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Original Article

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

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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

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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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

by Minto et al.[3] When the value is 0, it denotes an additive effect. It is synergistic or antagonistic when >0 or <0, respectively.

Pharmacokinetic profiles, including plasma and effector-site concentrations, were estimated using the TIVA trainer simulation program (version 8, Build5, Guttabv, EuroSIVA, Netherlands). We used the Maitre et al's[14] model for alfentanil and the Zomorodi et al's[15] model for midazolam.

The C_{50} values given by Minto et al[3] were 0.144 mg/kg for midazolam and 0.0936 mg/kg for alfentanil. The reported response surface model was built on the raw data given by Short et al,[12] and the volunteers were all females. By inputting average height, weight, and age into the simulation software, the estimated maximum plasma concentration at such a dosage yielded 311 ng/mL for midazolam and 705 ng/mL for alfentanil. A modified response surface model was then constructed using the above approximations. The investigation endpoint was the patient's arousal status as binary data, $E = 1$ for OAA/S score <4 or $E = 0$ for OAA/S score ≥4. The primary aim was to validate the model in terms of accuracy. Accuracy of prediction is assessed by calculating the difference between the true response (OAA/S scores < 4 and ≥ 4) and the model-predicted probability. The model is considered "accurate" if the difference is < 0.5. The total percentage of accurate predictions was obtained for both the original (mg/kg) and the modified (ng/mL) response surface models.

3. Results

Forty patients were initially enrolled; however, five were excluded, two because of previous known neurologic diseases and three because of inadequate records. The demographic data are summarized in Table 2. EGD and colonoscopy were completed in all our patients. Forty-one observations were eligible for pooling among the 35 patients studied. Six additional observations were available from the period between EGD and colonoscopy when the patient became arousable and the OAA/S score was ≥4. Each observation produces two concentration pairs, one is at the maximal model-predicted chance of an OAA/S score of <4 ($E = 1$, which all occurred after initial boluses during induction) and the other is at true patient arousal at the end of the procedure (OAA/S score ≥ 4 or $E = 0$). A total of 82 concentration pairs for midazolam and alfentanil were available. The average body mass index was 22.1 ± 2.3 kg/m^2. The mean cumulative dose for midazolam was 0.047 ± 0.015 (standard deviation) mg/kg and that for alfentanil was 0.012 ± 0.004 mg/kg. The plasma concentration ranged from 27 ng/mL to 112 ng/mL and from 12 ng/mL to 106 ng/mL for midazolam and alfentanil, respectively. Accuracy of prediction was 0% for the OAA/S score <4 group, since the difference between the true response and prediction was >0.5 in all 41 observations (Fig. 1). Drug synergy for producing hypnosis is clearly delineated as bowing of the isoboles toward the origin. 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 at maximal model-predicted probability (OAA/S score < 4). All the observations were below the 50% probability isobole.

The modified response surface model is shown in Fig. 2. Significant synergy is seen between midazolam and alfentanil. At a commonly used dosage, alfentanil alone is insufficient to produce an OAA/S score of <4. Maximum drug concentrations at an OAA/S score of <4 are plotted, which show a large discrepancy between the predicted and true patient responses (Figs. 2 and 3).

The original response surface model in units of mg/kg is plotted as a contour graph. The cumulative patient drug dose is marked as black dots (Fig. 4). Two out of 35 patients (6%) reached > 50% predicted probability of an OAA/S score of <4 using the model. One patient had difficult EGD and colonoscopy, and the examination time was much longer than average. The second patient was not remarkably different from others, but was simply manifested as more resistant to midazolam and alfentanil and required more boluses.

Table 2
Patient demographic data.

Age (y)	49.1 ± 9.4
No. of males	19 (54.3)
No. of females	16 (45.7)
Weight (kg)	60.5 ± 9.3
Height (cm)	165.1 ± 7.8
Body mass index (kg/m^2)	22.1 ± 2.4
Examination time	
Colonoscopy (min)	6.5 ± 2.3
Esophagogastroduodenoscopy (min)	3.3 ± 2

Data are presented as *n* (%) or mean ± standard deviation.

