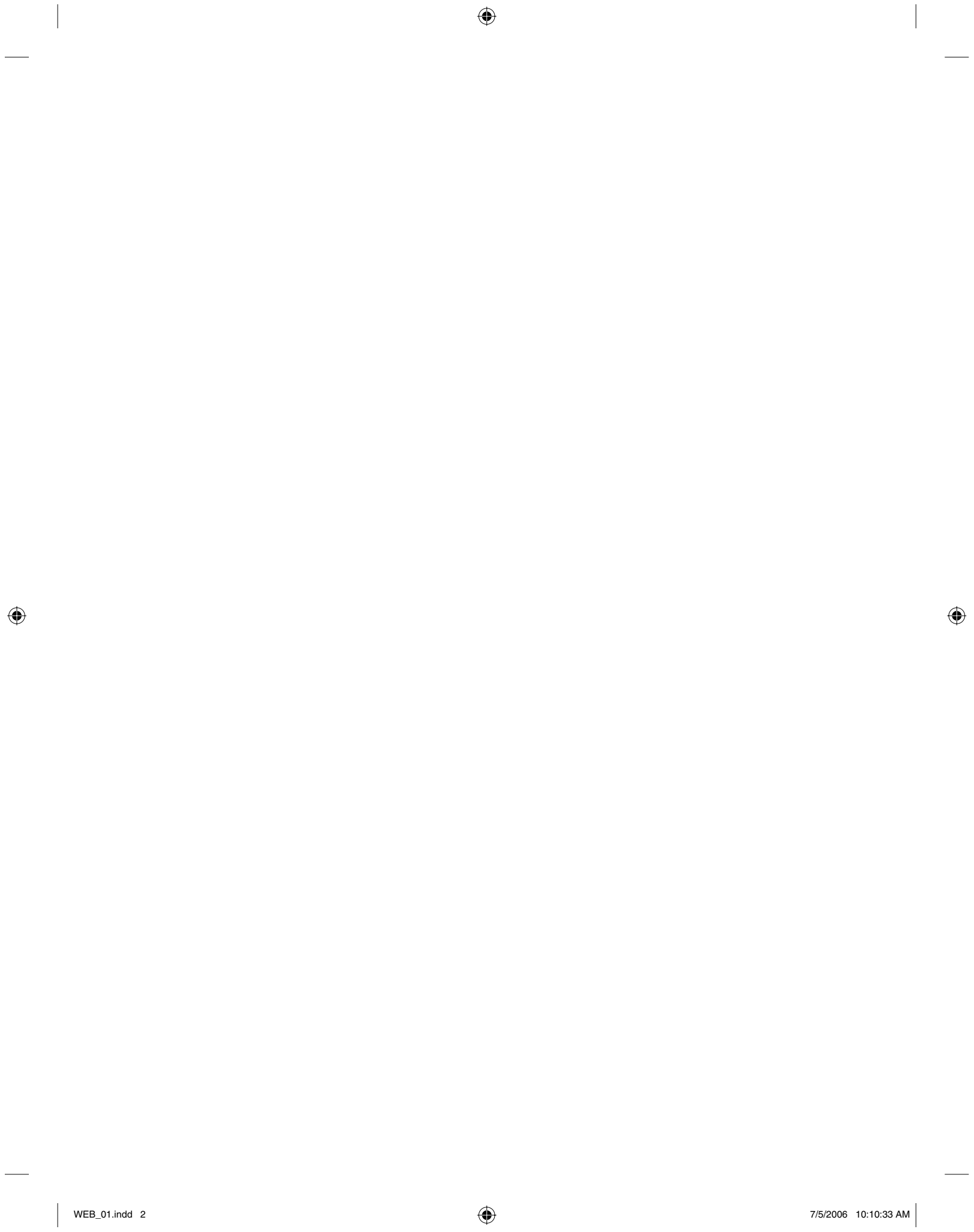


PART 1

Pharmacology



CHAPTER 1

Pharmacokinetic principles

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Introduction

Pharmacokinetics can be defined as the characterization and prediction of the time course of the concentration of a drug in the body. This includes the characteristics of drug absorption, distribution, metabolism and elimination. Pharmacokinetic models can be used to predict the time course of this drug concentration. Variations in body composition or organ function — for example, in children, in pregnant women and fetuses *in utero*, in elderly populations and in patients with organ dysfunction — may affect anaesthetic drug distribution and elimination and therefore drug responses. In this chapter, we first briefly describe some of the basic concepts governing pharmacokinetics. Secondly, we focus on the concepts of pharmacokinetic modelling and, thirdly, the influence of various physiological changes on the pharmacokinetics of drugs is described.

Drug absorption

Transfer of drugs across membranes

To reach a therapeutic concentration at their site of action, drugs need to pass through the cell membranes that separate different compartments in the body [1]. These membranes are 5–10 nm wide and are arranged in a lipid bilayer structure. This bilayer is present in a fluid state embedding a mosaic of dispersed proteins that can penetrate both outer or inner leaflet of the lipid sheet [1,2]. The structure of the lipids in cell membranes varies widely, although all of them are amphipathic. The membrane lipids comprise phospholipids, sphingolipids and cholesterol, and most membrane proteins are glycoproteins carrying carbohydrates on their outer surface. In the same way, some phospholipids are glycolipids. The

molecules in cell membranes are orientated in such a way that non-polar elements are confined to the core and polar elements are exposed on either side. The hydrophobic core favours the crossing of lipid-soluble molecules and hampers the movement of water-soluble ones across the cell membranes [2]. The nature of the compartmentalization by membranes strongly depends on the specific structure of the barrier in different tissues. In some tissues, such as the gastrointestinal tract, the lining cells are closely connected. In other tissues, such as the glomerulus of the kidney, there are gaps between cells allowing filtration [1]. The permeability of vascular endothelium throughout the body also varies. There are gaps between endothelial cells of the capillary wall, but in some tissues, such as the central nervous system (CNS), there are tight junctions between the endothelial cells of the capillaries forming the blood–brain barrier [1,3].

Theoretically, drugs can move across cell membranes by passive mechanisms or by active processes [4]. Lipophilic drugs cross cell membranes very easily by simple diffusion. The rate of diffusion across the membrane depends on the concentration gradient, the size of the molecules (smaller molecules diffuse more easily than large ones), the lipid solubility, membrane properties such as the membrane area and thickness, and the diffusion coefficient. Drugs in a charged, ionized form cannot pass through membranes by simple diffusion; only the uncharged fraction can [1]. The Henderson–Hasselbalch equation makes it possible to calculate the uncharged fraction of a drug, given its pKa and the ambient pH. From:

$$\text{pH} = \text{pK}_a + \log \text{base/acid} \quad (1)$$

For acidic drugs, this results in:

$$\text{pH} = \text{pK}_a + \frac{\log \text{ionized concentration}}{\text{unionized concentration}} \quad (2)$$

For basic drugs, this results in:

$$\text{pH} = \text{pK}_a + \frac{\log \text{unionized concentration}}{\text{ionized concentration}} \quad (3)$$

Ionization is not only important in determining the rate of which a compound can move across a membrane, it is also important in determining the partition of a drug between compartments with a different ambient pH. Diffusion of water-soluble drugs is restricted by passage through aqueous pores that span the cell membrane. However, these channels are too small to let most drugs pass through them. Endothelial membranes in the capillaries can have larger pores allowing bulky molecules to pass through [4]. Diffusion can also be facilitated by carrier-mediated mechanisms that operate along a concentration gradient without making use of an energy source. This is called 'facilitated diffusion' [1].

Active transfer mechanisms require energy. The energy can be supplied by the hydrolysis of adenosine triphosphate (ATP) directly, as for instance in the case of Na^+/K^+ ATPase, or indirectly by the coupling of the passive transfer of one compound along its ionic gradient with the movement of another molecule against its concentration gradient [3]. An example of such a transport system is the absorption of amino acids from the small bowel lumen into intestinal cells [1]. This transfer is achieved by a coupling with Na^+ diffusion that occurs down its electrochemical gradient. Maintenance of the latter requires energy and ultimately depends on the Na^+/K^+ ATPase system [3].

Pinocytosis transports large molecules [3]. In this process a part of the cell membrane is invaginated to form a vesicle, which engulfs extracellular material, and is removed via exocytotic mechanisms.

Drug administration techniques in anaesthesia

There are many ways in which a drug can be given. Although most drugs are given orally, in anaesthesia many drugs are administered intravenously. Because absorption is bypassed, drug action is very fast

by this route. However, for all other routes of drug administration, the drug must be absorbed from the site of application before being carried in the circulation to its site of action.

Intramuscular or subcutaneous administration

Many factors affect the rate of absorption after intramuscular or subcutaneous injection. The molecular weight of the compound, the vehicle in which the drug is dissolved, the volume that is given and, last but not least, the local perfusion of the muscle and fat tissue are important [5]. Some drugs are absorbed very easily, but for others the absorption is poor or unpredictable (e.g. diazepam) [6]. After the injection of water-soluble drugs, the plasma level can increase rapidly, because these compounds enter the circulation very fast. This is especially true for drugs with low molecular weight, which can reach the systemic circulation by entering the capillaries directly [5]. The use of vasoconstrictors or vasodilators, as well as individual patient haemodynamics, can also markedly influence the rate of absorption.

