

Target concentrations of remifentanyl with propofol to blunt coughing during intubation, cuff inflation, and tracheal suctioning

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Background. The target blood concentrations of propofol and remifentanyl, when used in combination, required to blunt the cough response to tracheal intubation, cuff inflation, and tracheal suctioning without neuromuscular blocking agents are not known.

Methods. In a randomized prospective study, 81 patients were enrolled to determine which of three target remifentanyl blood concentrations was required to blunt coughing during intubation, cuff inflation, and tracheal suctioning. Anaesthesia was achieved with propofol at a steady effect-site concentration of $3.5 \mu\text{g ml}^{-1}$. The target blood remifentanyl concentrations were 5, 10, or 15 ng ml^{-1} . These concentrations were maintained for 12 min before intubation.

Results. There was no cough response to intubation in more than 74% of patients and no significant difference in the incidence of coughing with intubation between the three groups. Significant difference in coughing, diminishing with increasing remifentanyl target concentration, was observed with cuff inflation ($P=0.04$) and tracheal suctioning ($P=0.007$). Bradycardia and hypotension was more frequent with the remifentanyl target concentration of 15 ng ml^{-1} . Tracheal suctioning resulted in more coughing than intubation ($P=0.01$) or cuff inflation ($P=0.004$).

Conclusion. Target remifentanyl blood concentrations of 5, 10, and 15 ng ml^{-1} associated with a $3.5 \mu\text{g ml}^{-1}$ propofol target blood concentration provided good intubating conditions and absence of cough about 75% of the time. Higher target remifentanyl concentrations were associated with less coughing during tracheal tube cuff inflation and tracheal suctioning.

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Remifentanyl has a rapid onset of action owing to a short blood–effect-site equilibration half-life and a rapid offset of action owing to its high clearance by non-specific blood and tissue esterases. The use, in combination, of propofol and remifentanyl results in a reduction in dose requirement of both agents.¹ The target blood concentration of remifentanyl, during propofol infusion, required to blunt the cough response during intubation and procedures such as neurosurgery, ear, and eye surgery where preventing coughing is recommended, is not known.^{2–4} Neuromuscular blocking agents effectively prevent coughing but may be associated with adverse effects such as prolonged paralysis, allergic reactions, and residual neuromuscular block.⁵ For these reasons, anaesthesia without

neuromuscular blocking agents may be deemed preferable, particularly for short surgical procedures.

Our objective was to determine the most appropriate target concentration of remifentanyl required to blunt the cough response, whilst maintaining a steady effect-site concentration of propofol, during three procedures that typically induce a cough reflex.

Methods

After local Medical Ethics Committee approval and written informed consent, 81 patients (47 female, 34 male) with American Society of Anesthesiologists (ASA) physical

status I, 18–60 yr, BMI <30, were invited and agreed to participate in the study. They were aware that propofol and remifentanil were drugs licensed for general anaesthesia, and only propofol but not remifentanil was approved for target-controlled infusion administration at the time of the study. All patients were to undergo maxillo-facial surgery, which required orotracheal intubation. Patients with known cardiac, pulmonary, or renal disease, drug misusers, those consuming more than 20 g alcohol daily, and patients with predicted difficult intubation were excluded. Participants received 1 mg kg⁻¹ of oral hydroxyzine 1 h before operation. Monitoring consisted of pulse oximetry, ECG, and non-invasive arterial pressure at 2 min intervals. All patients breathed oxygen 100% before induction of anaesthesia. In a double-blind allocation, patients were randomly allocated to receive one of three remifentanil target concentrations; 5 ng ml⁻¹ (Group A), 10 ng ml⁻¹ (Group B), and 15 ng ml⁻¹ (Group C) using PaMoTM software (Viviand, Marseilles, France).⁶ A syringe pump (Pilote C, Fresenius, Grenoble, France) was driven by a personal computer using the pharmacokinetic model described by Minto and colleagues.^{6,7} The target propofol concentration, using a Diprifusor[®] (Astra Zeneca Inc., UK) was 3.5 µg ml⁻¹. The target plasma concentration was maintained for 12 min before intubation to permit equilibration with the effect site.⁸ During this 12-min period, oxygen 100% was provided and breathing was assisted manually. End-tidal carbon dioxide was maintained between 4.0 and 5.3 kPa. An experienced anaesthetist attempted laryngoscopy and intubation, inflated 10 ml of air into the cuff of the tracheal tube over 10 s, and then passed a standardized suction catheter through the tracheal tube until it could pass no further or resistance was met. The vocal cords were noted to be open, moving, or closed. Intubation was attempted only when vocal cords were open and not moving. When the vocal cords were noted to be moving or closed, lidocaine 100 mg was administered, by aerosol, to the cords under direct vision. During intubation, cuff inflation, and passage of a tracheal suction catheter, the cough response was documented as absent or present. Intubation conditions were assessed to be good when there was no cough during passage of the tracheal tube. Heart rate and mean arterial pressure (MAP) were assessed before intubation and after passage of the suction catheter. Ephedrine (6 mg increments) was administered if the MAP fell below 55 mm Hg, and atropine (500 µg increments) if heart rate fell below 45 beats min⁻¹ for more than 60 s.

