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ORIGINAL ARTICLE

EC_{50} of remifentanil to prevent withdrawal movement associated with injection of rocuronium

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Abstract
Purpose Various strategies have been studied to reduce the discomfort of rocuronium injection. This study was designed to determine the effect-site target concentration (Ce) of remifentanil at which there was a 50% probability of preventing movement from pain in response to the injection of rocuronium (EC_{50}).
Methods Anesthesia was induced with a propofol target-controlled infusion (TCI, Marsh model) and remifentanil TCI (Minto model). Effect-site target concentration of propofol was 3 μg/ml. Ce of remifentanil for the first patient started at 2.0 ng/ml. Ce of remifentanil for each subsequent patient was determined by the response of the previous patient by the Dixon up-and-down method with an interval of 0.5 ng/ml. After both drugs reached target concentration, rocuronium 0.8 mg/kg was administered, and the pain response was observed.
Results The EC_{50} of remifentanil was 1.5 ± 0.45 ng/ml by Dixon's up-and-down method. From probit analysis, the EC_{50} of remifentanil was 1.37 ng/ml (95% confidence limits, 0.69–2.15 ng/ml), and the EC_{95} was 3.19 ng/ml (95% confidence limits, 2.31–11.24 ng/ml).
Conclusion The EC_{50} of remifentanil to blunt the withdrawal responses to rocuronium injection was 1.37–1.5 ng/ml during 3 μg/ml propofol TCI anesthesia.

Keywords EC_{50} · Remifentanil · Rocuronium · Up-and-down method

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Introduction

Pain on injection is one of the main disadvantages of rocuronium during induction of anesthesia. When rocuronium was administered in subparalyzing doses, 50–100% of patients reported a severe, burning pain [1]. Pain on rocuronium injection is a common side effect, reported in 50–80% of the patients [1, 2]. Even after loss of consciousness during induction of anesthesia, intravenous rocuronium can still elicit withdrawal movements such as withdrawal of the injected hand and arm or a generalized movement of the body [1]. These withdrawal movements may cause dislocation or displacement of the IV catheter, causing difficulty in administrating additional drugs and subsequent risk of cardiovascular activation.

Several reports using different opioids have been published to prevent withdrawal reactions during rocuronium injection in adults with varying results [3–5]. Recently, there are a few reports of preventing rocuronium-induced withdrawal movement with a remifentanil injection [6]. Remifentanil 1 μg/kg without the venous occlusion technique was reported to reduce the incidence of rocuronium-induced withdrawal movement in children [7]. Remifentanil is a synthetic and esterase-metabolized opioid with a rapid onset, an ultrashort duration of action, and a stable, short context-sensitive half-time compared with other opioids [8]. Because of these advantages of remifentanil, it has often been used as a target-controlled infusion (TCI) combined with propofol for induction or maintenance of anesthesia. Despite the benefits of remifentanil, many have been reluctant to use it as a bolus injection because of side effects such as muscle rigidity, bradycardia, and hypotension.

There are no studies about the effect-site target concentration (Ce) of remifentanil at which there is a 50% probability of preventing rocuronium injection pain movement

(EC_{50}). This study was designed to evaluate the EC_{50} of remifentanil to prevent the withdrawal response associated with a rocuronium injection in an adult population.

Materials and methods

The study enrolled 45 male and female patients of ASA class I or II, aged 16–71 years. Written informed consent was obtained from all patients, and the study was approved by Hospital Ethics Committees. All patients received diazepam 0.05 and 0.2 mg/kg glycopyrrolate intramuscularly 1 h before induction of anesthesia, and the intravenous line was kept at the forearm with a 21-gauge IV cannula for hydration and drug infusion.

We excluded all patients with difficult venous access, those requiring rapid sequence, those with an allergy to any of the anesthetic medications or a history of major neurological or psychiatric problems, and those unable to provide informed consent. Patients were informed that they would be receiving a drug at the start of the anesthetic that may or may not cause pain. When the patients arrived at the operating rooms, electrocardiogram, noninvasive blood pressure, and SpO_2 were monitored. All patients were preoxygenated for 5 min before induction of anesthesia.

All patients received anesthesia with a combination of propofol and remifentanil on a concomitant use of running fluid. Propofol was administered via a target-controlled infusion system based on a Marsh pharmacokinetic model using a TCI device (Orchestra; Fresenius-Vial, Brezins, France). The dose of propofol was an effect-site target-controlled infusion (TCI) of 3 μg/ml. Because the median effective concentration of remifentanil in the presence of propofol was not known, the sample size was calculated using the up-and-down experimental design described by Dixon [9, 10].

Remifentanil was administered based on a Minto pharmacokinetic model [11]. The target effect-site remifentanil concentration for the first patient was 2.0 ng/ml; For each subsequent patient, the concentration was determined by the response of the previous patient. If a patient was adequately anesthetized (i.e., had no response to rocuronium injection), the target effect-site remifentanil concentration for the subsequent patient was decreased by 0.5 ng/ml. If a patient had a response to injection ("response" defined as withdrawal movement of the wrist, arm, elbow, or shoulder and even generalized withdrawal movement in more than one extremity), the target effect-site remifentanil concentration for the subsequent patient was increased by 0.5 ng/ml. After both of the two drugs reached target concentrations, 0.8 mg/kg rocuronium bromide, which was used as an induction dose in our hospital, was injected over 10–15 s at room temperature.

The Dixon up-and-down method was used to determine the mean and standard deviation of remifentanil EC_{50}. The EC_{50} was determined by calculating the mean of the midpoint dose of all independent pairs of patients who manifested crossover from "response to injection" to "nonresponse to injection" after eight crossover points. At least seven pairs of failure–success are necessary for statistical analysis.

Heart rate (HR) and mean arterial pressure (MAP) were recorded and compared between before drug infusion and after the target Ce of both drugs was reached. If the MAP decreased below 50 mmHg, ephedrine 0.25 mg/kg was scheduled.

Data were also analyzed using a probit regression model. The probit regression model is used to estimate the effect of the explanatory variables when the response is a series of binomial results. The changes of HR and MAP were analyzed with a paired *t* test or a signed-rank test. Data were plotted and analyzed using Sigma Plot 9.0 and SPSS 12.0 (SPSS, Chicago, IL, USA). Values were expressed as mean ± SD, mean (95% confidence intervals, CI), or number of patients. $P < 0.05$ was considered to be statistically significant.

Results

Forty-five subjects aged 16–71 years were enrolled, and all subjects completed the study protocol. No patient had bradycardia, hypotension, or oxygen desaturation. The patient demographics are included in Table 1. No patient experienced clinically significant hemodynamic changes during the study.

Even though HR and MAP decreased in statistical significance, the decrease of HR and MAP was not of clinical importance (Table 2). Those changes were not so low that the patients needed inotropics such as ephedrine.

The effect-site concentration of propofol and remifentanil reached the targets after start of infusion within 3 min 40 s and 1 min 30 s, respectively. Dose–response data for each patient, which were obtained by the up-and-down method, are shown in Fig. 1. The predicted EC_{50} of

Table 1 Patient demographics

Characteristics	Data
Age (years)	41.4 ± 16.1
Height (cm)	164.7 ± 9.6
Weight (kg)	62.5 ± 10.1
Gender (M/F)	20/25

Data are shown as mean ± SD or frequency

Table 2 Changes in mean arterial blood pressure and heart rate

	HR		MAP	
	Beats/minute	*P* value	mmHg	*P* value
Baseline	77.3 ± 17.4 (median, 79)		93.0 ± 16.8	
After infusion	66.9 ± 13.6 (median, 69)	<0.001	84.2 ± 14.2	<0.001

Data are shown as means ± SD

HR heart rate, *MAP* mean arterial pressure

Baseline, before administration of drugs; after infusion, after Ce (effect-site target concentration) of both remifentanil and propofol reached target concentration

remifentanil was 1.5 ± 0.45 ng/ml by the Dixon up-and-down method.

Probit analysis resulted in the EC_{50} of remifentanil of 1.37 ng/ml (95% confidence limits, 0.69–2.15 ng/ml) and the EC_{95} of 3.19 ng/ml (95% confidence limits, 2.31–11.24 ng/ml) (Fig. 2).

