Hyperthyroidism Patients Have Shorter Onset and Duration Time of Rocuronium than Euthyroidism Patients

Yong-guang Wang[1], Xiao-jun Song[2], Shan-wu Feng[1], Ya-li Ge[1], Jian-jun Yang[1], Liang-liang He[1]

[1]Department of Anesthesiology and [2]Department of Pharmacy, Jinling Hospital, School of Medicine, Nanjing University, Nanjing, P.R. China.

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ABSTRACT - PURPOSE. The possibility of altered response to nondepolarizing muscle relaxants in hyperthyroidism patients has not been documented. The present study was conducted to observe the onset and duration of rocuronium-induced neuromuscular blockde in hyperthyroidism patients. **METHODS.** Eighteen hyperthyroidism patients undergoing subtotal thyroidectomy (H group) and eighteen euthyroidism patients undergoing operation on neck (E group) were studied. Anesthetized with propofol and fentanyl, all patients received rocuronium 0.6 mg/kg. The twitch high of adductor pollicis muscle was monitored by acceleromyography. The onset, the duration of the initial dose, the durations of the repeated maintenance doses, the repeated times, and the total doses of rocuronium were observed. **RESULTS.** The onset time of rocuronium in H group was significantly shorter than that in E group ($P<0.05$). The duration of the initial dose as well as the durations of the repeated maintenance doses in H group was significantly shorter than that in E group ($P<0.05$). The repeated times and the total dosage of rocuronium in H group were significantly more than that in E group ($P<0.05$). **CONCLUSIONS.** Hyperthyroidism patients experience a shorter onset time, a shorter duration, and require larger doses of rocuronium than euthyroidism patients.

INTRODUCTION

Hyperthyroidism is a common and severe endocrine disease mainly characterized by for example weight loss, hypermetabolism, hypertension, tachycardia, pulse pressure augmentation, and sweatiness (1-3). The critical anesthetic concerns include rational administrations of analgesics, the type of anesthetic, when using nondepolarizing neuromuscular blocking agents (NMBA), and appropriate suppression of stress reaction. Rocuronium is a nondepolarizing NMBA with an intermediate duration time, but with a rapid onset of action whereby good intubating conditions are achieved within 60 to 90 seconds after rocuronium 0.6 mg/kg (4,5). A search in PubMed yielded nearly one thousand articles on rocuronium but no report regarding administration of rocuronium or other nondepolarizing NMBA in the hyperthyroidism patients.

Hyperthyroidism patients show a more rapid clearance and need a larger dosage of some drugs, such as propranolol, theophylline, and propofol than euthyroidism patients (6,7). We hypothesized that rocuronium also could be cleared more rapidly and larger doses of rocuronium should be needed in hyperthyroidism patients compared with euthyroidism patients. The objective of the present preliminary study was to observe the onset and duration of rocuronium-induced neuromuscular blockde in hyperthyroidism patients who received subtotal thyroidectomy.

Corresponding Author: Jian-jun Yang, MD, Department of Anesthesiology, Jinling Hospital, 305 East Zhongshan Road, People's Republic of China. E-mail: zbfcj@hotmail.com.

METHODS

Ethics Consideration

The present study was approved by the Ethics Committee of Jinling Hospital and conducted according to the Helsinki Declaration and prior written informed consents were obtained from all the patients.

Inclusion and Exclusion Criteria of Patients

Thirty-six adult patients, 18 to 50 years of age, 43 to 73 kg of weight, undergoing scheduled elective operation on neck, were sequentially enrolled from January 2003 to January 2006. They consisted of 18 hyperthyroidism patients (H group, ASA II, American Society of Anesthesiologists Physical Status II) underwent subtotal thyroidectomy. Eighteen gender- and age-matched, duration of time of anesthesia-matched euthyroidism patients (E group, ASA I, American Society of Anesthesiologists Physical Status I) served as controls.

Patients with coronary artery disease, heart failure, hematopathy, diabetes, water-electrolyte disturbances, acid-base imbalances, or neuromuscular disorders were excluded from the present study. None of the patients received any other drug known to interact with neuromuscular blocking drugs before surgery except that all hyperthyroidism patients received antithyroid premedication with oral potassium iodide compound solution and propranolol. All the patients had normal liver and renal functions.

Anesthesia Techniques

Demographics, pulse pressure (mmHg), hart rate, antithyroid drugs, and laboratory test results two weeks before surgery [free triiodothyronine (FT3), free thyroxine (FT4), thyrotropic stimulating hormone (TSH)] were recorded when patients were visited the day before surgery.

