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Targeting smooth emergence: the effect site concentration of remifentanil for preventing cough during emergence during propofol–remifentanil anaesthesia for thyroid surgery

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Background. The administration of short-acting opioids can be a reliable and safe method to prevent coughing during emergence from anaesthesia but the proper dose or effect site concentration of remifentanil for this purpose has not been reported. We therefore investigated the effect site concentration (Ce) of remifentanil for preventing cough during emergence from anaesthesia with propofol–remifentanil target-controlled infusion.

Methods. Twenty-three ASA I–II grade female patients, aged 23–66 yr undergoing elective thyroidectomy were enrolled in this study. EC_{50} and EC_{95} of remifentanil for preventing cough were determined using Dixon's up-and-down method and probit analysis. Propofol effect site concentration at extubation, mean arterial pressure, and heart rate (HR) were compared in patients with smooth emergence and without smooth emergence.

Results. Three out of 11 patients with remifentanil Ce of 1.5 ng ml^{-1} and all seven patients with Ce of 2.0 ng ml^{-1} did not cough during emergence; the EC_{50} of remifentanil that suppressed coughing was 1.46 ng ml^{-1} by Dixon's up-and-down method, and EC_{95} was 2.14 ng ml^{-1} by probit analysis. Effect site concentration of propofol at awakening was similar in patients with a smooth emergence and those without smooth emergence, but HR and arterial pressure were higher in those who coughed during emergence. Clinically significant hypoventilation was not seen in any patient.

Conclusions. We found that the EC_{95} of effect site concentration of remifentanil to suppress coughing at emergence from anaesthesia was 2.14 ng ml^{-1}. Maintaining an established Ce of remifentanil is a reliable method of abolishing cough and thereby targeting smooth emergence from anaesthesia.

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Various techniques have been proposed as ways of reducing coughing during emergence including deep extubation,[1] the administration of dexmedotomidine,[2] i.v. or topical lidocaine,[3 4] or lidocaine applied inside the tracheal tube cuff.[5] Each method has its limitations.

Of the techniques proposed, the administration of short-acting opioids is promising as it can be maintained during emergence and the effects are short-lived. Although there are data regarding the beneficial effect of opioids for suppressing cough during emergence,[6–8] no study has presented the proper dose or effect site concentration of remifentanil for preventing cough during emergence. We therefore hypothesized that maintaining an optimum effect site concentration of remifentanil by target-controlled infusion (TCI) could safely and effectively suppress cough during emergence.

The purpose of this study was to evaluate the EC_{50} and EC_{95} of remifentanil in effect-site TCI for preventing cough in total i.v. anaesthesia (TIVA) with propofol and remifentanil.

Methods

After approval from the institutional ethics committee, written informed consent was obtained from 23 patients (all females, ASA I–II, aged 23–66 yr undergoing general anaesthesia for elective thyroidectomy compared with thyroid neoplasm) who were enrolled in this study. Exclusion criteria were signs of difficult airway, increased risk of perioperative aspiration, history of chronic respiratory disease such as chronic obstructive pulmonary disease or asthma, recent respiratory tract infection, current smokers, and significant cardiovascular, hepatic, or renal disease.

All patients were premedicated with midazolam 0.05 mg kg^{-1} i.m. 30 min before and glycopyrrolate 0.5 mg i.v. just before induction of anaesthesia. ECG, Sp_{O_2}, E'_{CO_2}, non-invasive blood pressure (NIBP), and nasopharyngeal temperature were monitored at 1–5 min intervals.

For effect-site TCI of propofol and remifentanil, a commercial TCI pump (Orchestra® Base Primea, Fresenius Vial, France) was used, and the pumps were operated by Schnider and colleagues'[9] and Minto and colleagues'[10] models for propofol and remifentanil, respectively; our protocol was based on targeted effect site concentration rather than measured plasma concentration from direct sampling.

