BJA

British Journal of Anaesthesia, ■ (■): 1–10 (2018)

doi: 10.1016/j.bja.2018.01.041
Advance Access Publication Date: xxx
Clinical Investigation

CLINICAL INVESTIGATION

Adaptation of non-linear mixed amount with zero amount response surface model for analysis of concentration-dependent synergism and safety with midazolam, alfentanil, and propofol sedation

J.-Y. Liou[1,2], C.-K. Ting[1,2], W.-N. Teng[1,2], M. S. Mandell[3] and M.-Y. Tsou[1,2,*]

[1]Department of Anaesthesiology, Taipei Veterans General Hospital, Taipei City, Taiwan, [2]National Yang Ming University, Taipei, Taiwan and [3]Department of Anaesthesiology, University of Colorado Hospital, Aurora, CO, USA

*Corresponding author. E-mail: mytsou8095@gmail.com

Abstract

Background: We use the non-linear mixed amount with zero amounts response surface model with triple drug combinations during sedation for endoscopy to describe drug interactions and predict loss of response to noxious stimuli and respiratory depression.

Methods: Sedation was monitored in 56 patients undergoing gastrointestinal endoscopy (modelling group) using modified alertness/sedation scores. A total of 227 combinations of effect-site concentrations were derived from pharmacokinetic models. Accuracy and the area under the receiver operating characteristic curve were calculated. Accuracy was defined as an absolute difference <0.5 between the binary patient responses and the predicted probability of loss of responsiveness. Validation was performed with a separate group (validation group) of 47 patients.

Results: Effect-site concentration ranged from 0 to 108 ng ml^{-1} for midazolam, 0–156 ng ml^{-1} for alfentanil, and 0–2.6 μg ml^{-1} for propofol in both groups. Synergy was strongest with midazolam and alfentanil (24.3% decrease in U_{50}, concentration for half maximal drug effect). Adding propofol, a third drug, offered little additional synergy (25.8% decrease in U_{50}). Two patients (3%) experienced respiratory depression. Model accuracy was 83% and 76%, area under the curve was 0.87 and 0.80 for the modelling and validation group, respectively.

Conclusion: The non-linear mixed amount with zero amounts triple interaction response surface model predicts patient sedation responses during endoscopy with combinations of midazolam, alfentanil, or propofol that fall within clinical use. Our model also suggests a safety margin of alfentanil fraction <0.12 that avoids respiratory depression after loss of responsiveness.

Keywords: Alfentanil; Endoscopy; Midazolam; Opioid; Pharmacodynamic

Editorial decision: March 10, 2018; **Accepted:** January 31, 2018

Editor's key points

- Combinations of two or more drugs, commonly used for sedation, result in complex interactions.
- In contrast with two drug combinations, little progress has been made with modelling triple drug interactions.
- The authors studied interactions among alfentanil, midazolam, and propofol using a non-linear mixed amount with zero amounts model.
- This model was able to predict loss of responsiveness and respiratory depression with reasonable accuracy.

Effective sedation aims to make patients comfort while minimising adverse effects such as respiratory depression (RD). Drugs that treat anxiety, pain, and awareness are usually given in combination to make patients comfortable during invasive procedures. This can increase the risk of adverse events such as RD or slow the workflow through sites of care that require rapid patient turnover.

Response surface models (RSMs) predict drug response by integrating isobolographic data with concentration effect curves and curve shift effects.[1–5] These models work well for dual drug combinations such as combinations of inhalation agents, i.v. hypnotics, opioids, α_2-agonists, or non-steroidal anti-inflammatory drugs.[6–9] However, triple drug interactions are difficult to study because of the complex model development process needed to describe all drug combinations.

Triple drug models have been developed for anticancer or antifungal therapy based on *in vitro* microbial kill rates.[10–12] Anaesthesia models differ by using patient response as an end measure.[2,13] Triple drug interaction models have been developed using hierarchy and non-RSMs, including double-sedative-single-opioid and sedative-opioid-volatile agent combinations.[13,14] However, practical clinical use of this approach is limited because these studies used drug doses calculated in milligrams per kilograms. It is difficult to translate this type of dose calculation into clinical practice where drugs are often given in multiple boluses and at varying intervals.

