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39 Intravenous Infusions for Sedation: Rationale, State of the Art, and Future Trends

Anthony R. Absalom

Introduction

Benefits of the Intravenous Route of Administration

When sedation outside of the operating room is required, possible routes of administration of the required sedative and analgesic agents include the inhalational, oral, intranasal, intramuscular, and intravenous routes.

Although administration of low doses of volatile anesthetic agents by inhalation can provide adequate sedation (and analgesia if nitrous oxide is also used), this mode of sedative administration is often not feasible outside the operating room. The bulky apparatus required to administer the agent, oxygen, and nitrous oxide, and to scavenge waste gases, is a significant limitation. Furthermore, distressed children are unlikely to cooperate sufficiently to tolerate a face mask or a "physiological" mouthpiece, as well as the odor and taste of the agent, throughout the period of administration.

With oral or enteral, transnasal, rectal, or intramuscular administration, the administered drug forms a depot that is absorbed slowly. Agents administered by the oral or enteral route are then subjected to significant first-pass metabolism. This problem is avoided with intramuscular injection, but this route is seldom used because it is painful. For all these routes, the rate at which the drug reaches the systemic circulation is highly variable, since it also depends on factors such as gastric emptying, peristalsis, local pH, other contents of the gut, cardiac output, and mucosal or muscular blood flow. This results in considerable inter- and intra-individual variability in bioavailability when these routes are used. In patients who are in pain, distressed, or unwell, absorption and systemic penetration of orally administered agents may be minimal. Thus, administration of standard doses of sedatives by these routes results in very variable blood concentrations and clinical effects, making it very difficult to judge in advance the required dose.

The problems of variable absorption and first-pass effects are avoided by intravenous administration as the entire administered dose reaches the systemic circulation. There remains considerable inter- and intra-individual variability in the relationship between administered dose and the blood concentration profile achieved (i.e., pharmacokinetics), but this variability is far less than with other routes of administration.

For any sedative agent, the blood and effect-site concentrations that will provide adequate sedation will depend on the sensitivity of the patient to the drug (pharmacodynamics), which can change with time and can be profoundly and unpredictably altered by co-administration of analgesics and other drugs. The required concentrations will also depend on the nature and severity of any noxious stimuli. Since the stimuli involved with any intervention change over time, as can the patient's susceptibility to the agent, so too will the effect-site concentration required for optimal sedation.

The inhalational route offers the ability to titrate the dose against the clinical effect, but suffers from the practical disadvantages previously discussed. Of the remaining available routes of administration, only the intravenous route enables fine control of the blood concentration and clinical effects, particularly with newer agents that have "fast" kinetics, such as propofol. When administered as a single bolus, propofol has both a rapid onset and offset of action—the rapid onset is because the drug crosses the blood–brain barrier rapidly, and the rapid offset is because extensive redistribution to well-perfused tissues causes a rapid fall in blood concentrations and thus a decline in effect-site concentrations. With repeated boluses or an infusion, there is extensive redistribution of the drug into different tissues, but overall the drug does not "accumulate" significantly, in the sense that when administration ceases, blood concentrations fall fairly rapidly

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because hepatic metabolism is rapid compared with the rate of return of drug from the peripheral tissues.

If sedation with propofol is inadequate, then blood and effect-site concentrations can be rapidly increased by the administration of one or more boluses, or an infusion. If on the other hand sedation is excessive, then cessation of further drug administration should result in a rapid decline in blood concentrations and clinical effect. The ability to make rapid and fine adjustments to the depth of sedation is probably the major advantage of intravenous administration.

With almost all intravenously administered anesthetic drugs, fixed-rate infusions result in blood concentrations that increase significantly over time. One exception is remifentanil, which reaches steady-state blood concentrations after about 15 min of infusion at a fixed rate. The problem of increasing blood concentrations at constant infusion rates can be a trap for the unwary, since the relationship between infusion rate and clinical effect will change over time. A patient who is initially safe and adequately sedated may later become excessively sedated, with potentially life-threatening compromise of the airway and respiratory drive, despite there being no increase in the infusion rate. Steady-state blood concentration profiles are made possible by target-controlled infusion (TCI) systems, which facilitate titration of the blood concentration to the clinical effect, and will be discussed in detail later in this chapter.

Naturally, a disadvantage of intravenous administration is that intravenous access is required. Many children find this distressing, particularly if venous access is difficult because of obesity or obliteration of the veins caused by prior administration of irritant drugs. The pain and discomfort of intravenous cannulation can be limited by prior application of a topical local anesthetic formulation, by distraction by a parent or play therapist, by the use of small gauge cannulae, and of course by rapid completion of the procedure by an experienced and skilled physician.

Choice of Agents

Pharmacokinetic and pharmacodynamic factors influence our choice of agents. Pharmacokinetics describe the relationship between drug dose and blood concentration, whereas pharmacodynamics is the study of the clinical effects themselves and of the relationship between blood concentration and clinical effect. Most current hypnotics lack analgesic properties, whereas most potent analgesics at best have weak sedative properties. For painful procedures, a combination of hypnotic and opioid is commonly used, but it should be remembered that these combinations result in pharmacokinetic and pharmacodynamic interactions (they are usually strongly synergistic—see below).

Ideally, a drug used for sedation should have a rapid onset of action and also a rapid offset of action. This requires an agent with a combination of favorable pharmacokinetic properties and pharmacodynamic properties, such as rapidly reached steady-state blood concentrations during infusion, a rapid rate of blood–effect-site equilibration, lack of accumulation, and a rapid decline in blood concentrations on stopping the infusion [and ideally a context-insensitive half-time (CSHT)]. By definition then, agents that are able to provide rapid, titratable, and controllable sedation must usually be administered by continuous infusion. Fentanyl is a good illustrative example. After a single dose, or a short-duration infusion, fentanyl has rapid kinetics. Once repeated doses or an infusion lasting more than an hour has been given, the kinetics become slower, and the CSHT increases significantly, making it unsuitable for use by infusion outside of the operating room (OR) or intensive care unit (ICU). Other intravenous agents that accumulate significantly and are not suitable for use by infusion or multiple bolus administration outside of the ICU are morphine, midazolam, and thiopentone. Perhaps the most promising drug, particularly with regard to pharmacokinetics and dynamics, is remimazolam, which is metabolized by nonspecific tissue esterases and has a fast onset and offset of effect [1, 2]. This drug is currently undergoing further phase III evaluation studies.

Of the currently available drugs, those with suitable pharmacokinetics for use by infusion include ketamine, etomidate, propofol, and dexmedetomidine. Remifentanil also has ideal properties for use by infusion [3], and although only a weak sedative, it is commonly used by infusion at low doses during sedation in combination with propofol.

Unfortunately, although ketamine has many suitable characteristics, such as maintained cardiorespiratory stability, bronchodilation, and potent analgesia, it can cause problematic psychiatric phenomena. In subsedative doses in adults, it has been shown to cause several of the negative symptoms of schizophrenia [4, 5]. At sedative and anesthetic doses, troublesome emergence phenomena are common, particularly when ketamine is used as the sole agent. These phenomena are less severe in children and can be attenuated by concomitant benzodiazepine administration. The use of bolus doses for procedural sedation in children in the emergency unit has been shown to be safe and associated with few complications [6].

Etomidate commonly causes pain on injection and nausea and vomiting, and when used by infusion, it is associated with significant adrenal suppression [7]. Indeed, in unwell adults, even single doses were shown to interfere with adrenal function for 24 h [8].

Another suitable agent is methohexitone, but unfortunately it is no longer widely available. Thus, the only remaining agents that are suitable for use by infusion are propofol and dexmedetomidine.

Pharmacodynamics of Commonly Used Agents

Propofol

The introduction into clinical practice of the intravenous hypnotic agent propofol, a $GABA_A$ agonist, has led to a significant increase in the popularity of the technique of total intravenous anesthesia (TIVA) in most of the world [9, 10]. TIVA is the exclusive use of the intravenous route for induction and maintenance of anesthesia. Strictly speaking, a technique involving intravenous infusions supplemented by nitrous oxide, for example, is not a TIVA technique. Exclusive use of the intravenous route for sedation is a natural extension of TIVA, since propofol and most other intravenous hypnotic agents produce anxiolysis and sedation at lower doses.

