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Priming with rocuronium or vecuronium prevents remifentanil-mediated muscle rigidity and difficult ventilation

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Abstract
Purpose. The aim of this study was to test our hypothesis that priming with rocuronium would prevent muscle rigidity and difficult ventilation due to remifentanil administration.
Methods. One hundred patients, American Society of Anesthesiologists (ASA) status I or II, were recruited into the study, and randomly allocated to one of four protocols (n = 25 each). Remifentanil was administered at 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in group A and at 0.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in groups B, C, and D. Priming with vecuronium (0.02 $mg \cdot kg^{-1}$) or rocuronium (0.06 $mg \cdot kg^{-1}$) was performed at the same time as the infusion of remifentanil in groups C and D, respectively. Anesthesia was induced with 1 $mg \cdot kg^{-1}$ propofol 2 min after the start of remifentanil infusion. After the patient had lost consciousness, the anesthesiologist performed mask ventilation, and watched for the presence of muscle rigidity. Ventilation and rigidity were evaluated using a scoring system.
Results. Of the 100 patients, 9 were excluded; the number of patients in group A was 24, while groups B and D had 22 patients each, and group C had 23 patients. A lower dose of remifentanil (group A) or priming with vecuronium or rocuronium (groups C, D) significantly reduced the incidence of some difficulty with ventilation ($P = 0.0010$, $P = 0.0053$, and $P = 0.021$, respectively, vs group B). Of the patients in group B, 10 (45.5%) developed some difficulty with ventilation, and ventilation was impossible in 2 of them. On the other hand, 1 (4.1%) of the patients in group A, 2 (8.7%) in group C, and 3 (13.6%) in group D developed some difficulty with ventilation.
Conclusion. The present study showed that priming with rocuronium or vecuronium reduced the incidence of difficult ventilation by avoiding the muscle rigidity caused by remifentanil.

Key words Rocuronium · Priming · Remifentanil · Rigidity · Ventilation

Introduction

Remifentanil is a selective μ-opioid receptor agonist with a very short context-sensitive half-life [1]. This drug is metabolized by a nonspecific tissue esterase without participation of the liver or kidneys [2–4]. Despite its special features, however, remifentanil induces adverse reactions common to the fentanyl family, among which muscle rigidity is well known. Such rigidity can occur when large doses of opioid are given by rapid intravenous administration [5]. Severe rigidity of the thoracic and abdominal muscles makes manual ventilation of the lungs extremely difficult [6]. It has been shown that rigidity of the laryngeal muscles may cause closure of the vocal cords, leading to difficult ventilation [7]. Life-threatening hypoxemia induced by such muscle rigidity can be treated with depolarizing and nondepolarizing muscle relaxants [5]. However, the decision to use muscle relaxants in this situation must be made carefully, because difficulties with manual ventilation can have many causes other than muscle rigidity due to opioid administration. Therefore, preventive procedures to avoid muscle rigidity are more important than treatment if it occurs.

Rocuronium is a nondepolarizing neuromuscular blocking agent and its main advantage is a short time of onset. Since the introduction of rocuronium, the use of priming has decreased significantly. However, pretreatment with or the concomitant use of pancuronium significantly decreases the incidence and severity of fentanyl-mediated rigidity [6].

The aim of the present study was to test our hypothesis that priming with rocuronium would prevent the muscle rigidity and difficult ventilation caused by remifentanil administration during the induction of anesthesia.

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Methods

Patient population

This study received institutional Ethics Committee approval (Aichi Cancer Center, Nagoya, Japan), and we obtained written informed consent from all patients. Patients with American Society of Anesthesiologists (ASA) physical status I or II and Mallampati classification I or II were recruited into the study. Between November 1 and December 28, 2007, 100 patients were randomly allocated to one of four protocols (n = 25, respectively), using a computer-generated random code. The following patients were excluded: (i) patients who were anticipated to have difficult intubation (patients who had cervical retroflexion limitation); (ii) patients who were anticipated to have a disfigured airway (patients with a history of oral and/or cervical surgery); (iii), patients who had received opioids in the preoperative period; and (iv) patients with hypotension during anesthesia induction who were treated with reduction of remifentanil infusion before signs of rigidity were watched for. Patients were allocated and excluded, using the above-mentioned criteria, by an anesthesiologist who did not participate in the observation and data interpretation.

