Contributions of PK/PD Modeling to Intravenous Anesthesia

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Pharmacokinetic (PK)/pharmacodynamic (PD) modeling has made an enormous contribution to intravenous anesthesia. PK/PD models have provided us with insight into the factors affecting the onset and offset of drug effect. For example, we are now able to describe the influence of cardiac output on the disposition of intravenous drugs within the first few minutes after administration of the drug. We are able to calculate intravenous loading doses that allow for the delay between the concentration of the drug in the plasma and the rising concentration at the site of drug effect. We are able to achieve and maintain a stable level of anesthetic effect using computerized infusion pumps that target the site of drug effect rather than the plasma. Importantly, on the basis of models of drug interaction and an understanding of how drug offset varies with duration of administration, we are now able to rationally combine hypnotics and opioids.

Pharmacokinetic (PK)/pharmacodynamic (PD) modeling is the process of constructing a mathematical model to relate the time course of dose to concentration (pharmacokinetics) and concentration to effect (pharmacodynamics). Intravenous anesthesia is concerned with the use of intravenous drugs to achieve the desired effects during the induction of anesthesia, during surgery, and in the early postoperative period. The main drug classes used for inducing general anesthesia are the hypnotics, the analgesics, and the muscle relaxants. These are given to ensure unconsciousness, to facilitate endotracheal intubation, to provide analgesia, and to suppress the hemodynamic and neuroendocrine responses to surgery. The main objectives are that the patient should rapidly lose consciousness and have no awareness during the operation; the level of analgesia should closely follow the level of surgical stimulation to ensure hemodynamic stability; the drug effects should rapidly wear off at the end of the operation so that the patient has no residual sedation, no residual muscle paralysis, and, ideally, no respiratory depression and no painful sensation from the surgical trauma. Therefore, as with PK/PD modeling, intravenous anesthesia is particularly concerned with an understanding of the time course of drug effect.

We anticipate that most readers of this article will have some familiarity with the “gold standard” parameters derived from noncompartmental or moment analysis of pharmacokinetic data, i.e., clearance, volume of distribution at steady state, and mean residence time. Although an understanding of these concepts serves as a foundation for the study of pharmacokinetics, the parameters derived from moment analysis cannot be used for providing a description of the time course of the predicted concentration after intravenous drug administration. It is for this reason that we are particularly interested in compartmental models (Figure 1). The reader will require some knowledge of clinical pharmacology (including some familiarity with one-, two-, and three-compartment mammillary models), some familiarity with the effect-site concept (characterized by the rate constant $k_{e0}$), and some familiarity with the Hill equation (which defines the concentration–effect relationship).

In his editorial “(Almost) Everything You Learned About Pharmacokinetics Was (Somewhat) Wrong!,” Fisher presented some of the problems associated with the application of conventional PK concepts to situations in which the plasma concentrations of the drug change rapidly.1 He highlighted the fact that many of the basic PK/PD equations are flawed when applied to the practice of anesthesiology.

In contrast to anesthesiology, which involves the administration of most of the drugs by intravenous bolus or infusion for procedures lasting minutes to hours, many other specialties involve the administration of drugs by repeated oral dosing for conditions lasting weeks, months, or years. Anesthesiology relies increasingly on drugs with a very rapid onset of effect (1–2 min), whereas in some medical specialties (for example, in psychiatry) the onset time is measured in weeks. As a result, many PK/PD studies outside of the anesthesiology literature

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focus on drug effects that are present after days or weeks of repeated oral drug administration when plasma drug concentrations are relatively constant. This is in marked contrast to PK/PD studies in the anesthesiology literature, which focus on the rapidly changing drug effect within minutes of intravenous drug administration.

**FRONT-END KINETICS**

Standard one-, two-, and three-compartment mammillary models have at least one obvious shortcoming, according to many anesthesiologists, and that is the obvious misspecification in the model with respect to the first 1–2 min after an intravenous bolus dose of an anesthetic drug. Most anesthesiologists tend to view their patients more from a physiological perspective than from a mathematical one. They tend to think of the body as a complicated system of organs in series and parallel, rather than as a one-, two-, or three-compartment mammillary model. They understand the distribution of cardiac output to the various organs and are concerned with regional blood flows and with how to maintain those flows in a variety of pathological states. Consequently, an anesthesiology trainee, when asked to describe what concentrations he or she would expect to measure in blood samples obtained every second from the radial artery after an intravenous bolus dose of a drug, would offer a “physiological” reply, such as: “I would expect that there would be a dozen or so samples where no drug is detected. This is because the drug has to reach the right heart via the superior vena cava, then be pumped through the pulmonary circulation to the left ventricle, and thereafter be pumped into the systemic circulation. Thus, after a brief delay, the drug levels will rapidly rise to a peak, then oscillate due to recirculation.”

However, (one can imagine that) most students of pharmacokinetics, when asked what happens to the concentration of a drug after an intravenous bolus, would offer something more “mathematical,” such as: “Assuming instantaneous mixing within the central compartment, the concentrations will decline monotonically according to a mono- or multiexponential disposition function, i.e., with the back-extrapolated concentration at time zero calculated as the dose administered divided by the central volume of distribution” (Figure 2).