Part of the reason for the popularity of propofol is the favorable pharmacokinetic profile (see above and later discussion) and the availability of infusion equipment to simplify and facilitate accurate and precise administration such as "calculator" infusion pumps and TCI systems. "Calculator" infusion pumps are simpler systems that can be programmed with the patient's weight so that the user can input a dose in mass-based units such as a bolus dose size in μ(mu)g/kg or an infusion rate in μ(mu)g/kg/min. Another reason for the increase in popularity of TIVA is propofol's beneficial pharmacodynamic profile. At subsedative doses, propofol induces anxiolysis and amnesia [11, 12].

For procedures and environments that are frightening to children, these effects are highly desirable. In addition to anxiolysis, it produces a sense of well-being and is associated with a very low incidence of nausea and vomiting [13]. In fact, propofol has been shown to possess direct antiemetic properties at subhypnotic doses [14]. This is particularly beneficial in painful procedures requiring supplementary use of opioid analgesics that are likely to induce nausea and vomiting. With increasing doses, propofol produces dose-dependent sedation, with a gradual, stepwise loss of higher cognitive functions. For example, although functional imaging studies suggest that neurophysiological responses associated with processing of complex sentences are lost at very light levels of sedation [12], basic auditory perception of words continues for some time after loss of responses to command [15]. Propofol does, of course, possess some undesirable pharmacodynamic effects. These include pain on initial intravenous injection and dose-related cardiorespiratory depression. Pain on injection can be attenuated by many methods and virtually eliminated by using a new propofol formulation containing medium-chain triglycerides with added lidocaine [16].

The problems of respiratory and cardiovascular depression are dose dependent, but can be somewhat unpredictable, particularly in unwell patients. Propofol causes modest reductions in myocardial contractility and more marked effects on systemic vascular resistance. At lower doses there is a reduction in respiratory rate and tidal volume, obtunded airway reflexes, and obtunded responses to hypercarbia and hypoxemia. An anesthetic induction dose commonly causes a brief period of apnea. Moreover, when other agents are co-administered, marked synergism can occur, particularly with the opioids. Modest doses of propofol and remifentanil have been shown to increase the apnea threshold and markedly obtund the ventilatory response to hypercarbia [17]. These adverse cardiorespiratory effects of propofol are part of the reason why, in some quarters, it is felt that sedation with propofol should only be administered by anesthesiologists [18].

The ASA guidelines on safe sedation practices are not quite as proscriptive in the use of propofol by nonanesthesiologists and rather only state that "practitioners administering propofol should be qualified to rescue patients from any level of sedation, including general anesthesia" [19].

Dexmedetomidine

Dexmedetomidine is an effective sedative agent, producing a state of sedation that is unique among intravenous agents because the patient remains rousable even from relatively deep sedation. This difference is probably related to the fact that most other intravenous sedatives exert their clinical effects via a different mechanism (an agonist effect on $GABA_A$ receptors on inhibitory neurons in the thalamus and other areas), whereas dexmedetomidine acts as a highly selective α(alpha)2 adrenergic agonist (i.e., having minimal effects on the α[alpha]1 receptor subtype), which results in enhanced activity in non-rapid eye movement (NREM) sleep-promoting pathways [20].

An agonist effect on α(alpha)2 receptors results in inhibition of the locus coeruleus, which is thought to disinhibit the ventrolateral preoptic (VLPO) nucleus, causing increased GABA release from VLPO neurons resulting in decreased activity in the tubo-mammillary nucleus (TMN). Natural NREM sleep is also associated with increased firing of VLPO neurons. Since the TBM is the only neuronal source of histamine, which causes arousal, this action on the TBM results in reduced histamine release and sleep or sedation.

In addition to the benefit of rousability, the promotion of natural sleep may bring other benefits such as the restorative functions of sleep. Disturbances of natural sleep are known to cause cognitive and mood changes and to have adverse

effects on immunity. In addition, recent work suggests that dexmedetomidine may modulate the inflammatory response in critically ill patients and in septic animals [21, 22].

Finally dexmedetomidine (and other α[alpha]2 adrenergic receptor agonists) has several other beneficial effects. These include analgesia and an opioid-sparing effect when used during painful procedures and slowing of the heart rate and protection against myocardial ischemia (shown in adults). In high doses dexmedetomidine can cause vasoconstriction, but in lower doses it causes mild vasodilation and only minor effects on the blood pressure. Respiratory drive is well maintained. In adult intensive care patients, sedation with dexmedetomidine is associated with less delirium than other agents [23].

These pharmacodynamic benefits, coupled with a pharmacokinetic profile that makes it suitable for use by infusion [24], have led to increased use of dexmedetomidine for sedation. When used as the sole agent for sedation for computed tomography (CT) and magnetic resonance imaging (MRI) studies, dexmedetomidine has been shown to produce reliable and effective sedation with acceptable hemodynamic stability and no adverse effects on respiratory parameters [25–28].

Ketamine

Ketamine is an NMDA antagonist, which has two optical isomers—the S(+) form and the R(−) form. In most countries it is sold as a racemic mixture, whereas in parts of Europe the purified and more expensive s(+) isomer (s-ketamine) is sold. The S- isomer is thought to be 2–4 times more potent than the racemic mixture [29, 30].

It is the only currently available sedative or hypnotic agent that possesses analgesic properties. At modest doses it causes a dissociated state that is unique to the currently available agents [31]. In this state, the eyes remain open, but the patient will stare blankly and usually not respond to noxious stimuli. Catatonia is sometimes also present. The sympathomimetic effects of ketamine can cause increases in heart rate, blood pressure, myocardial contractility, cardiac output, and systemic vascular resistance. It has little effect on ventilatory drive and promotes bronchodilation (through an adrenergic mechanism). Airway reflexes are commonly preserved, although there can be an increase in oral and airway secretions. Intramuscular ketamine is a useful way to induce anesthesia in children and in those patients where venous access is difficult; it is associated with little pain on injection. Infusions are seldom used, except on ICU, and for procedural sedation, single doses are more usual, either alone or in combination with other agents (e.g., propofol or a benzodiazepine and sometimes an analgesic) [32].

Remifentanil

Remifentanil is a pure μ-opioid receptor antagonist and therefore has a similar range of clinical effects to those of the other opioids [33]. It is a potent analgesic, at best a mild anxiolytic, and can cause nausea and vomiting. Remifentanil has vagotonic effects, with a resultant reduction in heart rate, but on its own has limited effects on blood pressure. Like the other opioids, it causes mioisis and impairs respiratory drive and the ventilatory responses to hypoxia and hypercarbia. At higher doses it inhibits coughing and will prevent movement responses to painful stimuli. Excessive doses may cause chest wall rigidity and difficulty with ventilation.

Basic Principles of Pharmacokinetics

What Is a Pharmacokinetic Model and How Is It Derived?

A pharmacokinetic model is a mathematical model that can be used to predict the blood concentration profile of a drug after a bolus dose or an infusion of varying duration. Some types of models, such as recirculatory models, approximate human physiology by estimating blood volume, cardiac output, and blood flow to different organs or groups of organs [34, 35].

The most commonly used models are the so-called mammillary, compartmental models, as illustrated in Fig. 39.1. In order to understand these models, some understanding of the mathematics of exponential processes is necessary (see below). It is important to remember that compartmental models are mathematical constructs. They are typically derived by measuring the arterial or venous plasma concentration of a drug after a bolus or infusion in a group of patients or volunteers and then estimating the pharmacokinetic parameters of the drug under investigation by performing nonlinear mixed effects modeling with software such as NONMEM® (Globomax LLC, Hanover, MD, USA). During this process, the investigators typically begin with a simple model and then make stepwise increases in the complexity of the model. Increases in complexity that do not significantly improve the ability of the model to predict measured blood concentrations are rejected in favor of the simpler model.