Anesthesia and study groups

None of the patients received any premedication and all were fasted for at least 8 h before surgery. On the patient's arrival at the operating room, a crystalloid solution was infused intravenously and routine monitoring equipment was applied. Remifentanil was administered at 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (group A) or 0.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (groups B, C, D) after preparation for general anesthesia at the same time that the patient received oxygen. The priming dose was determined according to the dose used in previously reported studies [8,9]. Briefly, priming with vecuronium (0.02 $mg \cdot kg^{-1}$) or rocuronium (0.06 $mg \cdot kg^{-1}$) was performed at the same time as the infusion of remifentanil in groups C and D, respectively. Ninety seconds after the start of remifentanil infusion, each patient was asked whether there were any changes in eye-opening or breathing. When the patient reported any changes, the patient was notified that these were normal reactions to anesthetic drugs. Propofol was administered as a bolus at 1 $mg \cdot kg^{-1}$ 2 min after the start of remifentanil infusion. All patients were asked to breathe deeply while they remained conscious. After the patient had lost consciousness, the observer delivered mask ventilation, and watched for signs of thoracic bulging, end-tidal carbon dioxide wave, and muscle rigidity. Subsequently, remifentanil was administered at 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and an intubating dose of muscle relaxant (vecuronium 0.1 $mg \cdot kg^{-1}$ in groups A, B, and C and rocuronium 0.6 $mg \cdot kg^{-1}$ in group D) was administered, and propofol was administered at 0.5 $mg \cdot kg^{-1}$ in group A. Ventilation and rigidity were evaluated using a previously reported scoring system (Table 1) [6,10]. In this scoring system, "moderate" and "severe" are defined in relation to "difficulty with ventilation". After intubation, the patients in all groups received remifentanil at 0.07 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and sevoflurane at 1% for end-tidal concentration. The observers were blinded to the drug protocol. Caregivers were not blinded, but they did not participate in data collection or data interpretation. After anesthesia induction, a questionnaire (Table 1) was handed to each observer and it was collected within the same day.

Rescue protocol

Patients in whom ventilation became impossible were treated as follows: (i) the caregiver withdrew remifentanil administration; (ii) the caregiver administered a muscle relaxant at the intubating dose; (iii) the observer used the ASA difficult airway management algorithm.

Patients with hypotension were treated as follows: when the systolic blood pressure fell to below 60 mmHg during anesthesia induction, the caregiver administered remifentanil at half the protocol dose and phenylephrine at 0.1 mg.

Statistical analysis

Statistical analysis was performed using the Statcel software package (OMS, 2003, Saitama, Japan). One-way analysis of variance (ANOVA) was used for comparisons of age, height, weight, and body mass index (BMI) data among the groups. Categorical data were analyzed

Table 1. Questionnaire on anesthesia induction for the observer, and scoring system

1. Did you confirm any difficulty with mask ventilation and/or rigidity?
2. How severe was the muscle rigidity and difficulty with ventilation?

No (no difficulty with ventilation during manual positive pressure ventilation and no clinical evidence of rigidity)
Mild (no difficulty with ventilation but some extremity or abdominal wall stiffness)
Moderate (some difficulty with ventilation ± the presence of marked extremity or abdominal wall stiffness)
Severe (virtually impossible to ventilate ± the presence of marked extremity or abdominal wall stiffness)

After anesthesia induction, this questionnaire including the rigidity scoring system was handed to each observer

by the χ^2 test. Differences of $P < 0.05$ were considered statistically significant.

Results

Of the 100 patients, 9 were excluded on the basis of the above-mentioned criteria (6 developed hypotension and received remifentanil reduction, 1 had undergone oral and cervical surgery, 1 had cervical retroflexion limitation, and 1 had received morphine preoperatively), and 91 were entered into the study. There were no significant differences in patient characteristics among the four study groups (Table 2).

A lower dose of remifentanil (group A) or priming with vecuronium or rocuronium (groups C, D) significantly reduced the incidence of some difficulty with ventilation ($P = 0.0010$, $P = 0.0053$, and $P = 0.021$, respectively, vs group B; Fig. 1). The incidence of difficult ventilation and muscle rigidity appeared to be dose related. Of the 22 patients in group B, 10 (46%) developed some difficulty with ventilation, of whom ventilation was impossible in 2. On the other hand, 1 (4%) of the 24 patients in group A, 2 (9%) of the 23 patients in group C, and 3 of the 22 patients (14%) in group D developed some difficulty with ventilation, but ventilation was impossible in none of them. The incidence and severity of muscle rigidity are summarized in Table 3.

All patients who developed any difficulty with ventilation were induced without serious complications. The two patients in whom ventilation was impossible were intubated immediately using the rescue protocol. Vocal cord closure was confirmed in one of them during intubation, and the vocal cords of the other patient could not be observed clearly. Emergence from anesthesia was smooth in all patients, and the postoperative courses were uneventful.

