Simulated Drug Administration: An Emerging Tool for Teaching Clinical Pharmacology During Anesthesiology Training

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A thorough understanding of the dose–response relationship is required for optimizing the efficacy of anesthetics while minimizing adverse drug effects.[1] Nowadays, except for the inhaled anesthetics (for which end-tidal concentrations can be measured online), most of the drugs used in clinical anesthesia are administered using standard dosing guidelines, without giving due consideration to their pharmacokinetics and dynamics in guiding their administration. Various studies have found that introducing pharmacokinetics and pharmacodynamics as part of the inputs in clinical anesthesiology could lead to better patient care.[2] With this in mind, it is extremely important that clinicians understand and apply the principles of clinical pharmacology that determine the time course of a drug's disposition and effect.

Clinical pharmacology is one of the most challenging topics to teach in anesthesiology. The development of simulators to illustrate the time course of a drug's disposition and effect provides online visualization of pharmacokinetic–pharmacodynamic information during the clinical use of anesthetics. The aim of this review is to discuss the importance of simulation as a clinical pharmacology teaching tool for trainees in anesthesiology.

LEARNING FROM SIMULATIONS

Basic knowledge of drug disposition and effect is an integral part of the clinical practice of anesthesiology. Unfortunately, the basic concepts of pharmacokinetics and pharmacodynamics are not always easy to understand or to apply directly to clinical practice. It might be difficult to extrapolate data relating to absorption, distribution, and clearance and their changes over a period of time directly into clinical practice. Predicting the onset and offset of drug effect during drug administration might be challenging, given that the plasma is not the site of drug effect for most anesthetic drugs.[3,4] Thanks to the availability of computer technology, this extended knowledge can be incorporated into simulation packages so that clinicians can simulate the time course of a drug's disposition and effect while the drug is being administered and its effect is being measured. Computer simulations are frequently used in various disciplines to evaluate control systems.[5,6] After learning clinical pharmacology through simulations, anesthesiologists will be able to answer the following questions: What plasma and effect-site concentration do I get when I inject 1 mg/kg of propofol and how long does it take to see the onset and offset? Does it take longer to see the offset of drug effect when administering fentanyl for 5 min or 5 h? How are sevoflurane and remifentanil interacting? How does a target-controlled drug infusion (TCI) work?

INCORPORATION OF CLINICALLY AVAILABLE PHARMACOKINETIC/PHARMACODYNAMIC TOOLS

New methods of drug administration have been developed and are now used clinically. Drug effects are more easily measured using more accurate and more specific monitoring devices. The aim of these developments is to use principles from the pharmacology of anesthetics to optimize drug titration, by better controlling the overall relationship between drug dose and the desired response. Various technologies are available in the operating room and can be used as online teaching tools.

For intravenously administered anesthetic drugs, including propofol, opiates, and muscle relaxants, TCI systems are commercially available. TCI is an infusion controlled in such a manner as to achieve a user-defined estimated drug concentration in a body compartment or tissue of interest. An anesthesiologist using a TCI system to administer an anesthetic agent is able to set and adjust a desired drug concentration, usually referred to as the "target concentration," based on clinical observation of the patient or measurement of drug effect. Multicompartmental pharmacokinetic models are used by TCI systems to calculate the infusion rates required for achieving the target concentration. A computer or microprocessor is required for performing the complex calculations and to

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control the infusion pump. Classically, plasma- or effect-site concentrations are targeted.[7]

As shown in **Figure 1**, commercially available systems 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 while administering the drug. Commercial pumps can also be connected to personal computer software programs to provide online predictions of plasma- and effect-site concentrations. A good example of such a program is RUGLOOP (Demed, Temse, Belgium), developed by De Smet and Struys and available at http://www.demed.be. Various investigators are also studying the time course between measurable end-tidal concentrations of inhaled anesthetics and drug effects. Hysteresis data are available for various inhaled drugs and will be incorporated in future applications of this technology.[8,9]

Aside from displaying predicted effect-site concentrations for inhaled and intravenous drugs, the measuring of specific drug effects is one of the major achievements in anesthesiology and has to be considered as an integral part of pharmacology anesthetic. Although end points, such as hypnosis and analgesia, can be measured only in terms of surrogate indices, spontaneous and evoked electroencephalographic derived indices can be monitored as real-time surrogate indices of hypnotic drug effect.[10] In an attempt to measure the balance between nociception and pharmacologically induced antinociception, various measures of the "status" of the autonomic nervous system during anesthesia have been studied, such as heart rate variability and the variability of the pulse plethysmography amplitude.[11–14] It is already possible in clinical practice to combine dose–response information both from the concentration and the drug effect monitors, to guide the administration of hypnotic drugs, and there is evidence that the simultaneous use of these two clinical pharmacological sources of information offers improved patient care.[15]

