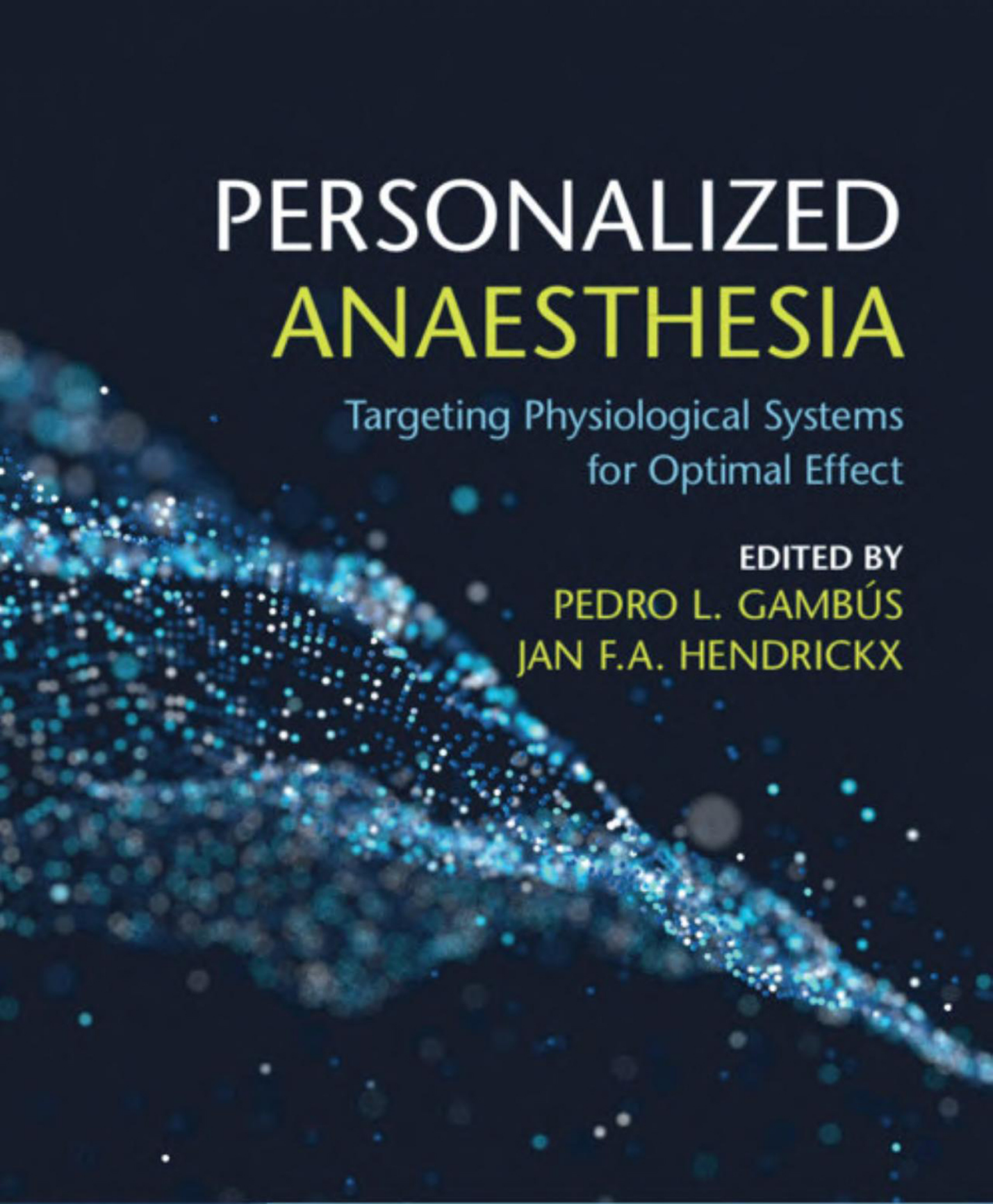
PERSONALIZED ANAESTHESIA

Targeting Physiological Systems for Optimal Effect

EDITED BY
PEDRO L. GAMBÚS
JAN F.A. HENDRICKX



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Foreword

Anaesthesia, the state of oblivion and non-responsiveness that permits surgical invasion of our bodies, is among the most important medical discoveries in history. In Henry Jacob Bigelow's famous report of William Morton's first public demonstration of ether anaesthesia, he not only describes successful surgery under ether anaesthesia, but also his subsequent investigations to determine the nature of the anaesthetizing agent. [1]

Morton, hoping to profit from his discovery, declined to reveal that ether was responsible for the miracle of anaesthesia. In his famous case report, Bigelow conducted his own experiments: 'The first experiment was with sulphuric ether, the odor of which was readily recognized in the preparation employed by Dr. Morton. Ether inhaled in vapor is well known to produce symptoms similar to those produced by nitrous oxide. In my own former experience, the exhilaration has been quite as great, though perhaps less pleasurable, than that of this gas, or of the Egyptian haschish.'

Bigelow then describes the drug delivery system: 'A small two-necked glass globe contains the prepared vapor, together with sponges to enlarge the evaporating surface. One aperture admits the air to the interior of the globe, whence, charged with vapor, it is drawn through the second into the lungs. The inspired air thus passes through the bottle, but the expiration is diverted by a valve in the mouth-piece and escaping into the apartment is thus prevented from vitiating the medicated vapor.'

Bigelow goes on to describe the time course of drug effect in a series of dental cases he observed: onset in 3–5 minutes, requirement for increased drug during dental extraction, and recovery ranging from 10 minutes to an hour. He notes the accumulation of anaesthetic effect with continued administration: 'When the apparatus is withdrawn at the moment of unconsciousness, it continues, upon the average, two or three minutes, and the patient then recovers completely or incompletely, without subsequent ill effects. But if the respiration of the vapor be prolonged much beyond the first period, the symptoms are more permanent in their character. In one of the first cases, that of a young boy, the inhalation was continued during the greater part of ten minutes, and the subsequent narcotism and drowsiness lasted more than an hour.'

Finally Bigelow describes measurement of anaesthetic effect: 'The pulse has been, as far as my observation extends, unaltered in frequency, though somewhat diminished in volume, but the excitement preceding an operation has, in almost every instance, so accelerated the pulse that it has continued rapid for a length of time. The pupils are in a majority of cases dilated; yet they are in certain cases unaltered.'

There it is! The very first published report about anaesthesia linked 1) the pharmacology of anaesthetic drugs, 2) the physiology of the body's response to the drugs, and 3) monitoring drug effect and patient status to the (now daily) miracle of rendering a person insensible to surgical pain.