Table 4 shows the incidences of side effects as a result of the priming with vecuronium or rocuronium. Of the patients in group C, 12 (52%) developed difficulty with

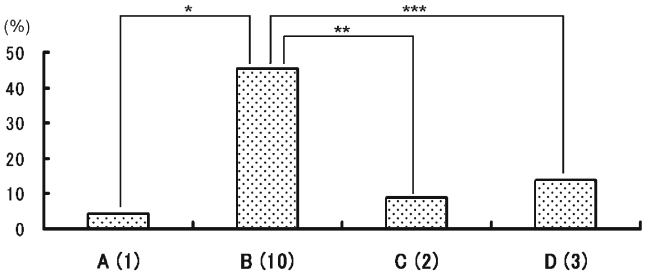

Fig. 1. Percentages of patients (*n*) showing incidence of some difficulty with ventilation. A lower dose of remifentanil (group *A*) or priming with vecuronium or rocuronium (groups *C*, *D*) significantly reduced the incidence of some difficulty with ventilation (*$P = 0.0010$; **$P = 0.0053$; ***$P = 0.021$ vs group B). *Numbers in parentheses* are numbers of patients in each group who showed some difficulty with ventilation

Table 2. Demographic data

Group	A ($n = 24$)	B ($n = 22$)	C ($n = 23$)	D ($n = 22$)	
Priming	—	—	Vecuronium	Rocuronium	
Remifentanil ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.2	0.7	0.7	0.7	*P*
Height (cm)	158.7 ± 8.6	159.5 ± 7.2	160.3 ± 9.4	157.8 ± 7.9	0.664
Weight (kg)	56.6 ± 10.4	55.5 ± 11.3	57.3 ± 13.5	56.5 ± 10.0	0.936
Body mass index	22.4 ± 3.2	21.8 ± 3.9	22.1 ± 3.9	22.9 ± 4.5	0.822
Age (years)	61.5 ± 13.9	59.4 ± 14.3	59.7 ± 16.0	63.7 ± 15.0	0.762
Sex (male/female)	9/15	7/15	11/12	10/12	0.680

Data are means ± SD, unless stated otherwise
There were no significant differences in any patient characteristics among the four groups

Table 3. Percentages of patients (*n*) with muscle rigidity

Group	A ($n = 24$)	B ($n = 22$)	C ($n = 23$)	D ($n = 22$)
Priming	—	—	Vecuronium	Rocuronium
Remifentanil ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.2	0.7	0.7	0.7
No	96% (23)	45% (10)	91% (21)	86% (19)
Mild	0	9% (2)	0	0
Moderate	4% (1)	36% (8)	9% (2)	14% (3)
Severe	0	9% (2)	0	0

Induction sequences (see "Methods" for full details): (i) priming with vecuronium or rocuronium was performed at the same time as infusion of remifentanil in groups C and D. (ii) Propofol was administered 2 min after the start of the remifentanil infusion

Table 4. Percentages of patients (n) with side effects of priming techniques

Group	A ($n = 24$)	B ($n = 22$)	C ($n = 23$)	D ($n = 22$)
Priming	—	—	Vecuronium	Rocuronium
Remifentanil ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.2	0.7	0.7	0.7
Difficulty with eye opening	0	0	52% (12)*	82% (18)**
Slight feeling of dyspnea	0	0	4% (1)	9% (2)
Difficulty with pronunciation	0	0	0	9% (2)
Difficulty with taking a deep breath	0	0	0	0
Decrease in oxygen saturation	0	0	0	0
Regurgitation	0	0	0	0

All of the patients could breathe deeply while they remained conscious. Priming with vecuronium or rocuronium significantly increased the incidence of difficulty with eye opening (*$P = 0.000076$; **$P = 3.4 \times 10^{-8}$ vs group B)

eye opening and 1 (4%) developed a slight feeling of dyspnea. Of the patients in group D, 18 (82%) developed difficulty with eye opening, 2 (9%) developed a slight feeling of dyspnea, and 2 (9%) developed difficulty with pronunciation. Priming with vecuronium or rocuronium significantly increased the incidence of difficulty with eye opening ($P = 0.000076$; $P = 3.4 \times 10^{-8}$, respectively, vs group B). However, all of the patients could breathe deeply while they remained conscious, and none of them developed decrease in oxygen saturation, regurgitation, or other serious complications.