Discussion

The purpose of this study was to describe the effect-site target concentration of remifentanil at which there is a 50% probability of preventing the rocuronium injection pain

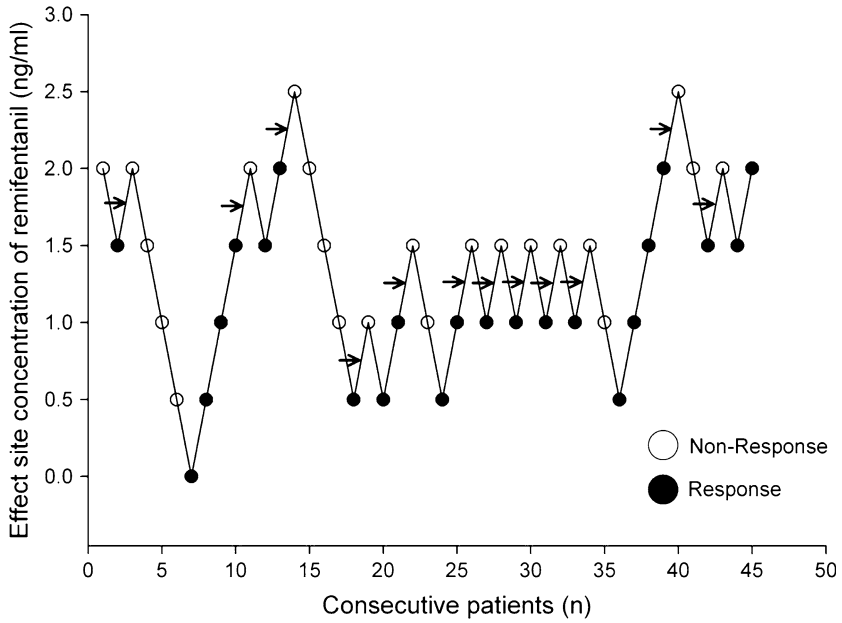

Fig. 1 Consecutive remifentanil concentration following the Dixon up-and-down method. *Arrows* represent the mean remifentanil concentration when crossing from a response (*black circles*) to a nonresponse (*white circles*) for rocuronium injection. The average of these concentrations is ED_{50}

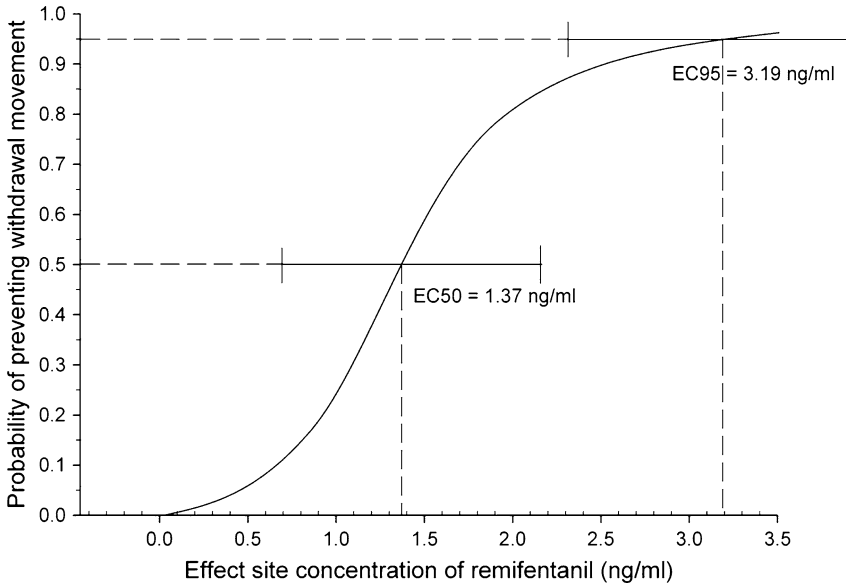

Fig. 2 Probit regression shows probability of preventing withdrawal movement from rocuronium injection as a function of effect-site concentration of remifentanil. *Horizontal bars* denote 95% confidence interval for efficient effect-site concentration of remifentanil in 50% and 95% of probabilities (EC_{50} and EC_{95}), respectively. The *right end* of the horizontal SD bar to which 95% probability corresponds is beyond the scale (11.24 ng/ml)

movement when used in combination with propofol TCI of 3 μg/ml.

The need to reduce withdrawal movement or pain during rocuronium injection has encouraged many different approaches such as using local anesthetics, opioids, sodium bicarbonate, and dilution [3–5, 7, 12]. The exact mechanism of rocuronium-induced localized pain has not been established, but it has been reported that the pain may be caused by the activation of nociceptors by the osmolality or pH of the solution, or activation by the release of endogenous mediators such as histamine, kinin, and other substances mediating inflammation [1, 13].

