ORIGINAL CLINICAL RESEARCH REPORT

A New Method for Comprehensive Analysis of Benzodiazepine, Opioid, and Propofol Interactions and Dose Selection Rationales in Gastrointestinal Endoscopy Sedation

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BACKGROUND: The aim of this study was to explore a new method for determining optimal dosing regimens for combinations of propofol, midazolam, and an opioid to achieve rapid on- and off-set of deep sedation.

METHODS: We simulated 16 published dosing regimens using a well-validated pharmacodynamic model. The study was divided into 2 parts. First, the regimen that best provided deep sedation and rapid recovery was selected. A deep sedation-time area-under-the-curve (AUC) method was used to compare published dosing regimens; a higher AUC indicated better sedation and faster recovery. Second, subgroup analysis of the best-performing dosing regimen was undertaken better to understand how each drug affected patient recovery.

RESULTS: The AUC method identified a combination of midazolam 1 mg, alfentanil 500 μg, and propofol target infusion effect-site concentration (Ce) 2 μg mL^{-1} as the optimal regimen ($P < .01$). Propofol correlated with high probability of sedation and increased AUC ($R^2 = 0.53$), whereas midazolam had a significant impact on time to return of consciousness ($R^2 = 0.86$). Subgroup analysis indicated that regimens consisting of a fixed dose of alfentanil and either 5 μg mL^{-1} Ce propofol, or 1 mg midazolam with 3–5 μg mL^{-1} Ce of propofol, or 2 mg midazolam with 2 μg mL^{-1} Ce propofol provided adequate sedation and rapid recovery. Midazolam >3 mg greatly prolonged recovery.

CONCLUSIONS: This study used a clinically relevant method and model simulation to determine suitable sedation regimens for use in gastrointestinal endoscopy. A balanced propofol, midazolam, and an opioid should be used. The AUC method was capable of providing objective assessments for model selection. (Anesth Analg 2025;140:1168–77)

KEY POINTS

- **Question:** Does a combination of propofol, midazolam, and an opioid exist that has a rapid onset of sedation, avoids oversedation, and provides brief periods of analgesia?
- **Findings:** A novel in silico model effectively evaluated several multi-drug sedation and analgesia dosing regimens and identified drug combinations that met the sedation goals described above.
- **Meaning:** Modeling could be used to explore the advantages and disadvantages of drug combinations to meet desired clinical outcomes in deep sedation for endoscopy procedures.

There are several drug combinations available for gastrointestinal endoscopy.[1,2] Systematic reviews have previously lacked a standardized tool, and so provided vague recommendations from pooled but heterogeneic studies.[1,3,4] Drug dosages expressed per kilogram of body weight have been offered for 2- or 3-drug regimens, but there were no guidelines on how to choose between regimens.

Pharmacodynamic response surface modeling (RSM) was introduced to anesthesiology in the 1990s,[5]

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and elaborate transformations have been performed to fit anesthesia-specific drug effects.[6–9] The models gradually advanced from 2-drug models to complex 3-drug models[8,10] that handle broader clinical scenarios.[11–13] The nonlinear mixed effect with zero amount (NLMAZ) model is a 3-drug RSM developed for patients undergoing gastrointestinal endoscopy and receiving a combination treatment of midazolam, propofol, and an opioid,[8] matching clinical outcomes from earlier studies.[14]

Target-controlled infusion (TCI) or infusion pumps are not always available in procedural sedation suites, especially in the United States. The aim of this study was to explore the utility of using NLMAZ RSM simulation to understand differences in sedation and recovery among published dosing regimens. In silico modeling offers the ability to evaluate numerous dosing regimens that minimize the risk of deep sedation as measured by "time area-under-the-curve" (AUC). This approach differs from clinical trials that are logistically limited to only a few dosing regimens, and it avoids the heterogeneity of systematic reviews. The study hypothesis was that by using a deep sedation-time AUC analysis aided by graphical illustrations, rational dosing deep sedation dosing regimens for endoscopy procedures could be identified that provided rapid induction and recovery.

PATIENTS/MATERIAL AND METHODS

This study was conducted in 2 parts. The first part was a comparison of published deep sedation dosing regimens and to select the best-performing available regimen in terms of rapid on- and off-set of deep sedation based on model simulation. The second part was a set of extended simulations exploring incremental dosing changes of the selected regimen identified in Part 1, to optimize the on and offset of deep sedation.

PART I

Regimen Setup

In this study, combination preferences, such as midazolam-heavy/alfentanil-light or balanced triple drug strategies were considered. Our primary purpose was to investigate published regimens rather than simulate every possible combination. Regimens were extracted from earlier pharmacodynamic simulations for gastrointestinal endoscopies and pooled for a direct comparison.[13,14]

Regimens using single, 2-drug, and 3-drug combinations of propofol, midazolam, and an opioid were searched using PubMed as previously described.[13,14] Studies that reported details on dosing, sedation quality, recovery, and had undergone model simulations were included. We excluded opioid-only and propofol-midazolam combinations because single opioid regimens do not reliably induce loss of consciousness[15] and are potentially harmful at doses that do. DS was defined as a score <2 on the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Scale (Supplemental Digital Content 1, Table S1, http://links.lww.com/AA/F50),[16] including unresponsiveness to endoscope insertion.

