British Journal of Anaesthesia **110** (5): 729–40 (2013)
Advance Access publication 6 February 2013 · doi:10.1093/bja/aes504

BJA

Remifentanil–sevoflurane interaction models of circulatory response to laryngoscopy and circulatory depression

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Editor's key points

- This study investigates the pharmacodynamic interaction of sevoflurane and remifentanil as described by the probabilities of no response to laryngoscopy and occurrence of circulatory depression using response surface modeling.
- Remifentanil reduces the amount of sevoflurane required to prevent circulatory response to laryngoscopy and occurrence of circulatory depression in a synergistic manner.
- The synergistic effect is bigger for the prevention of circulatory response to laryngoscopy than for the occurrence of circulatory depression.

Background. Sevoflurane and remifentanil are commonly combined to produce the hypnotic and analgesic effects required for clinical anaesthesia. Previous studies have characterized interactions between several i.v. drugs and inhalation agents. Aiming to extend this effort, we developed two new mathematical models to characterize the interactions manner and strength between sevoflurane and remifentanil.

Methods. Sixty-five adult Chinese patients undergoing elective operations received a target-controlled infusion of remifentanil (0–10 ng ml^{-1}) and inhaled sevoflurane (0.3–3.4 vol.%) at various randomly selected target concentration pairs. After reaching pseudo-steady-state drug levels, the circulatory response to laryngoscopy and any circulatory depression (a side-effect) were observed for each pair of target concentrations. The pharmacodynamic interactions between sevoflurane and remifentanil were investigated by response surface methodology. NONMEM software was used to estimate the model parameters.

Results. The response surface models revealed significant synergy between sevoflurane and remifentanil. When the target remifentanil concentration was increased from 0 to 10 ng ml^{-1}, the $C_{50,sevo}$ decreased from 2.6 to 0.38 vol.% for the prevention of circulatory response to laryngoscopy and from 3.53 to 1.46 vol.% for the induction of circulatory depression.

Conclusions. The new models can be used to characterize the interactions between these two drugs both qualitatively and quantitatively. Remifentanil significantly decreased the amount of sevoflurane required to eliminate patient response to clinical stimuli, thus reducing the likelihood of side-effects, specifically circulatory depression.

Keywords: anaesthetics volatile, sevoflurane; analgesics opioid, remifentanil; model, mathematical; model, pharmacodynamic

Accepted for publication: 20 October 2012

Modern anaesthetic drugs are often co-administered to efficiently create the desired anaesthetic state and to avoid the adverse effects. For example, the induction and maintenance of anaesthesia may involve a hypnotic to achieve and maintain loss of consciousness, and an opioid to blunt the response to noxious stimulation. One of the advantages of combining an opioid and a hypnotic over the use of single agent is the synergistic increase in a desired anaesthetic effect.[1] It is important to quantitatively understand the pharmacodynamic interactions of these agents to optimize drug dosing. Various quantitative approaches have been developed to describe drug interactions.[2–6]

The anaesthetic state consists of both a hypnotic and an analgesic component and therefore cannot be considered as a single universum of the drug effect. Somatic responses (e.g. movement) and circulatory responses [e.g. heart rate (HR) and mean arterial blood pressure (MABP)] may be used as perioperative pharmacodynamic endpoints. Various hypnotic–analgesic interaction models have been described.[7–19] Minto and colleagues[7] described a

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mathematical approach based on response surface methods for evaluating drug–drug interactions between several i.v. anaesthetic drugs. This method is an extension of previous models, such as the ones proposed by Greco and colleagues[8] and Short and colleagues.[10] Minto co-workers hypothesized that any given ratio of two drugs behaves as a 'new drug' with its own sigmoidal concentration–response relationship. The Minto model has been applied in various studies focusing on either multiple i.v. anaesthetic drugs[11] or opioid-volatile anaesthetic synergy.[18] By using the Minto model, they introduced terms of normalized concentrations of drug A, drug B, and the 'new drug' such as U_A, U_B, and U_{50}.[7 11 18]

Dahan and colleagues[19] made two modifications to the Minto model. First, drug interactions were taken into account by a function $I(Q)$ for which they chose a spline with two interpretable parameters. Secondly, they chose a general linear dose–response relationship for the model. The introduction of the $I(Q)$ function which was considered variation in the cubic-spline approach is reasonable; however, the response surface model established by Dahan and his colleagues is appropriate for continuous data at lower concentration pairs of alfentanil and sevoflurane.

