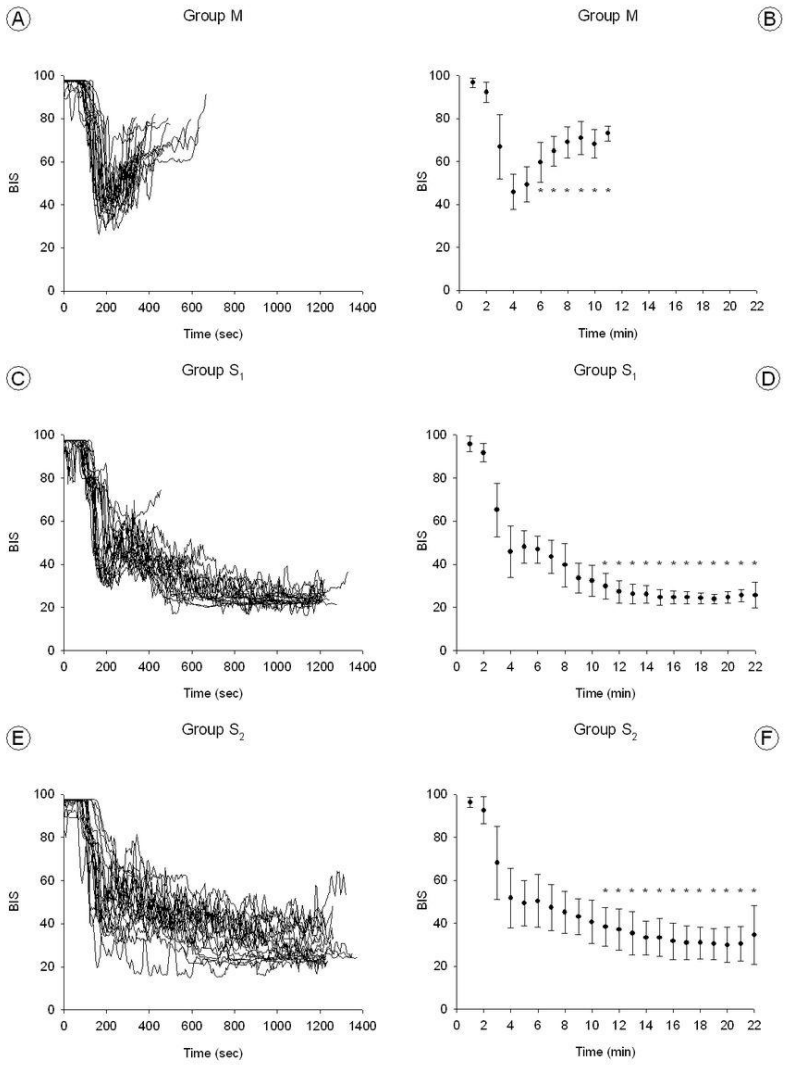

Fig 2 The individual BIS values versus time and their respective mean BIS values (SD) in Group M (Marsh's model) (A and B), Group S1 (Schnider's model with a fixed k_{e0}) (C and D), and Group S2 (Schnider's model with a fixed TTPE) (E and F).*steady state condition in BIS (non significant BIS changes).

BIS showed a more pronounced hypnotic drug effect during steady-state (min 11) compared with the mean BIS at LORNC. (Table 3) Additionally, between minutes 11 and 20, BIS of group S1 was always significantly lower compared to BIS in group S2. (Table 3)

Table 2: Demographics

Table 2: Demographics	Mean Age(SD) years	Mean weight(SD) kg	Mean height(SD) cm	Sex(M/F)	Time to LORNC (sec)	Mean BIS at LORNC (sec)
Group M	33.05(7.69)	62.2(10.53)	170.8(5.66)	2/18	163(59)	59(12)
Group S1	33.1(6.81)	65.75(9.2)	169.3(7.66)	3/17	163(25)	59(14)
Group S2	33.6(5.98)	67.55(13.2)	170.3(6.74)	7/13	176(49)	59(13)

Group M: Marsh group, Group S1: Schnider pharmacokinetics with fixed ke0, Group S2: Schnider pharmacokinetics with fixed time to peak effect. SD: Standard deviation.

Discussion

In an accurate PK-PD model for propofol, any predicted Ce_{PROP} should be time independently and unequivocally related to hypnotic effect. Although the estimated Ce_{PROP} at LORNC was kept constant in our study, we found that all three studied PK-PD models failed to maintain a constant hypnotic effect over time. When using the Marsh PK-PD parameter set, all patients woke up and BIS increased over time. In contrast, when using two PD variations of the Schnider PK model, BIS decreased for several minutes, indicating a progressively intensifying hypnotic effect. Only after 11 minutes of effect-site controlled TCI titration, both Ce_{PROP} and BIS remained constant over time.

The discrepancy in performance results from differences between models, both on a PK and PD level. First, Schnider et al.[2] estimated a smaller central compartment volume for propofol compared with Marsh et al. When the volume of the central compartment of any PK-PD model is decreased, a continuous infusion of propofol will result in a faster increase of Cp_{PROP}, provided that the other volumes and equilibration constants remain identical. Therefore, the larger central compartment of the Marsh model might be a determinant of the slower increase in Cp_{PROP} in group M compared with groups S1 and S2. The significantly lower Cp_{PROP} at LORNC in group M unavoidably affects Ce_{PROP} at LORNC, which was also significantly lower in group M compared with the other groups.

Table 3: mean BIS at LORNC versus mean BIS at minute 11 (Steady-state)

Table 3	Group S1		Group S2	
	LORNC	Min 11	LORNC	Min 11
mean BIS	59*	29*$	59*	37*$
STDEV	14	6	13	10
N	20	20	20	20

*p<0.001 (paired T-test) between mean BIS at LORNC and mean BIS at Min 11
$p<0.001 (unpaired t-test) between mean BIS at Min 11 in Group S1 versus S2
BIS: Bispectral Index; LORNC: Loss of Response of Name Calling

After LORNC, we switched to effect-site controlled TCI, using the respective predicted Ce_{PROP} at LORNC as a target. At that time, the pump will temporarily stop infusing propofol until Cp_{PROP} and Ce_{PROP} are in equilibrium. The time to equilibrate Cp_{PROP} and Ce_{PROP} is determined both by the characteristics of the three compartmental PK model and k_{e0}. A higher k_{e0} reflects a more rapid equilibration between the central compartment and the effect-site. The fixed k_{e0}=0.456min^{-1} of group S1, and the variable k_{e0}=0.362 (+/-0.04) min^{-1} of group S2 are both considerably larger than the k_{e0}=0.26 min^{-1} of group M.[8-9] Theoretically, the combination of both PK and PD model differences between groups, might have resulted in a comparable equilibration time. However, in our study, the pump in groups S1 and S2 was prompted to restart propofol administration before return of consciousness could occur, whereas in group M, the pump did not deliver any propofol for a long time and all patients regained consciousness. (Table 4)

We stopped measuring once ROC occurred, as our patients were undergoing elective surgery. We manually administered additional propofol after ROC to evoke anesthesia compatible with the planned surgery. One can only speculate what would have happened if we had continued the TCI titration in group M. Either patients might have remained responsive while experiencing a light level of sedation (in steady-state) or at the other hand, we might equally observe patients who lose consciousness again, once propofol restarts, as instructed by the PK-PD model. Our study design does not allow a conclusive statement on this possibility.

Comparing results in group S1 and S2, we observed a comparable behaviour in clinical observations and BIS. In group S1, one patient woke up after 505 sec, whereas, in group S2, all patients remained unconscious. Apart from the only exception in group S1, mean BIS decreased in both groups during 11 minutes, indicating a progressively intensified hypnotic drug effect over time in most patients. This observation can be a reflection of inaccuracy of the PK-PD model. On the other hand it might equally be a correct detection of two distinguishable clinical conditions, “the momentum of LORNC” versus

"the condition of maintaining unconsciousness after LORNC has occurred". If a patient needs a higher concentration of propofol for falling asleep compared with maintaining the unresponsiveness, the BIS is expected to go down even when Ce_{PROP} at LORNC is kept constant over time. Some evidence is available that loss of consciousness and return of consciousness are the result of separate neurophysiological pathways.[11] Additionally, the level of adrenergic activity in the awake might be involved in a higher need for propofol to evoke LORNC compared to maintaining a comparable level of unresponsiveness when the adrenergic tone is suppressed. If these assumptions are confirmed in future studies, a temporary decrease in BIS is to be expected in our study setting. After reconsideration of these assumptions, we conclude that an overlapping time course of the BIS effect and Ce_{PROP} as hypothesized in this study is not something we can expect as a proof of accuracy of the PK-PD model. This will only be true in the special case that "Ce_{PROP} and effect" relate in a constant function (relationship) between each other over time. (e.g. Effect = some parameter x Ce_{PROP})

A better understanding of the covariates that determine the duration of inconsistency between a constant Ce_{PROP} and an observed hypnotic effect could help researchers to better target anesthetic steady state conditions. Many covariates can be suspected that affect the time to obtain steady state. First, a

Table 4: Time of the pump inactivity after LORNC *P<0.001(ANOVA) between Groups M and S1, and Groups M and S2. $ P>0.05(ANOVA) between Groups S1 and S2

	Group M	Group S1	Group S2
Mean pump inactivity time (s)	233*	102*$	81*$
SD	105	32	20
n	20	20	20

high induction speed (of more than 6000 ml/h) interferes with the estimation of k_{e0}, as published by Struys et al.[12] In contrast, moderate induction speeds appear to be a relevant covariate in the PK rather than in the PD part of the model.[13] In our study, we administered propofol at moderate speed of 3000 mg/h. The time to reach steady state could therefore be different with induction speeds other than 3000 mg/h. Secondly, the value of the measurement of hypnotic drug effect must be considered. Different clinical endpoints or surrogate measures of cerebral hypnotic drug effect relate differently with Ce_{PROP} and will affect time to reach steady state. When using solitary effect-site controlled TCI of propofol, it remains challenging to predict the time course of a corresponding effect. It seems inevitable to use a surrogate quantification of cerebral hypnotic drug effect (such as BIS) to detect the exact onset time of the steady-state condition. Additionally, such measurements can help to readjust Ce_{PROP} towards a predefined hypnotic drug effect. The major strength of the effect-site controlled TCI technology lies

not in predicting the resulting hypnotic effect in the individual patient, but rather in its ability to maintain the pharmacological condition once a predefined clinical effect has been reached.

In conclusion, when targeting a constant Ce_{PROP} at LORNC by means of effect-site controlled TCI using three different PKPD models, we observed either recovery (Marsh model) or intensifying hypnotic effect (Schnider PK model with fixed k_{e0} or fixed TTPE). Therefore, surrogate measures of hypnotic drug effect, such as bispectral index (BIS), remain a valuable tool to provide the clinician with additional information on the correlation between time courses of Ce_{PROP} versus the observed clinical effect.

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CHAPTER 5

An Evaluation of Using Population Pharmacokinetic Models to Estimate Pharmacodynamic Parameters for Propofol and Bispectral Index in Children

Anesthesiology 2011; 115:83–93

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Introduction

In the first study it was shown that using flawed estimated plasma concentrations could result in pharmacodynamic parameters of poor accuracy.

The following article is a validation of the Kataria model. We showed that the Kataria model is biased and inaccurate. When the Kataria model (just like any other currently used model) is used to estimate plasma concentrations the PD parameters of the combined PK-PD model are also inaccurate.

Rigouzzo used the Schnider model to estimate plasma concentrations and concluded that the Schnider model is accurate to describe the PD of propofol in children. We agree with Rigouzzo that the model is accurate in describing the PD of propofol but warn for the complete inaccuracy of the Schnider model for describing the PK of propofol..Additionally we propose a new combined PK-PD model for propofol TCI in children.

An Evaluation of Using Population Pharmacokinetic Models to Estimate Pharmacodynamic Parameters for Propofol and Bispectral Index in Children

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ABSTRACT

Background: To study propofol pharmacodynamics in a clinical setting a pharmacokinetic model must be used to predict drug plasma concentrations. Some investigators use a population pharmacokinetic model from existing literature and minimize the pharmacodynamic objective function. The purpose of the study was to determine whether this method selects the best-performing pharmacokinetic model in a set and provides accurate estimates of pharmacodynamic parameters in models for bispectral index in children after propofol administration.

