Recommended dose of sufentanil during induction of general anesthesia to avoid coughing and drastic hemodynamic fluctuations in patients undergoing surgery

Ping Chen*, Ping Zeng* , Yuan Gong* and Xiang Long

Abstract

Background: Sufentanil-induced cough (SIC) is a common complication during anesthesia induction. We explored the recommended sufentanil dose that effectively avoids cough during general anesthesia using a clinical trial to analyze the effective dose (ED)50 and ED95 of sufentanil that avoids cough, hemodynamic fluctuations, and adverse reactions.

Methods: On the basis of sufentanil dose, 136 patients (ASA class I–II) were randomly allocated into the following groups: I, 0.1 μg/kg; II, 0.3 μg/kg; III, 0.5 μg/kg; or IV, 1.0 μg/kg. The number of coughing incidents, dizziness, panic, and chest tightness within 1 minute after sufentanil injection, and the patient’s heart rate (HR) and blood pressure 5 minutes after intubation were recorded and analyzed. Cough was assessed as follows: none, 0 times; mild, 1 to 2 times/minute; moderate, 3 to 4 times/minute; and severe, 5 times/minute or more.

Results: The ED50 and ED95 of cough incidence induced by intravenous sufentanil in patients during general anesthesia induction was 0.332 μg/kg and 1.423 μg/kg, respectively. The cough rate in group I was lower than the other groups. The incidence of dizziness, panic, chest tightness, hypertension, bradycardia, and tachycardia were not significantly different.

Conclusions: The recommended sufentanil dose during general anesthesia induction is 0.1 μg/kg.

*Chen Ping, Zeng Ping, and Gong Yuan are co-first authors of this paper.

Corresponding author:
Yuan Gong, The First College of Clinical Medical Science, China Three Gorges University; Department of Anesthesiology, Yichang Central People’s Hospital, Hubei 443000, China.
Email: gy-yc@163.com
Keywords
Sufentanil-induced cough, sufentanil, anesthesia induction, hemodynamics, recommended dose, clinical trial, ED50, ED95

Date received: 19 December 2019; accepted: 22 January 2021

Introduction
Sufentanil is a μ-opioid receptor agonist that has been widely used in anesthesia since it was synthesized in the mid-1970s, and its use has reflected the rapid increase in surgery worldwide. While providing safe anesthesia and a powerful analgesic effect, it is also associated with adverse reactions in patients such as sufentanil-induced cough (SIC) during induction of general anesthesia. Agarwal et al. showed that the cough rate of sufentanil and fentanyl was 15% and 32%, respectively. This cough is usually sudden and irritating, and it may lead to a sudden increase in blood pressure, tachycardia, and pneumothorax, and especially in the absence of strict fasting, the gastric contents could reflux into the mouth, causing life-threatening asphyxia via inhalation into the lungs. Thus, finding an effective way to suppress cough is of important clinical significance.

Opioids, which are nonbarbiturate intravenous anesthetic agents, have been studied since 1950. The μ-opioid receptor is encoded by the OPRM1 gene, which is the primary activity site of many endogenous opioid peptides, including β-endorphin and encephalin, and the major target of opioid analgesics. This is why opioids are so effective at relieving pain. Sufentanil is approximately five- to ten-times stronger than fentanyl in terms of analgesia. However, although it has a strong analgesic effect, sufentanil also has some side effects, such as SIC, which is a common phenomenon during the induction of anesthesia.

Although SIC can be prevented by adding dezocine or dexmedetomidine (Dex) before sufentanil injection, dezocine was reported to be associated with myocardial depression in the presence of enflurane, and Dex was reported to be associated with an increased incidence of bradycardia and hypotension. Moreover, some patients do not comply with the indication for analgesics or sedatives, which limits the use of dezocine.

Solanki et al. found that nonpharmacological methods such as acupressure and drug dilution also have positive effects on avoiding fentanyl-induced cough in female cancer patients. Liu et al. found that application via mechanical dropper can alleviate sufentanil-induced cough (2% vs. 21%, P<0.001). Using this nonpharmacological method, sufentanil was diluted using the original liquid that was present in the dropper, and the drug infusion rate was limited via a long fluid line. This led us to suggest that SIC may be related to the speed at which drugs enter the body, and that different speeds are associated with different blood concentrations. Thus, we hypothesized that different doses of sufentanil may be related to different incidences of SIC, which requires further study.

