Rocuronium Bromide Intravenous Solution Maruish® is more suitable than ESLAX Intravenous® during rapid-sequence induction of anesthesia

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Abstract

Purpose: Rocuronium Bromide Intravenous Solution® (Maruishi Pharmaceutical Co., Ktd, Osaka, Japan) is a newly developed generic drug, and we have noticed that, compared with conventional rocuronium formulations (e.g. Esmeron (Eslax), MSD Co. Ltd., Tokyo, Japan), rocuronium Maruishi appeared to cause less pain or withdrawal movement. The aim of this study was to assess the hypothesis that injection of rocuronium Maruishi causes less body movement than rocuronium MSD does, during rapid-sequence induction of anesthesia.

Methods: Sixty patients were allocated randomly to one of two groups. In one group, rocuronium MSD was used, and in the other group, rocuronium Maruishi was used. After induction of general anesthesia, a test drug (containing rocuronium) 0.9 mg/kg was injected. Patient's withdrawal movement was graded with the scale. Primary outcome measure was the incidence of moderate or severe movement after injection of rocuronium. Secondary outcome measure was the degree of movement between the groups.

Results: Moderate or severe withdrawal movement was observed after injection of rocuronium MSD in 11 of 30 patients (37%), and after injection of rocuronium Maruishi in 3 of 30 patients (10%). There was a significant difference in the incidence between the groups ($P = 0.013$, 95%CI for difference: 26-28%). The degree of movement was also significantly greater for rocuronium MSD than for rocuronium Maruishi ($P = 0.015$).

Conclusion: Compared with rocuronium MSD , rocuronium Maruishi is more suitable than conventional rocuronium formulations, for rapid-sequence induction of anesthesia.

Key words: Rocuronium, Pain on injection, Withdrawal movement

Introduction

Rapid-sequence induction of anesthesia is indicated when the patient is at increased risk of pulmonary aspiration of gastric contents. Originally, anesthesia was induced with thiopental (or thyamylal), and neuromuscular blockade achieved with suxamethonium [1], and the trachea is intubated approximately 1 min after induction. Currently, anesthesia is frequently induced with propofol [2], and neuromuscular blockade with rocuronium at a high dose (0.9-1.2 mg/kg), because a high dose of rocuronium can produce the optimal neuromuscular blockade for tracheal intubation as fast as suxamethonium does [3].

One major problem with the use of propofol and a high-dose rocuronium is pain on injection [4, 5]. Pain during injection of these drugs while the patient is losing consciousness frequently causes withdrawal movement of the wrist, the arm, and even the body trunk [5-7] . Bending the arm may prevent anesthetic drugs to reach the effect sites, and movement of the body may increase the intragastric pressure, causing regurgitation and pulmonary aspiration of gastric contents. The reported incidence of withdrawal movement varies between 50 and 80% [5-7].

Rocuronium Bromide Intravenous Solution® (Maruishi Pharmaceutical Co., Ktd, Osaka, Japan) is a newly developed generic drug, and we have noticed that, compared with conventional rocuronium formulations (e.g. Esmeron (Eslax), MSD Co. Ltd., Tokyo, Japan), rocuronium Maruishi appeared to cause less pain or withdrawal movement. If this is the case, rocuronium Maruishi is theoretically more suitable than other conventional rocuronium formulations for rapid-sequence induction of anesthesia.

We hypothesized that injection of rocuronium Maruishi causes less body movement than rocuronium MSD does, during rapid-sequence induction of anesthesia. The aim of this study was to assess this hypothesis.

Methods

The institutional research ethics committee approved the study, and written informed consent was obtained from all the patients. The study was registered in a publicly accessible database before recruitment of the first subject (UMIN000032466).

We studied 60 patients, aged between 20 and 65 yr, American Society of Anesthesiologists (ASA) physical status 1or 2, who were scheduled for elective surgeries under general anesthesia, and in whom tracheal intubation was deemed necessary during anesthesia. We excluded patients when at least one of the followings was present: body weight > 100 kg, pregnant, history of bilateral mastectomy, chronic pain syndromes, cardiovascular disease, asthma, respiratory disease with hypoxia, neurological deficits, thrombophlebitis, dyskinesia, alcoholic, a history of drug abuse, regular use of analgesics or sedatives, the use of an analgesic within the previous 24h, difficult airways, difficult venous access, or contraindicated to any drug used in this study. In addition, because of ethical concern, we excluded patients at increased risk of pulmonary aspiration.

