Optimizing intravenous drug administration by applying pharmacokinetic/pharmacodynamic concepts

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Editor’s key points

- Developments in pharmacokinetic modelling, effect-site monitors, and computer technology that are driving better optimization of anaesthetic drug administration are reviewed.
- The authors emphasize that anaesthetists are now able to differentiate and measure hypnosis and analgesia, the two main facets of anaesthetic effect.
- An important extension of this work is the development of advisory and closed-loop feedback systems combining effect-site monitoring and pharmacokinetic modelling.

Summary. This review discusses the ways in which anaesthetists can optimize anaesthetic–analgesic drug administration by utilizing pharmacokinetic and pharmacodynamic information. We therefore focus on the dose–response relationship and the interactions between i.v. hypnotics and opioids. For i.v. hypnotics and opioids, models that accurately predict the time course of drug disposition and effect can be applied. Various commercial or experimental drug effect measures have been developed and can be implemented to further fine-tune individual patient-drug titration. The development of advisory and closed-loop feedback systems, which combine and integrate all sources of pharmacological and effect monitoring, has taken the existing kinetic-based administration technology forwards closer to total coverage of the dose–response relationship.

Keywords: hypnotics; intravenous; opioids; pharmacokinetics

A wide spectrum of pharmacological actions (analgesia, hypnosis, and suppression of somatic and autonomic responses to noxious stimuli) are needed to control the general anaesthetic state.1 When administering (i.v.) drugs, a thorough understanding of the dose–response relationship is essential for achieving the specific therapeutic drug effect while minimizing side-effects. Rational drug dosing depends on an understanding of both the pharmacokinetics and pharmacodynamics (PK/PD) of the compounds in use and their drug interactions.2 With an ageing population, and growing demand for more complex surgical procedures in patients with limited physiological reserves, the need to fine-tune anaesthetic management in order to optimize perioperative care is greater than ever.

In the current practice, i.v. drugs are commonly administered using standard dosing guidelines, an approach which ignores inter- and intra-individual variability in the dose–response relationship. It has been proven that incorporating PK/PD information as an additional input to guide clinical anaesthesia can result in better patient care.3 As such, it is important that anaesthetists learn and understand basic anaesthetic pharmacological principles and apply the available pharmacology-based technology to their daily clinical practice. This review discusses the possible ways in which clinical pharmacology information can be used to optimize i.v. drug administration. For this purpose, we will focus on the dose–response relationship and interactions among i.v. hypnotics and opioids.

‘Everything starts with education’

Knowledge on drug disposition and effect should be considered as essential for the practice of anaesthesia. Although most of the established residency programmes worldwide do incorporate basic pharmacology teaching, clinical pharmacology remains a challenging topic to teach, and the extrapolation of theoretical principles such as drug distribution and clearance into clinical practice in the operating theatre remains difficult.

Modern computer technology has facilitated the incorporation of this theoretical knowledge into pharmacokinetic simulation software packages, enabling clinicians to simulate the time course of drug disposition and drug effect while drugs are being administered and their effects are being measured. Computer simulations are frequently used in anaesthesia as part of training and assessment.4 Simulation technology and teaching methods have advanced significantly over recent years and have the potential to improve the competency of anaesthetists and ensure a safer use of i.v. anaesthetic drugs.5 By teaching clinical pharmacology through simulations, anaesthetists will be able to answer questions such as: Which plasma and effect-site concentration are reached when injecting propofol 2 mg kg⁻¹? Is the offset of drug effect when administering alfentanil different if it is administered for 30 min compared with 5 h? In what way do propofol and remifentanil interact? The various software packages available are able to predict...
hypnotic and opioid drug behaviour, helping the clinician to make the transition from ‘dose thinking’ towards ‘concentration thinking’.3

**PK/PD-based drug administration**

The dose–effect relationship can be divided into three parts: the relationship between dose administered and blood concentration (the pharmacokinetic part), the relationship between effect organ concentration and therapeutic effect (the pharmacodynamic part), and the coupling between PK/PD (Fig. 1). Figure 2 shows that the time course of drug concentration for most i.v. hypnotics and opioids can be described by compartmental models depicting drug distribution and clearance. As the plasma is not the site of drug effect, hysteresis (the retardation or lagging of a clinical effect behind the cause of the effect being a specific plasma concentration) exists between the blood concentration and the clinical effect. Extending the pharmacokinetic model with an effect compartment enables modelling of the effect-site concentration of the drug, which represents this delay. This extension only requires one additional transfer constant, called $k_{eo}$. The relationship between the effect-site concentration and clinical drug effect is thought to be governed by a static (time-independent), non-linear (sigmoidal) relationship. In theory, a change in effect-site concentration should directly translate into a change of clinical effect without time delay. However, with currently available models, various technological limitations and biological sources of variability might alter this relationship and as a result, in clinical practice, targeting the effect-site concentration to that associated with a specific clinical endpoint (e.g. loss of consciousness) may be associated with changes in clinical effect over the next few minutes.7