Our aim was to design and describe a new anaesthetic interaction model predicting patient response during sedation that could be adapted for practical use. We chose the non-linear mixed amount with zero amount (NLMAZ) as a response surface approach for model development, because it allows independent flexibility expressed as functions in all of the Hill's parameters.[15] These functions can capture local differences in synergism, additivity, or antagonism in a single data set. We hypothesise that an integrated model from upper and lower endoscopy sedation also adequately describes responses in a separate group of patients. A secondary aim was to use our model design to improve sedation safety by predicting the risk of RD. We anticipate that this type of model could have practical clinical application and warrants further evaluation.

Methods

Study group

This was a single-centre observational study. Institutional Review Board approval at the Taipei Veterans General Hospital was obtained before recruitment (IRB number: 2016-04-003C and 2017-03-003B). Written informed consent was obtained from all subjects. ASA (class 1 or 2) patients aged between 20 and 80 yr scheduled for oesophagogastroduodenoscopy (OGD) or colonoscopy were candidates for the study. Our estimated sample size was 60 patients. A previous study[16] showed an efficient criss-cross design requiring 20 patients, while the radial and slice design required 40 patients to define a reliable dual-drug response surface. Our study manifested non-steady state drug concentrations and the drug administration shared similarities with the radial design.

Patients were excluded if they had documented impairment in verbal communication, history of facial or neck surgery, pre-examination SpO_2<95%, or a history of sedative, opioid, or chronic alcohol use. Two groups of patients were enrolled: a modelling group to construct the RSM, which included both upper (OGD) and lower (colonoscopy) endoscopy; and a validation group. The latter sample only received upper endoscopy and was used to evaluate the model's clinical applicability.

Anaesthesia management

Anaesthetic drugs were given through a 22-gauge i.v. catheter placed in a distal arm. Patients were monitored using standard non-invasive equipment: electrocardiography, pulse oximetry, and non-invasive blood pressure. Supplemental oxygen was administered by nasal cannula at 5 L min^{-1}. One anaesthesiologist in each session administered bolus i.v. doses of midazolam, alfentanil, or propofol based on clinical preferences.

The Modified Observer Assessment of Alertness/Score (MOAA/S)[17,18] was used to measure arousal by clinical observation on a 0–5 scale where 5 was awake and 0 was unresponsive to noxious stimuli. Endoscopy began when the patient reached loss of response (LOR), defined by MOAA/S<2 (no response to prodding or noxious stimuli). Additional alfentanil was given if the patient appeared uncomfortable. Midazolam or propofol was given if the patient's MOAA/S was >4 with or without pain. After each bolus, the medication was flushed with 3 ml of normal saline. RD was defined as severe hypoxaemia shown by a reliable pulse oximetry reading <90%, regardless of the duration. Two health care providers trained in MOAA/S scored depth of sedation at the start and the end of the examination, or at critical events (occurrence of RD, endoscope insertion, painful expression) for each study patient. Loss of response was defined as MOAA/S<2. We pooled upper and lower endoscopy into one single session based on previous findings showing a similar pain intensity.[19]

Pharmacodynamic response surface model

We use the NLMAZ model as our response surface model. It is an extension to the mixed amount with zero amount observation model and was first proposed by White and colleagues.[15] The original form is as follows:

$$E = \frac{(E_{max} - E_0) \times \left(\frac{U}{U_{50}}\right)^n}{1 + \left(\frac{U}{U_{50}}\right)^n} + E_0 \quad (1)$$

where E is the effect, defined as the probability of LOR. E_{max} is the maximal drug effect possible and E_0 is the baseline probability when no drugs are present. U_{50} is the value of U resulting in 50% of the maximal effect, that is, to achieve 50% chance of LOR. U resembles that in the Minto model, which can be interpreted as a new drug and is the sum of the