

Title: Validation of a remifentanyl propofol response surface model for sedation in patients undergoing surgery

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Introduction: Recent work in our laboratory has characterized the synergistic interaction between remifentanyl and propofol in volunteers using surrogate measures of sedation and analgesia (1). Using a response surface approach, isobols representing a 50 and 95% probability of loss of consciousness (LOC) were created. The aim of this present work is to explore how well the isobols predict the LOC and return of consciousness (ROC) in patients undergoing a propofol-remifentanyl based anesthetic for elective surgery. Our hypotheses were that the LOC isobols would accurately predict the probability of LOC during induction of anesthesia and ROC on emergence from anesthesia.

Methods: After Internal Review Board approval, 21 patients scheduled for elective surgery were enrolled in the study. Each patient subject received a total intravenous anesthetic with remifentanyl, propofol, succinylcholine and/or rocuronium, and fentanyl. Doses of all drugs were recorded. The Observer's Assessment of Alertness/Sedation (OAA/S) scale was assessed (i) every 20 seconds during the induction of anesthesia until LOC (OAA/S < 2) and (ii) every 20 seconds once delivery of remifentanyl and propofol were terminated until ROC (OAA/S ≥ 2). Pharmacokinetic (PK) models of remifentanyl and propofol were used to estimate their respective effect site concentrations at every OAA/S assessment. Propofol and remifentanyl effect site concentration pairs associated with LOC and ROC were compared to probability of LOC as predicted by the sedation model. Data are presented as mean ± SEM

Results: The remifentanyl and propofol effect site concentrations at which patients achieved LOC and ROC are presented in Figure 1, Panels A and B respectively. The PK models predicted higher propofol and remifentanyl effect site concentrations at the time of LOC than ROC. The mean probability of OAA/S < 2 at the time of LOC and ROC for all patients as predicted by the sedation response model surface were 95 ± 1% and 55 ± 7% respectively.

Figure 1

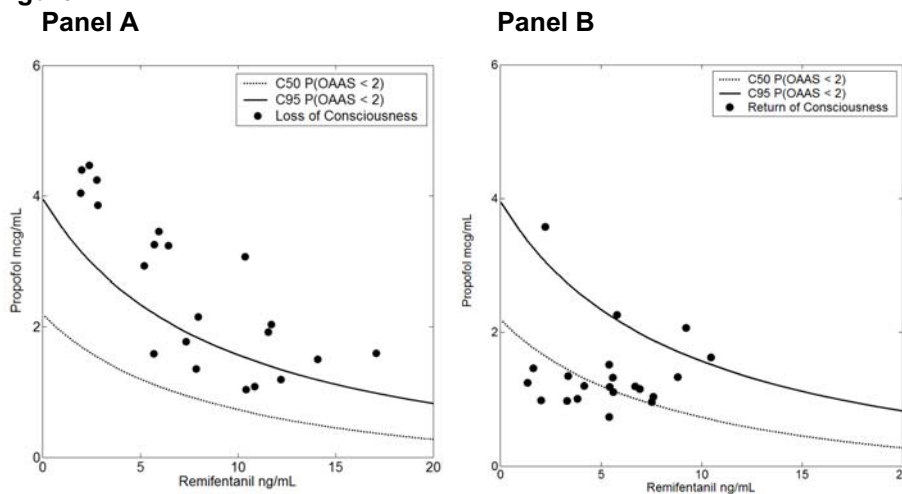


Figure Legend: Remifentanyl and propofol effect site concentration pairs at LOC and ROC are presented in panels A and B. The sedation response surface model was used to plot the remifentanyl propofol concentration pairs necessary to achieve a 50% and 95% probability of an OAA/S < 2. The 50 and 95% probability of LOC are presented as the solid and dashed lines respectively. These lines are known as the C50 and C95 isobols.

Discussion: The sedation response surface model predicted a mean probability of 95% that all 21 patients would have a LOC at the remifentanyl-propofol concentrations where LOC actually occurred. However, LOC occurred well beyond the 95% isobol in 15 patients. All patients were above the 50% isobol. This sedation response surface model misspecification may be due to rapidly changing remifentanyl and propofol effect site concentrations during the induction of anesthesia reflective of non steady state conditions (i.e. actual concentrations were not as high as the PK models predicted they were). When the subject's drug concentrations are not at steady state, the PK models are not expected to perform as well as under steady state conditions. The sedation response surface model predicted the probability of ROC in patients emerging from anesthesia near the 50% isobol. PK model estimates of remifentanyl and propofol effect site concentrations were more likely closer to steady state levels at this segment of the anesthetic.