Manual bolus, continuous infusion schemes, or both do not easily result in steady-state concentrations (except after long-lasting infusions) and so, technology which enables accurate maintenance of targeted concentration can be beneficial. A target-controlled infusion (TCI) is an infusion controlled by a computer or microprocessor in such a manner as to achieve a user-defined drug concentration in a ‘body compartment’ of interest. These systems use multi-compartmental pharmacokinetic models to calculate the infusion rates required to achieve the target concentration.

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**Fig 1** Dose–response relationships and interaction between hypnotics and analgesics. (Reprinted with permission from Sahinovic and colleagues)8 The green areas represent the kinetic process. The pink areas represent the relationship between the effect-site concentration and effect. Both pharmacokinetic and pharmacodynamic interactions are shown. Feedback control is shown for both hypnotics and analgesics, taking the interactions into account.
A clinician using a TCI system to administer an i.v. hypnotic or opiate is thus able to set a desired (‘target’) drug concentration, and then adjust it based on clinical observation of the response of the patient or on measurements of drug effect. A computer or microprocessor performs the complex calculations, and controls the infusion pump. Classically, plasma or effect-site concentrations are targeted. The development of TCI technology has enabled the clinicians to better manage the complex relationship between dose, blood-concentration, effect-site concentration, and clinical effect.

For most of the i.v. hypnotics and opioids used in daily practice, PK/PD models with clinically acceptable accuracy are programmed into commercially available TCI pumps. For propofol, two adult models are commercially available—the Marsh and the Schnider model. Masui and colleagues recently combined measured plasma concentration data from four different studies in which various propofol infusion regimens were used—bolus, short infusion, long infusion, and TCI—and then tested the ability of different pharmacokinetic models to predict the concentrations for all of the regimens. They concluded that the model published by Schnider and colleagues, although imperfect, should be recommended to be used for TCI and advisory displays. Unfortunately, the Schnider model effect-site control algorithm has been implemented differently in various commercially available infusion pumps and as such users need to be informed and exercise caution when using specific equipment, as this might result in different dosing and effect.

Masui and colleagues studied the front-end PK and PD of propofol and concluded that a combined PK/PD model consisting of a multi-compartmental model with a lag time, presystemic compartments, and a sigmoidal maximum possible drug effect model accurately described the early phase pharmacology of propofol during infusion rates between 10 and 160 mg kg\(^{-1}\) h\(^{-1}\). They also found that age was a covariate for lag time and that the infusion rate influenced kinetics, but not dynamics. Further studies are required to reveal whether this more complex model is clinically relevant or not compared with the classical model.

For the opioids, a better consensus exists than for propofol, and so only one model for remifentanil (‘Minto’), sufentanil (‘Gepts’), and alfentanil (‘Maitre’) has been selected for use in commercially available TCI systems. As most of the models mentioned above have been developed using specific populations, their use in children the elderly and morbidly obese patients is still limited. Caution should be applied when extrapolating and using the models in groups differing from the original validating population. Cortinez and colleagues proved that an allometric model using total body weight as the size descriptor of volumes and clearances was superior to other size descriptors to characterize propofol PK in obese patients.

For the opioids, there are no models suitable for use in children, whereas for propofol, two models have been implemented for control of TCI in children in commercially available pumps—the Kataria and Paedfusor model.
integrated PK/PD model enabling effect compartment control TCI for children is still lacking and the accuracy of these paediatric propofol models is still under debate. For children, various limitations are still present and have been described in recent reviews by Anderson and Hodkinson and Constant and Rigouzzo. Additionally, more experimental modelling strategies have been applied.

The first commercially available TCI system was the Diprifusor® (AstraZeneca, UK), which incorporated the Marsh model. It only allowed plasma-controlled TCI as the importance of the effect compartment was not fully appreciated at the time it was developed. Initial reports suggested benefits of this technology compared with manual infusion. More recently, others have not shown that plasma-controlled propofol TCI systems facilitate more accurate control of anaesthetic depth than manually controlled infusions. This might be due to the fact that the plasma is not the site of drug effect. Effect compartment-controlled TCI may offer better control of the dose–response relationship. For deep sedation in spontaneously breathing patients, Moerman and colleagues found that the combination of remifentanil and propofol offered better conditions for colonoscopy than propofol alone; and that TCI remifentanil administration was associated with reduced propofol dosing and a lower incidence of apnoea and respiratory depression, compared with manually controlled administration. Others have confirmed this finding. For other opioids such as sufentanil, TCI administration has proved to be accurate and safe.