Anaesthesia was induced using targeted effect-site TCI remifentanil and propofol. After the patient was unable to respond to verbal stimulus, rocuronium 1 mg kg^{-1} was given i.v. Tracheal intubation was performed in all patients using a 7.0 mm [internal diameter (I.D.)] reinforced endotracheal tube and cuff pressure was maintained at 20–25 mm Hg throughout the procedure. Mechanical ventilation was maintained with a tidal volume of 8 ml kg^{-1}, and ventilatory frequency was adjusted to maintain E'_{CO_2} at 4.6–5.2 kPa. Temperature was maintained at 36–37°C. The effect-site TCI of propofol and remifentanil was titrated to maintain blood pressure and heart rate (HR) within 10–20% of pre-induction values, and was kept within the range of 2.5–4 μg ml^{-1} and 2–5 ng ml^{-1}, respectively.

Two practitioners were involved during the emergence phase. The first anaesthetist controlled the TCI pump and recorded the effect site concentration of propofol and remifentanil, the E'_{CO_2} of the patient during extubation, and arterial pressure and HR during emergence. The second anaesthetist, who was blinded to the patients' effect site concentration of remifentanil and propofol, was instructed to extubate the patient, and record the number of coughs and other adverse events during the emergence phase.

During skin suture, effect-site TCI of remifentanil was titrated to a predetermined concentration (initial concentration being 1.5 ng ml^{-1} for the first patient). The predetermined concentration was maintained throughout emergence until extubation for at least 15 min, so that effect site concentration and plasma concentration can be expected to be stable. After completion of suture, ketorolac 0.5 mg kg^{-1} (maximum dose 30 mg) was given for pain control and glycopyrrolate 0.004 mg kg^{-1} with neostigmine 0.02 mg kg^{-1} was given for reversal of neuromuscular block, which was confirmed as more than 90% response of train-of-four (TOF). Propofol was then titrated to 1.5 μg ml^{-1} effect-site TCI. After the surgical dressings were applied, propofol infusion was discontinued. Mechanical ventilation was then converted to manual ventilation and PE'_{CO_2} was maintained at 4.9–6.3 kPa. The patient was not disturbed, other than continuous verbal requests to open their eyes, and all other stimulus was avoided. When the patients opened their eyes, deep breathing was encouraged, and after spontaneous respiration and adequate tidal volume and ventilatory frequency were confirmed, the trachea was extubated. Immediately after extubation, oxygen was supplemented via a facemask for 5 min. Hypoventilation, defined as RR<8 bpm or a Sp_{O_2} below 95% despite oxygen supplement, and other respiratory complications were recorded. HR and mean arterial pressure (MAP) during emergence were recorded at three points—at the point when remifentanil TCI reached the predetermined concentration, before, and after immediate extubation.

Cough was defined as a strong and sudden contraction of the abdomen. If the patient did not cough during emergence, the extubation was defined as a smooth emergence, and the predetermined concentration for the subsequent patient was decreased by 0.5 ng ml^{-1}. Similarly, if the patient coughed anytime around extubation, it was considered a failed smooth emergence and the predetermined concentration was increased by 0.5 ng ml^{-1} for the next patient. After extubation, patients received 100% oxygen by facemask and were observed for 5 min, and then transferred to the post-anaesthetic care unit (PACU). In the PACU, the post-anaesthetic recovery scores[11] were recorded, and fentanyl 1 μg kg^{-1} was given when pain scores exceeded 5 by visual analogue scales.

Patient data are presented as median and range or mean (SD). The Dixon's up-and-down method needs at least six pairs of smooth emergence–failed smooth emergence for statistical analysis,[12] and 23 patients were collected on the basis of Dixon's method. EC_{50} was defined as the mean of the cross-over concentrations. The smooth emergence–failed smooth emergence sequences were also analysed by the probit test, which enabled us to derive the remifentanil effect site concentration for cough suppression, with 95% confidence limits of the mean. Comparison between smooth emergence patients and failed smooth emergence patient for propofol effect site concentration at extubation, PE'_{CO_2} at extubation, recovery score at admission, duration of PACU stay was performed using Fisher's exact test of χ^2 analysis. MAP and HR during emergence between smooth emergence patients and failed smooth emergence patients were analysed by RMANOVA. SPSS package (version 13.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. $P<0.05$ was considered to be statistically significant.

