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Optimizing IV drug administration by applying PK/PD concepts.

M.M.R.F.Struys¹ ², M Sahinovic ¹, B.J. Lichtenbelt ¹, H.E.M. Vereecke ¹, A.R. Absalom¹

¹ Department of Anesthesiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands
² Department of Anesthesia, Ghent University, De Pintelaan 185, 9000 Gent, Belgium

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 interactions between intravenous hypnotics and opioids. For intravenous hypnotics and opioids, models that accurately predict the time course of drug disposition and effect can be applied. Various commercially or experimentally drug effect measures have been developed and can be implemented to further fine-tune patient individualized 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 towards a total coverage of the dose-response relationship.
Introduction:

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. When administering (intravenous) 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 the understanding of both the pharmacokinetics and dynamics of the compounds in use and their drug interactions. 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 peri-operative care is greater than ever.

In current practise, intravenous drugs are commonly administered using standard dosing guidelines, an approach which ignores inter- and intra-individual variability in the dose-response relation. It has been proven that incorporating pharmacokinetic-dynamic information as an additional input to guide clinical anaesthesia can result in better patient care. As such, it is important that anaesthetists learn and understand basic anaesthetic pharmacological principles and apply the available pharmacology-based technology into their daily clinical practice. This review discusses possible ways in which clinical pharmacology information can be used to optimize intravenous drug administration. For this purpose we will focus on the dose-response relationship and interactions among intravenous 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 programs world-wide 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 practise 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 a
part of training and assessment. Simulation technology and teaching methods have advanced significantly over the last years and have the potential to improve the competency of anaesthetists and ensure a safer use of intravenous anaesthetic drugs. 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 2mg/kg? Is the offset of drug effect when administering alfentanil different if it is administered for 30 minutes compared with 5 hours? In what way are propofol and remifentanil interacting? 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”.

**Pharmacokinetic-dynamic 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 pharmacokinetics and dynamics (figure 1, partially). Figure 2 shows that the time course of drug concentration for most intravenous 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 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. Manual bolus and/or continuous infusion schemes 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. A clinician using a TCI system to administer an intravenous 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\(^8\). The development of target-controlled infusion (TCI) technology, have enabled clinicians to better manage the complex relationship between dose, blood-concentration, effect-site concentration and clinical effect.

![Diagram of Hypnotics and Analgesics](image)

**Figure 1**: dose-response relationship and interaction between hypnotics and analgesics.

For most of the intravenous 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\(^9\)-\(^11\). Masui and colleagues\(^12\) 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. He concluded that the model
published by Schnider and coworkers, 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 the various commercially available infusion pumps, so, users have to be informed and cautious when using specific equipment as this might result in different dosing and effect. Masui et al. studied the front-end PK and PD of propofol and concluded that a combined pharmacokinetic-dynamic 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 infusion rate influenced kinetics, but not dynamics. Further studies are required to reveal if or not these more complex model is clinically relevant compared with the classical one.

Figure 2: Dose-response relationship for one drug. Pharmacokinetics are depicted as a multicompartmental model. Pharmacodynamics are shown as a sigmoidal Emax model. Kinetics and dynamics are linked by a effect-site compartment. (Modified from with permission).
For the opioids a better consensus exists than for propofol, and so only one model for remifentanil ("Minto"\textsuperscript{15, 16}), sufentanil ("Gepts"\textsuperscript{17}) and alfentanil ("Maitre"\textsuperscript{18-20}) has been selected for use in commercially available TCI systems.