PK/PD models have other potential operating theatre applications. Commercially available systems called ‘drug-displays’ also provide online information of the predicted plasma and effect-site concentrations of the given drugs. This allows the clinician to learn more about the concentration–clinical effect relationship when administering the drug in a combined bolus and continuous infusion model.

In addition, commercial pumps can also be connected to PC software programs to provide online predictions of plasma and effect-site concentrations. An example of such a program is RUGLOOP, developed by De Smet and Struys and available at ‘http://www.demed.be’.

**Measuring clinical drug effects**

Beneficial kinetics and a fast onset and offset facilitate optimal drug administration and titration during anaesthesia. In contrast to ‘slow’ drugs, the clinical effect of i.v. hypnotics and opioids can be measured online in a minute to second time frame. Better monitoring of therapeutic effects has become available with the introduction of hypnotic effect monitors. As these monitors measure cerebral drug effect, this has to be considered as an integral part of anaesthetic pharmacology. For the first time in the history of the speciality, anaesthetists are able to differentiate and measure the two chief components of anaesthetic effect, hypnosis and analgesia, by using specific effect monitors. However, much work still has to be done. Various commercially available systems exist, but the extent to which they have been validated is variable, and some require further work to be validated as measures of cerebral drug effect. To facilitate this, the relationship between drug effect-site concentration and clinical effect has to be better defined. As shown in Figure 2, a sigmoidal $E_{\text{max}}$ model is mostly used for this, but in specific conditions, more complex models might be required. In addition, validation based on clinical endpoints such as loss and return of consciousness is required. Clinical usefulness will need to be demonstrated and patient outcome should be enhanced by applying this new technology. For some of these monitors, some of these goals have already been reached and there are publications in the literature. For others, major research is still required.

In contrast to the hypnotic cerebral drug effect monitors, real ‘analgesic drug effect monitors’ do not yet exist. This is due to the complexity of pain physiology and the fact that what is required is a measure of the balance between nociception and anti-nociception during anaesthesia. The nature and severity of surgical stimuli change constantly and responses to noxious stimuli, such as movement and haemodynamic changes, are modulated by multiple factors. In an attempt to optimize the titration of opioids in relation to the noxious stimulus and the resulting adrenergic activation, various measures of the status of the autonomic nervous system have been studied. The success of these based on skin conduction, heart rate variability, and variability of pulse plethysmography has been variable. Recently, the multivariate surgical stress index (SSI) (GE Healthcare, Helsinki, Finland) (now commercially called ‘SPI’ or ‘Surgical Pleth Index’), based on a sum of the normalized beat interval (PBI) and the pulse plethysmographic pulse wave amplitude (PPWA), has been developed as a measure of nociception–anti-nociception balance. Some correlations between SSI during stimulation and remifentanil concentrations have been found. Using SSI to titrate remifentanil compared with standard clinical practice during surgery resulted in reduced remifentanil usage, improved haemodynamic stability, and less movement during surgery.

If immobility is considered as an important clinical endpoint of hypnotic and analgesic drug titration, then prediction of movement responses to noxious stimuli during anaesthesia is beneficial. The RIII reflex, a component of the nociceptive flexion reflex, is a polysynaptic spinal withdrawal reflex elicited by stimulation of nociceptive Aδ afferents. It is assessed by analysing the biceps femoris muscle electromyogram during electocutaneous stimulation of the ipsilateral sural nerve. This approach remains experimental and is not commercially available for clinical use.

