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Recent advances in control of sedation

Jeff E. Mandel, MD, MS*

Anesthesiology & Critical Care, Perelman School of Medicine, University of Pennsylvania, 780B Dulles Building, 3400 Spruce Street, Philadelphia 19104-4283, Pennsylvania

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ABSTRACT

Procedural sedation is commonly employed in endoscopic procedures, and increasingly uses propofol. The use of propofol is commonly restricted to anesthesia providers, and this may increase the cost of care. Administration of propofol requires a special set of skills to deal with the variability of patient response and the consequences of improper dosing. This has stoked interest in the use of automated systems to reduce manpower costs associated with propofol. This article examines why propofol poses challenges for human control, and how various automated systems have been used to address these challenges. We examine target-controlled infusions, patient-controlled sedation, the SEDASYS System, and optimized ramp induction. The article emphasizes on how the various approaches deal with the range of variability in propofol response. No single system is capable of dealing with all patients without some human supervision and intervention.

1. Introduction

Procedural sedation is frequently employed during endoscopic procedures. Although there are certainly examples of unsedated endoscopy, this is the province of the true believer. Additionally, a considerable fraction of diagnostic procedures are completed with nurse-administered midazolam and opiates such as fentanyl. Although there is no reason that these drugs could not be administered via automated systems, there has been little interest to date in such systems. Most of the interest in control of endoscopic sedation is directed at propofol. New agents such as remimazolam and cyclopropyl-methoxycarbonyl metomidate (AP-700) [1] are intended for infusion, although it is unclear whether these agents would make inroads into endoscopic sedation over the next few years. Thus, this article focuses on automated control of propofol.

2. Why is propofol difficult to administer?

The average endoscopist who uses midazolam or opioid sedation successfully may wonder why propofol is difficult to control. To illustrate this, I would use data derived from work done with my research group over the last decade. First, patients exhibit considerable variability in the dose required to obtund consciousness, as illustrated in Figure 1. This figure depicts the cumulative probability of tolerance of endoscopy with increasing effect-site concentrations of propofol in 40 patients undergoing sedation for esophagogastroduodenoscopy (EGD). Although the median effect-site concentration in this cohort of patients is 4.8 μg/mL, there are patients adequately sedated below 3 μg/mL, and several requiring more than 10 μg/mL. It should be noted that these effect-site estimates utilize age and weight in their calculation.

Second, attempts to anticipate patient dosing requirements by clinicians meet with limited success. Clinicians typically initiate sedation with an initial plan, for example, a bolus of 90 mg followed by an infusion of 110 μg/kg/min, and modify the plan giving additional propofol at their discretion. Analysis of control performed by anesthesia providers indicates that the initially selected propofol administration accounts for only 85% of that ultimately given. Further, the discretionary administration of propofol is correlated with the estimated target with regression coefficient of 0.64, as depicted in Figure 2. This suggests that predictions of dosing requirements by skilled practitioners were responsible for at most 36% of the discretionary dosing. Although it is possible that clinicians can predict which patients require "a big dose," translating this into an actual number has limited accuracy.

Third, propofol produces airway obstruction. This is depicted in Figure 3, using additional data not presented in our previous publication [2]. In this cohort of 136 patients with known obstructive sleep apnea, the median dose of propofol necessary to intentionally produce airway obstruction was 3.98 μg/mL. This is only slightly lower than the dose necessary to permit elective endoscopy, albeit in a cohort not selected for known obstructive sleep apnea. In this study, we also observed patients who exhibited airway collapse and were simultaneously combative in

* Corresponding author.
E-mail address: jemandel@verizon.net

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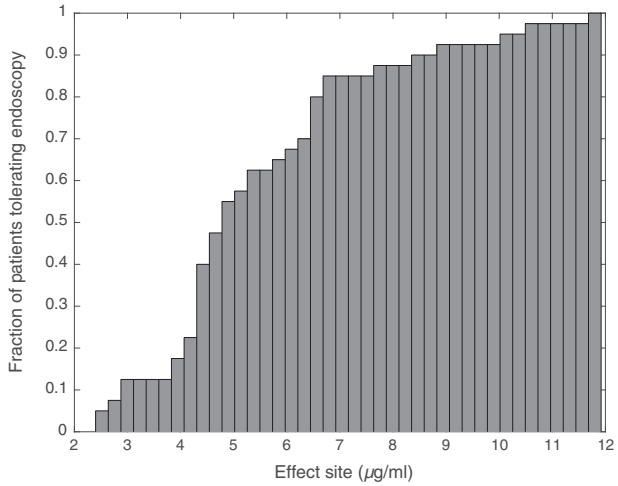

Fig. 1. Cumulative probability of tolerance of endoscopy vs estimated effect-site concentration for propofol. (Adapted with permission from Mandel, unpublished data.)

response to nasopharyngolaryngoscopy. This suggests that even under ideal conditions, there is a narrow window for sedation without airway obstruction.

Given these challenges, propofol-based gastrointestinal sedation has been limited to anesthesia providers and selected experienced clinicians who have undergone advanced airway training. The additional providers represent an added expense, and acquisition of the skills required to control propofol takes time and exposes patients to risk during the learning phase. Can automated systems reduce the need for skilled providers such as anesthesiologists? Several approaches have been described. We would focus on how these work, rather than consider whether they are superior to traditional approaches.