As most of the above mentioned models have been developed in 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\textsuperscript{13}. Cortinez et al\textsuperscript{21} 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 pharmacokinetics 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\textsuperscript{22, 23}. An 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\textsuperscript{24, 25}. For children, various limitations are still present and have been described in recent reviews by Anderson\textsuperscript{26} and Constant.\textsuperscript{24} 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 important of the effect compartment was not fully appreciated at the time it was developed. Initial reports suggested benefits of this technology compared to manual infusion\textsuperscript{27-30}. More recently, others have not shown that plasma controlled propofol TCI systems facilitate more accurate control of anaesthetic depth than manually controlled infusions\textsuperscript{31, 32}. 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\textsuperscript{33-35}. For deep sedation in spontaneously breathing patients Moerman and colleagues\textsuperscript{36} 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 apnea and respiratory depression, compared to manually controlled administration. Others have confirmed this finding\textsuperscript{37}. For other opioids such as sufentanil, TCI administration has been proven to be accurate and safe\textsuperscript{38}.

Pharmacokinetic and dynamic models have other potential operating room applications. Commercially available systems called “drug-displays” also provide on-line 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 on-line 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 with “slow” drugs, the clinical effect of intravenous hypnotics and opioids can be measured online in a minute to second time frame. Better monitoring of the therapeutic effects has become available with the introduction of hypnotic effect monitors. As this equipment measures cerebral drug effect, it has to be considered as an integral part of anaesthetic pharmacology. For the first time in the history of the specialty, 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 has still to be done. Various commercially available systems exist, but the extent to which they have been validated is variable, and some required further research 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 Emax model is mostly used for this, but in specific conditions more complex models might be required. In addition, validation on clinical endpoints such as loss and return of consciousness is required. Clinical utility should be proven and finally, patient outcome should be enhanced by applying this new technology. For some of these monitors, some of these goals are already reached and published 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 antinociception during anaesthesia. The nature and severity of surgical stimuli change constantly and responses to noxious stimuli, such as movement and hemodynamic 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 \(^{43}\) and variability of pulse plethysmography, \(^{44}\) has been variable \(^{45, 46}\). 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 pulse beat interval (PBI) and the photoplethysmographic pulse wave amplitude (PPGA), has been developed as a measure of the nociception-antinociception balance \(^{47}\). Some correlations between SSI during stimulation and remifentanil concentrations have been found. \(^{48}\) Using SSI to titrate remifentanil compared with standard clinical practice during surgery resulted in less remifentanil usage, improved hemodynamic stability and less movement during surgery \(^{49}\).

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 \(^{50-52}\). The RIII reflex, a component of the nociceptive flexion reflex, is a polysynaptic spinal withdrawal reflex elicited by stimulation of nociceptive A\(\delta\) afferents. It is assessed by analyzing the biceps femoris muscle electromyogram during electrocutaneous stimulation of the ipsilateral sural nerve. This approach remains experimental and is not commercially available for clinical use \(^{51, 52}\).

Given the close relation between the propofol effect-site concentration and BIS \(^{53}\), Luginbühl and colleagues hypothesised 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**:

Target-controlled infusions, 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.

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 mentioned therapeutic effect monitors, 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 anyhow, 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”.

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.

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. Accurate titration can produce clinical benefits but requires a high standard of clinical expertise and is a labor-intensive process that may divert the clinician’s attention from critical actions resulting in paradoxically suboptimal therapy or even threatening the patient’s safety. “Closed-loop controllers” are computer programs designed to maintain a targeted effect by adapting and optimizing the 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: 1) a continuously available control variable representative for the targeted therapeutic effect; 2) a clinically relevant set-point or target value for this variable 3) a control actuator which is, in this case, the infusion pump driving the drug; 4) a system, in this case a patient 5) an accurate, stable control algorithm. Although closed-loop systems to control hypotics 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 (!) years. 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.
Unfortunately, PID control might suffer from a lack of patient individualization leading to oscillation during control and therefore, Struys and De Smet developed a model-based patient-individualized closed loop control system for propofol administration using the Bispectral Index as a controlled variable. They tested their system, which uses Bayesian methodology for patient-individualization, during anaesthesia for ambulatory surgery and found a high level of accuracy and feasibility. As all previous examples lack the possibility of predictive control, Ionescu et al. developed the Robust Predictive Control Strategy which can be applied for propofol dosing using BIS as a controlled variable during anesthesia. So far, 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-antinociception balance during anaesthesia.

