

Pharmacodynamic interactions: hypnotics and opioids

In anesthesiology, unlike most medical disciplines, pharmacodynamic drug interactions are frequently produced by design. Anesthesiologists take advantage of the pharmacodynamic synergy that results when two drugs with different mechanisms of action but similar therapeutic effects are combined. These synergistic combinations can be advantageous because the therapeutic goals of the anesthetic can often be achieved with less toxicity and faster recovery than when the individual drugs are used alone in higher doses. In fact, except for specific, limited clinical circumstances wherein a volatile agent or propofol alone are acceptable approaches (e.g., a brief procedure in a pediatric patient such as tympanostomy tubes or radiation therapy), modern day anesthesia is at least a two drug process consisting of an analgesic (typically an opioid) and an hypnotic agent. Therefore, from a strictly pharmacological perspective, anesthesiology can be thought of as the practice of pharmacologic synergism using central nervous system depressants.¹

The synergistic interaction between sedatives and opioids (e.g., propofol-remifentanyl or sevoflurane-remifentanyl as prototypes) has now been characterized using sophisticated "response-surface" methodology.²⁻⁵ The response-surface approach creates a three-dimensional plot of the sedative and opioid concentrations *versus* drug effect, quantitatively describing the pharmacodynamic interaction of the two drugs.

The response-surface method is an advance because it describes the drug interaction over the entire range of drug effect and thereby enables simulation from one clinical state to another. This is critical in anesthesia pharmacology because, unlike other therapeutic areas, anesthesiologists must quickly produce and then expeditiously reverse very profound drug effects. Therefore, understanding how best to transition from the anesthetized state to the awake state is a key challenge for every anesthetic.

The response-surface approach provides a scientific foundation to address this challenge. Combined with pharmacokinetic information, opioid-hypnotic response surfaces can be used to identify target concentrations of the two drugs that provide adequate anesthesia and yet optimize the recovery process (or other outcomes of interest such as drug acquisition cost or the analgesic state upon emergence).⁶

Consider for example, the pharmacodynamic interaction of propofol and remifentanyl, a commonly used combination for the provision of total intravenous anesthesia (TIVA). Isoboles (i.e., "cuts" through the surface) for sedation and analgesia can be drawn to identify combinations of the drugs that produce the same probability of adequate effect. The key question, of course, is which of the infinite number of possible combinations is best? When combined with pharmacokinetic information (and pharmacodynamic knowledge about recovery), it is possible to identify the combination that produces not only adequate anesthesia but also the fastest recovery. Because of pharmacokinetic influences, of course, the optimal combination changes with the length of the infusions. A similar approach has also been used to identify the optimal combination of opioids and volatile anesthetics using sevoflurane and remifentanyl as prototypes.⁵

The clinical application of these drug interaction models through the use of computer simulation constitutes a revolutionary advance in our understanding of anesthetic drug clinical behavior. Clinical display systems incorporating these response-surface drug interaction models are now being tested for real time use in the operating room as an approach to drug dosage optimization.⁷⁻¹⁰

Thinking about the clinical pharmacology of the modern general anesthetic in terms of response-surfaces represents a new conceptual framework to guide the formulation of rational dosing strategies. The response surface is "navigated" in the sense that various points on the surface "map" are targeted at different times during the anesthetic to achieve the goals of the anesthetic (e.g., immobility, hemodynamic control, rapid emergence, good analgesia upon emergence, etc.). Rather than simply thinking about sedatives and opioids in isolation, the response surface approach enables an in depth, clinically relevant understanding of the tremendous synergy that results when sedatives and opioids are administered together.

1. Stanski DR, Shafer SL: Quantifying anesthetic drug interaction. Implications for drug dosing [editorial; comment]. *Anesthesiology* 1995; 83: 1-5

2. Minto CF, Schnider TW, Short TG, Gregg KM, Gentilini A, Shafer SL: Response surface model for anesthetic drug interactions. *Anesthesiology* 2000; 92: 1603-16.
3. Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, Shafer SL: Pharmacodynamic interaction between propofol and remifentanyl regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. *Anesthesiology* 2004; 100: 1353-72
4. Kern SE, Xie G, White JL, Egan TD: A response surface analysis of propofol-remifentanyl pharmacodynamic interaction in volunteers. *Anesthesiology* 2004; 100: 1373-81
5. Manyam SC, Gupta DK, Johnson KB, White JL, Pace NL, Westenskow DR, Egan TD: Opioid-volatile anesthetic synergy: a response surface model with remifentanyl and sevoflurane as prototypes. *Anesthesiology* 2006; 105: 267-78
6. Minto CF, Schnider TW: Contributions of PK/PD modeling to intravenous anesthesia. *Clin Pharmacol Ther* 2008; 84: 27-38
7. Johnson KB, Syroid ND, Gupta DK, Manyam SC, Egan TD, Huntington J, White JL, Tyler D, Westenskow DR: An evaluation of remifentanyl propofol response surfaces for loss of responsiveness, loss of response to surrogates of painful stimuli and laryngoscopy in patients undergoing elective surgery. *Anesth Analg* 2008; 106: 471-9, table of contents
8. Struys MM, De Smet T, Mortier EP: Simulated drug administration: an emerging tool for teaching clinical pharmacology during anesthesiology training. *Clin Pharmacol Ther* 2008; 84: 170-4
9. Syroid ND, Johnson KB, Pace NL, Westenskow DR, Tyler D, Bruhschwein F, Albert RW, Roalstad S, Costy-Bennett S, Egan TD: Response Surface Model Predictions of Emergence and Response to Pain in the Recovery Room: An Evaluation of Patients Emerging from an Isoflurane and Fentanyl Anesthetic. *Anesth Analg* 2009
10. Johnson KB, Syroid ND, Gupta DK, Manyam SC, Pace NL, Lapierre CD, Egan TD, White JL, Tyler D, Westenskow DR: An Evaluation of Remifentanyl-Sevoflurane Response Surface Models in Patients Emerging from Anesthesia: Model Improvement Using Effect-Site Sevoflurane Concentrations. *Anesth Analg* 2009