All the patients were premedicated with intramuscular phenobarbital 0.1g half an hour before anesthesia. After the patients were admitted to the operation room, electrocardiography, pulse oximetry saturation, and invasive blood pressure through left radial artery cannulation were monitored. After left cephalic vein cannulation, intravenous Ringer's lactate was infused at the rate of 10±2 ml/kg/h.

General anesthesia was induced with midazolam 0.04-0.06 mg/kg, fentanyl 3.0 μg/kg and propofol 2-3 mg/kg. Rocuronium (Organon, Holland) 0.6 mg/kg was intravenously administered within 3 s to facilitate orotracheal intubation. After orotracheal intubation, all the patients were mechanically ventilated to keep the end tidal carbon dioxide tension 32–35 mmHg. Ten minutes later, anesthesia was maintained with continuous intravenous infusion of fentanyl 3 μg/kg/h and propofol 4–12 mg/kg/h adjusted on the basis of physiological signs, such as heart rate, arterial blood pressure, and pupil size. Esmolol 0.25 mg/kg was intravenously administered to the patients once mean arterial blood pressure increased more than 15% of the baseline associated with tachycardia when the propofol infusion rate had already achieved 12 mg/kg/h.

Neuromuscular Blocking Effects

Neuromuscular transmission was monitored by acceleromyographic (NMT mechanosensor) using train-of-four-sequence (TOF) (Datex-Ohmeda S/5 Anesthesia Monitor, Datex-Ohmeda Divisin, Instrumentarium Corp., Helsinki, Finland). The right forearm was prepared for monitoring. The hand and the forearm were immobilized in a splint allowing free mobility of the thumb. Skin temperature was monitored and maintained above 32°C. The monitor automatically determined the supramaximal current and response reference level, and then the ulnar nerve was stimulated at

the wrist via surface electrodes by supramaximal current in a TOF (0.2 ms duration, 2 Hz, four consecutive square wave impulses). These stimuli were delivered every 20 s throughout the present investigation. To determine onset time and recovery of rocuronium, the response of the adductor pollicis muscle to stimulation, which was quantified using an acceleromyographic probe fixed to the volar surface of the distal phalanx of the thumb, of the ulnar nerve was monitored. The TOF monitor was connected to a personal computer for online data recording and processing.

The time from administration of rocuronium to complete clinical recovery was monitored. The effects of NMB were monitored as following steps: 1) recoded the time between rocuronium initial administration and complete depression of the first twitch (onset time); 2) recorded the time between rocuronium initial (1^{st}) administration and recovery of the first twitch of the TOF response to 25% (1^{st} T25); 3) once the recovery of first twitch of the TOF response achieved 25%, an additional dose of rocuronium 0.15 mg/kg should immediately been administered; 4) recorded the time from rocuronium 2^{nd}, 3^{rd}, 4^{th}, and 5^{th} administration to recovery of first twitch of the TOF response to 25% (2^{nd}, 3^{rd}, 4^{th}, and 5^{th} T25), respectively; 5) calculated the average dosage of rocuronium needed to maintain clinical neuromuscular blockade effect in per unit time (the total doses of rocuronium was 1.2 mg/kg/h in both groups). In addition, the average esmolol consumption and the average propofol infusion rate in this period were also calculated.

Body temperature was monitored throughout the study in all patients by means of nasopharyngeal temperature probes with the room air temperature controlled at about 24 °C.

Statistical Analysis

Data were expressed as mean ± SD or proportions. Statistical analysis was performed by a computer program, Statistical Product for the Social Sciences (SPSS version 11.5). Between the two groups, sex distribution and ASA physical status were compared using Chi–square test and body temperature at the end of the study was compared using one-way analysis of covariance (dependent variable: body temperature at the end of the study; fixed factor: group; covariate: body temperature before anesthesia).

The other comparisons between the two groups, after a test for homogeneity of related variances, were performed using the independent samples Student's t-test (equal variances) or t'-test (unequal variances). Differences were considered to be significant at $p<0.05$.

RESULTS

Study Population

Two female patients, one in H group and the other in E group, didn't achieve complete depression of the first twitch after rocuronium 0.6 mg/kg intravenously administered, and then they seceded from the present study. Hence, we studied 34 patients, 17 with hyperthyroidism and 17 with euthyroidism. Demographics and preoperative laboratory test results, antithyroid drugs, and hemodynamics of these patients were collected and statistically analyzed (Table 1). Patients did not differ with respect to age, sex or height ($P>0.05$), but differed with respect to weight, body mass index, ASA physical status, FT3, FT4, TSH, pulse pressure, HEART RATE, propranolol consumption and potassium iodide solution consumption ($P<0.05$). FT3, FT4, and TSH were significantly higher or lower, respectively, than their reference normal range of value in H group (in our hospital normal range of

FT3: 3-9 pmol/L; normal FT4: 9-25 pmol/L; normal TSH: 0.5-5.0 mU/L) (P<0.05), while not in E group.