Important Mathematical Concepts for Understanding of Pharmacokinetic Models

Many physiological processes depend on concentration gradients and so display first-order kinetics (Fig. 39.1). For most anesthetic agents, the enzymes involved in metabolism are

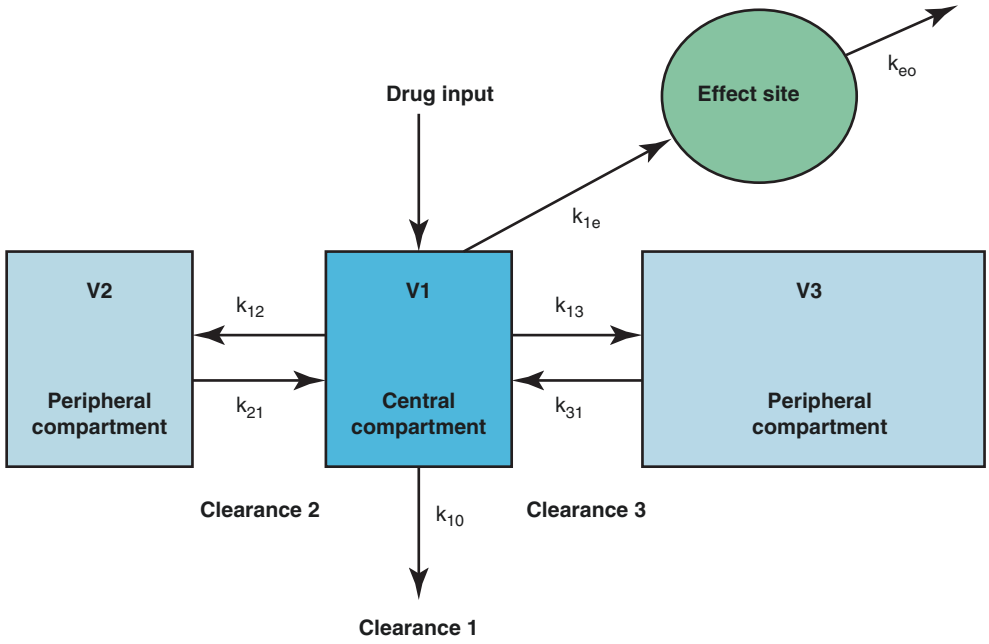

Fig. 39.1 The three-compartment pharmacokinetic model enlarged with an effect compartment. (Adapted from Absalom and Struys [36])

not saturable at clinical concentrations, and thus the amount of drug metabolized during any unit of time depends on the plasma drug concentration at that time. Similarly, redistribution of most anesthetic drugs is a passive process in which the rate and direction of redistribution depend on the concentration gradient between the blood and other tissues.

For any first-order process, the variable of interest changes in an exponential manner. Depending on the process, the variable may either increase or decrease exponentially. When the variable of interest is an amount (e.g., the mass of drug or the number of millimoles of drug), then the changes in this variable over time can be described mathematically in the following general way (the formula applies equally well to other exponential process such as population growth or the arterial blood pressure changes during diastole):

$$A(t) = A(0) \times e^{k.t}$$

where $A(0)$ is the amount at time zero, t is the time since the start of the process, $A(t)$ is the amount at time t, k is the rate constant (with units of the inverse of time—typically min^{-1}), and e is an irrational constant approximately equal to 2.7182. The rate constant k describes the proportional change over a unit of time. If $k = 1$, then $A(t)$ increases by a multiple of e^1 in each unit of time, i.e., $A(t)$ increases by 271.8% in each unit of time. On the other hand, if $k = -1$, then $A(t)$ changes by a factor of e^{-1} (=1/e = 0.367) in each unit of time, which means that $A(t)$ decreases by 63.3% in each unit of time.

The rate of change of $A(t)$ at time t can be calculated mathematically as the first differential of $A(t)$ as follows:

$$\frac{dA(t)}{dt} = k \times A(0) \times e^{k.t} = k \times A(t)$$

Thus although the proportional change is constant, the absolute change over a unit of time changes according to the amount, $A(t)$, present during that unit of time.

In pharmacology we are often more interested in concentrations than amounts, and we are commonly dealing with situations where gradients decline over time. For these situations the following general equation will apply:

$$C(t) = C(0) \times e^{-k.t}$$

where $C(0)$ is the concentration at time zero, t is the time since the start of the process (e.g., the time since drug administration), $C(t)$ is the concentration at time t, and k is the rate constant.

Half-Life, Time Constant, and Rate Constant

The time constant, τ(tau), is another rate descriptor, but with units of time. Mathematically it is the inverse of the rate constant (i.e., $1/k$) and represents the time taken for a change by a factor of e (i.e., an increase of 271% or a decrease of 63%).

Rate and time constants are not intuitively easy to understand, and thus the pharmacology literature often uses half-lives to describe the time course of exponential processes. Simply put, the half-life describes the time it takes for a change by a factor of 2, i.e., for the amount to change to double or half the initial value. By definition the half-life is shorter than the time constant. Mathematically the half-life can be calculated as follows:

$$t\,\frac{1}{2} = \tau(\text{tau}) \times \ln\ 2 = \tau(\text{tau}) \times 0.693 = \frac{1}{k} \times 0.693$$

Volume of Distribution

If serial measurements of the concentration of a drug can be performed, then it is possible, with knowledge of the time course of drug administration, and appropriate mathematical techniques, to calculate a volume of distribution (an apparent volume in which the drug has been distributed). Few drugs distribute uniformly throughout the body. Most distribute into different tissues at different rates. In these situations, an "initial volume of distribution" (V1 or Vc) is often described. It can be calculated as follows:

$$\mathrm{Vd} = \frac{\mathrm{Dose}}{C(0)}$$

Since drugs do not mix instantaneously on injection, $C(0)$ is calculated by extrapolating the time–concentration curve back to time zero. If the volume of distribution, Vd, is larger than the circulating blood volume, then the drug is likely to have rapidly mixed in the blood and extracellular fluids.

The volume of distribution at steady state, Vdss, is the apparent volume of distribution once adequate time has been allowed for complete equilibration of the drug across all tissues. In multicompartmental models, Vdss is the mathematical sum of the volumes of all compartments in the model. For drugs with extensive protein binding and/or high lipid solubility, the peripheral tissues will have a large capacity to absorb the drug, resulting in a Vdss greater than the volume of the entire body.

Single Compartment Pharmacokinetic Models

The behavior of a drug that does not undergo redistribution can be described by a single compartment mathematical model. On injection, the drug distributes uniformly throughout a single volume, V, and the drug concentration in this compartment is the same as the plasma concentration. After a single bolus or an infusion, the drug concentration will decline because of metabolism or elimination, as described by the following equation:

$$C_{\mathrm{p}}(t) = C_{\mathrm{p}}(0) \times \mathrm{e}^{-k\mathrm{el}.t}$$

where $C_{\mathrm{p}}(t)$ is the plasma concentration at time t, $C_{\mathrm{p}}(0)$ is the initial plasma concentration, k_{el} is the elimination rate constant, and $t = 0$ is the time of the bolus or the time at which the infusion ceased. Clearance (mL/h) can be calculated from k_{el} as follows:

$$\mathrm{Clearance, Cl} = k_{\mathrm{el}} \times \mathrm{V}$$

If the relationship between drug concentration and time is plotted on linear axes, then the exponential decline results in a curved graph (Fig. 39.2). If, however, a semilogarithmic graph is used (i.e., the logarithm of the concentration is plotted), a straight line will result. Figure 39.3 shows the relationship between $\log_{\mathrm{e}} C_{\mathrm{p}}(t)$ and time.