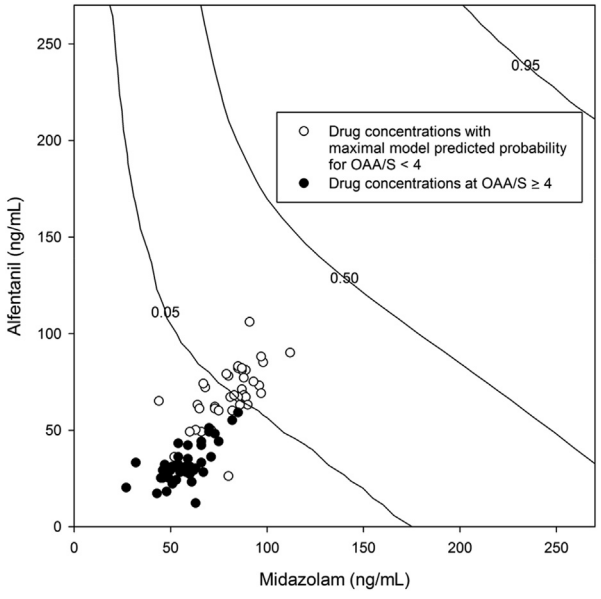

Fig. 1. Contour graph of the modified response surface model versus plasma concentration. Solid lines represent the 95%, 50%, and 5% chances of patients having an OAA/S score of <4. All the observations lie below the 50% line, regardless of the patient's actual response. OAA/S = Observer's Assessment of Alertness and Sedation scale.

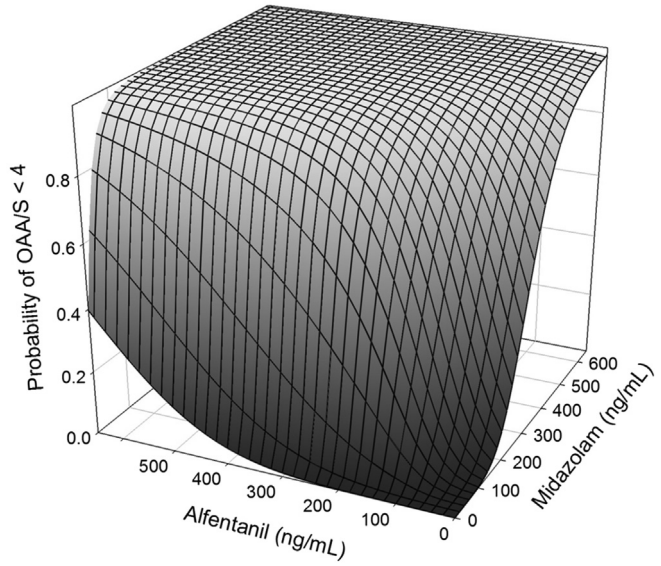

Fig. 2. The modified response surface model for midazolam–alfentanil interaction showing significant synergy between the two drugs. As shown by the model surface, an OAA/S score of <4 cannot be reliably achieved with alfentanil alone, even at high doses. OAA/S = Observer's Assessment of Alertness and Sedation scale.

