Priming with Rocuronium to Accelerate the Onset Time of Cisatracurium During Intubation

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Background: The priming technique, in which a small dose of nondepolarizing muscle relaxant is administered 3–6 minutes before giving the intubation dose, can speed up the onset of muscle relaxation in patients with paralysis during intubation. We investigated the priming technique and compared 2 different priming agents (rocuronium and cisatracurium) at a priming time of 3 minutes and its effect on decreasing the onset time of cisatracurium.

Methods: A total of 60 patients with ASA physical status I–II scheduled for elective surgery were enrolled. After induction with propofol and fentanyl, the patients were randomized into 1 of 3 groups. Group 1 received rocuronium 0.06 mg/kg as a priming dose. Group 2 received cisatracurium 0.01 mg/kg as a priming dose. Group 3 received normal saline and constituted the control group. After a 3-minute priming time, intubation doses of cisatracurium were given (Groups 1 and 2, 0.14 mg/kg; Group 3, 0.15 mg/kg). First twitch height percentage (T1/T0%; % of control) and train-of-four percentage (T4/T1%) were recorded every 10 seconds from baseline until T1/T0% reached 0.

Results: Rocuronium (Group 1) and cisatracurium (Group 2) significantly accelerated the onset of cisatracurium (Group 1, 117.0 ± 29.0 seconds; Group 2, 151.0 ± 37.5 seconds; Group 3, 221.5 ± 36.6 seconds; all $p < 0.001$).

Conclusion: Priming with rocuronium or cisatracurium for 3 minutes significantly accelerated the onset of cisatracurium. Priming with rocuronium for 3 minutes improved the onset time of cisatracurium even more than priming with cisatracurium itself. [*J Chin Med Assoc* 2009;72(1):15–19]

Key Words: cisatracurium, precurarization, rocuronium

Introduction

Cisatracurium, a unique nondepolarizing neuromuscular blocker, degrades in plasma at physiologic pH by organ-independent Hoffmann elimination.[1] It has potency approximately 4 times higher than that of atracurium, with a very stable cardiovascular effect during induction,[2] even at a dose 8 times as high as 95% effective dose (ED95).[3] However, its relatively long onset time deters its suitability for rapid-sequence intubation. We were interested in speeding up the onset time of cisatracurium. Mak and Irwin demonstrated that the onset time of cisatracurium is significantly shortened by priming with cisatracurium or rocuronium 6 minutes before administration.[4] According to a computer simulation, the priming interval for cisatracurium should be at least 6 minutes and as little as 3 minutes for rocuronium.[5] Therefore, we performed this prospective, double-blind, randomized and controlled study to determine the effectiveness of rocuronium or cisatracurium as the priming agent 3 minutes before an intubation dose of cisatracurium was given.

Methods

After approval by the Institutional Review Board of Taipei Veterans General Hospital, 60 patients with American Society of Anesthesiologists (ASA) physical status I–II scheduled for elective surgery were enrolled. Excluded from the study were patients who had known difficult airway, fever, diabetes mellitus with neuropathy, pregnancy, high risk of aspiration, neuromuscular disease or any premedication that might influence

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neuromuscular function. Prior to the study, informed consent was obtained from each subject, which also included an explanation of what the procedure was about. An independent study nurse recorded all the data.

After the patient's arrival in the operating room, 2 stimulating electrodes were placed over the ulnar nerve at the wrist and 2 recording electrodes were attached over the adductor pollicis muscle. An intravenous line was set on the hand opposite the electrodes. The 4 fingers were immobilized with belts on the arm board beside the operating bed, but the thumb was allowed to move freely.

No premedication was given; anesthesia was induced with propofol 2–2.5 mg/kg and fentanyl 2 μg/kg; propofol infusion of 6–10 mg/kg/hr was used for maintenance. Train-of-four (TOF) stimuli were applied to the ulnar nerve (M-NMT module; Datex-Ohmeda Inc., Finland) after loss of eyelid reflex to prevent any feeling of unpleasantness or pain by the patients. The corresponding electromyographic (EMG) amplitudes were measured using the neuromuscular transmission module, and were displayed on an anesthetic monitoring system (Anesthetic Monitoring System A/S3, Datex-Ohmeda Inc.). The TOF stimuli module automatically searched for the supramaximal current. Once the supramaximal current had been established, the EMG amplitude of T1 was considered to be the control response, T0.