Inhalation

Depending on the particle size, inhaled drugs will mainly reach airway mucosa from the larynx to the bronchioles, creating local effects, or reach the alveolus, allowing largely systemic effects. However, systemic absorption may still occur in both cases [5]. Volatile molecules readily reach the alveolar space and can enter the systemic circulation within seconds. The rate of absorption of volatile anaesthetics is determined by adequacy of pulmonary ventilation, cardiac output, inspired concentration and anaesthetic solubility [7].

Epidural, intrathecal and perineural administration

Epidural, intrathecal or perineural administration of drugs is used for providing regional analgesia and anaesthesia. The onset time depends on the concentration of unionized local anaesthetic around the axon. Because local anaesthetics are bases, adding sodium bicarbonate reduces onset time in epidural solutions. Addition of a vasoconstrictor increases the duration of the block [1].

Oral administration

Multiple factors are involved in the absorption of the drug from the gastrointestinal tract to the systemic circulation. First-pass metabolism, unpredictable pharmacokinetics and a latent period before maximal concentration in plasma make this route unsuitable for many anaesthetics [8].

Rectal administration

The rectal blood flow partly drains directly into the systemic circulation, avoiding first-pass metabolism, although absorption is unpredictable [1].

Sublingual, buccal and nasal administration

While permitting very fast absorption of certain drugs, these routes directly drain into the systemic circulation, avoiding first-pass effect [5].

Bioavailability

Bioavailability is generally defined as the fraction of an extravascularly administered dose that reaches the systemic circulation [5]. An orally administered dose is only partially absorbed from the gut and partially metabolized in the gut wall and liver before reaching the systemic circulation.

Drug absorption and first-pass effect

Before the drug can cross the mucosal membranes after oral intake, the tablets must disintegrate and dissolve. Pharmaceutical factors such as chemical formulation, particle size, coatings or the inclusion of inert fillers influence this dissolution process [8]. Because most drugs only pass the lipid membranes in their unionized form, the regional pH greatly influences absorption. Consequently, acidic drugs would mainly be absorbed in the stomach, but the large surface area and anatomical properties of the small intestine make this the main absorption site for all drugs [4]. The speed of gastric emptying, simultaneous intake of other drugs or food and pathological conditions also influence the speed and degree of drug absorption [1]. Before reaching the systemic circulation, the drugs need to pass through the intestinal mucosa and the liver [8]. Metabolism of the drug may occur in the gut wall or by the liver,

further reducing the amount that reaches the target organ.

Drug distribution

The basic pharmacokinetic parameter to describe drug distribution is the apparent volume of distribution (V_d), calculated as:

$$V_d = \text{amount of drug} / \text{concentration} \quad (4)$$

It must be noted, however, that this has been simplified by assuming that the drug is administered into a single, well-mixed compartment. If the drug remains unbound in the plasma and does not distribute into other tissues, the V_d would be the same as the plasma volume. However, most drugs leave the plasma and distribute into and bind to other tissues. Drug distribution throughout the body depends largely on organ blood flow and physicochemical properties of the drug, such as lipid solubility and protein binding.

Blood flow

Shortly after a drug enters the systemic circulation, tissue concentrations rise in the more highly perfused organs, such as the brain and liver. Organs with lower blood flow will take longer to equilibrate, and, in some cases, this may take several hours or even days [4].

Lipid solubility

After passing into the extravascular space, water-soluble drugs are mostly limited to the extracellular fluid, while lipid-soluble drugs easily cross cell membranes and can accumulate in certain tissues. For instance, lipophilic drugs such as thiopental may accumulate in fat, and be redistributed to other organs afterwards, prolonging the duration of drug action [4]. This indicates that drug distribution throughout the body depends largely on physicochemical properties.

Protein binding

In plasma, many drugs are bound to a variable degree to plasma proteins and, because only free unbound drug is able to move across capillary membranes, this protein-bound fraction cannot be

regarded as pharmacologically active [4,9]. The plasma proteins have multiple binding sites and the amount of drug bound depends on its total concentration, the competition for binding by other compounds for the same binding sites, the concentration of protein and the affinity between drug and protein [10]. As a rule, neutral and acidic drugs bind to albumin and basic drugs bind also to α_1 -acid glycoprotein and lipoproteins [1]. Plasma protein binding is particularly important for drugs that occupy a large portion of the available binding sites at therapeutic concentrations. With these drugs, a small increase in the bound fraction can increase the unbound fraction out of proportion [1,6].

Special membranes

Blood–brain barrier

Contrary to most tissues, where capillary membranes are freely permeable, cerebral capillaries form tight junctions, restricting free diffusion of drugs into the cerebral extracellular fluid. Besides this structural barrier, astrocytes form a metabolic or enzymatic blood–brain barrier that neutralize certain agents before they reach the CNS. Penetration of drugs into the brain depends on ionization, molecular weight, lipid solubility and protein-binding [5]. However, peptides such as bradykinin and enkephalins and certain conditions such as inflammation can increase the blood–brain barrier permeability, allowing normally impermeable substances to enter the brain [6].

Placental barrier

Most low molecular weight, lipid-soluble drugs can easily cross the placental barrier while large molecular weight or polar molecules cannot [8]. Differences in fetal blood pH, placental blood flow, protein binding and fetal metabolism influence fetal free drug levels [1]. As a rule, drugs that affect the CNS — and consequently pass the blood–brain barrier — can also cross the placenta [8].

Drug metabolism

After administration, most drugs (certainly if they are lipid-soluble) have to be metabolized before they

can leave the body. In most cases metabolism reduces the activity of a drug, but in some cases metabolic conversion of a drug may increase or only partially decrease its activity. Generally, metabolism results in a more water-soluble molecule that can be excreted more easily. The main organ for drug metabolism is the liver [8], but processes also take place in the gut, plasma, gastric mucosa, lung or other organs [1]. Metabolism consists of two phases.

Phase I

In phase I, molecules are chemically activated to prepare for possible phase II reaction [5]. Three types of enzymatic reactions may occur: oxidation, reduction and hydrolysis.

Oxidation

Many oxidative reactions take place in the endoplasmic reticulum of the liver, the microsomes, and are catalysed by the cytochrome P450 system. The P450 superfamily comprises more than 30 different isoenzymes in humans. However, the majority of P450s involved in drug metabolism belong to three distinct families: CYP1, CYP2 and CYP3. These are essential in the elimination of drugs as well as in the synthesis or metabolism of endogenous compounds. Monoamines are metabolized by monoamine oxidase in the mitochondria. Alcohol dehydrogenase is localized in the cytoplasm.

Reduction

These reactions typically take place in the hepatic endoplasmic reticulum and cell cytoplasm. As in oxidation, the cytochrome P450 system is responsible for many reduction reactions [8].

Hydrolysis

Esterases are active in plasma as well as in the liver. They are able to hydrolyse an ester to the alcohols and the carboxylic acid.

Phase II

Conjugation or synthesis

These reactions include glucuronidation, sulphonation, acetylation, methylation or glycation. This generally increases the water solubility, favouring renal or biliary excretion, and most of these reactions

take place in the liver microsomes, but the lung is also involved [1].

Drug excretion

Either directly or after biotransformation, drugs are eliminated out of the body in urine or bile. Small amounts are also excreted in saliva, sweat and milk, but this is usually of little quantitative significance [5]. Small molecules are mainly excreted in urine; high molecular weight molecules (>400–500 Da) are preferentially eliminated in bile.

Renal excretion

Three processes account for renal drug excretion: filtration, secretion and diffusion.

Glomerular filtration

Glomerular filtration is a passive process involving filtration of mainly unbound fraction of water-soluble molecules. Large or highly protein-bound molecules will not cross the glomerular membrane [8].

Tubular secretion

Tubular secretion is an active carrier-mediated secretion that may take place against a concentration gradient. For some drugs, complete clearance may be achieved in a single renal circulation [8].

Tubular diffusion

In the distal renal tube, depending on urine pH, important passive diffusion may take place between the urine and the plasma. This mechanism is restricted to substances capable of crossing tubular cell membranes and can result in marked reabsorption of excreted drugs. In addition, the elimination of certain drugs can be increased by alterations in urine pH; after diffusion of the non-ionized fraction of certain basic drugs from the relatively alkaline plasma to the acid urine, they are trapped as cations and excreted [8].

Biliary excretion

Hepatocytes actively transport high molecular weight molecules, such as the steroid-based muscle relaxants, to the bile. This is a saturable process which

can be inhibited by other drugs. Active transport may result in significant concentration of certain drugs, up to 100 times the plasma level [5]. Some drugs require conjugation, but others are excreted unchanged in bile. Conjugated drugs excreted in the bile may be subsequently hydrolysed by bacteria in the gut and reabsorbed, increasing their biological half-life [1], a process called enterohepatic recirculation.