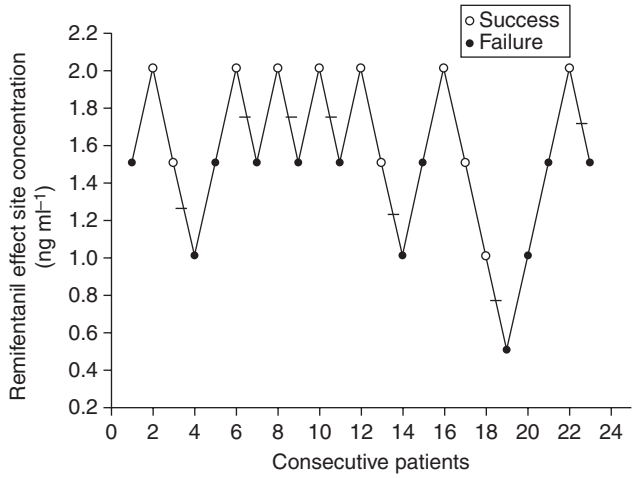

Fig 1 Data of consecutive smooth emergence and failed smooth emergence over predetermined concentration (PRC) of remifentanil (with initial PRC being 1.5 ng ml^{-1} for the first patient). Seven pairs of smooth emergence–failed smooth emergence sequences were received for statistical analysis with the Dixon's up-and-down method. The effect site concentration of remifentanil for abolishing emergence cough in 50% of patients was 1.46 (0.39) ng ml^{-1}.

Results

We enrolled 23 female patients of median age 57 (range 23–66) yr and weight 55 (44–70) kg. Anaesthesia lasted a median 147 (range 94–255) min. The sequences of smooth emergence and failed smooth emergence are shown in Figure 1. Smooth emergence was observed in three out of 11 patients with effect-site concentration (Ce) of remifentanil 1.5 ng ml^{-1} and seven out of seven patients with Ce 2.0 ng ml^{-1}. By Dixon's method, the EC_{50} of remifentanil for emergence without cough was 1.46 (SD 0.39) ng ml^{-1}. A logistic regression curve of the probability of no coughing showed that the 50% effective concentration for abolishing cough during emergence was 1.53 ng ml^{-1} (95% CI 1.18–1.81 ng ml^{-1}), and the 95% effective concentration was 2.14 ng ml^{-1} (95% CI 1.89–3.57 ng ml^{-1}). Significant respiratory complications including hypoventilation did not occur in any of the patients. Emergence profile between smooth emergence patients and failed smooth emergence patients are compared in Table 1. Both groups were comparable with awakening effect site concentration of propofol, recovery score at admission, and duration of stay in the PACU.

Haemodynamic values of smooth emergence and failed smooth emergence patients are compared in Table 2. MAP and HR were statistically higher in failed smooth emergence patients who had coughed during emergence (P=0.002 and P=0.038, respectively).

Table 1 Comparison between smooth emergence patients and failed smooth emergence patients. Values are expressed as mean (range), mean (SD) or number. Ce, effect site concentration; F'_{CO_2}, end-tidal carbondioxide tensions; PAR, post-anaesthesia room; PACU, post-anaesthesia care unit. *P<0.05 between groups.

	Smooth emergence	Failed smooth emergence
Number of patients	11	12
Age	43.8 (23–66)	46.5 (23–66)
Number of coughs	0	3 (3–6)
Propofol Ce at extubation (μg ml^{-1})	1.1 (0.7–1.5)	1.0 (0.8–1.7)
Remifentanil Ce at extubation (ng ml^{-1})	2.0 (1.0–2.0)*	1.5 (0.5–1.5)
$P_{E'CO_2}$ at extubation (kPa)	5.5 (4.9–6.0)	5.3 (4.9–6.3)
PAR score at admission	9.1 (0.6)	8.9 (0.4)
Duration of PACU stay (min)	41.3 (12.2)	39.8 (7.1)