Given the close relationship between propofol effect-site concentrations and bispectral index (BIS), Luginbuhl and colleagues hypothesized that the predicted effect-site concentrations of propofol and remifentanil together with an appropriate interaction model could provide sufficient information to predict responsiveness of an anesthetized patient to noxious stimuli. Thus, they developed the novel...
noxious stimulation response index (NSRI), computed from hypnotic and opioid effect-site concentrations using a hierarchical interaction model and found that NSRI conveys information that better predicts the analgesic component of anaesthesia than EEG-derived measures.54

Individualizing the dose–response relationship

TCIs, as described above, are based on population-based PK/PD models. The model parameters in the infusion device are those of the typical patient and are usually adjusted for factors known to influence these parameters, such as weight, height, age, and gender. As such, TCI ignores residual inter-individual variability, thereby limiting the accuracy of the estimated drug concentration for the individual. Fortunately, this inaccuracy can be limited if the model is built during a study which explores a wide variety of possible covariates using parametric modelling, ideally non-linear mixed-effects modelling.55 56 Caution is needed when applying model-based drug information to an individual patient with co-morbidity such as cardiac disease, obesity, diabetes, nephropathy, alcoholism, and to children and the elderly, if similar subjects were not part of the original study population. Because of this, no single regimen applies to all patients. Some guidance can be found in the effective concentrations at which 50% and 95% of patients have accurate clinical effect.57

The resulting inaccuracy of absolute concentrations based on population models requires the clinician to manually titrate the dose regimen or target concentration for the individual patient based on observations of the desired therapeutic effect. Using one of the therapeutic effect monitors mentioned, the clinician is able to do so rationally. As a result, one could argue that if one has to titrate to a specific therapeutic effect, advanced drug administration systems are not required. In defence of TCI, it has been shown that the use of TCI technology facilitates rapid achievement of therapeutic concentrations at the site of drug action, the so-called ‘effect-site concentration’.33–35 It is already possible in clinical practice to combine both sources of dose–response information—the effect-site concentrations displayed by the TCI system, and drug effect information shown by the hypnotic effect monitors, to guide hypnotic drug administration. Proof exists that the combined information offers a higher degree of care.58

Clinicians usually apply a reactive approach, by selecting a dose based on a variety of considerations, observing the effect thereof, and adjusting the dose if required.59 Accurate titration can produce clinical benefits but requires a high standard of clinical expertise and is a labour-intensive process that may divert attention from critical actions, resulting in paradoxically suboptimal therapy or even threatening patient safety. ‘Closed-loop controllers’ are computer programs designed to maintain a targeted effect by adapting and optimizing drug administration. In closed-loop control, the user (patient or clinician) only selects and enters the desired effect variable to be maintained. The application of closed-loop systems for drug administration is complex and requires a perfect balance for all the basic components of such a system: (i) a continuously available control variable representative for the targeted therapeutic effect; (ii) a clinically relevant set-point or target value for this variable; (iii) a control actuator which is, in this case, the infusion pump driving the drug; (iv) a system, in this case, a patient; and (v) an accurate, stable control algorithm. Although closed-loop systems to control hypnotics and analgesics using continuously measured pharmacodynamic drug effect measures are not yet available commercially, various experimental systems have been developed and tested over the last 40(!) yr.60–61 Recently, various groups tested BIS-guided propofol administration using proportional-integral-derivative (PID) closed-loop control and found that it was clinical feasible and outperformed manual drug titration.62–66

Unfortunately, PID control might suffer from a lack of patient individualization, leading to oscillation during control and therefore, we (Struys and De Smet)67–69 developed a model-based patient-individualized closed-loop control system for propofol administration using the BIS as a controlled variable. We tested this system, which uses Bayesian methodology for patient-individualization, during anaesthesia for ambulatory surgery and found a high level of accuracy and feasibility.67 71 As all previous examples lack the possibility of predictive control, Ionescu and colleagues72 developed the Robust Predictive Control Strategy which can be applied for propofol dosing using BIS as a controlled variable during anaesthesia. To date, most closed-loop systems offer only ‘single-input–single-output control’. As hypnotics and analgesics are mostly co-administered during anaesthesia, multiple-input–multiple-output controllers are a logical next step, but have yet to be developed and tested. In addition to a measure of hypnotic drug effect, these systems will also require an accurate measure of the nociception–anti-nociception balance during anaesthesia.73

During sedation and postoperative analgesia, patient-controlled drug delivery allows the patient to optimize drug titration, and as such this can also be defined as a closed-loop system. Patient demands represent positive feedback, whereas lack of responsiveness can be used for negative feedback. Doufas and colleagues74 75 showed previously that failure to respond to an automated responsiveness monitor (ARM) precedes potentially serious consequences of loss of responsiveness. Recently, they showed that ARM dynamics in individual subjects compare favourably with clinical and electroencephalogram endpoints and that the ARM could be used as an independent guide of drug effect during propofol-only sedation.76 This technology has now been implemented in Sedasys76 (Ethicon endoSurgery, Cincinnati, OH, USA) to provide propofol sedation during endoscopic procedures.77 Previously, others have also shown the applicability of patient-controlled drug administration for hypnotic78 and analgesic79–81 drugs.
Combining hypnotics and analgesics

To reach the highest standards of care, optimal titration of both anaesthetic and analgesic drugs is required. Classically, opiates are used to manage the balance between nociception and anti-nociception and short-acting hypnotics are widely used to titrate the hypnotic component of anaesthesia. When optimizing the balance between hypnotic and analgesic action, the primary concern is to ensure an accurate level of the hypnotic component of anaesthesia. Both awareness caused by inadequate anaesthesia, and the haemodynamic side-effects caused by an excessive anaesthetic depth should be avoided as they may compromise outcome.