Drug clearance

The two main organs responsible for drug excretion are the liver and kidneys. Clearance is defined as the volume of plasma from which a drug is completely removed per time unit. Many drugs are metabolized by the liver and although their metabolites may stay in the blood for some time before actual excretion, they often have no or little residual pharmacological effect. On the other hand, a drug may be removed from the body both by urinary excretion of unchanged drug and by hepatic metabolism.

Clearance values can be considered as the sum of the clearances by the various organs involved for a certain drug:

$$Cl = Cl_R + Cl_H + Cl_X \quad (5)$$

whereby Cl_R is renal clearance, Cl_H is hepatic clearance and Cl_X is clearance by other routes. The clearance of most drugs is mainly dependent on the liver, either by hepatic metabolism and/or biliary excretion [8].

The pharmacokinetic concept of hepatic clearance takes into consideration that the drug is transported to the liver by the portal vein and the hepatic artery and leaves the organ by the hepatic vein [11]. It diffuses from plasma water to reach the metabolic enzymes. There are at least three major parameters to consider in quantifying drug elimination by the liver: blood flow through the organ (Q), which reflects transport to the liver; free fraction of drug in blood (f_u), which affects access of drug to the enzymes; and intrinsic ability of the hepatic enzymes to metabolize the drug, expressed as intrinsic clearance (Cl_{int}). Intrinsic clearance is the ability of the liver to remove drug in the absence of flow limitations and blood binding. Taking into account these three parameters, the hepatic clearance can be expressed by:

$$Cl = \frac{Q \cdot f_u \cdot Cl_{int}}{Q + f_u \cdot Cl_{int}} \quad (6)$$

It is obvious that the hepatic clearance cannot be larger than the total volume of blood reaching the liver per unit time (i.e. the liver blood flow Q). The ratio of the hepatic clearance of a drug to the hepatic blood flow is called the extraction ratio of the drug (E), which can be expressed as:

$$E = \frac{C_a - C_v}{C_a} = \frac{f_u \cdot Cl_{int}}{Q + f_u \cdot Cl_{int}} \quad (7)$$

where C_a is the concentration in the mixed portal venous and hepatic arterial blood and C_v is the hepatic venous blood concentration. The value of the extraction ratio can vary between 0 and 1. It is 0 when $f_u \cdot Cl_{int}$ is zero (i.e. when the drug is not metabolized in the liver); it is 1 when the hepatic clearance equals hepatic blood flow (approximately 1.5 L/min in humans).

The extraction ratio can be generally classified as high (>0.7), intermediate ($0.3-0.7$) or low (<0.3) according to the fraction of drug removed during one pass through the liver. The effect of critical illness on hepatic clearance depends on these extraction characteristics of the drug as explained below (see p. 18). Table 1.1 lists the hepatic extraction ratio in humans for some sedative and analgesic drugs.

Table 1.1 Some example drugs with various hepatic extraction ratios (ER).

Low ER (ER < 0.3)	Intermediate ER (ER 0.3–0.7)	High ER (ER > 0.7)
Diazepam	Alfentanil	Fentanyl
Lorazepam	Chlorpromazine	Flumazenil
Methadone	Diphenhydramine	Ketamine
Pentobarbital	Droperidol	Morphine
Chlordiazepoxide	Etomidate	Nalmefene
	Haloperidol	Naloxone
	Hydromorphone	Propofol
	Midazolam	Sufentanil
	Pethidine	

High extraction drugs

Drugs with a high hepatic extraction have a high intrinsic hepatic metabolizing capacity ($f_u \cdot Cl_{int} \gg Q$) and are rapidly and extensively cleared by the liver from the blood. Their clearance depends primarily on hepatic blood flow, and binding to blood components is not an obstacle for extraction; the extraction is said to be non-restrictive or blood flow dependent. This results in a simplification of equation 6:

$$Cl \approx Q \quad (8)$$

Changes in protein binding will have no influence on the clearance of high extraction drugs. The importance of changes in protein binding must also be assessed by evaluating the influence on the drug concentrations, particularly on the free drug concentrations as they determine the drug effect. This is made clear by the following equations, which illustrate the relationship between total (C_{ss}) and unbound ($C_{ss,u}$) drug concentrations at steady state, and Cl following intravenous drug administration:

$$C_{ss} = \frac{R_0}{Cl} \quad (9)$$

and

$$C_{ss,u} = \frac{f_u \cdot R_0}{Cl} \quad (10)$$

where R_0 represents the rate of drug input. Because $Cl \approx Q$ (equation 8) for high extraction drugs, one can substitute Q for Cl in equations 9 and 10. It is apparent that C_{ss} is not affected by changes in protein binding, whereas $C_{ss,u}$ changes directly with f_u . The latter implies that for high extraction drugs, changes in free drug fraction may result in alterations in drug effect.

Low extraction drugs

Drugs with a low hepatic extraction have a low intrinsic hepatic metabolizing capacity ($f_u \cdot Cl_{int} \ll Q$) and are extracted less avidly and incompletely from hepatic blood. Their clearance is relatively independent of hepatic blood flow, and is primarily determined by the intrinsic metabolizing capacity of the liver and by the free drug fraction; the extraction

is said to be restrictive or capacity limited. This results in a simplification of equation 6:

$$Cl \approx f_u \cdot Cl_{int} \quad (11)$$

Changes in free fraction may occur during critical illness and will result in alterations of clearance of low extraction drugs. When substituting equation 11 into equations 9 and 10, it is clear that for low extraction drugs changes in protein binding are inversely related to C_{SS} , but have no effect on $C_{SS,u}$.

Intermediate extraction drugs

The clearance of drugs with intermediate extraction is dependent on hepatic blood flow, the intrinsic metabolizing capacity of the liver and free drug fraction.

Pharmacokinetic analysis of the time course of the drug concentration

Pharmacokinetic analysis in the individual patient

The study of the time course of drug concentrations in plasma, urine and other sampled sites has been helped by the development of sensitive analytic techniques such as high performance liquid chromatography (HPLC), mass spectrometry and radioimmunoassay. Changes in measured drug concentration in relation to time are used to derive pharmacokinetic constants that describe the behaviour of drugs in the body. The two most important pharmacokinetic constants to describe the characteristics of a drug are the volume of distribution (V_d) and clearance (Cl). The volume of distribution represents the apparent volume available in the body from the distribution of the drug. The clearance represents the body's ability to remove drug from the blood or plasma. Both V_d and Cl can be determined from a decline in their plasma concentration after drug administration.

Two methods to determine V_d and Cl are discussed in this chapter. Although model-independent analysis still represents the gold standard by which the estimates of other techniques should be compared, this approach does not offer sufficient information to facilitate the development of rational drug dosing

guidelines. Therefore, compartmental or physiological model-dependent analysis is mandatory.

Model-independent pharmacokinetic analysis

Model-independent pharmacokinetics represents a straightforward approach based purely on mathematical descriptions of blood or plasma profiles of drugs or metabolites without invoking a particular model. In many situations, such as during drug development, it is sufficient to characterize plasma profiles in terms of maximum plasma concentration levels, C_{max} , time of maximum level, t_{max} , and area under the plasma curve, AUC. These parameters can be obtained by simple inspection of the plasma or blood concentration of the drug versus time, as seen in Fig. 1.1. From AUC, one can determine the clearance and volume of distribution [12].

The AUC, representing the change in concentration (C) during time (t) (starting at the moment of drug administration) can be calculated by using the integral:

$$AUC = \int_0^{\infty} C(t) \cdot dt \quad (12)$$

In practice, the AUC can be estimated using the 'trapezoidal rule'. Because the total amount of drug eliminated between the moment of drug administration and infinity must be equal to the dose, we can rewrite equation 12 as follows:

$$\text{Dose} = Cl \cdot AUC \quad (13)$$

From equation 13, we can calculate the drug clearance (Cl) as:

$$Cl = \text{Dose}/AUC \quad (14)$$

The second basic pharmacokinetic parameter, volume of distribution (V_d), can also be determined as:

$$V_d = Cl \cdot MRT \quad (15)$$

Whereby MRT stands for the 'mean residence time', calculated as the ratio between the total area under the first moment of the plasma concentration–time curve (i.e. the area under the plasma concentration \times time versus time curve, extrapolated to infinity) or AUMC and the AUC:

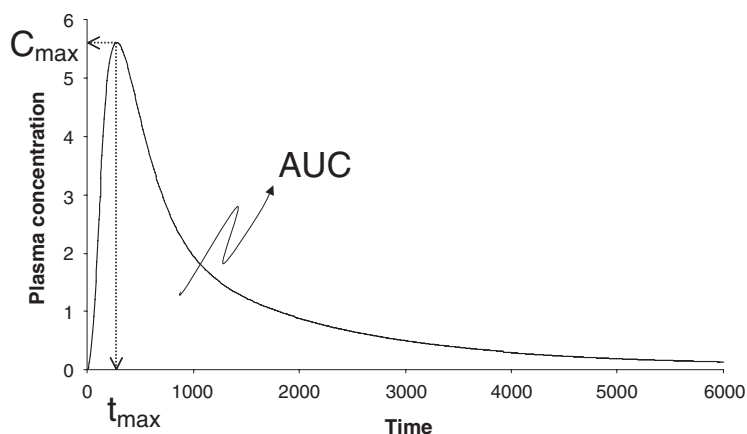


Figure 1.1 Time course of the plasma concentration of a drug after bolus injection. AUC, area under the curve; C_{\max} , maximum plasma concentration; t_{\max} , time at C_{\max} .

$$\text{MRT} = \text{AUMC} / \text{AUC} \quad (16)$$

It has to be stated that the V_d calculated here is the apparent volume of distribution. If the drug remains unbound in the plasma and does not distribute into other tissues, the V_d would be equal to the plasma volume. As most drugs distribute through extravascular sites in the body and bind to other tissues, the apparent V_d might be much larger than the whole body volume. In contrast, the initial volume is usually reported, which, for an intravenous bolus dose, is determined using equation 16:

$$V_d = \text{Amount} / \text{Concentration} = \text{dose} / C_0 \quad (17)$$

whereby the drug concentration is 'back-extrapolated' to time zero (C_0).