Statistics

The hypothesis of this study was that there would be a clinically meaningful difference in the incidence of coughing during intubation among the three groups according to remifentanil target blood concentrations. In order to detect a decrease in the cough response from 50 (the highest incidence) to 10% (the lowest incidence), 25 patients would be

required in each of the three groups with a power of 80% and a *P*-value of 0.05.

Descriptive statistics, means and SD, were calculated for continuous variables, and frequencies for qualitative variables. Comparative statistics used included, χ^2 or Fisher's tests to compare qualitative variables, and Student's *t*-test or non-parametric tests to compare quantitative variables. The level of significance was set at 0.05.

Results

Twenty-seven patients were included in each group with no significant difference between groups with respect to age and BMI. One patient from Group C was excluded for unexpected difficult intubation (inability to see epiglottis). No significant difference in vocal cord position was observed in the three groups. Cords were open and immobile in 20, 23, and 21 patients of Groups A (*n*=27), B (*n*=27), and C (*n*=26), respectively. Good conditions for intubation were observed in 19, 24, and 21 patients, respectively (*P*>0.05). A cough response was associated with cuff inflation in nine, four, and two patients of Groups A, B, and C, respectively (*P*=0.04). Tracheal suctioning induced a cough in 18, nine, and seven patients, respectively (*P*=0.007) (Fig. 1). Lidocaine was used in 16 patients with closed or moving vocal cords, including seven, four, and five in Groups A, B, and C, respectively. The incidence of coughing during intubation was not significantly different among the three groups irrespective of whether or not the patients who received lidocaine were included in the analysis. Of those who did not receive lidocaine, a cough reflex was associated with tracheal suctioning in 13 out of 20 patients (Group A), seven out of 24 patients (Group B), and four out of 21 patients (Group C) (*P*=0.007).

There was no significant difference among the three groups with respect to MAP and heart rate before and after the procedures. Ephedrine (6 mg) was used in one

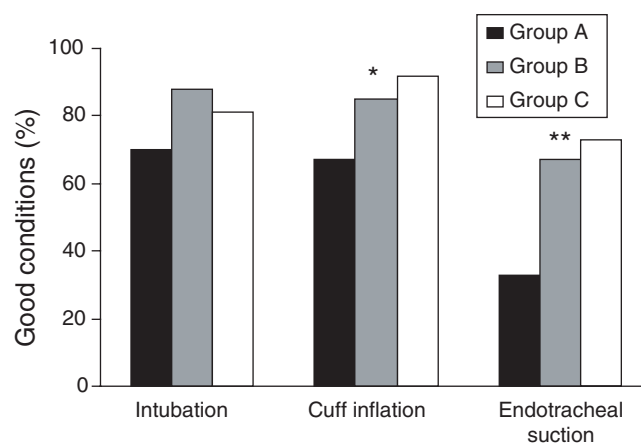


Fig 1 Incidence of good conditions (no or slight cough reflex during intubation, cuff inflation, and tracheal suction) for the three remifentanil target concentrations (5, 10, and 15 ng ml⁻¹). **P*=0.04; ***P*=0.007.

patient in each group. Atropine (500 mg) was administered in one patient of Group C. During the procedure, MAP (mm Hg) was lower in Group C (62 (9)) than in Groups A (74 (17)) and B (68 (8)) ($P=0.05$). Heart rate (beats min^{-1}) decreased significantly in Group C (55 (10)) compared with Groups A (66 (15)) and B (61 (10)) ($P=0.005$).

Tracheal suctioning resulted in more coughing than intubation (43 vs 21%, $P=0.01$) and cuff inflation (43 vs 19%, $P=0.004$). No significant difference in coughing was observed between intubation and cuff inflation. If we excluded the subgroup of patients requiring lidocaine spray, the absence of coughing was achieved in 62% of patients during tracheal suctioning compared with 87% during intubation ($P=0.005$) and 84% during cuff inflation ($P=0.01$). In the same subgroup of patients, who did not receive lidocaine, a significant association between the target blood concentration of remifentanyl and coughing during tracheal suctioning was shown ($P=0.007$). This association was not found for intubation and cuff inflation.

Discussion

Our results suggest that, with a target blood propofol concentration of $3.5 \mu\text{g ml}^{-1}$, all three remifentanyl target blood concentrations (5, 10, and 15 ng ml^{-1}) result in immobile open vocal cords in 75% of patients. This high rate of failure may be explained by the effect of opioids on vocal cords. A previous study, which demonstrated a 93% incidence of difficult ventilation after a 3 mg kg^{-1} dose of sufentanil, proposed closure of the glottis and supraglottic structures as the cause of difficult ventilation.⁹ Lidocaine spray onto the vocal cords allowed passage of a tracheal tube in the remaining patients.