The anesthesiology trainee is typically surprised to learn that there is such an obvious difference between the predictions for an intravenous bolus dose according to a mammillary compartment model when compared with observed reality. Most trainees find this information troubling, because it is within the first few minutes after an intravenous bolus that they are particularly concerned with monitoring drug effects and side effects. It would seem obvious that the so-called front-end kinetics play a large part in determining the rate and extent of drug distribution to the site of drug effect and that it is the early distribution kinetics that should be most accurately characterized.

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**Figure 1** Commonly used pharmacokinetic/pharmacodynamic (PK/PD) model. (a) A three-compartment mammillary pharmacokinetic model with effect site. Subscripts of microrate constants ($k$) indicate direction of arrows. In this example, the central compartment represents the plasma concentration ($C_p$); the other two compartments are numbered 2 and 3. The box at lower left represents the effect-site concentration ($C_e$), not drawn to scale ($C_e$ is several orders of magnitude smaller than $C_p$). At steady state, we assume $C_e = C_p$. (b) The direct sigmoid relationship between $C_e$ and effect described by one form of the Hill equation. $C_{50}$ is the concentration associated with half the maximum effect ($E_{max}$). The steepness of the curve is determined by the parameter $n$ (for the curve shown, $n = 4$).

**Figure 2** Arterial blood thiopental concentrations (open circles) measured for the first 5 min (illustrating the first- and second-pass peaks) after rapid right atrial injection of 100 mg into a dog. Fitted to a recirculatory model (solid line). Predicted arterial concentrations (dashed line) over the first 1 min by back extrapolation on the basis of just five data points (filled circles). Redrawn with permission from ref. 2.
The standard PK equations used for describing the plasma concentration after an intravenous bolus dose are relatively simple and appealing. PK data obtained after an intravenous bolus dose facilitate the estimation of the central volume of distribution by the method of back-extrapolating the concentration to time zero. However, such simplicity comes at a great price, i.e., that the predicted plasma concentrations at time zero are highest, whereas in reality they are zero. Mathematically, a “bolus” dose of a drug is assumed to be given instantaneously (over an infinitesimal period) and to mix instantaneously throughout the central compartment. In the clinical setting, however, bolus doses are given relatively slowly. We note that, from a PK modeling perspective, the simple decision to treat an intravenous “bolus” (e.g., one given over 30 s) as a rapid infusion over the same time interval already goes a long way toward dealing with the gross model misspecification, because for an infusion (in contrast to a bolus dose) the predicted plasma concentration is zero at time zero.

The traditional mammillary compartmental model is certainly well accepted and sufficient for describing the pharmacokinetics of many drugs. This model has contributed to a much greater understanding of the comparative pharmacokinetics of different drugs within the same class. However, we now recognize its limitation when applied to the rapid administration of many of the anesthetic drugs, particularly those with a rapid onset of effect.1

Physiologically based pharmacokinetic (PBPK) models are able to describe the early drug distribution kinetics accurately. However, PBPK modeling requires anatomical tissue weights, blood flows, and tissue/blood partition data to enable the construction of a system of differential equations that can predict blood and tissue concentrations. That is, a PBPK model requires actual measurements of organ blood flow and tissue drug concentrations, and these are not readily available in human patients. Wada et al. have developed a graphical simulator for PBPK.3 Using this approach, a PBPK model for thiopental developed in rats was scaled to humans and used for understanding the important role that changes in cardiac output play in determining much of the variability in the early disposition of thiopental. The simulator has also been used for exploring the impact of a number of physiological changes on the pharmacokinetics of fentanyl, alfentanil, and midazolam.

Upton and Ludbrook developed a six-compartment hybrid physiological model of the kinetics and dynamics of induction of anesthesia with propofol in a chronically instrumented sheep model.4 Their model included a description of initial bolus kinetics allowing for initial vascular mixing, lung kinetics and cardiac output; a description of the effects of propofol-induced changes in cerebral blood flow; and a combined description of systemic kinetics as two tissue pools. They showed that increased cardiac output decreased the duration of anesthesia, whereas increased cerebral blood flow increased the depth (but not the duration) of anesthesia.5 In another publication, these authors have shown that the initial arterial concentrations of propofol after intravenous administration are inversely related to cardiac output. On the basis of such evidence, we could speculate that a reduction in cardiac output caused by the coadministration of drugs such as midazolam and fentanyl to anxious patients might be part of the mechanism by which these drugs reduce the required induction dose of propofol.

The recirculatory multicompartment PK model includes some of the best aspects of traditional multicompartmental PK and PBPK models while also offering some advantages over both.6 Although it is considerably simpler than the PBPK, the recirculatory model nevertheless incorporates the influence of cardiac output on the distribution kinetics. It is simpler to develop than the PBPK because it estimates blood flow to tissue compartments on the basis of the calculated intercompartmental clearance of a flow-limited tissue distribution marker rather than requiring actual organ blood flows and tissue concentrations. A distinguishing feature of the recirculatory model is the use of the drug concentrations of the recirculation peak to model a fraction of the cardiac output as “nondistributive blood flow” (a “PK shunt”). This model has been used for demonstrating that halothane-induced changes in cardiac output alter the balance of distributive and nondistributive blood flows to various tissues.7

THE EFFECT COMPARTMENT CONCEPT

All anesthesiologists are aware that there is a significant delay between administering an intravenous bolus dose and observing the drug effect. A physiology-minded anesthesiologist will understand that some of this delay is caused by events relating to circulation and cardiac output as discussed earlier. However, an accurate description of the “front-end kinetics” is not sufficient, because the plasma is not the site of drug effect. If the drug action requires that it must cross cell membranes, then factors such as molecular weight, lipid solubility, and degree of ionization will affect how readily a drug can access its receptor. Conceivably, additional delays relating to receptor-binding and postreceptor signal transduction will also contribute to the time lag between plasma concentration and the desired effect. Obvious differences between the time of peak effect after an intravenous bolus for drugs of the same class, e.g., alfentanil and morphine, underscore how important such drug factors can be in determining the delay between dose and effect.