Next, optimal and rationale opioid titration is required. As such, the dose–response relationship of both drugs should be optimized. I.V. hypnotics and opioids demonstrate both kinetic and dynamic interactions and this should be taken into account.

Pharmacodynamic interactions between opioids and I.V. hypnotics are clinically very significant and have been studied in detail using response surface methods. Response surface models are powerful sources of information on drug interactions as they combine information about any isobole (i.e. a graph showing an equi-effective combination of two drugs) and the concentration response curve of any combination of the drugs involved. Using the various response surfaces one can predict the corresponding drug effect for any two (or more) concentrations of the interacting drugs.

The information of hypnotic–analgesic drug interaction together with data from estimated drug concentration and online effect-monitoring can be combined in a powerful pharmacodynamic advisory tool that estimates the complete dose–response relationship, facilitates optimal dose titration, and improves patient care.

Recently, various display systems have been developed and tested. Schumacher and colleagues proposed an advisory system that leaves the anaesthetist in complete control of dosing but provides real-time information about the estimated drug concentrations, predicted combined effect, and estimated wake-up time resulting from the anaesthetists’ actions. Additionally, this device displays the optimal drug concentration ratio for a given effect in the typical patient. Albert and colleagues developed a pharmacological display system that can be used to accurately model the concentration and effect of anaesthetic drugs administered alone and in combination, online, in the operation theatre, thereby visualizing the sedation, analgesia, and muscle relaxation.

Fig 3 Smart Pilot View (Dräger, Lübeck, Germany). This display represents a balanced anaesthetic case using a volatile agent, propofol, remifentanil, and fentanyl. It uses a topographical plot of the interaction between hypnotic and analgesic drugs (left plot) and represents the vital signs and bispectral index scale (BIS), dose and effect over time. Furthermore, it introduces the noxious stimulus response index (NSRI) as a new parameter (right plots). The topographical plot on the left illustrates the synergistic interaction of hypnotic and analgesic drugs with grey-scaled isoboles. MAC 50 and 90 indicate the probability of loss of response to skin incision (MAC, minimum alveolar concentration). MAC awake indicates the probability of wake-up. Fentanyl is converted into remifentanil equivalents, so its contribution can be accounted for on the isobole plot. The plots on the lower right represent the time course for each drug over the previous 40 min to 4 h and 20 min into the future. A series of symbols (light green buttons) are used as Event Markers during a surgical procedure (e.g. loss of consciousness, intubation, and incision). These are useful to mark the individual reaction or non-reaction of the patient and determine if the patient’s individual reaction corresponds to the level of anaesthesia, which is represented by the isoboles calculated from the behind lying algorithms. (SmartPilot® View, reprinted with permission, © Dräger Medical GmbH, Lübeck, Germany.)
status of a patient based on general population models that have been corrected for body mass, age, and sex. Various advisory systems have recently become commercially available. Two examples, Smart Pilot View (Dräger, Lübeck, Germany) and GE Navigator (GE Healthcare, Helsinki, Finland), are depicted in Figures 3 and 4, respectively.

In conclusion, by implementing PK/PD-based information, the anaesthetist should be able to optimize anaesthetic–analgesic drug administration. For both i.v. hypnotics and opioids, models to accurately predict the time course of drug disposition and effect can be applied. Various commercially available and some experimental drug effect measures have been developed and can be implemented to further fine-tune patient individualized drug titration. All sources of pharmacological and effect monitoring can be combined into anaesthetic advisory and closed-loop feedback systems enlarging the existing kinetic-based administration technology towards a total coverage of the dose–response relationship.

Conflict of interest
The departments involved in this work have received grants from companies mentioned in this work, being (i) GE Healthcare, Helsinki, Finland, (ii) Dräger, Lübeck, Germany, and (iii) Ethicon endoSurgery, Cincinnati, OH, USA. M.M.R.F.S. is a co-owner of the RUGLOOP system, licensed to DEMED, Temse, Belgium.

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