The optimal target blood concentration of remifentanyl for blunting coughing during procedures such as intubation, cuff inflation, and tracheal suctioning appears to be at least 10 ng ml^{-1} . A target blood concentration of 5 ng ml^{-1} does not blunt the cough reflex in about 30% of patients during procedures but this was improved at 10 ng ml^{-1} . This is comparable with a previous study, which concluded that an effect-site concentration of remifentanyl 8 ng ml^{-1} with an effect-site concentration of propofol $3 \mu\text{g ml}^{-1}$ provides satisfactory conditions for intubation.¹⁰ The intubation in that study¹⁰ occurred 4 min after the induction of anaesthesia, whereas a 12-min period was chosen in the present study. This longer time interval was chosen to allow both drugs to reach a 'steady state' at the time of intubation.⁸ Rapid injection of propofol produces significantly higher peak arterial propofol concentrations.¹¹ The different rate of drug injection may explain the higher concentrations required in the present study to achieve a similar rate of good conditions during intubation. Moreover, a target of $3.5 \mu\text{g ml}^{-1}$ is in agreement with the reported propofol concentration at which consciousness was lost in 50% of the patients, $3.4 \mu\text{g ml}^{-1}$.¹² Although a computer simulation suggested that the optimal blood propofol and remifentanyl

concentrations with respect to satisfactory intraoperative anaesthetic conditions were $2.0 \mu\text{g ml}^{-1}$ and 6.3 ng ml^{-1} , respectively, such concentrations, in our clinical experience, do not prevent a cough response to powerful stimuli like intubation and tracheal suctioning.¹

Remifentanyl has been recommended for neurosurgery,² and is widely used for eye and ear surgery.⁴ During such delicate surgery, the inhibition of coughing is recommended to avoid surgical complications.⁴ Tracheal suctioning, a powerful stimulus for coughing, may occasionally be indicated during anaesthesia. When coughing is stimulated during eye surgery, complications such as suprachoroidal haemorrhage may occur.¹³ Our study suggests that tracheal suctioning is a stronger cough-inducing stimulus than intubation or cuff inflation, as remifentanyl 5 ng ml^{-1} was associated with coughing in 66% of patients, whereas there was no cough reflex with tracheal suctioning in 73% of patients with a 15 ng ml^{-1} target blood concentration. Such target concentrations induce hypotension and bradycardia. This is consistent with the finding that opioids blunt somatic and autonomic responses to tracheal stimulation in a concentration-dependent manner.¹⁴

The present study has several limitations. The use of lidocaine in patients with closed or moving vocal cords could have resulted in a decreased cough reflex. However, the results in this study were the same for all end points whether or not the patients who received lidocaine were included in the analysis. The target concentrations are based on mathematical pharmacokinetic models, and actual plasma concentrations were not measured. We did not assess the vocal cord damage and postoperative hoarseness. A recent study¹⁵ showed that the quality of tracheal intubation contributes to laryngeal morbidity; good intubating conditions are less frequently associated with postoperative hoarseness and vocal cord damage. Adding atracurium to a propofol–fentanyl induction regimen significantly improved the quality of tracheal intubation and decreased postoperative hoarseness and vocal cord damage.¹⁵ Our results suggest that induction without neuromuscular blocking agents may not provide optimal conditions for intubation in a large proportion of patients, even with the highest target remifentanyl concentration (15 ng ml^{-1}).

In conclusion, a suitable target remifentanyl concentration to decrease the likelihood of a cough reflex during intubation may be at least 10 ng ml^{-1} , with a propofol target concentration of $3.5 \mu\text{g ml}^{-1}$. This combination is associated with coughing in ~30% of patients during tracheal suctioning. The addition of a neuromuscular blocking agent, or possibly a higher target propofol concentration, is advisable when the cough reflex could induce surgical complications.

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Appendix

For clinicians who do not have access to TCI software for remifentanil, target remifentanil concentrations may be achieved as follows.

A remifentanil infusion of $0.2 \mu\text{g kg}^{-1} \text{min}^{-1}$ during 12 min in 70 kg male adults typically results in blood concentrations of 5 ng ml^{-1} , and a $0.6 \mu\text{g kg}^{-1} \text{min}^{-1}$ infusion typically results in blood concentrations 15 ng ml^{-1} of remifentanil. A blood concentration of 15 ng ml^{-1} may be achieved in 4 min with a $1.5 \mu\text{g kg}^{-1}$ bolus for 1 min followed by $1 \mu\text{g kg}^{-1} \text{min}^{-1}$ infusion until the fourth minute.

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