Forty years ago, Segre investigated the kinetics of norepinephrine and its effect on the circulatory system in cats and concluded that the site of action was “quite apart from the blood compartment.”8 He developed a model that included a “receptor biophase” compartment. Ten years later, Hull et al. showed that, by the simple addition of a biophase compartment to a two-compartment mammillary model developed for pancecuronium, they could remove the hysteresis between plasma concentration and drug effect.9 Independently, in a now highly cited publication, the late Prof. Sheiner et al. postulated the effect-site concept: a hypothetical effect compartment modeled as an additional compartment linked to the plasma compartment by a first-order process (Figure 1) but whose exponential did not enter into the PK solution for the mass of drug in the body.10 The hypothetical amount of drug in the effect compartment was then related to the observed effect of D-tubocurarine. Stanski,
coauthor of this publication, went on to develop a highly successful research program based on high-resolution PK/PD modeling that relied heavily on the use of the electroencephalogram (EEG) as a surrogate measure of drug effect.

Stanski et al. investigated the relationship between the serum concentrations of intravenous anesthetic agent thiopental and its effects on the EEG. They found that, with arterial samples, the significant hysteresis that was present could be resolved by applying the effect compartment modeling approach (Figure 1). They published similar investigations that now provide the basis for our understanding of the PK/PD of other intravenous anesthetic agents, including ketamine isomers, etomidate, and midazolam. Scott et al. used PK/PD effect-site modeling to investigate two commonly used intravenously delivered opioids, alfentanil and fentanyl. They were able to show that the more rapid effect of alfentanil’s central volume of distribution (resulting in relatively higher initial concentrations after an intravenous bolus) and its more rapid equilibration with the effect site (resulting in relatively higher concentrations after an intravenous bolus). The cited publication provides perhaps the best illustration of how the effect-site concept has changed our thinking. It has become absolutely clear that neither the central volume (V$_C$) nor the steady-state volume of distribution (V$_{dss}$) is a useful parameter in calculating the bolus dose required for achieving a desired effect (effect-site concentration). The use of V$_C$ or V$_{dss}$ results in a calculated loading dose that is too small or too large, respectively. We cannot scale bolus doses merely on the basis of differences in steady-state potency. In order to calculate equipotent intravenous bolus doses for different drugs of the same class, we have to use the effect-site model to determine the apparent volume of distribution at the time of the peak effect-site concentration. Similar defining studies were conducted for two other commonly used opioids, sufentanil and remifentanil, and for two others that never made it to the market, mifentanil and trefentanil. By this time, it had become absolutely clear that neither the central volume (V$_C$) nor the steady-state volume of distribution (V$_{dss}$) is a useful parameter in calculating the bolus dose required for achieving a desired effect (effect-site concentration). The use of V$_C$ or V$_{dss}$ results in a calculated loading dose that is too small or too large, respectively. We cannot scale bolus doses merely on the basis of differences in steady-state potency. In order to calculate equipotent intravenous bolus doses for different drugs of the same class, we have to use the effect-site model to determine the apparent volume of distribution at the time of the peak effect-site concentration. Similar defining studies were conducted for two other commonly used opioids, sufentanil and remifentanil, and for two others that never made it to the market, mifentanil and trefentanil. By this time, it had become absolutely clear that neither the central volume (V$_C$) nor the steady-state volume of distribution (V$_{dss}$) is a useful parameter in calculating the bolus dose required for achieving a desired effect (effect-site concentration). The use of V$_C$ or V$_{dss}$ results in a calculated loading dose that is too small or too large, respectively.

Kazama et al. also studied more than one site of drug effect for propofol. They used an effect-site model to investigate the effect on the EEG and on systolic blood pressure in patients of different ages. They found that the effect of propofol on EEG occurs more rapidly than its effect on systolic blood pressure. Importantly, they found that plasma:effect-site equilibration half-times for the EEG effect did not change with increasing age, but that the half-times for systolic blood pressure were doubled in the elderly. This finding, combined with their finding of an increased sensitivity to the hemodynamic effects of propofol in the elderly, emphasizes the need for careful hemodynamic monitoring in the elderly when propofol is used. This remains true even when the administered dose has been carefully titrated to achieve the desired EEG effect.

For many of the drugs used by anesthesiologists, the relationship between effect-site concentration (C$_E$) and drug effect is direct; i.e., there is a static relationship between the effect-site concentrations and the PD model (Figure 1). However, this is not always the case. Indirect PD models are based on the effects of the drug (inhibition or stimulation) on the factors controlling either the input or the dissipation of the drug response. Bouillon et al. used an indirect PD model to describe non-steady-state carbon dioxide data during and after administration of remifentanil. Their work has provided new insights into the acute effect of rapidly acting opioids on ventilatory control. Simulations based on their model have shown that remifentanil effect-site concentrations that are poorly tolerated when administered by intravenous bolus will be well tolerated when achieved more gradually by infusion. The reason for the discrepancy is that slow administration of the remifentanil allows the carbon dioxide to increase, partially offsetting the ventilatory depressant effect of the opioid. Bouillon et al. also used an indirect PD model to accurately describe the magnitude and time course of propofol-induced ventilatory depression.