Drug combinations from each identified study were used for the simulation session. The simulation sessions consisted of a 3-minute induction period (Figure 1, portion A), a procedure period containing 5-minute esophagogastroduodenoscopy (EGD) plus a 21-minute colonoscopy (Figure 1, portion B), and a 31-minute recovery period (Figure 1, portion C). Total simulation time was 60 minutes. The dosages and administration procedures were based on the outcomes of previous studies combined with reasoning based on the pharmacokinetic properties of each drug. The modified dosing strategies are shown in Table 1. Effect-site drug concentrations (Ce) were calculated using simulation software (TIVAtrainer, Version 9.1, Build 5, Euro SIVA). The models used for simulation were Schnider for propofol,[27] Maitre for alfentanil,[15] Zomorodi for midazolam,[28] Shafer for fentanyl,[29] and Minto for remifentanil.[30] Opioid concentrations were converted to alfentanil equipotency concentrations for model input using the ratio a fentanyl:alfentanil :remifentanil ratio of 1:0.0625:1.2.[12,31] A hypothetical 50-year-old female patient with a height of 170 cm and a weight of 60 kg was used as the patient model for the simulation based on the demographic results of earlier studies.[13,14]

Objective Assessment of Regimen Performance

An AUC approach was used to identify the regimen of choice, which served as the primary outcome measure (Figure 1). The ideal sedation achieved instantaneous DS when administered (Figure 1, upper panel portion B), and an instantaneous return to full consciousness when the procedure ended (Figure 1, upper panel portion C). Therefore, the probability of DS during the induction and recovery periods should be zero and the probability of DS during the procedure should be 1. AUC was calculated using the following equation:

$$AUC = AUC_B - AUC_A - AUC_C \quad [1]$$

AUC_A, AUC_B, and AUC_C are the AUCs corresponding to portions A, B, and C in Figure 1. The AUC was calculated for every regimen simulation using the built-in trapezoid method in MATLAB software (R2021a, The MathWorks, Inc). We illustrate a sedation course example using Regimen 16 to demonstrate the AUC concept (Figure 1, lower panel).

We used parameter variabilities from the NLMAZ model for simulation. Each regimen underwent 2000 simulations using the new parameters from the parameter variability pool. The regimen with

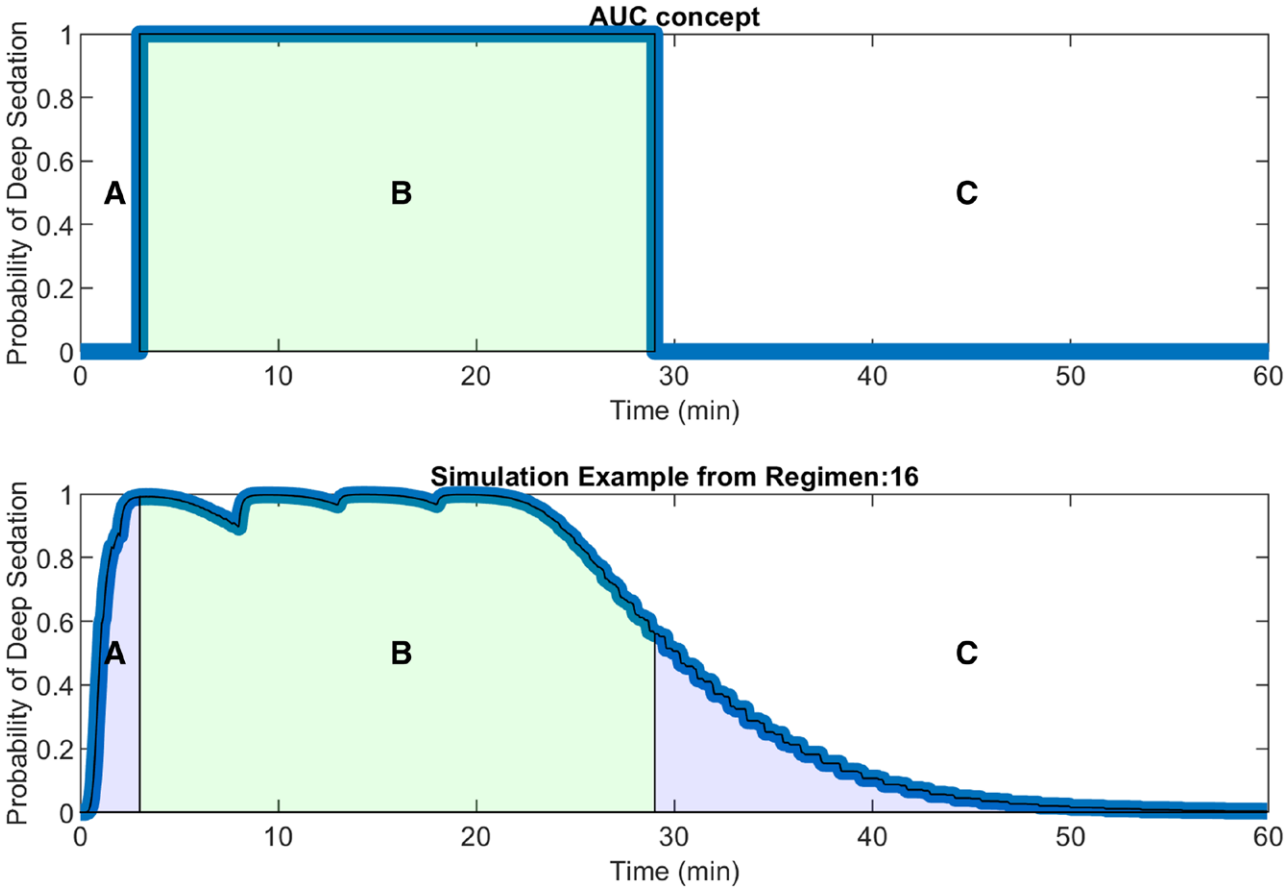

Figure 1. Illustration of the AUC method and its calculation. Panels **A** (blue), **B** (green), and **C** (blue) represent the sedation induction, procedure, and recovery periods, respectively, of simulated sedation regimens for use in gastrointestinal procedures. The sedation probability course is shown as a blue line. The upper panel describes an ideal sedation scenario in which patients are instantaneously sedated at the start of the procedure and instantaneously return to consciousness when the procedure ends. The lower panel depicts the sedation course of Regimen 16. The larger the AUC obtained by calculating $AUC_B - AUC_A - AUC_C$, the closer the regimen was to the optimal scenario. AUC indicates area under the curve.

the highest average AUC was deemed to perform best in terms of adequacy of sedation and speed of recovery. The 2-tailed Wilcoxon ranked sum test with Bonferroni correction was used to compare the pairwise AUCs with the highest AUC. Considering an original *P*-value significance level of <.01, a corrected $P < .00071$ was considered significant.