Currently, achieving an optimal level of anesthesia requires the combined use of hypnotic and opiate drugs. An accurate level of the hypnotic component as well as an optimal level of the analgesic component are required for anesthesia in patients who are to undergo surgery. The noxious stimulus should be identified properly and blocked at the spinal level. Classically, this is done by using opioids and/or locoregional anesthetic techniques. Recently, inhaled anesthetics have been shown to exert some of their effects at the level of the spinal cord and could offer an alternative method of blocking ascending stimuli from reaching the cerebral cortex, where they cause an arousal reaction.[16–18] If an opioid is used along with a hypnotic drug, their interaction has to be considered. The most detailed study of this interaction uses response surface methods.[19] The hypnotic–opiate balance has been described for intravenous drugs.[20–23] Recently, Manyam *et al*.[24] have studied the interaction between sevoflurane and remifentanil. Response surface pharmacodynamic interaction models were built using the pooled data for sedation and analgesic end points. Apart from the hypnotic–opioid interaction, one has also to consider an interaction between two hypnotics. Classically, an induction bolus of one drug is given intravenously, followed by an inhaled drug for maintenance of hypnosis. It was found recently that the combined effect of propofol and sevoflurane on loss of consciousness and movement of the patient at the time of skin incision, during general anesthesia, is additive and not synergistic.[25]

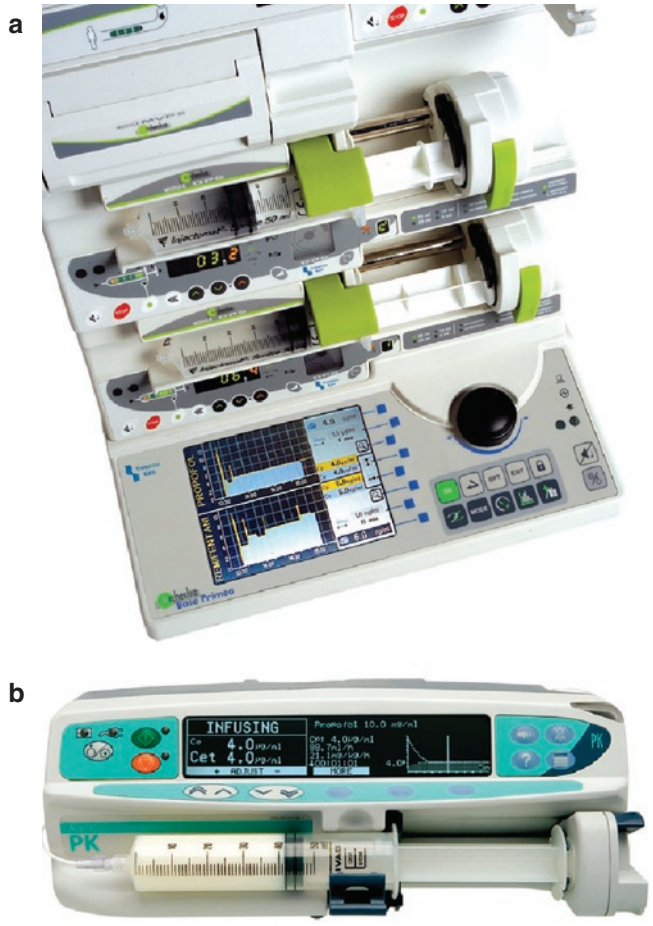

Figure 1 Commercially available target-controlled infusion devices. (**a**) Shows the BASE PRIMEA system (Fresenius, Brézins, France), including two pumps and the target-controlled infusion controller with color display. (**b**) Shows the ASENA PK TCI pump (Cardinal Health Alaris Products, Basingstoke, UK). Both systems can control the predicted plasma and effect-site concentrations of the given drugs. The displays show the trend and prediction of the time course of drug concentrations. Reprinted with permission of the respective companies.