Methods: Twenty-eight children classified as American Society of Anesthesiologists physical status 1 who were given general anesthesia for dental treatment were studied. Anesthesia was given using target-controlled infusion of propofol based on the Kataria model. Propofol target plasma concentration was 7 μg/ml for 15 min, followed by 1 μg/ml for 15 min or until signs of awakening, followed by 5 μg/ml for 15 min. Venous blood samples were taken 1, 2, 5, 10, and 15 min after each change in target. A classic pharmacokinetic-pharmacodynamic model was estimated, and the methodology of other studies was duplicated using pharmacokinetic models from the literature and (re-)estimating the pharmacodynamic models.

Results: There is no clear relationship between pharmacokinetic precision and the pharmacodynamic objective function. Low pharmacodynamic objective function values are not associated with accurate estimation of the pharmacodynamic parameters when the pharmacokinetic model is taken from other sources.

Conclusion: Minimization of the pharmacodynamic objective function does not select the most accurate pharmacokinetic model. Using population pharmacokinetic models from the literature instead of the 'true' pharmacokinetic model can lead to better predictions of bispectral index while incorrectly estimating the pharmacodynamic parameters.

PROPOFOL is widely used to manage the hypnotic component of anesthesia in children because of its beneficial pharmacologic characteristics, although caution is warranted in relation to side effects such as the propofol infusion syndrome.[1] Pharmacokinetic-pharmacodynamic (PK-PD) models predicting the time course of drug concentration and effect might be helpful to optimize drug administration if found to be an accurate prediction of reality. A number of population pharmacokinetic models have been developed to predict propofol plasma concentrations in children for arterial blood samples,[2–4] venous blood samples,[5–7] or both.[8] In two recent studies, Rigouzzo e*t* al.[9,10] suggested that a propofol model describing the PK-PD relationship in adults[11,12] might be used in children. Some of these population pharmacokinetic models are used in target-controlled infusion (TCI) regimens to modulate predicted propofol plasma concentrations. However, plasma concentrations are only of secondary importance in anesthesia because plasma is not the site of drug effect. For propofol anesthesia, cerebral drug effects can be measured and are quantal (*e.g.*, loss and return of consciousness, tolerance to noxious stimulus) or continuous (*e.g.*, electroencephalographic data) in nature. The Bispectral Index (BIS, Covidien, Norwood, IL), a quantitative parameter derived from the frontal electroencephalogram, has been validated as a measure of propofol cerebral drug effect in children older than 1 yr.[9,10,13,14]

To study propofol pharmacodynamics in a clinical setting, where dosing varies according to patient requirements, a pharmacokinetic model must be used to predict drug plasma concentrations. The methodologically best approach is the classic PK-PD approach in which population and individualized pharmacokinetic models are estimated using blood samples drawn from the study patients and the individualized pharmacokinetic model used for subsequent pharmacodynamic estimation. However, drawing blood samples is not always practical or possible in some clinical situations. Some investigators have instead applied what we describe in this investigation as the PK(predicted)-PD approach, where the individualized pharmacokinetic model is replaced by a population pharmacokinetic model obtained from existing literature. This fixed population model is then used to produce the pharmacokinetic predictions necessary to study the pharmacodynamics. In this investigation, to clarify the particular pharmacokinetic model used, the word "predicted" can be changed to indicate the origin of the pharmacokinetic model. For example, a PK (Kataria)-PD model indicates that the Kataria model[6] was used for pharmacokinetic predictions.

The PK (predicted)-PD approach leads to questions about the accuracy of the population predictions for individuals in a particular clinical situation. One approach is to simply take the accuracy for granted.[15] This seems difficult to justify because a number of pharmacokinetic models

are available in the literature, each giving different predictions for a given situation. Another approach is to consider a number of pharmacokinetic models and choose the best one based on some quality of the corresponding pharmacodynamic estimation, such as the objective function.[10,16] This approach assumes that the best-performing pharmacokinetic model can be identified by the lowest objective function from the corresponding pharmacodynamic estimation. However, this relationship has not yet been experimentally demonstrated. Studies using this approach also estimate important pharmacodynamic model parameters, such as effect-site equilibration constant (k_{e0}) or the effect-site concentration for 50% effect (Ce_{50}), by minimization of the pharmacodynamic objective function. However, there is no evidence that low values for the objective function are associated with accurate estimation of these parameters when the pharmacokinetic model is taken from other sources. It has been recently shown that fundamental flaws can be introduced when applying predicted instead of measured propofol plasma concentration when investigating the half-life for the effect-site equilibration in adults.[17–19]

The purpose of the current study was to test two hypotheses: that the PK (predicted)-PD approach selects the best-performing pharmacokinetic model from those considered, and that the PK (predicted)-PD approach provides accurate estimates of pharmacodynamic model parameters. We performed propofol TCI-driven anesthesia on children and obtained propofol plasma concentrations from blood samples and BIS values as a measure of cerebral drug effect. From these data we estimated a classic PK-PD model, where both a pharmacokinetic and pharmacodynamic model is estimated. We also duplicated the methodology of other studies by estimating PK (predicted)-PD models, *i.e.*, using pharmacokinetic models from the literature and (re-)estimating only the pharmacodynamic models. By comparing the estimation results of the different approaches we determined the ability of the PK (predicted)-PD approach to identify the best-performing pharmacokinetic model and provide informative estimates for the true pharmacodynamic parameters.

Materials and Methods

Clinical Protocol

After Ethics Committee approval (Ghent University Hospital, Gent, Belgium), clinical trial registration (EUDRACT 2005-001797-27), written informed consent of the parents or legal representative obtained by the dentist, and a clinical examination done by the anesthesiologist, 28 children classified as American Society of Anesthesiologists physical status 1 were enrolled in the study. Patients were divided in four groups according to age: 7 children age 3–5 yr in group 1, 7 children age 5–7 yr in group 2, 7 children age 7–9 yr in group 3, and 7 children age 9–11 yr in the fourth group. All children

were scheduled for dental treatment under general anesthesia.

Exclusion criteria were allergy to any of the constituents of propofol or local anesthetics, previous adverse anesthetic experience, evidence of major preexisting disease, suspected difficult airway, concomitant disease, or antibiotic treatment. No premedication was offered to the patients. The skin was locally anesthetized by applying eutectic mixture of local anesthetic cream (EMLA, AstraZeneca, Ukkel, Belgium) over the site of the peripheral veins 1 h before the procedure.

Noninvasive monitoring (heart rate, noninvasive blood pressure monitoring, saturation, end-tidal carbon dioxide) was established before induction of anesthesia. The propofol cerebral drug effect was continuously monitored using the bispectral index (BIS). BIS (version 4.0, XP) was derived from the frontal electroencephalogram and calculated by the A-2000 BIS Monitor® (Covidien, Newton, MA) using three BIS-Sensor electrodes (pediatric size) or the four-sensor electrode, depending on the patient's age. The BIS value ranges from 100 to 0. The smoothing time of the BIS monitor was set to 15s.

Venous access was established with two 20-or 22-gauge peripheral intravenous cannulae. The first cannula was connected to the infusion pump, and the second cannula was used for blood sampling. The TCI system used to control the propofol infusion comprised a syringe infusion pump (Asena, Carefusion, Basingstoke, United Kingdom) controlled by a computer programmed with RUGLOOPII (Demed, Temse, Belgium) using a pharmacokinetic model for propofol administration in children, in a study previously published by Kataria et al[6]. Propofol was started at a target plasma concentration of 7 µg/ml for 15 min, followed by a target concentration of 1 µg/ml for another 15 min or until signs of awakening (BIS more then 80, movement, eye opening). Finally, the infusion was followed by a target plasma concentration of 5 µg/ml for 15 min. After initial loss of consciousness a laryngeal mask was inserted. No opioid was administered. All children received a crystalloid infusion of 4–5 ml/kg/h during the study. Each blood sample (2 ml per sample) was replaced by 2 ml of crystalloid solution. During the procedure the children were kept warm with a Bair Hugger (Arizant Healthcare, Eden Prairie, MN). The complete study was executed before the start of surgery.

Venous blood samples were collected at baseline (upon placement of the cannula) and after 1, 2, 5, 10, and 15 min at a target of 7 µg/ml. After decreasing the target concentration to 1 µg/ml, blood was withdrawn after 1, 2, 5, 10, and 15 min when possible. After increasing the target concentration to 5 µg/ml, blood samples were obtained at 1, 2, 5, 10, and 15 min. At that time the study period was completed and the anesthesia was continued at the discretion of the anesthesiologist in charge. The collected blood samples (EDTA) of each child were centrifuged, and the obtained plasma was stored in a refrigerator at a temperature at -80°C for further analyses. Propofol (bound and free) plasma concentrations were analyzed using a validated liquid chromatographic fluorescence detection method.

In short, plasma (500 µl) was treated with 1 ml acetonitrile (containing the internal standard 2,4-di-tert-butylfenol) to initiate plasma protein precipitation. After centrifugation, 10 µl of the clear supernatant is injected into the liquid chromatography system (Kontron 325 pump system, Kontron Instruments, Milano, Italy) and Hitachi AS2000A autosampler (Hitachi, Tokyo, Japan). Separation was obtained on a Discovery C18 column (5 µm, 50 X 2.1 mm; Supelco, Sigma-Aldrich, Bornem, Belgium) using a water/acetonitrile gradient. Detection was achieved using a Shimadzu RF-10AXL fluorescence detector (Shimadzu, Kyoto, Japan) (λex 276 and λem 310 nm). Validation (according to Food and Drug Administration guidelines: Bioanalytical Method Validation, Guidance for Industry) data include: limit of detection 0.0935 µg/ml; limit of quantification 0.2 µg/ml, weighted (1/x) linear regression model calibration curves from 0.20 to 15.0 µg/ml (11 calibrators + blank), R^2 = 0.9961 (n = 6). Selectivity was assured on the basis of the analysis of multiple blank human plasma batches and injection of potential comedication standards. Independently prepared quality control samples (0.5, 0.75, 3.5, and 12.5 µg/ml) were used to evaluate precision (repeatability 2.55– 8.37 relative SD %); (reproducibility 4.60–6.84 relative SD %, n = 6) and accuracy (-7.59 to -3.39 bias % relative error), and later to accept individual sample runs.

Pharmacokinetic Dynamic Model

A three-compartmental mammillary model with parameters V1, V2, V3, CL, Q_2, and Q_3 was applied enlarged with an effect-site. The effect-site was assumed to be linked to the central pharmacokinetic compartment with a first-order equilibrium constant of $k_{e}0$. A classic sigmoidal maximal possible drug effect model (E_{max}) was used to describe the relationship between propofol effect-site concentration (*Ce*) and the BIS as a measure of propofol cerebral drug effect:

$$\text{Effect} = E_0 + (E_{max} - E_0)\frac{Ce^{\gamma}}{Ce^{\gamma} + Ce_{50}^{\gamma}}$$

where Effect is the measured BIS value, E_0 is the baseline measurement when no drug is present, E_{max} is the maximal possible drug effect, *Ce* is the calculated propofol effect-site concentration, Ce_{50} is the *Ce* associated with 50% maximal drug effect, and γ is the steepness of the concentration-*versus*-response relation. The delay in the reported BIS index was assumed to be 10 s as published previously.[17] For the current study E_{max} was fixed to 0 and E_0 to 95.

Unless otherwise stated, interindividual variability was assumed to be log-normally distributed:

$$\theta_i = \theta_{TV} \cdot e^{\eta i}$$

here θ_i is the parameter value in the *i*th patient, θ_{TV} is the typical value of the parameter in the

population, and η_i is a random variable in the *i*th patient with a mean of 0 and a variance of ω^2. Interindividual variability is reported as ω, the SD of 1 in the log domain, which is approximately the coefficient of variation in the standard domain.

Residual intraindividual variability for the observed propofol central compartment concentration was modeled using constant coefficient of variance model, and for BIS index this was modeled using an additive error model. Model estimation was performed using NONMEM VI 2.0 (ICON, Dublin, Ireland).

Classic PK-PD Approach. The sequential method[20,21] was used. More specifically, a population pharmacokinetic model was estimated using patients' individual measured blood samples first, producing a population pharmacokinetic model and individual (*post hoc*) pharmacokinetic estimates. In the second stage, the pharmacodynamic model population parameters are estimated with the individual pharmacokinetic model parameters fixed to their *post hoc* estimates.

PK (Predicted)-PD Approach. In this approach, the patient pharmacokinetic model is fixed to one of the previously published population pharmacokinetic models; these are shown in table 1. No pharmacokinetic estimation is performed because the time course of the propofol plasma concentration is calculated from the fixed pharmacokinetic model, the patient covariates in the model, and the given propofol dose per time. The pharmacodynamic model is estimated with a population approach using the patient's individual BIS data.