The probability of DS was calculated using drug concentrations from each regimen and the established NLMAZ model. Recovery times, as secondary end points, were defined as the time needed from the end of the procedure to achieve 50% (t_{50}) and 5% (t_5) probabilities of DS; t_{50} denoted the time needed to reach moderate sedation from deep sedation, and t_5 denoted the time needed to return to consciousness based on the results of an earlier study.[14] These variables were calculated independently and represent different states of wakefulness. Parameter variances were also included for t_{50} and t_5 analyses. Correlations between individual drug doses to the times to recovery (t_{50} and t_5), and AUCs were analyzed by linear regression. R^2 values were used for comparisons. Variance represents the proportion of an independent variable that explains the observed outcome. All statistical analyses were performed using MATLAB's built-in functions.

Sedation Isoplane Navigation Using the NLMAZ Model

In dual-drug pharmacodynamic studies, drug effect can be visualized 3-dimensionally, with the 2 drugs on the *x*- and *y*-axes and the effect on the *z*-axis. The drug concentrations that produce a certain percentage of effect can be plotted on a 2-dimensional (2D) graph as isoboles as effect projections from a 3-dimensional (3D) surface onto a 2D graph.[32] Isoboles are important for identifying the degree of drug interaction and for navigating drug effects.[12,13] The same approach can be applied to the 3-drug NLMAZ model. In this model, the drug's effect was projected from 4-dimensional (4D) data onto a 3D graph as isoplanes. We constructed isoplanes from 1 million random drug combinations to cover a wide range of concentrations and ensure stable isoplane geometry. Concentration pairs of 50%

Table 1. Summary of the Doses of 16 Simulated Sedation Regimens for Use in Gastrointestinal Endoscopy

Regimen number	Reference	Drug combination in the original study protocols	Dosing regimen used for simulation
1	Milligan et al[17]	Midazolam: 6 mg	Midazolam: 3 mg at 0 min, 1.5 mg at 3 and 5 min
2	Milligan et al[17]	Midazolam: 4 mg Alfentanil: 900 μg	Midazolam: 3 mg at 0 min, 1 mg at 3 min Alfentanil: 300 μg at 0, 3, and 5 min
3	Lera dos Santos et al[18]	Midazolam: 6 mg Fentanyl: 50 μg	Midazolam: 4 mg at 0 min, 1 mg at 3 and 5 min Fentanyl: 50 μg at 0 min
4	Moon[2]	Midazolam: 3.8 mg Fentanyl: 200 μg	Midazolam: 0.8 mg at 0 min, 1 mg at 3,5, and 8 min Fentanyl: 50 μg at 0 min, 25 μg at 3, 5, 7, 9, 11, and 13 min
5	Usta et al[19]	Midazolam: 1.8 mg Alfentanil: 1000 μg	Midazolam: 1.8 mg Alfentanil: 500 μg at 0 min, 100 μg at 2, 4, 6, 8, 10 min
6	Avramov et al[20]	Midazolam: 6 mg Remifentanil: 0.1 μg kg^{-1} m^{-1} infusion	Midazolam: 2 mg at 0, 2, and 4 min Remifentanil: infusion of 30 μg min^{-1} at 1 min, stopped at 23 min.
7	Gurunathan et al[21]	Midazolam: 0.04 mg kg^{-1} Fentanyl: 77.5 μg Propofol: 276 mg	Midazolam: 2.5 mg Fentanyl: 75 μg Propofol: 30 mg at 0, 2, 4, 6, 8, 10, 12, 14, and 16 min
8	Gurunathan et al [21]	Fentanyl: 66.9 μg Propofol: 329 mg	Fentanyl: 75 μg Propofol: 30 mg at 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 min
9	Levitzsky et al[22]	Midazolam: 1 mg Fentanyl: 50 μg Propofol: 10 mg at induction, 5–10 mg every 30s after assessment, total 50 mg	Midazolam: 1 mg Fentanyl: 50 μg Propofol: 10 mg at 0 min, 20 mg at 2 and 8 min
10	Levitzsky et al[22]	Midazolam: 3 mg Fentanyl: 100 μg	Midazolam: 3 mg Fentanyl: 100 μg
11	Chan et al[23]	Midazolam: 3.8 mg Alfentanil: 800 μg Propofol: 23mg	Midazolam: 3 mg, 0.8 mg at 8 min Alfentanil: 600 μg Propofol:10 mg at 2 and 11 min
12	Chan et al[23]	Midazolam: 3 mg Alfentanil: 600 μg Propofol: 10 mg	Midazolam: 3 mg at 0 min Alfentanil: 600 μg at 0 min and 200 μg at 8 min Propofol: 10 mg at 2 min
13	Hsu et al[24]	Midazolam: 1.1 mg Fentanyl: 52.5 μg Propofol: 159 mg	Midazolam: 1 mg Fentanyl: 50 μg Propofol: TCI Ce 5.0 at 0 min, 3.0 at 8 min, stopped 5 min before procedure end (at 24 min)
14	Hsu et al[24]	Midazolam: 1.1 mg Fentanyl: 52.5 μg Propofol: 159 mg	Midazolam: 1 mg Alfentanil: 500 μg Propofol: TCI Ce 2.0 at 0 min, stopped 5 min before procedure end (at 24 min)
15	VanNatta and Rex[25]	Midazolam: 1 mg Fentanyl 50 μg Propofol: 82.5 mg	Midazolam: 1 mg Fentanyl 50 μg Propofol: 30 mg at 2 and 13 min, 20 mg at 8 min
16	Lee et al[26]	Midazolam: 0.05 mg kg^{-1} Fentanyl 50 μg Propofol: 145.64 mg	Midazolam: 3 mg Fentanyl 50 μg Propofol: 30 mg at 0, 8, 13, and 19 min 20 mg at 2 min