AVAILABILITY OF SIMULATION PROGRAMS

Simulation technology and pedagogy have advanced dramatically in recent years and have the potential to improve the competency of anesthesiologists and ensure a safer use of anesthetic drugs in practice.[26] A wide range of simulation technology products is available for teaching the pharmacology of anesthetics, ranging from Excel spreadsheets through the new generation of computer-driven, screen-based, realistic, and virtual reality simulators. Various tools are available to simulate the time course of plasma- and/or effect-site concentrations when using one or more drugs. These packages also offer instruction in TCI.

Several early software simulation programs such as STANPUMP, STELPUMP, STANGRAPH, RUGLOOP I, and

IVA-SIM have been collected by Dr. Steven Shafer at Stanford University and are still available at http://anesthesia.stanford.edu/pkpd/. Minto and Schnider developed a complete set of add-in tools for Excel (Microsoft Corporation, Redmond, WA). This software, called "PKPDTOOLS," is available from http://www.pkpdtools.com/. These spreadsheet applications are becoming very popular for data handling in research and education and provide user-friendly tools covering all the basic situations commonly encountered in pharmacokinetic/pharmacodynamic modelling. PKPDTOOLS has additional reparameterization functions, can simulate TCI, and has context-sensitive half-time functions. Additional dedicated pharmacokinetic/pharmacodynamic simulations with Excel are available at http://www.demed.be.

A user-friendly simulator is TIVATRAINER, developed by Dr. F. Engbers at Leiden University (available at http://www.eurosiva.org) (**Figure 2a**). This simulation program is capable of showing the plasma- and effect-site concentrations of various intravenously administered anesthetics. There are various modes of administration, including manual, TCI, effect-site controlled infusion, as well as an intravenous-assist mode whereby the "ideal" manual input is calculated by the

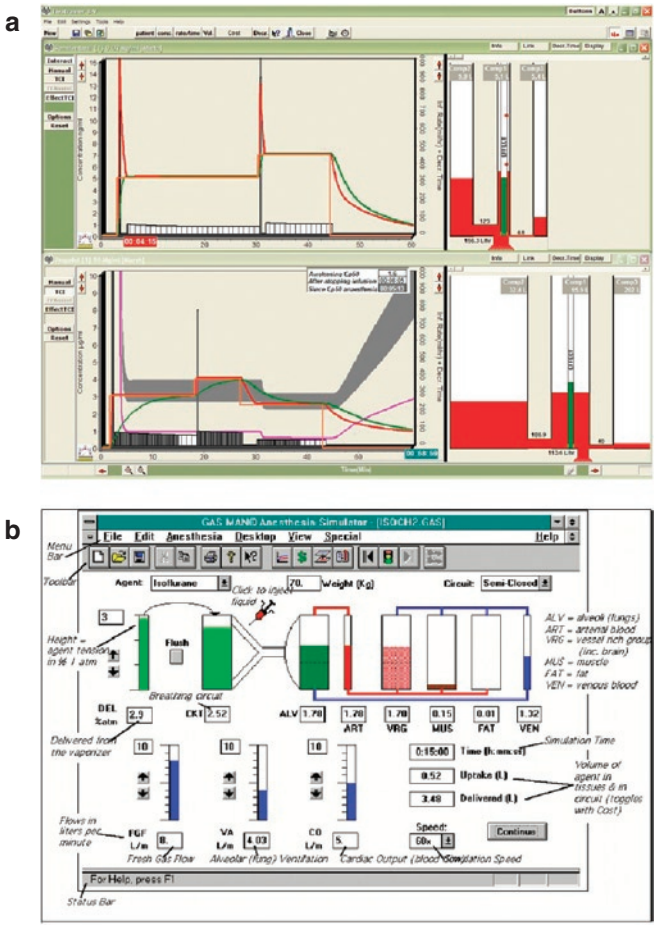

Figure 2 Examples of personal computer–based simulation programs. The upper part shows a screenshot from TIVATRAINER software and the lower part shows a screenshot from GASMAN. Reprinted with permission of Dr. F. Engbers and Dr. J. Philip.