As a double-blind randomized controlled study, patients were allocated randomly to one of two groups. In one group, rocuronium MSD was used, and in the other group, rocuronium Maruishi was used. Random allocation was made using a block randomization (in blocks of 4), and each allocation was described in a card placed into a sealed opaque envelope. Shortly before induction of anesthesia, a personnel who was not involved to clinical part of the study, opened an envelope, confirmed the allocation, and aspirated the allocated drug to a 10-ml syringe, and affixed a label of “Rocuronium” to the syringe. Both drugs are colorless transparent liquid with the same volume (50 mg/ 5.0 ml), so that it was impossible to distinguish which rocuronium was being contained.

No premedication was given. On arrival at the operating room, a non-invasive blood pressure cuff, an electrocardiogram and a pulse oximeter were applied. A 20-gauge intravenous cannula was inserted into the vein of the back of the hand, a macrodrip tubing was connected to the cannula, and a roller clamp was fully open so that acetated Ringer's solution was infused with the maximum dripping speed, with the bottle hang approximately 1 m above the patient's heart.

After preoxygenation with 100% oxygen through a facemask more than 3 min, anesthesia was induced as a rapid sequence. To avoid possible pain by propofol, thiamylal 4.5 mg/kg was used to induce general anesthesia. Immediately after injection of thiamylal, a test drug (containing rocuronium) 0.9 mg/kg was injected. Patient's withdrawal movement was graded by an independent person with the following scale: None: no response; Mild: movement at the wrist only; Moderate: movement/withdrawal involving arm only (elbow or shoulder); Severe: movement/withdrawal in more than one extremity or body trunk, cough, or breath holding. Sixty seconds after the injection of the test drug, the trachea was intubated. A 7.0-mm ID tracheal tube was used in females, and a 8.0-mm ID tube in males. If the anesthesiologist judged that it would be unsuitable to intubate the trachea due to insufficient neuromuscular blockade of the glottis, tracheal intubation was not attempted. In such a case, the study was terminated at this point, and tracheal intubation was judged as failure. Either an additional dose of rocuronium or an analgesic was injected intravenously, and if necessary, manual ventilation using a facemask was attempted with initiating administration of an inhalational agent in oxygen.

Once tracheal intubation was confirmed with the appearance of the end-tidal carbon dioxide waveforms, anesthesia was deepened immediately. If the blood pressure or the heart rate either increased or decreased markedly, or if arrhythmia occurred, the anesthesiologist judged whether or not treatment was required, and if treatment was made, the details of the treatment

was recorded. Subsequent anesthetic management was at the discretion of the attending anesthesiologist.

Statistics analysis

Primary outcome measure was the incidence of moderate or severe movement after injection of rocuronium. Fisher's exact test was used to compare the incidence between the groups. For secondary outcome measures, Chi-squared for trend was used to compare the degree of movement between the groups, and Fisher's exact test was used to compare the incidence of suboptimal neuromuscular blockade at tracheal intubation. $P<0.05$ was taken as a significant. The 95% confidence intervals (CI) for the difference in the incidence between the groups were also calculated.

The incidence of moderate or severe movement after injection of Eslax was 78% in one report [6] and in 47% in another report [7]. Our preliminary observation indicated that the incidence would be 40-50% after injection of rocuronium, whereas the incidence would be 10-15% after injection of rocuronium Maruishi. We considered that difference in the incidence of moderate or severe body movement of 35% (50% versus 15%) would be clinically important. To detect this, with a power of 80% and $P = 0.05$, approximately 60 patients would be required.

Results

Patients' characteristics were similar between the two groups (Table 1).

Moderate or severe withdrawal movement was observed after injection of rocuronium MSD in 11 of 30 patients (37%), and after injection of rocuronium Maruishi in 3 of 30 patients (10%) (Table 2). There was a significant difference in the incidence between the groups (P = 0.013, 95%CI for difference: 26-28%). The degree of movement was also significantly greater for rocuronium MSD than for rocuronium Maruishi (P = 0.015). No withdrawal movement was observed after injection of rocuronium Maruishi in 21 of 30 patients (70%).

In all the patients in both the groups, the anesthesiologists judged that the degree of neuromuscular blockade was optimal and tracheal intubation was attempted. In all the patients, tracheal intubation was successful, without vocal cord responses or straining. In no patient, were there hemodynamic abnormalities which required treatment.

Discussion

We have shown that the incidence of moderate or severe withdrawal movement was significantly less after injection of rocuronium Maruishi than after injection of rocuronium MSD, during rapid-sequence induction of anesthesia. In addition, the degree of withdrawal movement was significantly less with rocuronium Maruishi than with rocuronium MSD.