Table 2 Comparison of haemodynamic profiles during extubation between smooth emergence patients and failed smooth emergence patients. Values are expressed as mean (SD). T1, time when operation was finished and effect site concentration of remifentanil was maintained at predetermined concentration; T2, immediately before extubation; T3, immediately after extubation; MAP, mean arterial pressure; HR, heart rate. *P=0.002; †P=0.038

		Smooth emergence patients	Failed smooth emergence patients*,†
MAP (mm Hg)	T1	82.6 (12.0)	89.8 (13.4)
	T2	87.7 (10.1)	95.8 (11.3)
	T3	88.4 (8.4)	98.6 (9.7)
HR (beats min^{-1})	T1	61.7 (9.2)	66.1 (11.8)
	T2	65.7 (9.9)	74.2 (11.5)
	T3	66.7 (7.3)	75.7 (10.5)

Discussion

In this study we used propofol–remifentanil TIVA with the goal of finding the effect site concentration of remifentanil for smooth emergence. Our results show that the EC_{95} of remifentanil that abolishes cough during emergence is 2.14 ng ml^{-1}. Several studies have demonstrated the use of opioids for preventing cough. During propofol anaesthesia, fentanyl modified airway reflexes and decreased the incidence of cough in a dose-related manner[6] and during isoflurane anaesthesia, fentanyl 2 μg kg^{-1} [7] or alfentanil 15 μg kg^{-1} [8] effectively attenuated cough and cardiovascular stimulation during emergence. However, a bolus dose of remifentanil 1 mg kg^{-1} attenuated the increase in blood pressure and HR during emergence, but failed to demonstrate a decrease in the incidence of cough.[13] The antitussive effect of opioids is primarily central,[14] and maintaining and predicting a certain plasma or effect site concentration by a single bolus administration is clinically difficult and unreliable, and could be the reason why a single bolus dose of remifentanil failed to suppress cough during emergence. We hypothesized that a method which targeted and maintained the effect site concentration of opioid could be more reliable.

The effect site TCI of remifentanil is desirable in this setting because the context-sensitive half-life of remifentanil is short and infusion with a TCI pump can predict and maintain the target concentration safely during emergence. It was previously reported that TIVA with propofol–remifentanil reduce the incidence of cough during emergence compared with balanced anaesthesia with fentanyl-sevoflurane-N_2O,[15] but the effect site

concentration of any drugs for preventing cough during propofol–remifentanil TIVA has not been determined. Our attention was on the antitussive effect of remifentanil, and therefore designed this study to demonstrate the remifentanil effect site concentration for preventing cough during emergence in propofol–remifentanil TIVA. None of the patients suffered hypoventilation, and all were discharged from the PACU without any adverse events. The main reason for delayed discharge was because of administration of fentanyl 1 $\mu g\ kg^{-1}$ for postoperative pain control, which occurred in six patients in our study. The rapid cessation of remifentanil's analgesic effect has shown to increase analgesic drug requirements during the postoperative period,[16] and although our study was limited to thyroid operations, more painful operations are expected to require more analgesics during recovery and thus may increase the incidence of other side effects. Further studies will be required to demonstrate the application of our result for other types of surgery.

A few limitations in our study should be kept in mind. First, pharmacodynamic and pharmacokinetic difference exists between women and men during propofol anaesthesia, and emergence is more rapid in female patients.[17] The study population is limited to females in this study, and therefore should be considered when interpreting the data. Secondly, because older patients are more sensitive to opioids, age variation should also be considered. Since our patients ranged from 23 to 66 yr, some patient characteristics should be considered. The mean age of smooth emergence patients was 43.8 yr and that of failed smooth emergence was 46.5 yr. It should also be stated that the oldest patient, aged 66 yr, received an infusion of remifentanil with a predetermined concentration of 1.5, and did not cough during emergence. We therefore believe that age variation of remifentanil sensitivity did not interfere with our data, although when the calculated EC_{95} value is clinically applied to older patients than our study groups, a lower concentration could be required for cough suppression. Thirdly, the presented concentration is a predicted value that is calculated from a pharmacokinetic model, and not real measurement from patients' plasma sampling. This predicted that effect site concentration is estimated from Minto's pharmacokinetic model, however it is known that remifentanil can be administered by this method with acceptable bias and inaccuracy in clinical situations.[18]

In conclusion, the EC_{95} of effect site concentration of remifentanil that suppresses coughing is 2.14 ng ml^{-1}. Maintaining this Ce of remifentanil during emergence is a safe and reliable method of abolishing cough and thereby targeting smooth emergence.