Indices for Assessment

For all pharmacokinetic models, goodness-of-fit plots were constructed for each data set using each model. The plots depict the predicted concentrations *versus* the observed concentrations of propofol. In addition, the predictive performances of the pharmacokinetic models were analyzed using prediction error analysis, as described by Varvel *et al*[22]

Prediction error (PE) for plasma concentrations was calculated using the following equation:

$$PE = \frac{Cplasma\ observed - Cplasma\ predicted}{Cplasma\ predicted} X\ 100$$

Prediction error for BIS values was calculated using the following equation:

PE = BIS observed -BIS predicted

PE is an indication of the bias of the achieved concentrations, and the absolute value of the PE (| PE |) is a measure of the precision.

PK model	Parameters
Kataria [7]	V1 = 0.41 * WGT V2 = 0.78 * WGT _ 3.1 * AGE _ 16 V3 = 6.9 * WGT CL _ 0.035 * WGT Q2 = 0.077 * WGT Q3 = 0.026 * WGT
Paedfusor [2,29]	V_1 = 0.4584 * WGT K_{10} = 0.1527 * $WGT^{-0.3}$ K_{12} = 0.114 K_{21} = 0.055 K_{13} = 0.0419 K_{31} = 0.0033
Marsh [5]	V_1 = 0.343 * WGT K_{10} = 0.1 K_{12} = 0.0855 K_{21} = 0.033 K_{13} = 0.021 K_{31} = 0.0033
Short [8]	V_1 = 0.432 * WGT K_{10} = 0.0967 K_{12} = 0.1413 K_{21} = 0.1092 K_{13} = 0.0392 K_{31} = 0.0049
Rigby-Jones [3]	V_1 = 0.584 * WGT V_2 = 1.36 * WGT V_3 = 5.67 * WGT + 103 CL = 0.0302 * WGT Q_2 = 0.0160 * WGT Q_3 = 0.0133 * WGT
Rigby-Jones (multicenter)	V_1 = 7.76 * PWT V_2 = 14.4 * PWT V_3 = 83.9 * PWT CL = 0.614 * $PWT^{0.75}$ Q_2 = 0.839 * $PWT^{0.75}$ Q_3 = 0.252 * $PWT^{0.75}$ PWT = WGT / 15
Schuttler [9]	V_1 = 9.3 * $PWT^{0.71}$ * $(AGE / 30)^{-0.39}$ * (1 + BOL * 1.61) V_2 = 44.2 * $PWT^{0.61}$ * (1 + BOL * 0.73) V_3 = 266 CL = 1.44 * $PWT^{0.75}$ Q_2 = 2.25 * $PWT^{0.62}$ * (1 – VEN * 0.40) * (1 + BOL * 2.02) Q_3 = 0.92 * $PWT^{0.55}$ * (1 + BOL * (-0.48)) PWT = WGT / 70 VEN = 1 (venous samples) BOL = 0 (infusion dosing, not bolus)
ShangGuan [4]	V_1 = 7.41 * PWT V_2 = 54.6 * PWT V_3 = 7.2 * PWT CL = 0.185 * $PWT^{0.75}$ Q_2 = 0.614 * $PWT^{0.75}$ Q_3 = 0.692 * $PWT^{0.75}$ PWT = WGT / 13.7
Schnider [13,14]	V_1 = 4.27 V_2 = 18.9 - 0.391 * (AGE - 53) V_3 = 238 CL = 1.89 + 0.0456 * (WGT - 77) - 0.0681 * (LBM - 59) + 0.0264 * (HGT - 177) Q_2 = 1.29 - 0.024 * (AGE - 53) Q_3 = 0.836 LBM_{male} = 1.1 * WGT - 128 * $(WGT / HGT)^2$ LBM_{female} = 1.07 * WGT - 148 * $(WGT / HGT)^2$

Table 1 Propofol pharmacokinetic models from the literature.

For each individual, median prediction error (MDPE) and median absolute prediction error (MDAPE) were calculated as measures of the accuracy and precision of the Cplasma prediction. In the *i*th subject:

$$\text{MDPE}i = \text{median}\{\text{PE}ij, j = 1, \ldots, Ni\}$$

where N_i is the number of PE values obtained for the *i*th subject. Hereby, an MDPE value of 0 means no bias.

MDAPE indicates the precision of the C_{plasma} prediction. In the *i*th subject:

$$\text{MDAPE}i = \text{median}\{|\ \text{PE}ij\ |, j = 1, \ldots, Ni\}$$

where N_i is the number of PE values obtained for the *i*th subject. The closer to 0, the more precise is the model.

To reflect the quality of the pharmacodynamic model and predictions the NONMEM objective function value was used. All of the objective function value comparisons concern estimation of the pharmacodynamic model using the BIS pharmacodynamic observations from the current study in conjunction with a fixed pharmacokinetic model, so the comparisons are valid.

Parameter	units	*Typical value*	*Relative standard deviation*
V_1	l/kg	0.174	84%
V_2	l/kg	0.234	0 fixed
V_3	l/kg	0.951	0 fixed
CL	l/min/kg	0.0393	15.2%
Q_2	l/min/kg	0.102	0 fixed
Q_3	l/min/kg	0.0333	24.7%
Residual SD	%	18.4	

Table 2 PK model estimated from the plasma concentration observations from the current study

Results. reasons Data from all included 28 patients were used in the analysis. In total, 443 venous blood samples were obtained and used for the analysis. In 5 patients, 1 blood sample was missing due to technical reasons (1-min sample at plasma concentration [Cp] 1 in patient 1, 1-min sample at Cp7 in patient 9, 15-min sample at Cp1 in patient 11, 1-min sample at Cp7 in patient 18, 1-min sample at Cp1 in patient 21). Nineteen boys and nine girls were included.

Their demographics were (median [min–max]) age, 6.5 y (range, 4–11 y); weight, 21.5 kg (range, 18–54 kg); height, 119 cm (range, 105–152 cm). All NONMEM runs successfully completed the covariance step and reported a condition number less than 1,000.

PK model	PK performance		PD estimation				
	MDPE (%)	MDAPE (%)	Objective function	k_{eo} (1/min)	Ce_{50} (μg/ml)	γ	SD(res)
Posthoc	0.8	8.6	77385.25	0.79	3.85	1.50	7.9
population	-0.6	14.0					
asymptotic standard error				0.12	0.11	0.06	2.2

Table 3 PK predictive performance and results from PD model estimation

Classic PK-PD Approach

For the classic PK-PD approach, a three-compartment model fit the data. The typical values, intraindividual and residual variability for the estimated population model, are shown in table 2. The interindividual variance (ω) values for V_2,V_3, and Q_2 were fixed to 0 to obtain a stable estimation. For all patients, the observed, population-predicted, and *post hoc* predicted plasma concentrations are shown in figure 1. The observed/population predicted and observed/*post hoc* predicted plasma concentrations *versus* time and *versus* observed plasma concentrations graphs are shown in figure 1. Except for some rather high plasma concentrations, an overall accurate fit was found as indicated by the smoothed curves. This is reflected by the population and *post hoc* median (absolute) prediction errors as shown in table 3.

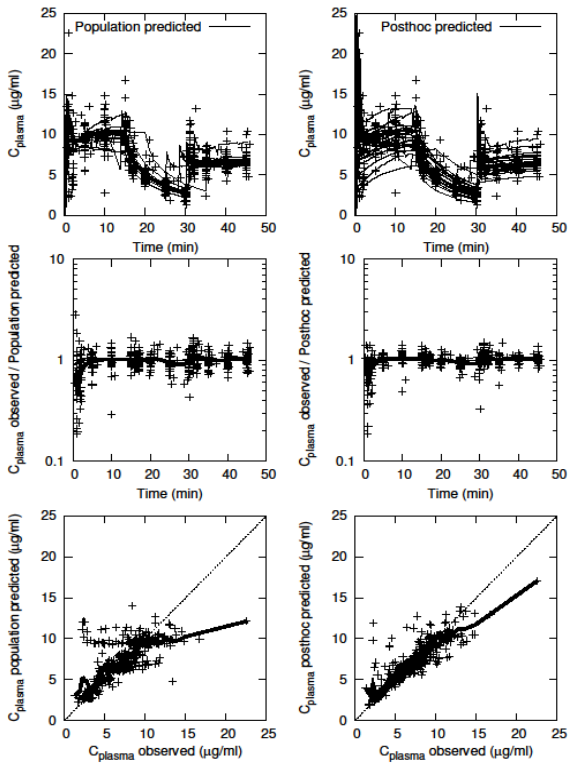

Fig 1 From the classic PK-PD approach, PK population and post-hoc predictions for the current study versus observed propofol plasma concentrations in time.

Sequentially, a sigmoid E_{max} model was used to describe the pharmacodynamic relationship between concentration and cerebral effect as measured by BIS.

For the pharmacodynamic model, the typical values and standard errors for k_{e0} and effect-site concentration Ce_{50} and the NONMEM objective function for the pharmacodynamic model are shown in table 3. Figure 2 shows the observed, population-predicted, and *post hoc* predicted BIS values for all patients. An overall observed *versus* predicted analysis revealed an acceptable pharmacodynamic model prediction (fig. 2). We did not find any statistically significant relationship ($P < 0.05$) between patient age, height, or sex on the estimated pharmacokinetic or pharmacodynamic model parameters.

PK (Predicted)-PD Approach

For the PK (predicted)-PD approach, the pharmacokinetic predictions are obtained from the fixed

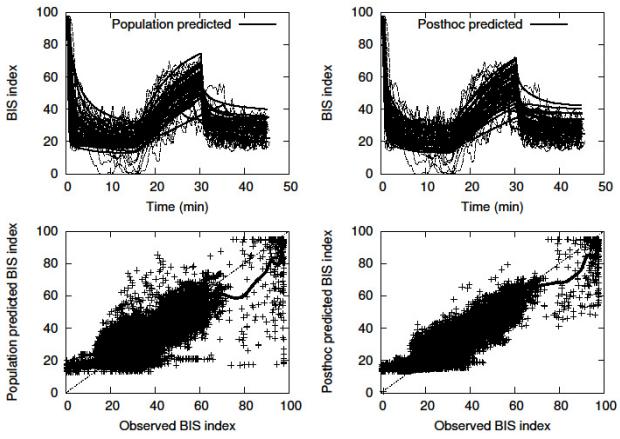

Fig 2 From the classic PK-PD approach, PD population and post hoc predictions for the current study vs observed BIS and time. Observations are marked as (+) or as (smoothed) dotted line.

models described in table 1. For these applied pharmacokinetic models, figure 3 shows the relationship between predicted *versus* observed propofol plasma concentrations and also depicts the ratio between predicted/observed propofol plasma concentration *versus* time. The predictive performance of the applied pharmacokinetic models is shown in table 4. The Marsh model shows the best and the Schnider model the worst pharmacokinetic performance as measured by MDPE and MDAPE. We did not see any advantage of pharmacokinetic models developed with venous samples to predict our (venous) samples. This suggests arterial *versus* venous sampling is dominated by other sources of variation. Differences in assay handling[23] between studies and the distinction between blood and plasma drug concentrations[24] may also influence model performance.

A sigmoid E_{max} model was used to describe the pharmacodynamic relationship between concentration and cerebral effect as measured by BIS. The typical values for k_{e0} and effect-site concentration Ce_{50} and the NONMEM objective function for the pharmacodynamic model are shown in table 4. The PK (Schnider)-PD model gave the best pharmacodynamic fit, and the PK (Rigby-Jones)-PD model gave the worst pharmacodynamic fit as indicated by the NONMEM objective function values.