The patients were randomized (using envelope randomization) into 3 groups. Group 1 received rocuronium 0.06 mg/kg, Group 2 received cisatracurium 0.01 mg/kg, and Group 3 received normal saline and constituted the control group. After a 3-minute priming period, an intubation dose of cisatracurium was given (Groups 1 and 2, 0.14 mg/kg; Group 3, 0.15 mg/kg). The priming and intubation doses of the drugs were diluted to volumes of 1 mL and 10 mL, and labeled as coded syringes by an independent anesthesiologist who was not involved in the management of the patients. Both percentage of the first twitch height (T1/T0%) and the percentage between the first and the fourth twitch (T4/T1%) were recorded from electromyography every 10 seconds during and after the priming period until T1/T0% reached 0. Intubation was then attempted and the study was ended after intubation.

Throughout the induction, only oxygen was given. Anesthetic gas was not administered. End-tidal carbon dioxide ($EtCO_2$) was controlled at around 25–35 mmHg by mask ventilation. The temperature of the adductor pollicis muscle of the measurement hand was kept between 35.5°C and 36.0°C by covering the forearm and hand with towels or a warm blanket. Intraoperative monitors, which included pulse oximetry, electrocardiography, noninvasive blood pressure and end-tidal capnography, were used in all patients.

Statistical analysis

ANOVA and χ^2 tests were used to analyze the patient characteristics. T1/T0%, T4/T1% and the intubation time (time interval between administration of intubation dose and the time when T1/T0% reached 0) were analyzed with 1-way ANOVA. Separate *post hoc* pair-wise comparisons were made with Bonferroni correction. Values were considered significant when $p < 0.05$. Parametric data are presented as mean ± standard deviation.

Results

A total of 60 patients enrolled into the study were evaluated successfully and completely. There were no obvious side effects, like bradycardia, difficult ventilation and hypoxemia, found during the priming period. Patient characteristics were not significantly different among the 3 groups as analyzed by ANOVA and χ^2 tests (Table 1).

T1/T0%, T4/T1% and intubation time were significantly different among the groups as calculated by 1-way ANOVA (Table 2). Further analyses with factorial ANOVA (Bonferroni multiple comparison test

Table 1. Patient characteristics*

	Group 1 (rocuronium; $n = 20$)	Group 2 (cisatracurium; $n = 20$)	Group 3 (control; $n = 20$)	p
Age (yr)	38.2 ± 14.6	36.3 ± 14.1	36.9 ± 11.8	0.81
Body weight (kg)	65.7 ± 12.5	71.0 ± 14.7	69.1 ± 13.4	0.69
Body height (cm)	160.4 ± 25.7	169.2 ± 11.5	168.2 ± 8.4	0.34
BMI (kg/m^2)	29.7 ± 25.1	24.6 ± 3.7	24.3 ± 3.8	0.51
Gender (M:F)	11:9	14:6	13:7	0.89
ASA class (1:2)	15:5	17:3	15:5	0.98

**Data presented as mean ± standard deviation or n. BMI = body mass index; ASA = American Society of Anesthesiologists.*

Table 2. T1/T0%, T4/T1% after 3-minute priming and intubation*

	Group 1	Group 2	Group 3	*p*
T1/T0%	89.6 ± 7.7†	90.7 ± 5.1†	96.4 ± 2.7	< 0.01
T4/T1%	88.4 ± 14.7†‡	97.9 ± 2.0	97.2 ± 1.3	0.01
Intubation time (s)	117.0 ± 29.0†‡	151.0 ± 37.5†	221.5 ± 36.6	< 0.01