Although the effect-site model has been very helpful in developing an understanding of the complex relationship between dose and effect, some important questions remain. This is particularly true for propofol. Kazama et al. investigated a wide range of infusion rates with undiluted and diluted propofol. The results of this investigation provide good evidence that induction dose and time are dependent on infusion rate in a complex manner that is not adequately described by the effect-site model. The data of Kazama et al. data provide additional evidence that rapid circulation begins to influence the induction with propofol at infusion rates of >60 mg/kg/h and that it becomes the main factor for induction at infusion rates of >150 mg/kg/h.

Recently, Struys et al. hypothesized a difference in plasma:effect-site equilibration rate half-times depending on the rate of delivery of propofol. Instead of measuring plasma concentrations of propofol, they estimated plasma concentrations using a “validated” set of pharmacokinetic parameters. Their initial analysis indicated that equilibration half-life differed twofold between the two modes of administration. However, by measuring arterial concentrations in a new group of patients, they were able to show that this finding was mostly a compensation for inaccurate predictions of the arterial concentrations.
after a bolus. Ludbrook et al. concluded, on the basis of their work in a chronically instrumented sheep model, that there were large discrepancies between predicted and measured arterial and brain propofol concentrations when these models were used for predicting drug concentrations across doses and dose rates. Unfortunately, these data suggest that the front-end kinetics may also be dose-dependent.

PREDICTORS OF ONSET AND OFFSET OF EFFECT
Anesthesiologists develop an intuitive understanding of “onset” and “offset” of drug effect. This is because many of the drug effects they observe are binary (yes or no) parameters. For these binary response parameters, the onset and offset of drug effect is usually defined as the time to a predefined event, such as the time to loss or return of eyelash reflex or the time to loss or return of verbal response. In contrast, for some drug effects, continuous measures of the effect are available. For example, it is possible to measure accurately the depression in the force of muscle contraction after the delivery of muscle relaxants and EEG changes for the hypnotic effects of intravenous anesthetic agents. On the basis of such continuous measures of drug effect we can develop somewhat arbitrary end points to define the onset and offset of effect. For example, when measuring the effect of muscle relaxants we can stimulate the ulnar nerve at the wrist and measure the time for the strength of the contraction in the adductor pollicis (thumb) muscle to decrease by 95%. Another descriptor of onset could be the time to “maximal effect.” Traditional predictors of onset, such as the time to a predetermined end point, lack general applicability because they are dose-dependent. Although they might be helpful in comparing different doses of the same drug, they are not particularly useful when comparing different drugs of the same group, even if the doses are normalized to some clinical end point.

The most commonly quoted and traditional descriptor of drug onset and offset is the drug’s “terminal” half-life. The focus on half-life probably originated with the concept that dosing intervals and time to steady state could be predicted from the elimination half-life. However, this is a flawed approach with respect to drugs for which the pharmacokinetics is described in terms of multicompartment models. With regard to onset, anesthetic drugs are rarely administered at a constant dosing interval or at a constant rate of infusion; rather, they are usually administered by loading doses to achieve the desired effect as rapidly as possible (i.e., to target an effect-site concentration with deliberate overshoot in the plasma). With regard to offset, some insight into the relative contributions of the “distribution” and “elimination” half-lives to the rate of decline of the plasma concentration can be obtained relatively easily by calculating the relative contributions of each half-life to the total area under the curve after a bolus dose of the drug. However, using the rate at which the plasma concentration falls during the terminal elimination phase as a guide to determine drug offset is misleading. Mean residence time is rarely reported in the anesthesiology literature, and its utility (or lack thereof) in comparing the offset of effect for drugs of the same class has not been reported.

Fortunately, PK/PD models can describe the predicted time course of plasma concentration, effect-site concentration, and effect (for continuous measures of drug effect) or probability of effect (for binary measures of drug effect) after any dosing scheme. Over the past 10 years, PK/PD modeling has contributed several new descriptors of onset and offset of drug effect, and these have been popularized in the anesthesiology literature.

ONSET
The time to peak effect-site concentration (tpeak) is an informative dose-independent descriptor of the onset of drug effect after an intravenous bolus dose. It is important to emphasize, however, that tpeak is determined by both the rate of equilibration between the plasma and the effect-site (ke0) and the plasma PK parameters. Many of our colleagues often assume (incorrectly) that a drug with a bigger ke0 (i.e., a shorter equilibration halftime) will always have a more rapid onset than a drug with a smaller ke0 (i.e., a longer equilibration halftime). This is true only if the two drugs being compared also have identical plasma pharmacokinetics.

We also note that tpeak is frequently (incorrectly) referred to as the “time of peak effect.” Although we might appear to be splitting hairs, it is important to understand that there is a difference, and that the difference is because of the sigmoid relationship between the effect-site concentration and the drug effect (Figure 1). With “supra-maximal” doses, the maximum effect will occur prior to tpeak (Figure 3). We also note that the tpeak parameter need not be determined solely from a submaximal intravenous bolus-dose study. Even if a drug has been administered by infusion and the maximum drug effect has been achieved, it is still possible to determine tpeak from the parameters of the effect-site model. However, a submaximal bolus-dose study has the advantage of providing the opportunity to observe tpeak directly from the effect data, independent of modeling assumptions. The time to peak effect-site concentration is a useful parameter, particularly when used as a means of comparing drugs of the same class, e.g., comparing the onset times for different opioids or muscle relaxants.