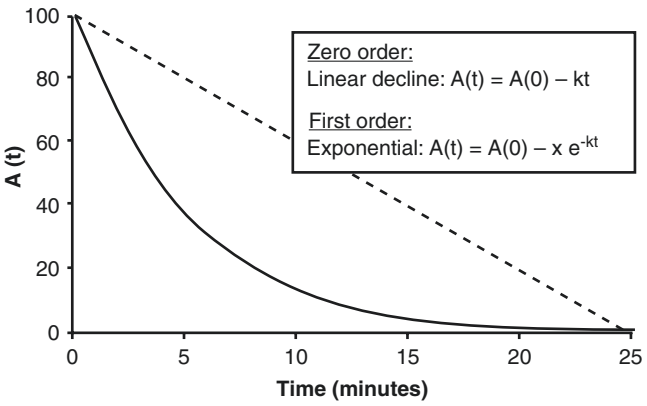

Fig. 39.2 Exponential versus linear decay. The (*dotted*) *straight line* represents linear decay, in which the amount of drug at time t is a linear function of the initial amount. The curve (*solid*) illustrates exponential decay in which the amount of drug at time t is an exponential function of the initial amount

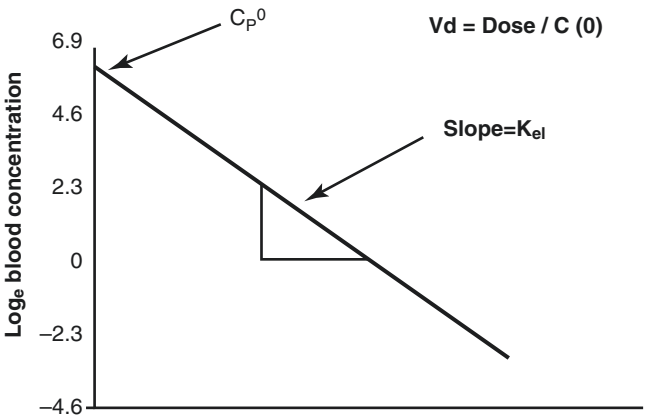

Fig. 39.3 The relationship between log e drug concentration and time after a bolus of a drug with single compartment kinetics. The slope of the elimination curve is constant

As shown the elimination rate constant can be calculated from the slope of the line in Fig. 39.3. If the natural logarithm ($\log_{\mathrm{e}}$ or "ln") of the drug concentration is plotted against time, then the slope is simply equal to k_{el}. As there is only one rate constant influencing the rate of decline in drug concentration, the decline in plasma concentrations has a constant $t_{1/2}$ that can be calculated from k_{el} as shown previously.

Three Compartment Models

The pharmacokinetics of most anesthetic drugs are best described by three compartment models. Each model describes the number of compartments and their volumes, the rate of drug metabolism or elimination, and the rate of

transfer of drug between the different compartments. The concept is summarized in Fig. 39.1.

By convention, the compartment into which the drug is injected is called the central compartment (V1 or Vc), which may be thought of as including the blood volume, although it can be larger than the blood volume. It is sometimes referred to as the initial volume of distribution. Elimination of active drug by metabolism usually occurs from within this compartment (as in the case of hepatic or renal metabolism). The rate of elimination is described interchangeably by a rate constant (k_{10}) or a clearance (Clearance = $k_{10} \times V1$). The second compartment, V2, is referred to as the "rapid redistribution" compartment since drug concentrations in V2 equilibrate rapidly with those in the central compartment. The rate constants k_{12} and k_{21} are used to describe the rate of drug transfer from V1 to V2 and from V2 to V1, respectively. Fast redistribution clearance, "Clearance 2," can be calculated as:

$$\text{Clearance } 2 = k_{12} \times V1 = k_{21} \times V2$$

The third compartment, V3, is often referred to as the "slow" compartment (because there is rather slower drug distribution between V1 and V3). Here the rate constants k_{13} and k_{31} are used to describe the rate of drug transfer from V1 to V3 and from V3 to V1, respectively. Slow redistribution clearance, "Clearance 3," can be calculated as:

$$\text{Clearance } 3 = k_{12} \times V1 = k_{21} \times V2$$

The second and third compartments are sometimes referred to as the "vessel-rich" and "vessel-poor" compartments, respectively, but these terms are best avoided since they encourage the false impression that these compartments represent distinct anatomical or physiological entities. The sum of V1, V2, and V3 gives the "volume of distribution at steady state," Vd_{ss}.

The site of action of the anesthetic agents is, of course, not in the vascular system, but in the brain at a vaguely defined "effect site." Thus, many models now also include the effect site as a fourth compartment, with the rate constant k_{eo} being used to describe the rate of equilibration between the central and effect-site compartments.

For a drug showing three compartment kinetics (such as propofol), the change in concentrations after a bolus or infusion cannot be described by a single rate constant or half-life. The decline in plasma concentration is more complex because it is influenced by several simultaneous exponential processes, each with a different rate constant, so that the time required for the concentration to fall by 50% (or any other proportion) changes over time. Figure 39.4 shows a typical curve of the relationship between blood concentration and time after a single bolus dose of an anesthetic drug. The time course of changes in plasma concentration shown in Fig. 39.4 can be described mathematically as the sum of three exponential processes as follows:

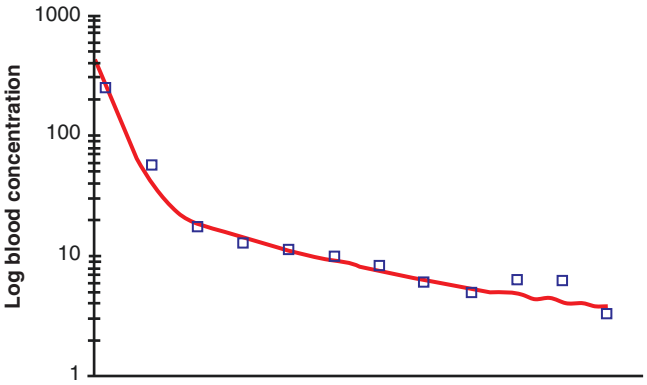

Fig. 39.4 Relationship between plasma concentration (after a bolus dose) and time for a typical anesthetic agent, displaying tricompartment kinetics. The *squares* represent typical measured concentrations, and the *red line* represents a curve generated the sum of three exponentials

$$C_p(t) = A \cdot e^{-\alpha(\text{alpha})t} + B \cdot e^{-\beta(\text{beta})\,t} + C \cdot e^{-\gamma(\text{gamma})t}$$

where A, B, C, α(alpha), β(beta), and γ(gamma) are constants. As can be seen in Fig. 39.4, in the early phase after a bolus dose, the plasma concentration falls rapidly, being mostly influenced by rapid redistribution (described by a rate constant α[alpha]). Later on the rate of decline in plasma concentrations is influenced mostly by redistribution to less well-perfused tissues (described by a rate constant β [1]). Eventually the predominant factor is elimination (rate constant γ[gamma]). From these parameters the time-honored redistribution and elimination half-lives can be calculated

During and after administration of repeated bolus doses or infusions, the changes in drug concentrations vary in a complex matter since they are influenced by several simultaneous exponential processes, and the relative contributions of the different processes change for most anesthetic drugs as the duration of infusion increases. These factors make it difficult to predict drug concentrations without the assistance of computer programs.

Context-Sensitive Half-Time

The concept of "context-sensitive half-time" (CSHT) has been introduced as a simple metric that provides a summary of the interplay of time and the different half-lives after an infusion [37].

It describes the time taken for blood concentration of a drug to fall by 50% after the end of an infusion of a specified duration—the context is thus the duration of infusion. The influence of duration of infusion on CSHT indicates the degree of drug accumulation and the balance between redistribution and metabolism/elimination. This metric only describes the time taken for the first decline of 50%—the time taken for subsequent 50% falls will be different. Also, it does not necessarily describe when clinical effects will cease, since these depend on the initial concentration and pharmacodynamic factors such as the sensitivity of the patient to the drug. Nonetheless, it gives the physician a use-

