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Original Article

Previously published midazolam–alfentanil response surface model cannot predict patient response well in gastrointestinal endoscopy sedation

Jing-Yang Liou [a], Chien-Kun Ting [a,b], Yu-Ying Huang [c], Mei-Yung Tsou [a,b,*]

[a] *Department of Anesthesiology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[b] *National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC*
[c] *Department of Anesthesiology, Cheng-Hsin General Hospital, Taipei, Taiwan, ROC*

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Abstract

Background: A response surface model is a mathematical model used to predict multiple-drug pharmacodynamic interactions. With the use of a previously published volunteer model, we tested the accuracy of the midazolam–alfentanil response surface model during gastrointestinal endoscopy.

Methods: We enrolled 35 adult patients scheduled for combined endoscopic procedures. Patients were sedated with intravenous midazolam and alfentanil, and monitored with real-time auditory evoked potential. Sedation Observer's Assessment of Alertness/Sedation (OAA/S) scores were recorded by an independent observer every 2 minutes. Patients with OAA/S scores of ≥4 were designated as "awake". Pharmacokinetic profiles were calculated using the TIVA trainer. The published response surface model was modified to make estimations more reasonable. Patient response (OAA/S score ≥ 4 or <4) was then estimated using the modified version of the model.

Results: The average procedural times were 3.3 ± 2 minutes and 6.5 ± 2.3 minutes for esophagogastroduodenoscopy and colonoscopy, respectively. The model poorly predicted patient response during gastrointestinal endoscopic procedure sedation. Accuracy in predicting an OAA/S score of <4 was 6% for the original model and 0% for the modified model. The estimated probability of loss of response ranged from 0.04% to 2.94% at the time of arousal (OAA/S score ≥ 4) and from 0.24% to 15.55% when the patient was asleep (OAA/S score < 4).

Conclusion: The model showed significant synergy between midazolam and alfentanil; however, it was inadequate in predicting the response of patients undergoing sedated gastrointestinal endoscopic procedures. Future model parameter adjustments are required.

Keywords: alfentanil; gastrointestinal endoscopy; midazolam; pharmacodynamic; response surface model

1. Introduction

Drug interactions have always been an important issue in daily anesthesia practice. Traditionally, isobolographic analysis is used to describe drug interactions, which can be characterized as additive, synergistic, or infra-additive (antagonistic).[1] Isobologram is limited to presenting drug interactions at a specified response endpoint, for example, 50% chance of movement during laryngoscopy. The response surface model is a combination of the drug concentration–effect relation and the isobologram. It displays drug effects in a wide range of drug concentrations for two or more drugs.[2,3] Various anesthetic combinations have already been evaluated, including hypnotic–hypnotic,[4,5] opioid–hypnotic,[6–8] and analgesic–analgesic[9] pairs.

The combination of midazolam and alfentanil can be used in some surgical procedures and examinations requiring

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* Corresponding author. Dr. Mei-Yung Tsou, Department of Anesthesiology, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.

E-mail address: mytsou8095@gmail.com (M.-Y. Tsou).

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moderate sedation and analgesia.[10,11] Both drugs are still used very commonly. Few studies have investigated the response surface model for midazolam–alfentanil interaction.[2,3] Minto et al[3] used the volunteer data from Short et al[12] and developed a response surface model for hypnosis without stimulus using midazolam and alfentanil. The aim of this study was to validate the accuracy of this published response surface model during the quiescent phases in gastrointestinal endoscopic procedure sedation.