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References

1 Neelakanta G, Miller J. Minimum alveolar concentration of isoflurane for tracheal extubation in deeply anesthetized children. *Anesthesiology* 1994; **80**: 811–3

2 Guler G, Akin A, Tosun Z, Eskitascoglu E, Mizrak A, Boyaci A. Single-dose dexmedetomidine attenuates airway and circulatory reflexes during extubation. *Acta Anaesthesiol Scand* 2005; **49**: 1088–91

3 Saghaei M, Reisinejad A, Soltani H. Prophylactic versus therapeutic administration of intravenous lidocaine for suppression of post-extubation cough following cataract surgery: a randomized double blind placebo controlled clinical trial. *Acta Anaesthesiol Taiwan* 2005; **43**: 205–9

4 Minogue SC, Ralph J, Lampa MJ. Laryngotracheal topicalization with lidocaine before intubation decreases the incidence of coughing on emergence from general anaesthesia. *Anesth Analg* 2004; **99**: 1253–7

5 Fagan C, Frizelle HP, Laffey J, Hannon V, Carey M. The effects of intracuff lidocaine on endotracheal-tube-induced emergence phenomena after general anaesthesia. *Anesth Analg* 2000; **91**: 201–5

6 Tagaito Y, Isono S, Nishino T. Upper airway reflexes during a combination of propofol and fentanyl anaesthesia. *Anesthesiology* 1998; **88**: 1459–66

7 Nishina K, Mikawa K, Maekawa N, Obara H. Fentanyl attenuates cardiovascular responses to tracheal extubation. *Acta Anaesthesiol Scand* 1995; **39**: 85–9

8 Mendel P, Fredman B, White PF. Alfentanil suppresses coughing and agitation during emergence from isoflurane anaesthesia. *J Clin Anesth* 1995; **7**: 114–8

9 Schnider TW, Minto CF, Shafer SL, *et al*. The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999; **90**: 1502–16

10 Minto CF, Schnider TW, Egan TD, *et al*. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* 1997; **86**: 10–23

11 Aldrete JA, Kroulik D. A postanaesthetic recovery score. *Anesth Analg* 1970; **49**: 924–34

12 Dixon WJ. Staircase bioassay: the up-and-down method. *Neurosci Biobehav Rev* 1991; **15**: 47–50

13 Shajar MA, Thompson JP, Hall AP, Leslie NA, Fox AJ. Effect of a remifentanil bolus dose on the cardiovascular response to emergence from anaesthesia and tracheal extubation. *Br J Anaesth* 1999; **83**: 654–6

14 Kamei J. Role of opioidergic and serotonergic mechanisms in cough and antitussives. *Pulmonary Pharmacol* 1996; **9**: 349–56

15 Hohlrieder M, Tiefenthaler W, Klaus H, *et al*. Effect of total intravenous anaesthesia and balanced anaesthesia on the frequency of coughing during emergence from the anaesthesia. *Br J Anaesth* 2007; **99**: 587–91

16 Coles JP, Leary TS, Monteiro JN, *et al*. Propofol anaesthesia for craniotomy: a double-blind comparison of remifentanil, alfentanil, and fentanyl. *J Neurosurg Anesthesiol* 2000; **12**: 15–20

17 Hoymork SC, Raeder J. Why do women wake up faster than men from propofol anaesthesia? *Br J Anaesth* 2005; **95**: 627–33

18 Mertens MJ, Engbers FH, Burm AG, Vuyk J. Predictive performance of computer-controlled infusion of remifentanil during propofol/remifentanil anaesthesia. *Br J Anaesth* 2003; **90**: 132–41