EVALUATION OF COMMON DOSING REGIMENS FOR MODERATE AND DEEP SEDATION USING A REMIFENTANIL PROPOFOL INTERACTION MODEL FOR RESPIRATORY COMPROMISE

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Introduction: Dosing schemes for propofol and propofol in combination with an opiate are commonly used in mildly stimulating procedures of short duration that require moderate to deep sedation. However, some adverse drug effects set in before therapeutic levels of drug are administered. The aim of this simulation study was to evaluate how common dosing regimens for upper endoscopy compare to a pharmacodynamic response surface model for respiratory compromise. We hypothesize that all published dosing regimens will experience a high probability of respiratory compromise.

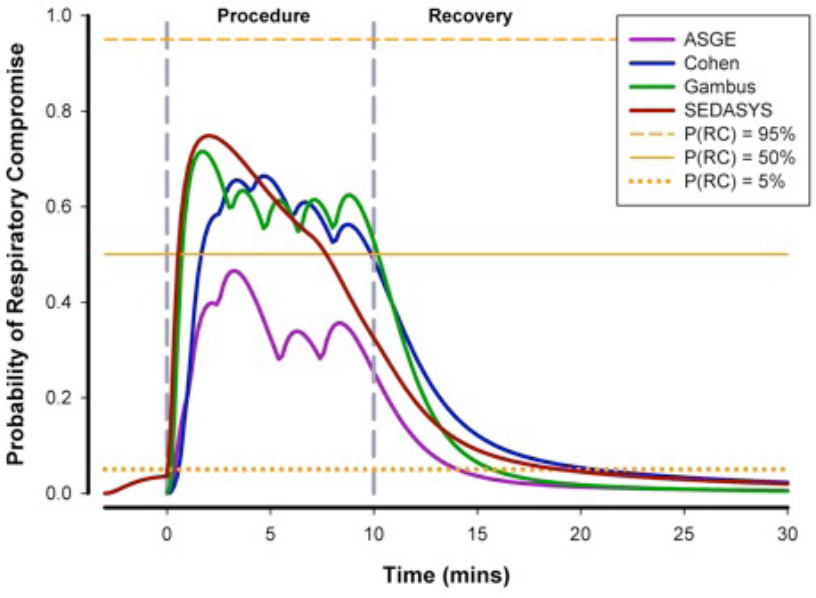
Methods: Keyword searches were performed in PubMed to identify published dosing regimens for upper endoscopy. Only those dosing schemes that administered propofol, remifentanil and/or fentanyl were considered. Searches all included the keyword propofol in combination with one or more of the following: dosing, endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), endoscopist-directed propofol sedation (EDP), endoscopy, esophagogastroduodenoscopy (EGD), nurse administered propofol sedation (NAPS), protocol and sedation. Additional studies were identified from tables included in large review papers.

We identified dosing regimens that were representative of four selected general dosing strategies:

1. propofol only – intermittent bolus technique
2. fentanyl-propofol – intermittent bolus technique
3. remifentanil-propofol – intermittent bolus technique
4. fentanyl-propofol – computer-assisted personalized sedation.

The dosing regimens and accompanying washouts were simulated for a total time of 60 minutes. Effect site concentrations of remifentanil, propofol and fentanyl were calculated using the pharmacokinetic models of Minto et al.(1), Schnider et al.(2) and Shafer et al.(3) respectively. Because the pharmacodynamic models were developed for remifentanil-propofol, a remifentanil:fentanyl equivalency of 1:1.2 was used to convert fentanyl effect-site concentration into remifentanil equivalents(4,5).

Results: Four published dosing recommendations were selected for simulation: intermittent boluses of propofol from the American Society for Gastrointestinal Endoscopy (ASGE) Standards of Practice Committee,(6) loading bolus of fentanyl with intermittent boluses of propofol from Cohen et al.,(7) and a loading bolus of fentanyl followed by a propofol infusion administered by SEDASYS as presented by Pambianco et al.(8) For remifentanil-propofol, instead of identifying a dosing regimen we identified recommended target effect-site concentrations for unstimulated patients.(9) We developed an intermittent bolus dosing regimen adapted from Cohen's that targets this region. Descriptions of the four recommendations are presented in Table 1.



Pharmacodynamic probability for respiratory compromise versus time for the simulated dosing regimens are shown in Figure. Additionally, Table 2 shows the total amount of time each simulation spent about the 5, 50 and 95% probability isoboles.

Simulation	Sim Time (min)	Respiratory Compromise 5%	50%	95%
ASGE Standards of Practice Com.	60	13.7	0.0	0.0
Cohen	60	20.0	8.3	0.0
Gambus	60	15.5	9.5	0.0
Pambianco (SEDASYS)	60	18.8	7.2	0.0

Author	Drug	Clinical Setting	Dosing Regimen
Standards of Practice Committee(21) (2008)	Propofol	GI Endoscopy	Initial bolus of 10-60 mg of propofol. Additional 10-20 mg boluses administered as needed with a minimum of 20 to 30 seconds between doses.
Cohen(22) (2003)	F/P	GI Endoscopy	Initial boluses of 75 mcg fentanyl and 5-10 mg propofol. Additional 5-15 mg boluses administered as needed with a minimum of 30 seconds between doses.
Gambus(23) (2011)	R/P	Ultrasonographic Endoscopy	Optimal sedation on an unstimulated patient is achieved by targeting effect-site concentrations of 2.8 to 1.8 mcg?ml^{-1} propofol and 0-1.5 ng?ml^{-1} remifentanil. Increased drug levels are required in the presence of stimulation.
Pambianco(4) (Sedasys) (2008)	F/P	GI Endoscopy	Initial boluses of 50-100 mcg fentanyl and, 3 minutes later, 0.5 mg/kg propofol. Initiate propofol infusion at 75 mcg/kg/min and titrate to effect with rate adjustments and/or 25 mg/kg propofol boluses as needed.

Cohen spent 8.3 minutes above the 50% isobole. Similarly, Gambus spent almost the entire procedure (9.5 mins) with a greater than 50% isobole. SEDASYS spent the least time above it but also provided the highest probability.

Discussion: The simulation results suggest that respiratory compromise should be worrisome during gastrointestinal endoscopic procedures. It is clear from the simulations that respiratory compromise occurs in the same region of drug concentrations that are used routinely. It is important to recognize that models of respiratory compromise are contructed from data in young healthy volunteers that for the most part are unstimulated. Predictions of respiratory compromise would undoubtedly be shifted up and to the right in a stimulated state. In other words, an endoscope inserted into the gastrointestinal tract would cause the patient become more awake and breathe. In addition, an endoscope placed into the esophagus, may help maintain an open airway relieving possible obstruction.

References:

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