Simulations started at 0 min, with a 3-minute induction period, a 26-minute procedure (5 min esophagogastroduodenoscopy and 21 min colonoscopy), and a recovery period of up to 60 min. The model simulation patient was a 60-year-old woman, with a height of 170 cm and a weight of 60 kg (ASA-PS 2).
Abbreviations: ASA-PS, American Society of Anesthesiologists-physical status; Ce, effect-site concentration; TCI, target-controlled infusion.

± 0.005% DS probabilities were identified and connected to form the 50% isoplane. The same procedure and margin were used for the 5% and 95% isoplanes. The alfentanil fraction threshold of 0.1, suggested by the NLMAZ model, was used for the respiratory depression isoplane. Concentration pairs that yield a data point outside the respiratory depression isoplane denote a higher risk of respiratory depression.

Fractions represented the proportions of individual drugs within the drug combination after normalization with respect to their C_{50} values.[8] A fraction error margin of 0.0001 was chosen, and the isoplane construction steps were repeated. The isoplanes represented changes in sedation depth. A good regimen, as indicated by a higher AUC, should traverse the isoplanes in a near-perpendicular manner for the fastest DS onset and recovery. Isoplane navigation with respect to time of the best-performing regimen from the assessment in part I demonstrated such characteristics.

PART II
Extended Analyses of the Best-Performing Regimen

The regimen identified in part 1, having a significantly higher average AUC than the others, was subjected to extended simulations using varying doses of

propofol and midazolam doses combined with a 500-µg fixed dose of alfentanil. From this regimen, midazolam doses of 0, 1, 2, and 3 mg and propofol doses that aimed to produce Ce of 2, 3, and 5 µg mL^{-1} were simulated with the fixed alfentanil dose, and this generated 12 subgroups for extended analysis. The simulation sessions were set at time intervals similar to that of induction, procedure, and recovery in part I.

The AUC and t_5 were calculated for each subgroup considering parameter variances with 500 simulations for each regimen. Multiple pairwise comparisons with the top-ranked regimen were performed, and a Bonferroni corrected p-value of 0.00083 was considered significant. Subgroups with AUCs that were higher than the regimen identified in Part I were considered feasible for clinical use.

RESULTS

Part I

Regimen Setup and Infusion Doses. The procedure described in a study by Hsu et al[24] was modified for propofol TCI in regimens 13 and 14. In regimen 14, the TCI was designed to approximate the original propofol doses. A higher TCI setting was used for Regimen 13. Multiple frequent propofol doses were given in regimens 7 and 8. Altering the propofol dosing schemes provided variety to our simulation and reflected the clinical situations in which TCI was commonly used. Remifentanil infusion rate was increased from 0.1 to 0.5 µg kg^{-1} min^{-1} to represent a scenario of midazolam-heavy/opioid-heavy combination.

Three of the simulated regimens used drug infusions. In Regimen 6, the total remifentanil dose was 792 µg. Propofol doses were 304 mg and 169 mg for regimens 13 and 14, respectively. Total remifentanil dose in Regimen 6 was 660 µg (11 µg kg^{-1}), which resulted in a Ce of 11 ng mL^{-1} before ceasing drug administration.

Regimen Performance. AUCs were calculated for 2000 simulations, but the average AUC and standard deviations stabilized after 500 simulations. The performances of the regimens are summarized in Table 2. Regimen 13 had the highest AUC ($P < .00071$) and so was chosen for Part II analysis.

Regimen 5 did not attain a 50% chance of DS at any point during its simulation session and had a low AUC, indicating insufficient sedation. Regimens 1, 3, 4, and 6 had average t_5 toward the end of the simulation. In fact, 33.6%, 26.2%, 96.4%, and 38.3% of regimens 1, 3, 4, and 6, respectively, did not reach t_5 during the 2000 simulations. Regimen 4 produced a negative AUC. A negative AUC or prolonged t_5 was indicative of excessive sedation that lingered far into recovery.

Isoplanes and Navigation. Figure 2A shows the isoplane projection from 4D data. The probability of DS increased as concentrations of propofol and midazolam increased, but not of alfentanil. This indicates that alfentanil alone was not sufficient to produce DS. In the clinically relevant dose range, the respiratory depression isoplane traversed the 5% probability isoplane but not the 50% and 95% isoplanes. Regimen 13 did not reach the respiratory depression isoplane during its navigation course (Supplemental Digital Content 2, Figure S1, http://links.lww.com/AA/F51).

Dose Correlations with AUC, t_{50}, and t_5. The total drug doses and their correlations with AUC, $t_{50,}$ and t_5 are shown in Figure 3. To maintain analyses relevant to clinical practice, the remifentanil used in Regimen 6 was omitted due to dose above the product's label recommendations (0.025–0.2 µg kg^{-1} min^{-1}) for monitored anesthesia care. Linear regression showed a good positive correlation between propofol and AUC ($R^2 = 0.53$) and between midazolam and t_5 ($R^2 = 0.86$) and t_{50} ($R^2 = 0.30$). Midazolam accounted for 85.9% of the variance in t_5, while propofol and opioids were poorly correlated. These results indicated that propofol plays a key role in the quality of sedation and midazolam had a significant negative impact on recovery.