**Data presented as mean ± standard deviation; †p < 0.05 vs. control group and ‡p < 0.05 vs. Group 2, ANOVA test with Bonferroni correction. Group 1 = priming with 3-minute rocuronium; Group 2 = priming with 3-minute cisatracurium.*

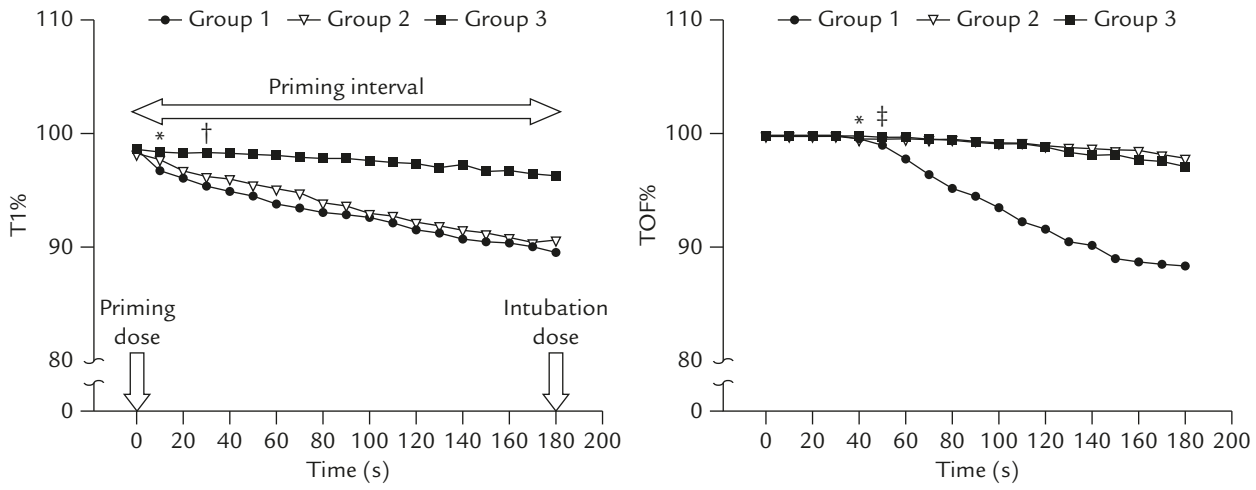

Figure 1. Time progression of mean T1% and TOF% during 3-minute priming. *First time point of $p < 0.05$ between Groups 1 and 3; †first time point of $p < 0.05$ between Groups 2 and 3; ‡first time point of $p < 0.05$ between Groups 1 and 2. All calculations by ANOVA test with Bonferroni correction. Group 1 = priming with rocuronium; Group 2 = priming with cisatracurium; Group 3 = control.

used as needed) were used for T1/T0%, T4/T1% and intubation time to measure between-group variables (Figure 1). Priming with rocuronium (Group 1) and cisatracurium (Group 2) for 3 minutes accelerated the intubation time of cisatracurium as compared with that of the control group (Group 3). Group 1 (rocuronium) had significantly shorter intubation time than Group 2 (cisatracurium) ($p = 0.001$). T1/T0% at the third minute in Groups 1 and 2 was not significantly different, but both were significantly depressed compared to that of the control group. T4/T1% at the third minute in Group 1 was significantly depressed compared to that found in Groups 2 and 3, but there was no difference between Groups 2 and 3 (Table 2).

Discussion

The present study indicates that priming with rocuronium or cisatracurium for 3 minutes can significantly shorten the onset time of cisatracurium. With a 3-minute priming interval, rocuronium significantly reduced intubation time associated with cisatracurium than did cisatracurium itself (Table 2).

Mak and Irwin reported that using cisatracurium and rocuronium as priming drugs at an interval of 6 minutes significantly reduced the onset time for cisatracurium.[4] According to Kopman et al, who used computer simulation with construction of onset model for vecuronium, the priming interval for cisatracurium should be at least 6 minutes, while it could be as little as 3 minutes for rocuronium.[5] Yavascaoglu et al found that a 3-minute priming interval was effective during rapid tracheal intubation with rocuronium.[6] A 3-minute priming interval appears to be optimal for rocuronium, while 6 minutes appears to be the optimal time for cisatracurium.