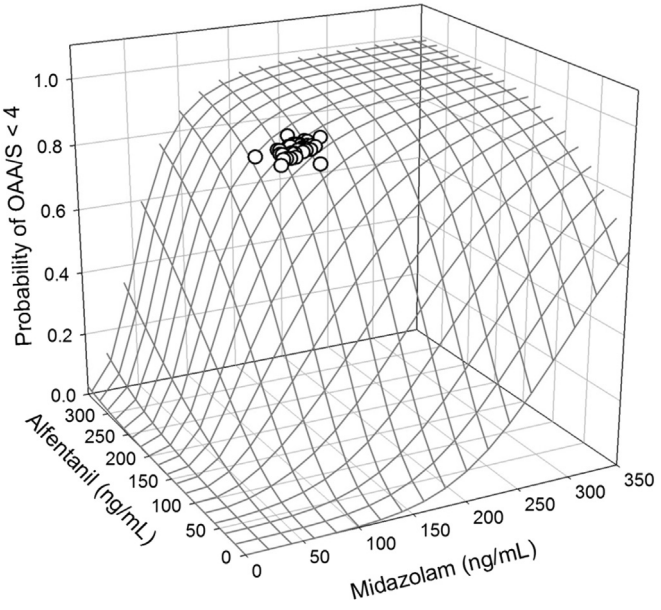

Fig. 3. The modified response surface model is rotated to a different perspective. Black circles are maximum drug concentrations. All patients have attained an OAA/S score of <4 despite the model predicting that they would not, even at plasma drug concentrations with maximal model-predicted probability of an OAA/S score of <4. OAA/S = Observer's Assessment of Alertness and Sedation scale.

4. Discussion

In this study, we assessed the ability of a previously reported response surface model of midazolam–alfentanil to predict patient response during gastrointestinal endoscopy sedation and wake-up time. The model reported by Minto et al[3] is in a class by itself and is the only available response surface model for the midazolam–alfentanil interaction to date. The model, which predicts hypnosis, was built based on the raw data collected by Short et al[12] from 400 Chinese female patients with an average weight of 50.3–54.1 kg and an average age of 30.6–32.6 years. In the literature, hypnosis was defined as failure to open the eyes on verbal command. This was equivalent to an OAA/S score of <4 in our study. Our population's average body weight and age were 60.54 kg and 49.1 years, respectively. The derived plasma concentration differed by < 10% for the age range of 29–60 years and body weight range of 40–60 kg under simulation for both drugs.

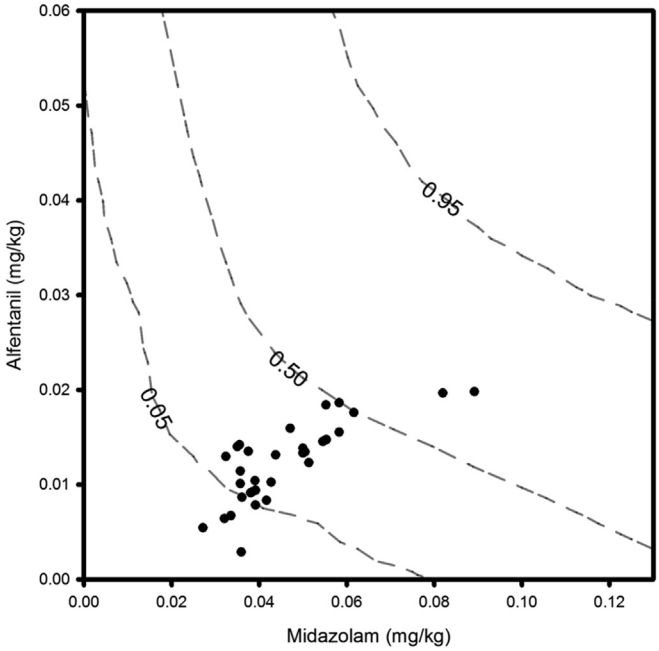

Fig. 4. This is the contour graph derived from the original response surface model. Dashed lines represent the 95%, 50%, and 5% probabilities of an OAA/S score of <4. The cumulative drug doses are mostly scattered below the 50% isobole. Only two out of 41 observations were considered accurate (difference between true and predicted probability <0.5). OAA/S = Observer's Assessment of Alertness and Sedation scale.

A midazolam and opioid combination has been used extensively for moderate conscious sedation during various examinations[11,16–20] by both anesthesiologists and non-anesthesiologists. The previously reported C_{50} values for midazolam and alfentanil were 0.144 mg/kg and 0.0936 mg/kg, respectively.[3] For a 60-kg patient, that would translate into 8.64 mg midazolam and 5616 μg alfentanil. The single-bolus dosage of alfentanil is extremely high and rarely used in modern anesthesia practice, especially for such a short procedure. Using the model, the predicted probability for hypnosis was inaccurate for all doses. All our observed patients have a <20% chance of being asleep (OAA/S score < 4). This implied that patients should be awake throughout the entire procedure, although actually most of the patients fell asleep in our 41 observations.