Model-dependent pharmacokinetic analysis

Two approaches towards model dependent pharmacokinetic analysis are discussed: *compartmental* and *physiological models*. In the *compartmental* model, the body is assumed to be made up of one or more compartments. These compartments might be special or chemical in nature but, in most cases, the compartment is used to represent a body volume or group of similar tissues or fluids into which a drug is distributed. In the physiological model approach, pharmacokinetic modelling is based on known anatomical or physiological values and the modelling of drug movement is based on the flow rates through partic-

ular organs or tissues and experimentally determined blood-tissue concentration ratios. Although compartmental models are dramatically simplifying the 'pharmacokinetic reality' and physiological models might be a more realistic approximation, compartmental models are often used clinically in anaesthesia to predict the plasma concentration of various drugs (e.g. propofol, opioids). Since the introduction of computer-controlled drug delivery systems into clinical practice (so-called target controlled infusion devices), it is crucial to understand the underlying theoretical concepts of compartmental models. Therefore, the development of these models is explained in more detail below.

Compartmental models

The simplest pharmacokinetic model is the 'one-compartment model' with a single volume (V) and clearance (CL), as shown in Fig. 1.2. Clearance is calculated as $k_{10} \cdot V$, whereby k_{10} is the rate constant for drug elimination. Although almost none of the drugs used in anaesthesia can be accurately characterized by the one-compartment model, it allows the introduction of some mathematical concepts. There are two forms of processes: zero-order and first-order. A zero-order process is one that happens at a constant rate. The mathematics of the rate of change (dx/dt) is simple:

$$\text{Constant rate of change} = k = dx/dt \quad (18)$$

where x is the amount of drug and t is time.

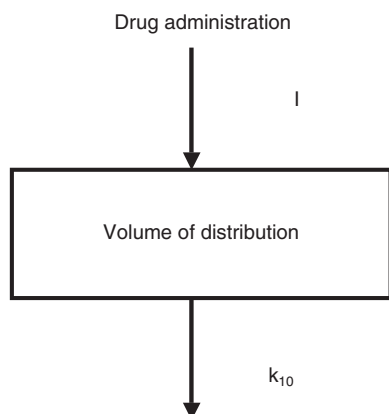


Figure 1.2 The one-compartment pharmacokinetic model.

If the value of x at time t is needed, $x(t)$, it is found as the integral of the equation 18 from time 0 to time t :

$$x(t) = x_0 + k \cdot t \quad (19)$$

where x_0 is the value of x at $t = t_0$. This is a straight line with a slope of k and an intercept of x_0 .

A first-order process is much more complex. The rate of change for a first-order process is:

$$dx/dt = k \cdot x \quad (20)$$

where the units of k are simply 1/time. If a value of x at time t is needed, $x(t)$, it can be found as the integral of the equation 20 from time 0 to time t :

$$x(t) = x_0 \cdot e^{-kt} \quad (21)$$

By using the equation $C_0 = x_0/V$, where C_0 is the concentration at time 0, x_0 is the initial dose of drug and V is the volume of the compartment, the plasma concentrations over time after an IV bolus of drug are then described by:

$$C(t) = C_0 \cdot e^{-kt} \quad (22)$$

This is the commonly used expression relating concentration to time and initial plasma concentration and the rate constants. It defines the 'concentration over time' curve for the one-compartment model and has a log-linear shape. The one-compartment model is frequently used in pharmacology to describe the pharmacokinetics of drugs. It demonstrates the

concepts of volumes, clearances and rate constants. In this model, no distribution phenomenon occurs. Unfortunately, none of the intravenous hypnotic anaesthetic drugs used in clinical anaesthesia can be characterized accurately by a one-compartment model because of their distribution into and out of the peripheral tissues. Therefore, it is necessary to extend this one-compartment model to a multicompartmental one.

Several multicompartment models are described in the literature [13,14]. Although a two-compartmental model is used commonly in general drug research, the most popular one in anaesthesia is the three-compartment mammalian model, as shown in Fig. 1.3. In anaesthesia, all clinically used, target controlled, infusion techniques and pharmacokinetic computer simulations are based on this model.

The fundamental variables of the compartment model are the volume of distribution (central, rapidly and slowly equilibrating peripheral volumes) and the clearances (systemic, rapid and slow inter-compartmental). As shown in Fig. 1.3, the drug is injected into and eliminated either by metabolism or renal excretion from this central compartment (compartment 1). The drug is quickly distributed into a rapidly equilibrating peripheral compartment (compartment 2) and this compartment quickly reaches equilibration with the central compartment. The drug is distributed more slowly into a third compartment (compartment 3). The sum of the compartmental volumes is the apparent volume of distribution during steady-state (V_{dss}) and is proportionally constant, relating the plasma drug concentration at steady-state to the amount of drug in the body [13].

Micro-rate constants, expressed as k_{ij} , define the rate of drug transfer from compartment i to compartment j . Compartment 0 is a compartment outside the model, so k_{10} is the micro-rate constant for those processes acting through biotransformation or elimination that irreversibly remove drug from the central compartment (compartment 1). The inter-compartmental micro-rate constants (k_{12} , k_{21} , etc.) describe the exchange of drug between the central and peripheral compartments. Each compartment has at least two micro-rate constants: one for drug entry and one for drug exit. The differential

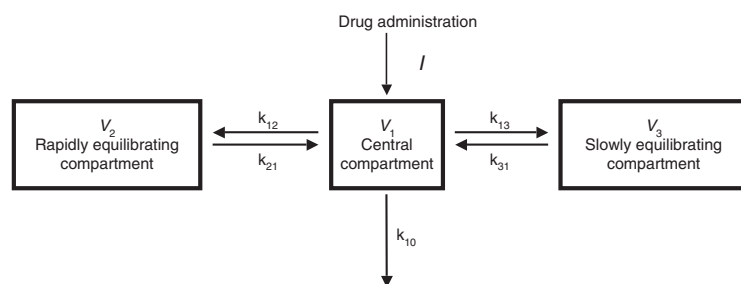


Figure 1.3 The three-compartment pharmacokinetic model.

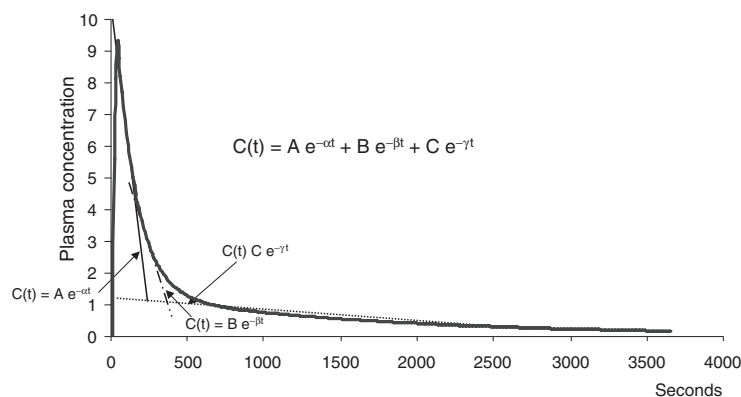


Figure 1.4 The triexponential curve representing the time course of a drug plasma concentration after intravenous injection. Each exponential term accounts for a portion of the curve. The individual lines associated with each exponential term are also shown. The triexponential curve represents the algebraic sum of the individual exponential functions. Solid, dashed and dotted lines are used to show how each exponential relates to different portions of the full curve.

equations describing the rate of change for the amount of drugs in compartments 1, 2 and 3, follow directly from the micro-rate constants (note the similarity to the one-compartment model).