Table 1. Demographics and preoperative laboratory test results, medications, and hemodynamics

	H group (n=17)	E group (n=17)
Age (yr)	36±10	38±11
Sex (M/F)	3/14	3/14
Height (m)	1.62±0.08	1.63±0.08
Weight (kg)	52±5#	61±7
Body mass index (kg/m^2)	19.7±1.5#	22.9±2.3
ASA physical status (I/ II)	0/17#	17/0
FT3 (pmol/L)	34.9±12.8#	5.7±2.1.
FT4 (pmol/L)	61±18#	15±5
TSH (mU/L)	0.03±0.02#	4.39±0.71
Pulse pressure (mmHg)	54±7#	46±6
Heart rate (beat/min)	96±8#	81±8
Propranolol consumption (mg/day)	48±13#	0
Potassium iodide solution consumption (drop/day)	48#	0

FT3=free triiodothyronine; FT4=free thyroxine; TSH= thyrotropic stimulating hormone; ASA=American Society of Anesthesiologists. Data were expressed as mean ± SD or proportions. Between the two groups, sex distribution and ASA physical status were compared using Chi–square test and the other comparisons were performed using independent samples Student's t-test (equal variances assumed) or t' test (equal variances not assumed). # P<0.05 significant difference in H group compared with E group.

Onset and Duration time of Rocuronium

The assessments of neuromuscular blockade and recovery of rocuronium in two groups were presented and compared in Table 2. The onset time, 1st, 2nd, 3rd, 4th, and 5th T25 in H group were significant shorter than those in E group (P<0.05). The shortest onset time in H group was only 42 s. The average dosage of rocuronium in per unit time in H group was significant more than those in E group (P<0.05). (Table 2)

Table 2. Onset and duration time, and dosage in per unit time, of rocuronium

	H group (n=17)	E group (n=17)
Onset time (s)	56±10#	71±13
1st T25 (min)	17±5#	31±8
2nd T25 (min)	11.1±2.6#	23.7±6.7
3rd T25 (min)	10.9±2.5#	22.6±4.4
4th T25 (min)	11.8±2.8#	22.8±4.9
5th T25 (min)	12.2±2.9#	22.1±4.6
Dosage in per unit time (mg/kg/h)	1.14±0.13#	0.59±0.09

1st, 2nd, 3rd, 4th, and 5th T25 represented the time from rocuronium 1st, 2nd, 3rd, 4th, and 5th administration to recovery of first twitch of the TOF response to 25%, respectively. Data were expressed as mean ± SD. Comparisons were performed using independent samples Student's t-test. # P<0.05 significant difference in H group compared with E group.

Propofol Infusion Rate, Esmolol Consumption, and Body Temperature

The average esmolol consumption (0.59 mg/kg) and the average propofol infusion rate

(10.4mg/kg/h) in H group were significantly higher than those in E group (0.06 mg/kg and 6.9 mg/kg/h, respectively; P<0.05). At 3rd,4th, and 5th T25 time points, body temperature had significant difference between the two groups (P<0.05). At 5th T25 time points, the body temperature increased significantly from 36.53 to 37.11°C in H group (P<0.05), while not in E group. (Table 3).

DISCUSSION

The two groups differed in weight, body mass index, ASA physical status, FT3, FT4, TSH, pulse pressure, heart rate, propranolol consumption and potassium iodide solution consumption (P<0.05). This, however, illustrated the characters of hyperthyroidism patients (1-3). Traditional preoperative preparation for hyperthyroidism patients with propranolol and iodides (8, 9) was adopted; however, euthyroidism state wasn't totally achieved according to the still presented augmentation in pulse pressure and increase in heart rate in H group.

There are two major findings in the present study: the administration of a standard dose of rocuronium (0.6 mg/kg) followed by an additional dosage of rocuronium 0.15 mg/kg in H group leads to both a shorter onset and a shorter duration from NMB compared with E group. Documented by the short persisting NMB, our results support the hypothesis that hyperthyroidism patients need larger doses of rocuronium due likely to a more rapid clearance. The more rapid clearance as a result of a higher liver blood floe had also been demonstrated for some other drugs (6, 7).

However, there were a few limitations in the present study. First, we didn't measure the cardiac output at the corresponing time points; second, we did not measure the drug concentration to ascertain an accelerated clearance as the cause of the differences between the two groups, hence, we have only speculated on the reasons for the findings of the present study.