It has also been proposed that tpeak can be used to address a common difficulty in clinical pharmacology simulation and control, namely, a wide choice of PK models, but only one or two published PK/PD models. The naive approach to combining separate PK and PD studies is to simply take the ke0 from the PD study and apply it to the pharmacokinetic study of interest. However, it is not possible to transport the ke0 from one set of PK parameters to another without also affecting the time of the peak effect-site concentration. In the tpeak approach, ke0 is recalculated using the pharmacokinetics of interest to preserve the tpeak. This method has been implemented in one of the target-controlled infusion (TCI) systems used in clinical anesthesiology.

OFFSET
In 1991, Shafer and Varvel introduced the concept of “recovery curves” to provide a guide to rational opioid selection. They investigated the time required for the effect-site concentration
to decrease by different percentages after an infusion designed to target and maintain a constant effect-site concentration for short-duration and long-duration infusions (Figure 4). The focus was to determine the time required for the relevant decrease in the effect-site concentration (from concentrations during the use of an anesthetic drug to concentrations associated with recovery) and how this changes as a function of the duration of infusion.

In 1992, Hughes et al. introduced the now popular term “context-sensitive half-time,” which they defined as the time required for a 50% decrease in plasma concentration after an infusion regimen designed to maintain a constant central compartment drug concentration. With reference to a three-compartment hydraulic model, they were able to provide an intuitive rationale for the role of distribution in determining postinfusion central compartment kinetics. At the termination of a very brief infusion of a drug described by a three-compartment PK model (Figure 1), neither peripheral compartment will have had time to equilibrate with the central compartment. Consequently, the concentration in the central compartment falls because of continued distribution into the two peripheral compartments and elimination from the central compartment. In contrast, after a very long infusion (of sufficient duration for the two peripheral compartments to equilibrate with the central compartment), the rate of fall in the central compartment is slowed by the redistribution of drug from the two peripheral compartments back into the central compartment. The context-sensitive half-time provides a better insight into the decline of a drug’s central compartment drug concentrations than the elimination half-life does. Indeed, Hughes et al. concluded that elimination half-life was of no apparent value for the six drugs that they investigated.

The “recovery curves” published by Shafer and Varvel were later referred to by Bailey as the “relevant effect-site decrement time” curves. These curves represent an extension and improvement of the context-sensitive half-time concept for two reasons: first, because they are based on the effect-site concentrations rather than on plasma concentrations, and second, because they focus not on the time taken to achieve a 50% decrement, but on the time taken for a percentage decrement that is relevant to the clinical scenario.

Context-sensitive half-time curves are often used to justify the selection of one drug rather than another in various clinical situations. For example, based on the context-sensitive half-time curves for four commonly used intravenous opioids it has been reasoned that, if the goal is rapid recovery, then sufentanil would be a better choice than alfentanil for operations up to 600 min, because the plasma concentration of sufentanil falls by 50% at a significantly faster rate (Figure 5a). It could also be reasoned that fentanyl should be avoided altogether because of its very long context-sensitive half-time. However, when we explore the four relevant effect-site decrement curves (based on simulations

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**Figure 3** Pharmacokinetic/pharmacodynamic (PK/PD) simulation of two doses of the nondepolarizing neuromuscular blocking drug vecuronium (1 and 4 mg, respectively) based on Rupp and colleagues’ PK/PD model for young patients. (a) The predicted plasma concentrations (solid line) and predicted effect-site concentrations ($C_e$) (dashed line). The two doses result in the same time to peak $C_e$ (arrows). (b) The predicted effect for the two doses. The onset of maximum neuromuscular blockade takes place earlier after a “supra-maximal” dose.

**Figure 4** Pharmacokinetic/pharmacodynamic (PK/PD) simulation of two propofol effect-site target-controlled infusions (TCIs) with the same target of 3 ng/ml but with different durations (10 and 40 min). (a) The falling predicted effect-site concentrations ($C_e$) after the cessation of the infusions (solid lines). $t_1$ and $t_2$ represent the time durations for the concentrations to fall from 3 to 1 ng/ml. (b) The relevant effect-site decrement times for the two infusions that are depicted in the upper figure by two open circles. The solid line represents values obtained after many simulations. The relevant decrement time increases with duration of TCI.
predict that 100% of patients will become consistently unresponsive only at infinite concentrations and that some patients will never awaken after anesthesia (i.e., the probability of no response never reaches 0). This shows that the mean effect time requires an accurate model of the probability of no response at low concentrations.

