Results from 404 drug-induced sleep endoscopies with probability ramp control: lessons for pharmacokinetic design of DISE protocols

Jeff E. Mandel, MD, MSa,*, Joshua H. Atkins, MD, PhDb

Introduction: Drug-induced sleep endoscopy (DISE) employs a drug such as propofol to allow observation of airway collapse to predict success in surgical interventions for obstructive sleep apnea. A number of protocols have been published for the administration of propofol during DISE, but these protocols do not make use of pharmacokinetic modeling to estimate the propofol concentration at airway collapse and the probability distribution for this quantity. We hypothesized that this information could be used to improve the delivery of propofol during DISE.

Methods: Deidentified data from 404 patients sedated with Probability Ramp Control was analyzed. The estimated effect site concentration at the time of airway collapse (ECac) was fit to a gamma distribution. Correlation between ECac and age/weight were performed using Spearman ρ. This probability distribution was utilized to assess the ability of a published protocol to produce airway collapse in a reasonable duration in a representative cohort of patients.

Results: The parameters of the gamma distribution were a = 8.3 (95% confidence interval, 7.2–9.5), b = 0.58 (95% confidence interval, 0.51–0.67). The mean ECac was 4.8 ± 1.7 μg/mL; 95% of ECac fell in the range 2.4–8.5 μg/mL. ECac was uncorrelated with age (ρ = −0.06, P = 0.27) and weight (ρ = −0.11, P = 0.03). The previously published protocol displayed variability across the cohort and failed to achieve effect site concentrations sufficient for the least sensitive patients in our cohort.

Conclusions: Effect site propofol concentrations at the time of airway collapse during DISE span a wide range with a skewed distribution. The lack of correlation with either age or weight suggests that the pharmacokinetic model is sufficient for describing the effect of age and weight on propofol dosing. The impact of these factors on propofol dosing during DISE is examined, and workable solutions to this clinical challenge are proposed.

Keywords: Drug-induced sleep endoscopy, Propofol, Pharmacokinetics

Drug-induced sleep endoscopy (DISE) is a technique for making anatomic observations of sites of airway collapse to predict the success of various interventions for the management of obstructive sleep apnea[1]. A number of recipes have been developed for DISE; our group described a method we termed Probability Ramp Control (PRC)[2], which employs a pharmacokinetic model to steadily increase the probability of obstruction over time. We now have experience with this technique in over 350 cases, making estimation of the probability distribution for effect site concentration at the time of airway collapse (ECac) feasible. While this estimated probability distribution is specific to the pharmacokinetic model employed and the rate of administration, it may be useful in improving results from other methods.

Methods

Approval for retrospective review (#828154) of deidentified data during DISE was obtained from the IRB of the Perelman School of Medicine at the University of Pennsylvania. The propofol titration was generated by our previously described technique that determines the optimal infusion sequence to traverse the cumulative probability distribution for propofol effect site concentrations at which airway collapse was observed[3]. This probability distribution is determined by infusing propofol in the defined manner while observing for airway collapse; the total amount of propofol used to achieve this condition is noted, and the effect site concentration estimated using the pharmacokinetic model of Cortínez et al[3], with an adjoined effect site. MATLAB code for the model is available on the Opentarget controlled infusion (TCI) website[4]. Note that the effect site is a hypothetical compartment that is in equilibrium with the plasma, but has a time constant that yields a peak concentration that coincides with the observed time to peak effect of propofol, ∼90 seconds[3].

All data analysis was performed with MATLAB 2020a (MathWorks, Natick, MA). Data from 404 cases were analyzed.
Ages were calculated from the date of birth to the resolution of a single day; the last available weight in the electronic medical record was recorded in kilogram. The effect site estimates were examined for distribution, found to have a positive skewness, and were fit to a gamma distribution. Note that a gamma distribution is an exponential distribution, and is undefined for negative values of the effect site concentration. The mean and SD of effect sites were determined, and linear correlation with age and weight performed using Spearman ρ.

The observed probability distribution was used to explore different strategies for conducting DISE without the assistance of a pharmacokinetic model. The administration sequence for the control group in De Vito et al.[6] (comprised of an initial bolus of 1 mg/kg propofol followed by 20 mg boluses every 2 min) was applied to the pharmacokinetic model using the age and weight of each of the 404 patients. This is termed approach 1. Next, an optimized bolus sequence was determined for 55.4-year-old, 96 kg patient (the average weight and age of the 404 patients). The sequence was designed to produce the fifth percentile ECₐ₋ₐc with the initial bolus with 10 additional boluses delivered at diminishing intervals to produce the 95th percentile ECₐ₋ₐc. This is termed approach 2. Finally, an optimal infusion sequence was constructed for the average patient using the PRC algorithm to track a target with a normal distribution of time to airway collapse of 5 minutes with a SD of 1.2 minutes. This is termed approach 3.

**Results**

Patient age averaged 55.4 ± 11.5 years, weight was 96.0 ± 17.2 kg. The parameters of the gamma distribution for effect site estimates at the time of airway collapse (ECₐ₋ₐc) were a = 7.3 (95% confidence interval, 6.3–8.4), b = 0.65 (95% confidence interval, 0.56–0.75). The mean ECₐ₋ₐc 4.7 ± 1.8 µg/mL. 95% of cases fell in the range 1.9–8.4 µg/mL. ECₐ₋ₐc was uncorrelated with age (ρ = −0.06, P = 0.24) and weight (ρ = −0.11, P = 0.03). A histogram of ECₐ₋ₐc with the fit probability distribution is depicted in Figure 1.