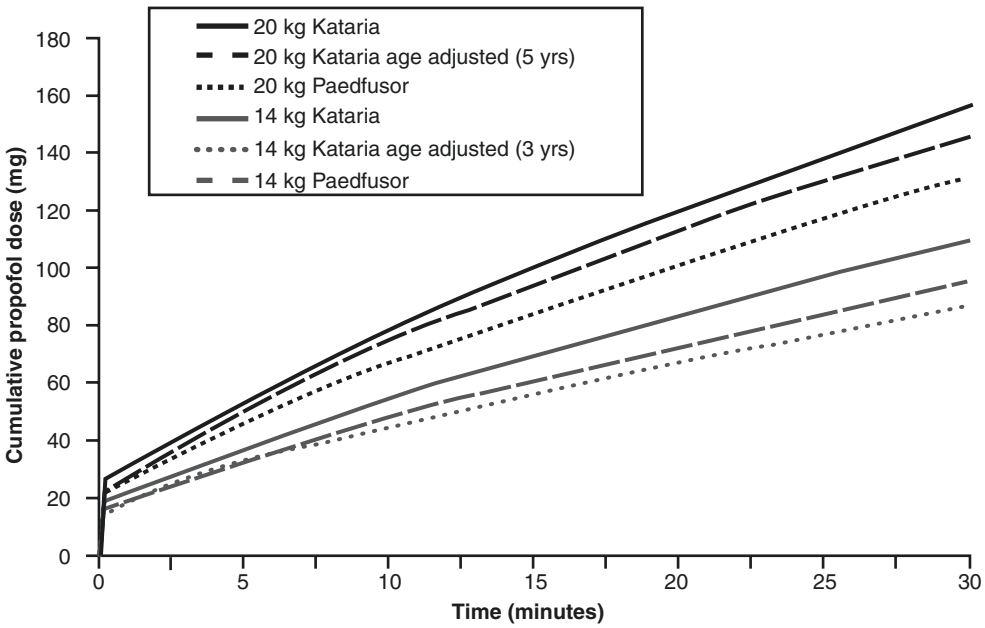

Fig. 39.5 Cumulative propofol doses administered to children weighing either 14 or 20 kg, by TCI systems programmed with the Kataria or Paedfusor pharmacokinetic models for propofol (target concentration 2.5 μ[mu]g/mL)

ful indicator of the rate at which drug concentrations will decline after an infusion and an indication of the influence of duration of infusion.

Pharmacokinetic Models for Propofol

During the early 1990s, a study of the predictive accuracy of the "Marsh" adult propofol model in 20 children showed that it significantly overestimated the blood concentrations (i.e., measured blood concentrations were less than expected) [38]. This was consistent with other work showing that the pharmacokinetics of propofol differ between children and adults [39, 40].

The Marsh model was then revised to produce a model specific to children (the size of the central compartment volume was increased, but remained a linear function of body weight), and when prospectively tested, the predictive performance was improved compared with the adult model [38].

Since then several other models specific to children have been produced. Schüttler published a complex model in 2000 based on a combined analysis of data from several other studies [41]. This model, which contains multiple covariates, and adjusts for mode of drug administration (bolus versus infusion) and sampling site (arterial versus venous), was designed for use in a wide range of patients including children. The Short model, on the other hand, was designed specifically for the pediatric population [42], but like the Schüttler model, it is seldom used in clinical practice.

The Kataria and Paedfusor models are the most commonly used models at present and are available in commercially available TCI systems available in most countries of the world (but not the USA). Despite the fact that the models were developed in different ways, and that weight is incorporated in a different way in each model, the overall model parameters are fairly similar. Figure 39.5 shows a comparison of the cumulative propofol dose for children weighing 14 and 20 kg when the Kataria and Paedfusor models are used to administer a target blood concentration of 2.5 μ(mu)g/mL.

Kataria et al. used three different pharmacokinetic modeling techniques in an extended group of children between 3 and 11 years and found that the pharmacokinetics of propofol could be described by a three-compartment model [43]. They found that a weight-proportional model performed significantly better than a model with fixed volumes and rate constants. Adjusting V2 (and hence k_{12} and k_{21}) according to age produced a further (modest) improvement. Although Kataria recommended that the weight-proportional model be used, some investigators have used the weight-proportional model with age adjustment. The equation used to adjust V2 for age is likely to yield an anomalous (negative) V2 for children younger than 3 years, and thus the age-adjusted, weight-proportional model should not be used in children younger than 3 years.

The Paedfusor model [44] was adapted from one of the preliminary models developed by Schüttler prior to the publication of his final model [41] and was incorporated in a pediatric TCI pump developed and used in Glasgow. In the Paedfusor model, the central compartment volume and clearance have a nonlinear correlation with weight, whereas in the final Schüttler model, all variables have a nonlinear correlation with age and weight.

A recent study investigated the predictive performance of eight existing pediatric propofol models in children between 3 and 26 months of age [45]. Most models performed accept-

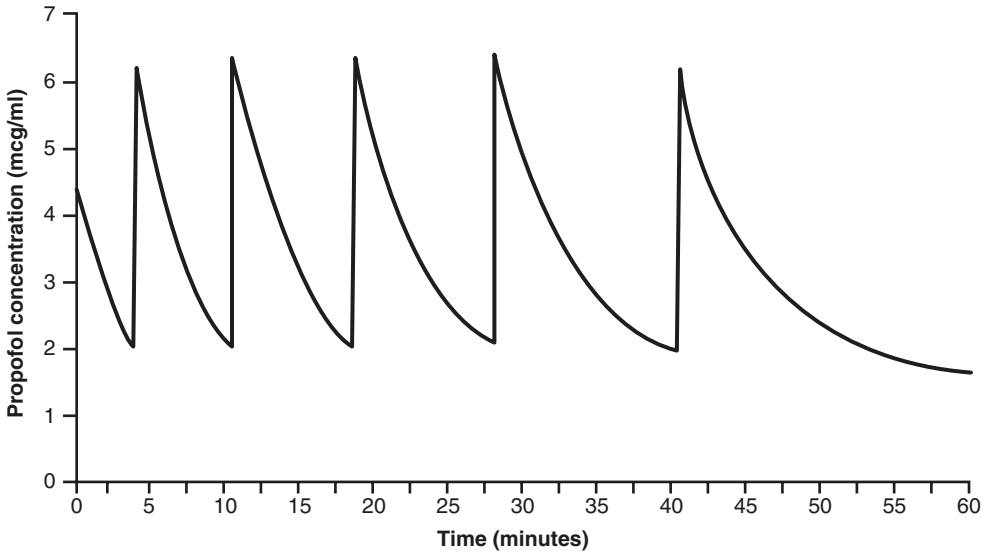

Fig. 39.6 Estimated blood propofol concentrations resulting from repeated 40 mg boluses of propofol in a 20 kg child. In this simulation, a repeat bolus was administered each time the estimated concentration fell to 2 μ(mu)g/mL. Note how the rate of decline in concentration after successive doses gradually decreases, resulting in an increase in the interval between doses

ably, but interestingly the Short model was found to perform best.

With increasing size, pharmacokinetic parameters change in a complex nonlinear way, and the scaling techniques used in the models described earlier do not deal optimally with size-related changes in very young and small children. It is increasingly being recognized that allometric scaling best describes the relationships between clearances and size [46]. Eleveld and colleagues have used the data from multiple published studies of the pharmacokinetics and pharmacodynamics of propofol to produce a single pharmacokinetic model for propofol. It uses allometric scaling for size, and a maturation function (to deal with changes in organ and enzyme function in the early months after month), and is designed to be used for patients from 6 months old through to old age [47]. In internal testing the model performed well or even better than specialist models developed specifically for use in children. More recently Eleveld has produced a general-purpose combined pharmacokinetic and pharmacodynamic model for propofol suitable for use in children and adults [48]. This combined model is currently undergoing prospective validation.

A summary of the model parameters for these propofol models has recently been published [36].

Pediatric Propofol Infusion Regimens

Disadvantages of Repeated Bolus Dose Administration

Although it is possible to maintain sedation or anesthesia with repeated boluses of an intravenous sedative agent, this is far from ideal. Firstly, stable levels of sedation are not possible since the blood and effect-site concentrations will be constantly either rising or falling. If the bolus size is too big, the patient state will oscillate from excessive sedation/anesthesia, with the attendant risks, to inadequate sedation. Secondly, it is difficult to judge the dose required to produce adequate, but not excessive blood concentrations. Finally, it is also difficult to judge the required interval between doses. Figure 39.6 shows the estimated blood concentrations arising from repeated 40 mg boluses of propofol administered to a 20 kg child. In these simulations, a bolus was administered each time the estimated concentration fell to 2 μ(mu)g/mL. As can be seen, as drug accumulates in peripheral tissues, the rate of decline in blood concentration after successive doses gradually decreases, resulting in an increase in the interval between doses.