**TCI**

TCI systems deliver intravenous drugs on the basis of PK models. It has been 40 years since Kruger-Thiemer derived the equations specifying the infusion rate profile necessary for achieving and maintaining a constant plasma concentration of a drug whose pharmacokinetics could be described in terms of a linear multicompartment model and >25 years since Schwilden first demonstrated the use of computer-controlled infusion pumps in anesthesia. In those early years, TCI systems developed by several research groups were used primarily as tools to achieve and maintain steady-state plasma levels in many important PK/PD studies. Then, in 1996, a collaboration between AstraZeneca Pharmaceuticals and the University of Glasgow Department of Anaesthesia led to the release of the "Diprifusor" TCI system for propofol. Since then, more than 10,000 systems have been introduced in over 25 countries (a notable exception is the United States), and more than 13 million TCI propofol-based anesthetics have been administered worldwide. The Diprifusor uses the three-compartment mammillary PK model for propofol published by Marsh et al. to achieve and maintain a target propofol plasma concentration selected by the anesthesiologist that can then be titrated up or down according to the observed effect. More recently, two companies have released so-called open TCI systems that can be used with generic propofol (unlike the Diprifusor, which requires the use of special prefilled syringes). These newer pumps also enable the administration of propofol, alfentanil, sufentanil, and remifentanil on the basis of effect-site TCI (Figure 6).

Hu et al. applied linear systems theory to characterize the relationship between the variability in concentrations achieved with TCI devices and the variability in concentrations after intravenous bolus injection. They found that the variability of any arbitrary infusion regimen, including TCI, is bounded by the variability after bolus injection. In other words, for any drug described by linear PK models, no infusion regimen, including TCI, can have higher variability than that observed after bolus injection. That is, TCI devices neither create nor eliminate biological variability. Therefore, there will always be some difference between the concentrations predicted by the TCI system and the real (measured) drug concentrations because of the unexplained PK variability between patients. However, even if we had an online measure of the actual arterial concentrations, we would still not be that much wiser, because we never know in advance exactly what effect-site concentration any given patient will require, given the unexplained interpatient PD variability.

Ideally, the PK model used in a TCI system should explain some of the interindividual PK variability by individualizing the PK parameters according to the patient's covariates.
A weight-proportional PK model, such as that used in the Diprifusor, means that all of the volumes and clearances of a multicompartment model are proportional to the weight of the patient. Interestingly, when using a weight-proportional PK model with a TCI pump, a doubling of the weight has exactly the same effect on the infusion rates as a doubling of the targeted concentration. Or, more practically, two pumps side by side will run identical rates for a 50-kg patient with a targeted concentration of 6 µg/ml and for a 150-kg patient with a targeted concentration of 2 µg/ml. Actually, one of the main advantages of TCI systems is that they have no difficulty handling more complex PK models such as those developed using mixed-effect modeling techniques. Two such models are currently used in the newer TCI systems. The use of covariate-adjusted models has the potential to contribute greatly to the anesthesiologist’s ability to titrate to effect, because such models have already accounted for up to half of the otherwise unexplained interindividual PK variability.

One feature of TCI pumps that contributes greatly to the anesthesiologist’s ability to accurately time the offset of drug effect is the ability of the pumps to calculate the “relevant effect-site decrement time” (explained earlier). For example, by careful titration to effect during the induction of intravenous anesthesia with remifentanil and propofol, the anesthesiologist can take note of the effect-site concentration values of the two drugs at which the patient requires some prompting to breathe and at which the patient ceases to respond to voice. The anesthesiologist can then enter these (individualized) relevant effect-site concentration values to help guide an assessment of when the patient will awaken and breathe spontaneously after the cessation of the infusions. By monitoring the relevant effect-site decrement times (in combination with the monitoring of the central nervous system effect of the drug using clinically available processed EEG variables), potential difficulties with slow wake-up times, particularly after very long operations, can usually be avoided. Indeed, some strategies, such as how to alter the mix of the two drugs so that the wake-up time is optimized, become much easier to implement.

DRUG INTERACTIONS
Total intravenous anesthesia commonly consists of the combination of propofol with one of the synthetic opioids. Propofol and opioid PD interactions form the subject of many recent studies that have provided many practical insights into how best to use these drugs in combination. Vuyk et al. contributed greatly to our understanding with a series of PK/PD simulations to investigate the optimal effect-site propofol-opioid concentration window that ensures adequate anesthesia in 50 and 95% of patients with combinations of propofol with alfentanil, fentanyl, sufentanil, or remifentanil for a wide range of infusion durations.27 They concluded that the time to return of consciousness after propofol-opioid anesthesia depends predominantly on the choice of opioid and only marginally on the duration of infusion. Remifentanil, which undergoes rapid ester hydrolysis, has a short, context-sensitive half-time and a rapid equilibration with the effect site. Relatively more remifentanil (as compared to the other opioids) combined with relatively less propofol was found to be the best strategy for a patient’s rapid re-emergence to consciousness.

Anesthetic drug interactions have traditionally been characterized using isobolographic analysis or multiple logistic regression. Unfortunately, both approaches have significant limitations. Minto et al. proposed a model based on response-surface methodology, which is mathematically consistent with models of the concentration–response relationship of single drugs.32 They then used the model to characterize the entire dose–response relationship among three drugs: midazolam, alfentanil, and propofol. On the basis of the response surface, the probability of response could be predicted for any combination of effect-site concentrations of the three drugs. They were able to simulate the predicted time course of effect after maximally synergistic bolus dose combinations.

Bouillon et al. used response-surface methodology to demonstrate that propofol and remifentanil are synergistic for the clinical end points of “no response to shouting and shaking” and “no response to laryngoscopy,” but that the interaction is additive for their combined effect on two different electroencephalographic measures of drug effect.33 More recently, Johnson et al. reported an assessment of a series of remifentanil–propofol interaction models demonstrating that these models can predict responses
to selected pertinent events during elective surgery. However, significant model error was evident during rapid changes in predicted effect-site concentrations.