We studied the probability of coughing in female patients who were administered different doses of sufentanil in operating rooms during surgery induction. In this study, we also investigated the side effects including dizziness, panic, chest tightness,
and hemodynamic fluctuations, and these data were recorded by two anesthesia nurses after sufentanil induction. We evaluated the importance of the sufentanil dose on SIC and other adverse reactions. We hypothesized that patients’ cough reactions can be linked to the dose of sufentanil during induction. This was of great clinical significance for determining an effective way to suppress cough without relying on other interventions besides the correct dosage.

**Methods**

This study was approved by Chinese Clinical Trial Registry (ChiCTR1900025149). It was a single-center, randomized, and controlled parallel-group superiority clinical trial in which the data analyst was blinded. One hundred thirty-six eligible patients who were undergoing general anesthesia for surgery (women, age 22–65 years; body mass index [BMI], 19–24 kg/m²) were enrolled, and each participant provided written informed consent. The inclusion criteria were as follows: all general anesthesia patients who were American Society of Anesthesiologists (ASA) class I and II. Exclusion criteria were as follows: (1) allergic to sufentanil; (2) serious cardiac and cerebrovascular diseases; (3) respiratory diseases such as chronic bronchitis, asthma, and respiratory infections in the past 2 weeks; (4) long-term use of steroids or bronchodilators and angiotensin-converting enzyme inhibitor (ACEI) drugs; (5) neurological and mental disorders; or (6) liver or kidney dysfunction. After providing written informed consent, 136 eligible participants were randomly allocated on the day of surgery to one of four groups (I, II, III, or IV), which are described below, using a computer-generated randomization table.

**Clinical protocol**

All patients fasted for 8 hours, and there was no drug pretreatment before surgery. Electrocardiogram (ECG), pulse oximetry, and blood pressure monitors were routinely used, and inhaled oxygen (oxygen flow rate: 3 L/minute) was administered through a nasal catheter after the patient entered the operating room; this was then changed to a facemask with an oxygen flow rate of 6 L/minute before anesthesia induction. Sufentanil 5 μg/mL (250 μg sufentanil dissolved in 50 mL saline; Yichang Renfu Pharmaceutical Industry, Hubei, China) was used. The four groups of patients were injected with different doses of sufentanil over 3 s via the distal upper limb intravenous access, as follows: I, 0.1 μg/kg; II, 0.3 μg/kg; III, 0.5 μg/kg; and IV, 1.0 μg/kg. Patients’ cough frequency was observed within 1 minute by two anesthesia nurses. The severity of cough was graded on the basis of the frequency, as follows: none (score of 0), 0 times; mild (score of 1), 1 to 2 times/minute; moderate (score of 2), 3 to 4 times/minute; and severe (score of 3), 5 times/minute or more. After 1 minute of sufentanil injection, general anesthesia was continued with propofol 2 mg/kg and succinylcholine 1 mg/kg. Intubation was started 1 minute after succinylcholine injection, and we then fixed the tracheal tube and turned on the sevoflurane volatilize tank. During the induction period, the patients’ dizziness, chest tightness, panic, sleepiness, mean arterial pressure (MAP) fluctuation over 20%, bradycardia (heart rate [HR] ≤50 beats/minute), and tachycardia (HR ≥100 beats/minute) were also recorded.

The hemodynamic parameters of patients in the different groups were measured at the following four time points: 1 minute before anesthesia (T0), 1 minute after anesthesia (T1), immediately after intubation (T2), and 5 minutes after
intubation (T3). The hemodynamic parameters that were studied at baseline (1 minute before anesthesia) and at T0, T1, T2, and T3 included MAP fluctuation over 20%, bradycardia, and tachycardia.

