Introduction and Outline of the Thesis
Introduction

In the clinical field of anesthesia, the sciences of physiology and pharmacology are almost touchable. With knowledge of the mechanisms involved in the behavior of anesthetic agents in a continuously changing environment, the anesthesiologist provides the best possible conditions for the performance of therapeutic and diagnostic procedures while safeguarding the patient.

The dose-concentration relationship of a drug, known as pharmacokinetics (PK), can be expressed in terms of bioavailability, absorption, distribution, metabolism and elimination. In anesthesia the preferred route of administration of a drug is intravenous, thus bypassing processes involved in the transfer of drug from the intestinal tract into the bloodstream. As a result, the reported pharmacokinetic profiles of anesthetic agents typically include the drug's distribution and elimination half-lives, volumes of distribution, and metabolic and distributional clearances. The importance of these pharmacokinetic parameters varies with the different phases of the anesthetic procedure. For example, during induction of anesthesia the initial distribution is affected by cardiac output and pulmonary uptake, while drug clearance may be less important. During maintenance of anesthesia, especially for prolonged procedures, drug elimination may gain clinical importance with time.

The studies in this thesis focus on the pharmacokinetics and pharmacodynamics (PD, the concentration-effect relationship) of anesthetic agents during induction of anesthesia. Since the pharmacology of the induction of anesthesia is still poorly understood, this translates in an often troubled induction phase. Induction of anesthesia is associated with frequent underdosing causing insufficient analgesia or awareness, but also undesirable overdosing causing hemodynamic and respiratory depression. In general the pharmacology of induction of anesthesia is described using compartmental modeling, despite the knowledge that this methodology describes the dose-concentration relationship at induction inaccurately.

In this thesis we looked for better ways to describe the early phase PK and PD of agents used in anesthesia through recirculatory modeling. As indocyanine green plays an important role in recirculatory modeling, the first chapters deal with the analysis and modeling of ICG in blood. The last chapters of this thesis deal with the recirculatory PK and PD of rocuronium, a muscle relaxant, and propofol, a hypnotic agent.
Outline of the thesis

The studies presented in this thesis were aimed at answering the following questions;

1. Is it possible to adequately measure ICG transcutaneously for determination of hemodynamic parameters?
2. Is it possible to adequately determine the plasma disappearance rate of ICG in a non-invasive manner and what is the range of this parameter in a “normal” population?
3. Is it possible to determine a circulatory model for rocuronium in humans, based on intravascular and diffusion kinetics, using ICG as a marker?
4. Can a recirculatory model based on ICG be developed for propofol in humans and what can be said about the role of the lung in the disposition and elimination of propofol?
5. How does the implementation of a recirculatory PK model for propofol reflect on the $k_{e0}$ of propofol and BIS in the early phase after bolus administration, using PK-PD modeling?

In chapter 2 a review is provided on pharmacokinetic modeling of anesthetic drugs. Besides a general overview of the various methods of pharmacokinetic modeling, the recirculatory model which has been described by Kuipers et al. for the muscle relaxant rocuronium, using ICG as intravascular marker, is discussed in detail.

In chapter 3 a study is presented in which the accuracy of the non-invasive transcutaneous measurement of ICG by the DDG-2001 is discussed. Two different probes were used to determine the concentration of ICG and the derived hemodynamic parameters cardiac output, central blood volume and total blood volume. These measurements were compared to the simultaneous measurements of ICG in arterial blood, and the derived hemodynamic parameters based on arterial measurements, acquired by rapid sampling.

In chapter 4 the findings are presented concerning the accuracy of the non-invasive measurement of the ICG-PDR versus arterial measurement of ICG, studied in the population described in chapter 3. As data on ICG-PDR measured transcutaneously in a population without liver failure is scarce, this has been explored. The implication of these findings upon clinical decision making in the treatment of patients, subject to imminent liver failure is discussed.
In chapter 5 a circulatory pharmacokinetic model for rocuronium is presented, based on intravascular and diffusion kinetics. The data upon which this model is based were the same as used for the model described in chapter 2. The model applying diffusion kinetics further explores the distribution into the interstitial space and its relationship with cardiac output.

In chapter 6 a recirculatory pharmacokinetic model for propofol in humans is presented. The model describes the distribution, recirculation and elimination of propofol, based on ICG pharmacokinetics, after the administration of an induction bolus dose. The role of the lung in the distribution and elimination of propofol is discussed.

In chapter 7 the recirculatory PK model for propofol is implemented in a PK-PD model for propofol. Effect is measured by BIS, which is transferred at high frequency from the A-2000 monitor. Two different PD models are implemented in the PK-PD model to explore the effect on the $k_{eq}$ and its correlation with flow.