Commonly Used Regimens

Typically, blood concentrations of the order of 2–3 μ(mu)g/mL are required for sedation in children. Naturally the concentration required is influenced by multiple other factors such as co-administered drugs. Thus, it is not surprising that after cardiac surgery, Murray et al. found that the mean measured propofol concentration at recovery of consciousness was only 0.97 μ(mu)g/mL [49], whereas Rigouzzo et al. found that the EC50 (of measured blood propofol concentration at steady state) associated with loss of consciousness in healthy children was 4.0 μ(mu)g/mL [50].

A commonly used deep sedation regimen for children is an initial bolus of 2 mg/kg followed by an infusion at 10 mg/kg/h (in children <1 year of age, higher doses may be required, e.g., an initial bolus of 3 mg/kg and higher initial infusion rates). Figure 39.7 shows a simulation of the regimen, with the concentrations estimated by the Paedfusor model. At about 10 min after the initial bolus, the blood con-

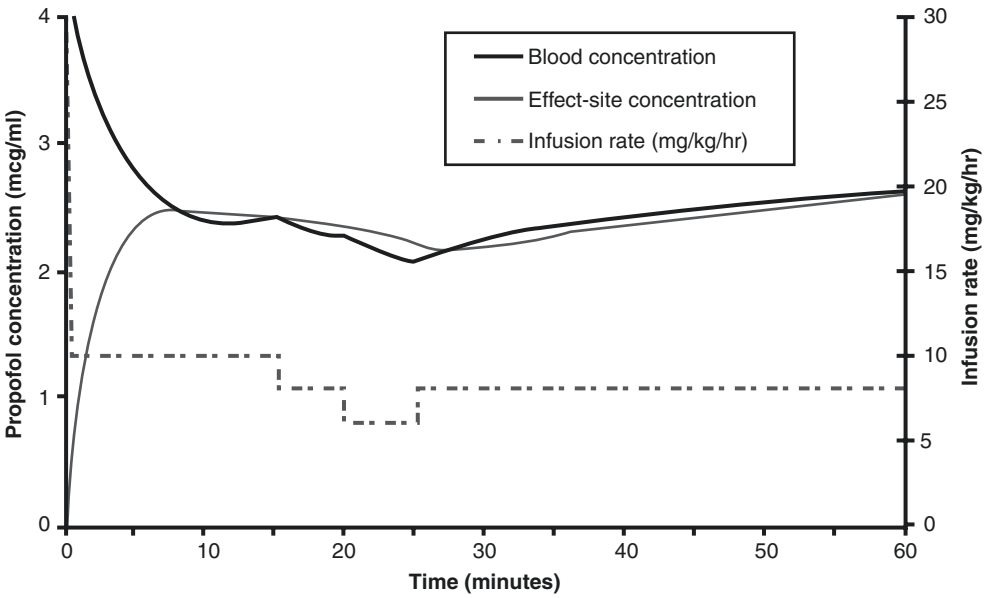

Fig. 39.7 Blood and effect-site concentrations (*heavy* and *light continuous lines*, respectively, as estimated by the Paedfusor model with a k_{eo} of 0.91 min^{-1}), arising from an initial bolus of 2 mg/kg, followed by an infusion initially at 10 mg/kg/h. Note the slow blood and effect-site concentration changes after step changes in infusion rate at 15, 20, and 25 min. Also, note that the concentrations continue to rise when the infusion rate is kept constant

centrations reach a nadir of ~2.5 μ(mu)g/mL. If the infusion rate is kept constant at 10 mg/kg/h, the blood and effect-site concentrations and clinical effect will gradually increase (reaching ~5 μ[mu]g/mL after several hours), which is why downward titration of the infusion rate is commonly required.

In a recent study, Koroglu and colleagues administered a 3 mg/kg bolus followed by infusions of 10–15 μ(mu)g/kg/min (i.e., 6–9 mg/kg/h) of propofol to 30 children between 1 and 7 years of age for sedation during MRI scans [25]. With this propofol regimen, sedation was adequate in 27 of the 30 children, cardiorespiratory stability was reasonable, and mean recovery and discharge times were 18 and 27 min, respectively.

PK Models for Dexmedetomidine

Pharmacokinetic models for dexmedetomidine in children have recently been produced from studies involving single bolus administration [51], after short infusions [52], and after longer infusions [53] for postoperative sedation. Further studies are needed to compare the predictive accuracy of these models to determine which perform optimally in clinically relevant situations.

Infusion Regimens for Dexmedetomidine

Despite the low α(alpha)1 affinity of dexmedetomidine, rapidly administered boluses cause bradycardia and hypertension. Typical infusion regimens thus usually comprise an initial bolus over 10 min, followed by a continuous infusion. Mason used an initial bolus of 2 μ(mu)g/kg over 10 min (repeated if Ramsay sedation score [54] of 4 not reached) followed by an infusion at 1 μ(mu)g/kg/min, in 62 patients with mean age 2.8 years and mean weight 15 kg, undergoing CT imaging [26]. Of these patients, 10% were able to undergo their scan during the initial loading dose, 16% required a second loading dose, and 90% required the maintenance infusion. Two patients became agitated during the loading dose and were given alternative agents for sedation.

Subsequently, Mason reported the results of a study of the use of higher doses of dexmedetomidine in >700 patients undergoing MRI scanning, which is more stimulating, and in which movement causes significant image degradation [27]. With time their regimen evolved from an initial bolus of 2–3 μ(mu)g/kg and from an initial infusion rate of 1 μ(mu)g/kg/h to 1.5 and 2 μ(mu)g/kg/h. The highest doses were associated with successful sedation and image acquisition in 97.6% of patients, but with reasonable cardiorespiratory safety.

Koroglu and colleagues used smaller doses for sedation during MRI scanning in 30 children with a mean age of 4 and mean weight of 14 kg; the bolus dose was 1.0 μ(mu)g/kg over 10 min, and this was followed by an infusion at 0.5 μ(mu)g/kg/h initially, but increased to 0.7 μ(mu)g/kg/h if a Ramsay score of 5 was not reached within 25 min [25]. With this regimen, additional midazolam was required in 16% of patients to facilitate successful scan completion.

PK Models for Ketamine

Ketamine is an enantiomer and is sold either as a racemic mixture or as a purified formulation containing only the S-ketamine enantiomer. The pharmacokinetics of ketamine have been described in adults [55], in children receiving a single bolus dose for procedural sedation [56], and in children receiving long-term infusions for intensive care unit sedation [57].

Infusion Regimens for Ketamine

For procedural sedation a bolus dose of 0.25–0.5 mg/kg is commonly used. Infusions are seldom used, but when used, the infusion rates are again commonly of the order of 0.25–0.5 mg/kg/h.

PK Models for Remifentanil

The most commonly used adult PK model for remifentanil is the Minto model, which can be used in children older than 12 years [58, 59]. There is limited data available on the pharmacokinetics of remifentanil in younger children. Rigby-Jones et al. studied a cohort of 26 neonates and children undergoing sedation with midazolam and remifentanil infusions after cardiac surgery [60]. They found that a two-compartment model, with metabolic and distribution clearances scaled allometrically with weight, best described the data. Ross studied a cohort of 42 children ranging in age from 5 days to 17 years [61]. The children each received a single 5 μg/kg bolus of remifentanil administered over 1 min. They only reported non-compartmental parameters, but showed age-related effects on volume of distribution and clearance. Using these and other data, Eleveld has produced a general-purpose combined pharmacokinetic and pharmacodynamics model for remifentanil that is suitable for use in children as well as in adults [3]. This model has yet to undergo formal prospective validation in children.

Infusion Regimens for Remifentanil

Remifentanil boluses can cause abrupt apnea, bradycardia, and chest wall rigidity and are best avoided or administered cautiously. If a rapid onset of analgesia is required, then loading doses of the order of 0.1–0.25 μ(mu)g/kg given over 1 min can be considered, if full monitoring and ventilator equipment are available. When infusions are used in spontaneously breathing patients, then infusion rates of 0.03–0.06 μ(mu)g/kg/min are usual.