The result of applying the infusion sequence of De Vito and colleagues to the 404 simulated patients (approach 1) is depicted in Figure 2, optimized bolus sequence (approach 2) is depicted in Figure 3, and the PRC sequence (approach 3) is depicted in Figure 4.

**Discussion**

There are 2 important results of this analysis. The first is that the effect site estimates at the time of airway collapse predicted by the Cortinez model were poorly correlated with age and weight, suggesting that these variables are sufficient to determine propofol dosing during DISE. The second is that ECₐ₋ₐc spans at least a 4-fold range with a skewed distribution.

Various approaches to titration of propofol during DISE have been described[7] but typically fall into 2 broad groups; bolus delivery and TCI. These approaches were compared by De Vito et al.[6]. This approach can be expected to suffer from 3 limitations.

The first is the lack of optimization of the bolus magnitude. Ideally, the initial bolus would be designed to produce an effect site concentration associated with a low probability of airway collapse to avoid excessive sedation in the most sensitive patients in the cohort. This is evident in Figure 2; the fifth percentile for ECₐ₋ₐc is 2.4 µg/mL; the initial bolus achieved an effect site of at least 3.4 µg/mL in our cohort. For patients in the first quartile of our distribution, and approach 1 may result in excessive sedation requiring intervention for complete airway collapse.

The second is that the constant interval between the 20 mg boluses will produce differing trajectories of propofol...
approach 3. PRC indicates Probability Ramp Control.

The examples presented in Figures 3 and 4 utilize a pharmacokinetic approach coupled with an understanding of the probability distribution for airway collapse to produce a predictable process. We do not know how much propofol an individual patient will require, only that the average time to airway collapse will be consistent irrespective of age and weight. An additional benefit is that it is possible to determine the administration sequence to maintain the effect site concentration near that identified at the onset of airway collapse to permit more extensive analysis of patterns of obstruction or interventions to overcome obstruction such as continuous positive airway pressure or mandibular advancement.

The desired results can be obtained with TCI (in countries where such devices are available), but to do so with an initial setting and 10 subsequent settings over 8 minutes will require modification of the target effect site at intervals of ~45 seconds. While this certainly is easier than approach 2, which requires refilling a syringe with 25 mg of propofol at least every 60 seconds, the estimated effect site concentrations are highly dependent on the choice of $k_{e0}$, as discussed in the appendix of Atkins et al.$^3$. Thus, choosing a target TCI setting to maintain the state based on the observation of the target at airway collapse is also fraught with error.

PRC (approach 3) utilizes a different approach. The infusion sequence is selected to minimize the difference in the estimated time to airway collapse and a normal distribution of time to airway collapse of $\pm 1.2$ minutes. This is depicted in Figure 4. For our “average patient,” this results in an initial bolus of 100.5 mg over 4 minutes followed by an infusion of 536 $\mu$g/kg/min until the obstruction is observed (or a limit of 262 mg, corresponding to the 95th percentile $EC_{ac}$). Once the observation of airway collapse is made, the infusion is paused for ~100 seconds and restarted at a new infusion rate designed to maintain stable conditions for up to 18 minutes. The first 2 parameters are available for programming the pump before initiation of sedation, the last 2 are determined when airway collapse is observed. While the advantages of PRC in comparison to bolus or TCI techniques have not been established, the simplicity of the process may prove useful in a busy clinical environment.

**Conclusions**

Effect site propofol concentrations at the time of airway collapse during DISE span a wide range with a skewed distribution. The lack of correlation with either age or weight suggests that these parameters will not improve the predictive value of a pharmacodynamic model. This does not mean that the effect site estimates are correct, only that they are sufficient to predict the probability of response to a dose of propofol. The impact of these factors on propofol dosing during DISE is examined, and a workable solution to this clinical challenge is proposed.

**Ethical approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Sources of funding**

This study received no funding.
Informed consent

This protocol was reviewed by the IRB of the Perelman School of Medicine at the University of Pennsylvania. Use of deidentified data from existing clinical records was deemed exempt from informed consent.

Conflict of interest disclosures

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Acknowledgments

The authors acknowledge the contributions of Erica R. Thaler, MD and David T. Kent, MD in performing the endoscopic examinations.

References

[1] Chong KB, De Vito A, Vicini C. Drug-induced sleep endoscopy in treatment options selection. Sleep Med Clin 2019;14:33–40.
[2] Atkins JH, Mandel JE, Rosanova G. Safety and efficacy of drug-induced sleep endoscopy using a probability ramp propofol infusion system in patients with severe obstructive sleep apnea. Anesth Analg 2014;119:805–10.
[3] Cortínez LI, Anderson BJ, Penna A, et al. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. Br J Anaesth 2010;105:448–56.
[4] Mandel JE. Propofol cortínez. 2010. Available at: http://opentci.org/code/matlab/mandel-propofol-cortinez-2010. Accessed March 8, 2019.
[5] Minto CF, Schnider TW, Gregg KM, et al. Using the time of maximum effect site concentration to combine pharmacokinetics and pharmacodynamics. Anesthesiology 2003;99:324–33.
[6] De Vito A, Agnoletti V, Berrettini S, et al. Drug-induced sleep endoscopy: conventional versus target controlled infusion techniques—a randomized controlled study. Eur Arch Otorhinolaryngol 2011;268:457–62.
[7] Atkins JH, Mandel JE. Drug-induced sleep endoscopy: from obscure technique to diagnostic tool for assessment of obstructive sleep apnea for surgical interventions. Curr Opin Anaesthesiol 2018;31:120–6.