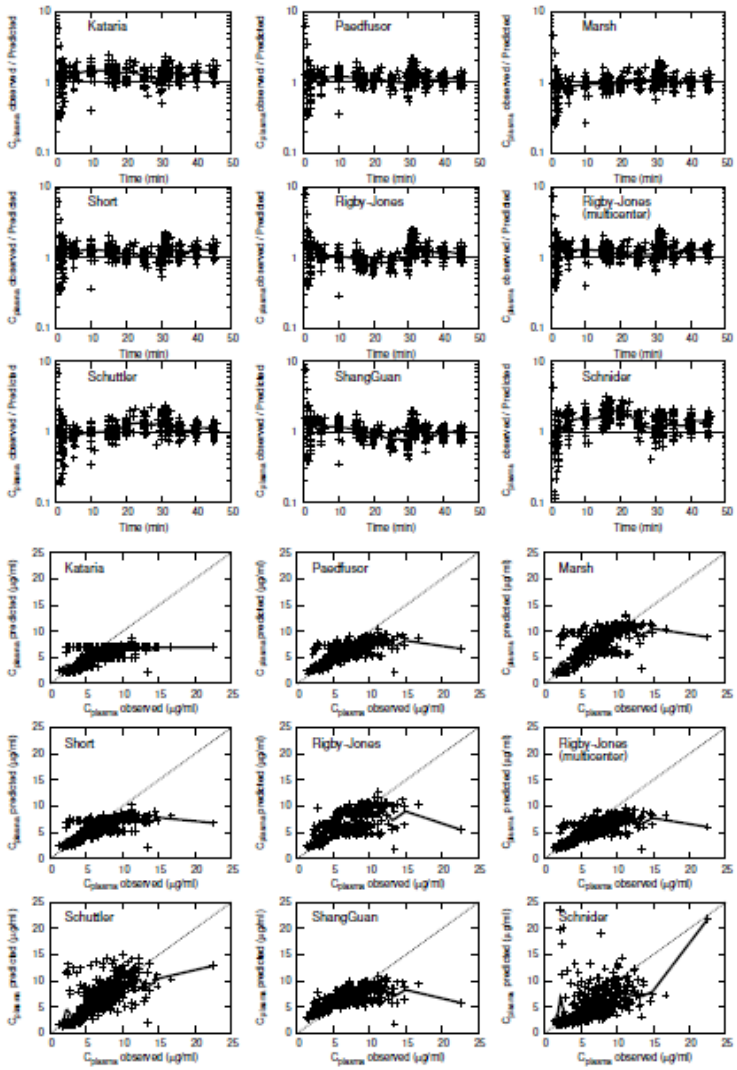

Fig 3 From the PK (predicted)-PD approach, predicted versus observed graphs for propofol plasma concentrations for the PK (predicted) models described in table 1.

PK model	PK performance		PD estimation					
	MDPE (%)	MDAPE (%)	Objective function	k_{eo} (1/min)	Ce_{50} (μg/ml)	γ	SD(res)	MDAPE (BIS)
Kataria	31.3	34.1	75619.64	0.89	2.98	1.53	7.5	5.26
Paedfusor	10.4	19.0	75334.11	1.38	3.53	1.53	7.4	5.17
Marsh	-1.3	15.9	76976.42	0.93	3.33	1.12	7.8	5.50
Short	17.0	23.1	76206.88	1.24	3.41	1.58	7.6	5.50
Rigby-Jones	4.4	21.6	80904.49	2.64	3.61	1.33	8.9	6.86
Rigby-Jones Multicenter	20.9	25.8	76001.34	1.47	3.18	1.47	7.6	5.36
Schuttler	10.2	21.8	77214.12	0.72	2.78	1.02	7.9	5.48
ShangGuan	-1.0	20.7	74351.15	3.30	4.52	2.07	7.2	4.96
Schnider	41.4	46.9	74334.83	0.33	2.80	1.58	7.1	4.85

Table 4: From the *PK(predicted)-PD approach,* pharmacokinetic predictive performance and results from pharmacodynamic model estimation. MD(A)PE is median (absolute) performance error.

This PK (predicted)-PD approach assumes that the best-performing pharmacokinetic model can be identified by the lowest objective function from the corresponding pharmacodynamic estimation. Figure 4 shows these relationships for the data from the current study. There does not seem to be a clear relationship between MDPE or MDAPE with the objective function from pharmacodynamic estimation. Thus, it should not be assumed that this approach selects the best-performing pharmacokinetic model. In fact, in our study, it selected the worst-performing pharmacokinetic model. Alternatively, one could rank the models based on root mean squared error of the predictions; this can be seen as the SD of the residuals (SD[res]) in table 4. In this case the ranking of models is identical to that from objective function value, and the findings are same. Yet another ranking could be based on the MDAPE of the predictions, also shown in table 4.

In this case the ranking of models is nearly identical, and the findings the same.

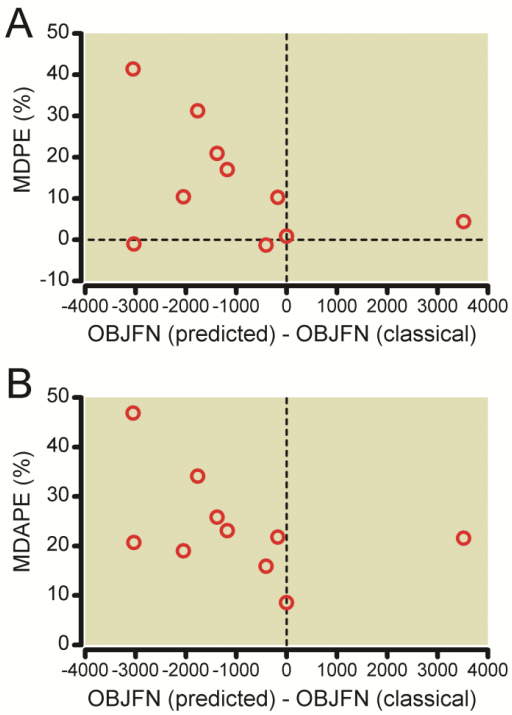

Fig 4 For the PK (predicted)-PD approach, the relationship between objective function and MD(A)PE for the PK models as decribed in table 1. The point from the classic PK-PD approach is included. There is no clear relationship between PK precision and the PD objective function.

Studies using the PK (predicted)-PD approach also estimate pharmacodynamic parameters $k_{e}0$, Ce_{50}, and γ, by minimization of the pharmacodynamic objective function. However, there is no evidence that low objective function values are associated with accurate estimation of these pharmacodynamic parameters when the pharmacokinetic model is taken from other sources. Figure 5 shows the relationship between objective function from the PK (predicted)-PD approach and its ability to estimate the "true" pharmacodynamic parameters estimated by the classic PK-PD approach, which are marked by crosshairs. It seems that for the PK(predicted)-PD approach, *i.e.*, using a population pharmacokinetic model taken from other sources, that minimization of the pharmacodynamic objective function does not necessarily result in accurate estimates of the pharmacodynamic parameters.

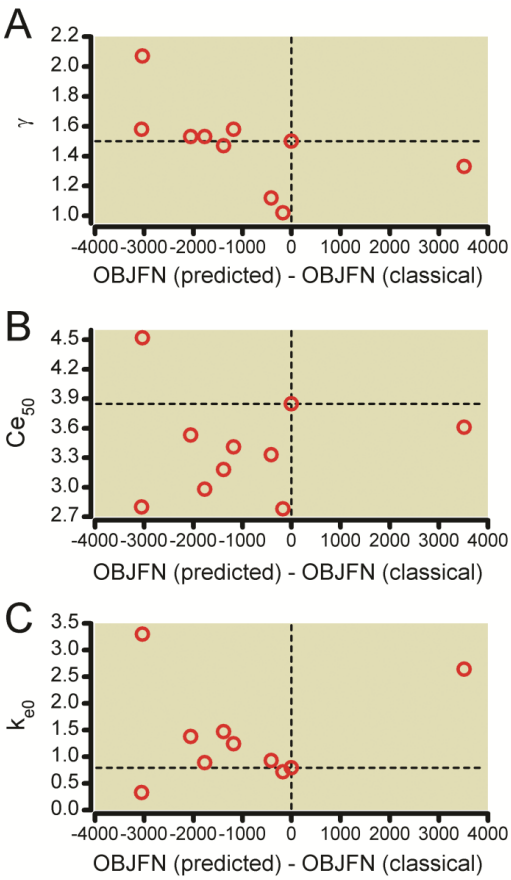

Fig 5 For the PK (predicted) – PD approach, the relationschip between objective function (OBJN) and the estimation of PD parameters estimated by the classic PK-PD approach (indicated by crosshairs). Low PD objective function values are not associated with accurate estimation of the PD parameters when the PK model is taken from other sources.

Discussion

We found that the classic PK-PD approach results in an accurate pharmacokinetic model as evidenced by low values for MDPE and MDAPE. Surprisingly, using a population pharmacokinetic model from another source, *i.e.*, the PK (predicted)-PD approach, can lead to lower pharmacodynamic objective function values than the classic approach, but offers no guarantee of an accurate pharmacokinetic model. Interestingly, the best pharmacodynamic fit was obtained using the PK (Schnider)-PD model, while at the same time this model produced the worst pharmacokinetic predictions. We found that the PK (predicted)-PD approach does not select the best-performing pharmacokinetic model.

Shafer *et al.* stated that the final validation of a model for TCI should be to apply it in a TCI setting and to measure the plasma concentration.[25] These validations have been performed for adults,[11,12] but not for children. Our study is a validation of the previously applied[15] Kataria model[6] for propofol plasma-controlled, TCI-driven anesthesia on children. Similar to other models,[10] we found that the Kataria pharmacokinetic model was biased and inaccurate, evidenced by poor MDPE and MDAPE. The Marsh and ShangGuan models showed low pharmacokinetic bias (MDPE) and the Marsh model the best precision (MDAPE). We also considered the Schnider model, despite its derivation from an adult population, because a recent publication suggested it may provide acceptable PK-PD performance in children.[26] However, in our study it showed pharmacokinetic bias and was inaccurate. Our results are in agreement with others,[10] who found an MDPE and MDAPE for the Schnider model of 44.3% and 44.3% and for the Kataria model of 52.2% and 52.5%, respectively. For the Paedfusor model, Absalom *et al.*[2] found lower values for MDPE (4.1%) and MDAPE (9.7%) compared with our studies. This might be because of the difference between arterial and venous blood sampling in their study and ours, respectively. The pharmacokinetic accuracy for the Short model are worse than expected, possibly because this model was developed in Chinese children, who may have altered kinetics compared with the European children used in our study.[7] On the other hand, the ShangGuan pharmacokinetic model developed in Chinese children was nearly unbiased and showed reasonable precision.

We were able to develop a three-compartmental model from the pharmacokinetic data scaled to total body weight. It showed unbiased population and *post hoc* individual predictions with an acceptable accuracy.[27] The difficulties we experienced in estimating the population variances for V_2,V_3, and Q_2 may be related to the fact that the pharmacokinetic observations were made during TCI-driven anesthesia. TCI dosing has been mathematically proven to have lower inter-individual variability compared with bolus dosing.[28] This reduced uncertainty in plasma propofol observations across the population makes the data less informative for estimation of a population pharmacokinetic model, thereby making the previously mentioned simplifications to the model structure necessary.

The pharmacokinetics and dynamics of a drug should be modeled within the same patient group to obtain an unbiased description of the dose-response relationship of a drug,[29] and the classic PK-PD approach is methodologically the best estimate of the "true" PK-PD model. In the current study we found a Ce_{50} of 3.85 μg/ml, a value similar to the "measured" Ce_{50} of 4.03 μg/ml found by Rigouzzo e*t* al.[9] Rigouzzo e*t* al. also found a "target" Ce_{50} using the Kataria pharmacokinetic model to be 2.94 μg/ml, which can be compared with that from our PK (Kataria)-PD model, 2.98 μg/ml.

In a different study,[10] the same authors found a Ce_{50} of 2.64 μg/ml when the Schnider pharmacokinetic model was used. This value can be compared with that of our PK (Schnider)-PD model, where a Ce_{50} of 2.80 μg/ml was found. It seems that the underprediction of the Kataria and Schnider pharmacokinetic models leads to too-low estimates of Ce_{50}. There does not seem to be any relationship indicating any particular Ce_{50} value. This suggests that the PK (predicted)-PD approach does not accurately estimate the true value of Ce_{50}. The same must also apply to covariate relationships with Ce_{50}, although this is claimed in other studies.[16]

A wide variability of k_{e0} values between the PK (predicted)-PD models is demonstrated, clearly illustrating the influence of the applied pharmacokinetic model on the estimated value of k_{e0}. There does not seem to be any relationship indicating any particular k_{e0} value. This suggests that the PK (predicted)-PD approach does not accurately estimate the true value of k_{e0}. We used a 10-s BIS delay in our calculations, which will influence the absolute value of k_{e0}, a previously described approach.[17] Similar to other studies,[19] we fixed the BIS values for E_0 and E_{max} to 0 and 95, respectively, although in other studies these values have been estimated.[16]

One may be tempted to argue that the limitations of the pharmacokinetic estimation may degrade the estimation of the true pharmacodynamic parameters, and thus the inability of the PK(predicted)-PD models to find the same values as the classic PK-PD approach, does not necessarily mean that the PK(predicted)-PD approach did not find the true pharmacodynamic parameters. However, it should be noted that for the PK (predicted)-PD models considered, there is no clear relationship between model fit (objective function or residual error) and any particular estimated pharmacodynamic parameter value. For example, the best two PK (predicted)-PD models estimate very different values for all of the pharmacodynamic parameters. Because the PK (predicted)-PD approach fails to indicate any particular pharmacodynamic value, it must also have failed at indicating the true pharmacodynamic parameter.