Target-Controlled Infusions

Definition

A TCI is an infusion of a drug administered by an infusion pump controlled by a computer or microprocessor that is programmed to calculate and implement the drug infusion rates required to achieve in a patient the blood or effect-site concentrations required by the user. Simply put, with these systems, the user inputs a desired "target" concentration, and the system uses the parameters of a pharmacokinetic model for that drug and the patient parameters included as covariates in the pharmacokinetic model to calculate the infusion rates estimated to be necessary to achieve that concentration [36].

Rationale for TCI

As previously explained, bolus doses of intravenous drugs for sedation are generally only suitable for short procedures. Although infusions do provide more stable conditions, they still do not provide stable blood concentrations. Even for propofol, a drug with rapid kinetics, blood concentrations continue rising for several hours when fixed-rate infusions are used (see Fig. 39.7). There is thus a poor correlation between infusion rate and clinical effect. During the course of any procedure, the effect-site concentration required for adequate sedation will vary widely according to several other factors such as the influence of co-administered drugs (especially opioid analgesics), the onset of natural sleep, changes in the environment, and the severity of any noxious stimuli. The changing relationship between infusion rate and effect-site concentration, and the delay in blood–effect-site concentration equilibration, makes rational, precise, and rapid titration of the infusion very difficult. As can be seen in Fig. 39.7, stepwise changes in the infusion rate of 2 mg/kg/h result in very slow changes in blood and effect-site concentrations, so that it is difficult to assess the response to an infusion rate adjustment. These difficulties form an important part of the rationale for TCIs, where a computer or microprocessor is used to implement the infusion rates required to maintain steady-state blood concentrations. Since steady-state blood concentrations arise quite quickly, TCI systems allow the user to judge the clinical effect of a blood concentration and to then adjust the target blood concentration accordingly, rather than adjusting the infusion rate accordingly. An analogy is to compare the control a car driver has over the speed of his car, when he has a speedometer and cruise control system versus the control he would have with only a gas pedal and no cruise control system or speedometer.

When k_{eo} values for children have been validated and effect-site targeting is sufficiently developed for use in children, then a further refinement will be added since users will then be able to titrate the effect-site concentration titrate according to observed patient responses.

With blood and effect-site concentration targeting, absolute accuracy of the pharmacokinetic model is not important, since steady-state concentrations arise very quickly, and there remains wide variability in pharmacodynamic sensitivity among different patients to given blood and effect-site concentrations. Thus, even with the most accurate models and systems, titration according to pharmacodynamic responses will be required.

Principles of TCI

With TCI the user is able to set and alter a desired "target" drug concentration. The target is usually a blood concentration (although algorithms do exist for effect-site targeting [62] and have been implemented for propofol, remifentanil, and sufentanil use in adults). TCI systems use compartmental pharmacokinetic models with complex mathematical algorithms to calculate and implement the infusion rates required to achieve the target concentration. The system software calculates the drug amount in each of the compartments every 10 s, taking into account the amount of drug infused over the previous 10 s, the movement of drug into and out of the central compartment by redistribution, and the rate of removal of active drug from the central compartment by metabolism or elimination. It then calculates and implements the infusion rate required to maintain the target concentration over the subsequent 10 s.

The theoretical foundations for a system designed to maintain and achieve steady-state blood concentrations were laid by Kruger-Thiemer in 1968 [63] and later developed and refined by Vaughan and Tucker [64, 65] and Schwilden [66] (who developed the first clinical application of this theory: the "computer-assisted total intravenous anesthesia system"). The schemes developed by these pioneers for drugs conforming to two-compartment models became known as BET (*B*olus, *E*limination, *T*ransfer) schemes, so-called because they comprised an initial bolus to fill the central compartment (size in mg = target concentration × V1), followed by two superimposed infusions: one to replace drug lost by elimination and one to replace drug lost by redistribution. Modern TCI systems continue to use methods based on this approach, except that most modern models comprise of three compartments. After the initial bolus, three superimposed infusions are computed. When the target concentration is constant, drug lost by elimination is replaced by a constant rate infusion, since a fixed proportion of the total amount of drug in the central compartment is eliminated in each unit of time. In contrast, the amount of drug distributed to peripheral tissues declines exponentially as the gradient between the central compartment and the peripheral compartments decreases. Thus, two infusions at exponentially declining rates are required to replace drug "lost" from the central compartment by fast and slow redistribution. The sum of these three infusions is an infusion at a decreasing rate.

When the user decreases the target concentration, the infusion system stops infusing drug until it calculates that the blood concentration has decreased to the target concentration, whereupon the infusion restarts (see Fig. 39.8).

The first commercially available TCI systems contained the Diprifusor®, a microprocessor that was embedded in intravenous infusion pumps sold by several manufacturers from 1996 onward (in numerous countries around the world, but not in the USA). The development of the Diprifusor® has been described in detail [10]. TCI pumps controlled by it could only administer TCIs of propofol, and only if the microprocessor was able to detect the presence of single-use prefilled glass syringes of 1% or 2% propofol purchased from AstraZeneca. These syringes contain a programmable metallic strip in the flange that is detected by a sophisticated process called programmed magnetic resonance.

In the years since the release of the first generation of TCI systems, the patent for propofol has expired, and significantly cheaper generic forms of propofol are now available. This has led to the development and launch of second-

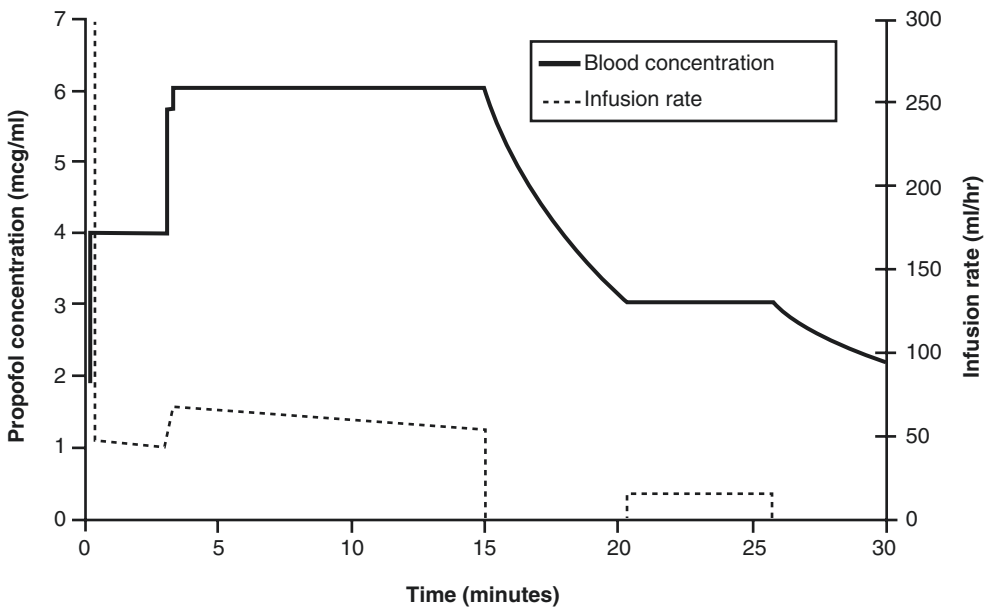

Fig. 39.8 Blood concentration targeted TCI, showing the infusion rates required by the Paedfusor model for a child weighing 20 kg. At time zero the target is set at 4 μ(mu)/mL, at 3 min it is increased to 6 μ(mu)g/mL, and at 15 min the target is reduced to 3 μ(mu)g/mL

generation TCI systems, the so-called Open TCI systems. In addition to the use of generic propofol, these systems also can be used for TCI of a variety of drugs, from a variety of syringe types and sizes. Two commonly used commercially available systems are the Alaris Asena PK® (BD, Wokingham, UK) and the Base Primea (Fresenius, Brezins, France).