For example, for a three-compartment model, the differential equations are:

$$\begin{aligned} dx_1/dt &= I + x_2 k_{21} + x_3 k_{31} - x_1 k_{10} - x_1 k_{12} - x_1 k_{13} \\ &= I + x_2 k_{21} + x_3 k_{31} - x_1 (k_{10} + k_{12} + k_{13}) \end{aligned} \quad (23)$$

$$dx_2/dt = x_1 k_{12} - x_2 k_{21} \quad (24)$$

$$dx_3/dt = x_1 k_{13} - x_3 k_{31} \quad (25)$$

where I is the rate of drug input, x is the amount of drug for a specific compartment and k is a micro-rate constant. Each of the above equations can be solved and the complete solution can be found in the literature [14].

How may we explore into how many compartments the pharmacokinetic behaviour of a specific drug fits? This can be done by taking plasma samples at specific time points after a bolus injection and de-

picting the results in a log (plasma concentration) over time graph, as shown in Fig. 1.4.

Three distinct phases can be distinguished. There is a *rapid 'distribution' phase* (solid line) that begins immediately after the bolus injection. This phase is characterized by very rapidly equilibrating tissues. There often is a *slower second distribution phase* (dashed line) that is characterized by a movement of the drug into more slowly equilibrating tissues and a return of the drug from the most rapidly equilibrating tissues (i.e. those that reached equilibrium with the plasma during phase I). The terminal phase (dotted line) is a straight line when plotted on a semi-logarithmic graph. The terminal phase often is called the *elimination phase* because the primary mechanism for decreasing drug concentration during the terminal phase is its elimination from the body [13].

Mathematically, a decreasing curve with a constant slope can be described, as in equation 21. This is for a one-compartmental model. Curves that continuously decrease over time, with a contin-

uously declining slope (Fig. 1.4), can be described by the sum of multiple equations 21, one for each compartment. This is the sum of exponentials describing the decrease of plasma concentration over time:

$$C(t) = A e^{-\alpha t} + B e^{-\beta t} + C e^{-\gamma t} \quad (26)$$

where t is the time after injection of the bolus, $C(t)$ is the drug concentration after a bolus dose, and A , α , B , β , C and γ are variables of a pharmacokinetic model. A , B , and C are called *coefficients* and express an equivalent of compartmental concentrations. At time 0,

$$C_0 = A + B + C \quad (27)$$

α , β and γ are called *exponents* (sometimes called *hybrid rate constants*). These exponents express the slope of each exponential decay, as shown in Fig. 1.4.

Equation 26 can be transformed mathematically from the exponential form to the 'compartmental' form (the form using the micro-rate constants). For the three-compartment mammillary model, this interconversion between the exponential form (equation 26) and the micro-rate constant form (equations 23–25) becomes exceedingly complex as more exponents are added. This is because every exponent is a function of every micro-rate constant and vice versa. It is not the purpose of this chapter to explain and solve all the equations. The complete solution of the three-compartment model can be found in the literature [13,14].

Front-end kinetics to optimize compartmental models

In a classical multicompartmental mammalian pharmacokinetic model, intravenously administered drugs are assumed to mix instantaneously in an initial distribution volume (V_c) that includes, at a minimum, the intravascular space. In reality, the volume of distribution of a drug expands with a time course dependent on the physiological environment and chemical characteristics of the drug. As a result, the estimate of V_c will be smaller when earlier blood sampling is applied. Nonetheless, conventional pharmacokinetic models overestimate because they ignore the complexity of intravenous mixing [15].

Recirculatory multicompartmental pharmacokinetic modelling can be applied to describe drug disposition from the moment of rapid intravenous injection. These models retain the relative simplicity of mammalian models, but incorporate descriptions of key physiological processes that have emerged as important determinants of intravenously injected drug disposition. In the fit of the recirculatory model to the data, the concentration at time zero is zero and there is a delay between the time the drug is administered and the time the drug appears at the sampling site. This model fits the early arterial concentrations of samples obtained soon after rapid intravenous input. Pulmonary uptake, injection rate, intravascular mixing and the influence of the cardiac output on this phenomenon are taken into account. First applications of these recirculatory multicompartmental models have recently been published [15,16].

Non-linear compartmental models

When drug behaviour is studied by pharmacokinetic models, it is mostly assumed that distribution and elimination are first-order processes resulting in a linear relationship between concentration at any time and dose. This assumption is only correct if elimination and transport processes never become saturated. When saturation occurs (e.g. saturation of an enzyme system), the rate of drug elimination reaches a maximum and becomes concentration independent [12]. For a single non-linear compartmental model, the elimination rate (ER) can be described as:

$$ER = \frac{V_n C_u(t)}{K_m + C_u(t)} \quad (28)$$

where $C_u(t)$ is the concentration of the unbound drug at time t and K_m is the Michaelis–Menten constant, which is the concentration at which the rate is half maximum, V_m . When $C_u \ll K_m$, then the process is not saturated and the rate is dependent on the concentration, described as:

$$ER = \frac{V_n}{K_m} \cdot C_u(t) = Cl \cdot C_u(t) \quad (29)$$

In contrast, when C_u is much greater than K_m , saturation occurs, the elimination rate approaches V_m and is concentration independent ($ER = V_m$).

Physiological models

The description of physiological drug models depends on the interpretation of drug distribution in terms of anatomical or physiological spaces, which have defined volumes, perfusion characteristics and partition coefficients. Individual compartments may have 'flow-limited' or 'membrane-limited' characteristics (depending on whether blood flow or transmembrane transport is the limiting factor governing drug uptake). This means that the time course of drug or metabolite levels in the various 'physiological' organs or compartments is calculated using blood flow rate through each particular region, diffusion of the drug between blood and tissue, and the relative affinity of drug for blood and the various tissues and organs [17].

These complex physiologically based pharmacokinetic models have been used to describe the disposition of volatile anaesthetics [18]. For intravenously administered agents, however, their application has been sporadic because of the large number of parameters involved in the studies to determine the models. Therefore, their application is justified only when detailed mechanisms of drug metabolism or excretion by liver, kidney, lung or other organs is required or when specific tissue localization should be depicted (e.g. anticancer drugs).

Connecting pharmacokinetics and dynamics

The time course of drug concentration, defined as the pharmacokinetics of the drug, cannot in itself predict the time course or magnitude of drug effect. In clinical practice, a delay is frequently observed between the moment of peak plasma concentration, peak concentration at the effect site and peak drug effect. This delay occurs when the plasma is not the site of drug action, but only a means of transport, and is called counterclockwise or anticlockwise hysteresis. Drugs exert their biological effect at the 'biophase', also called the effect site, which is the immediate area where the drug acts on the body, and includes membranes, receptors and enzymes. The study of the concentration–effect relationship is called pharmacodynamics and is covered elsewhere in this book. Problems resulting from temporal disequilibrium (hysteresis) can be overcome by using

the concept of the effect compartment model [19,20] in which drug response is modelled against drug concentration in a hypothetical effect compartment. The concentration of the drug in this theoretical compartment is directly related to the measured drug effect.

The effect compartment is an additional compartment linked to the central compartment of the mammillary pharmacokinetic model, as shown in Fig. 1.5. The effect compartment receives drug from the central compartment by a first-order process, expressed by a first-order rate constant, k_{e1} . The actual mass of drug reaching the effect compartment is negligible. It is assumed that the effect compartment kinetics do not affect the pharmacokinetic model. Given these assumptions, the effect compartment can be considered a compartmental model with an input defined by a first-order rate constant (k_{e1}) and a first-order rate constant defining the output (k_{e0}). The time to reach a steady-state concentration in this effect compartment is dependent on the elimination from the effect compartment. A clarification of this statement is found in equation 30

$$C_e = C_{SSe} (1 - e^{-k_{e0}t}) \quad (30)$$

The term C_e defines the drug concentration in the effect compartment, C_{SSe} refers to the concentration at steady-state or the concentration that will be reached in the effect compartment after equilibration with the concentration in the central compartment of the pharmacokinetic model. The time to reach a steady-state is solely dependent on the k_{e0} . This rate constant can precisely characterize the temporal aspect of equilibration between plasma concentration and drug effect. The rate constant k_{e0} in the pharmacokinetic model, together with a pharmacodynamic model (e.g. the sigmoid E_{max} model) driven by the predicted effect site concentration, allows us to characterize the effect data directly to the plasma concentration using non-linear regression analysis. This step simultaneously yields estimations of the pharmacokinetic and pharmacodynamic variables. The exact equations for the combination of an effect compartment with a three-compartment mammillary model can be found in the literature [19].

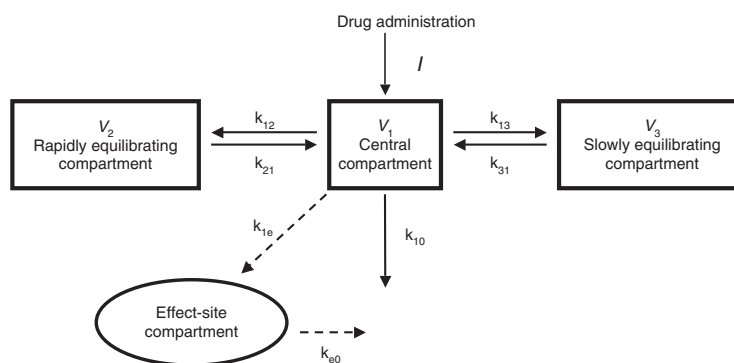


Figure 1.5 The three-compartment pharmacokinetic model enlarged with an effect site compartment.