However, that was only the start of the enduring entwining of anaesthesia, pharmacology, technology and patient safety. The *following year* John Snow published an account of eighty operations with ether anaesthesia. [2] He begins by describing five 'degrees' of ether anaesthesia: a first degree 'whilst he still retains a capacity to direct his volunteer movements', a second degree with 'voluntary actions performed, but in a disorganized manner', a third degree with 'no evidence of mental function', a fourth degree with 'no movements … except those of respiration' and patients 'incapable of being influenced by external impressions' (sounds like 1 MAC), and a fifth degree, where 'respiratory movements are more or less paralyzed.' He also notes ether uptake, which starts at 'about two drachms of ether per minute.' The ensuing chapter describes each stage in detail. Snow then presents the basic concepts of anaesthetic uptake and distribution. He has already figured out some of the subtle details. For example, recovery is initially rapid, but slows because 'when he is inhaling the vapour he is quickly removed

from {the second} into the third degree, but when inhalation is discontinued the vapour is got rid of, in a ratio varying directly with the quantity in the blood, which is a constantly decreasing ratio.' Snow then introduces a novel drug administration technology, a temperature controlled ether vaporizer, because 'a knowledge of the strength of the vapour as being essential to a correct determination of the state of the patient at all times.'

Snow concludes this book, published just a year after Morton's demonstration, with an appendix describing his experiments anaesthetizing frogs! John Snow is widely credited as having founded two scientific disciplines: anaesthesiology and epidemiology. In our minds, John Snow should also be recognized as the founder of clinical pharmacology.

It has been nearly two centuries since Bigelow's report and John Snow's book(!). The fundamentals of anaesthesia practice to which these authors alluded have not changed. What has changed is the precision of our practice. Our drugs target their biological sites of action more precisely than ether. The onset and offset of our anaesthetics is far faster than with ether, enabling more precise control of anaesthetic depth. Our knowledge of physiology is far more precise. We can achieve desired drug effects and mitigate adverse effects by targeting specific ligands in nearly every tissue in the body. Our monitoring is more precise, with the ability to capture neurological and cardiopulmonary status in real time.

Despite these advances, anaesthesia remains a mystery. We understand precisely where the intravenous hypnotics bind, but we have not been able to translate that knowledge into understanding how they induce and maintain the anaesthetic state. Decades of research using the most advanced tools in pharmacology and neuroscience have failed to identify the site of action of inhaled anaesthetics. We have no idea how isoflurane, sevoflurane, nitrous oxide and xenon produce unconsciousness. Understanding the mechanism of inhaled anaesthetic action remains among the oldest and most puzzling mysteries in pharmacology and neuroscience.

Although anaesthesia remains mysterious, mathematics is infinitely more so. Mathematics can describe paradoxes of the quantum world that defy common sense. Mathematics can describe the behaviour of distant galaxies, the expansion of the universe, the relative sizes of infinities and the first moments after the Big Bang. As noted by physicist Eugene Wigner, 'The miracle of the appropriateness of the language of mathematics for the formulation of the laws of physics is a wonderful gift which we neither understand nor deserve. We should be grateful for it and hope that it will remain valid in future research and that it will extend, for better or for worse, to our pleasure, even though perhaps also to our bafflement, to wide branches of learning.' [3]

Personalized anaesthesia, as described in this book, is the marriage of these two mysteries: anaesthesia and mathematics. Personalized anaesthesia applies the power of mathematics to the elements of anaesthesia described in Bigelow's report and Snow's book. This, too, has a long history in our specialty. John Severinghaus built a career from applying mathematics to physiological measurement. [4] E.I. ('Ted') Eger II developed mathematical models of inhaled anaesthetics while stationed at Fort Leavenworth, Kansas. [5] His mathematical models predicted the second gas effect, verified clinically.

We had the good fortune to be among dozens of investigators combining mathematics and computer modelling with precise measurements of drug concentrations following intravenous administration and with precise measurements of drug effect. [6] The authors of this book represent the current generation of leaders in personalized anaesthesia. They are not the intellectual descendants of Morton, who pursued anaesthesia solely to find fame and fortune, but of Bigelow, who presciently described anaesthesia as 'one of the most important discoveries of the age' [1] and Snow, who turned Morton's clinical parlour trick into a science. [2] Seeking to advance scientific understanding and patient care, the authors of this book combine the latest scientific findings and the most sophisticated tools of technology with the nearly infinite power of mathematics.

We are proud to have contributed to this long and distinguished history. We applaud the authors for their continuing efforts advancing the daily miracle and mystery of anaesthesia.

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Introduction

Pedro L. Gambús and Jan F. A. Hendrickx

This book aims to provide the modern anaesthesiologist and interested clinician with the tools to understand how anaesthesia and surgery influence human physiology, how information about the anaesthetic state and the different homeostatic systems of the human body is collected and processed, and how this information can be integrated to optimize and individualize care to the patient by helping us to swiftly respond to changes: personalized anaesthesia.

The book is based upon the concept of general anaesthesia being a constellation of galaxies (see Fig. 1). By providing hypnosis, antinociception/analgesia and immobility, anaesthesia makes surgery possible. But anaesthesia and surgery also generate a number of changes in different systems of the body. Some of these are expected and intended to protect the patient against the harmful effects of the surgical process. Others are a consequence of the relative non-specificity of the drugs used or derive from the procedure *per se*. It is the anaesthesiologist's task to keep this galaxy stable.

Current knowledge about physiology and pharmacology allows the anaesthesiologist to understand to some degree what is going on in the human body. Concurrently, technology has grown exponentially. We are now able to determine the 'depth' of the anaesthetic state. We measure signals from almost any organ system in the body that provide us with an indication of the well-being of the homeostatic systems in the individual patient. All this allows us to titrate drugs, fluids, blood products, heat and other