During sedation and post-operative 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 et al. 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 favorably with clinical and electroencephalogram endpoints and that the ARM could be used as an independent guide of drug effect during propofol-only sedation. This technology has now been implemented in Sedasys (Ethicon endoSurgery, Cincinnati, Ohio, USA) to provide propofol sedation during endoscopic procedures. Previously, others have also shown the applicability of patient-controlled drug administration for hypnotic and analgesic 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 antinociception and short acting hypnotics are widely used to titrate the hypnotic component of anesthesia. When optimizing the balance between hypnotic and analgesic action, the primary concern is to ensure an accurate level of the hypnotic component of anesthesia. Both awareness caused by inadequate anesthesia, and the hemodynamic side-
effects caused by an excessive anaesthetic depth should be avoided as they may compromise outcome. 82-84

Next, optimal and rationale opioid titration is required. As such, the dose-response relationship of both drugs should be optimized. It should be taken into account that intravenous hypnotics and opioids demonstrate both kinetic and dynamic interactions. Pharmacodynamic interactions between opioids and intravenous hypnotics are clinically very significant and have been studied in detail using response surface methods 85-89. Response surface models are powerful sources of information on drug interactions as they combine information about any isobole and the concentration response curve of any combination of the drugs involved 90. Using the different mathematically described response surface, one can predict the corresponding drug effect for any two (or more) drug concentrations of the interacting drugs 91.

The information of hypnotic-analgesic drug interaction together with data from estimated drug concentration and on-line effect-monitoring can be combined in a powerful pharmacodynamic advisory tool that estimates the complete dose-response relation, facilitates optimal dose titration, and improves patient care 92, 93. Recently, various display systems have been developed and tested. Schumacher et al. 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 wakeup time resulting from his actions. Additionally, this device displays the optimal drug concentration ratio for a given effect in the typical patient 94. Albert and co-workers developed a pharmacological display system that can be used to accurately model the concentration and effect of anaesthetic drugs administered alone and in combinations, on-line, in the operation room, thereby visualizing the sedation, analgesia and muscle relaxation status of a patient based on general population models that have been corrected for body mass, age, and sex 95. Various advisory systems became recently 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.
Figure 3: Smart Pilot View (Dräger, Lübeck, Germany). This display represents a balanced anesthetic 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 gray-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 past 40min to 4h and 20 minutes 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, incision). These markers are useful to mark the individual reaction or non reaction of the patient and see if the patients individual reaction will correspond to the level of anesthesia, which is represented by the isoboles calculated from the behind lying algorithms. (SmartPilot® View, reprinted with permission, © Dräger Medical GmbH, Lübeck, Germany).
Figure 4: GE Navigator (GE Healthcare, Helsinki, Finland) display provides a tool for modelling and visualization of PK/PD models for common anaesthetic (inhaled and i.v.) drugs. In addition, it provides a model for the synergistic effects of propofol (or inhaled agents) and the fentanyl family. The calculated effect-site concentrations are displayed in a time-based graphical format. The total effect trace (the black line shown in the sedation and analgesia windows) visualizes the combined synergistic effect of the analgesic and sedative drugs. The displayed effects include level of sedation according to loss of consciousness probability, level of analgesia according to the probability of response to intubation (high pain stimuli), and level of neuromuscular block. The drug models are calculated for up to 1 h into the future providing predictive drug modelling for drug concentration and quantitative complex drug interactions. (Navigator Therapy Display, reprinted with permission, © 2010 General Electric Company, Helsinki, Finland).

In conclusion, by implementing PK/PD based information, the anaesthetist should be able to optimize anaesthetic-analgesic drug administration. For both intravenous 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 relation.
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