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Review Article

Response surface models in the field of anesthesia: A crash course

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ABSTRACT

Drug interaction is fundamental in performing anesthesia. A response surface model (RSM) is a very useful tool for investigating drug interactions. The methodology appeared many decades ago, but did not receive attention in the field of anesthesia until the 1990s. Drug investigations typically start with pharmacokinetics, but it is the effects on the body clinical anesthesiologists really care about. Typically, drug interactions are divided into additive, synergistic, or infra-additive. Traditional isobolographic analysis or concentration-effect curve shifts are limited to a single endpoint. Response surface holds the complete package of isobolograms and concentration effect curves in one equation for a given endpoint, e.g., loss of response to laryngoscopy. As a pharmacodynamic tool, RSM helps anesthesiologists guide their drug therapy by navigating the surface. We reviewed the most commonly used models: (1) the Greco model; (2) Reduced Greco model; (3) Minto model; and (4) the Hierarchy models. Each one has its unique concept and strengths. These models served as groundwork for researchers to modify the formula to fit their drug of interest. RSM usually work with two drugs, but three-drug models can be constructed at the expense of greatly increasing the complexity. A wide range of clinical applications are made possible with the help of pharmacokinetic simulation. Pharmacokinetic-pharmcodynamic modeling using the RSMs gives anesthesiologists the versatility to work with precision and safe drug interactions. Currently, RSMs have been used for predicting patient responses, estimating wake up time, pinpointing the optimal drug concentration, guide therapy with respect to patient's well-being, and aid in procedures that require rapid patient arousal such as awake craniotomy or Stagnara wake-up test. There is no other model that is universally better than the others. Researches are encouraged to find the best fitting model for different occasions with an objective measure.

1. Introduction

The collective of anesthetic drugs share a common but unique property. Rapid onset and offset are required to ensure ease of titration to cope with surgical stimuli, provide good surgical condition, and prevent excessive and prolonged postoperative somnolence. Anesthesiologists practice rapid drug interactions every day. Since no single drug is capable of producing all the elements of a balanced anesthesia[1] alone, we rely on the combined effects of multiple drugs. Many anesthesiologists build their regimens based on years of experience. The ultimate goal is to produce the desired effect: loss of response to various stimuli or suppression of the autonomic reflexes to noxious stimuli while avoiding excessive cardiovascular or respiratory depression, and the concentration range can sometimes be therapeutically narrow. Cutting back months or years of training is possible with an existing guide, such as a drug model. One good example is the advent of target controlled infusions.[2]

The search for drug interaction began since more than 100 years ago.[3] Evolution of the pharmacodynamics analysis to response surface models (RSM) has been around for decades. Box and Wilson[4] came up with the first idea of optimization using RSM. The introduction into the field of anesthesia occurred in the 1990s,[5,6] and later blossomed with a number of works. The study of RSMs only considers the pharmacodynamics, the type of interaction most relevant to anesthesia. Investigations primarily focused on effects such as loss of response to verbal command,[7–13] reduced perception,[14,15] or loss of response to noxious stimuli (pain surrogates,[9–12,16,17] laryngeal mask insertion,[16] esophageal instrumentation,[18–20] laryngoscopy[8–11,16,21–23]), the appearance of unwanted side effects (cardiovascular depression,[23,24]

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respiratory depression[19,25]), predicting certain physiology-based monitor values[22] (Bispectral Index,[13,16,24–28] entropy,[8,16,28] composite variability index[28]) and even an index of well-being.[29] RSMs can be extended to simulate patient's recovery and arousal time.[20,21,30] They have important clinical implications and many are already incorporated into real-time displays.

2. Drug interactions

2.1. Isobolograms

To begin with, a basic understanding of drug interactions is required. Several methods exist. Isobolographic analysis was very common but is still used today.[31] It is not universally applicable since it illustrates only a single effect endpoint each time. However, by simply looking at the isobolograms, we can easily identify the type of drug interaction. Three types of drug interactions exist: (1) additive; (2) synergistic; or (3) infra-additive. A commonly used reference for additive drug effect is the Loewe additivity (simple form expressed in Eq. 1):

$$Interaction\ \ index = \frac{C_A}{C_{50A}} + \frac{C_B}{C_{50B}} \begin{cases} < 1 : synergy \\ = 1 : additivity \\ > 1 : infra - additive \end{cases} \quad [1]$$

C_A denotes the concentration of Drug A, and C_{50A} is the concentration required for Drug A to reach half maximal effect. The same applies for Drug B. Other references lines such as Bliss independence[32] or the Median-effect method[33] are available. Greco et al.[5] advocated the use of Loewe additivity as the universal reference line for RSM and until now, RSMs in the field of anesthesia still adopt it. Drug interactions are anticipated with drugs that hold different mechanisms of action. Most of the anesthetics bear more than one site of action and the magnitude of interaction becomes utterly important for anesthesiologists.