Statistical analysis and endpoints

The study was conducted as a randomized, single-central, controlled pilot trial, and patients who were included in the study provided written informed consent. However, the patients were not aware of their group assignment. The primary outcome of the study was to record the number of different coughing events and their severity at different doses of sufentanil. The values 0, 1, 2, or 3 were assigned according to the degree of cough. Further endpoints were the mean effective dose (ED)50 and ED95 of cough incidence and the number of other adverse reactions. Statistics were performed using commercially available analysis software (GraphPad Prism 5 for Windows [GraphPad Software, San Diego, CA, USA, www.graphpad.com]; SPSS v.17.0 [SPSS Inc., Chicago, IL, USA]; and Excel [Microsoft Corp., Redmond, WA, USA]). Values of variables among the four groups were compared using a two-way analysis of variance (ANOVA). Categorical variables are presented as frequencies and continuous variables are summarized as the mean values with 95% confidence intervals (95% CIs). Enumeration data and rate were compared using the Chi-square test (2 × 2 table). The ED50 and ED95 for sufentanil were calculated using probit regression analysis. A Student’s t-test was also used in this study. The values of p were calculated between all possible pairs of the four groups. Significance was considered at p<0.05 based on a two-tailed probability.

A sample size of 76 patients was calculated on the basis of our previous study that showed a cough rate from 0.137 to 0.902, and using an α-error of 0.05 and 90% power. Because there were enough female surgical patients, we recruited 136 patients.

Results

Patient characteristics

There were 34 female patients in each of the study groups (I, II, III, and IV). The average age of the patients in the study groups was 43.18±10.28 years, 43.69±12.68 years, 43.21±11.54 years, and 42.26±11.98 years, respectively. The patients’ BMI ranged from 21.24 to 22.2 kg/m² and the MAP (1 minute after anesthesia) ranged from 86.03 to 91.59 mmHg in the four groups. There was no statistically significant difference (as shown using a t-test) between age, BMI, or MAP at baseline (Table 1).

Cough severity graded on the basis of its frequency

The ED50 and ED95 for cough that was induced by intravenous sufentanil in patients during general anesthesia induction were 0.332 μg/kg and 1.423 μg/kg, respectively (Figure 1). The incidence of SIC in group I was significantly lower compared with group III (p<0.05) and group IV (p<0.05). The incidence of SIC in group II was significantly lower compared with group III (p<0.05) and group IV (p<0.05) (Figure 2).

Mild cough in group I was significantly lower compared with groups II (p<0.05), III (p<0.05), and IV (p<0.05). Moderate cough in group I was significantly lower compared with group III (p<0.05). Severe cough in groups III (p<0.05) and IV (p<0.05) was significantly higher compared with group I and group II (Table 2).
The incidence of dizziness, panic, chest tightness, and sleepiness, which could seriously affect the patients’ postoperative comfort, was observed for 1 minute after intravenous sufentanil injection. There was no statistical difference between these indicators (Table 3).

Different doses of sufentanil and hemodynamic parameters

Hemodynamic parameters were evaluated at four time points (T0–T3), as described above. There were no significant differences at these time points. Additionally, MAP fluctuation over 20%, bradycardia, and tachycardia showed no significant differences except for the incidence of MAP fluctuation over 20%

Table 1. Patient characteristics and clinical groupings.

| Group | Female patients | Age (years) | ASA classification | BMI (kg/m²) | MAP (mmHg) |
|-------|-----------------|-------------|--------------------|-------------|------------|
| I     | 34              | 43.18±10.28 | 3                  | 22.06±2.11 | 87.57±12.49|
| II    | 34              | 43.68±12.68 | 2                  | 21.44±2.27 | 91.59±11.38|
| III   | 34              | 43.21±11.54 | 3                  | 22.21±1.90 | 89.02±10.24|
| IV    | 34              | 42.26±11.98 | 2                  | 21.24±2.17 | 86.03±12.89|

There was no significant difference in age, BMI, and MAP (1 minute after anesthesia) between the groups. Student’s t-test for age.

ASA, American Society of Anesthesiologists; BMI, body mass index; MAP, mean arterial pressure.

Figure 1. Dose–effect curve of the SIC incidence.
SIC, sufentanil-induced cough.

Figure 2. The incidence of SIC in each group. The incidence of SIC in group I was significantly lower compared with group III (p<0.05), and the incidence of SIC in group I was significantly lower compared with group IV (p<0.05); the incidence of SIC in group II was significantly lower compared with group III (p<0.05), and the incidence of SIC in group II was significantly lower compared with group IV (p<0.05).

SIC, sufentanil-induced cough.

The incidence of dizziness, panic, chest tightness, and sleepiness

The incidence of dizziness, panic, chest tightness, and sleepiness, which could seriously affect the patients’ postoperative comfort, was observed for 1 minute after intravenous sufentanil injection. There was no statistical difference between these indicators (Table 3).
fluctuation over 20% in group I compared with group III at T3 ($p<0.05$; Table 4).

Table 2. Cough severity at different sufentanil doses.

| Group | Sufentanil dose (μg/kg) | None | Mild | Moderate | Severe |
|-------|-------------------------|------|------|----------|--------|
| I     | 0.1                     | 0    | 1    | 0        | 2      |
| II    | 0.3                     | 0    | 6*   | 1        | 2      |
| III   | 0.5                     | 0    | 6**  | 5#       | 8&$    |
| IV    | 1.0                     | 0    | 8*** | 1        | 12&&$$ |

Mild cough in group I was significantly lower compared with groups II (*, $p<0.05$), III (**, $p<0.05$), and IV (***, $p<0.05$); moderate cough in group I was significantly lower compared with group III (*, $p<0.05$) and IV (**, $p<0.05$); severe cough in group I was significantly lower compared with groups III (#, $p<0.05$) and IV (&&, $p<0.05$); severe cough in group II was significantly lower compared with group III ($, $p<0.05$); severe cough in group II was significantly lower compared with group IV ($$, $p<0.05$).

Table 3. The incidence of dizziness, panic, chest tightness, and sleepiness.

| Group | Sufentanil dose (μg/kg) | None | Dizziness | Panic | Chest tightness | Sleepiness |
|-------|-------------------------|------|-----------|-------|----------------|------------|
| I     | 0.1                     | 10   | 24        | 0     | 0              | 0          |
| II    | 0.3                     | 12   | 20        | 0     | 0              | 2          |
| III   | 0.5                     | 6    | 28        | 1     | 0              | 0          |
| IV    | 1.0                     | 10   | 23        | 1     | 4              | 0          |

There was no statistical differences between these indicators.

Table 4. Hemodynamic evaluation.

| Group | Sufentanil dose (μg/kg) | MAP fluctuation over 20% | Bradycardia | Tachycardia |
|-------|-------------------------|---------------------------|-------------|-------------|
|       |                         | T1 | T2 | T3 | T1 | T2 | T3 | T1 | T2 | T3 |
| I     | 0.1                     | 6  | 10 | 9* | 1  | 1  | 7  | 0  | 0  | 0  |
| II    | 0.3                     | 4  | 6  | 5  | 2  | 4  | 2  | 3  | 0  | 0  |
| III   | 0.5                     | 2  | 6  | 2  | 2  | 5  | 1  | 0  | 0  | 0  |
| IV    | 1.0                     | 5  | 7  | 3  | 1  | 2  | 1  | 1  | 0  | 1  |

*The incidence of MAP fluctuation over 20% in group I was higher than that in group III at T3 ($p<0.05$).

MAP, mean arterial pressure.

Discussion

The incidence of cough that is associated with sufentanil induction remains a concern in clinical practice. Cough is a defensive airway reflex that protects the trachea from mechanical or chemical stimulation. Sufentanil, which functions as a potent opioid drug, can inhibit the pharyngeal reflex and stress response. Hoffmann et al.17 found that the observed arm-to-head time was 14.3±3.0 s between the injection of echo-contrast agent into the antecubital vein and the beginning of signal amplification in the carotid artery. Although SIC usually occurs within 1 minute after induction of anesthesia. Ricciardolo18 showed that citric acid release after sufentanil injection can stimulate
terminals of peripheral primary sensory neurons and cause a large release of the tachykinins substance P and neurokinin A, which then causes neurogenic inflammation. However, citric acid can initiate the cough reflex by stimulating C-fibers\textsuperscript{19} and histamine release\textsuperscript{20} in the airway, which also contribute to SIC. Researchers found that histamine release is related to the opioid dose or concentration, and histamine release increases when the drug dose increases or the infusion time decreases.\textsuperscript{21} This could explain the correlation between the sufentanil dose and the occurrence of SIC in our research.

The ED50 and ED95 for cough that were induced by intravenous sufentanil in patients during general anesthesia induction were 0.332 μg/kg and 1.423 μg/kg, respectively. These results suggest that sufentanil below 0.332 μg/kg would not cause half the incidence of cough in patients during induction of general anesthesia. Additionally, 0.1 μg/kg of sufentanil in group I showed less mild cough than groups II (0.3 μg/kg, \(p<0.05\)), III (0.5 μg/kg, \(p<0.05\)), and IV (1.0 μg/kg, \(p<0.05\)); less moderate cough than group III (0.5 μg/kg, \(p<0.05\)); and less severe cough than groups III (0.5 μg/kg, \(p<0.05\)) and IV (1.0 μg/kg, \(p<0.05\); Table 2). Moreover, a dose of 0.1 μg/kg was also associated with a lower incidence of SIC compared with groups II and III (Figure 2). These data indicated that the lower the dose of sufentanil, the milder is the resulting cough.

We also studied and analyzed the fluctuation of hemodynamics at different sufentanil doses at the same time points to determine an effective dose of sufentanil that did not cause cough or severe hemodynamic fluctuations. In our research, we compared and analyzed adverse reactions at different sufentanil doses, including cough, dizziness, panic, chest tightness, MAP fluctuation over 20%, bradycardia, and tachycardia. We found that there were no significant differences among the incidences of these side effects (dizziness, panic, and chest tightness), which may be because the incidence of these side effects was low and the sample size was not large enough. Additionally, there was no significant difference in hemodynamics (MAP fluctuation over 20%, bradycardia, and tachycardia), which is also a reason for us recommending 0.1 μg/kg of sufentanil during general anesthesia induction. The incidence of SIC was also low and there were no obvious hemodynamic fluctuations at this sufentanil dose. General anesthesia was then continued using propofol 2 mg/kg and succinylcholine 1 mg/kg, which was also a potential limitation for side effects in this study.

Sufentanil has a wide range of safe doses. For example, it can be used at a high dose of 30 μg/kg\textsuperscript{22} for coronary artery bypass grafting and at 0 μg/kg\textsuperscript{23} for opioid-free surgery cesarean section under general anesthesia. Additionally, 0.1 μg/kg was less than the ED50, and the incidence of cough showed varying degrees of severity but was the lowest at this dose. There was also no statistically significant difference in the hemodynamic fluctuations in group I (0.1 μg/kg) and group II (0.3 μg/kg). Moreover, 0.1 μg/kg sufentanil can reduce the use of opioid drugs, which is consistent with opioid-free anesthesia, and thereby reduce the incidence of postoperative nausea and vomiting, which are other side effects of opioids. Thus, we recommend the use of 0.1 μg/kg of sufentanil during general anesthesia induction.

The ED50 of SIC that was induced by intravenous sufentanil in patients during general anesthesia induction was 0.332 μg/kg (95% CI 0.332–1.423), and thus, the recommend dose of sufentanil is 0.1 μg/kg. This method avoids additional drugs, and it also increases the safety of anesthesia.
Declaration of conflicting interests
The authors declare that there is no conflict of interest.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research has been supported by the Wujieping foundation (320.6750.17567).

Author contributions
Y.G. contributed to the study design, data analysis, and article editing. P.Z. contributed to article writing. X.L. contributed to study design and article editing. P.C. contributed to the interpretation. P.Z., P.C., and Y.G. are the co-first authors of this paper. They had full access to all the data in the study and take responsibility for the integrity and accuracy of the data.

ORCID iD
Ping Zeng https://orcid.org/0000-0002-2719-1009

References
1. Maciejewski D. Sufentanil in anaesthesiology and intensive therapy. Anaesthesiol Intensive Ther 2013; 44: 35–41.
2. Deeks ED. Sufentanil 30 μg sublingual tablet: a review in acute pain. Clin Drug Investig 2019; 39: 411–418.
3. Agarwal A, Gautam S, Nath SS, et al. Comparison of the incidence and severity of cough induced by sufentanil and fentanyl: a prospective, randomised, double-blind study. Anaesthesia 2007; 62: 1230–1232.
4. Nguyen TTT, Higashi T, Kambayashi Y, et al. A longitudinal study of association between heavy metals and itchy eyes, coughing in chronic cough patients: related with non-immunoglobulin E mediated mechanism. Int J Environ Res Public Health 2016; 13: 110.
5. Stanley TH. The history and development of the fentanyl series. J Pain Symptom Manage 1992; 7: S3–S7.
6. Xu GH, Gao M, Sheng QY, et al. Opioid receptor A118G polymorphism does not affect the consumption of sufentanil and ropivacaine by patient-controlled epidural analgesia after cesarean section. Ther Drug Monit 2015; 37: 53–57.
7. Liu XS, Xu GH, Shen QY, et al. Dezocine prevents sufentanil-induced cough during general anesthesia induction: a randomized controlled trial. Pharmacol Rep 2015; 67: 52–55.
8. Sun S and Huang SQ. Effects of pretreatment with a small dose of dexmedetomidine on sufentanil-induced cough during anesthetic induction. J Anesth 2013; 27: 25–28.
9. Hall RI, Murphy MR, Szlam F, et al. Dezocine-MAC reduction and evidence for myocardial depression in the presence of enflurane. Anesth Analg 1987; 66: 1169–1174.
10. Constantin JM, Momon A, Mantz J, et al. Efficacy and safety of sedation with dexmedetomidine in critical care patients: a meta-analysis of randomized controlled trials. Anaesth Crit Care Pain Med 2016; 35: 7–15.
11. Solanki SL, Doctor JR, Kapila SJ, et al. Acupressure versus dilution of fentanyl to reduce incidence of fentanyl-induced cough in female cancer patients: a prospective randomized controlled study. Korean J Anesthesiol 2016; 69: 234–238.
12. Liu M, Li Z, Wang S, et al. Application via mechanical dropper alleviates sufentanil-induced cough: a prospective, randomized, single-blinded trial. Trials 2019; 20: 170.
13. O’Shaughnessy MA and Adams JE. Perioperative management of hypertension in hand surgery patients. J Hand Surg Am 2015; 40: 1684–1687.
14. Trappe HJ. ECG results: tips and tricks for the correct diagnosis: bradycardia and tachycardia rhythm disorders. Herz 2018; 43: 177–194.
15. Kurokochi N. Age-corrected intraoperative tachycardia correlates with postoperative electrocardiographic alterations. J Anesth 2001; 15: 11–16.
16. Chen X, Thee C, Gruenewald M, et al. Comparison of surgical stress index-guided analgesia with standard clinical practice during routine general anesthesia: a
pilot study. *Anesthesiology* 2009; 112: 1175–1183.

17. Hoffmann O, Weih M, Schreiber S, et al. Measurement of cerebral circulation time by contrast-enhanced Doppler sonography. *Cerebrovasc Dis* 2000; 10: 142–146.

18. Ricciardolo FL. Mechanisms of citric acid-induced bronchoconstriction. *Am J Med* 2001; 111: 18–24.

19. Tanaka M and Maruyama K. Mechanisms of capsaicin- and citric acid-induced cough reflexes in guinea pigs. *J Pharmacol Sci* 2005; 99: 77–82.

20. Bailey PL. Possible mechanism(s) of opioid-induced coughing. *Anesthesiology* 1999; 90: 335.

21. Baldo BA and Pham NH. Histamine-releasing and allergenic properties of opioid analgesic drugs: resolving the two. *Anaesth Intensive Care* 2012; 40: 216–235.

22. Philbin DM, Rosow CE, Schneider RC, et al. Fentanyl and sufentanil anesthesia revisited: how much is enough. *Anesthesiology* 1990; 73: 5–11.

23. Enten G, Shenouda MA, Samuels D, et al. A retrospective analysis of the safety and efficacy of opioid-free anesthesia versus opioid anesthesia for general cesarean section. *Cureus* 2019; 11: e5725.