Population pharmacokinetic analysis

The pharmacokinetic characteristics of a specific drug are usually reported as mean population variables. However, it is crucial to reveal additional information about the magnitude of variability in the population receiving the drug. The analysis of pooled data from many subjects, or summary statistics derived from individual pharmacokinetic studies, are generally considered to be unsatisfactory methods for population analysis. Although this *pooled approach* will describe the observations well most of the time (because the objective function for the regression model is precisely that — to minimize the error between model prediction and the observed value), this pooled approach is 'naïve' and does not take into account specific population variability. Failure to appreciate the magnitude of variability in the pharmacology of a drug can compromise fixed dose clinical trials outcomes by making the drug appear less effective or more toxic [21].

Population pharmacokinetic analysis is crucial during every drug development as it has considerable predictive value. Previously, a '*two-stage*' approach was applied to characterize population variability. In this case, pharmacokinetic data are derived for every individual from the population and then population mean (and standard deviations) are calculated to depict the population and its variability. Although reported frequently in the literature, the major problem of the two-stage approach is that it fails to address the two major sources of population variability: intra- versus interindividual variability [22].

When obtaining multiple blood samples from various patients to calculate the population pharmaco-

kinetic model, two problems are faced. First, there is a random intra-individual variability resulting from unavoidable (small) errors in the assay method or individual variability. Secondly, there is an interindividual variability which can be defined as randomized effects (not measurable difference between individuals) or fixed effects (measurable, also defined as covariates). Even after having entered all possible covariates (e.g. age, weight, height, gender, body surface, lean body mass), randomized effects will still exist. To be able to reveal all possible sources and explanations of population variability, sophisticated statistical analysis, called *non-linear mixed effect modelling*, is required. Various commercially available software packages are able to process population data using such modelling [20,23–27].

Pharmacological changes resulting from physiological and pathophysiological alterations

The different pharmacokinetic processes explained above may be altered because of physiological and pathophysiological effects leading to changes in free concentration at the effect site, and eventually to alterations in drug effect. Changes in drug effect may also result from changes in pharmacodynamics such as alterations in intrinsic drug efficacy or end organ sensitivity to the drug. These events make up the pharmacodynamics of a drug. Both pharmacokinetics and pharmacodynamics are susceptible to physiological processes and pathophysiological conditions. The potential impact of age, pregnancy, chronopharmacology, obesity and renal, liver,

circulatory and respiratory failure, head injury and cardiopulmonary bypass on the pharmacology of the drug are discussed. The examples used to illustrate this section focus on drugs frequently used during anaesthesia.

Age

With increasing age, multiple physiological and pathophysiological changes occur in the cerebrovascular, cardiovascular, respiratory, renal and hepatic systems, resulting in pharmacological changes such as a reduction in excretion and metabolism, and an increased CNS sensitivity [28]. The changes may result in an increased drug effect, reduced elimination rate and prolonged duration of drug action. The increase in body fat, reduction in muscle mass and decrease in total body water with age may result in an increase of distribution volume for lipophilic drugs, and decrease for hydrophilic drugs.

For most intravenous hypnotic agents, such as midazolam [29] and propofol [30], and for the inhalational anaesthetic agents, the increased sensitivity with age is, at least in part, explained by altered pharmacodynamics. For opioids, the pharmacodynamic involvement is not always clear. The prolonged opioid effect of sufentanil in elderly patients has been attributed to alterations in pharmacodynamics [31], whereas for alfentanil changes in pharmacokinetics have been suggested to account for the lower dose requirement in elderly patients [32]. For neuromuscular agents, the increased effect in the elderly appears to be caused by altered pharmacokinetics resulting in a decreased clearance because of an age-related decrease in renal and hepatic function.

Physiological changes also influence the pharmacokinetics of drugs in children [33]. The neonatal phase is characterized by rapid and dramatic changes of organ function. Changes in body composition and the content of plasma proteins influence volume of distribution, the drug distribution to different compartments and the amount of free drug in plasma. A decrease in extracellular fluid space during the first year of life influences distribution volume of neuromuscular blocking agents which are polar drugs whose distribution is restricted to the extracellular fluid space [34]. Thus, weight-normalized doses of

neuromuscular blocking agents yield smaller plasma concentrations in neonates or infants than in children or adults. Pharmacokinetics of propofol in children are characterized by a larger central compartment volume, which is consistent with the higher induction dose requirement reported for children [35]. As a result of the immaturity of the hepatic microsomal systems there is decreased metabolism of agents such as diazepam, midazolam and morphine [33]. In the first year of life, capacity of the enzymatic systems increase, which is accompanied by increased drug clearance. For remifentanyl, which is metabolized by tissue and plasma esterases, the opposite is observed, with an increased clearance in young infants compared with older children and young adults [36]. Beyond the neonatal period, the pharmacology of most opioid analgesics are not markedly different from those of adults [37]. Maturation changes may also occur in pharmacodynamics (e.g. increased sensitivity to neuromuscular blocking agents in younger patients) [34].

Pregnancy

Throughout pregnancy there are marked physiological changes that may have a significant influence on the pharmacokinetics of drugs [38]. The increased minute ventilation, decreased functional residual capacity and increased cardiac output may result in increased pulmonary uptake of gases, leading to decreased anaesthetic requirement in pregnancy. However, the rate of induction with inhalational anaesthetic agents is not necessarily faster because this depends on both pulmonary equilibration kinetics and tissue distribution kinetics. Apparent distribution volumes of drugs may increase during pregnancy because of the expansion of fluid volume and the presence of fetal and placental tissues resulting in an increased elimination half-life. However, contrary to what one would expect, these changes in distribution volume are not observed with the polar neuromuscular relaxants, for which distribution volumes are unchanged during pregnancy [39]. The increased cardiac output may accelerate the onset of action of induction agents and neuromuscular blockers. Unbound drug fraction may increase during pregnancy because of reduced albumin concentration and endogenous displacing substances. With re-

gard to metabolism, both inhibition and induction of enzymes have been reported during pregnancy. The increased thiopental clearance during pregnancy has been attributed to hormonal enzyme induction. Hepatic blood flow is thought to be unchanged during pregnancy, although clearance of propofol, which is considered blood flow dependent, has been reported to be increased during pregnancy, and increased extrahepatic clearance can probably account for this observation. Renal plasma flow is increased, resulting in increased renal drug excretion, and the increased clearance of pancuronium during caesarian section has been explained by the increased glomerular filtration rate [39]. Elimination of inhalational anaesthetics is expected to be enhanced by the increased minute ventilation. Apart from pharmacokinetic changes, pharmacodynamics of drugs, although not well investigated in pregnancy, may also be influenced by the physiological processes occurring. For instance, an increased pain threshold during pregnancy, mediated by endorphins, may theoretically influence opioid effects. The prolonged apnoea following large doses of succinylcholine in pregnancy may be explained by decreased plasma pseudocholinesterases [39].

Chronopharmacology

Chronopharmacology is the influence of circadian rhythm on the pharmacology of drugs. Pharmacological parameters are influenced by different physiological functions displaying circadian rhythm [40]. Information regarding circadian rhythms for general anaesthesia remains fragmentary. Barbiturates are more effective in the evening than in the morning, which has been explained by endogenous variation in hepatic drug metabolism and by diurnal changes in GABAergic activity. A temporal pattern in pharmacology has also been observed for midazolam, with a higher clearance after an intravenous dose in the late afternoon than after a morning dose and a circadian fluctuation in the sensitivity of the CNS. No data are currently available regarding circadian changes for propofol or etomidate. Diurnal changes in the efficacy of halothane has been investigated and it was found that its greatest efficacy occurred in the early morning, which may theoretically be explained by circadian rhythmicity in receptor activity

as well as distribution and metabolism. Circadian changes in pancuronium requirements could be explained by time-dependent changes in renal elimination and cholinesterase activity. Diurnal variation in pain perception has been shown to be highly relevant to the daily practice of pain management, leading to variations in the need for analgesics at different times of day.

Obesity

Obesity can significantly alter the tissue distribution and elimination of drugs, and may necessitate modified loading and/or maintenance doses [41]. The altered pathophysiology of the obese body can affect drug distribution because of changes in body composition, regional blood flow and binding to plasma proteins. In obese people, the percentage of fat per kilogram of total body weight is markedly increased, whereas that of lean tissue is reduced. Cardiac performance may be impaired and tissue blood flow per gram of fat can be significantly decreased. There is also uncertainty about the binding of drugs to plasma proteins in obese patients. Increased α_1 -acid glycoprotein acid levels may lead to increased protein binding of drugs. The behaviour of molecules with weak or moderate lipophilicity (e.g. vecuronium, rocuronium) is generally rather predictable, as these drugs are distributed mainly in lean tissues, and the dosage of these drugs should be based on the ideal body weight. For highly lipophilic drugs (e.g. remifentanyl), there are great discrepancies in distribution in obese individuals, and the size of the distribution volume is not always correlated with the degree of lipophilicity.

