

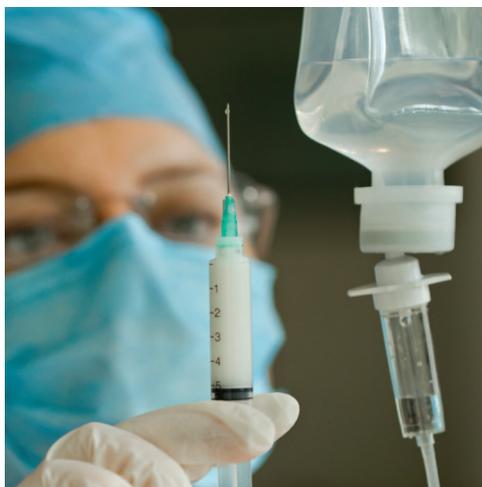
Making Sedation Safer

Is Simulation the Answer?

ANESTHESIOLOGY is sometimes called the practice of clinical pharmacology, but there is a tenuous connection between pharmacology as presented in textbooks and the practical knowledge needed to titrate drugs in anesthetic practice. A drug ED₅₀, minimum alveolar concentration, or half-life is an average with limited value for characterizing a therapeutic or toxic dose in an individual patient. Furthermore, it is almost impossible to find a textbook or paper with data that can guide the titration of two or more drugs. As a result, anesthesiologists rely on empirical approaches to dosing; we titrate to effect when we can, or we make an educated guess, and treat the results of overdose (usually hypoventilation or hypotension), if they occur.

The situation is quite different when drugs such as propofol and fentanyl are administered by those lacking anesthesia training. A range of safe and effective doses must be defined, because overdosing is no longer an acceptable option. Unfortunately, these dose ranges have not been determined. The lack of adequate information to guide safe sedation practice was recognized by the Food and Drug Administration in 2010 when it put out a Request For Assistance on the clinical development of sedation products.* American Society of Anesthesiologists members have recently provided guidance to the agency in May 2012.

What sort of information should anesthesiologists be recommending? Drugs should ideally be studied in the way they will actually be used, and a range of doses should be tested that allows the estimation of both desired and toxic effects. In



“... there should be little argument that a model capable of simulating real-life use of these drugs has the potential to make sedation safer and more effective for everyone.”

this issue of ANESTHESIOLOGY, La Pierre *et al.*¹ have attempted to provide this information in a very creative way: Using healthy volunteers, they tested various combinations of propofol and remifentanyl for their ability to blunt responses to insertion of an esophageal bougie (to mimic upper gastrointestinal endoscopy). Next, they determined the combinations that produced ventilatory depression or airway obstruction. These data were used to create a concentration-response model for desired effects (“satisfactory sedation”) and toxic effects (“respiratory compromise.”) Finally — and this is the new part — the model was used to simulate several published propofol-opioid “recipes” used by gastroenterologists for sedation during endoscopy. The conclusions were provocative: these protocols were all quite unlikely to cause prolonged sedation or respiratory compromise, but they were also unlikely to produce satisfactory conditions for endoscopy! I believe

this demonstrates the great potential of simulation for comparing complex dosing schemes.

Bear in mind, this initial study has some important limitations:

- It describes model development, so there must still be a prospective validation in a new population. The investigators will hopefully obtain sufficient data to predict drug effects in individual subjects.
- Simulations based on healthy volunteers undergoing 10-min procedures cannot be applied to many clinical circumstances.
- Remifentanyl was studied, and “remifentanyl equivalents” were used to predict the behavior of fentanyl. This is a reasonable first approximation, but remifentanyl is not a dilution of fentanyl!
- The drugs were administered by target-controlled infusion, a technology that is still unavailable in the United

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* [Docket No. FDA-2010-N-0547] Clinical Development Programs for Sedation Products; Request For Assistance. Available at: <http://www.gpo.gov/fdsys/pkg/FR-2010-11-29/pdf/2010-29927.pdf>. Accessed January 14, 2011.

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◆ This Editorial View accompanies the following article: LaPierre CD, Johnson KB, Randall BR, Egan TD: A simulation study of common propofol and propofol-opioid dosing regimens for upper endoscopy: Implications on the time course of recovery. ANESTHESIOLOGY 2012; 117:252-62.

States. The model must be modified for typical dosing with a constant rate propofol infusion and intermittent fentanyl bolus. Some of these limitations will undoubtedly be addressed in additional studies by these investigators.

This is a difficult paper, and clinicians may be excused for asking whether such a complex analysis is necessary. The value of pharmacokinetic-pharmacodynamic modeling of sedatives was demonstrated after midazolam was introduced. More than 80 deaths occurred during procedural sedation in radiology and gastrointestinal endoscopy.² It was difficult to understand why excessive doses of midazolam were administered, because the drug was supposedly titrated to a sedative endpoint in responsive patients. The synergistic interaction with opioids was partly to blame, but diazepam had previously been used safely with the same opioids in the identical clinical setting. Bühner *et al.*³ performed a pharmacokinetic-pharmacodynamic study comparing midazolam and diazepam, and the results were surprising. Using an electroencephalographic measurement, these investigators found that the $t_{1/2ke0}$ (half-time to effect-site equilibrium) was 1.6 min for diazepam and 4.8 min for midazolam—three times slower! In this case, the shorter-acting drug had a much slower onset, a fact that had never emerged during extensive clinical studies. It seems likely that clinicians who were used to administering incremental doses of diazepam every minute or so were not waiting long enough to see the full effect of midazolam, and excessive doses were accumulating. In this instance, pharmacokinetic-pharmacodynamic modeling provided guidance on not only dose (concentration) *versus* effect, but also how to titrate, information not easily obtainable by other means.

In the LaPierre study, response-surface modeling adds another level of information. The investigators targeted effect-site concentrations ranging from subtherapeutic to toxic. The effects of excessive propofol or remifentanyl are obvious (prolonged sedation and respiratory depression, respectively), but how does one determine an optimal ratio? For that, the response surface is used to compare and analyze data for a series of drug combinations. This

method can be used to analyze combinations of drugs with different dose-limiting toxicities, (*e.g.*, propofol and dexmedetomidine) or combinations that are additive or synergistic for one effect but antagonistic for another. For example, combining midazolam with butorphanol (a highly sedating opioid agonist-antagonist) increases sedation, but decreases anterograde amnesia.⁴

To summarize, LaPierre *et al.* have simulated propofol-opioid combinations in a way that mimics their actual clinic use. They have created their model with a range of doses sufficient to study both desired and undesired drug effects simultaneously. If validated, this model will allow them to predict the safety and efficacy of a wide variety of sedation protocols.

The rapidity with which intravenous sedation can produce injury has been the basis for numerous publications, educational programs, and of course, American Society of Anesthesiologists guidelines and videos. Who should be allowed to administer powerful mixtures such as propofol and fentanyl remains a contentious issue, but there should be little argument that a model capable of simulating real-life use of these drugs has the potential to make sedation safer and more effective for everyone.

Carl E. Rosow, M.D., Ph.D., Harvard Medical School, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts. croswow@partners.org

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