2.2. Concentration-effect curve

Second in line is the concentration-effect curve, or dose-response curve. Most anesthetic drugs can be described using the sigmoid E_{max} model, or the Hill model for a single drug (Eq. 2):

$$E = E_0 + \frac{(E_{max} - E_0)U^\gamma}{1 + U^\gamma} \quad (2)$$

E is the effect, or the probability of the investigating endpoint. E_0 is the effect while no drug is present, and E_{max} is the maximal effect attainable. When dealing with binomial data, e.g., response or no response, E_0 would be 0 and E_{max} would be 1. This will reduce the equation to a simpler form (Eq. 3):

$$E = \frac{U^\gamma}{1 + U^\gamma} \quad (3)$$

U is the normalized ratio of the drug concentration with respect to C_{50}. C_{50} is the concentration required to reach half maximal drug effect and γ is the steepness of the curve. Eq. (3) delineates the basis of all the RSMs to come, with different modifications done to U.

2.3. Response surface models

The reader must now aware of the limitations of the above analyses. Only a few effect endpoints can be analyzed each time and in order to characterize all the possible interactions, multiple separate studies are needed. The concept of the response surface is simple: to create a surface that encompass the complete set of isobolograms, concentration-effect curves and the shift of concentration-effect curve in the presence of another drug. As with isobolograms, the shape of the three-dimensional surface can give readers clues on how the drug combinations interact (Figure 1). We will look into some of the most commonly used models. The models can be generalized into two categories. First are the models that carry one interaction parameter, while the second group converts the interaction parameter into a mathematical function. The first group includes the Greco model[5,6] in both full and reduced forms, Machado model,[34] Plummer model,[35] and Carter model.[36] They assume the surface is smooth and interactions outside the scope of synergism, additivity, and infra-additivity are not adequately described. Those with an interaction function include Minto model,[7] Fidler model,[37] and Kong model.[38] These models, albeit with increased complexity, can graph virtually any type of drug interaction. Drug interactions are often assumed to interact equally throughout the entire concentration range, as with the single interaction models. In reality, different levels of synergism, additivity, or even antagonism may actually be at play interspersed throughout the surface. Isoboles from such response surface would appear zigzagged and nonuniform. Another model, with a more physiological approach, is the Boullion Hierarchy model. We will take a closer look at some of the most commonly cited models: Greco model, Minto model, and the Hierarchy model.

2.4. Full Greco model

The full Greco model:

$$E = \frac{E_{\max} \times \left[\frac{C_A}{C_{50A}} + \frac{C_B}{C_{50B}} + \alpha \times \left(\frac{C_A}{C_{50A}} \times \frac{C_B}{C_{50B}}\right)\right]^\gamma}{\left[\frac{C_A}{C_{50A}} + \frac{C_B}{C_{50B}} + \alpha \times \left(\frac{C_A}{C_{50A}} \times \frac{C_B}{C_{50B}}\right)\right]^\gamma + 1} \quad (4)$$

E is the model calculated effect. For binomial data, it is often referred to as the probability of reaching E_{max}, ranged from 0 to 1. E_{max} is the maximal achievable effect, often set to 1 (100% chance of loss of response to certain stimuli) and thus is often omitted during parameter estimation. C_A and C_B are the drug concentrations for Drug A and Drug B. C_{50}s are the concentrations of either Drug A or Drug B alone that will reach 50% maximal effect. The interaction parameter is α. Interaction is synergistic when $\alpha > 0$, infra-additive when $\alpha < 0$, and additive when α equals 0. As mentioned previously, RSMs are extensions with modification to U in the sigmoid *Emax* model (Eq. 3). In the Greco model, $U = [C_A/C_{50A} + C_B/C_{50B} + \alpha \times (C_A/C_{50A} \times C_B/C_{50B})]$. γ is the steepness of the surface. Bol et al.[39] also proposed a model that is very similar to the original Greco model but adjusted for categorical data, and looks identical to the Greco model presented here. The Greco model assumes that both Drug A and Drug B can exert a targeted effect alone. One downside to this is when applying opioids to a hypnosis model, it would infer that opioids can produce hypnosis alone. This would not be true since opioids are known to produce hypnosis unreliably.[40] The results the Greco model give when an opioid and a hypnotic agent are combined to attain hypnosis does give us some hints. Opioid C_{50} are often magnitudes higher than clinically used concentrations. As such, the reduced Greco model can be derived to solve the opioid C_{50} parameter problem.

2.5. Reduced Greco model

A C_{50} orders higher than C will end up with a very small and negligible ratio C/C_{50}. The effect of opioids (assume Drug B) alone can be dropped out. We then rewrite the full Greco model as: