Pharmacometric Models in Anesthesia and Analgesia

MARCUS BJÖRNSSON
Modeling is a valuable tool in drug development, to support decision making, improving study design, and aid in regulatory approval and labeling. This thesis describes the development of pharmacometric models for drugs used in anesthesia and analgesia.

Models describing the effects on anesthetic depth, measured by the bispectral index (BIS), for a commonly used anesthetic, propofol, and for a novel anesthetic, AZD3043, were developed. The propofol model consisted of two effect-site compartments, and could describe the effects of propofol when the rate of infusion is changed during treatment. AZD3043 had a high clearance and a low volume of distribution, leading to a short half-life. The distribution to the effect site was fast, and together with the short plasma half-life leading to a fast onset and offset of effects. It was also shown that BIS after AZD3043 treatment is related to the probability of unconsciousness similar to propofol.

In analgesia studies dropout due to lack of efficacy is common. This dropout is not at random and needs to be taken into consideration in order to avoid bias. A model was developed describing the PK, pain intensity and dropout hazard for placebo, naproxen and a novel analgesic compound, naproxcinod, after removal of a wisdom tooth. The model provides an opportunity to describe the effects of other doses or formulations. Visual predictive checks created by simultaneous simulations of PI and dropout provided a good way of assessing the goodness of fit when there is informative dropout.

The performance of non-linear mixed effects models in the presence of informative dropout, with and without including models that describe such informative dropout was investigated by simulations and re-estimations. When a dropout model was not included there was in general more bias. The bias increased with decreasing number of observations per subject, increasing placebo effect and increasing dropout rate. Bias was relatively unaffected by the number of subjects in the study. The bias had, in general, little effect on simulations of the underlying efficacy score, but a dropout model would still be needed in order to make realistic simulations.

Keywords: Pharmacometrics, Anesthesia, Analgesia, Dropout, NONMEM

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To Life
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


II Björnsson MA, Norberg Å, Kalman S, Simonsson USH. Population model for pharmacokinetics and bispectral index after intravenous infusion of the sedative and anesthetic AZD3043 in healthy volunteers. *Submitted*


IV Björnsson MA, Friberg LE, Simonsson USH. Performance of non-linear mixed effects models in the presence of informative dropout. *Submitted*

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### Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>BIS</td>
<td>Bispectral index</td>
</tr>
<tr>
<td>$B_{\text{max}}$</td>
<td>Maximum binding capacity</td>
</tr>
<tr>
<td>$C_e$</td>
<td>Drug concentration at effect site</td>
</tr>
<tr>
<td>CL</td>
<td>Clearance</td>
</tr>
<tr>
<td>$\text{EC}_{50}$</td>
<td>Concentration giving 50% of maximum effect</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencefalogram</td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>Maximum effect</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and drug administration</td>
</tr>
<tr>
<td>FO</td>
<td>First Order method</td>
</tr>
<tr>
<td>FOCE</td>
<td>First Order Conditional Estimation method</td>
</tr>
<tr>
<td>FOCE-I</td>
<td>First Order Conditional Estimation method with Interaction</td>
</tr>
<tr>
<td>$F_{\text{rel}}$</td>
<td>Relative bioavailability</td>
</tr>
<tr>
<td>$h(t)$</td>
<td>Hazard at time $t$</td>
</tr>
<tr>
<td>$h_e$</td>
<td>Hazard dependent on effect score</td>
</tr>
<tr>
<td>$h_0$</td>
<td>Baseline hazard</td>
</tr>
<tr>
<td>IIV</td>
<td>Inter-individual variability</td>
</tr>
<tr>
<td>iv</td>
<td>Intravenous</td>
</tr>
<tr>
<td>$k_{e0}$</td>
<td>Rate constant for equilibration between plasma and effect site.</td>
</tr>
<tr>
<td>$k_{e12}$</td>
<td>Rate constant for distribution from central to peripheral effect site</td>
</tr>
<tr>
<td>$k_{e21}$</td>
<td>Rate constant for distribution from peripheral to central effect site</td>
</tr>
<tr>
<td>$K_m$</td>
<td>Concentration at half of maximum protein binding</td>
</tr>
<tr>
<td>$k_{pl}$</td>
<td>Rate constant for onset of placebo effect</td>
</tr>
<tr>
<td>MBDD</td>
<td>Model-based drug development</td>
</tr>
<tr>
<td>MOAA/S</td>
<td>Modified Observer’s Assessment of Alertness/Sedation</td>
</tr>
<tr>
<td>MTT</td>
<td>Mean transit time</td>
</tr>
<tr>
<td>NN</td>
<td>Number of transit compartments</td>
</tr>
<tr>
<td>OFV</td>
<td>Objective Function Value</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>PC-VPC</td>
<td>PRED-corrected visual predictive check</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamics</td>
</tr>
<tr>
<td>PI</td>
<td>Pain intensity</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PKPD</td>
<td>Pharmacokinetic/pharmacodynamic</td>
</tr>
<tr>
<td>PL&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum placebo effect</td>
</tr>
<tr>
<td>PRED</td>
<td>Population prediction</td>
</tr>
<tr>
<td>PsN</td>
<td>Perl speaks NONMEM</td>
</tr>
<tr>
<td>Q</td>
<td>Distribution clearance</td>
</tr>
<tr>
<td>RMSE</td>
<td>Root mean square error</td>
</tr>
<tr>
<td>RSE%</td>
<td>Relative standard error in percent</td>
</tr>
<tr>
<td>SSE</td>
<td>Stochastic Simulation and Estimation</td>
</tr>
<tr>
<td>S(t)</td>
<td>Probability of remaining in study at time t</td>
</tr>
<tr>
<td>TCI</td>
<td>Target controlled infusions</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>VPC</td>
<td>Visual Predictive Check</td>
</tr>
<tr>
<td>V</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>V&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>Volume of distribution at steady state</td>
</tr>
<tr>
<td>ε</td>
<td>Difference between observation and individual prediction</td>
</tr>
<tr>
<td>ω&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Variance of η</td>
</tr>
<tr>
<td>σ&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Variance of ε</td>
</tr>
<tr>
<td>θ</td>
<td>Typical value of a parameter</td>
</tr>
<tr>
<td>η</td>
<td>Difference between individual value and typical value of a parameter</td>
</tr>
</tbody>
</table>
Introduction

Drug development is facing challenges with fewer drugs to the market and escalating costs [1,2]. According to an analysis by Forbes, the average cost for developing a new drug is 4 billion US$ (10 February 2012, www.forbes.com). These issues were highlighted by the US Food and Drug Administration (FDA) in a white paper in 2004, where they identified model-based drug development (MBDD) as an important way of improving drug development [3]. MBDD was defined as pharmaco-statistical models of drug efficacy and safety from preclinical and clinical data to improve drug development knowledge management and decision-making. The concept has been adopted and developed by pharmaceutical industry [1,2,4-6] and is also appreciated by other regulatory agencies [7].

Pharmacometrics, which is an important part of MBDD, has become broadly used within drug development, and were shown in a survey among ten large or mid-sized pharmaceutical companies to positively affect internal decision making [8]. It has also been increasingly used, and has had an increased importance, in New Drug Applications to the regulatory authorities to support drug approval, labeling, and trial design decisions [9,10].

Pharmacometrics

Pharmacometrics has been defined as “the science of developing and applying mathematical and statistical methods to characterize, understand, and predict a drug’s pharmacokinetic, pharmacodynamic, and biomarker-outcome behavior” [11]. Important tasks in pharmacometrics are to find the optimal dose or dosing regimen, improve decision making, and decrease time and cost of drug development.

Pharmacometric models are useful tools to aid drug development, therapeutic decisions and regulatory decisions [7,9]. The models can provide a quantitative basis for informed decisions, and they also have the potential for increasing power in clinical studies [12,13]. Pharmacometrics has evolved from pharmacokinetics (PK), to pharmacodynamics (PD), and also involves other aspects of drug treatment, such as disease progression, dropout and placebo response.
Pharmacokinetics

PK describes the processes and rates of absorption of a drug, distribution into tissues and the elimination by metabolism or excretion [14]. The pharmacokinetic properties of a drug can usually be investigated by collecting repeated plasma concentrations of the drug after administration. A model including parameters describing the absorption, distribution and elimination processes is then fitted to the data, and conclusions about the PK can be made.

Pharmacodynamics

While PK has been described as “what the body does to the drug”, PD can be described as “what the drug does to the body” [14]. PD quantifies the relationship between drug concentrations at the site of action and the desired or undesired effects. When PK is linked to PD, the drug effect over time after drug administration can be described. As PD involves the concentrations at the effect site, and PK typically describes concentrations in plasma, there might be a need to find a link between these concentrations. The concentrations at the effect site can often be difficult to measure, and therefore a model describing a hypothetical effect site can be used. The effect compartment model assumes that there is a distribution of drug between plasma and the effect compartment, leading to a delay in effects in relation to the plasma concentrations. This delay is quantified by the rate constant $k_{e0}$. A large $k_{e0}$ means that equilibrium between plasma and effect site is fast, and a small $k_{e0}$ implies that equilibrium is slow. There can also be other reasons for a delayed effect in relation to plasma concentrations, e.g. indirect effects, when it takes time for the measurable effects to appear after the drug has interacted with the target [15].

In order to describe the drug effects over time it is sometimes of importance to describe the progression of the disease, and the effects of placebo. Sometimes it is difficult to separate the disease progression and the placebo effects, especially when there are existing treatments, and it is unethical to study the disease without treating the patient.

Non-linear mixed effects models

Non-linear mixed effects modeling is an important tool in pharmacometrics. It is suitable for biological systems, as biological data are in general best described by non-linear functions, and there is usually a natural variability in biological systems, which can be described by mixed effects models.

Non-linear mixed effects models consist of fixed effects and random effects. The fixed effects describe the structure, or the trend of the data, in the typical individual. The fixed effects parameters are usually denoted $\theta$. The
random effects describe different levels of variability in data, typically variability between subjects as well as residual unexplained variability, for example measurement error. Other levels of variability can also be estimated, for example variability between different occasions within a subject [16].

The difference between an individual value for a parameter and the population mean of that parameter is usually denoted \( \eta \). The variability in the parameter can have any distribution but in parametric models they are typically normally distributed or any transformation of a normal distribution. For a parameter with a normal distribution, the value of parameter \( P \) in individual \( i \), \( P_i \), can be described as

\[
P_i = \theta^P + \eta_i^P
\]

where \( \eta_i^P \) is normally distributed with mean zero. The variance of \( \eta_i^P \), \( \omega^2 \), is estimated in the non-linear mixed effects model. As many physiological parameters tend to be log-normally distributed the parameter can be described as

\[
P_i = \theta^P \times \exp (\eta_i^P)
\]

The residual unexplained variability, usually denoted \( \varepsilon \), describes the difference between an observation and the individual model predicted value at that particular time-point. The \( j \)th observation in individual \( i \), \( y_{ij} \), can be described as

\[
y_{ij} = f(x_{ij}, P_{ij}) + \varepsilon_{ij}
\]

where \( f(x_{ij}, P_{ij}) \) is the individual prediction described by a function of all parameters and the independent variables \( x_{ij} \), which typically are time and dose. \( \varepsilon \) is normally distributed with mean zero, and the variance \( \sigma^2 \), which is estimated in the model. Often measurement errors are proportional to the value of the observed variable, for example a plasma concentration. The residual unexplained variability can be parameterized in different ways, so that for example the magnitude of the residual variability is proportional to the prediction. Combinations of proportional and additive residual errors are also possible [17].

Covariates, such as demographics, genetics, or organ function can be added to the model in order to explain the reasons for variability. For example, a drug that is eliminated through the kidneys is likely to be eliminated slower in patients with poor renal function than in patients with normal renal function. The magnitude of the covariate effects on the model parameters can be estimated in the non-linear mixed effects model. The covariate relationships can be used to individualize the dosing regimen, so that a patient that is likely to have a fast elimination, based on its set of covariates, can receive a
higher dose or a shorter interval between doses in order to reach the therapeutic concentrations of the drug.

As all data from all individuals are analyzed simultaneously, both sparse and rich data, as well as data from unbalanced study designs, can be used [18], which is an advantage when sampling is difficult, e.g. in small children, or not possible to do at the same times in all subjects.

The parameter estimates of a model are found by iteratively searching for the most likely parameter estimates, given the data. This is done by minimizing the objective function (OFV), which represents minus twice the log-likelihood of the data. For hierarchical models, where the more complex model can be collapsed into the simpler one, the difference in OFV is approximately chi-square distributed, which means that a difference of 3.84 in OFV corresponds to a p-value of 0.05 when there is one more parameter in the more complex model. There are several different estimation methods that can be used to minimize the OFV. The first-order (FO) and first-order conditional (FOCE) methods use a first-order Taylor-series expansion at $\eta=0$ or the conditional value of $\eta$ [19,20]. The FOCE method can also be applied with interaction between $\eta$ and $\varepsilon$ (FOCE-I). The Laplacian method uses a second-order Taylor-series expansion [20,21], and needs to be used for modeling non-continuous data, such as categorical or time-to-event data.

**Anesthesia**

Anesthesia is the blocking of sensations, including pain. In local or regional anesthesia a specific part of the body, e.g. the tooth while at the dentist, is deprived of its sensations, while in general anesthesia all sensations in the whole body are blocked and the patient becomes unconscious. General anesthesia can be obtained using inhaled anesthetic gasses or by intravenous (iv) administration of anesthetic agents.

In general anesthesia practice, it is desirable to reach anesthesia quickly, to easily adjust the dose to keep the patient at an appropriate depth of anesthesia, and for the patient to quickly become conscious and recover from the anesthesia after the procedure [22]. In contrast to many other therapeutic areas, where patients are chronically dosed and it may take days or weeks to reach appropriate effects, anesthesia deals with very fast onset and offset of effect, within minutes, and short durations where concentrations and effects are not at steady state.

PK and PD models are widely used in iv anesthesia in order to optimize dosing. Dosing regimens are often based on covariates such as body weight, age, and disease status. To achieve a rapid onset and smooth anesthesia varying infusion rates are often administered, e.g. starting with a short high-rate infusion followed by a slower maintenance infusion. The infusion rate is then further adjusted and titrated to the desired effects. This can also be done
by using target controlled infusions (TCI). In TCI systems a PKPD model, including covariate effects, is driving the infusion pump, and the infusion rate is automatically adjusted in order to achieve and maintain the target effect site concentrations of the drug. If proper effects are not achieved a new target effect site concentration can be entered and the infusion rates are automatically altered to rapidly reach the new target concentration. Commercial TCI systems are available in most parts of the world [23], and algorithms are available for several drugs, e.g. propofol, fentanyl, remifentanil, alfentanil, sufentanil, midazolam and ketamine [24-30].

In order to give dosing recommendations, not only on the starting dose but also on how to titrate to the desired effects, it is important to be able to describe the effects after different infusion rates so that the PKPD model is as accurate as possible.

To describe the delay between plasma concentration and effect of iv anesthetics an effect-compartment model is commonly used. For propofol, different estimates of $k_{e0}$ have been reported, depending on the rate and duration of administration. A higher $k_{e0}$ has been observed for bolus doses and high rate, short infusions compared to longer, slow rate infusions [31]. Therefore, a single effect compartment model is not suitable for modeling or simulations when the rate of infusion changes during the treatment.

BIS

Bispectral index (BIS) is a dynamic measure of anesthetic depth derived from the electroencephalogram (EEG) [32]. The EEG signals are transformed into a scale ranging from 0 (isoelectric EEG) to 100 (fully awake). At BIS below 60 the probability of consciousness is very low. BIS is dependent on the anesthetic agent, and has been shown to reflect the depth of anesthesia well for some anesthetics, e.g. propofol, midazolam and isoflurane [33], but cannot accurately capture the depth of anesthesia for others, e.g. ketamine and nitrous oxide [34, 35]. BIS is used in anesthesia practice to monitor the anesthetic depth in real time, but can also be used to document the effects of new anesthetics in drug development, and be used in pharmacokinetic-pharmacodynamic models to optimize dosing regimens.

Analgesia

While anesthesia refers to the blocking of all sensations, analgesia is the blocking of the sensation of pain. Pain is a condition that affects most people, up to 70% of the population in western countries use analgesics regularly [36]. Pain is also the most common reason for consulting a physician [36]. There are several different types of pain, e.g. nociceptive pain, in which peripheral specialized sensory nerves, nociceptors, are activated, and neuro-
pathic pain, in which the nerve fibers are damaged or dysfunctional, sending signals although there is no stimulus that normally should be painful. There are many existing treatments, especially for nociceptive pain, but due to variability in the efficacy between patients, and adverse effect, there is still an unmet medical need for better analgesics.

As pain is a personal and subjective experience [37], the measurement of pain need to be done by the patients themselves. One of the more sensitive methods to measure pain is the Visual Analogue Scale (VAS) [38]. On the VAS, the patients rate their pain by marking a line between “No pain” and “Worst pain imaginable”, or similar wordings. The investigator could then measure how many millimeters from the “No pain” side the patient put their mark.

**Dental pain model**

Surgical removal of an impacted wisdom tooth is a painful procedure. The pain is well described and characterized, short-lasting, and responds well to nociceptive pain treatment, such as non-steroidal anti-inflammatory drugs and opioids [39]. This makes it a good model for studying novel drugs targeted for the treatment of nociceptive pain.

The impacted wisdom tooth is removed under local anesthesia, using standard surgical procedures. Patients that experience pain when the effect of the local anesthetic vanishes are randomized to study drug, comparator or placebo. The effect on the pain intensity could then be studied over time using a pain scale, such as the VAS.

For ethical reasons, patients that require additional pain relief during the study are given an active analgesic. Once this rescue medication is given no further measurements of pain intensity are performed, as these measurements would not only reflect the effects of study drug, but also the effects of the rescue medication. In order to allow for the study drug to be absorbed and start giving an effect, the patients are sometimes asked to refrain from rescue medication during the first hour or two, but they are still allowed to take rescue medication if they cannot wait.

**Dropout**

In longitudinal studies data are collected repeatedly over time in each subject. However, some patients might not be able to participate for the whole planned study duration. The patients are then dropping out of the study, and no further assessments of the study variables are being performed in that patient. Dropout can be due to various reasons, including adverse events or lack of efficacy of the study drug, but also due to other reasons not related to
the disease or drug under investigation [40]. When dropout occurs in a study the interpretation of the results can become more difficult.

Dropout has been classified as *missing completely at random*, when the dropout does not depend on observed or unobserved values of the dependent variable, *missing at random* when the dropout is dependent on the observed, but not the unobserved, value of the dependent variable, and *missing not at random* when the dropout is dependent on the unobserved value of the dependent variable [41-44]. Dropout can also be classified as ignorable, when the interpretation of the results is valid even if the dropout is ignored [42]. This is the case when the dropout is completely at random, and not dependent on the studied disease, treatment or procedures. When the interpretation of the results is affected by the dropout it is not ignorable, and needs to be taken into account to make valid inferences of the drug effects [42]. Dropout missing not at random is non-ignorable and can also be referred to as informative dropout [45]. This could be the case for example when dropout is dependent on the effects of the study drug. The fact that a patient has dropped out of the study could provide information about the treatment effect in that patient. Such informative dropout could be important to handle in non-linear mixed effects modeling in order to avoid bias in the parameter estimates [46-48]. In the dental pain model, the patients with the most pain tend to request rescue medication, i.e. the probability of dropping out is dependent on the pain intensity. At the same time the observed pain intensity is dependent on the dropout. At the end of the study period the differences in pain intensity is small between placebo and active treatment, as the patients that remain in the study are those who are no longer in pain, regardless of treatment.

When analyzing dropout the time of dropout is recorded for the subjects that drop out during the study. Other subjects may still be remaining in the study at the time of terminating the study procedures. This is called censoring. When it is known that a subject still has not dropped out at a certain time, but it is unknown what happens after that time it is called right censoring. Censored observations can be modeled using a survival function, in which the probability of still remaining in the study (not having dropped out) at time t, S(t), can be described as

\[
S(t) = \exp \left( - \int_0^t h(t) \, dt \right)
\]

where h(t) is a function describing the hazard over time. For subjects that drop out, the probability density of dropping out at time t, f(t) is modeled as

\[
f(t) = S(t) \times h(t)
\]
If the exact time of dropout is not known, but rather that a subject has dropped out any time between two visits, it is called interval censoring, and the probability of dropping out during that interval could be modeled as the difference between the probability of remaining in the study at the beginning of the interval and the probability of remaining in the study at the end of the interval.
Aims

The aim of this thesis was to improve the understanding of the time course of drug effect in anesthesia and analgesia by using non-linear mixed effects modeling.

The specific aims were to:

- Investigate the influence of target site distribution on the onset and offset of propofol anesthesia
- Describe the PK and PD for a novel investigational anesthetic compound, AZD3043
- Assess the validity of BIS as a marker for anesthesia for AZD3043
- Describe the analgesic effects of naproxcinod and naproxen in a study with a large proportion of informative dropout
- Investigate the need of handling informative dropout in non-linear mixed effects modeling, including factors affecting bias and imprecision in parameter estimates
Material and Methods

Study drugs
This thesis describes the PK and PD of propofol (Paper I), AZD3043 (Paper II), naproxcinod and naproxen (Paper III). Propofol is a widely used anesthetic, while AZD3043 is a novel compound under development for induction and maintenance of anesthesia [49]. Similarly, naproxen is a widely used non-steroidal anti-inflammatory analgesic, while naproxcinod [50-52] is under the development for analgesia. Naproxcinod is rapidly metabolized to naproxen in the intestines and in blood [53]. No real drugs were described in the simulation study in Paper IV.

Data
The data used in Papers I-III were obtained from clinical studies. All studies were performed in accordance with the Declaration of Helsinki and Good Clinical Practice. The studies were approved by an Independent Ethics Committee or Research Review Committee, and written informed consent was obtained from all subjects. In Paper IV only simulated data were used.

Propofol study
Data on arterial plasma propofol concentrations and BIS were obtained in a randomized cross-over study in 21 healthy male and female volunteers. The subjects received a 1-minute iv infusion of 2 mg/kg of propofol at one occasion, and a 1-minute iv infusion of 2 mg/kg of propofol immediately followed by a 29-minute iv infusion of 12 mg/kg/hour of propofol at another occasion. Arterial plasma concentrations of propofol were measured repeatedly up to 4 hours after the infusion. BIS was measured until the subjects were regarded as awake after the anesthesia. As arterial concentrations are more closely related to the concentrations at the effect site, arterial rather than venous concentrations were studied [54-55].
AZD3043 studies

Data on arterial AZD3043 plasma concentrations and BIS were obtained in two parallel group dose escalation studies. In the first study AZD3043 was administered iv in 9 panels of 6 healthy male volunteers (53 in total due to one missing subject in one of the panels). Each volunteer received one 30-minute infusion of AZD3043, with the infusion rate ranging from 1 mg/kg/h in the first panel to 81 mg/kg/h in the last panel. The second study was divided into two parts. In part A, a total of 40 healthy male or female volunteers (5 panels of 8 subjects) received a 1-minute infusion of AZD3043, with the dose ranging from 1 to 6 mg/kg (60 to 360 mg/kg/h). In part B a total of 32 healthy male or female volunteers (4 panels of 8 subjects) received a 1-minute infusion (dose ranging from 0.8 to 4 mg/kg, or 48 to 240 mg/kg/h) immediately followed by a 30-minute infusion of AZD3043 (10 to 40 mg/kg/h). Arterial plasma concentrations of AZD3043 were measured repeatedly up to 2 h after the infusion. BIS was recorded until the subjects were regarded as awake according to clinical signs. Consciousness was assessed using the Modified Observer’s Assessment of Alertness/Sedation score (MOAA/S) [56], where a MOAA/S of 2 or less was classified as unconscious.

Naproxcinod, naproxen and placebo study

Data on naproxen plasma concentrations, pain intensity and time of dropout were obtained in a randomized, double-blind, parallel-group study in 242 patients undergoing surgical removal of a wisdom tooth [52]. Patients who experienced pain after the effects of local anesthetics had vanished were randomized to one of four different doses of naproxcinod (375, 750, 1500 or 2250 mg), naproxen (500 mg) or placebo. Total and unbound plasma concentrations of naproxen were obtained repeatedly in a subset of patients (n=90) up to 8 hours after administration of study drug, and pain intensity was measured in all patients on a visual analogue scale for 8 hours, or until request of rescue medication. Patients were asked not to take rescue medication during the first 1.5 h after administration of study drug, but they were still allowed to take it if they could not wait. The time of request of rescue medication was recorded, and was used for the dropout analysis.

Simulation study

Paper IV is based on simulations from a model adapted from the one presented in Paper III. The model simultaneously simulated an efficacy variable, and dropout that was dependent on the efficacy variable. A one-compartment PK model with a constant-rate infusion was used to simulate individual concentration-time profiles, which were used as an input to the
PD-model. The PD-model consisted of an exponential placebo effect model, and an inhibitory $E_{\text{max}}$-model describing the concentration-effect relationship. The dropout hazard was related to the efficacy variable, where the hazard increased exponentially with increasing efficacy score. Parameter values used in the simulations are shown in Table 1, and the plasma concentrations, effect variable and probability of dropout for a typical individual for the Base Model are shown in Figure 1.

Table 1. Parameter values used in the simulation of the Base Scenario (Scenario 1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical value</th>
<th>Inter individual variability (%)$^a$</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>50</td>
<td>30</td>
<td>Efficacy variable at baseline</td>
</tr>
<tr>
<td>$P_{\text{max}}$ (%)</td>
<td>20</td>
<td>120</td>
<td>Maximum placebo effect</td>
</tr>
<tr>
<td>$k_{\text{pl}}$ (h$^{-1}$)</td>
<td>0.25</td>
<td>44</td>
<td>Rate constant for onset of placebo effect</td>
</tr>
<tr>
<td>$E_{50}$ (units/L)</td>
<td>20</td>
<td>122</td>
<td>Concentration leading to 50 % of maximum efficacy</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>10</td>
<td>30</td>
<td>Clearance</td>
</tr>
<tr>
<td>V (L)</td>
<td>10</td>
<td>30</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>$h_0$ (h$^{-1}$)</td>
<td>0.01</td>
<td>-</td>
<td>Baseline hazard</td>
</tr>
<tr>
<td>$h_2$</td>
<td>0.05</td>
<td>-</td>
<td>Parameter for relationship between hazard and effect variable</td>
</tr>
<tr>
<td>$\sigma$ (effect units)</td>
<td>7.5</td>
<td>-</td>
<td>Additive residual variability</td>
</tr>
</tbody>
</table>

$^a$ Inter individual variability expressed as coefficient of variation.

Figure 1. Drug concentrations, effect variable and probability of remaining in the study for a typical individual based on the true model parameters from the Base Model. Solid line – placebo, dashed line – low dose, circles – medium dose, dotted line – high dose.

Different scenarios with varying system-specific properties (dropout rate, magnitude of placebo effect), and design specific properties (number of patients, number of observations), were simulated (Table 2). In the simulations the exact time of dropout was recorded and used in the estimations. For the scenarios where number of observations was varied, simulations were also performed without recording the exact time of dropout, but rather recording...
that a subject had dropped out any time between two observations of the efficacy variable (interval censoring).

The simulations, one thousand simulations per scenario, were performed using the stochastic simulation and estimation (SSE) functionality in the software PsN.

Table 2. Parameters and design variables varied in the different simulation scenarios. For each scenario, the grey cells gives the value of the variable that was changed compared to the Base Scenario (Scenario 1).

<table>
<thead>
<tr>
<th>Scenario</th>
<th>N per group</th>
<th>PL_{max}^a (%)</th>
<th>Observation interval (h)</th>
<th>Observations per patient</th>
<th>h_e^b</th>
<th>Dropout^c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Base)</td>
<td>45</td>
<td>20</td>
<td>1</td>
<td>9</td>
<td>0.05</td>
<td>22-52</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>20</td>
<td>1</td>
<td>9</td>
<td>0.05</td>
<td>22-52</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>20</td>
<td>1</td>
<td>9</td>
<td>0.05</td>
<td>22-52</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>20</td>
<td>1</td>
<td>9</td>
<td>0.05</td>
<td>22-52</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>10</td>
<td>1</td>
<td>9</td>
<td>0.05</td>
<td>23-57</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>40</td>
<td>1</td>
<td>9</td>
<td>0.05</td>
<td>20-43</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>80</td>
<td>1</td>
<td>9</td>
<td>0.05</td>
<td>16-30</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>20</td>
<td>0.5</td>
<td>17</td>
<td>0.05</td>
<td>22-52</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>20</td>
<td>2</td>
<td>5</td>
<td>0.05</td>
<td>22-52</td>
</tr>
<tr>
<td>10</td>
<td>45</td>
<td>20</td>
<td>4</td>
<td>3</td>
<td>0.05</td>
<td>22-52</td>
</tr>
<tr>
<td>11</td>
<td>45</td>
<td>20</td>
<td>1</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
<td>20</td>
<td>1</td>
<td>9</td>
<td>0.025</td>
<td>13-22</td>
</tr>
<tr>
<td>13</td>
<td>45</td>
<td>20</td>
<td>1</td>
<td>9</td>
<td>0.06</td>
<td>27-68</td>
</tr>
<tr>
<td>14</td>
<td>45</td>
<td>20</td>
<td>1</td>
<td>9</td>
<td>0.07</td>
<td>34-83</td>
</tr>
</tbody>
</table>

^a Maximum placebo effect  
^b Parameter relating the hazard to the effect variable. A high value represents a larger probability of dropout.  
^c The range of probability of dropout for a typical individual between treatment groups, where the lower number represents the highest dose and the highest number represents placebo.

Software

All non-linear mixed effects analyses performed in this thesis were performed using NONMEM (versions VI and 7) [20]. The PsN toolkit [57] was used together with NONMEM for automation of estimations and simulations. The Xpose [58] package in R (http://www.r-project.org) was used for goodness of fit assessments and production of graphs.

Model development

For each study the model building was done sequentially, starting with a model for the PK. After finalizing the PK model, the PD model was developed. In Paper I the individual empirical Bayes estimates of the parameters were used as an input to the PD-model, while in Papers II and III PK and PD data were analyzed simultaneously, with the PK parameter estimates fixed.
based on the final PK model [59]. In Paper III a dropout model was then added, and the PD and dropout models were refined simultaneously.

Propofol

The pharmacokinetics of propofol has been described in various ways in numerous papers [60-64], and the starting point for the PK modeling was a commonly used three-compartment model. In order to get an as good as possible input to the PD model, further components were added, such as a third disposition compartment, a lag-time to describe the time for the drug to transfer from the site of administration to the site of sampling, and time-dependency in the clearance parameters. Log-normally distributed inter individual variability was added to the parameters were it was supported by the data. Additive, proportional and combined additive and proportional residual unexplained variability models were explored, as well as a different residual error during the first minutes after start of infusion as the variability was larger during that time. Body weight was investigated as a covariate on clearance and volumes of distribution.

Individual empirical Bayes estimates of the PK parameters were used as an input to the PD-model. As there are several publications modeling the effects of propofol on BIS as an effect compartment model combined with a sigmoid $E_{max}$ model [31,62,64-68] this was used as the starting point for the modeling. In order to describe the different onset and offset rates after different infusion rates, a second effect-site compartment was added, allowing for distribution within the brain. The decrease in BIS was linked to the central effect site compartment concentrations through a sigmoid $E_{max}$ model. $k_{e0}$ as well as the rate constants to and from the peripheral effect site compartment were estimated.

AZD3043

To describe the arterial PK of AZD3043 two- and three-compartment models were applied. A lag-time was used to describe the time from administration to the time of appearance of drug at the sampling site. Log-normally distributed inter individual variability was added to the parameters were it was supported by the data. Additive, proportional and combined additive and proportional residual unexplained variability models were explored. Body weight was included as a covariate on clearance and volume parameters in an allometric fashion [69]. Dose-dependency in the parameters was investigated, as well as the effects of sex, age and esterase activity on CL.

An effect-compartment model with a sigmoid $E_{max}$ model was used as the starting point for the PD-model. A two-compartment effect-site model was also investigated.
To assess the usefulness of BIS as a measure of depth of anesthesia after AZD3043 administration logistic regression was performed. The logit of the probability of unconsciousness was modeled as a slope-intercept model. Inter-individual variability was investigated in both slope and intercept. The values of BIS where there was a 50% and a 95% probability of unconsciousness were derived by simulating from the model.

**Naproxcinod and naproxen**

Naproxcinod is rapidly metabolized to naproxen in the intestines and only a small fraction of the dose is present unchanged in plasma [53]. Naproxen is also believed to be responsible for the effects after naproxcinod administration, and therefore only naproxen concentrations were modeled. As naproxen is highly bound to albumin [70] and this binding is saturable at high concentrations, both total and unbound concentrations of naproxen were modeled. One- and two-compartment disposition models were evaluated for the PK, as well as several different absorption models, including first-order, zero-order, sequential zero- and first order absorption, with and without lag-time, and a transit compartment model [71]. Unbound oral clearance and volume of distribution of naproxen were assumed to be the same regardless of treatment, while the absorption properties were different for naproxcinod and naproxen. A binding model was used to describe the relationship between total and unbound naproxen concentrations. Log-normally distributed inter individual variability was added to the parameters were it was supported by the data, and additive, proportional and combined additive and proportional residual unexplained variability models were explored. The predicted unbound concentrations were used as an input to the PD model.

PK and PD data were then analyzed simultaneously while the PK parameters were fixed in the subsequent PD analysis. When analyzing the pain intensity, a preliminary model for the PI after placebo administration was first established. Exponential, inverse Bateman and Weibull functions were explored for the placebo model. Thereafter the effects of naproxen were added to the model, as an inhibitory sigmoid $E_{\text{max}}$ model, as well as a model for dropout. Exponential, Weibull and Gompertz models were explored for the dropout hazard, and linear and exponential models for the influence of pain intensity and baseline pain intensity on the hazard were investigated. All parts of the PD and dropout models were then refined simultaneously.

**Model selection**

The selection of a more complex model compared with a simpler model was based on goodness of fit plots, precision in the parameter estimates, scientific plausibility and statistically using the OFV.
Visual predictive checks (VPC) were used to assess the simulation properties of the developed models. A VPC is produced by simulating a large number of studies using the model. The means and different percentiles of the simulated data at each time point are then compared with the corresponding means and percentiles of the observed data. In cases where dosing is individualized, or where there is a large range of doses with few individuals per dose, PRED-corrected VPC (PC-VPC) were used [72]. In a PC-VPC the data are normalized with the population prediction for each individual before calculating the means and percentiles. All VPC were performed using PsN [57] and Xpose [58].

Simulations and re-estimations

In paper IV, the simulated data from each scenario was analyzed using two different models; 1) the same model as used for the simulations, e.g. including a model describing the dropout, 2) the same model as used for the simulations, but ignoring the part of the model describing the dropout. In the cases where the dropout was ignored, both the FOCE-I and Laplace estimation methods were used. In addition, for the scenarios where the exact time of dropout was not simulated, interval censoring was used in the estimation of the dropout model.

From the results of the estimations, bias and imprecision in the parameter estimates were calculated. Bias was calculated as

\[
\text{Bias} = 100\% \times \frac{\text{mean}(\text{Est} - \text{True})}{\text{True}}
\]

where Est and True are the estimated and true values of the parameter. Imprecision is described as the root mean square error, calculated as

\[
\text{RMSE} = 100\% \times \sqrt{\frac{\text{mean}((\text{Est} - \text{True})^2)}{\text{True}^2}}
\]

Bias and imprecision were then compared for the different simulated scenarios and estimation models.

To illustrate the need of modeling informative dropout in order to make realistic simulations, VPCs were created. An arbitrarily simulated dataset, simulated from the Base Scenario, served as the “observed” data. In addition, a dataset simulated with 40% dropout completely at random was simulated to serve as “observations”. Simulations were then performed with or without including a dropout model, and were compared with the “observations”.

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Results

Anesthesia

Propofol PKPD model
When the commonly used 3-compartment PK model was fitted to the arterial concentrations of propofol, it was shown that it could not adequately be fitted to the two dosing regimens simultaneously. Even if analyzed by itself, the dosing regimen that started with a high-rate 1-minute infusion and was followed by a slower rate 29-minute infusion could not be adequately described with the 3-compartment model. In order to get an as good as possible input to the PD-model, a third disposition compartment, a lag-time between the site of administration and the site of sampling, and a time-dependency in CL, were added to the model (Figure 2).

As with the PK, the BIS could not be accurately described for the two different dosing regimens when analyzed together, nor could the primed constant infusion by itself, with the previously used model, the effect-site model. This was true both when using the 3-compartment model and the more complicated newly developed PK-model as an input to the PD-model. After the 1-minute infusion a higher $k_{e0}$ was estimated than for the other regimen, even though both regimens were studied in the same individuals.

Using a two-compartment effect-site model (Figure 2) the fit of the BIS data significantly improved, allowing for different onset and offset rates for the different treatment regimens. This was true both when the standard 3-compartment model and the new PK model were used as an input to the PD-model (Figure 3). The rate constant for distribution within the effect site, $k_{e12}$ and $k_{e21}$ were 0.114 min$^{-1}$ and 0.0214 min$^{-1}$, implying that the volume of the peripheral part of the effect site was approximately 5 times larger than the central part of the effect compartment. PK and PD parameter estimates are shown in Tables 3 and 4.
Figure 2. Final PK/PD-model for the relation of arterial propofol concentrations and BIS. CL is the clearance from V1, the central compartment, V2, V3 and V4 are volumes of the peripheral compartments, Q2, Q3 and Q4 are distribution clearances between central and peripheral compartments, $t_{\text{lag}}$ is the lag-time for dose into central compartment, $I_{\text{max}}$ is the maximum fractional decrease in elimination and distribution clearances, $t_{50}$ is the time-point for 50% of the maximum fractional decrease in elimination and distribution clearances, $k_{e0}$ is the rate constant for distribution from effect compartment, $E_{\text{max}}$ is the maximum effect, $EC_{50}$ is the effect site concentration ($C_e$) needed to reach 50% of $E_{\text{max}}$, $\gamma$ is the shape factor, $k_{e12}$ and $k_{e21}$ are rate constants for distribution between central and peripheral effect compartments.
Figure 3. Population prediction corrected visual predictive check (PC-VPC) for the standard effect compartment model (left) and the final two-compartment effect site model (right) after the primed constant infusion (top panel) and bolus administration (bottom panel). Open circles represent the population prediction (PRED) corrected observations. The dotted lines represent the median, 2.5th and 97.5th percentile of the PRED-corrected observations. The shaded areas represent the 95% confidence intervals for the PRED-corrected simulated median and 2.5th and 97.5th percentiles.
Table 3. Parameter estimates of the final 4-compartment propofol PK model with time-dependent elimination and distribution.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (RSE%)</th>
<th>IIV (RSE%)</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/min)</td>
<td>1.60 (4.1)</td>
<td>8.7 (39)</td>
<td>Clearance</td>
</tr>
<tr>
<td>V1 (L)</td>
<td>2.88 (9.0)</td>
<td>19 (100)</td>
<td>Volume of central compartment</td>
</tr>
<tr>
<td>Q2 (L/min)</td>
<td>1.29 (16.1)</td>
<td>-</td>
<td>Distribution clearance between compartments 1 and 2</td>
</tr>
<tr>
<td>V2 (L)</td>
<td>4.47 (19.6)</td>
<td>48 (48)</td>
<td>Volume of peripheral compartment</td>
</tr>
<tr>
<td>Q3 (L/min)</td>
<td>0.680 (12.1)</td>
<td>-</td>
<td>Distribution clearance between compartments 1 and 3</td>
</tr>
<tr>
<td>V3 (L)</td>
<td>12.4 (12.6)</td>
<td>23 (50)</td>
<td>Volume of peripheral compartment</td>
</tr>
<tr>
<td>Q4 (L/min)</td>
<td>0.458 (9.7)</td>
<td>-</td>
<td>Distribution clearance between compartments 1 and 4</td>
</tr>
<tr>
<td>V4 (L)</td>
<td>71.2 (10.0)</td>
<td>12 (120)</td>
<td>Volume of peripheral compartment</td>
</tr>
<tr>
<td>t_{lag} (s)</td>
<td>5.23 (32.2)</td>
<td>-</td>
<td>Lag-time for appearance of drug at site of sampling</td>
</tr>
<tr>
<td>I_{max} (%)</td>
<td>75.7 (4.7)</td>
<td>-</td>
<td>Maximum fractional decrease in elimination and distribution clearance</td>
</tr>
<tr>
<td>t_{50bolus} (s)</td>
<td>50.5 (26.3)</td>
<td>78 (35)</td>
<td>Time-point for 50% of the maximum fractional decrease in elimination and distribution clearances for the bolus dose</td>
</tr>
<tr>
<td>t_{50-PCI} (s)</td>
<td>70.2 (34.4)</td>
<td>78 (35)</td>
<td>Time-point for 50% of the maximum fractional decrease in elimination and distribution clearances for the primed constant infusion</td>
</tr>
<tr>
<td>σ (%)</td>
<td>12.9 (3.9)</td>
<td>-</td>
<td>Proportional residual error</td>
</tr>
<tr>
<td>σ_{2min} (%)</td>
<td>21.6 (16.3)</td>
<td>-</td>
<td>Proportional residual error first 2 min</td>
</tr>
<tr>
<td>θ_{WT-CL} (%/kg)</td>
<td>0.726 (22.2)</td>
<td>-</td>
<td>Effect of body weight on CL</td>
</tr>
</tbody>
</table>

RSE% - relative standard error calculated as the ratio between the standard error and the estimate, and multiplied by 100. IIV - inter-individual variability in % of the parameter estimate.

Table 4. Parameter estimates for the final two-compartment effect site BIS model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (RSE%)</th>
<th>IIV (RSE%)</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>k_{e0} (min^{-1})</td>
<td>0.159 (5.96)</td>
<td>15 (38)</td>
<td>Rate constant for distribution from effect compartment</td>
</tr>
<tr>
<td>Baseline BIS</td>
<td>92.5 (0.75)</td>
<td>3.5 (35)</td>
<td>Maximum decrease in BIS from baseline</td>
</tr>
<tr>
<td>E_{max} (%)</td>
<td>90.4 (2.74)</td>
<td>-</td>
<td>Effect site concentration needed to reach 50% of E_{max}</td>
</tr>
<tr>
<td>EC_{50} (ng/mL)</td>
<td>2550 (4.78)</td>
<td>18 (36)</td>
<td>-</td>
</tr>
<tr>
<td>γ</td>
<td>2.93 (4.98)</td>
<td>-</td>
<td>Shape factor</td>
</tr>
<tr>
<td>k_{e12} (min^{-1})</td>
<td>0.114 (13.16)</td>
<td>-</td>
<td>Rate constant for distribution from central to peripheral effect compartment</td>
</tr>
<tr>
<td>k_{e21} (min^{-1})</td>
<td>0.0214 (9.44)</td>
<td>-</td>
<td>Rate constant for distribution from peripheral to central effect compartment</td>
</tr>
<tr>
<td>σ</td>
<td>6.55 (3.51)</td>
<td>-</td>
<td>Additive residual error</td>
</tr>
</tbody>
</table>

RSE% - relative standard error calculated as the ratio between the standard error and the estimate, and multiplied by 100. IIV - inter-individual variability in % of the parameter estimate.
AZD3043 PKPD model

The PK of AZD3043 was described by a 3-compartment disposition model, with a lag-time for the drug to appear at the site of sampling. Clearance was high, 2.14 L/min, which is higher than the expected liver blood flow. This is consistent with AZD3043 being metabolized by esterases, both in plasma and in the liver. Despite this, the esterase activity was not found to influence CL. However, only subjects with a normal esterase activity were included in the study. Sex and age did not have a statistically significant influence on CL. Volume of distribution was low but dose-dependent. At the lowest administered dose, 1 mg/kg/h, $V_{ss}$ (the sum of central and peripheral volumes of distribution) was 12 L, and increased to 35 L at the highest administered dose, 81 mg/kg/h. PK parameters are shown in Table 5, and plasma concentration-time plots for the different dose-groups are shown in Figure 4.

### Table 5. Parameter estimates of the final PK model for arterial concentrations of AZD3043.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (RSE%)</th>
<th>IIV (RSE%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/min)</td>
<td>2.14 (1.5)</td>
<td>13 (15)</td>
<td>Clearance</td>
</tr>
<tr>
<td>V1 (L)</td>
<td>2.52 (10)</td>
<td>73 (27)</td>
<td>Volume of central compartment</td>
</tr>
<tr>
<td>Q2 (L/min)</td>
<td>3.77 (7.5)</td>
<td>-</td>
<td>Distribution clearance between compartments 1 and 2</td>
</tr>
<tr>
<td>V2 (L)</td>
<td>4.68 (7.3)</td>
<td>68 (18)</td>
<td>Volume of peripheral compartment 2</td>
</tr>
<tr>
<td>Q3 (L/min)</td>
<td>0.772 (6.2)</td>
<td>-</td>
<td>Distribution clearance between compartments 1 and 3</td>
</tr>
<tr>
<td>V3 (L)</td>
<td>8.37 (4.6)</td>
<td>22 (25)</td>
<td>Volume of peripheral compartment 3</td>
</tr>
<tr>
<td>$t_{lag}$ (min)</td>
<td>0.412 (0.56)</td>
<td>-</td>
<td>Lag-time for appearance of drug at site of sampling</td>
</tr>
<tr>
<td>$\theta_{Dose-V2}$ (%/mg/kg)</td>
<td>0.00122 (16)</td>
<td>-</td>
<td>Effect of dose on V2</td>
</tr>
<tr>
<td>$\theta_{Dose-V3}$ (%/mg/kg)</td>
<td>0.000212 (17)</td>
<td>-</td>
<td>Effect of dose on V3</td>
</tr>
<tr>
<td>$\sigma_{add}$ (μmol/L)</td>
<td>0.0202 (8.6)</td>
<td>-</td>
<td>Additive residual variability</td>
</tr>
<tr>
<td>$\sigma_{prop}$ (%)</td>
<td>16.9 (5.7)</td>
<td>-</td>
<td>Proportional residual variability</td>
</tr>
</tbody>
</table>

RSE% relative standard error calculated as the ratio between the standard error and the estimate, and multiplied by 100, IIV inter-individual variability in % of the parameter estimate. Parameter estimates are for a typical individual of median weight (77 kg) and at a dose of 6 mg/kg.