It was an unexpected result that the classic PK-PD approach did not lead to the lowest objective function from pharmacodynamic estimation because it does provide the best estimates of the true pharmacokinetic model for each individual. The reason for this is probably the shortcomings of k_{e0} and the sigmoidal E_{max} model to describe the relationship between BIS and plasma compartment concentration. BIS is a complex variable measured from the brain, a very complex organ. There may be time-dependent and/or level-dependent components to the BIS that are not properly described with the sigmoidal E_{max} model. When such pharmacodynamic model misspecification is present, some specific pattern of misprediction of the pharmacokinetic model might lead to better pharmacodynamic predictions, by "compensating" for specific shortcomings of the pharmacodynamic model.

This phenomenon may be occurring in the PK-PD models studied here. The evidence for this is that the PK (Schnider)-PD model performs quite well for predicting pharmacodynamic responses but poorly predicts the pharmacokinetic responses. Therefore, an improved pharmacodynamic model for BIS may allow the PK (predicted)-PD approach to perform better, and it also would improve the classic PK-PD approach. Another study[9] did not find pharmacodynamic model misspecification; however, only nearly steady-state conditions were considered. At the same time, other pharmacokinetic model structures, such as physiologically-based models[30] or the use of transit compartments,[31] may also help "unify" pharmacokinetic and pharmacodynamic accuracy within a single model but these need to be properly scaled for application in children. Rigouzzo *et al.*[10] suggested that the adult Schnider model might be useful for TCI of propofol in children. Their reasoning was based on good results from the PK (Schnider)-PD approach, which they used in their study. The current study confirmed the good pharmacodynamic performance of this model but found that its pharmacokinetic accuracy in children is poor, worse than all other models tested. Therefore, one cannot argue for use of the Schnider pharmacokinetic model in children on the grounds of its pharmacokinetic accuracy. On the other hand, one could argue that for some anesthesiologic applications, pharmacokinetic accuracy is of little importance provided the pharmacodynamic accuracy is good. This approach represents a paradigm shift in the application of TCI systems where, instead of a target constant drug concentration, the target is some desired pharmacodynamic response. Drug-dosing profile is then adjusted to achieve a constant pharmacodynamic target, possibly requiring a non-constant time course of drug concentration. The good pharmacodynamic performance of the PK (Schnider)-PD model coupled with its poor pharmacokinetic accuracy gives us a hint that these drug dosing profiles may exist. Of course, the Schnider pharmacokinetic model may not be optimal for this purpose and other optimized models could be applied. Future studies may address whether this approach has any advantages to the current TCI approach in anesthesiologic applications.

We conclude that for PK-PD models of BIS in children after propofol administration using fixed pharmacokinetic models from the literature and estimating the pharmacodynamic model does not ensure good pharmacokinetic accuracy or provide informative estimates for pharmacodynamic parameters. It can, however, provide for better pharmacodynamic model fit than the classic PK-PD approach. It seems that there is some misspecification of the sigmoidal E_{max} pharmacodynamic model for BIS response in children. If the sigmoidal E_{max} pharmacodynamic model is used, then some specific pattern of misprediction of the pharmacokinetic model might lead to better pharmacodynamic predictions, by "compensating" for specific shortcomings of the pharmacodynamic model. For applications where pharmacodynamic accuracy is of primary importance these dosing profiles may prove useful.

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CHAPTER 6

DISCUSSION AND GENERAL CONCLUSIONS

CHAPTER 6 DISCUSSION AND GENERAL CONCLUSIONS

The aim of drug titration in anaesthesia is to reach and maintain a stable therapeutic drug concentration at the site of drug effect. In inhalational anaesthesia the measured end-tidal concentration of the gaseous agent is a reliable estimate of its concentration in the brain. For propofol, as an intravenous anaesthetic, we have to rely on estimated/calculated concentrations. The basis for the estimations of propofol plasma concentrations are PK models. Furthermore we want to be in control of the time course and degree of the hypnotic effect of propofol which necessitates the use of PD models. The essential link between a PK and PD model is the k_{e0} the mathematical representation of the plasma/effect-site equilibration rate. Essential for TCI is the accuracy of the applied model. PK-PD models have been developed in rather low numbered populations, most often healthy volunteers, with limited demographic variability which limits their universal application in patients not resembling the typical patient.

The goal of the research we included in this thesis was to study the performance of popular and frequently used PK-PD models We showed that PK and PD estimations are closely linked to one another and that optimal PK-PD model building should always be estimated simultaneously within one study population. We pointed out major differences between models as choice of a wrong model can have detrimental consequences for the patient; either inadequate hypnotic effect or to much effect with potentially harmful side-effects. At the same time we warned for model inaccuracies that arise when models are built without blood sampling.

In chapter 3 we hypothesized[1] a different plasma-effect site equilibration time depending on the injection rate of propofol. To face this problem we administered 2,5 mg/kg propofol as either a bolus or a rapid infusion (duration of 1,2 or 3 minutes). BIS was measured and a PD model was developed (classic sigmoidal and combined fixed plus sigmoidal model). Propofol concentrations were estimated using the Schnider model. We initially concluded that plasma-effect site equilibration for bolus injection is faster than for infusions because two k_{e0}'s , one for bolus injection and another for the three infusion groups best fitted our data. Yet otherwise stated the time course of drug effect is different for bolus injection versus infusion.

However one of the reviewers[2] assessing the original manuscript suggested that these results were potentially flawed because of misspecification of propofol concentrations during the very first minutes after bolus administration. Additional ethics committee approval was requested for the collection of propofol arterial concentrations in 10 additional patients to evaluate the accuracy of the Marsh and Schnider PK models in the first 5 minutes after intravenous propofol bolus. We showed poor performance of these models to predict arterial propofol concentrations in the first minutes after propofol bolus. This is not surprising as it is merely a reflection of the misassumption that there is an

instantaneous mixing of drug in the central compartment. So the definitive conclusion was that the actual rate of blood-brain equilibration may not differ between bolus and infusion methods of administration. Analogous to chapter 5, this reflects the inaccuracy that arises when PD data are linked to PK data generated by poorly performing models.

Masui[3] and colleagues studied the front-end PK and PD of propofol and conclude that a combined PK/PD model consisting of a multi-compartmental model with a lag-time, presystemic compartments, and a sigmoidal maximum possible drug effect model accurately described the early phase pharmacology of propofol.

In chapter 4 we showed[4] that both the Marsh model and the Schnider model failed to maintain a constant hypnotic effect over time. We hypothesized that these models would be able to accurately estimate the C_e of propofol at loss-of-consciousness and consequently that targeting this C_e using TCI would result in a stable effect, i.e. unconsciousness at the same level of anesthesia. Using the Marsh PK-PD parameter set all patients woke up and BIS increased over time. The opposite effect was observed using two PD variations of the Schnider model; a decrease in BIS was observed for several minutes, indicating a progressively intensifying hypnotic effect. The question arises whether this is due to inaccuracy of the PK-PD model or to a lack of understanding the exact underlying neuro-physiological pathways.

On a PK level there are essential differences between the Marsh and Schnider model. Marsh used slow infusion rates in his original population and hence found a large V_c, whereas Schnider used boluses and subsequently found a lower V_c. When the V_c of any PK model is decreased, a continuous infusion of propofol will result in a faster increase in C_p. In our study the 'Marsh group' and the two 'Schnider groups' were administered a continuous infusion of propofol with comparable times to loss of response to name calling (LORNC) and hence comparable doses. Due to the large V_c in the Marsh model the predicted plasma and effect-site concentrations were lower in the 'Marsh group'. The plasma and effect-site concentrations were higher in the two 'Schnider groups' as the V_c is typically lower for the Schnider model. After switching to effect-site controlled TCI, PD differences arose; the k_{e0} of Marsh (0.26 min^{-1}) is lower then the k_{e0}'s in our Schnider groups (k_{e0} = 0.456 min^{-1} and 0.362 min^{-1}). Therefore the equilibration between plasma and effect site concentration is slower for the Marsh group and so the infusion pump waits considerably longer to restart propofol infusion in the Marsh group. The Schnider groups started from higher C_e concentrations and together with higher k_{e0}'s and hence more rapid equilibration times, this resulted in the pump to restart much earlier and therefore deeper levels of anesthesia.

In the Schnider groups there was a progressively intensified hypnotic drug effect over time. One may hypothesize that the conditions to induce unconsciousness are different from those required to maintain unconsciousness. For instance higher adrenergic activity in the awake may result in a higher need for propofol to induce LOC compared to the dose needed to maintain a comparable level of unconsciousness in the unresponsive patient in whom adrenergic tone is suppressed. The neural mechanisms that play a role in anesthesia induction and emergence are insufficiently resolved for the moment but are continuously under investigation[5,6]. It is now accepted that emergence of anesthesia is not simply the reverse process of induction due to the elimination of anesthetic drugs from the effect-site concentration. At least in inhalation anesthesia, it has been shown that for sevoflurane the parameters of the sigmoidal E_{MAX} model (EC_{50} , slope γ) are different for induction and recovery. In the mean time it seems inevitable to use surrogate measures of hypnotic effect such as BIS to detect the exact onset time of steady-state conditions and hence keep the hypnotic effect at a constant level.

In the study, discussed in chapter 5 we validated the Kataria PK model[7] for propofol in TCI for children. 28 children were anesthetized using TCI, plasma controlled according to the Kataria model, which was very popular at that time. 448 venous blood samples were drawn, and analysed for propofol concentration. Subsequently our own PK model was developed using NONMEM. BIS values were monitored and a PD model was developed. A k_{e0} of 0,79 min^{-1} links PK and PD model. We found that the Kataria model was biased and inaccurate. The Coppens' model resulted in an accurate PK prediction. In a next phase we estimated plasma concentrations and BIS values with PK-PD models found in the literature. Using the same approach Rigouzzo[8] concluded that the Schnider model for adults is useful for TCI in children. However in our study we showed that the Schnider model in children was biased and inaccurate on a PK level but performed fairly well at a PD level. Other PK-PD models were also simulated and we concluded that the use of estimates of plasma propofol concentrations using published PK models and estimating the PD model does not ensure good pharmacokinetic accuracy or provide estimates for PD parameters. An accurate estimation of k_{e0} demands an integrated PK-PD study, combining blood samples with frequent measurements of drug effect, resulting in an overall model for the dose-response behavior of the drug. The relationship between the effect-site concentration and clinical drug effect is thought to be governed by a static (time-independent), non-linear (sigmoidal) relationship. Probably the biologic reality is more complex and the E_{max} model is an oversimplification to generate a k_{e0} and to describe the relationship between BIS and plasma concentration. BIS is a complex variable from the brain, a very complex and yet not well understood organ. With such pharmacodynamic model misspecification, some pattern of misprediction of the PK model might lead to better PD predictions, by 'compensating' for specific shortcomings of the PD model. Although the literature suggest that the adult Schnider model might be useful for TCI of propofol in children, our study confirms the good PD performance but evenly

demonstrated that its PK performance in children is poor. One could argue and state that in anesthesia practice TCI should focus more on some desired PD response as target, rather than trying to predict and simulate concentrations, both plasma and effect-site concentrations.

A way to counteract the inaccuracy of PK/PD models is the use of these models in closed-loop circuits[9,10]. A closed loop controlled drug delivery system uses a PK/PD model, which forms the basis for drug input. A continuous measure of drug effect (BIS) delivers feedback to the drug delivery device. A control system measures the error between the target and observed effects and adapts the drug infusion rate in a manner that is proportional to the magnitude of the error. This is a promising method to deal with PK/PD model inaccuracy caused by inter-individual pharmacological variability.

The development of a 'universal' model covering a wide patient population (extremes of age, co-morbidities, obese,…) will definitely end the discussion on which model is best performing.

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SUMMARY

When the anaesthetist injects a particular dose of a hypnotic drug, he aims a specified clinical effect. To obtain this effect a specific therapeutic drug concentration in the blood and subsequently in the brain of the patient is necessary. Anaesthetists are able to gain control over the blood concentration of the inhalational agents by using a vaporizer to administer the volatile anaesthetic, with measured end-tidal concentration as immediate feedback.

For intravenous anesthesia it is impossible to measure on-line the plasma concentration so we have to rely on pharmacokinetic models to estimate the plasma concentration. If we want to control the time course of drug effect we need pharmacodynamic models, and link them with the pharmacokinetic models.