Part II

Regimen Subgroups. Regimen 13 was identified as the regimen of choice. It was broken down into subgroups of 0, 1, 2, and 3 mg doses of midazolam and propofol TCI with Ce of 2, 3, and 5 µg $mL^{-.1}$ Alfentanil was fixed at 500 µg. This gave a total of 12 subgroups.

Subgroup Performance Comparisons. The probability of DS was plotted against time for each subgroup. The subgroups are shown in Figure 4A–4D, with their AUCs displayed in the legends. Propofol Ce of 2 µg mL^{-1} did not produce sufficient sedation; however, an increase in the probability of DS was seen with propofol Ce of 2 µg mL^{-1} when midazolam dose was increased from 0 to 1 mg (Figure 4A, 4B). An observable prolongation of recovery could be seen with increased doses of midazolam as a gentle downslope.

Subgroup AUCs that were higher than regimen 13 (AUC =261.7) were 267.5, 265.4, and 261.8. A subgroup had an AUC of 261.5 but did not reach statistical significance (taking into account adjustment for multiple comparisons) when compared to 261.8 ($P = .0012$). Therefore, the 4 regimens were considered feasible for clinical use, and none of these were in the 3 mg midazolam subgroups.

Table 2. Performance of Simulated Sedation Regimens for Use in Gastrointestinal Endoscopy

Regimen	AUC	t_{50} (min)	t_5 (min)
1	89.93	15.67	NA
2	180.50	3.83	20.42
3	101.26	15.75	NA
4	−14.17	20.83	NA
5	33.10	NA	−4.25
6	90.00	17.58	NA
7	225.90	1.92	15.08
8	244.30	−4.67	−3.17
9	39.24	−18.17	−14.58
10	141.32	−7.08	10.50
11	188.56	4.00	21.00
12	167.92	−6.25	10.50
13	261.70	−2.17	2.17
14	231.85	−3.83	−0.58
15	91.82	−11.92	−8.92
16	224.10	1.25	15.17

The times needed to achieve 50% (t_{50}) and 5% (t_5) probabilities of DS were defined starting from the end of the procedure to the probability cutoff. A negative value was indicative of a premature return to consciousness before the conclusion of the procedure. Regimens with t_{50} or t_5 marked as NA did not reach the given probability during the 60-min simulation because of inadequate anesthesia or prolonged recovery.

Abbreviations: AUC, area under the curve; DS, deep sedation; NA, not achieved.

The subgroup recovery times (t_5) are shown in Figure 4E. Subgroups without midazolam regained consciousness before the procedure ended, demonstrating the significance of the effect of midazolam on t_5. Propofol Ce of 2–5 μg mL^{-1} without midazolam was found to be an acceptable dose. Midazolam doses ≥3 mg significantly prolonged t_5. Dosages identified as optimal for initiating sedation included propofol Ce of 5 μg mL^{-},^{1}1 mg midazolam with propofol Ce of 3 or 5 μg mL^{-},^{1} and 2 mg midazolam with propofol Ce of 2 μg mL^{-},^{1} all with a fixed 500 μg dose of alfentanil.

Subgroup analyses identified midazolam as the primary cause of prolonged recovery (Figure 4). This effect was evident with only 2 mg of midazolam. Our AUC analysis identified 4 regimens that were suitable candidates for gastrointestinal endoscopy sedation:

1. Propofol Ce, 5 μg mL^{-1} + alfentanil, 500 μg
2. Propofol Ce, 5 μg mL^{-1} + midazolam, 1 mg + alfentanil, 500 μg
3. Propofol Ce, 3 μg mL^{-1} + midazolam, 1 mg + alfentanil, 500 μg
4. Propofol Ce, 2 μg mL^{-1} + midazolam, 2 mg + alfentanil, 500 μg

DISCUSSION

The study was an in silico analysis of published dosing regimens for procedural sedation during endoscopy. Through simulations and an objective AUC