The rate constant for effect-site distribution, $k_{e0}$, was high, 0.69 min$^{-1}$, corresponding to a half-life of the distribution of 1 minute. A two-compartment effect-site model, as developed for propofol in Paper I, did not improve the fit, suggesting that distribution within the effect site is limited or rapid. EC$_{50}$ was estimated to 54 μmol/L, with an inter-individual variability of 35%. Plots of BIS over time for the different dose-groups are shown in Figure 5, and final parameter estimates for the BIS model are shown in Table 6.
Figure 4. Individual observed (grey) and predicted typical (black) arterial plasma concentrations of AZD3043 versus time, stratified for different dosing regimens.
The analysis showed that BIS could serve as an indicator of anesthetic depth, as the relationship between BIS and the probability of being unconscious was similar to that for e.g. propofol. The values for BIS where 50% and 95% of the subjects are unconscious were estimated to 65 and 48, respectively. A VPC of the relationship is shown in Figure 6.
Table 6. Parameter estimates of the final BIS model for AZD3043.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (RSE%)</th>
<th>IIV (RSE%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>94.1 (0.31)</td>
<td>3.3 (18)</td>
<td>Baseline BIS</td>
</tr>
<tr>
<td>EC&lt;sub&gt;50&lt;/sub&gt; (µmol/L)</td>
<td>54.3 (6.2)</td>
<td>35 (28)</td>
<td>Concentration needed to reach 50% of E&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td>γ</td>
<td>1.51 (5.7)</td>
<td>-</td>
<td>Shape factor</td>
</tr>
<tr>
<td>k₀&lt;sub&gt;e&lt;/sub&gt; (min⁻¹)</td>
<td>0.689 (9.1)</td>
<td>78 (42)</td>
<td>Rate constant for delay of effect</td>
</tr>
<tr>
<td>σ</td>
<td>5.07 (3.7)</td>
<td>-</td>
<td>Additive residual variability</td>
</tr>
</tbody>
</table>

RSE% relative standard error calculated as the ratio between the standard error and the estimate, and multiplied by 100, IIV inter-individual variability in % of the parameter estimate.

The short half-life, limited distribution, and fast equilibration between plasma and effect-site provided possibilities for a rapid onset and offset of anesthesia. The between-subject variability in EC<sub>50</sub> and in the relationship between BIS and the probability of being unconscious makes individual titration necessary in order to provide and maintain a proper depth of anesthesia.

Figure 6. Visual predictive check of the relationship between BIS and the probability of consciousness (MOAA/S>2) after administration of AZD3043. Circles represent the observed proportion of conscious subjects at each value of BIS, and the shaded area represents the 95% prediction interval based on the simulations. The solid line represents the model simulated probability of consciousness at each value of BIS.
Analgesia

Naproxcinod, naproxen and placebo PKPD model

The pharmacokinetics of naproxen, during the first 8 hours after administration, was best described by a one-compartment model with transit compartment absorption into the central compartment. Mean transit times for the absorption were 1.8 hours after naproxcinod and 0.5 hours after naproxen administration, respectively. The saturable protein binding was modeled using a binding model, with a $K_m$ of 0.55 $\mu$mol/L. Final PK parameter estimates are shown in Table 7.

Table 7. Parameter estimates for the final PK model of total and unbound naproxen.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (RSE%)</th>
<th>IIV (RSE%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$CL_u/F$ (L/h)</td>
<td>515 (12.1)</td>
<td>25 (37)</td>
<td>Oral unbound clearance</td>
</tr>
<tr>
<td>$V_u/F$ (L)</td>
<td>4,290 (13.6)</td>
<td>44 (29)</td>
<td>Oral unbound volume of distribution</td>
</tr>
<tr>
<td>$MTT_{naproxcinod}$ (h)</td>
<td>1.77 (10.8)</td>
<td>58 (24)</td>
<td>Mean transit time for naproxcinod</td>
</tr>
<tr>
<td>$NN_{naproxcinod}$</td>
<td>3.58 (9.9)</td>
<td>58 (26)</td>
<td>Number of transit compartments for naproxcinod</td>
</tr>
<tr>
<td>$MTT_{naproxen}$ (h)</td>
<td>0.500 (23.8)</td>
<td>100 (60)</td>
<td>Mean transit time for naproxen</td>
</tr>
<tr>
<td>$NN_{naproxen}$</td>
<td>4.23 (24.8)</td>
<td>64 (68)</td>
<td>Number of transit compartments for naproxen</td>
</tr>
<tr>
<td>$B_{max}$ (µmol/L)</td>
<td>643 (7.1)</td>
<td>17 (44)</td>
<td>Maximum binding of naproxen to plasma proteins</td>
</tr>
<tr>
<td>$K_m$ (µmol/L)</td>
<td>0.549 (10.2)</td>
<td>-</td>
<td>Naproxen concentration at half maximum binding</td>
</tr>
<tr>
<td>$F_{rel}$ (%)</td>
<td>59.7 (14.6)</td>
<td>-</td>
<td>Relative naproxen bioavailability compared to naproxen dosing</td>
</tr>
<tr>
<td>$\sigma_{T,add}$ (µmol/L)</td>
<td>6.19 (22.3)</td>
<td>-</td>
<td>Additive residual variability for total naproxen concentrations</td>
</tr>
<tr>
<td>$\sigma_{T,prop}$ (%)</td>
<td>8.43 (8.0)</td>
<td>-</td>
<td>Proportional residual variability for total naproxen concentrations</td>
</tr>
<tr>
<td>$\sigma_{U,prop}$ (%)</td>
<td>18.6 (11.0)</td>
<td>-</td>
<td>Proportional residual variability for unbound naproxen concentrations</td>
</tr>
<tr>
<td>Corr. $MTT_{naproxcinod}$-NN_{naproxcinod} (%)</td>
<td>-52 (38)</td>
<td>-</td>
<td>Correlation between $MTT_{naproxcinod}$ and $NN_{naproxcinod}$</td>
</tr>
</tbody>
</table>

RSE% - relative standard error calculated as the ratio between the standard error and the estimate, and multiplied by 100, IIV inter-individual variability in % of the parameter estimate.

The placebo effect, and/or the natural course of the progression of pain, after removal of an impacted wisdom tooth was described using an exponential model, where the pain intensity declined or increased towards a new level with a rate constant of the equilibration of 0.24 $h^{-1}$. On average, the placebo effect on pain intensity was a decrease by 20%, but with a large variability, allowing the pain intensity to decrease to 0 or increase to 100 mm on the VAS.
A sigmoid $E_{\text{max}}$ model described the effect of unbound naproxen concentrations on the pain intensity. EC$_{50}$ was estimated to 0.135 μmol/L.

A Weibull time-to-event model described the time to request of rescue medication. The Weibull model suggests a higher hazard at early times and a lower hazard at later times. Pain intensity was found to have a large impact on the hazard, with the hazard increasing exponentially with increased pain intensity. The pain intensity at baseline was also found to influence the hazard. Subjects entering the study with a high pain intensity had a lower hazard at a given pain intensity than those entering the study with low pain intensity. Parameter estimates for the pain intensity and dropout model are shown in Table 8. Visual predictive checks for the dropout are shown in Figure 7.

Figure 7. Visual predictive check of time to request of rescue medication after administration of naproxcinod 375 mg, 750 mg, 1500 mg and 2250 mg, naproxen 500 mg or placebo, based on the final PK/PD model. Solid line represents the observed Kaplan-Meier curve and the shaded area represents the 90% prediction interval for the simulated Kaplan-Meier curve.
Table 8. Parameter estimates for the final pain intensity and dropout model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (RSE%)</th>
<th>IIV (RSE%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI_{baseline} (mm)</td>
<td>52.7 (13.4)</td>
<td>32 (27)</td>
<td>Baseline pain intensity</td>
</tr>
<tr>
<td>P_{max} (%)</td>
<td>20.2 (12.2)</td>
<td>120 (16)</td>
<td>Maximum placebo response</td>
</tr>
<tr>
<td>k_{pl} (h^{-1})</td>
<td>0.237 (68.8)</td>
<td>43 (39)</td>
<td>Rate constant for placebo effect</td>
</tr>
<tr>
<td>EC_{50} (μmol/L)</td>
<td>0.135 (10.4)</td>
<td>120 (21)</td>
<td>Unbound concentration needed for half maximum effect</td>
</tr>
<tr>
<td>γ</td>
<td>1.61 (12.4)</td>
<td>-</td>
<td>Shape factor</td>
</tr>
<tr>
<td>σ_{PI} (mm)</td>
<td>7.82 (13.3)</td>
<td>-</td>
<td>Residual variability for pain intensity</td>
</tr>
<tr>
<td>λ</td>
<td>0.00999 (15.6)</td>
<td>-</td>
<td>Scale parameter in the Weibull distribution</td>
</tr>
<tr>
<td>α</td>
<td>0.729 (9.9)</td>
<td>-</td>
<td>Shape parameter in the Weibull distribution</td>
</tr>
<tr>
<td>θ_{PI}</td>
<td>0.0782 (9.2)</td>
<td>-</td>
<td>Influence of current PI on the hazard</td>
</tr>
<tr>
<td>θ_{baseline}</td>
<td>-0.00261 (19.2)</td>
<td>-</td>
<td>Influence of baseline PI on the hazard</td>
</tr>
</tbody>
</table>

RSE% relative standard error calculated as the ratio between the standard error and the estimate, and multiplied by 100, IIV inter-individual variability in % of the parameter estimate.