PK-PD models have been studied for decades. Different models have been built in very specific patient populations and are therefore difficult to use in other patient groups. PK-PD models try to reduce patient intervariability by identifying and incorporating covariates. The models are used in target controlled anesthesia where a plasma concentration or effect-site concentration is chosen.

PK-PD models sometimes are inaccurate. Comparing the Marsh and Schnider models in effect site controlled TCI, we found significant shortcomings. When the predicted effect-site concentration was maintained at the moment of loss of consciousness, the patients woke up in the Marsh group, while the effect was even more pronounced in the Schnider group. We proved that PD models of BIS in children developed by predictions of plasma propofol concentrations using published PK models and estimating the PD model does not ensure good PK accuracy or provide informative predictions for PD parameters. We also confirmed that three compartmental models fail to accurately predict arterial propofol concentrations in the first minutes following bolus administration. This is the result of the flawed assumption that a drug, added to the central compartment is instantaneously and completely mixed.

PK-PD models will be studied further in the future. Further fine-tuning of TCI will be the goal. The information of hypnotic-analgesic drug interactions with data from estimated drug concentration is used in advisory systems that provide real-time information concerning the full dose-response curve. These online display systems informs the anaesthetist about the anaesthetic depth, degree of sedation, the expected wakeup time, extent of muscle relaxation… The ultimate goal is to develop the ideal model that can be universally used in children, adults, obese patients, patients with comorbidities or critical illnesses. This will bring us to a closed-loop system completely covering the dose-effect relationship. We hopefully expect that this will make anesthesia even safer than it ever was before.

In somno maxima securitas !

SAMENVATTING

Wanneer de anesthesist een welbepaalde dosis van een hypnoticum toedient, verwacht hij een specifiek effect bij de patiënt. Om dit effect te bekomen moet een welbepaalde concentratie van het hypnoticum bereikt worden in het bloed en de hersenen. Wanneer een patiënt in slaap gedaan wordt met een inhalatieanestheticum kan de anesthesist zeer gemakkelijk de bloedspiegel controleren door middel van de verdamper en bovendien kan hij de concentratie meten in de uitgeademde lucht om onmiddellijk de verdamper instellingen aan te passen.

Bij intraveneuze anesthesie is het niet mogelijk om onmiddellijk de plasmaconcentratie van het product te meten, en dus moeten we gebruik maken van wiskundige farmacokinetische modellen om de plasmaconcentratie te schatten. Als we het effect willen voorspellen in de tijd moeten we gebruik maken van farmacodynamische modellen en combineren met het farmacokinetisch model.

PK-PD modellen worden reeds zeer lang bestudeerd. Een model wordt bestudeerd in een welbepaalde patiëntenpopulatie en is soms moeilijk te gebruiken voor een groep patiënten die sterk verschilt van de oorspronkelijke populatie. PK-PD modellen trachten de variabiliteit tussen verschillende patiënten te verminderen door rekening te houden met zoveel mogelijk patëntgebonden eigenschappen. Deze modellen worden gebruikt in ‘target’ gecontroleerde toediening van anesthetica; de anesthesist kiest de concentratie van het anestheticum die hij wil bereiken in het bloed of thv de hersenen van de patiënt.

Een wiskundig model is soms niet voldoende accuraat. Wij vergeleken het model van Schnider met dat van Marsh en vonden enkele belangrijke tekortkomingen. We brachten patiënten in slaap met een propofol infuus tot ze het bewustzijn verloren. De concentratie thv de hersenen werd geschat met het Schnider of Marsh model en op het moment van bewustzijnsverlies werd de geschatte concentratie verder aangehouden. In de Marsh groep werden de patiënten wakker. De patiënten in de Schnider groep gingen nog dieper slapen.

Wij brachten kinderen in slaap en ontwikkelden een farmacokinetisch model op basis van gemeten plasmaconcentraties. Tegelijk maten we de BIS waarden en gebruikten deze voor het opstellen van een farmacodynamisch model. Nadien schatten we de plasmaconcentratie door middel van een aantal farmacokinetische modellen beschikbaar in de literatuur. We toonden aan dat deze ‘schattingen’ niet in staat waren om een accuraat farmacokinetisch en farmacodynamisch model te bepalen.

We bevestigen tevens dat drie compartimentele modellen niet in staat zijn om de arteriële plasmaconcentraties te schatten in de eerste minuten na propofol toediening. Deze modellen gaan er verkeerdelijk vanuit dat propofol zich onmiddellijk en gelijk verdeelt over het ganse bloedvolume.

Het onderzoek naar PK-PD modellen zal ongetwijfeld verder gevoerd worden. De ‘target’ gecontroleerde toediening van intraveneuse anesthetica zal hierdoor nog verder verfijnd worden. De

modellen zullen tevens gebruikt worden om voorspellingen te doen van het verloop van de concentratie en het bijhorend effect van het hypnoticum om het verloop van de anesthesie nog beter te sturen. Deze systemen zullen de anesthesist informeren over de graad van sedatie, diepte van anesthesie, het vermoedelijke moment van ontwaken, de graad van spierverslapping,…Uiteindelijk zal een model ontwikkeld worden dat universeel toepasbaar is voor kinderen, volwassenen, obese patiënten, patiënten met co-morbiditeit, kritisch zieke patiënten…

Deze evolutie leidt naar een gesloten systeem waar de ganse dosis-effect curve gemonitord en automatisch gecontroleerd wordt. Hopelijk maakt dit de anesthesie nog veiliger dan ze al was.

In somno maxima securitas.

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Secundair onderwijs:
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Academisch (Universitair) Onderwijs:

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- Opleiding tot geneesheer-specialist in Anesthesie en Reanimatie : 1/08/1994 – 31/07/1999
  - 1ste jaar : UZ Gent
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  - 3de, 4de en 5de jaar: UZ Gent

  Erkenning als specialist in Anesthesie-reanimatie: 6/08/1999

<u>Aanvullende opleidingen</u>

- 3 Day Course on Obstetric Anaesthesia and Analgesia: 6 – 12/12/1999
  Obstetric Anaesthetist's Association (OAA), Church House Conference Center Westminster London,

- Cursus Basic Life Support, Automated External Defibrillation: mei 2000
  European Resuscitation Council, Antwerpen

- Fellowship Obstetrische anesthesie : 10/02-30/04/2003
  Queen Charlotte and Chelsea Hospital/ Londen, Departement van Dr. J Crowhurst,

- 3 Day Course on Obstetric Anaesthesia and Analgesia: 22-24/11/2004
  OAA, Church House Conference Centre Westminster London

- 3 Day Course on Obstetric Anaesthesia and Analgesia: 5-7/11/2007
  OAA, Church House Conference Centre Westminster London

3. BEROEPSLOOPBAAN

- Resident Dienst Anesthesie UZGent: 1/08/1999 - 31/07/2002
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- 1999: actief betrokken bij oprichting en dagelijks beleid Chirurgisch Dagziekenhuis (CDZ)
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  - oftalmologische anesthesie (incl. loco-regionale)
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- 2009: Afdelingshoofd Chirurgisch Dagcentrum UZGent
- Bestuurslid BARA: Belgian Association of Regional Anesthesia
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Onderwijs UGent

- EHBO en Reanimatie: medelesgever en examinator aan de studenten Geneeskunde,Tandheelkunde en Revalidatie en Kinesitherapeutische wetenschappen (REVAKI):
  Theorie en practica EHBO en Reanimatie voor
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  Practica EHBO en Reanimatie voor 2e, 3e ba Gen., 1e, 2e en 3e mast Gen.
  Academiejaar 1999-2000 tot 2008-2009

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  Academiejaar 1999-2000 tot heden

- Examinator Stationsproef 4de proef Gen.
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- Tandheelkundige anesthesie: voor 3e ba Tandhlk.
  4 theorielessen , 4u en 2 practicalessen, 2x4u
  1999 tot heden

- Capita Selecta 4e mast ziekenhuisarts:
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  lessen: Wat is anesthesie en Beademingsapparaat, 3,5u, 2010-heden

- 'Update on resuscitation and automated external defibrillation'
  Postgraduaat Revaki
  Theorie en praktische training, 4 uur/ jaar
  Academiejaren 1999-2000, 2000-2001, 2001-2002

- AVU interuniversitaire cursus voor ASO 2de opleidingsjaar: vanaf 2004 tot heden
  'Anesthetisch beleid bij pathologische zwangerschap'; KULeuven, 2/10/2004, 1/10/2005, 30/09/2006; UZGent, 29/09/2007

  'Advanced Life Support'; VUB Jette, 24/03/2007

  'Basic and Advanced Life Support'; UZGent 13/09/2008
  'Zwangerschap: 'Anesthesie voor sectio', UZGent 13/09/2008

  'Anesthesie voor de pathologische zwangerschap', UA Wilrijk, 28/11/2009
  Basic and Advanced Life Support ; VUB 16/01/2010

  Basic life support and advanced life support; e-learning 2011

Anesthesie voor de pathologische zwangerschap, 22/10/2011; ZOL

Basic life support and advanced life support; e-learning 2012
Anesthesie voor de pathologische zwangerschap, e-learning 2012

- 'Basic Life Support van de volwassene en het kind; Automatische defibrillatie',
  Praktijklessen ABC, nascholing voor tandartsen (organisator prof. dr. Luc Marks)
  Faculteitszaal UGent , jaarlijks van 2008 tot heden

- Stagebegeleider voor een 10-tal studenten (jaarlijks) uit 1e, 2e en 4e mast Geneeskunde

Onderwijs UZGent

- 'Pre-eclampsie en zwangerschapsverwikkelingen'
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- Basic life support, provider
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  Basic life support en Automated external defibrillation, instructor
  European Resuscitation Council
  Medelesgever
  Nederoverheembeek, 8, 9 en 10/10/2000

- 'Speciale technieken in anesthesie: anesthesie voor Neus-, Keel- en Oorheelkunde'
  27/01/2001

- 'Anesthesie en extra-uteriene zwangerschap'
  Bijscholing voor verpleegkundigen
  Februari 2001

- 'Locoregionale anesthesie technieken voor arbeid en sectio'
  Bijscholing voor vroedvrouwen
  UZGent: 12-13/01/2002 en 24/04/2002

- 'Anesthesie voor ambulante heelkunde: van preoperatieve onderzoeken tot ontslag van de patiënt'
  Bijscholing voor verpleegkundigen
  UZGent : 8/02/2002

- Introductie van de cursus EHBO als onderdeel van de V-lijn op
  RUG opendeurdagen,
  Gent, 2/03/2002

- 'Anaesthesia for the pathologic delivery'
  Antwerpen, september 2002

- 'Zwangerschap en Pediatrie'
  5/10/2002, 4/10/2003, 1/10/2005

- 'Medicatie bij anesthesie en reanimatie in de verloskunde'
  Vorming verpleegkundigen verloskwartier en materniteit
  UZGent, 4/03/2008

5. WETENSCHAPPELIJK CURRICULUM

PUBLICATIES

Boeken

(b_1) co-auteur van boeken

1. L. Versichelen, M. Coppens
   EHBO / First Aid
   Handboek voor studenten
   Academia Press, herwerkte en vernieuwde uitgave 2001

2. L. Versichelen, M. Coppens
   EHBO / First Aid
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3. Versichelen L F M, Coppens MJ, et al.
   EHBO / First Aid
   Handboek voor studenten
   Academia Press, herwerkte en vernieuwde uitgave 2007

(b_2) hoofdstukken in boeken

1. Coppens M
   'Respiratoire insufficiëntie tijdens en na de zwangerschap'
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2. Coppens M
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7. Struys MMRF, Coppens MJ, De Neve N, Mortier EP, Doufas AG, Van Bocxlaer JFP, and Shafer SL
   Influence of administration rate on propofol plasma - effect site equilibration. Anesthesiology 2007, 107(3): 386-96

8. Femke Delporte, Kristien Roelens, Marc Coppens, Annick Viaene, Karel Everaert, Hans Verstraelen, Marleen Temmerman
   Obstetrisch handelen bij tetraplegische patiënte
   Tijdschrift voor Geneeskunde. 2009 65(10). p.468-469

9. Marc Coppens, Jurgen Van Limmen, Thomas Schnider, Barbara Wyler, Sjoert Bonte, Frank Dewaele, Michel MRF Struys, Hugo EM Vereecke.
   Study of the Time Course of the clinical effect of propofol versus the time course of the predicted effect-site concentration of propofol. performance of three pharmacokinetic-dynamic models in steady-state conditions.
   British Journal of Anaesthesia 2010, 104 (4):452-8