3. Target-controlled infusion

Target-controlled infusion (TCI) systems use one of many published pharmacokinetic models of propofol to guide delivery by adjusting the infusion rate of the drug to achieve and maintain a specified target concentration in either the plasma or the effect

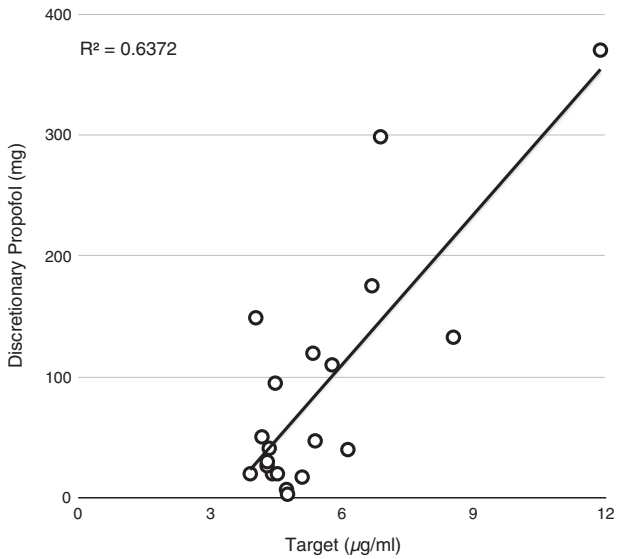

Fig. 2. Discretionary propofol (additional propofol given after the initial boluses and infusion rate) vs estimated effect-site concentration for propofol. (Adapted with permission from Mandel, unpublished data.)

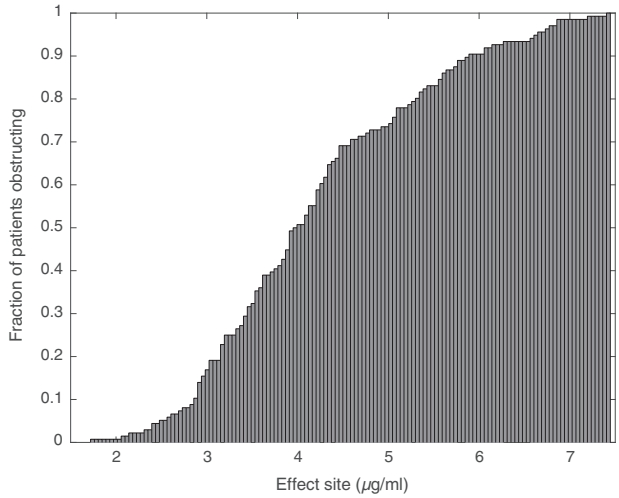

Fig. 3. Cumulative probability of airway collapse during drug-induced sleep endoscopy vs effect-site concentration for propofol. (Adapted with permission from Mandel, unpublished data.)

site. The effect site (a compartment whose diffusion time constant of drug explains the delay between the measured blood concentration and some measured clinical effect) is a modeling convenience. The concentration in the effect site cannot be measured, only inferred, but we are more interested in the clinical effect than the blood concentration. Targeting the effect-site concentration yields a more predictable clinical effect, but may lead to transiently high plasma concentrations with accompanying cardiovascular effects [3]. Newer systems such as the Fresenius Orchestra Base Primea (Fresenius Kabi, Bad Homburg, Germany) and the B. Braun Space (B. Braun, Bethlehem, PA) allow selection of either plasma or effect-site targets. TCI systems are available worldwide with the notable exception of the United States, while the United States of Food and Drug Administration (US FDA) is yet to approve a TCI device, this may change [4]. Consideration of TCI in this article is appropriate even for the North American reader. Commercially available devices tend to be based on the Diprifusor, which uses relatively simple algorithm to obtain initial control—specification of a maximum infusion rate and a target concentration. The maximum infusion rate is limited by the performance of the pump, typically 1200 mL/h. Although this may seem to be a large number, it is possible to manually deliver 10 mL of propofol in less than 5 seconds, a rate of 7200 mL/h, and delivering this bolus over 30 seconds would challenge the patience of many clinicians. As the predicted effect-site concentration approaches the target, the infusion rate is decreased, and quickly approaches a steady-state rate that decreases slowly as the peripheral compartments fill with propofol. When designing a medical device, transmitting a new infusion rate to a pump every 10 seconds is trivial, but it is quite possible to achieve similar results using a small number of adjustments, and United States providers should not feel that they are at a significant disadvantage to Europeans if they are willing to adjust the infusion rate at specified times, as depicted in Figure 4. In this example, the optimal values for a sequence comprised a propofol bolus given over 1 minute, a pause, and a constant infusion for the remainder of a 15-minute period has been determined by constrained minimization. The derived values—37 mg, a pause of 44 seconds, and an infusion rate of 100 μg/kg/min yield an effect-site concentration of 2 μg/mL with a mean error of 1.5%, which is better than the accuracy of most clinical infusion pumps or of the pharmacokinetic model, and yet this sequence is easily produced with a pump and a stopwatch.

The earliest report of TCI in endoscopic sedation was that of Church et al [5], which employed a prototype of the Diprifusor