When using the model for simulations, for example for visual predictive checks of the efficacy variable, it was shown to be necessary to include the dropout model in the simulations in order to produce realistic plots (Figure 8). If the simulations are performed without using the dropout model, higher pain intensity would be simulated at the later time points, as those patients with the higher pain intensity are the ones that tend to drop out.

*Figure 8.* Visual predictive check of pain intensity (PI) versus time after administration of naproxcinod 375 mg, 750 mg, 1500 mg and 2250 mg, naproxen 500 mg or placebo, based on the final PK/PD model. The top row is simulated without dropout and the bottom row is simulated with dropout. Open circles represent the observations and the lines represent the median, 2.5th and 97.5th percentile of the observations. The shaded areas represent the 95% confidence intervals for the simulated median and 2.5th and 97.5th percentiles.
Simulations and estimations of dropout

In the Base Scenario, average dropout ranged from 22% in the highest dose group, to 52% in the placebo group. When the simulated data were analyzed with the same model as used for the simulations, i.e. including a model for the dropout, bias in the fixed effects parameters was low, less than 5%. When a dropout model was not included in the analysis, bias was larger, but still less than 8% when the Laplace method was used. When FOCE-I was used, bias increased further in the fixed effects parameters, to more than 20% for EC$_{50}$. The effect of the bias on the underlying efficacy profile was, however, not much affected (Figure 9).

![Figure 9](image)

**Figure 9.** Simulated effect variable for a typical individual given Placebo, Low Dose, Medium Dose and High Dose for a) Scenario 1, b) Scenario 14 (increased dropout rate, on average 57%), and c) Scenario 10 (observations every 4th hour only). Simulations are based on true parameters (thick solid line), parameters estimated with dropout model (dotted line, hidden by thick solid line), parameters estimated without dropout model using Laplace (dashed line) or FOCE-I (thin solid line). A lower value of the effect variable indicates a better effect, and hence a higher dose.

Bias in EC$_{50}$ increased with increasing magnitude of placebo effect, increasing dropout rate, and decreasing number of assessments of the efficacy variable (Figure 10). Bias in EC$_{50}$ was relatively unaffected by number of patients per treatment group, although there was a trend towards higher bias with lower number of subjects per group, especially when the FOCE-I method was used.

When the exact time of dropout was not recorded in the simulations, but rather the information that dropout occurred at some time between two measurements of the efficacy variable (interval censoring), bias was higher than when the exact time of dropout was recorded. This was more obvious the longer time between the observations.
Figure 10. Bias in EC\textsubscript{50} when estimating with a dropout model (white), without a dropout model, using the Laplace method (grey), and without a dropout model, using the FOCE-I method (black), when varying a) observation interval, b) extent of dropout (relation between hazard and effect score, $h_e$), c) maximum placebo response ($\text{PL}_{\text{max}}$), and d) number of patients per group.

The imprecision in the parameters was affected similar to the bias, with higher imprecision with increased placebo effect, higher dropout rate and fewer observations. In contrast to the bias, imprecision was affected by number of subjects, with a higher imprecision with decreased number of subjects (Figure 11).

VPCs showed that in order to make realistic simulations in the presence of informative dropout a model describing the dropout is necessary. The VPCs created when not simulating with a dropout model showed clear differences between the “observed” and simulated medians and percentiles (Figure 12a). This was most apparent for the placebo group, where the patients had the highest effect score, and hence the largest dropout rate. The “observed” median was lower than the simulated median as the patients with
the highest effect score had dropped out in the “observed” data. For the active treatment groups it was apparent that the simulated 97.5\textsuperscript{th} percentile was high, while in the “observed” data most patients with a high effect variable had dropped out. When a dropout model was included in the VPC simulations the resulting VPCs showed a good fit and agreement between “observed” and simulated medians and percentiles (Figure 12b). When the dropout was completely at random, however, a dropout model was not needed in order to produce realistic VPCs (Figure 12c).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure11.png}
\caption{Root mean square errors (RMSE) in EC\textsubscript{50} when including a dropout model (white), without a dropout model, using the Laplace method (grey), and without a dropout model, using the FOCE-I method (black), when varying a) observation interval, b) extent of dropout (relation between hazard and effect score, h\textsubscript{e}), c) maximum placebo response (PL\textsubscript{max}), and d) number of patients per group.}
\end{figure}
Figure 12. Visual Predictive Checks, a) without inclusion of dropout model for data containing informative dropout (Scenario 1), b) with dropout model for data containing informative dropout (Scenario 1) and c) without inclusion of dropout model for data with 40% dropout completely at random. Circles represent “observations” in an arbitrarily simulated dataset. Solid and dashed lines are the median, 2.5th and 97.5th percentiles of the “observations”. Shaded areas represent the 95% confidence interval of the simulated median, 2.5th and 97.5th percentiles.
Discussion

Anesthesia

Pharmacokinetics

In anesthesia, a fast onset of effect is often wanted. In order to induce anesthesia, short-duration, high-rate infusions or bolus doses are often used. This makes it very difficult to capture the PK, partly because it is difficult to collect enough blood samples in a very short time-frame, but also because the traditional PK models are not adequate for describing the pharmacokinetics during the first minutes after a short infusion. Henthorn et al. showed, by frequently sampling arterial concentrations of indocyanine green after a bolus injection in dogs, that there is a delay before the substance reaches the site of sampling [73]. Thereafter the concentrations oscillate during the first one to two minutes before starting to decrease monotonically. The same pattern was later shown in humans [74]. This behavior is not captured by the traditional compartmental models. Recirculatory PK models have been proposed to describe the early oscillating concentrations [75], but they require more frequent sampling than what is possible in a first-time-in-man study, like the studies described in Paper II. In Papers I and II a lag-time was used to describe the delay between site of administration and site of sampling. In the studies used in Papers I and II the drug was not given as a bolus dose, but rather as a constant infusion, even if the duration of some of the infusions were only 1 minute. This may have decreased the fluctuations in concentrations during the first minutes after start of administration. Due to the oscillations, also the timing of sampling is of importance during the first two minutes. There could be a large difference in the measured concentrations if a sample happens to be collected at the peak or the trough of the oscillations. In addition, when the concentrations are changing fast, any error in the recording of sampling time may have a large influence on the model. In Paper I a higher residual unexplained variability was used during the first two minutes to account for the possible model misspecification and potential errors in sampling time.

The effects of propofol on cardiac output and liver blood flow could potentially alter the PK after administration [76,77]. In Paper I it was also not-
ed that with a time-dependency in CL, possibly due to effects on liver blood flow, the model could better describe the PK of propofol.

The purpose of the propofol PK model was to get a good input to the PD model. It was speculated that the differences in $k_{e0}$ seen after different infusion rates of propofol could be due to the use of an inadequate PK model. Therefore additional components were added to the PK model to improve the fit in each patient. However, different $k_{e0}$ were found with the different infusion rates also with the more complex PK model, suggesting that the difference in $k_{e0}$ was not due to an inadequate PK model.

In Paper II the peripheral volumes of distribution after AZD3043 administration were estimated to be dependent on the dose. The larger the dose, the larger was the volume of distribution. As AZD3043 is a lipophilic compound, and was administered as an emulsion, it is possible that the distribution of the lipids in the emulsion could affect the distribution of AZD3043. The higher the dose, the more lipids were infused, and the higher was the volume of distribution. Administration of lipid emulsions is used as a treatment for overdoses or accidental iv administration of local anesthetics, leading to a distribution of the anesthetic to the lipids in the emulsion [78]. It has also been shown that plasma concentrations of bupivacaine decrease and volume of distribution increase after treatment with iv administration of a lipid emulsion [79]. Similar to AZD3043, propofol is also a lipophilic compound administered as an emulsion. However, as only two different dosing regimens of propofol were studied in Paper II, and there were other differences between the two treatments, any possible dose-dependent distribution was not noted for propofol.

Pharmacodynamics

In contrast to the commonly used single effect-compartment model, where a $k_{e0}$ that changes with infusion rate would be needed, a two-compartment effect site model could describe the different rates of onset and offset of measured BIS effects between the two dosing regimens of propofol, with a set of parameters that were independent of rate and duration of administration. The two-compartment effect site model allows for distribution within the effect site, without influencing the plasma PK. The shorter the administration, the shorter the time is for distribution, leading to a fast offset rate of effects. With increasing duration of infusion there is more time for distribution, and the offset of effects on BIS becomes more and more dependent on re-distribution from the peripheral effect-site compartment.