10. Marc Coppens, DouglasJ Eleveld, Johannes H Proost, Luc Marks, Jan Van Bocxlaer, Hugo Vereecke, Anthony R Absalom and Michel Struys
    An evaluation of using population pharmacokinetic models to estimate pharmacodynamic parameters for propofol and bispectral index in children.
    Anesthesiology 2011; 115 (1):83-93

11. Alicia Borderé, Annelies Stockman, Barbara Boone, Ann-Sophie Franki, Marc J. Coppens, Hilde Lapeere and Jo Lambert
    A case of anaphylaxis caused by macrogol 3350 after injection of a corticosteroid (pages 376–378)
    Contact Dermatitis 2012,vol 67, issue 6

a3) artikels in nationale tijdschriften die gebruik maken van een leescomité

1/ G. Rolly, L Versichelen, M Coppens
Het belang van de anesthesie voor de ontwikkeling van heelkunde in dagopname.
The role of anesthesiology in the development of ambulatory surgery.
Tijdschrift voor Geneeskunde 2001, 57(12):854-8

2/ Verbraeken H and M Coppens
Postoperatieve zorgen en verwikkelingen bij cataractchirurgie: de rol van de huisarts na de daghospitalisatie.
Tijdschrift voor Geneeskunde 2004, 60(8): 552-8

3/ Pijnbestrijding gedurende de partus
X Schyns-van den Berg, M Coppens
A&I,nr 2, 2010

a4) artikels in tijdschriften niet begrepen in (a1), (a2) en (a3)

1) Laten we 't nuchter houden: pro's en contra 's over voeding prepartum.
Inge Tency, Ellen Roets, Marc Coppens,and Marleen Temmerman
Tijdschrift voor vroedvrouwen 2010; 16(5): 279-86

c) artikels in Proceedings van wetenschappelijke congressen

1. Single dose intravenous tropisetron in the treatment of established postoperative nausea and vomiting: a double-blind, multicentre, dose-comparison study.
M Coppens, F Christiaens, C De Pauw, M Van Boven, V Capouet, B Ickx, L De Ritter, V Grimaudo, F Hulstaert
Acta Anaesthesiol. Belgica 1997, 48 (3):195

2. Do we need inhaled anaesthetics to blunt arousal and haemodynamic responses to intubation after intravenous induction with propofol, remifentanul and rocuronium?
Ndjekembo Shango D, Coppens M, Versichelen L, Mortier E, Struys M
Acta Anaesthesiologica Belgica 2007, 58(1): 75

3. Comparison of the ability of two pharmacokinetic models to maintain a predicted effect-site concentration of propofol compatible with loss of consciousness.
J Van Limmen, H Vereecke, M Coppens, E Mortier, M Struys
Acta Anaesthesiologica Belgica 2008, 59 (3): 211

4. Tramadol IV: influence of dose and intervals on the therapeutic accuracy and side effects when used for postoperative pain relief after ambulatory surgery.
D Devriese, B Vandervennet, L Van Praet, M Coppens, E Mortier, M Struys
Acta Anaesthesiologica Belgica 2009, 60 (2):131

5. Combined spinal epidural for labor using sufentanil epidurally versus intrathecally: influence on fetal heart rate.
N Everaert and M Coppens
European Journal of Anaesthesiology 2012; 29 (suppl 50):172

WETENSCHAPPELIJKE ACTIVITEITEN

(a) studieverblijf in het buitenland van langere duur (minimum 1 maand)

Queen Charlotte and Chelsea Hospital/ Londen
Departement van Dr. J Crowhurst
Fellowship Obstetrische anesthesie: 10/02-30/04/2003

(b) door mezelf georganiseerde internationale of nationale congressen en symposia

Medeorganisator Workshop: 'Abdominale blocks en wondkatheters: technieken van het verleden of strategie voor de toekomst? ' i.s.m. Endogent en BARA
Gent, 18/02/2009

(c) internationale congressen en lezingen waarop een actieve bijdrage

1. Abstract: 'Automatic online computing of delivered inhalation anaesthetics is now possible in clinical practice'.
   L Versichelen, G Rolly, M Struys, K Fonck, M Coppens.
   21st Annual Meeting of the European Academy of Anaesthesiology.
   Boedapest, 26-28/08/1999

2. 'Update Preoperative assessment of the ambulatory surgery': Presentatie sessie A
   International Winter Symposium, Update in Anesthesia, Intensive Care Medicine and Emergency Medicine
   Leuven 10-11/01/2003

3. 'Voordracht:'How to reduce maternal morbidity and mortality'
   Chairman session 1: Anesthesia for the Obstetric patient
   20th International Winter Symposium 'Update in Anesthesia, Intensive Care Medicine, Emergency Medicine'
   UZ Leuven, 6/01/2005

4. 'Effect of neuraxial labour analgesia on the fetus''
   Voordracht sessie 2 op 22nd International Winter Symposium Update in Anesthesia, Intensive Care Medicine, Emergency Medicine and Algology
   Leuven, 12-13/01/2007

5. 'The future of neuromuscular blocking drugs',
   'Neuroaxial analgesia for labor effect on the foetus'
   'How to reduce maternal mortality and morbidity'
   Voordrachten 4th Annual Meeting of Indonesian Society of Obstetric Anesthesia
   16-17/02/2007

6. 'Anesthesia and the beginning of life':
   Chairman Sessie 3 op 23th International Winter Symposium Update in Anesthesia, Intensive Care Medicine, Emergency Medicine and Algology
   Leuven, 11-12/01/2008

(d) idem voor nationale congressen en symposia

1) Abstract: 'Single dose intravenous tropisetron in the treatment of established postoperative nausea and vomiting: a double-blind, multicentre, dose-comparison study.'
M Coppens, F Christiaens, C De Pauw, M Van Boven, V Capouet, B Ickx,
L De Ritter, V Grimaudo, F Hulstaert
Annual Meeting BVAR (Belgische Vereniging voor Anesthesie en Reanimatie)
Louvain-La-Neuve, 30 /11/1996

2) Abstract :'Single dose intravenous tropisetron in the treatment of established postoperative nausea and vomiting: a double-blind, multicentre, dose-comparison study.'
M Coppens, F Hulstaert, C De Pauw, M Van Bever, V Capouet, B Ickx,
L De Ritter, V Grimaudo, F Christiaens.
Residents' Meeting BVAR
Gent, 21/06/1997

3) Workshop: 'Difficult intubation in pregnancy.'
L Versichelen, M Coppens, L Veeckman
Annual Meeting BSAR (Belgian Society of Anesthesia and Resuscitation) :
Women in Anesthesia, Anesthesia for women
Brussel, 30/11/2002

4) Abstract : 'Comparison of the ability of two pharmocokinetic models to maintain a predicted effect-site concentration of propofol compatible with loss of consciousness.'
J Van Limmen, H Vereecke, M Coppens, E Mortier, M Struys
Research Meeting SARB
Sint-Lambrechts Woluwe, 14/06/2008

5) 'Obstetric Hemorrhage: organisational aspects and medical treatment, including activated factor VII.' Voordracht 8th Annual Meeting BARA (Belgian Association for Regional Anesthesia) ' Obstetric Anesthesia' sessie : Maternal mortality and morbidity'
en Chairman sessie : Miscellaneous
Brussel, 04/10/2008

6) Abstract: 'Tramadol IV: influence of dose and intervals on the therapeutic accuracy and side effects when used for postoperative pain relief after ambulatory surgery'.
D Devriese, B Vandervennet, L Van Praet, M Coppens, E Mortier, M Struys
Research meeting SARB
Leuven, 20/06/2009

7) G-ENT Rounds georganiseerd door dienst Neus-, Keel- en Oorheelkunde van het UZGent. Inleiding: Basisprincipes van het pre-operatief onderzoek. *Dr. Marc Coppens. Chirurgisch dagcentrum. UZ Gent*, Locatie: Zaal Oude Infirmerie, Het Pand, Onderbergen 1, 9000 Gent, 26/04/2012

e) lezingen aan universiteiten en wetenschappelijke instellingen

1. 'Sedatie voor locale anesthesie tijdens oftalmologische ingrepen'
Postacademische bijscholing Anesthesie UZG
UZGent, 20/10/1999

2. ‘Organisatie van het Chirurgisch Dagziekenhuis in het Universitair Ziekenhuis Gent.’
   Postgraduaat heelkunde UZG
   UZGent, 8/11/1999

3. ‘Pre-eclampsia and medical complications during pregnancy’.

4. ‘Sedatie in oftalmologische anesthesie’,
   Postacademische bijscholing Anesthesie UZG
   UZGent, december 1999

5. ‘Anesthesie voor ambulante heelkunde’
   Lokgroep Anesthesie Kortrijk
   Kortrijk, oktober 2000
   ‘

6. ‘Complicaties van locoregionale anesthesie’.‘Management of the adult ambulatory patient’
   Postacademische bijscholing Anesthesie UZG
   UZGent, november 2000

7. ‘Behandeling van de anafylactische reactie’
   Voordracht ter gelegenheid van cursus Allergology
   15.09.2001

8. ‘Behandeling van de postoperatieve pijn in oogheelkunde’
   Voordracht voor Academia Ophtalmologica Belgica
   23.11.2001

9. ‘Remifentanil in obstetrische anesthesie’
   Gemeenschappelijke Staffvergadering: Verloskunde – Neonatologie – Genetica - Anesthesie
   January 2002

10. Aspecten van bifasische defibrillatie’
    Postacademische bijscholing Anesthesie UZG
    UZ Gent, 6/03/2002

11. ‘Anafylaxis en behandeling’
    LOK vergadering Neus- Keel- en Oorheelkunde
    Gent, 24/04/2002

12. ‘Postdurale hoofdpijn’
    Perinatale stafvergadering voor verloskunde-neonatologie-genetica-anesthesie
    UZGent, 30/09/2003

13. ‘CSE voor partus: praktische en economische aspecten’
    Voordracht voor LOK 0703
    Gent, 16/12/2003

14. ‘Medische urgenties in de tandartspraktijk’: voordracht
    ‘Basic Life support’: praktische oefeningen
    Vlaamse Wetenschappelijke Vereniging voor Tandheelkunde - Scientific Association of Dentists: Voorjaarssymposium ‘Cardio Pulmonaire Reanimatie’
    Gent, 7/02/2004

15. ‘Welke vasopressor bij sectio?’
    Perinatale stafvergadering verloskunde-neonatologie-genetica-anesthesie
    UZGent, 24/02/2004

16. ‘Anesthesie voor de zwangere bij niet-obstetrische chirurgie.’
    Perinatale stafvergadering verloskunde-neonatologie-genetica-anesthesie
    UZGent, 11/05/2004

17. ‘Analgesie voor partus’
    Postacademische vorming Anesthesie
    UZGent, 29/09/2004

18. Wintersymposium Leuven
    Voordracht.’How to reduce maternal mortality and morbidity ?’
    7/1/2005

19. ‘How to reduce maternal mortality and morbidity?’
    Postacademische vorming Anesthesie
    UZGent, 12/01/2005

20. What mothers want?!’
    Perinatale stafvergadering verloskunde-neonatologie-genetica-anesthesie
    UZGent, 25/01/2005

21. ‘Reanimatie in 2005’
    voordracht voor LOK 0703
    UZGent, 18/06/2005

22. ‘The difficult back: implications for neuraxial anesthesia in the obstetric patient’
    Postacademsiche bijscholing anesthesie
    UZGent, 22/06/2005

23. Maternele temperatuur en de foetus’
    Perinatale stafvergadering verloskunde-neonatologie-genetica-anesthesie
    UZGent, 20/09/2005

24. Voordracht: ‘Reanimatie van de zwangere’
    Praktijkoefeningen: ‘Basic Life Support tijdens de zwangerschap’
    Cursus ‘Praktische vaardigheden in de verloskunde’ van de Vlaamse Vereniging voor Obstetrie en Gynaecologie
    Diegem, 14-15/10/2005

25. ‘Effecten van anesthetica en analgetica op de neonaat.
    Perinatale stafvergadering verloskunde-neonatologie-genetica-anesthesie
    UZGent, 27/12/2005

26. ‘Advanced Life Support, nieuwe richtlijnen’
    Postacademische bijscholing anesthesie
    UZGent, 22/02/2006

27. ‘Obstetrische anesthesie in het UZGent- een update’
    Postacademische bijscholing anesthesie UZG
    UZGent, 22/03/2006