Some data suggest that the activities of hepatic cytochrome P450 isoforms are altered in obesity, but no clear overview of drug hepatic metabolism is currently available. Pharmacokinetic studies provide differing data on renal function in obese patients. Clearance and distribution volumes of propofol have been correlated with total body weight in obese patients, so that the values of the elimination half-life in non-obese and obese individuals are similar. This can explain why there are no signs of drug accumulation in obese patients. For sufentanil, clearance and distribution volume corrected per kilogram of total body weight were similar in obese and

non-obese patients, whereas for remifentanyl these parameters were significantly smaller in obese patients. Accordingly, remifentanyl doses for obese patients should be based on ideal body weight.

Liver failure

The liver is the major route for elimination of a wide variety of drugs. Biotransformation, liver blood flow, protein binding and biliary excretion, which can all potentially influence drug pharmacokinetics, depend upon the normal functioning of the liver. Impaired liver function may therefore lead to significant alterations in the pharmacokinetics of many drugs, necessitating dosage adjustment. Most information about the influence of liver insufficiency on the pharmacokinetics of drugs comes from patients with hepatic cirrhosis. However, other disease conditions such as hypothermia, hypotension and sepsis may also be associated with impaired liver function. Studies show that more than 50% of critically ill patients have hepatic dysfunction.

In order to fully understand the impact of liver failure on the pharmacokinetics of a particular drug, the underlying determinants of hepatic drug clearance must be well understood (see above). Measurement of endogenous substances such as bilirubin, bile pigments, albumin and enzymes have been used to assess liver function. However, unlike the assessment of renal function by measuring creatinine clearance, these parameters have not proven to be generally useful. Liver function tests do not generally correlate well with important physiological determinants of drug disposition such as liver blood flow and intrinsic clearance.

The histopathological changes occurring in liver cirrhosis are associated with a reduction in liver blood flow, the presence of portosystemic shunting and a reduction in the number and in the activity of the hepatocytes. The clinical manifestations of cirrhosis such as varices, oedema and ascites may also contribute to alterations in the pharmacokinetic behaviour of many drugs [42]. Impaired albumin production in cirrhotic patients may reduce plasma binding and thus increase the free drug fraction. In addition, drug absorption may be markedly altered in cirrhosis. A decrease in the fraction of the mesenteric blood flow passing through the liver (due to

portosystemic shunts) and decreased activity of drug metabolizing enzymes may result in an increased bioavailability of some orally administered drugs, such as midazolam and morphine. Drug distribution of certain drugs in cirrhotic patients may be increased because of reduced plasma protein levels and changes in body composition (ascites, oedema). An increased distribution volume of rocuronium in patients with liver disease results in a longer elimination half-life and a prolonged recovery time [43]. Hepatic clearance of high extraction drugs in cirrhotic patients is expected to be decreased because of impaired hepatic blood flow resulting from extra- and intrahepatic shunts. Morphine clearance was found to be decreased in cirrhosis [44]. However, contrary to what one would expect, there was no reduction in clearance of the high extraction drugs propofol [45,46], fentanyl and sufentanil [47] in cirrhotic patients. Clearance of low extraction drugs may be impaired because of hepatocellular damage, whereas an increase in free drug fraction may facilitate hepatic clearance of these drugs. Oxidative metabolic reactions, catalysed by CYP enzymes, appear to be more affected than glucuronidation in cirrhotic patients; reduced oxidation of alfentanil in patients with cirrhosis resulted in a decreased clearance [48]. Reduced midazolam clearance in cirrhotic patients was also observed [49], which may be explained by a reduced CYP3A4 isoenzyme activity. The pharmacokinetics of remifentanyl, which is metabolized by tissue and plasma esterases, appear to be unaffected in liver disease [48]. In liver cirrhosis, extrahepatic metabolism may compensate, at least in part, for the impaired metabolism of the drug by hepatic enzymes. Biliary obstruction in liver cirrhosis may also lead to impaired biliary excretion of drugs and/or their metabolites.

Cardiovascular failure, resulting from, for instance, sepsis, cardiogenic and hypovolaemic shock, may also affect hepatic clearance [50–53]. Inadequate hepatic perfusion during cardiovascular failure is expected to decrease clearance of high extraction drugs, as has been shown for morphine in septic shock patients. Respiratory failure, requiring mechanical ventilation, often develops during cardiovascular failure. The reduction in cardiac output and liver blood flow induced by mechanical ventila-

tion is also expected to decrease clearance of high extraction drugs. The use of vasopressor agents may also alter hepatic blood flow, thereby influencing drug clearance. Hepatocellular enzyme activity is often reduced during cardiovascular failure, leading to decreased clearance of low extraction drugs, and is presumably influenced by factors such as organ perfusion, intracellular oxygen tension and cofactor availability. The CYP enzyme system has been shown to be markedly altered in critical illnesses, and to a greater extent than the phase II enzymes. This may be because the CYP enzyme system is located in the more hypoxic central region of the liver lobule and therefore is more sensitive to hypoxia. Hypoxaemia results in reduced enzyme production in the liver, reduced efficiency of the enzyme present and decreased oxygen available for drug oxidation. Exposure of isolated human hepatocytes to hypoxia for several days resulted in a reduction in the CYP enzymes, with certain CYP families more affected than others. In patients with congestive heart failure, clearance of antipyrine was reduced; this is a low extraction drug independent of hepatic blood flow, often used as a model substrate for microsomal oxidative metabolism [54]. Clearance of midazolam was also found to be decreased in these patients [55]. Hepatic drug metabolism in sepsis may also be reduced by the nitric oxide mediated inhibition of CYP-dependent drug metabolism. *In vitro* experiments using human hepatocytes showed that cytokines may also reduce CYP expression. Temporary failure of midazolam metabolism in patients with sepsis, attributed to changes in hepatic blood flow and/or hepatic enzyme activity, has been reported [56]. Interestingly, serum from septic patients decreased CYP3A4-mediated metabolism of midazolam *in vitro*, which has been attributed to the depressant effects of cytokines.

Renal failure

The kidneys are responsible for the excretion of many drugs, both the parent drug and its metabolites. The urinary excretion of a drug is the net result of filtration, secretion and reabsorption. The causes of renal impairment are numerous and can be divided into prerenal, renal and postrenal causes. Septic shock, for instance, initially results in a pre-

renal type of acute renal failure, which then leads to the full picture of tubular/obstructive acute renal failure. In renal failure, both the parent drug and metabolites may accumulate.

Renal failure may also influence drug distribution [52]. A decrease in albumin concentration, changes in albumin structure, and competition between endogenous substances and drugs at albumin binding sites may increase free drug fraction during renal failure. This may theoretically increase drug effect for intravenously administered high extraction drugs extensively bound to albumin, and drug distribution volume. Both distribution volume and clearance of midazolam were found to be increased in patients with chronic renal failure, which has been attributed to reduced protein binding and a higher free drug fraction [57]. Metabolic acidosis occurring during renal failure may also be expected to affect drug distribution. For drugs that are weak acids, a decrease in pH will result in an increase in the non-ionized fraction, which may theoretically enhance drug distribution, whereas for weak bases the opposite may occur. Fluid retention is also a feature of renal failure, resulting in changes in total body water and the distribution of many drugs.

The kidneys have a modest capacity for autoregulation, and when renal blood flow is moderately reduced (10–20%), the glomerular filtration rate does not fall. Further reductions in blood flow resulting from, for example, cardiovascular failure, may compromise kidney perfusion as part of homeostasis, resulting in decreased glomerular filtration and a reduction in renal drug clearance. Clearance of drugs that are only filtered and not secreted or reabsorbed, is determined by both glomerular filtration rate and the free drug fraction. The pharmacokinetics of morphine and its glucuronide metabolites, morphine-3-glucuronide and morphine-6-glucuronide, have been investigated in intensive care patients with renal failure [58]. The two metabolites are eliminated by renal filtration only, and a linear relationship between renal function and the renal clearances of the two metabolites was found. Renal failure may thus result in higher plasma concentrations of these active metabolites. The latter was confirmed in another study in which the increased susceptibility to morphine in patients with

renal failure was explained by the observed accumulation of the active metabolite morphine-6-glucuronide in cerebrospinal fluid. The pharmacokinetics of the synthetic opioids alfentanil, sufentanil and remifentanil have been found to be little changed in patients with renal failure whereas continuous administration of fentanyl, although primarily metabolized in the liver, was found to result in prolonged sedation [59]. Prolonged sedation has also been observed after administration of midazolam in critically ill patients with renal failure, which has been attributed to accumulation of the active conjugate metabolite. No changes in pharmacokinetics of propofol, which is mainly metabolized in the liver, were found in patients with end-stage renal disease [60]. One study even found higher propofol requirements in patients with end-stage renal disease, which has been attributed to the hyperdynamic circulation caused by anaemia in these patients [61]. In patients with chronic renal failure, plasma clearance of vecuronium, which mainly undergoes hepatic elimination [62] resulting in an active metabolite, was found to be decreased. Also for rapacuronium [63], pancuronium and their potent metabolites, decreased clearance was observed in patients with renal failure. However, pharmacokinetics of atracurium were found to be unaffected by renal failure, explained by its spontaneous chemical degradation and ester hydrolysis. However, concern has been expressed about possible accumulation of its principal metabolite laudanosine in patients with renal failure. Renal failure was found to have little impact on the duration of action of rocuronium and cisatracurium [64]. Besides renal filtration, urinary drug secretion may also be part of the renal excretion process for certain drugs. Urinary drug secretion may be influenced by protein binding, depending on the efficiency of the secretion process, and on the contact time at the secretory sites. By analogy with hepatic metabolism, drugs that are almost completely removed from blood within the time they are in contact with the active transport site, secretion is dependent on blood flow but independent of protein binding, and reduced renal blood flow may be expected to slow elimination.