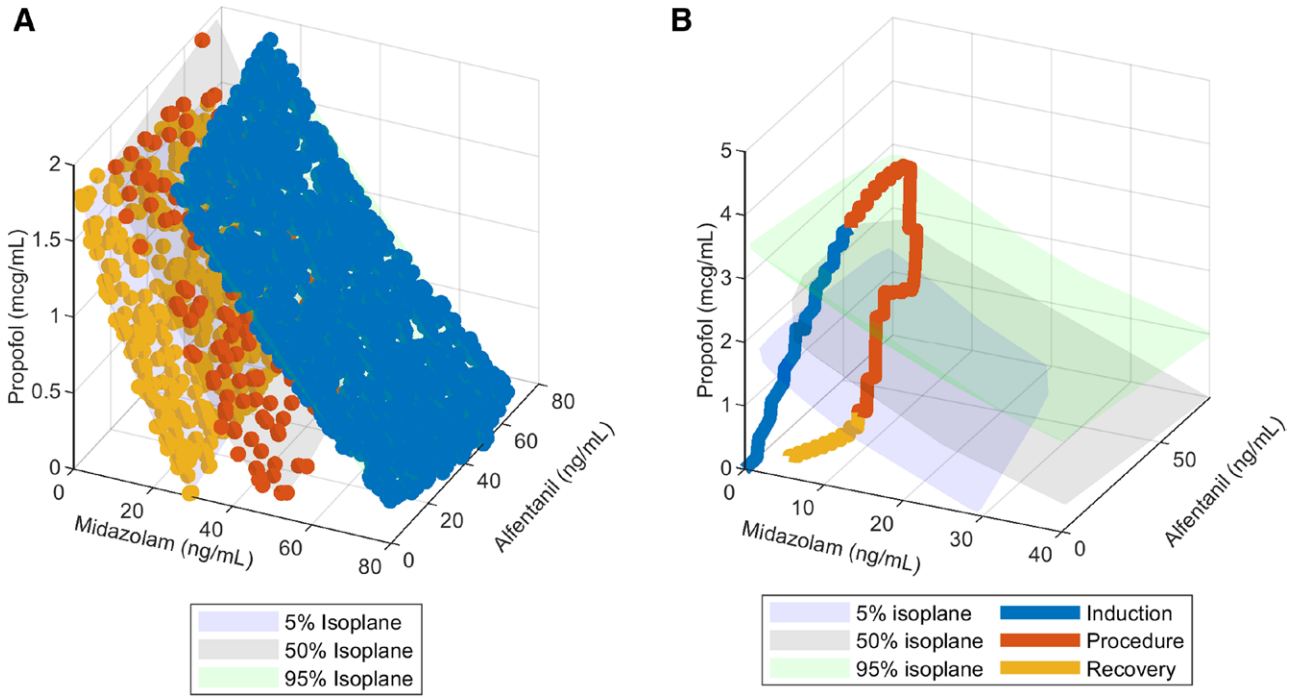

Figure 2. Isoplanes and navigation used in the simulation of sedation regimens. Isoboles with 5%, 50%, and 95% probabilities of deep sedation are shown. **A**, Showing how the surface was constructed. Random concentration sets were scattered. The 5%, 50%, and 95% probability (MOAA/S <2) concentration sets are connected to form a plane. **B**, Regimen 13 was used as a navigation example. A route from induction, through the procedure (esophagogastroduodenoscopy and colonoscopy), and the recovery period was traced. Probabilities above the 50% isoplane during the procedure indicates adequate sedation. Navigation that rapidly dropped to a 5% isoplane reflects rapid recovery. MOAA/S indicates Modified Observer's Assessment of Alertness/Sedation Scale.

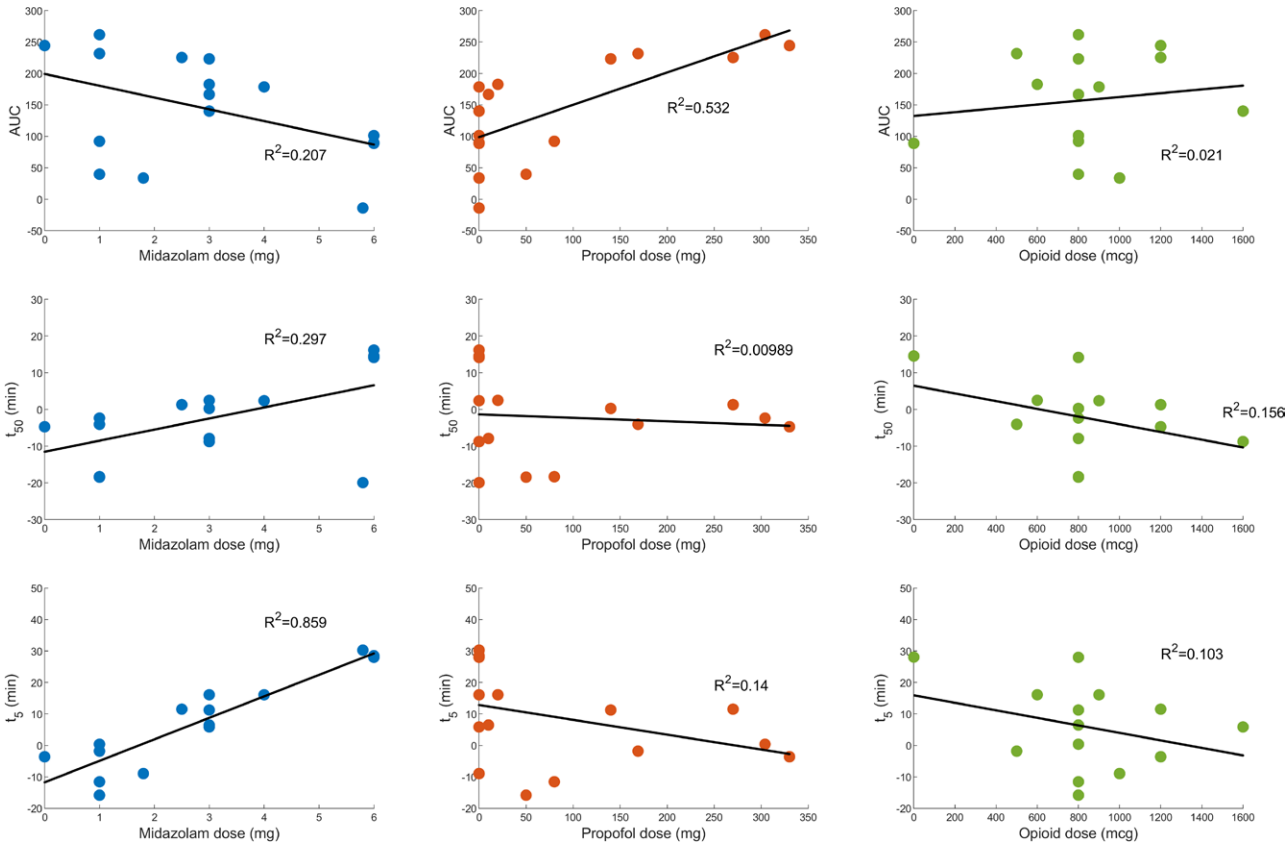

Figure 3. Correlations of total doses with areas-under-the-curve, t_{50} and t_5 for midazolam, propofol, and alfentanil in sedation regimens. Dose-AUC correlations reflect the overall quality of sedation, which was largely controlled by propofol (R^2 = 0.5229). Midazolam explained 76.5% and 71.2% of the variance observed at t_{50} and t_5, respectively. Larger midazolam doses significantly prolonged recovery. Fentanyl doses were converted to alfentanil equipotent doses by a factor of 4. Remifentanil was ignored due to the unusually high dose used in the regimen in which it was used since such doses are not used in clinical practice. AUC indicates area-under-the-curve: t_5, time to 5% isoplane (probability of deep sedation); t_{50}, time to 50% isoplane (probability of deep sedation).