28. ‘Nieuwe richtlijnen in de reanimatie’
    Voordracht voor LOK 1667
    UZGent, 30/03/2006

29. Voordracht:’Respiratoire insufficiëntie tijdens de zwangerschap’
    Jaarlijks congres van de Vlaamse Vereniging van Intensieve Zorgen voor Verpleegkundigen: ‘Binnenste buiten, Intensief bekeken’
    Gent, 24/11/2006

30. Voordracht: ‘Medische urgenties in de tandartspraktijk’
    Praktische oefeningen: ‘ Basic Life Support’
    Vlaamse Wetenschappelijke Vereniging voor Tandheelkunde - Scientific Association of Dentists; Najaarssymposium: ‘Onverwachte medische complicaties tijdens de tandheelkundige behandeling’
    Gent, 25/11/2006

31. ‘Update on general anaesthesia for Caesarean section’
    Voordracht Bara-meeting
    Tienen, 30/11/2006

32. ‘General Anesthesia for Caesarean Section’
    Perinatale stafvergadering verloskunde-neonatologie-genetica-anesthesie
    UZGent, 05/12/2006

33. Congres Gynaecologie De Doelen Rotterdam
    voordracht:’Combined Spinal Epidural voor bevalling’
    Rotterdam 4/2007

34. Voordracht:‘Opvang van de patiënt thuis na dagopname’
    102e Reeks Avondcolloquia voor de Practicus ‘ Het perioperatief gebeuren’
    UZGent, 23/05/2007

35. ‘The future of neuromuscular blockers after the introduction of Sugammadex’
    Postacademische bijscholing Anesthesie
    UZ Gent, 20/06/2007

36. ‘Congenitale hernia diafragmatica’ en ‘Appendectomie bij de zwangere’
    Moderator Journal Club Assistenten - casusbesprekingen
    Postacademische bijscholing Anesthesie
    UZGent, 05/09/2007

37. Voordracht: ‘Reanimatie van de zwangere’
    Praktijkoefeningen: ‘Basic Life Support tijdens de zwangerschap’
    VVOG (Vlaamse Vereniging voor Obstetrie en Gynecologie), cursus Praktische Vaardigheden in de Verloskunde
    Zemst, 23/11/2007

38. ‘Dental Restauration under general anesthesia: the anaesthetist’s view
    Voordracht KUL: Academie voor Kindertandheelkunde
    Leuven, 29/11/2007

39. ‘’Zenuwletsels bij neuraxiale anesthesie’
    Voordracht Perinatale stafvergadering verloskunde-neonatologie-genetica-anesthesie
    UZGent, 11/12/2007

40. ‘LMA-Supreme’
    Voordracht op uitnodiging van The Surgical Company
    Den Haag/ NL, 24/01/08

41. ‘Laryngeal mask supreme in Oftalmologie’
    Postacademische bijscholing Anesthesie
    UZGent, 27/02/2008

42. ‘De moeilijke rug in obstetrische anesthesie’
    Voordracht LOK 0703
    UZGent, 17/06/2008

43. ‘De moeilijke rug in obstetrische anesthesie’
    Postacademische bijscholing Anesthesie UZG
    UZ Gent, 24/09/2008

44. ‘LMA Supreme’ voordracht
    Stafvergadering ZNA Middelheim
    Antwerpen, 26/09/2008

45. ‘Obstetrische bloedingen’ voordracht
    Perinatale stafvergadering verloskunde-neonatologie-genetica-anesthesie
    UZGent, 14/10/2008

46. ‘Medische Urgentie in de tandartspraktijk’ voordracht
    ABC voor de tandartspraktijk (organisator prof. dr. Luc Marks)
    UZ Gent, 28/11/2008

47. ‘Het Chirurgisch Dagziekenhuis in het UZ Gent’
    Postacademische bijscholing Anesthesie
    UZ Gent, 10/12/2008

48. ‘Obstetrische bloedingen: medicamenteuze behandeling’
    Postacademische bijscholing Anesthesie
    UZ Gent, 21/01/2009

49. ‘Topics in de obstetrische Anesthesie’
    Postgraduaat meeting Anesthesiologie
    UZ Brussel, 30/04/2009

50. Congres BARA
    Voordracht: Bloedingen in de verloskundige anesthesie
    3/9/2009

51. ‘10 taboes rond Suprane’
    Postacademische bijscholing Anesthesie
    UZ Gent, 21/10/2009

52. ‘Medische Urgentie in de tandartspraktijk’ voordracht
    ABC voor de tandartspraktijk (organisator prof. dr. Luc Marks)
    UZ Gent, 03/12/2009

53. Wintersymposium Leuven, januari 2010
    Voordracht: “Effects of epidural analgesia on labour outcome

54. Refresher course obstetrische anesthesie BARA en NVA
    Voordracht: Pijn en pijnbestrijding tijdens normale arbeid en verlossing
    19/3/2010

55. 'Neuraxial analgesia and the outcome of labour'
    Postacademische bijscholing Anesthesie
    UZ Gent, 28/04/10

56. 'Nieuw chirurgisch dagcentrum'
    Postacademische bijscholing Anesthesie
    UZ Gent, 15/09/2010'

57. Congres reanimatie in tandheelkunde L Marks
    2/12/2010
    voordracht Medische urgenties in de tandheelkunde

58. Voorstelling van het nieuw Chirurgisch DagCentrum UZGent
    voordracht voor LOK 0703
    Gent, 7/12/2010

59. Openingssymposium Chirurgisch Dagcentrum
    Voordacht: 'Rol van de anesthesist in CDC'
    19/3/2011

60. Congres vroedvrouwen Oostende
    29/3/2011
    Voordracht: Nieuwe tendensen in pijnstilling na sectio

61. Refresher course obstetrische anesthesie NVA en BARA
    8/4/2011
    les:'Anesthesie voor sectio'

62. Cursus lachgassedatie Tandheelkunde: 3/5/2011
    voordracht: Biologische, chemische en fysische aspecten van lachgas
    Voordracht: Medische urgenties in de tandheelkunde

63. Studieclub Tandheelkunde
    voordracht medische urgenties in de tandheelkunde

64. Studieclub Tandheelkunde Kortrijk
    1/9/2011
    voordracht Medische urgenties in de Tandheelkunde

65. Congres Luc Marks Reanimatie in de Tandheelkunde
    1/12/2011
    voordracht: Medische urgenties in de tandheelkunde

66. Cursus Lachgassedatie in de Tandheelkunde
    Voordracht: 'Chemische,biologische en fysische eigenschappen van Lachgas'
    Voordracht:'Medische urgenties in de tandheelkunde en basic life support'
    8/5/2012

67. 'Algemene anesthesie voor sectio'
    voordracht voor LOK 1667
    Gent, 31/01/2012

68. ‘Centraal veneuze catheters: antimicrobiële en technische aspecten ‘
voordracht voor LOK 0703
UZGent, 24/09/2012

69. Symposium georganiseerd door het Allergienetwerk
Voordracht: ‘Perioperatieve anaphylaxie’
25/10/2012

70. ‘De perioperatieve anaphylaxie’
Postacademische bijscholing Anesthesie
UZ Gent, 21/11/2012

71. Congres van de Royal Belgian Society for Ear Nose Throat and Head and Neck surgery’
Voordracht:’Pediatric anesthesia for ENT surgery’
24/11/2012

72. Cursus Vlaamse Vereniging voor Wetenschappelijke Tandheelkunde
Voordracht: Medische urgenties in de tandheelkunde
10/11/2012

73. Cursus L Marks Tandheelkunde
Voordracht: Medische urgenties in de tandheelkunde
6/12/2012

74. Refresher course obstetrische anesthesie. Nederlandse Vereniging voor Anesthesie en BARA
Voordracht:’Beleid na keizersnede’

75. Cursus Lachgassedatie in de Tandheelkunde
Voordracht: ‘Chemische,biologische en fysische eigenschappen van Lachgas’
Voordracht:’Medische urgenties in de tandheelkunde en basic life support’
23/4/2013

(d) promotorschap of dagelijkse leiding van scripties en doctoraatsproefschriften

Co-promotor scriptie Pauline De Bruyne, 2e proef Gen, ‘Kwaliteitscontrole bij ambulante arthroscopie van de knie: invloed van type anesthesie en organisatorische aspecten.’ Academiejaar 2003-2004

Co-promotor Tramadolstudie studenten 2e proef Gen: B Vandervennet, L Van Praet, ‘veiligheid en therapeutische accuraatheid van perorale versus intraveneuze toediening van postoperative pijnstilling met tramadol’. Academiejaar 2007-2008

Co-promotor Tramadolstudie van Heleen Apostel, 2e mast Gen, Academiejaar 2008 -2009

Begeleider van Nele Everaert voor de Z-lijn Masterproef 1 – 1ste master Gen., ‘Incidentie van foetale bradycardie tijdens locoregionale analgesie voor bevalling: sufentanil epiduraal versus sufentanil spinaal.’ Academiejaar 2010 – 2011

Co-promotor ‘Anatomische afwijkingen van de wervelzuil: impact op epidurale anesthesie Van den Daele Daphne, Academiejaar 2011-2012

Dienstverlening

Wetenschappelijke en maatschappelijke dienstverlening, adviesverlening, lidmaatschap wetenschappelijke commissies, editoraat wetenschappelijke tijdschriften, lidmaatschap beroepsorganisaties e.d.

- Vertegenwoordiger Stuurgroep Reanimatie UZGent vanaf 1/8/2007
- Werkgroep Reanimatie UZGent, lesgever ALS voor verpleegkundigen
- Afgevaardigde Anesthesie in de Werkgroep P3 P4, sector Man-Vrouw-Kind 2008
- Lid van BARA Board (Belgian Association for Regional Anesthesia), 8 oktober 2005
- Lid van de BVAR (Belgische Vereniging voor anesthesie en reanimatie)
- Lid van The European Society of Regional Anaesthesia (ESRA)
- Lid van the Obstetric Anaesthetists Association (OAA), UK
- Verslaggever LOK 1667: sinds 2005
- Lid Kernteam Anesthesie
- Lid Kernteam Chirurgisch Dagcentrum
- Reviewer British Journal of Anaesthesia
- Reviewer Acta Anaesthesiologica Belgica
- Lid Werkgroep Pediatrie CDZ
- Lid Multidisciplinaire werkgroep van het project Acute Pijn bij Kinderen
- Lid Commissie Heelkunde
- Lid Werkgroep CDZ

MEDEWERKING AAN STUDIES

- Co-investigator bij de klinische studie:
  "Single dose intravenous tropisetron in the prevention of postoperative nausea and vomiting following gynaecological surgery: a double blind, multicentre, dose-comparison study."
  V Capouet, C De Pauw, B Vernet, D Ivens, V Derijcke, L Versichelen, H Van Aken, B Ickx, L Ritter, F Hulstaert.
  Acknowledgements to G Rolly, M Coppens etc. (BJA 1996; 76: 54-60)

- Co-Investigator in multicentre study: USB 31-20 : "Randomised, double-blind, comparative study to investigate the safety and efficacy of Ultiva versus Fentanyl for patients undergoing coronary arterial bypass grafting."
  A Moerman, M Coppens juni-december 1997.

- Co-investigator klinische studie:
  "Single dose intravenous tropisetron in the treatment of established postoperative nausea and vomiting: a double blind, multicentre, dose-comparison study."
  E. Alon, E. Buchser, E. Herrera, F. Christiaens, C. De Pauw, L. De Ritter,
  F. Hulstaert, V. Grimaudo. (Anesthesia Analgesia 1998 ; 86 :617-23)

- Co-investigator multi-centre, randomised, double blind, double dummy, placebo controlled, parallel group, phase II study to evaluate the safety, efficacy and pharmacokinetics of oral (25 mg) and intravenous (3 mg and 18 mg) formulations of the neurokinin-1 receptor antagonist, GW597599, when administered with intravenous ondansetron hydrochloride for the prevention of post-operative nausea and vomiting and post-discharge nausea and vomiting in female subject with known risk factors for PONV who are undergoing surgical procedures associated with an increased emetogenic risk. Project 2004/370, 2005
  M Struys, M Coppens

- Co-investigator multicentrische, gerandomiseerde, parallelle groep, vergelijkende, actief gecontroleerde, geblindeerde veiligheidsadviseur, fase IIIa, centrale studie, in volwassen patiënten die org 25969 vergelijkt met neostigmine administratie als omkering agens voor een neuromusculaire blok geïnduceerd door toediening van rocuronium of vecuronium bij herverschijning van T2. Number 2005-001135-30, project . 2005/339, december 2005
  M Struys, M Coppens, 12.12.2005