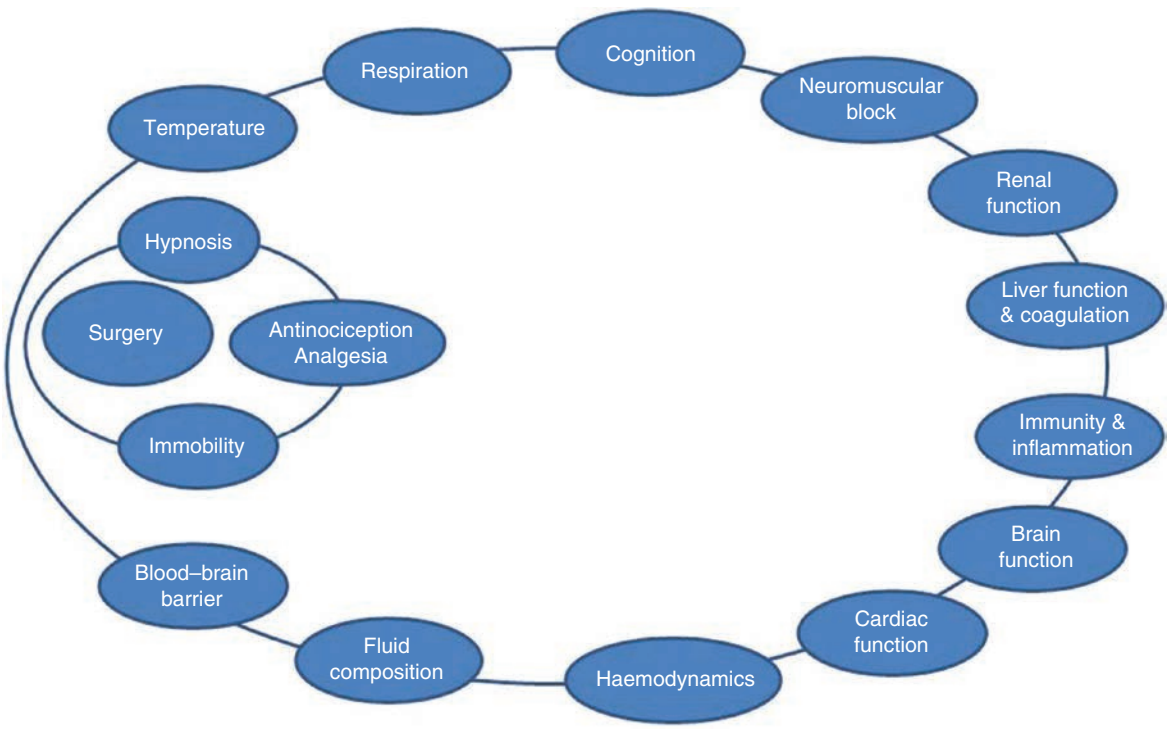

Fig. 1 Cascade of changes triggered by surgery and anaesthesia. The combined effects of surgery and anaesthetic drugs generate direct and indirect physiological changes that should be kept within normal limits.

factors, more and more with the help of automated closed-loop systems to maintain the anaesthetic state 'on target' while also preserving internal homeostasis in the individual patient. This is the basis of 'personalized anaesthesia'.

Being able to titrate anaesthesia to an individual's personal needs is bound to become more and more important because we face an increasingly older population of patients. Some patients are in good physical condition, but others are very sick, not only because of their surgical diagnosis *per se* but also and mainly because of concurrent chronic conditions. The number of patients presenting for ever-more complex surgery keeps increasing at a rate that prompted the World Health Organization (WHO) to warn of a future shortage of anaesthesia providers.

Integration of clinical knowledge, technology that allows us to measure parameters indicative of the anaesthetic state and organ homeostasis, data collection and mathematical modelling allows us to move from the old 'reactive' paradigm, where we take action after changes have taken place, to not only a 'proactive' paradigm, where we take action before something happens, but ultimately a 'predictive' paradigm where past and present information are processed and analysed into predictions about short- or long-term outcomes.

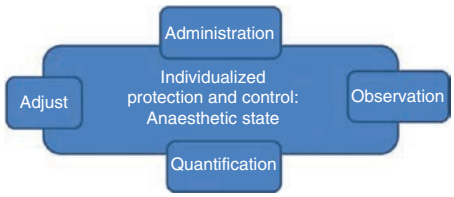

Fig. 2 Scheme of proactive and predictive anaesthesia action. Clockwise: drug administration will induce effects that are quantitated with adequate technology. In the event that prior and present information has been processed and analysed, adjustments will be done according to information-based predictions to avoid undesired outcomes.

We challenged ourselves to integrate this vision about 'personalized anaesthesia' in this book (Fig. 2), which has two parts. The first part presents the fundamentals of the quantitative approach: pharmacological concepts, signal and response analysis, modelling principles, covariate analysis, individualization principles and how they are integrated in an updated view of 'anaesthesia'. The second part describes the different effects of surgery and anaesthesia on each galaxy component from a common quantitative perspective, and where applicable the automated closed-loop systems that can help keep these systems stable. For each of these chapters we invited the world's experts.

Without any doubt, time will make the content of a book that seeks to explain personalized anaesthesia outdated – and for the better: new technologies, new information, new data analysis methods, different approaches to information, etc. are bound to be developed in the future. Artificial intelligence, including machine learning and other related approaches, is certainly going to be one of the major forces that will drive this change. New knowledge and technological innovations will continue to contribute more and more to individualized anaesthesia care, ultimately improving patient safety, outcomes and quality of life.

The editors want to thank the Gambús family members, the Hendrickx family members, their own mentors, the many expert authors that contributed to this book, and the patient staff of Cambridge University Press.

Chapter 1

Principles of Quantitative Clinical Pharmacology

Pedro L. Gambús and Sebastián Jaramillo

Introduction

Because there is no disease condition that can be treated with the administration of anaesthetic medications, the specialty of anaesthesiology does not possess a curative effect in itself. Nevertheless, achieving the state of anaesthesia or the anaesthetic state relies completely on the use of drugs. Drugs used in anaesthesia are very powerful and able to transiently break the most deeply rooted physiological defence mechanisms. Some of the effects induced include lack of consciousness, absence of response to pain, absence of muscle tone, immobility, lack of breathing and dysfunction of the autonomic nervous system, to name just a few. Some of these effects might be considered target or 'therapeutic effects', such as unconsciousness, analgesia or immobility, but others are 'side effects' that are induced because of the relative low specificity of currently used anaesthetic drugs.

Both the therapeutic and side effects are highly dynamic in their time course and they reach clinically effective ranges in a matter of seconds or minutes. If some of the collateral effects like respiratory depression are not adequately managed with measures such as securing the airway and providing mechanical ventilation, severe morbidity or even mortality might result. Fortunately, the current practice of anaesthesia relies on preoperative evaluation of patients as well as on several technological advances to try to predict and control the physiological changes in the patient. In addition, the effects of modern short-acting anaesthetic drugs fade very fast after discontinuing their administration.

It is of high importance to understand the fundamentals of pharmacology to be able to rationally dose anaesthetic drugs. Dosing has to be adjusted and individualized according to the characteristics of the patient, to the characteristics of the surgical or diagnostic procedure, and to the timing and events occurring during every procedure.

The present chapter will review basic concepts of clinical pharmacology. A quantitative perspective will be used. For instance, we will explain how mathematical models help understand drug effects, and how this will help us to define such concepts as onset of effect, peak effect and its time course, offset of effect after a bolus or continuous administration, context-sensitive decrement times, and the relevance of interindividual variability in anaesthetic drug response. These will serve as the basis for rational individualized drug dosing. Other chapters in this book will introduce topics such as estimating and characterizing inter-individual variability in drug response, incorporating covariate factor effects to decrease variability, signal analysis to measure actual responses to drugs with the goal of understanding, quantitating and individualizing drug responses in individual patients, for specific procedures, and for specific events during surgery.