Pharmacokinetic studies on alfentanil reported a large discrepancy in C_{50} concentration. Jhaveri et al[21] reported a loss of response C_{50} of 1012 ng/mL for loss of consciousness

in healthy volunteers when alfentanil was the sole agent used. Loss of consciousness was defined by failure to respond after three consecutive commands to take a deep breath. Plasma concentration for suppressing response to skin incision in combination with 70% N_2O was 200−300 ng/mL.[22] Ausems et al[23] also reported a similar plasma C_{50} when supplemented with 66% N_2O. The C_{50} for alfentanil was 475 ± 28 ng/mL for tracheal intubation, 279 ± 20 ng/mL for skin incision, and 150 ± 23 ng/mL for skin closure. Vuyk et al[24] studied the interaction between propofol and alfentanil during lower abdominal surgery in women. At low propofol plasma concentrations (2 μg/mL), the C_{50} for alfentanil was 170 ng/mL for laryngoscopy, 280 ng/mL for intubation, 259 ng/mL for opening of the peritoneum, and 209 ng/mL for intra-abdominal surgical stimuli. Albeit under noxious stimuli, the reported alfentanil C_{50} values with concomitant propofol or N_2O were below 500 ng/mL. The wide range of the pharmacokinetic profile may reflect a great interindividual pharmacodynamic response and poor ability to reliably produce a loss of response when opioids are used alone.[14]

One study, which involved 54 intensive care unit patients who had undergone coronary artery bypass graft surgery, reported a midazolam C_{50} of 171 ng/mL at a Ramsay score of 3 and 260 ng/mL at a Ramsay score of 5.[25] Another study conducted by Vinik et al[26] also investigated the hypnotic synergism between propofol, midazolam, and alfentanil in their binary and triple combinations. In the midazolam−alfentanil group, the C_{50} values were 0.04 mg/kg and 0.03 mg/kg for midazolam and alfentanil, respectively. The pharmacokinetic profile was magnitudes smaller than that adopted in this study. The unexpectedly high alfentanil and midazolam C_{50} values in Minto et al's[3] model may partly explain the poor predictive ability of the response surface model. We have plotted the cumulative doses against the contour graph derived from the original response surface model. It may seem slightly more accurate (6% and 0%), but prediction is still poor and should be interpreted carefully. Drugs are given in multiple boluses during the examinations. The cumulative dose increases with examination time and does not correlate well with plasma concentrations. It will most likely overestimate the predicted loss of response probability.

Endoscopic procedures are associated with discomfort and pain, both during and after the procedure.[27] Postprocedural pain can occur in up to 36% of the patients. Our study did not assess the response to instrumentation, but the presence of postprocedural pain may imply that drug concentrations lower than those in our study may be sufficient to produce an OAA/S score of <4 for such procedures.

Instead of volunteers, patients were used in this study. This is a strength but also a weakness. The patient population was limited and may underestimate the model's capabilities. We derived the C_{50} value from Minto et al's[3] model based on the mean body weight and height of the study population. The original C_{50} unit was mg/kg, and the derived plasma concentrations given by TIVA trainer were in ng/mL. Age difference had little effect on the three-compartment pharmacokinetic model used in the program, and the change was very small. Although assumptions were made to simplify the model, the variation in derived C_{50} plasma concentration is unlikely to alter the results. Plasma concentration equilibrated with effect site relatively quickly for alfentanil,[28] but that was not the case with midazolam.[15] Effect-site concentrations peaked minutes after bolus administration for both studied drugs, and cannot be reliably assumed and fitted for model modification.

In conclusion, the reported response surface model poorly predicted patient response during gastrointestinal endoscopy sedation. Minto et al's[3] model was constructed with volunteer data and a single bolus of drugs, which makes it difficult to be implemented into clinical practice. Analysis of the noxious stimulations during gastrointestinal endoscopy with respect to plasma or effect-site concentrations will make the model more accessible to clinicians. Further research is required in order to adjust the response surface parameters to provide a good prediction, as well as to develop new models for different circumstances.

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