Rapid-sequence induction of anesthesia was developed in 1950's, to minimize pulmonary aspiration [8]. The original method was preoxygenation, induction of general anesthesia with an ultra short-acting barbiturate (thiopentone) and suxamethonium, and no manual ventilation via a facemask [8]. Nevertheless, pulmonary aspiration frequently occurred [8]. The induction method was firmly established by introducing cricoid pressure in 1960"s [9].

Since the mid 1980's, a variety of modified methods have been proposed [10]. One major modification was the use of propofol instead of a barbiturate, and another the use of a high-dose rocuronium instead of suxamethonium. In addition, several drugs, such as opoids, calcium channel blockers, or beta blockers, have been suggested to minimize sympathetic responses to laryngoscopy and tracheal intubation.

During rapid-sequence induction of anesthesia, it is crucial to induce anesthesia as rapid as possible, so that it is necessary to minimize the number of drugs to be injected. In addition, it would be necessary to avoid injecting drugs which may increase the risk of pulmonary aspiration. Both propofol and rocuronium may frequently produce body movements, which may delay the onset of drugs and may increase the intragastric pressure (and subsequent pulmonary aspiration) [5-7, 11]. Opioids may also frequently induce excessive hypotension and bradycardia, and cause difficulty in mouth opening, difficult tracheal intubation, and difficult mask ventilation [12-16]. Studies have shown that the incidence of difficult airway management was 7-17% of cases [13, 14], and thus administration of an opioid may not be

suitable during rapid-sequence induction of anesthesia. A recent systematic review has shown that there is no evidence to support that drugs which prevent sympathetic responses to tracheal intubation would reduce the morbidity or mortality [16]. Therefore, there is no clear evidence as to which drugs should be used during rapid-sequence induction and intubation. Commercially available rocuronium are generally known to produce frequently pain and withdrawal movement, and several different drugs have been suggested to prevent pain and withdrawal movement [4, 5, 10]. We have found that rocuronium Maruishi caused moderate or severe withdrawal movement in only 3 of 30 patients (10%), and no withdrawal movement was observed in 21 of 30 patients (70%).

The mechanism is not known for rocuronium-induced pain or withdrawal movement, but it is believed that the pain is induced not by rocuronium in itself, but the osmolality or pH of their formulations is the likely cause [17-19]. Jimbo reported that the vascular pain on rocuronium injection was caused by hydrogen ions produced by weak acid, and low acid concentration buffer solution would eliminate vascular pain in a rat model [20]. The buffer for rocuronium MSD contains sodium acetate, whereas the buffer for Rocuronium Maruishi contains low acid concentration glycine/hydrochloric. These differences may the reason for the difference in the incidence of pain and withdrawal movement.

One possible problem with rocuronium Maruishi is that the onset time may not be as rapid as rocuronium MSD. In our study, there was no apparent difference in these drugs in the onset time, and tracheal intubation was successful, without vocal cord responses or straining, 1 min after injection. In addition, in no patient was it necessary to treat cardiovascular abnormalities after tracheal intubation.

In conclusion, compared with rocuronium MSD, rocuronium Maruishi is more suitable than conventional rocuronium formulations, for rapid-sequence induction of anesthesia.

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Table1. Patients' characteristics (Mean (SD) [range])

	Rocuronium MSD* (n=30)	Rocuronium Maruishi* (n=30)
Sex (males/ females)	11/19	12/18
Age (yr)	47 (11.7) [26-65]	47 (12.1) [22-65]
Height (cm)	163 (9.5) [147-180]	164 (9.1) [150-185]
Weight (kg)	60 (11.3) [42-89]	65 (13.3) [44-91]

*: Rocuronium MSD: ESLAX Intravenous® rocuronium
Rocuronium Maruishi: Rocuronium Bromide Intravenous Solution Maruishi ®

Table 2 Degree of withdrawal movements after injection of rocuronium

	None	Mild	Moderate	Severe
Rocuronium MSD* (n=30)	13	6	4	7
Rocuronium Maruishi* (n=30)	21	6	1	2

None: No response
Mild: Movement at the wrist only
Moderate: Movement/withdrawal involving arm only (elbow or shoulder)
Severe: movement/withdrawal in more than one extremity or body trunk, cough, or breath holding

*: Rocuronium MSD: ESLAX Intravenous® rocuronium
Rocuronium Maruishi: Rocuronium Bromide Intravenous Solution Maruishi ®

CONSORT 2010 Flow Diagram