The study of the principles governing the relation between dose and drug concentrations in the body constitutes pharmacokinetics (PK), and will be treated first. The relationship between drug concentration and effect will be presented in the pharmacodynamic (PD) concepts section.

Pharmacokinetic Concepts

Pharmacokinetics is the branch of pharmacology that studies the time course of the concentration of a drug resulting from initial drug dosing, its distribution to the different organs and tissues, and its disposal by the body through biotransformation and elimination. It also describes how it is absorbed when the drug is not intravenously administered. In real life, these processes occur simultaneously. The fundamental PK concepts are volume of distribution and clearance, the basic building blocks of the compartment models that are used to explain PK and PD of intravenous drugs (Fig. 1.1). For inhaled agents, physiological models are most often (but not exclusively) used.

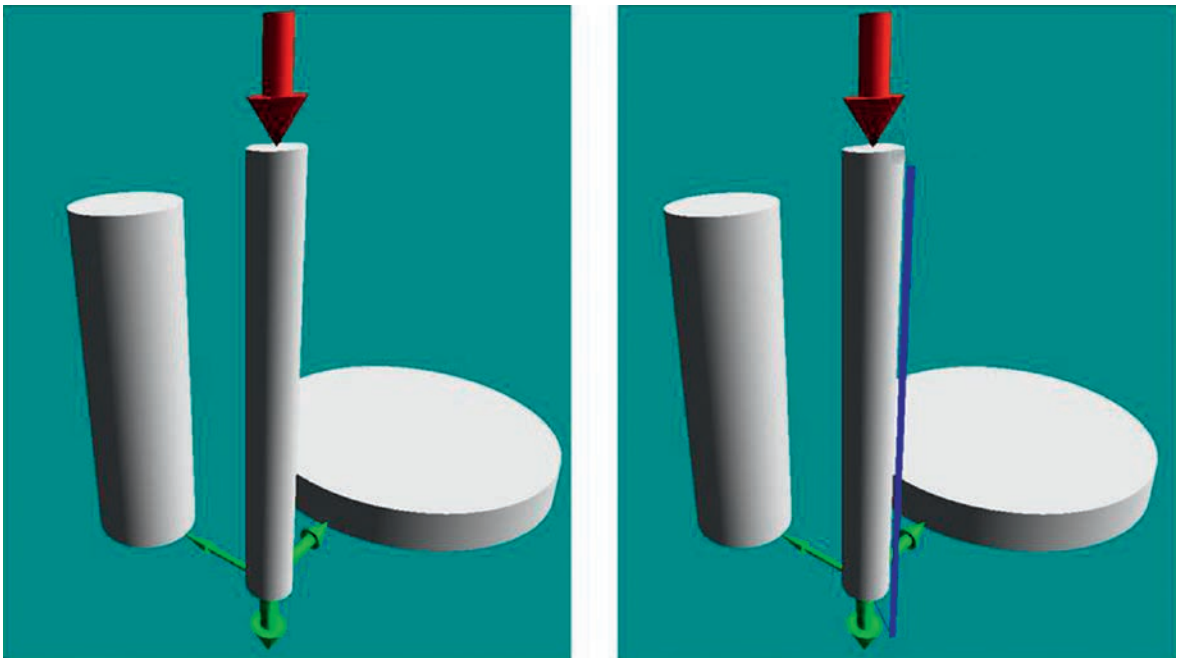

Fig. 1.1 Classical compartment model description. The left panel shows a three-compartment pharmacokinetic model. Drug input is marked by the red arrow and clearance, metabolic and intercompartmental, by the green arrows. The right panel shows a PK model with the addition of an effect site in the form of a long blue rectangle with no volume to meet the assumptions required for the modelling approach (generated with the use of the Cylinders software available at www.pkpdtools.com).

Volume of Distribution

The volume of distribution describes the relationship between the amount of drug in the body and its blood concentration [1]. When a bolus dose of any drug is administered intravenously, the drug gets diluted by and in the blood. It can be seen as analogous to introducing a substance into a bucket of water or fluid where physical laws regulate the speed and degree of dissolution. However, in the case of drugs and tissues, the degree to which a substance is diluted or how it reaches the tissues will also depend on drug properties such as lipophilicity, protein binding, partitioning into tissues and the flow of blood to the different organs and tissues.

Once the drug is in the fluid, which most often is the blood within the context of anesthesia, its presence can be measured as a concentration. If the concentration of a drug and the amount of drug administered are known, the volume of distribution can be estimated:

$$\textit{Volume of distribution} = \textit{Dose of drug} \,/\, \textit{Concentration of drug} \quad (1)$$

A volume of distribution is an apparent volume, i.e. a calculated value that does not have to bear a resemblance to any anatomical entity; it does not need to be equal to the volume of tissues in the body. For example, if a drug is highly bound to tissues, its concentration in blood will be very low, and therefore the estimation of the distribution volume can be very high, higher than any rational estimate of human body volume.

Volume of Distribution in the Central Compartment versus Peripheral Compartments

The central compartment is defined as the compartment into which a drug is initially injected and from which samples are taken for measurement. In the context of anaesthetic drugs, it is usually the volume of blood contained in the heart and blood vessels. The volume of distribution of the central compartment is the ratio of the administered dose over the first measured drug concentration. The 'maximal' concentration, i.e. at the time of injection, is obtained by back extrapolation of the concentration–time curve to time zero. The 'volume of distribution' concept is calculated with this concentration, which obviously is a theoretical construct because there is not yet a single drug molecule in the circulation at time zero because it takes some time for the drug to be transported from the vein to the central circulation.

There are several factors that affect estimation of the volume of distribution of the central compartment. Some are related to study design, for instance the sampling site and the timing of the samples. The sampling site, venous versus arterial blood, may affect the estimation because the concentration is lower in the venous than in the arterial blood: the estimation of volume of distribution based on venous blood samples thus will be significantly larger than that based on arterial blood. Timing of the first sample also has an effect: the longer it takes to obtain the first sample, the lower the 'initial' concentration will be because distribution and elimination start immediately after the drug enters the body, and thus the larger the calculated volume of distribution will be, leading to an overestimate. Erroneous distribution volume estimates will have consequences when they are going to be used for dosing guidelines because the recommended dose to achieve a given concentration will be much larger if the volume of distribution has been overestimated. This will result in excessively high actual concentrations. It also underscores the need for prospective testing of a model.

While it is known that several anaesthetic drugs undergo some initial distribution and degradation in the lungs, estimates of central volume do not usually take this into account. The study and integration of the changes taking place during the initial phase of mixing and distribution of drugs in the blood, its first-pass through the lung circulation, and possible degradation of drugs by the lungs is what is known as 'front-end kinetics'. Front-end kinetics has been studied and characterized, and more complex models have been proposed that could be implemented in infusion devices [2–4].