Upton et al. has suggested that distribution occurs within the brain, both in sheep [80] and in man [81]. In their human model the peripheral brain volume was estimated to 2.2 times larger than the central brain volume, whereas our results in Paper II suggest the peripheral compartment to be approximately 5 times larger. In the model developed by Upton et al., how-
ever, it was assumed that the total rather than the central brain concentration was related to the effect, and that the cerebral blood flow changed during treatment, which might have impacted the parameters. Furthermore, it has also been shown that the rate of distribution of drug to the brain was slower than suggested by the \( k_{\text{e}0} \) derived from efficacy data [82-84]. This indicates that distribution to the whole brain is slower than the distribution to the effect site, which supports the rationale of the two-compartment effect site model. The two-compartment effect-site model has subsequently been used successfully in modeling the effects of propofol in morbidly obese patients [85].

The two-compartment effect-site model did not improve the fit of BIS for AZD3043. This suggests that distribution within the brain is limited, or that equilibration within the brain is very fast. This is also in accordance with the low volume of systemic distribution and the high \( k_{\text{e}0} \) that was found for AZD3043. The fast equilibration between plasma and effect-site and the limited distribution within the brain, together with the high clearance and low volume of distribution provides a possibility of a fast offset of effect even after longer infusions. However, the dose-dependent volume of distribution could potentially lead to a slower offset of effects when the duration of the infusion increases.

The fact that the relationship between BIS and the probability of unconsciousness for AZD3043 is similar to that for propofol is not surprising, giving the similar mechanisms of action. It is still of importance to know the relationship if one would use BIS as a marker for efficacy when selecting dosing regimens for future studies.

### Analgesia

#### Pharmacokinetics

The pharmacokinetics of naproxen, after both naproxen and naproxcinod dosing, were described using a one-compartment model with saturable protein binding and transit compartment absorption. The systemic parameters, clearance and volume of distribution, were assumed to be the same regardless of in which form naproxen entered the systemic circulation. The absorption parameters were different, however, after administration of naproxen and naproxcinod. For naproxcinod, the transit compartment parameters describe not only the absorption, but also the metabolism to naproxen. In the study in Paper III, naproxen concentrations were collected for only 8 hours, while the half-life of naproxen is 14 hours [86]. Therefore the PK model might not be suitable for extrapolation to repeated dosing, although the first 8 hours are well described.
Pharmacodynamics

In Paper III, plasma samples for analysis of naproxen concentrations were not collected in all patients. The patients without concentration measurements could still be included in the development of the PD-model. Keeping the concentration data in the PD-dataset and fixing the PK-parameters provide a way of allowing for the most likely PK profile for those individuals, given the PK model and their PD data [59].

The pain scale used in Paper III, the VAS, is bounded between 0 and 100. In this case the model for the typical effect did not allow values below 0, and observations at 100 were very rare. However, with residual variability the model could still simulate values below 0 and above 100, and in order to avoid this, the simulations were truncated at these values. Different transformations of the VAS, such as logit transformation, could be used to avoid truncation, but this makes the scale and the effects difficult to interpret. There are also other pain scales available, for example categorical scales, which have been used in similar studies [87-89]. These scales do not have the same issues with boundaries, and make the dropout modeling easier as there is typically one value for the hazard at each pain score.

Dropout

In Paper IV it was shown that bias in the PD-parameters in general were higher when a dropout model was not included in the analysis, but the bias was still in most cases low and did not have a large influence on the simulations. This was true also in Paper III, where an analysis of pain intensity only, without including a dropout model, gave very similar parameter estimates as in the final model where a dropout model was included. This is probably because the pain intensity data was frequently sampled, the exact time of dropout was collected, and the patients were asked to refrain from rescue medication during the first 90 minutes, which contributed to keep the bias low. In other situations, with larger bias, the development of the PD model and dropout model simultaneously could be needed. Even though bias was small, a dropout model was still necessary to use in order to find a good model for pain intensity, as it was not possible to select a good model based on goodness of fit plots produced without accounting for the dropout.

A larger bias and imprecision was seen with increasing dropout rate, and the more dropout the more important it is to take the dropout into account. This seems obvious, not only because the more dropout there is the more information of the efficacy does the dropout contain, but there is also a decreased number of efficacy measurements with increasing dropout, making the dropout information more and more important in relation to the efficacy data.
With an increasing placebo effect, the number of dropouts due to lack of efficacy will decrease. Despite this, the bias and imprecision increased with increasing placebo effect. This could be due to the fact that the efficacy score used in the studies presented here is bound to be above 0. The larger the placebo effect, the less room is left for drug effect, and the smaller the drug effect is in relation to the placebo effect, the larger the bias and imprecision in \( \text{EC}_{50} \).

When the number of observations per subject was decreased, bias in the parameters increased. As the dropout hazard was dependent on the predicted efficacy score continuously, and not only the observed efficacy score, the dropout carried information on what happens with the efficacy between observations. As the observation interval becomes longer, the more important is the dropout to describe the efficacy score between measurements, and hence the dropout model becomes more important. As the number of measurements decrease, there is less information on the efficacy score, and the imprecision in the parameters increase. If the exact time of dropout is not available, there is less information about the efficacy score between observations, and therefore the bias increase if interval censoring is used.

The bias was relatively unaffected by the number of subjects in the study. By changing the number of subjects the structure of the data is not changed, but only the amount of data. This was reflected in the higher imprecision found when number of subjects was decreased.

Bias in baseline score was low in all scenarios in Paper IV. This could be explained by the fact that baseline scores were collected in all subjects and were not affected by the subsequent dropout.

In the simulation study, the estimation models, both for the efficacy variable and for the dropout in the cases where a dropout model was used, was always the same as the model used for the simulations. If modeling had instead been performed in a stepwise manner, like modeling analyses normally are, the analysis might have ended in a final model with a different structure.
Conclusions

The distribution to peripheral parts of the effect site can explain why different $k_{e0}$ have been observed for different infusion rates of propofol. A two-compartment effect-site model can be used to describe the effects of propofol on BIS after different rates of administration, or when the rate of administration is changed during treatment.

The probability of being unconscious is related to BIS after AZD3043 administration, similar to after propofol administration. AZD3043 has a high clearance, low but dose-dependent distribution, and a fast equilibration with the effect site, providing a rapid onset and offset of anesthesia. Variability makes individual titration of AZD3043 necessary in order to provide an appropriate depth of anesthesia.

In the dental pain model, dropout carries information on the efficacy variable, pain intensity. Both the current pain intensity and the pain intensity at baseline affect the hazard of requesting rescue medication. High pain intensity increases the hazard exponentially, and subjects with a low baseline pain have a higher dropout hazard than patients with a high baseline, at the same level of pain intensity.

Ignoring informative dropout leads to biased parameter estimates. Using the Laplace method may lead to lower bias than if FOCE-I is used. Bias increases with increasing placebo effect, increasing dropout rate, and decreasing number of observations per subject, but is relatively unaffected by number of subjects. Knowing the exact time of dropout leads to lower bias than using interval censoring, especially if the interval between observations is long.

Although bias produced by ignoring informative dropout may be small and have a small influence on the underlying predictions, the dropout is important to consider in order to making realistic simulations, such as visual predictive checks or clinical trial simulations.
Populärvetenskaplig sammanfattning

Det har blivit allt dyrare att ta fram nya läkemedel och antalet nya läkemedel som tas fram per år minskar. Ett sätt att göra utvecklingen av läkemedel mer effektiv är att använda sig av matematiska modeller för att beskriva och förklara resultaten av olika läkemedelsstudier.

Smärta drabbar i stort sett alla människor någon gång och är den vanligaste orsaken till att man besöker sjukvården. Inom smärtlindring, analgesi, vill man ta bort smärtupplevelsen utan att påverka andra känsloupplevelser. Anestesi, det vill säga narkos, innebär att alla patientens känsloupplevelser, inklusive eventuell smärta, blockeras och patienten blir medvetslös.

Denna avhandling beskriver utvecklingen av olika modeller för hur läkemedel för smärtlindring och anestesi tas upp och sprids i kroppen, bryts ner och utsöndras, samt hur detta är relaterat till de effekter läkemedlet ger upp hov till.

En av modellerna beskriver hur ett anestesiläkemedel, propofol, sprider sig i hjärnan. Modellen kan förklara varför det tar olika lång tid för läkemedlets effekt att avta efter olika långa behandlingar. En annan modell beskriver hur ett nytt anestesiläkemedel, AZD3043, sprider sig i kroppen och bryts ner samt hur detta påverkar de effekter man ser av läkemedlet. Modellerna är till stor nytta när man ska bestämma hur man ska dosera läkemedlet för att snabbt få effekt, behålla effekten på rätt nivå, samt öka eller minska effekten efter behov.

Ett vanligt sätt att undersöka effekten hos nya läkemedel mot smärta är att ge dem till patienter som dragit ut en visdomstand. Det går då att studera hur patienternas smärta förändras över tiden efter ingreppet. Om det nya läkemedlet inte ger tillräcklig effekt får patienterna ett befintligt fungerande läkemedel och man kan inte längre studera effekten av enbart det nya läkemedlet. Att de patienter som har mest ont i större utsträckning vill ha ytterligare smärtlindring än de patienter där smärten minskat leder till obalans i de data man samlar in. Detta kan hanteras med hjälp av en modell som beskriver hur sannolikheten att vilja ha ytterligare smärtlindring är relaterat till den smärta patienten har. Modellen användes för att beskriva effekten av två smärtläkemedel, naproxen och naproxcinod. I avhandlingen studeras också hur systematiska fel uppstår om man inte tar hänsyn till sambandet mellan smärta och sannolikheten att vilja ha ytterligare smärtlindring, samt olika faktorer som kan påverka storleken av det systematiska felet.
Acknowledgements

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