Among these agents, pretreatment with opioids has been shown to prevent withdrawal movements during rocuronium injection with varying results [3–5, 7]. Ahmad et al. [3] suggested that the central analgesic effect of opioid only occurs if adequate time is allowed for the onset of analgesia, whereas pretreatment with drugs with local anesthetic property is effective when the drug is administered immediately before, or with, a venous occlusion technique.

To have interaction with peripheral opioid receptors, opioids must remain in the body for a certain period of time. Roehm et al. [14] reported this period for remifentanil infusion to be 60 s in the prevention of propofol-induced injection pain. In this study, remifentanil was administered over 90 s with a TCI pump on running fluid without the venous occlusion technique; thus, the peripheral effect of remifentanil is less likely.

Remifentanil 1 or 0.5 μg/kg was already known to be effective in preventing rocuronium-induced withdrawal movement [15]. The incidence of withdrawal movements was reduced further with remifentanil at 1 μg/kg compared with that at 0.5 μg/kg. Considering these result, a dose-dependent effect of remifentanil in attenuating withdrawal is suspected. Regardless of the mechanism, it is likely that pretreatment with remifentanil has resulted in a deeper level of anesthesia, which elevates the pain threshold, and thus explains the decreased incidence of withdrawal movements. Further research to determine the optimal bolus dose of remifentanil required for the prevention of withdrawal movement with better hemodynamic stability is needed.

As compared with these previous studies, we tried to maintain a relatively low target effect-site concentration of propofol to minimize hemodynamic instability [16, 17]. Taylor et al. [18] reported that patients lost consciousness at a blood concentration of propofol of 9 μg/ml when a single bolus dose of propofol 2.5 mg/kg was administered, but the concentration at the effect site is only about 3.5 μg/ml. There was a positive interaction between remifentanil and propofol when used in combination. The concentration of propofol alone associated with a 50% probability of no response to esophagogastroduodenoscopy was 3.7 μg/ml, and this level was decreased to 2.8 μg/ml when used in combination with remifentanil in children [19].

The pharmacokinetics and pharmacodynamics of remifentanil are known to be influenced by patient age. We delivered remifentanil with effect-site TCI according to the Minto model. Minto et al. [11] stated that the pharmacokinetics and pharmacodynamics of remifentanil are influenced by age, not by gender, and they developed remifentanil dosing guidelines in consideration of age, sex, and lean body mass. This study was not focused on a specific population but on the general population including elderly patients. Even though the age of the population in this study varied from young to elderly persons, the study population passed the normality test of Kolmogorov–Smirnov, and the pharmacological effect of remifentanil on age was already reflected in the Minto's TCI model.

The Dixon up-and-down method has been commonly used in anesthesia research and has advanced in regard to its methodology. In some reports, the target concentration was selected in a logarithmic manner [20], and in other reports, the concentration was not transformed to a logarithmic scale. Logarithmic scale transformation could be performed merely for mathematical reason, not because of pharmacological problems. A slightly more accurate EC_{50} is seen with the logarithmic scale if the number of objects is the same as with the nontransformed method, and the logarithmic scale can help researchers to reduce the number of objects if the accuracy is same as with the nontransformed method.

One of the limitations is that we administered midazolam to patients for premedication. Midazolam would have an influence on the EC_{50} of remifentanil, even though the exact interrelationship such as an additive or synergistic effect on the analgesic effect of remifentanil was not known.

Another limitation of this study is the wide range of confidence intervals of EC_{50} and EC_{95}. Basically, the precision of the estimator may be narrowed by increasing the sample size, but that is not the purpose of up-and-down methods. The sample size of this study is sufficient for the up-and-down method. In addition, the precision of up-and-down methods is dependent on the gap between doses and starting dose. If the gap between doses is larger than the standard deviation, the CI is larger and depends somewhat on the starting level [9]. To increase the precision of the final estimator, altering the test space could be done in the course of an up-and-down sequence. That is, this modified up-and-down sequence is composed of two stages. The first stage consists of an original up-and-down sequence on the predetermined equally spaced test levels until three to four changes of response type are observed. The second stage consists of reducing the initial test space and restarting the

up-and-down sequence at the nearest level to the average and continuing the experiment at the next higher or the next lower level according to the response type on the reduced test space. Applying the foregoing modified up-and-down methods to this study, narrowing the gap between the doses after the fourth pairs of "response–nonresponse" would have resulted in a more precise confidence interval.

