Modeling Cognitive Function After Deep Sedation Procedures: Nonlinear Mixed Effects Approach

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Background: Anesthetic drugs used during sedation impair cognitive function (COG-F) even after the sedation procedures have finished. The amount and extent of cognitive impairment has not been adequately explored because objective and fast methods to quantify cognition at the bedside have been lacking. Recently several instruments able to objectively quantify some of the cognitive domains have been commercialized. CogState^{TM} is a software package designed as a battery of psychological tests that can be performed by patients with a laptop in the recovery area. The main objective of this project was to model the dynamics of recovery of cognitive function, measured using CogState^{TM} after sedation-analgesia.

Methods: Under IRB Approval and informed consent 80 patients undergoing deep sedation for gastrointestinal endoscopy in Hospital Clinic of Barcelona were enrolled in the study.
Propofol and remifentanil were administered through Target Controlled Infusion (TCI) system and COG-F was objectively quantified before and at least two more times after the end of sedation. To measure the speed of performance "LMN" the mean of the log10 transformed reaction times for correct responses was used as detection test.
Modeling was performed using a nonlinear mixed effects approach with NONMEM 7.3. Model selection was based on the evaluation of the minimum value of the objective function and goodness of fit plots (GOFs). Visual Predictive Check plots (VPC) and 500-Bootstrap Analysis were performed to evaluate the obtained final model. Covariates evaluated included demographic information, duration and initial hour of sedation procedures and results of Mini-COG test.

Results: The final model selected considers a synergistic interaction between remifentanil and propofol. Parameter values (RSE) were obtained with enough precision: basal LMN value *LMN0* = 2.75 (0.2), slope of the dose-response relationship *SLP* = 94.85 (25), k_{e0PRO} = 2.23 (46) min^{-1}, k_{e0REM} = 1.26 (62) min^{-1} and C_{50P} = 0.55 (6) µg/mL. Significant interindividual variability values (RSE) [SHR] found were *IIV LMN0* = 1.8 (10)[12] and *IIV SLP* = 36 (55)[71].
Age and sex on remifentanil k_{e0} and duration of sedation on basal LMN parameter were the covariates that significantly improved the model.

Conclusions: A population mixed effects model for COG-F recovery after propofol and remifentanil administration has been developed.

Since age, sex and duration of procedures are significant covariates, individualized strategies might be implemented and they should be taken into account when planning a procedure.

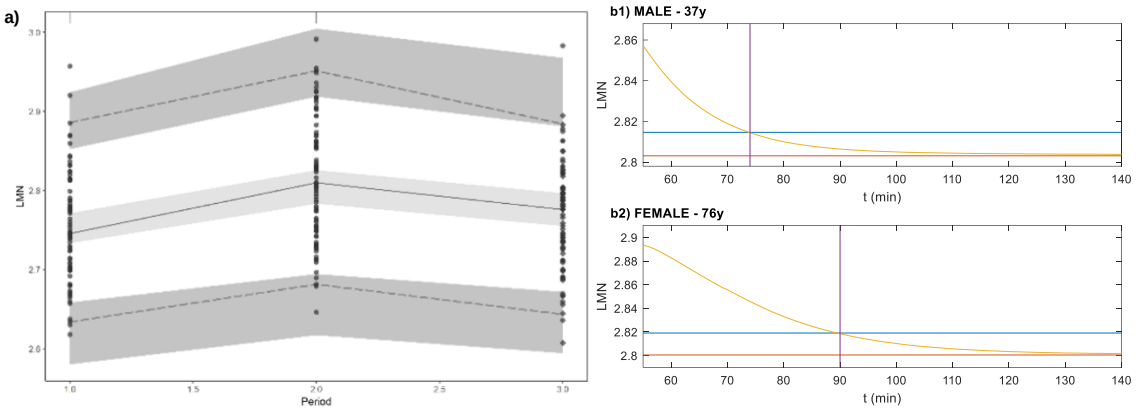

Figure 1. (a) VPC results. Data points represent raw data and lines correspond to its 2.5th, 50th and 97.5th percentiles. Grey shaded areas represent the 95% prediction intervals of the 2.5th, 50th and 97.5th percentiles of 500 simulated datasets. (b) Model simulation results of (b1) a 37y male and (b2) 76y woman. Horizontal red and blue lines show the basal (100%) and the 80% of the LMN value, yellow line corresponds to LMN profile and purple vertical line indicates when LMN curve and 80%LMN line intersect.