

Anesthesia: A Discipline That Incorporates Clinical Pharmacology Across the DDRU Continuum

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The dawn of the modern discipline of anesthesia can be traced to 16 October 1846, when William Morton administered ether to a patient who was undergoing surgical removal of a vascular malformation. The event took place in the surgical amphitheater in the Bullfinch Building of Massachusetts General Hospital, now known as the Ether Dome, and was memorialized by Robert C. Hinckley in a painting that is reproduced on the cover of this issue. Although Crawford Long first administered ether as a general anesthetic in 1842, this operation was not recorded, so official credit went to Morton. By today's evidentiary standards, Morton's experiment lacked the statistical safeguards of placebo control, double-blinding, and randomization, but the crowd shown in Hinckley's painting certainly documents substantial peer review.

Subsequent to this demonstration, anesthesia developed slowly as a medical discipline—the American Board of Anesthesiology not being founded until 1937—but it can be argued that anesthesia today stands out as the major primary medical specialty that routinely incorporates clinical pharmacology principles in patient care. In turn, scientists trained in anesthesia

or working with compounds used in anesthesia have made major contributions to clinical pharmacology across the entire continuum of drug discovery, development, regulation, and utilization (DDRU). Most notable have been major contributions in the areas of physiological pharmacokinetics, pharmacokinetic–pharmacodynamic (PK-PD) modeling, and pharmacogenetics.

Physiological pharmacokinetics

Teorell¹ made the first attempt to analyze drug distribution using a two-compartment model in which the central compartment represented intravascular space, and a physiological PK model was first described by Price and his colleagues in the Department of Anesthesia at the University of Pennsylvania.² Interestingly, this analysis of thiopental pharmacokinetics was published in the very first issue of *Clinical Pharmacology and Therapeutics*. Later development of physiologic PK models also stems from a study of thiopental pharmacokinetics by Bischoff and Dedrick,³ and these authors were careful to emphasize that this type of model was suitable for making *a priori* predictions that could be compared with experimental results, rather than for actual analysis of PK data.

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Although most PK analyses lack the resolution to characterize intravascular mixing, this process is significant for anesthetic agents that have a very rapid onset of action. Progress in this area has been made by Henthorn and his colleagues and is reviewed in this issue.⁴

PK–PD modeling

Segre⁵ can be credited with first developing a PK model in which drug concentrations in a hypothetical biophase compartment were linked to drug effects. This concept was subsequently incorporated in PK-PD models of skeletal muscle relaxants used in anesthesia by Hull *et al.*⁶ and Sheiner *et al.*⁷ PK-PD modeling incorporating an effect compartment was subsequently applied to numerous anesthetic drugs and played a critical role in optimizing dosing guidelines for the use of midazolam as an intravenous anesthetic agent. Based on traditional studies, initial dose recommendations for midazolam were derived from estimates that midazolam was no more than twice as potent as diazepam. However, Stanski and his colleagues⁸ used electroencephalograph waveform analysis as a biomarker to compare midazolam and diazepam PK-PD. By this means, they demonstrated that midazolam was five to six times as potent as diazepam and took three times longer to reach the peak biophase concentrations. More recent applications of this technology to enhance the development and utilization of intravenous anesthetics are described in this issue by Kern and Stanski.⁹ These contributions and others are summarized by Minto and Schnider¹⁰ in an overview of the contributions of PK-PD modeling to advances in intravenous anesthesia that also impact our more general understanding of the kinetics of early drug distribution and the analysis of pharmacologic effect.

Pharmacogenetics

Pharmacogenetic variation in patient response can reflect either PK differences in drug metabolism or PD abnormalities. Individual differences in response to succinylcholine, primaquine, and isoniazid were the first pharmacokinetically based variants to be evaluated from a genetic standpoint. In 1953, Forrat, Lehmann, and Silk¹¹ described a patient who experienced severe apnea following succinylcholine administration. Because both the patient and his brother had low cholinesterase levels, these investigators proposed that this abnormality had a hereditary basis. By 1956, both Lehmann and Ryan¹² and Kalow¹³ had established the pharmacogenetic basis for this atypical response to succinylcholine.

In 1960, Denborough and Lovell¹⁴ described a family with a high incidence of malignant hypothermia complicating general anesthesia and ascribed it to inheritance of a dominant gene. Subsequent investigations have linked this potentially fatal PD abnormality to a defect in the calcium ion release channel of the sarcoplasmic reticulum and have proposed the ryanodine receptor gene (*RYR*) as a candidate gene for the malignant hypothermia phenotype.¹⁵

An example of more recent pharmacogenetic investigations in this area is a study by Kharasch *et al.*¹⁶ on the influence of CYP3A5 variants on the pharmacokinetics and pharmacodynamics of alfentanil and midazolam, two CYP3A probes.

Future challenges and opportunities

Although it has been 162 years since Morton demonstrated the efficacy and safety of ether anesthesia, much remains to be learned about the mechanism of action of general anesthetic agents. In this issue, Eckenhoff *et al.*¹⁷ summarize

how our current understanding of anesthesia therapeutic mechanisms may contribute to drug discovery. Kharasch¹⁸ reviews progress that has been made in understanding the mechanisms by which halogenated anesthetics cause potentially fatal liver and kidney damage and describes how this understanding has led to the development of safer anesthetic agents. In addition, Alkire¹⁹ describes a future in which general anesthetics are used as probes in neuroimaging studies of brain function, as potential diagnostic tools, and as possible therapeutic agents.

Over the past 60 years, the improved understanding of the drugs used in anesthesia and a concerted effort to improve patient safety have reduced anesthesia-related mortality in the United States by more than an order of magnitude, even though more older, sicker patients are undergoing more complex operative procedures.²⁰ This has been due in part to improved anesthetic drugs and improved understanding of the PK and PD perturbations associated with aging and other altered physiologic states. One way to further improve the safety of drug delivery is to use closed-loop controllers to deliver potent drugs. Such controllers are being pioneered in the field of anesthesia but may find application in other areas of medicine, such as diabetes management. Gupta and Eger²¹ detail developments by which anesthesiologists can precisely control inhaled anesthetic effect-site concentrations by monitoring and controlling end-tidal volatile anesthetic concentrations. This enables the anesthesiologist to be a sufficient controller and eliminates the need for closed-loop inhaled anesthetic systems. This is in contrast to intravenous anesthetics for which there currently are no continuous monitors of plasma drug concentration. To overcome these difficulties in the field of intravenous anesthetics, closed-loop

controllers based on monitors of the depth of anesthesia are being developed. Manberg and colleagues²² emphasize the potential benefit of these systems while pointing out the substantial regulatory and other concerns that need to be addressed before they can be applied in routine clinical practice.

A continuing challenge is the increasing evidence that the way an anesthetic is administered may have deleterious consequences long after anesthesia and surgery are over and may contribute to one-year postoperative mortality.²³ Choice of anesthetic agent may also have an impact on the occurrence of postoperative delirium and cognitive dysfunction that are particular problems in the elderly.²⁴

It should be apparent that the contemporary practice of anesthesia requires a thorough understanding of clinical pharmacology principles. In addition, anesthesia provides an unusual opportunity for investigators to conduct research that illuminates clinical observations. However, both optimal clinical practice and full exploitation of this “bedside-to-bench” research paradigm are contingent on the inclusion of clinical pharmacology training in anesthesia residency and fellowship programs. Struys *et al.*²⁵ emphasize the importance of this training and describe didactic approaches that might well serve as a much-needed model for other medical disciplines.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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