technique, the 2 regimens identified as optimal for DS were a fixed alfentanil dose (500 µg) combined with 1 mg midazolam and 3 or 5 µg mL^{-1} Ce propofol, and a fixed alfentanil dose (500 µg) combined with 2 mg midazolam and 2 or 3 µg mL^{-1} Ce propofol.

The existing guidelines for gastrointestinal endoscopy sedation provide general dosing directions but do not help in determining initial doses of drug combinations.[1,4] Our results suggest a balanced sedation regimen is indicated.[4]

The AUC design was a simple method to screen for regimens of choice and allows simultaneous consideration of sedation adequacy and recovery speeds at equal weights. The approach penalized inadequate anesthesia or prolonged recovery. The design could be mathematically weight-adjusted for procedures with different sedation and recovery requirements.

Regimen 8 was a good alternative to Regimen 13 when TCI pumps were unavailable. Regimens that resulted in low or negative AUCs were 1-drug or 2-drug combinations of midazolam and an opioid. Since such combinations neither provided sufficient sedation nor rapid recovery in the simulations, we surmised that propofol inclusion was essential for quality sedation.

It was important to highlight that pharmacokinetic analysis inherently has a median absolute performance error of approximately 20%.[33] Between-subject variability is generally larger in pharmacodynamic than in pharmacokinetic approaches, sometimes reaching 300% error.[34] However, in this study we managed variability by including pharmacodynamic parameter variances. Different patient demographics altered pharmacokinetics and pharmacodynamics, but the original NLMAZ model did not consider age- or sex-related details. The chosen patient demographics in this study closely matched the original modeling and validation conditions to minimize pharmacodynamic uncertainties. Currently, RSM parameters were unavailable for the 3 selected drugs in special populations, such as elderly, obese, and underweight individuals. This study did not aim to prove superiority, rather, it presented a rationale for regimen selection.

Midazolam doses correlated with t_5 (Figure 3), with progressive prolonging of recovery time as the dose escalated. This effect was not seen for either propofol