Response-surface PK/PD models have contributed to our ability to design optimal anesthetic drug regimens. Additionally, improved “navigational” displays will evolve to convey the information to the anesthesiologist (Figure 7). By defining the (EEG) response surface for the interaction of propofol and remifentanil, these models bring us one step closer to closed-loop control of intravenous anesthesia.

FEEDBACK CONTROL

For decades, anesthesiologists have been interested in working toward automatic control of anesthesia. In 1950, Bickford explored the possibility of using the EEG to control the depth of anesthesia automatically in animals.35 One year later, Soltero et al. published an article in Anesthesiology titled “The Clinical Application of Automatic Anesthesia.”36 The article contains a picture of an “automatic anesthetizer designed for use in the operating room.” This application of automatic control of anesthesia more than 50 years ago was based on ether, which was administered via a vaporizer. At this time intravenous anesthetics were not frequently used for the maintenance of anesthesia. Even so, in 1954, Kiersey et al. used a similar setup to that used for ether for automatic control of thiopental administration in patients during surgery.37 They concluded: “It has been demonstrated that it is clinically feasible to employ electronic control of anesthesia.” The control algorithm they used at the time was fairly simple. The rate of thiopental administration was controlled directly by the EEG signal without any intervening PK model; that is, the infusion rate was proportional to the electrical activity of the brain.

It is interesting to note that for nearly 30 years after this initial research on automatic control, the interest in this area was rather small. It was not until the early 1980s that new research began to emerge. This was probably because of the availability of better equipment for measuring drug effects and for administering drugs, the availability of drugs with better PK properties, and a better understanding of pharmacokinetics and pharmacodynamics. With the availability of the personal computer, it became possible to take an automatic control system into the operating room. These early computers were already powerful enough to handle the control algorithms efficiently. Syringe pumps also became more commonly used, and many were equipped with serial communication ports, making it possible for the computer to control the infusion rate directly.

An automatic control system consists of three elements: the actuator, the sensor, and the controller. The actuator is responsible for administering the drugs to the patient. In the case of anesthetics, these are typically syringe pumps and vaporizers. The effect of the drug is measured objectively by the second element of the system, the sensor. Accurate, reliable, and fail-safe sensors are crucial for closed-loop control. Given that these sensors are sensing and processing biological signals, artifacts are common. The third element of the automatic control system is the controller. The controller compares the measured effect with the desired or target effect and calculates the optimal input for the next time interval. The hardware infrastructure (i.e., a computer) is readily available, powerful, and now small enough to fit inside a syringe pump casing. The control loop (the actuator–patient–sensor–controller loop) is closed in automatic control. The operator interacts with the system only at the level of the controller, by setting the control target (the set point).

The most commonly used signals for control of the “depth of anesthesia” are blood pressure, heart rate, EEG, and auditory evoked potentials. In addition, because the effects of neuromuscular blocking agents can be estimated objectively and reliably by measuring the response (force, acceleration, electromyography) of a muscle to electrical stimulation of a corresponding nerve, many research groups have developed automatic control systems for this class of drugs. Although objective measures of depth of anesthesia or depth of sleep are already very useful in clinical practice, the anesthesiologist still “senses and processes” many more signals from the patient than can be measured with the equipment available. Additionally, the anesthesiologist’s ability to anticipate events, e.g., a painful stimulus, is an important component of optimal administration of anesthetic drugs. All this cannot be achieved automatically.

Many different types of control algorithms have been used for feedback control in anesthesia. In general terms, the goal of any controller is to reach the targeted effect as rapidly as possible, with no overshoot, and to maintain the targeted effect with no systematic bias. Different types of controllers

**Figure 7** Pharmacokinetic/pharmacodynamic (PK/PD) simulation of an 8-h anesthesia for two different effect-site target-controlled infusions of propofol and remifentanil based on the Schnider and Minto models in a 70-kg, 170-cm, 40-year-old male; combination A (pro 2, remi 8) and B (pro 5.5, remi 2). Isoboles show equipotent combinations for 95% probability of no response to laryngoscopy (broken line) and 5% probability of no response to shaking and shouting (dotted line).33 The trajectory for each combination is shown for 60 min after the infusions are simultaneously stopped. The trajectories, starting at A and B, cross the dotted line in ~14 and 26 min, respectively. Novel displays could indicate the optimal combination for rapid recovery, given the patient’s covariates and the dosing history. Cp effect-site concentrations; pro, propofol; remi, remifentanil.
use PK/PD principles to different extents. On the basis of PK/PD principles, the process from drug input to effect can be divided into three steps: (i) drug input to plasma concentration, (ii) plasma concentration to effect-site concentration, and (iii) effect-site concentration to effect. Also, because they describe time delays, PK/PD principles are important parts of the design of feedback control systems. The use of intermediate models also permits the use of intermediate responses such as plasma concentration and effect-site concentration as the manipulated variable.