Discussion

The present study showed that priming with rocuronium or vecuronium reduced the incidence of difficult ventilation due to muscle rigidity caused by remifentanil during anesthesia induction. Previously reported investigations have suggested that priming with rocuronium or vecuronium led to the development of partial neuromuscular block and serious complications (regurgitation, decrease in oxygen saturation, severe muscle weakness) [11–13]. When applying priming to patients, special attention should be paid to these complications. In our series, although most of the patients with priming developed side effects (difficulty with eye opening, slight difficulty with breathing, and difficulty with pronunciation), none of the patients developed any serious complications with priming. To ease their anxiety, it is better to let patients know of the possible reaction of difficulty with eye opening and breathing before administering the priming dose. With the priming dose of vecuronium at $0.02\ mg \cdot kg^{-1}$, the train-of-four ratio in the fifth and sixth min is significantly lower when compared with that in the first min [9]. We should regulate the waiting time for induction to within 4 min with vecuronium at this dose. Further studies are required to determine the ideal priming dose and waiting time. One possible mechanism of the prevention of remifentanil-mediated rigidity by priming is that the asymptomatic partial block prevents the excessive hypertonia that can lead to muscle rigidity and vocal-cord closure, thus making ventilation easier. Further research is required to clarify the precise mechanisms underlying the prevention of rigidity produced by priming.

The mechanism responsible for opioid-induced muscle rigidity is thought to involve alterations in the central nervous system. One pharmacological investigation has suggested that opioid-induced muscle rigidity is due primarily to the activation of central μ-receptors, whereas δ_1 and κ_1 receptors attenuate this effect [14]. Remifentanil is a selective μ-opioid receptor agonist. Its rapid plasma effect-site equilibration causes the effect-site concentration to rise rapidly and produce a peak in a short time. When applying remifentanil to patients, attention should be paid to the possible development of muscle rigidity. The final common pathway of opioid-induced rigidity may also be shared by the motor abnormalities seen in parkinsonism and extrapyramidal drug reactions, implying a possible dopaminergic mechanism [15]. In our series, global rigidity and inability to ventilate occurred in a patient without priming who had received drugs (sulpiride, fluvoxamine maleate) that can cause extrapyramidal symptoms.

The incidence of pain on injection of rocuronium has been reported previously [16]. In our series, although none of the patients developed severe pain (pain or discomfort reported spontaneously by the patient and stated to be severe), mild or moderate pain could have developed. Some investigations have suggested that pretreatment with lidocaine, fentanyl, sufentanyl, or esmolol could reduce the incidence of pain on the injection of rocuronium [16–18]. When applying priming with rocuronium, the use of these palliative methods could be considered.

Rigidity of the laryngeal muscles may cause closure of the vocal cords, leading to difficult ventilation [7]. Therefore, an increase in ventilatory compliance can be seen as the prodrome of muscle rigidity [19]. The incidence of rigidity noted with opioid anesthetic techniques varies greatly with differences in the dose and speed of

opioid administration, the concomitant use of N_2O or midazolam, and patient age [6, 20]. Moreover, in obese patients, breathing work is increased [21]. It can be difficult to differentiate remifentanil-mediated rigidity from difficult mask ventilation in a patient with unfavorable anatomy. In the present study there were no significant differences in patients' characteristics among the groups, and patients with potential problems of the upper airway were excluded. None of the patients received N_2O or midazolam. Furthermore, the incidences of difficult ventilation and muscle rigidity appeared to be dose related. In our series, difficulty with ventilation was considered to be due to muscle rigidity induced by high-dose remifentanil.

Alexander et al. [22] did not report muscle rigidity after induction with remifentanil 3–5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and propofol 2 $mg \cdot kg^{-1}$. Our results showed a higher tendency toward muscle rigidity than has been shown in previous investigations [8,22,23]. The loosely defined grades in the rigidity scoring system we used might explain our results in relation to previously reported results. The assessment of "some difficulty" and "some stiffness" was left to the judgment of each observer. There is a limit to the precise evaluation of muscle rigidity using this scoring system.

Various doses of remifentanil (continuous dose up to 0.5–1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, bolus dose up to 1.0–5.0 $\mu g \cdot kg^{-1}$) were used during anesthesia induction in previously reported investigations [22–25]. Global standards for the optimum dosage of remifentanil for anesthesia induction have not been established. Our study showed that the administration of high-dose remifentanil increased the incidences of rigidity and difficulty with ventilation, and these results suggest that the maximum dose of remifentanil should be regulated during anesthesia induction without priming.

In conclusion, priming with rocuronium or vecuronium reduced the incidences of muscle rigidity and difficulty with ventilation induced by high-dose remifentanil.

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