Choice of Propofol Target Concentration

In general, blood concentrations between 2 and 3 μ(mu)g/mL are required for sedation in children. However, there are no hard and fast rules, and it is important to remember that use of a TCI system does not remove the requirement for titration of the target concentration according to the clinical response, since there is very broad intra- and inter-individual pharmacodynamic variability. Unfortunately there is very little data at present on the target concentrations required during sedation. There have been some studies of the concentrations required for loss of consciousness, and so, for safe sedation, it is worth bearing these in mind. Hammer and colleagues investigated the TCI propofol requirements for preventing a movement or hemodynamic response to esophagogastroduodenoscopy in 12 children between 3 and 11 years of age [67]. The EC50 (i.e., the propofol concentration estimated by the age-adjusted Kataria model at which 50% of patients did not respond) in this group was 3.55 μ(mu)g/mL when calculated using Dixon's up–down method [67] and 3.7 μ(mu)g/mL when recalculated using logistic regression [68]. In 45 children between 6 and 13 years of age, Rigouzzo found that the mean target propofol concentration (Kataria age-adjusted model) associated with a BIS (bispectral index) of 50 (i.e., surgical anesthesia) was 3.0 μ(mu)g/mL and the mean measured propofol concentration associated with BIS 50 was 4.3 μ(mu)g/mL [50].

Predictive Performance of PK Models During TCI

Most studies of the validity and accuracy of models used for TCI have used the parameters recommended by Varvel for assessing the predictive performance of a model during TCI: bias, imprecision, wobble, and divergence [69]. Generally, bias <20% and imprecision <40% are considered acceptable [70, 71]. Although not yet common in clinical practice, there is a growing body of experience of TCI administration of propofol in children. Some studies have studied predictive performance of TCI systems during anesthesia in children. Absalom and colleagues assessed the predictive performance of the Paedfusor model in 29 children aged between 1 and 15 years who were undergoing cardiac surgery or cardiac catheterization [44]. Predictive performance was well within the acceptable range. Bias was 4.1% indicating that on average the measured blood concentrations were 4% higher than predicted, while the imprecision was 9.7%, indicating that 50% of measured blood concentration samples were in the range from 90.3% to 109.7% of the target concentration. Engelhardt and colleagues used a simple manual infusion regimen designed to manually target three different propofol concentrations in children and then assessed the ability of the Kataria model to predict the measured concentrations [72]. In this study the bias was 6.98% and the imprecision 17.3%. Rigouzzo and colleagues used the age-adjusted Kataria model for TCI administration of propofol at target concentrations varying between 2 and 6 μ(mu)g/mL [50]. They did not perform a formal analysis of predictive performance, but reported that the Kataria model generally underestimated measured concentrations; mean measured concentrations at target concentrations of 2, 3, and 6 μ(mu)g/mL were 2.4, 4.7, and 12.2 μ(mu)g/mL, respectively.

There are, as yet, no studies of the predictive performance of PK models for dexmedetomidine in children and no studies specifically investigating the predictive performance of pharmacokinetic models for propofol in children undergoing sedation.

Choice of Dexmedetomidine and Remifentanil Target Concentrations

As with all modes of administration of sedative and analgesic drugs, with TCI administration close observation of the patient is required, with careful titration to effect. It is always safest to apply the adage "start low and go slow." TCI dexmedetomidine is not currently clinically available. If it does become available, then for sedation, target concentrations of 0.5–1.0 ng/ml should provide effective anxiolysis and sedation. For remifentanil, target concentrations in the range of 0.5–2.0 ng/ml can be used for procedural sedation, bearing in mind that when used in combination with propofol, higher target concentrations can result in unpredictable and potent interactions, with resultant respiratory depression.

Future Directions

Model Development and the Open TCI Initiative[1]

TCI systems are in common use for propofol sedation and anesthesia in adult patients in more than 100 countries [9]. A factor that is limiting the use of this technology in the pedi-

[1] http://opentci.org/. Accessed 4 February 2020

atric population is the paucity of published data verifying the validity and accuracy of the current pediatric models in different settings and patient groups. One of the goals of the recently established "Open TCI Initiative" was to set up multicenter collaborations to investigate model performance at the extremes of age. The group have done just that with the development of the general-purpose Eleveld model for propofol. It is hoped that the availability of this "universal" model [48] will lead to increased use of TCI technology for sedation and anesthesia in children.

Drug Interactions

Studies in adults over the past 20 years have made advances in our understanding of interactions between different classes of anesthetic agents. These interactions include pharmacokinetic interactions, in which the presence of one drug causes measured concentrations of another drug to be different from those expected, and pharmacodynamic interactions, in which the presence of one drug alters the clinical effects of another drug. It is clear that in adults, pharmacokinetic interactions are common among anesthetic agents and usually result in higher than expected concentrations and that pharmacodynamic interactions between hypnotics and opioids result in potent synergism for the sedative, anesthetic, respiratory, and cardiovascular effects of the hypnotic agents [73–77]. Newer monitors, which incorporate real-time information about the strength of pharmacodynamic interactions in adults, have been developed [78, 79].

Drover studied the pharmacodynamic interaction of propofol and modest doses of remifentanil in children undergoing endoscopy and found that remifentanil reduced the target propofol concentration (Kataria age-adjusted model) required for tolerance of endoscopy from 3.7 to 2.8 μ(mu)g/mL [68].

At present there is very little other published data concerning the magnitude and significance of anesthetic drug interactions in children. An understanding of this subject is important since it enables anesthesiologists to practice more safely and sometimes to use these interactions for the benefit of patients. It is thus likely that much more work will be done on this subject and that infusion and monitoring systems for children will display advisory messages based on real-time estimates of the interactions between co-administered agents.

Effect-Site Targeted TCI Systems

So far we have focused on blood-targeted TCI systems, which attempt to achieve the target blood concentration set by the user, while the effect-site concentration follows passively with a time delay determined by the rate of blood–effect-site equilibration. When a suitable k_{eo} exists for a given drug, pharmacokinetic model, and population group, then it can be used in conjunction with the pharmacokinetic parameters to "target" the effect site instead of the blood concentration. Because the anesthetic drugs have their mechanism of action in the brain rather than the blood, effect-site targeting is intuitively more appealing than blood concentration targeting and offers the potential for more rapid and precise control of the depth of sedation or anesthesia.

TCI systems operating in effect-site targeting mode manipulate the blood concentration to bring about the target (effect-site) concentration as rapidly as possible, by implementing an overshoot in blood concentration when the user increases the target effect-site concentration, and a blood concentration undershoot when the user decreases the target effect-site concentration. For effect-site targeting, the choice of k_{eo} value is critical, since it will determine the degree of overshoot or undershoot required. If the k_{eo} is too small for the patient and model, then excessively large under- and over-shoots will occur, and these may compromise patient safety. Effect-site targeting has been implemented in commercially available TCI systems programmed with pharmacokinetic models suitable for use with propofol and remifentanil in adults. Unfortunately, there are differences in the way that effect-site targeting with the Schnider model is implemented in the different pumps, resulting in different infusion profiles for the same model in some patient groups [80]. It is hoped that with widespread adoption of the Eleveld general-purpose model, this problem will be resolved.

Although the commercially available TCI devices generally are also programmed with one or more pediatric propofol models, effect-site targeting has not yet been implemented for children in these pumps. The Eleveld model does include a pharmacodynamic component [48], and so when implemented in TCI pumps, it will enable effect-site targeting. Further studies are likely to be necessary to demonstrate the safety and benefit of effect-site targeting in children before this technique is widely used in pediatric practice.

Closed-Loop Control

Automated control systems are almost omnipresent in modern life and are accepted without question. They control household appliances, fly airplanes, and control the flow of road and train traffic. Computer systems capable of automatic control of anesthesia and sedation have been developed and tested in adults [81–85].

More recently, Liu and colleagues have developed a system capable of dual control of propofol and remifentanil infusions and tested its performance in many hundreds of patients [86, 87]. Their system has been shown to improve the stability and control of anesthesia and to reduce anesthe-

siologist workload [88]. In a study in sedated adult intensive care patients, the system achieved more accurate control of sedation while reducing propofol requirements by half and decreasing vasopressor requirements [89]. In another study among adults undergoing rigid bronchoscopy, system performance was equivalent (but not superior) to manually controlled TCI infusions [89].

Since the problems of dose titration for sedation and anesthesia apply to children as well as to adults, it is likely that this technology will 1 day be used to improve the accuracy of drug administration for sedation in children. Indeed, preliminary work on closed-loop systems for children is already underway [90, 91].

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