The simplest type of controller is the so-called on–off controller. It administers the drug until the target effect is reached, then it turns off. The controller turns on again as soon as the measured effect is less than the targeted effect. This simple type of controller has not been used in any of the recently developed systems for the control of intravenous anesthetics. A classic type of controller is the so-called PID controller. (PID stands for “proportional, integral, and derivative.”) In this type of controller, the actuator setting is determined by the sum of three different properties extracted from the error curve, which is the difference between the desired and measured effects over time. The first contribution is proportional to the actual error of the system and helps in reaching the desired effect quickly. The second contribution is proportional to the derivative (steepness) of the error curve and helps anticipate the changes in the effect. The third contribution is proportional to the integral of the error curve and provides an effective control action in the proximity of the target and minimizes steady-state deviations. Combinations of these three control objectives are possible. The controller implemented by Soltero et al.36 in 1951 was a “P – controller,” which adjusted the infusion rate in proportion to the activity of the EEG signal. However, at that time the pharmacokinetics of intravenous anesthetics had not been well investigated. In particular, the models ignored the obvious time delays between plasma concentration and drug effect. More recently, Absalom et al. implemented a PID controller that uses the plasma propofol concentration as the manipulated variable.38 It must be noted that, although the control algorithm used by Absalom is “model-based,” it is not “model-predictive.” This type of controller has also been used with the effect-site concentration as the manipulated variable.39

Schwinden et al. used methohexital to control a variable derived from the EEG.40 The required infusion rate for the next control step was based on the difference between the set point and the measured EEG effect, and both the PK and PD models were used. Their control algorithm was both model-predictive and model-adaptive; however, their controller did not include a link model for the correction of the time delay between the time course of concentration in the plasma and at the effect-site, and it did not adapt all the model parameters. Nevertheless, Schwinden’s research advanced the understanding not only of automatic control but also of the role of the processed EEG as a measure of drug effect.

Many of the more recent publications describe controllers (for anesthesitics) that use the processed EEG as the control signal. For example, Struys et al. have developed a model-based adaptive controller for propofol.41 De Smet et al. further developed the adaptive part of the controller using Bayesian optimization.42 The Bayesian approach attempts to balance a priori information relating to the statistical distribution of the model parameters against the observation of the measured effect. Classically, the statistical distribution of the model parameters is obtained from a population analysis. De Smet et al. did not use the variances in the distribution of the parameters from previous studies, but instead estimated these values by simulation.

Kalman filters—a special case of Bayesian filters—have been used extensively for automatic control in the past. The hundreds of publications concerning Kalman filters (not just in the engineering literature but also in the medical literature) are evidence of their significance. Sartori et al. demonstrated how they can be applied to control anesthesia.43 Self-tuning and adaptation of PK model parameters are popular in feedback control for anesthesia. For example, Kern et al. proposed an approach of model adaptation based on fuzzy logic,44 and Gentilini et al.45 explored how the $k_{eq}$ can be individualized on the basis of an initial bolus dose and estimation of the time to peak effect.

Although anesthesiologists do not have a direct measure of “intraoperative analgesia,” an increase in heart rate and blood pressure in response to a painful (surgical) stimulus is generally considered a sign of inadequate analgesia. Clinically, such a response during surgery is usually treated with opiates. Gentilini et al. developed a model-predictive control system that controls the invasively measured blood pressure with the opiate alfentanil.46 This system also includes PK models for the prediction of alfentanil concentration. Constraints for the alfentanil concentrations can be entered into the system by the anesthesiologist. For control purposes, a linear model, rather than the more commonly used sigmoid $E_{\text{max}}$ model, was used to describe the relationship between alfentanil concentration and blood pressure. In a proof-of-concept study in patients, the system’s set-point precision was found to be similar to the precision reported from controllers of hypnotics.47

Besides PID and model-based approaches, other artificial intelligence–based control paradigms, such as fuzzy logic and neural networks, have been explored.48,49 Some of these controllers also make use of PK/PD principles. In a comparative study of feedback control vs. manual control of blood pressure during skin incision, Zbinden et al. showed that the automatic controller performed better than the anesthesiologist.50 In this investigation, in which the blood pressure was controlled as a measure of “depth of anesthesia,” it was also interesting to observe that the anesthesiologist anticipated the painful skin incision and therefore increased the concentration of isoflurane in advance. Despite this obvious advantage of having a human controller, the overall performance of the automatic control system was better.

PK/PD principles are used in closed-loop control systems for the administration of anesthetics. Despite recent advances in the development of sensors and promising results from studies
in patients, and more than 50 years after the first demonstration of its feasibility in patients, automatic control of anesthesia is not yet available for clinical use.

**CONCLUSION**

PK/PD modeling has made an enormous contribution to the practice of intravenous anesthesia. However, this is only part of the story. A pharmacologist armed with a thorough understanding of the necessary PK/PD principles would have little success in the operating room. This is because anesthesia remains an “art” as well as a science and is learned by experience over many years. It requires many technical skills involving needles and airways, the ability to think from the viewpoint of physiology, the skills to solve problems in a crisis, the capacity to perceive trends and anticipate events, eternal vigilance, and, perhaps most important, the humility to learn every day. As the end of a surgical operation approaches, the anesthesiologist must prepare to awaken the patient while simultaneously making certain that the patient does not wake up before the surgeon is finished! Unfortunately, if it takes 15 min longer than expected for a patient to awaken and breathe spontaneously after a 12-h operation (that may have originally been scheduled to last 6 h), surgical colleagues begin to doubt the anesthesiologist’s skills … such is the life of an anesthesiologist! However, there is absolutely no doubt that PK/PD modeling has made our lives as anesthesiologists very much easier.

**CONFICT OF INTEREST**
The authors declared no conflict of interest.

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