In conclusion, the EC_{50} Ce of remifentanil to prevent the withdrawal response was 1.5 ± 0.45 ng/ml with Dixon's up-and-down method using a Ce of 3.0 μg/ml propofol TCI. From the probit analysis, the EC_{50} and EC_{95} of remifentanil were 1.37 ng/ml (95% CI, 0.69–2.15 ng/ml), and the EC_{95} was 3.19 ng/ml (95% CI, 2.31–11.24 ng/ml), respectively.

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References

1. Borgeat A, Kwiatkowski D. Spontaneous movements associated with rocuronium: is pain on injection the cause? Br J Anaesth. 1997;79:382–3.
2. Shevchenko Y, Jocson JC, McRae VA, Stayer SA, Schwartz RE, Rehman M, et al. The use of lidocaine for preventing the withdrawal associated with the injection of rocuronium in children and adolescents. Anesth Analg. 1999;88:746–8.
3. Ahmad N, Choy CY, Aris EA, Balan S. Preventing the withdrawal response associated with rocuronium injection: a comparison of fentanyl with lidocaine. Anesth Analg. 2005;100:987–90.
4. Turan A, Memis D, Karamanlioglu B, Sut N, Pamukcu Z. The prevention of pain from injection of rocuronium by magnesium sulphate, lignocaine, sodium bicarbonate and alfentanil. Anaesth Intensive Care. 2003;31:277–81.
5. Memis D, Turan A, Karamanlioglu B, Sut N, Pamukcu Z. The prevention of pain from injection of rocuronium by ondansetron, lidocaine, tramadol, and fentanyl. Anesth Analg. 2002;94:1517–20.
6. Choi BI, Choi SH, Shin YS, Lee SJ, Yoon KB, Shin SK, et al. Remifentanil prevents withdrawal movements caused by intravenous injection of rocuronium. Yonsei Med J. 2008;49:211–6.
7. Kim JY, Kim JY, Kim YB, Kwak HJ. Pretreatment with remifentanil to prevent withdrawal after rocuronium in children. Br J Anaesth. 2007;98:120–3.
8. Egan TD, Minto CF, Hermann DJ, Barr J, Muir KT, Shafer SL. Remifentanil versus alfentanil: comparative pharmacokinetics and pharmacodynamics in healthy adult male volunteers. Anesthesiology. 1996;84:821–33.
9. Dixon WJ. Staircase bioassay: the up-and-down method. Neurosci Biobehav Rev. 1991;15:47–50.
10. Dixon WJ. Efficient analysis of experimental observations. Annu Rev Pharmacol Toxicol. 1980;20:441–62.
11. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology. 1997;86:10–23.
12. Tuncali B, Karci A, Tuncali BE, Mavioglu O, Olguner CG, Ayhan S, et al. Dilution of rocuronium to 0.5 mg/mL with 0.9% NaCl eliminates the pain during intravenous injection in awake patients. Anesth Analg. 2004;99:740–3.
13. Blunk JA, Seifert F, Schmelz M, Reeh PW, Koppert W. Injection pain of rocuronium and vecuronium is evoked by direct activation of nociceptive nerve endings. Eur J Anaesthesiol. 2003;20:245–53.
14. Roehm KD, Piper SN, Maleck WH, Boldt J. Prevention of propofol-induced injection pain by remifentanil: a placebo-controlled comparison with lidocaine. Anaesthesia. 2003;58:165–70.
15. Kim JY, Kwak HJ, Kim JY, Park KS, Song JS. Prevention of rocuronium-induced withdrawal movement in children: a comparison of remifentanil with alfentanil. Paediatr Anaesth. 2008;18:245–50.
16. Shafer SL, Gregg KM. Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer-controlled infusion pump. J Pharmacokinet Biopharm. 1992;20:147–69.
17. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology. 1998;88:1170–82.
18. Taylor IN, Kenny GN. Requirements for target-controlled infusion of propofol to insert the laryngeal mask airway. Anaesthesia. 1998;53:222–6.
19. Drover DR, Litalien C, Wellis V, Shafer SL, Hammer GB. Determination of the pharmacodynamic interaction of propofol and remifentanil during esophagogastroduodenoscopy in children. Anesthesiology. 2004;100:1382–6.
20. Wang LP, McLoughlin P, Paech MJ, Kurowski I, Brandon EL. Low and moderate remifentanil infusion rates do not alter target-controlled infusion propofol concentrations necessary to maintain anesthesia as assessed by bispectral index monitoring. Anesth Analg. 2007;104:325–31.