Depending on the characteristics of drugs and their ability to reach peripheral tissues, compartments other than the central compartment might be added and estimated. For most anaesthetic drugs it is assumed that the drug permeates rapidly from the central compartment to a group of highly perfused tissues, considered to be a fast peripheral compartment, and more slowly to a group of poorly perfused tissues, a slow peripheral compartment, mainly composed of fat. A drug that has reached fat tissues slowly will also slowly return to the central compartment. However, the possibility of a drug returning from fat to blood in significant quantities is very unlikely with the rapidly acting drugs that we use nowadays, therefore the probability of significant side effects related to significant amounts of drug back from fat to blood is very low.

To determine whether a one, two, or three compartment model best describes the time course of drug concentration, an adequate number of blood samples has to be drawn at predefined times, otherwise the whole PK process may not be accurately described.

At this point it is important to remark that PK not only describes the relation between dose and concentration of drugs, but that it is an important driver for pharmacological effect over time. Volumes of distribution and clearances not only have a combined influence on the PK, but also on the time course of the effect of each drug. This can be seen in Fig. 1.2 where a larger volume of distribution slows the onset of effect and decreases the duration of effect as well.

Clearance

Clearance describes the relation between the concentration of a drug and the rate of elimination of the drug from the body. Clearance reflects a real

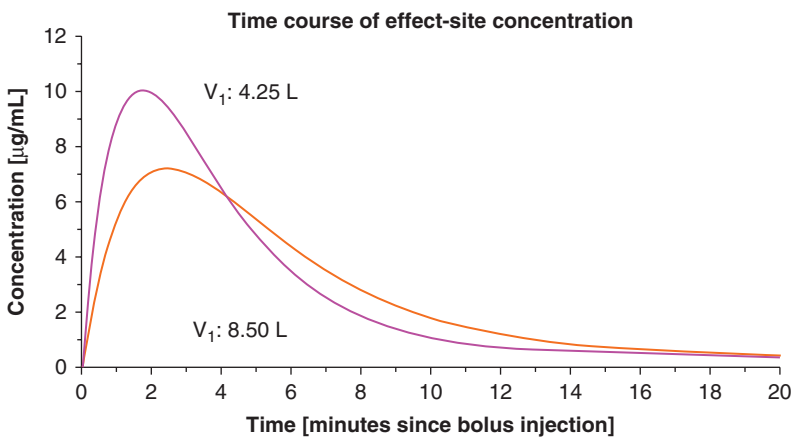

Fig. 1.2 Decay of effect-site concentration at two extreme values of volume of distribution. Doubling volume of distribution alters the dynamics of the effect by delaying onset, decreasing intensity and slowing the fall of effect site concentration.

physiological phenomenon, namely the ability of the body to eliminate an external substance, in this case a drug. It is measured in flux units (volume per time unit, i.e. litres/hour), and it describes how many litres of blood are irreversibly cleared of the drug in one hour.

Intuitively, clearance can be compared to a vacuum cleaner absorbing dust from the air in a room: clearance deals with the ability to clear 'the solvent (air or plasma)' from 'the solute (dust or drug)' per unit of time rather than with the amount of the solute (dust or drug) that is being removed. It can apply to a single organ (hepatic clearance for instance) or to the whole body (sometimes referred to as 'metabolic clearance') [5].

Clearance describes the intrinsic ability of the body to extract drugs from blood or plasma – it is not the rate of elimination or removal of the absolute amount of the drug per time unit. The amount of drug eliminated will depend on the concentration of the drug present in the blood at any moment. If drug clearance is constant at 1 L/h, the drug elimination rate will be zero if there is no drug but would be 1 mg/h if the concentration is 1 mg/L, and 100 mg/h if the concentration is 100 mg/L. Clearance is the proportionality constant that relates the rate of elimination to the measured concentration.

Clearance parameters, expressed in units of flow (L/min or L/kg/min), simply quantify the volume of plasma from which the drug is completely cleared per unit of time. Clearance is constant and independent of drug concentration for drugs that have a so-called linear behaviour meaning that doubling the dose will result in doubling of the drug concentration.

Clearance has been extensively used to calculate drug dosing schemes:

$$\textit{Maintenance dose rate} = \textit{Clearance} \times \textit{Target Concentration} \quad (2)$$

Age affects clearance: as adults grow older, their capacity to clear a drug is also decreasing. Organ failure can also affect the clearance by that particular organ. Concomitant drugs can also affect the clearance of a subject, for instance by altering cardiac output or simply by interfering with metabolic mechanisms. The two main organs with clearance ability are the liver and the kidneys.

As mentioned before for volume of distribution, clearance is a key component of the PK of any drug, but it also has an important influence on the time course of effect. Figure 1.3 presents the predicted effect-site concentration of propofol with normal and with doubled (metabolic) clearance to illustrate the effect of PK changes on drug effect.

Hepatic Clearance

From a clearance point of view, the liver is the most important organ. The liver clears drugs from the blood or the plasma. Two different drug classes are discerned, those with a high and those with a low extraction ratio. The first class are those drugs for which the only limiting factor for hepatic clearance is the flow of blood to the organ, and these drugs are said to have a high 'extraction ratio', close to one, as is the case for propofol. Drugs in the second class are those where the ability of the liver to clear blood or plasma is limited by the function of the hepatocyte, due to its internal

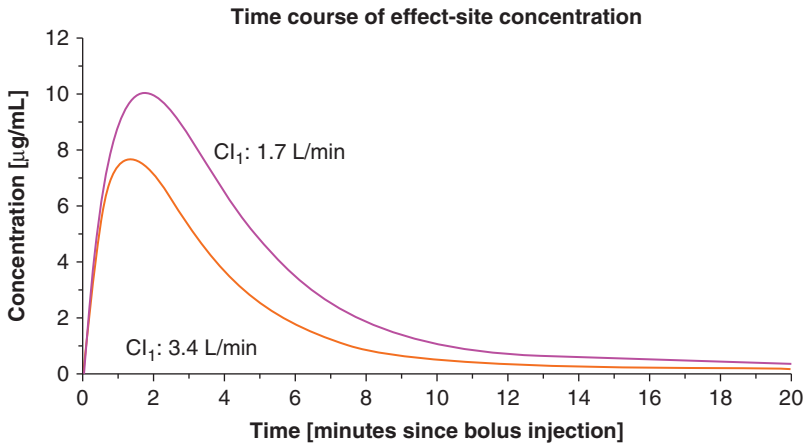

Fig. 1.3 Decay of effect-site concentration at two extreme values of clearance. Doubling clearance hastens the peak of effect but decreases its intensity and hastens the fall of the effect-site concentration.

enzymatic mechanisms or because some drug characteristics make it difficult to enter the cell. Drugs with these characteristics are said to have a low extraction ratio (well below one). Alfentanil is a good example of this class of drugs.