Tubular reabsorption may also occur with certain drugs. During cardiovascular failure, reabsorption

may be expected to increase as a consequence of decreased urine flow accompanying a decrease in glomerular filtration rate, but documentation of clinically important decreases in drug excretion as a result of this mechanism is lacking.

Circulatory failure

Circulatory failure caused by, for example, sepsis, cardiac failure or haemorrhage, is a common cause of altered pharmacokinetics [50–53,65,66]. A dramatic illustration of the impact of haemorrhage on the pharmacology of anaesthetics has been provided by Halford [67], who, in 1943, described an increased mortality rate in wounded military personnel during surgery under thiopental anaesthesia at the beginning of the Second World War. Regardless of aetiology, circulatory failure results in a redistribution of cardiac output with blood shunted away from less vital organs such as kidneys, spleen and gut to vital organs such as heart and brain. This may result in a disproportionate fraction of the available cardiac output delivered to the heart and brain. These changes in blood flow during haemodynamic shock may theoretically be expected to influence the pharmacokinetics of a drug by affecting absorption, distribution, metabolism and excretion. The pharmacodynamics may also be altered by changes in, for example, end organ sensitivity.

Circulatory dysfunction results in a decreased perfusion of muscles, skin and splanchnic organs. Absorption of drugs from sites with impaired blood flow is slow, sometimes incomplete, and subject to changes in circulatory status. Thus, the oral, transdermal, subcutaneous and intramuscular routes may not be reliable in critically ill patients, and an intravascular route is preferred. Cardiovascular failure will indeed result in a reduced enteral absorption of drugs not only because of the decreased forward flow (reduced organ perfusion), but also because of the increased back pressure (venous congestion) in the gut circulation. Gut hypoperfusion and poor absorption of drugs may theoretically also be worsened by mucosal oedema caused by hypoproteinaemia. Moreover, gastrointestinal failure is often present in the critically ill patient because of gut hypomotility (e.g. after surgery) caused by the constellation of organ failure associated with sepsis or

as a result of the administration of opioids for analgesia.

The rate and extent of distribution of a drug is determined by cardiac output, regional blood flow, the drug permeability of the tissue membranes and the relative distribution of the drug between tissue and blood. The latter is dependent on the binding of the drug in blood and tissues, the tissue mass, the lipid solubility of the drug and, for ionizable drugs, the pKa and the pH of the environment. All these determinants of distribution may change during circulatory failure, thereby altering the drug distribution volume.

Cardiovascular failure with a reduction of cardiac output may result in decreased drug distribution resulting in the homeostatic redistribution of blood flow away from less vital organs with preservation of blood flow to heart and brain. This phenomenon may be important for rapidly intravenously administered drugs with a high degree of lipid solubility, such as anaesthetics, and may result in an increased risk of CNS effects. Benowitz *et al.* [68] illustrated this principle by using a computer simulation of lidocaine kinetics for a 70-kg person in normal and hypovolaemic conditions following simulated removal of 30% of the blood volume. Following lidocaine administration, the amount of drug in the blood pool is higher during haemorrhage because the blood volume is smaller and because perfusion of other tissues is decreased. As a result of the higher blood concentrations and the autoregulation of brain blood flow, lidocaine content in the brain is much higher in early phases, explaining why CNS toxicity may result when standard lidocaine doses are administered to patients with circulatory failure. The slower and decreased distribution of lidocaine to the muscles during haemorrhage results from the homeostatic vasoconstriction in this organ.

Systemic inflammatory response syndrome has a widespread effect on the endothelium leading to increased capillary permeability which may result in accumulation of fluids in the interstitial space. This so-called 'third spacing' phenomenon may affect the distribution of drugs, particularly those with a small distribution volume. Endothelial barrier disruption may also lead to leakage of proteins away from the blood pool thereby influencing drug distribution.

Sepsis may also be expected to influence other tissue membranes, and meningeal inflammation, for instance, has been shown to increase the permeability of the blood–brain barrier. This is important for hydrophilic drugs, whereas penetration of more lipophilic compounds was found to be less dependent on the function of the blood–brain barrier.

Changes in the plasma protein binding of drugs during circulatory failure may be caused by changes in the concentration of the plasma proteins to which they are bound, by competition of endogenous substances for binding sites or by changes in the binding characteristics. Critical illness can cause increased concentrations of acute phase reactant proteins like α_1 -acid glycoprotein which is a major binding protein for basic drugs such as alfentanil. Increases in the concentration of α_1 -acid glycoprotein will decrease the unbound fraction of drugs that bind to this protein in the plasma, and result in a decreased distribution volume. In contrast, reduction in the level of serum albumin during critical illness because of reduced dietary protein intake, increased capillary permeability, haemodilution, renal loss and/or reduced hepatic synthesis may increase the free drug fraction of drugs that bind to albumin resulting in an increased distribution volume. For midazolam, which is extensively bound to albumin, a negative correlation was found between its distribution volume and the plasma albumin concentration in intensive care patients [69].

Fluid retention, as part of the homeostasis in response to a failing heart and as a result of fluids administered during resuscitation, may increase the volume of distribution. Alterations in distribution volume may also be expected from changes in tissue volume. Changes in general lean body mass and total body fat are likely to be of importance for the drug distribution volume. For instance, total body fat will decrease during sepsis because of stimulation of lipolysis and reduction of lipogenesis.

Reduced organ perfusion causes anaerobic metabolism and metabolic acidosis which may alter the distribution of ionizable drugs. The latter may also result from pH changes resulting from respiratory and kidney failure. No data are available on the influence of changes in pH on drug distribution during

circulatory failure. For drugs that are weak acids, a decrease in pH will result in an increase in the non-ionized fraction, which may theoretically enhance drug distribution, whereas for weak bases the opposite may occur.

Respiratory failure

Respiratory disorders induce several pathophysiological changes involving gas exchange and acid–base balance, regional haemodynamics, and alterations of the alveolar-capillary membrane which may affect absorption, distribution and elimination of drugs [70]. Changes in blood pH are expected to alter plasma protein binding and volume of distribution. Decreased cardiac output and hepatic blood flow in patients resulting from right ventricular failure or mechanical ventilation are expected to cause an increase in the plasma concentration of drugs with a high hepatic extraction ratio (see above). The same mechanisms may be responsible for a decreased renal elimination of drugs during respiratory failure. Acute and chronic lung disease can result in hypoxia, which may have significant effects on the enzymes responsible, leading to decreased biotransformation of drugs with a low extraction ratio [51]. However, clinical data on the effects of lung disease on the clearance of drugs are lacking.

Head injury

Patients with head injury may develop profound metabolic changes resulting in a hypermetabolic, hypercatabolic and hyperdynamic state. These changes may be expected to alter pharmacokinetics. Hepatic oxidative and conjugative metabolism have indeed been shown to be significantly increased over time in patients after acute head injury [71], resulting in increased metabolism of, for instance, pentobarbital, thiopental and lorazepam [72]. Hypoalbuminaemia and a rise in α_1 -acid glycoprotein accompanying the acute phase response in patients with head injury are expected to alter both drug distribution and metabolism.

Cardiopulmonary bypass

Cardiopulmonary bypass is accompanied by profound changes that may alter the pharmacokinetics of drugs [73,74]. For many drugs, such as midazolam, propofol, etomidate, pancuronium, fentanyl,

alfentanil and sufentanil, an abrupt decrease in serum concentration has been observed upon initiation of bypass which is explained by haemodilution and an increase in distribution resulting from decreased protein binding. For opiates, adsorption to the bypass apparatus was shown to be important. The gradual increase in serum concentrations seen during cardiopulmonary bypass after the initial fall as has been observed for midazolam, etomidate and sufentanil is usually explained by redistribution of the drug from tissues to the serum and/or a decrease in its elimination. The latter can be caused by impairment of renal or hepatic clearance resulting from lowered perfusion and hypothermia. The same phenomena are thought to explain why in the post-bypass period a concentration increase occurs, or at least a slower decrease than expected; this has been observed for drugs such as midazolam, etomidate and fentanyl.

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