Figure 3 Online advisory displays including characteristics of drug behavior and interaction. (**a**) The SmartPilot (Dräger, Lübeck, Germany). The two-dimensional display shows the effect-site concentrations of combined drugs (opioids/intravenous hypnotics or inhalation anesthetics) based on pharmacokinetic models, and the resulting anesthesia effect based on pharmacodynamic models. Gray-shaded areas indicate different levels of anesthesia. The white point indicates the current combination of effect-site concentrations, the light gray line shows the retrospective concentrations, and the black point and arrow mark the 10- and 15-min predictions, respectively, already calculated at the time of presetting the delivery of the drug. Event markers may be set to show the specific states of the patient in relation to the level of anesthesia. The time-based real-time curves, trends, and prediction of effect-site concentrations of individual drugs, the resulting anesthesia effect (Noxious Stimulus Response Index) and correlated BIS, vital signs, and event markers as reference for interpretation. (**b**) The Medvis display (Medvis, Salt Lake City, UT) shows a real-time visualization of the pharmacology of anesthetic drugs, using pharmacokinetic and pharmacodynamic models to predict drug effect-site concentrations and drug effects in the past, current time, and 10 min into the future. Drug doses administered in the form of boluses and infusions are controlled through separate data interfaces or user interfaces. Drugs are categorized according to sedation (top plot), analgesia (middle plot), and muscle relaxation (bottom plot). Effects are depicted as a population-based probability of producing unconsciousness (top plot), no response to tracheal intubation (middle plot), and no twitch response to a train of four stimuli (bottom plot). In addition, a second pharmacodynamic end point, POST-OP ANALG, represents a guideline therapeutic window for postoperative pain. Synergistic interactions of sedative/hypnotics and analgesics are shown as white lines in the plot. For example, the top plot shows that, with the use of propofol alone, the probability of producing unconsciousness is between 50 and 95% (yellow line) but, because propofol interacts with the opioids, the probability of unconsciousness is >95% (white line). Similarly, propofol potentiates the effect of the opioids in the middle plot.

program. Drug–drug interactions between opiates and hypnotics can be pictured using data from Vuyk *et al*.[27] A personal computer screen–based solution for simulating the time course of the pharmacokinetics and dynamics of inhaled anesthetics is GASMAN (http://www.gasmanweb.com), developed by Dr. J. Philip at Harvard Medical School. **Figure 2b** shows the time course of the uptake of an anesthetic drug in critical body compartments—lungs, heart, and brain—as well as in the breathing circuit and vaporizer.

Several academic centers have developed simulation tools to aid the learning and better understanding of clinical pharmacology. The University of Florida Department of Anesthesiology has developed the "Virtual Anesthesia Machine" website (http://vam.anest.ufl.edu/), which offers teaching tools such as compartment PK models, pill dosage/compliance simulations, anesthesia machine simulation with inhaled anesthetics, and many others. The commercially available software BODY Simulation (Advanced Computer Simulations, Point Roberts, WA) simulates human physiology and pharmacology, runs on standard personal computers, and is built around a collection of models of the cardiopulmonary system originally published by Fukui and Smith.[28] In this program, a detailed user interface has been customized to represent the operating room environment. Aside from personal computer screen–based simulators, various realistic high-end interactive patient simulators are available that use a full-size mannequin for full case–based training in anesthesiology.[26]

In the near future, all sources of pharmacological and effect monitoring will be combined into anesthetics advisory and feedback systems, expanding the existing kinetics-based technology available for administration of anesthetics so as to include total coverage of the dose–response relation. By measuring the patient's individual response to a given drug dose, drug administration could be guided by a pharmacodynamic advisory system that estimates the complete dose–response relation. Recently, various display systems have been developed and tested. Schumacher *et al*.[29] proposed an advisory system that leaves the anesthesiologist in complete control of dosing but enables him to obtain real-time information about the predicted drug concentrations, predicted combined effect, and predicted wakeup time resulting from his actions. Simultaneously, the system displays, in an intuitively appealing format, the optimal drug concentration ratio for a given effect in the typical patient. Albert *et al*.[30] have developed a pharmacological display system that can be used online in the operation room for accurately modeling the concentration and effect of anesthetic drugs administered alone and in combinations. This enables the anesthesiologist to visualize the sedation, analgesia, and muscle relaxation status of a patient on the basis of general population models that have been corrected for body mass, age, and sex. Thereby, it gives the anesthesiologist the ultimate tool to fully integrate clinical pharmacology into daily practice so as to achieve better patient care.[31,32] A commercially available system is shown in **Figure 3**.

Ultimately, when technology is considered to have become mature enough, closed-loop technology could be used for making automated dosing decisions to reach and maintain a preset target.[33] These systems might help the anesthesiologist to titrate drug administration without overshoot, to guide the monitoring of variables, and to optimize control of physiological functions.

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CONFLICT OF INTEREST

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