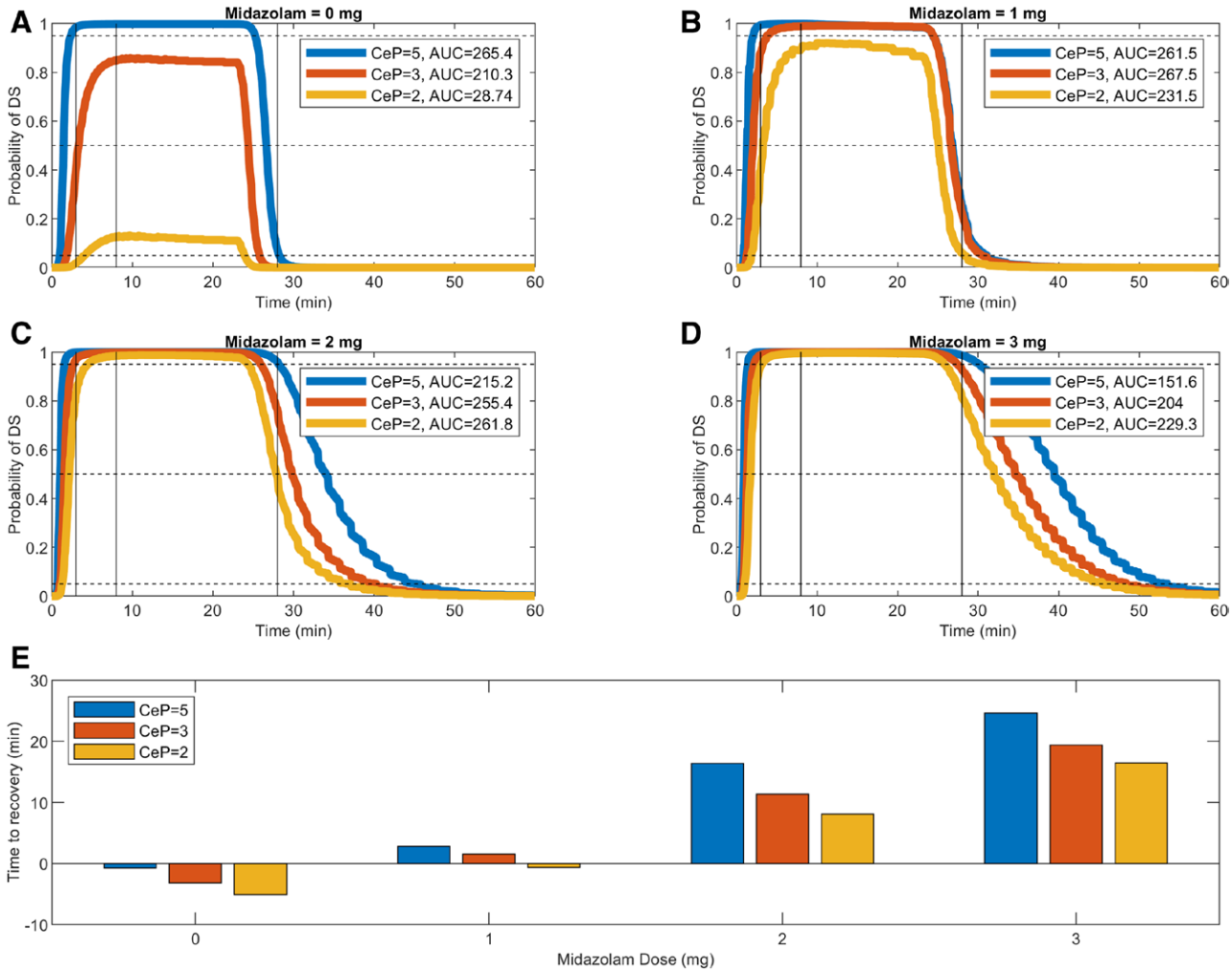

Figure 4. Extended simulation and time to recovery (t_5) of Regimen 13. Regimen 13 had the highest AUC. This regimen was divided into 12 subgroups comprising different doses of midazolam and propofol. **A**–**D**, Showing increasing midazolam doses. Propofol concentrations were simulated as TCIs of 2 (yellow line), 3 (red line), and 5 (blue line) mcg mL^{-1}.[1] Alfentanil was fixed at a dose of 500 µg. The AUCs were calculated using equation 1. Propofol and midazolam acts synergistically to provide rapid sedation and recovery. **D**, Showing low AUCs resulting from prolonged recovery due to a higher dose of midazolam. **E**, Propofol concentrations were simulated as TCIs of 2 (yellow bars), 3 (red bars), and 5 (blue bars) mcg mL^{-1}.[1] Alfentanil dose was fixed at 500 µg. Recovery time prolonged as midazolam doses increased. Prolonged recovery was also observed with propofol but to a lesser extent. AUC indicates area under the-curve; C_eP, propofol effect-site concentration; TCI, target-controlled infusion; t_5, time to 5% isoplane (probability of deep sedation).

or opioids. Our conclusion regarding opioids differed from that of other reports that had found high doses of opioids to prolong recovery.[35] This could be partially explained by context-sensitive decrement times.[36] Repeated or prolonged administration caused drug accumulation and lengthened the time taken for a drug to decay after it was stopped. Our simulation did not consider prolonged infusion, which, while common in surgical anesthesia, was less frequently used in procedural sedation. Opioids did not prolong recovery time in the simulations.

Any of these 4 regimens in the summary of 4 suitable choices (see Results, Part II) was a suitable choice, and clinical considerations should be determined on a case-by-case basis. Regimens that include midazolam should be chosen if anterograde amnesia is desired.[37] As older patients are known to be more sensitive to the lingering effects of sedatives,[38] dose reduction[39] would be suitable. Conversely, a healthy young patient might benefit from higher initial concentrations.

Fentanyl 50 or 100 µg boluses, replacing alfentanil 500 µg, were analyzed in comparison to alfentanil in the 12 regimens from Figure 3. The resulting AUCs for both doses were within 5% of their alfentanil counterparts and did not change the study results. This could be explained by the large alfentanil C_{50} in the original model, which dampened the effects of opioids on achieving MOAA/S <2.

The original NLMAZ model had 76% accuracy in the validation group. A follow-up validation of the NLMAZ model found that the model accurately

predicted 5 of 7 (71.4%) clinical study sedation outcomes and 8 of 9 (88.9%) recovery outcomes.[14] One RSM study had an accuracy of 82%–85% in gastrointestinal endoscopy sedation.[9] Another RSM study reported an inaccuracy rate of 25% ± 13% for the bispectral index.[40] The accuracy of the original model reflected the pharmacodynamic variations observed between patients, which should be considered using drug selection.

This study had several limitations. First, not all documented variations, in terms of drugs or procedure durations, were simulated as the study focused on those regimens most used in an average clinical practice. This was because there were countless combinations. For the same reason, the alfentanil dose was not varied in the subgroup simulations.

Second was the argument that simulation does not reflect clinical practice. However, a valid model that matched clinical outcomes[14] could provide important insights without the need for clinical trials, which sometimes may be difficult to design. Traditional clinical research would struggle to simultaneously evaluate the 16 regimens restricted by patient numbers, cost constraints, and safety considerations. Thus, this approach offered direct regimen comparisons that would not otherwise be possible.

Third, the possibility of oversedation was not discussed. The AUC method used in this study did not consider adverse effects, primarily because of the lack of a 3-drug adverse effect RSM. Oversedation was difficult to define, and adverse events, such as respiratory depression, were often cited as surrogates for oversedation. Published regimens already assessed for safety were used. The initial NLMAZ modeling considered a safety profile for respiratory depression, represented by the respiratory depression isoplane. In the original research from which the selected regimens were drawn, an alfentanil fraction exceeding 0.1 was found to be associated with respiratory depression.[8] During the simulation, the fraction only exceeded 0.1 for Regimen 6. Regimen 6 was not among the regimens deemed optimal; therefore, the recommended regimens should carry low risks of respiratory depression.

Finally, significant interindividual variations in the effects of most drugs were too idiosyncratic to be effectively incorporated into simulations, and not always required.[12,41] As such, these variations should be anticipated and allowed. Some unmodifiable conditions affect patient sensitivity or resistance to sedatives; age being a prime example. Previous research had proposed a general rule that stipulates a 7% reduction in anesthetic requirements for every decade increase of age.[42] The change in anesthetic requirements warrants a specific pharmacodynamic model for the elderly. With this in mind, it was reasonable to choose regimens with lower total drug doses for older or frail patients. Clinical studies are needed to validate the clinical benefit of our pharmacodynamic model. ■

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DISCLOSURES

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