2. Methods

2.1. Patient selection and anesthesia

After approval from the Institutional Review Board (IRB) at Taipei Veterans General Hospital, Taipei, Taiwan (IRB 2014-12-001BC), 40 adults—aged < 65 years—scheduled for combined esophagogastroduodenoscopy (EGD) and colonoscopy were enrolled. All patients had documented written consent. Patients were assessed as being at a physical status of I or II, according to the American Society of Anesthesiologists classification system. Exclusion criteria included hearing impairment, neurologic or behavioral disorders, habitual sedative use, and allergy to midazolam or alfentanil. Strict fasting and colon preparation protocols were followed. A 22-gauge intravenous catheter was secured for drug administration. Each patient received standard anesthetic care monitoring comprising electrocardiography, pulse oximetry, and noninvasive blood pressure monitoring. Supplemental oxygen was given via a nasal cannula, with the SpO_2 being maintained above 90%. Bolus intravenous doses of midazolam and alfentanil were administered by an experienced anesthesiologist. The patient was monitored with an auditory evoked potential monitor (AEP Monitor/2; Danmeter A/S, Odense, Denmark). Instrumentation began after a loss of response, as evaluated by the anesthesiologist, or an A-line auditory evoked potential index (AAI) of <60. The mean auditory evoked potential index values for various Observer's Assessment of Alertness/Sedation (OAA/S) scores were 81.2 at Score 5, 63.2 for Score 4, 48.8 for Score 3, 36.5 for Score 2, and 29 for Score 1 in patients undergoing gastrointestinal endoscopy sedation. According to the manufacturer of auditory evoked potential monitor monitors, an auditory evoked potential index value of >60 is indicative of the awake state.[13] Intolerable desaturation was managed with mask ventilation or insertion of a nasal airway. Additional alfentanil boluses were given if the patient expressed pain or showed facial expressions of pain. Midazolam boluses were given if the patient had an OAA/S score of ≥4 with or without pain expressions. EGD was performed first, followed by colonoscopy. At the end of the procedure, the patient was observed until verbal arousal was possible. Sedation OAA/S (Table 1) scores were recorded by an independent observer. Patients with an OAA/S score of ≥4 were designated as "awake". Each patient's response to a specific concentration of the midazolam and alfentanil pair was recorded during induction and emergence.

Table 1
Observer's Assessment of Alertness/Sedation scale.[a]

Observation	Score
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly &/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1

[a] An Observer's Assessment of Alertness/Sedation score of ≥4 indicated the awake status in this study.

2.2. Response surface model

Using SigmaPlot 12.5 (Systat Software, Inc., San Jose, CA, USA), patient response was calculated by a midazolam–alfentanil response surface model published by Minto et al[3] [Eq. (1)].

$$E = E_0 + (E_{\max}(\theta) - E_0)\frac{\left(\frac{U_{mid}+U_{Alf}}{U_{50}(\theta)}\right)^{\gamma(\theta)}}{1+\left(\frac{U_{mid}+U_{Alf}}{U_{50}(\theta)}\right)^{\gamma(\theta)}} \quad (1)$$

E represents the drug effect, which is the probability of a loss of response. It ranges from 0 to 1, with 0 indicating no drug effect and the patient having 100% probability of response, and 1 indicating no response to stimuli. $E_{\max}(\theta)$ is defined as the maximal drug effect (effect to achieve an OAA/S score of <4), whereas E_0 is the baseline effect when no drug is present. Their values are designated as 1 and 0 for $E_{\max}$ and E_0, respectively, to simplify the equation. C_{50} stands for the effective drug concentration that is required to achieve 50% maximal effect. U is the unitless normalized potency of the drug relative to a plasma concentration of 50% drug effect [Eq. (2)].

$$U = \frac{C}{C_{50}} \quad (2)$$

The model introduces a central concept, θ, to represent a new drug as a ratio of the drugs under investigation [Eq. (3)]. The term θ should not be confused with an actual measurable drug concentration; it is a concept developed for the model parameters. The range of θ varies from 0 (only midazolam present) to 1 (only alfentanil present).

$$\theta = \frac{U_{Alf}}{U_{mid}+U_{Alf}} \quad (3)$$

In our research, the drugs under investigation were midazolam (*Umid*) and alfentanil (*UAlf*); γ is the sigmoidicity factor, a function of θ, that determines the steepness of the effect. $U_{50}(\theta)$ is the potency of the new drug, at ratio θ, which yields half the maximal response. It can be calculated according to Eq. (4):

$$U_{50}(\theta) = 1 - \beta_{2,U_{50}}\theta + \beta_{2,U_{50}}\theta^2 \quad (4)$$

The parameter $\beta_{2,U_{50}}$ is an interaction parameter that originated from a fourth-order polynomial function, as described