Manyam and colleagues have analysed the interactions between sevoflurane and remifentanil by using logistic regression method. In our preliminary study, to retain the feature of quantitative analysis of interactions, the response surface methodology was here applied to investigate sevoflurane and remifentanil interactions. We preliminarily combined the Minto and Dahan models to create our response surface model in which each of the model parameters is given its physiological meaning and estimation takes place within a clinical reasonable range. Several effects such as loss of responsiveness, loss of response to painful stimuli, and other endpoints for sevoflurane and remifentanil combination have previously been reported. We choose the probabilities of no response to laryngoscopy and occurrence of circulatory depression (a side-effect) for patients as the pharmacodynamic effects.

Materials and methods

Patient selection and monitoring

Data were collected between 2007 and 2009. After approval from the local Medical Ethics Committee (Peking University, Beijing, China, IRB00001052-06078), 65 adult patients (30 men and 35 women, aged 20–50 years) were enrolled. All participants gave written informed consent. All enrolled patients had an American Society of Anesthesiologists physical status of I (ASA I), were non-smokers, deviated from their ideal body weight by no more than 25%, and were scheduled to undergo elective surgeries. Patients with a history of significant alcohol or drug abuse, a history of allergy to opioids, a history of cardiac, pulmonary, or renal disease, or a history of chronic drug use or medical illness known to alter the pharmacokinetics or pharmacodynamics of opioids or inhalation anaesthetics and patients with oesophageal reflux or hiatal hernia were excluded.

After 8 h of fasting, patients received an i.v. catheter for fluid and drug administration. In each patient, inspired and expired sevoflurane concentration, expired carbon dioxide concentration, pulse oximetry, and a five-lead electrocardiogram were measured. Non-invasive blood pressure was measured every 3 min (Anaesthesia Monitor, PHILIPS Intellivue MP60, Germany).

Study design and drug delivery

This was a prospective, open-label, randomized, parallel group study using a slices design as described by Short and colleagues to assess the drug–drug interactions.[11] Patients received no premedication. The primary drug in this study was sevoflurane. The concentration of sevoflurane was maintained at no more than two minimal alveolar concentration (the end-tidal concentration of volatile anaesthetic where there is a 50% probability of moving in response to a skin incision), ranging from 0.3 to 3.4 vol.%. Each patient was randomly assigned to one of 13 different sevoflurane concentration study groups (n=5 each). The assigned concentrations of sevoflurane were 0.3, 0.5, 0.7, 0.9, 1.1, 1.3, 1.5, 1.7, 2.0, 2.3, 2.6, 3.0, and 3.4 vol.% for the 13 groups, respectively.

The patients were studied in two phases, single drug and drug combination, the second phase taking place immediately after the first. In the first phase, the patients received sevoflurane alone at a fixed concentration. Thereafter, the second phase commenced with the administration of remifentanil. Remifentanil was administrated as target-controlled infusion (TCI) using a computer-controlled infusion device (Orchestra® Base Primea, Fresenius Vial, France). The pump was programmed with the remifentanil pharmacokinetic parameters reported by Minto and colleagues.[20] The TCI concentration of remifentanil for every patient was increased from 0 to 10 ng ml^{-1} in a stepwise ascending fashion (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 ng ml^{-1}), so that interactions could be characterized throughout the entire concentration range. Because of ethical issues, patient compliance and the fact that remifentanil caused sufficient sedation and analgesia, the concentration of remifentanil for TCI was no more than 10 ng ml^{-1}. If the patient had no pharmacodynamic effect at remifentanil concentration of 10 ng ml^{-1}, the probability was recorded as 0.

Anaesthesia was induced with sevoflurane and oxygen, first during spontaneous ventilation. Ventilation was assisted if the tidal volume was too small to provide adequate end-tidal sampling for the measurement of anaesthetic concentrations. The inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration at a constant value according to a pre-selected concentration. This concentration was maintained for at least 15 min. Sevoflurane was administered with oxygen (3 litre min^{-1}) and fresh air (3 litre min^{-1}) through a tight-fitting mask, using a standard breathing circuit and anaesthesia machine (Penlon Prima, Abingdon, UK).