Renal Clearance

Renal clearance is composed of two different mechanisms: glomerular filtration, and secretion at the tubular level. As with any other organ, ageing affects kidney function and consequently drug clearance, causing drug concentrations after the same dose to be higher and thus causing their effects to last longer. Some anaesthetic agents undergo liver biotransformation to generate water soluble compounds that can be excreted through the kidney. A classical, now historical, example is the neuromuscular blocking agent pancuronium, 85% of which is excreted by the kidneys. Many anaesthetic drugs also alter kidney function by altering renal blood flow.

Distributional Clearance

Distributional clearance reflects the transfer of a drug from the central volume of distribution, blood or plasma, to peripheral tissues. It will depend on the blood flow to each tissue or organ and on the permeability of capillary walls to different drugs. For propofol, a highly lipophilic hypnotic drug, the sum of metabolic clearance plus distribution clearance is almost as high as cardiac output, and this is because it is avidly captured by peripheral tissues. When it comes to drugs undergoing plasma enzymatic metabolism, such as remifentanil or Dynorphin A 1–13, the sum of metabolic and distributional clearance is higher than cardiac output. Distributional clearance is responsible for terminating a drug's effect after the initial bolus.

Compartment Models Applied to Pharmacology

When a bolus of a drug is administered and blood samples are collected to quantitate plasma drug concentrations, a certain concentration decay pattern can be observed. This pattern is similar when the same drug dose(s) and blood sampling sequence are repeated in a number of individuals. As can be seen in Fig. 1.4, Panel A, there is a common trend or tendency: there is a fast decay after the initial administration that subsequently slows down. Panel B represents how there is

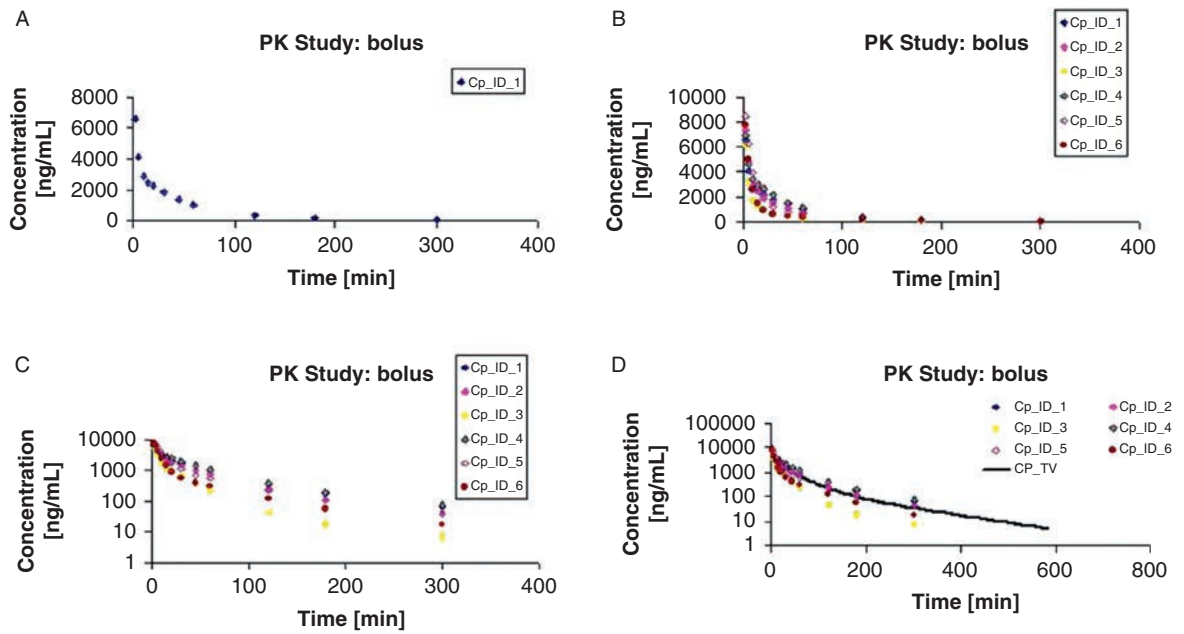

Fig. 1.4 Constructing a PK model. Panel A shows the time course of concentrations for a single subject. Panel B shows the common time course pattern for six individuals. If the results are plotted on a graph with a semi-logarithmic concentration on the Y-axis, three different decay phases can be observed in Panel C. Panel D shows the typical curve describing the time course of drug concentrations for all individuals and for the curve representative of the population or 'typical' individuals.

a common pattern for all blood samples from all individuals studied: three different decay parts can be visually identified in the curves, especially when a semi-log representation is used (Panel C). This pattern (Panel D) can be represented by an equation of the form:

$$Cp(t) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} + C \cdot e^{-\delta t} \quad (3)$$

A, B, C, α, β and *δ* are the parameters that define the intercept and the slope of each of the terms, describing the different parts of the concentration decay curve. These parameters can be estimated by nonlinear regression techniques. These parameters define the equation for a particular drug. The equation defining the curve is called the Unit Disposition Function (UDF), and it is the curve for a dose of one unit of the particular drug. UDF serves as a definition of the kinetic properties of the drug and as a way to compare different drugs.

Volumes of distribution and clearances can also be used as a way to describe the above drug concentration course. These are called compartment models. The values of distribution volumes and clearances are mathematically related to the above parameters in a complex manner. The drug concentration course is envisioned as being the result from injecting the drug into a closed compartment where it immediately gets diluted. As the drug gets diluted, it also simultaneously and irreversibly is cleared from the compartment to the environment. This simple approach is called the one compartment model. This compartment is called the central compartment because it can be connected to other 'peripheral' compartments. They are called multicompartment mammillary models because there is one central compartment from which the other compartments 'receive' the drug. The drug concentration in the central compartment decreases not only due to clearance to the environment but also by disappearing to one or two compartment(s), a process called inter-compartmental or distributional clearance. The drug concentration course of most anaesthetic drugs is best described by a three compartment mammillary model: a central compartment where the drug is administered and from where it is eliminated to the environment, connected to two different peripheral compartments that are not interconnected and are not open to the environment. Once a drug has been administered into the central compartment, elimination to the environment as well as distribution to the peripheral compartments simultaneously occurs. When drug administration ceases, drug flux can be reversed: the drug can return from the peripheral compartment(s) to the central compartment.

The transfer of drug from central compartment to the environment and from central to peripheral compartments can be quantitated by transfer constants that are usually denoted by a letter *k* and sub-index that defines the direction of drug transfer. For instance, k_{31} is the transfer constant regulating the direction of drug from compartment three, one of the two slow peripheral compartments, to the central compartment, while k_{10} denotes the 'final' elimination from the central compartment to the environment.

Although the physiological meaning is not clear or is even absent, the three compartment model envisions the human body to be a combination of three compartments. The central compartment is the compartment where the drug is injected and where it 'mixes instantaneously'; the fast peripheral compartment could be considered to be composed of well perfused tissues and organs where the drug arrives relatively fast; and the slow peripheral or third compartment could be considered to be composed of poorly perfused tissues, with the drug arriving slowly out of the central compartment. When the gradient is reversed, the drug returns from the slow to the central compartment sluggishly, and usually without having any clinical repercussion. Not all drugs need to be described by a three compartment model. The choice between a one, two, or three compartment model depends on drug characteristics and also on study design. The main point to consider is that enough blood samples have to be drawn to be able to estimate the different parameters of the function that describes the concentration decay curve. If the experiment consists of injecting the drug plus drawing a blood sample five minutes and three hours after injection, it is very likely that the decay would be represented by a straight line, and thus no reliable information about the concentration course can be extracted from what happens between five and 180 minutes. A good example of general study design for PK in anaesthesia can be found in the study of propofol PKPD by Schnider et al [6, 7] or remifentanil PKPD by Minto et al [8, 9].

The use of a compartment model to describe the time course of drug concentrations comes to the clinician in a more physiologically intuitive way. As mentioned before, the equation defining the drug disposition curve (Equation 3) can be represented in other ways using different parameters: equilibration constants, slope and coefficients and also as volumes of

distribution and clearances. The parameters of equations that underlie each of these different approaches bear a complex relationship to one another. Software solutions such as PKPD Tools for Excel [10] or convert.xls (available at www.nonmemcourse.com/convert.xls) are very helpful in re-parameterizing. The exponents and coefficients of Equation (3) for example can be converted into volumes of distribution and clearances with these tools. Most publications of PK and PKPD models in anaesthesia literature show the parameters of the model as volumes and clearances terminology.

Variability

Figure 1.4 shows the time course of the plasma concentration of a drug. Panel B shows the plasma decay curves of six different subjects, and Panel D shows all individuals plus the common descriptor of all them, the 'typical individual'. The 'typical individual' or 'population model' represents the sample or population. Between the population model and each one of the individual time courses there are differences. The differences between individuals are the 'inter-individual variability'. Variability can be decomposed into different factors that could potentially influence the PK of a drug. Some of those factors are easily identified with an appropriate study design (age, weight or gender of the subject, concomitant medication or diseases) and can be considered to explain part of the inter-individual variability (see Chapter 2 about PKPD Modelling and Chapter 3 about covariate factors).

Variability is an important issue when it comes to dosing anaesthetic drugs; new methods of data analysis, especially those based on nonlinear mixed effects modelling, permit one to study in detail the expected variability in the response after a dose of any anaesthetic, ultimately with the goal of improving drug titration in such a manner that effects can be individualized.

Pharmacodynamics

Pharmacodynamics (PD) is the part of pharmacology that studies the relation between drug concentration and effect(s). Drug effects can be therapeutic or can be side effects. In our specialty the term 'therapeutic effects' does not apply well, but still we refer to it as such when we define the effect we are looking for: hypnotic effect (unconsciousness, sedation), analgesia, immobility, or potentially dangerous side effects (respiratory depression, bradycardia, arterial hypotension). It is as important to reach the therapeutic effect and intensity of that effect as it is to avoid potentially dangerous side effects.

The Concept of Effect Site

Figure 1.5 represents the time course of drug concentration versus effect. The drug has been administered as a short intravenous infusion. It can be seen that there is a delay between achieving the maximal concentration and the maximal effect. This delay matches our clinical impressions well: after injecting a bolus dose of an anaesthetic drug, it takes a while before the maximal effect is achieved.

When graphically representing plasma drug concentrations versus effect, it can be noted that for a given concentration there can be two different intensities of effect. The type of curve that is generated is called 'hysteresis'. In pharmacology there are two types of hysteresis that relate concentrations to effect: one is clockwise and it corresponds to the phenomenon of

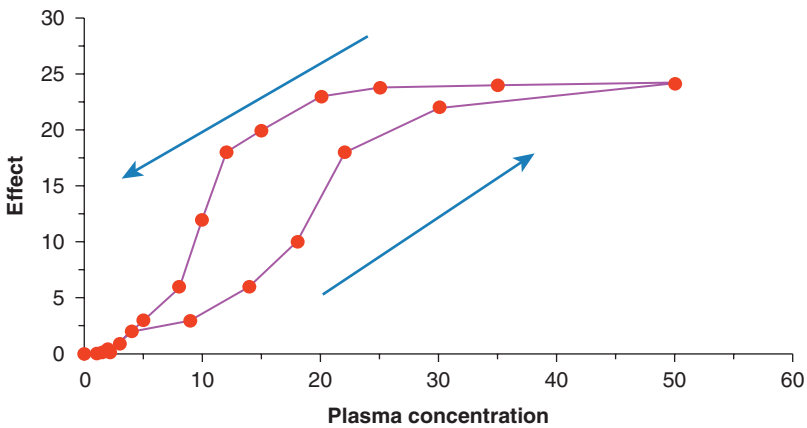

Fig. 1.5 The concept of effect site: hysteresis of plasma concentrations versus effect. As drug concentration starts to increase, the effect increases very slowly until a maximum point has been reached. Therafter, drug concentrations start to decrease but the effect disappears with a different pattern as compared to the onset of effect. This phenomenon that happens in a counterclockwise pattern is called hysteresis, and it is due to the fact that plasma is not the site of drug effect.

'drug tolerance'. The counterclockwise hysteresis is associated with the inaccurate match between plasma concentrations and effect. Ideally, counterclockwise hysteresis would be absent: if it were possible to measure drug concentrations at the site of drug effect, and if these could be plotted against the measurements of effect, the data points would fall on the same line because every concentration would be associated with only one level of effect. Hysteresis is caused by transport and signal processing delays: blood has to transport the drug to the target organ, where it will have to activate a receptor and trigger a chain of events ranging from subcellular to organ level, ultimately generating the observed effect.

How do we solve the hysteresis problem, i.e. the fact that the same clinical effect can occur in the presence of two different blood or plasma concentrations? As mentioned, we could consider measuring concentrations at the site of drug effect, but this is not yet possible for most of the cases. We could wait for steady state conditions, i.e. a condition where there is equilibrium between drug input and output. This is usually reached after continuous administration of a drug during at least five elimination half-lives. After reaching steady state conditions, we could draw blood samples and assume that there is equilibrium between the concentrations at the effect site and at all organs. However, again this proves to be an impossible approach because it takes too much time to reach such conditions, outlasting surgery itself.

We therefore need another solution: the theoretical 'effect site', a concept that links plasma concentrations to effect measurements. The effect site, also known as the biophase, was initially proposed to explain the relation between concentrations of d-tubocurarine and neuromuscular blockade, first by the Italian pharmacologist G. Segre in 1968 and then, almost simultaneously, by Sheiner [11] and Hull [12]. The effect site is a theoretical mathematical construct that can be considered to be yet another 'special' compartment, linked to the central compartment. After entering the effect site it is assumed that the drug directly and immediately exerts its effect. Another assumption is that the size of the effect site compartment and the amount of drug in it is very small, almost negligible, as compared to the size of the other compartments in the model, so that it has no influence on the PK or the mass balances of the drug. By definition, at steady state, the concentration at the effect site is the same as that in the central compartment because mixing is considered to be instantaneous, because the volume of the effect site is infinitesimally small and because the blood/effect-site partition coefficient is assumed to be one.

The delay between the plasma and effect-site concentration, and thus the clinical effect, is mathematically described by a single parameter, k_{eo}, the effect-site equilibration-rate constant, which is a first-order process. k_{eo} can be expressed as the equilibration half-life between plasma and the effect site according to the following equation:

$$t_{1/2}k_{eo} = ln2/k_{eo} = 0.693/k_{eo} \quad (4)$$

k_{eo} has units of 1/time (time^{-1}). A large $t_{1/2}k_{eo}$ (small k_{eo} value) implies a longer equilibration between plasma and effect site and a slower onset of effect. Small $t_{1/2}k_{eo}$ means fast onset and large k_{eo}. k_{eo} can be estimated from plasma concentrations and measured effect, or from PK parameters and measured effect. The original paper by Sheiner refers to the constant as k_{eo}. Several authors name it k_{e0}, in this book we will refer to it as k_{eo} to be consistent with the original proposal.

So, by definition, one concentration in the effect site, or biophase, is directly linked to one single effect. Different clinical end-points will have different k_{eo} values, e.g. the k_{eo} describing propofol induced arterial hypotension will differ from the propofol k_{eo} for Bispectral Index (BIS) changes, and the k_{eo} for BIS will differ from that for the 95% Spectral Edge of the electroencephalogram.

Sometimes the relations between drug concentration and effect are not as obvious as in the case of anaesthetics. Different approaches have been proposed to establish the link between plasma concentrations and effect in those situations where the effect compartment approach does not help. A common method is the use of 'indirect effect models' [15]. In those models the main assumption is that there are intermediate steps that can be estimated as well. Such steps may include interposed mechanisms, molecular or cellular mediators.

To summarize, the effect site compartment concept is the most commonly used approach to link the plasma concentration of a drug to its effect. It has been a key concept to derive rational dosing that achieves and maintains a defined level of effect. Based on these principles, Target Controlled Infusion (TCI) systems are able to target both plasma and effect site concentrations. The k_{eo} is the mathematical construct that allows PK models to be connected to PD models (see below)

and thus allows drug dosing to be linked to clinical effect. It allows us to make estimations or predictions of onset and offset of effect after a given drug dose.

Relation between Effect-site Concentration and Effect

For most anaesthetic drugs, the relationship between effect site concentration (Ce) and clinical effects takes a sigmoidal shape, modelled by the so-called sigmoidal Emax model (Fig. 1.6). As Ce increases from zero, there will initially be no or only a very small increase in effect, but as Ce is further increased, the effect will start to increase rapidly until it reaches a Ce above which the intensity of effect increases no further.

The equation that describes the sigmoid Emax model is known as the Hill equation [13]:

$$E = E_0 + (E_{max} - E_0)\frac{C_e^{\gamma}}{C_e^{\gamma} + IC_{50}^{\gamma}} \quad (5)$$

Four parameters define the model. E_0 is the baseline effect when no drug has been administered. E_{max} is the maximal effect that could be eventually reached. IC_{50} is the effect site concentration that induces 50% of the maximum effect. Gamma (γ) is the exponent that defines the steepness of the linear part of the curve, and is also referred to as alpha (α) or as the Hill coefficient.

IC_{50} reflects the potency of the drug for a given effect and thus allows drugs from the same drug class to be compared: because the IC_{50} of sufentanil is lower than that of fentanyl and remifentanil (which have a similar IC_{50}) which in turn is lower than that of alfentanil [14], sufentanil is said to be more potent than fentanyl and remifentanil, while the latter two are more potent than alfentanil [14].

Integration of Pharmacokinetics and Pharmacodynamics

PK and PD models and the effect site concept that links them permit us to estimate the onset, intensity, duration and offset of effect after a given dose. To be able to accurately predict the intensity of effect in an individual patient, covariate effects have to be incorporated into the parameters of the PKPD models (see Chapter 4).

Application to Rational Dosing Guidelines

The clinically most useful aspect of PKPD concepts is the ability to predict the 'right dose' that will result in the desired clinical effect at the right time and only during the period that is necessary for every patient. This means that a PKPD model will help the clinician to predict onset, duration and offset of the therapeutic effect. In addition, unwanted side effects have to be avoided or minimized.

Drug concentrations should fall within a therapeutic window, the range of concentrations within which the expected effect is safely attained. Below the therapeutic window, the effect in the patient is not intense enough because the drug is underdosed. Above the therapeutic window, the effect is much more intense than required because the drug has been overdosed and the patient is at risk of developing excessive or significant side effects. Given the special nature of the drugs used in anaesthesia, both under- and overdosing might be a source of serious problems like awareness, unexpected movement causing iatrogenic trauma, excessive haemodynamic depression (hypotension or tissue hypoperfusion), or even death. This is the reason

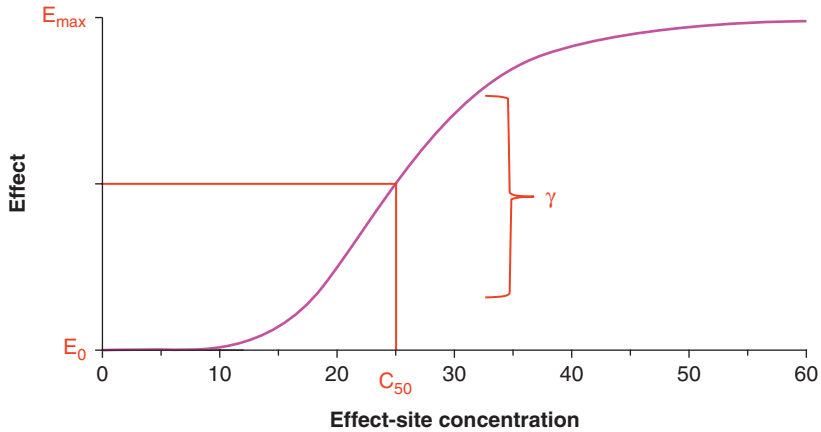

Fig. 1.6 The relation between effect-site concentration and effect. The sigmoid E_{max} model is defined by the effect when no drug is present (E_0), the maximal effect possible (E_{max}), the effect-site concentration that causes 50% of effect between E_{max} and E_0, and the exponent γ defining the steepness of the rectilinear part of the curve.