The speed of onset is inversely proportional to the potency of the nondepolarizing neuromuscular blocker,[7] except for atracurium.[8] Rocuronium has a molar potency that is only 9% that of cisatracurium.[9] Thus, more rapid onset of priming rocuronium to achieve its 90% peak effect as that of cisatracurium during a 3-minute priming interval is not unexpected.

Interestingly, after priming for 3 minutes with rocuronium, T1/T0 decreased to 89.6%, with a corresponding T4/T1% decrease to 88.4%. But with 3 minutes of cisatracurium, T1/T0 decreased to 90.7%,

and T4/T1% to 97.9%. Nondepolarizing neuromuscular blockers, in addition to depressing the amplitude of contractions (T1/T0), also cause tetanic and TOF fade (T4/T1).[10] TOF fade (T4/T1%) is thought to represent the degree of prejunctional neuromuscular block, impairing the mobilization of acetylcholine during rapid stimulation.[10,11] In contrast, T1/T0% reflects the postjunctional effects of neuromuscular junction. In this study, both priming agents showed equal postjunctional effect during the 3-minute priming interval. However, priming rocuronium produced more prejunctional effect than did cisatracurium (Figure 1).

What the optimal priming dose of a nondepolarizing neuromuscular blocking agent is has been discussed in the anesthesia literature. It is generally accepted that the priming dose should be limited to 10–20% of its ED95.[12] We chose 20% of ED95 as the priming dose to achieve the maximal priming effect with the fewest possible adverse effects. No definite values of T1 amplitude (T1/T0) and TOF fade (T4/T1) relevant to neuromuscular blocking symptoms were demonstrated because individuals might experience different symptoms (e.g. heavy eyelids, blurred vision, difficulty in swallowing) despite similar values of T1/T0 and T4/T1. Kopman et al demonstrated that T4/T1 ≤ 0.90 was accompanied by diplopia and difficulty in tracking moving objects in all subjects.[13] Symptomatic neuromuscular block could be present when T4/T1 is < 0.9. In our Group 2 (cisatracurium), T1/T0 decreased to 90.7%, with a corresponding decrease in T4/T1 to 97.9%. None of the patients in Group 2 had TOF <90%. Our results suggest that 3 minutes priming with cisatracurium will speed up the onset of cisatracurium without inducing significant neuromuscular blocking effect. However, variability in response to a priming dose in individuals has been found. Little fade may be seen at the onset despite profound neuromuscular blockade.[14] Caution should still be taken when using this technique.

Stable cardiovascular effect and unique independent Hoffmann elimination make cisatracurium a good choice for induction of patients with renal or hepatic function impairment or who are elderly. However, its relatively longer onset time prolongs the duration of induction and deters its application in rapid-sequence induction. The priming principle has been a good choice for accelerating the onset of nondepolarizing neuromuscular blockers since it was first introduced by Foldes[15] and Schwarz et al.[16]

Priming for 3 minutes with rocuronium on cisatracurium will significantly decrease the onset time of cisatracurium, therefore improving the clinical usefulness and reducing the risk of maintained airway. It can be useful during induction of general anesthesia to accelerate onset time of cisatracurium before or after administering sedative agents. In this study, in order to avoid unpleasant and painful feelings for the patients, we performed TOF stimuli after induction of general anesthesia and thus we did not evaluate the symptoms of conscious patients during the priming period. Otherwise, there were no obvious side effects, like bradycardia, difficult ventilation or hypoxemia found during the priming period. Further study needs to be done.

In conclusion, priming with rocuronium for 3 minutes will significantly improve the onset time of cisatracurium. However, patients should be reminded of possible neuromuscular blocking symptoms. Priming with cisatracurium for 3 minutes will also improve the onset time of cisatracurium. Knowledge of time sequences for priming and associated side effects can help us make plans for safe and comfortable induction in patients.

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