Table 3. Propofol infusion rate, esmolol consumption, and body temperature in the study

	H group (n=17)	E group (n=17)
Propofol infusion rate (mg/kg/h)	10.4±1.4＃	6.9±1.2
Esmolol consumption (mg/kg/h)	0.59±0.23＃	0.06±0.11
Body temperature at the end of the study (°C)	37.10±0.20＃	36.53±0.19
(Body temperature before anesthesia)	(36.53±0.19)	(36.51±0.18)

Data were expressed as mean ± SD. Comparisons of propofol infusion rate and esmolol consumption were performed using independent samples Student's t-test; comparison of body temperature at the end of the study was performed using one-way analysis of covariance (dependent variable: body temperature at the end of the study; fixed factor: group; covariate: body temperature before anesthesia). ＃P<0.05 significant difference in H group compared with E group.

The faster and larger blood flow could shorten the time and increase the dosage in per unit time, respectively, of rocuronium from intravenous administration to the neuromuscular junction. We speculated that the high dynamia status, especially the increased cardiac output, should mainly account for a shorter onset time (6, 7). Faber and coworkers have observed that cardiac output is 11.4 L/min or so in patients with hyperthyroidism as compared with 5 L/min in healthy subjects, and it still 8.5 L/min or so after the treatment of the overt hyperthyroid (3). Santiveri et al have reported that premeditation with ephedrine 10 mg decreases the onset time of rocuronium but does not affect the timing of atracurium (10).

The pharmacokinetics of rocuronium is altered by renal and hepatic disease (4, 5). Sandker and coworkers (11) and Proost and coworkers (12), however, have demonstrated that rocuronium is eliminated primarily by the liver. It is taken up into the liver by a carrier-mediated active transport system (13, 14). Khuenl-Brady K and coworkers found that only a small fraction (10%) of rocuronium is eliminated in urine (15). The quicker and increased blood flow to the liver rushes rocuronium quicker through when the transporters in the liver aren’t fully saturated (13, 14). Hence a quicker and shorter duration from NMB was observed in the present study.

Hyperthermia could shorten the duration of action of nondepolarizing NMBA (16, 17). It seemed that the shorter duration time of rocuronium in hyperthyroidism patients was somewhat due to the higher temperature. This may be an unlikely explanation since there was only 0.57 °C difference between hyperthyroidism and euthyroidism patients. In addition at 1st and 2nd T25 time points, when there were no significant differences in the body temperature, the blocking duration of rocuronium was still significantly different between hyperthyroidism and euthyroidism patients.

Higher propofol infusion rate was observed in H group. Tsubokawa et al (7) have suggested that this may be due to a rapid plasma clearance and an increased distribution volume of propofol. We administered esmolol to suppress the over expressed stress reaction though propranolol or esmolol does not invariably prevent "thyroid storm"(18). Loan and coworkers (19) reported that the onset and duration time changed insignificantly in patients receiving beta-adrenoreceptor blockers. Body mass index was significant lower in hyperthyroidism patients compared with euthyroidism patients. This is interesting since Puhringer et al (20) have concluded that there is no significant difference in the onset time and the duration of action of rocuronium between underweight and normal patients. Additionally, the larger esmolol consumption per unit time, due likely to a faster clearance, the increase in average body temperature after surgery, and the higher average propofol infusion rate in H group suggest a higher dynamic status in the hyperthyroidism patients.

In conclusion, hyperthyroidism patients experienced a shorter onset time, a shorter duration time, and need larger doses of rocuronium than euthyroidism patients. Accordingly, an increased dose of rocuronium is recommended. The question of whether other nondepolarizing NMBA have altered effect kinetics in hyperthyroidism patients should be studied in further investigation.

REFERENCES

[1]. Klein I and Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med, 344: 501-509, 2001.

[2]. Woeber KA. Thyrotoxicosis and the heart. N Engl J Med, 327: 94-98, 1992.

[3]. Faber J, Wiinberg N, Schifter S and Mehlsen J. Haemodynamic changes following treatment of subclinical and overt hyperthyroidism. Eur J Endocrinol, 145: 391-396, 2001.

[4]. Sparr HJ, Beaufort TM and Fuchs-Buder T. Newer neuromuscular blocking agents: how do they compare with established agents? Drugs, 61: 919-942, 2001.

[5]. Atherton DP and Hunter JM. Clinical pharmacokinetics of the newer neuromuscular blocking drugs. Clin Pharmacokinet, 36: 169-189, 1999.

[6]. O'Connor P and Feely J. Clinical pharmacokinetics and endocrine disorders: therapeutic implications. Clin Pharmacokinet, 13: 345-364, 1987.

[7]. Tsubokawa T, Yamamoto K and Kobayashi. Propofol clearance and distribution volume increase in patients with hyperthyroidism. Anesth Analg, 87: 195-199, 1998.

[8]. Feek CM, Sawers JSA, Irvine WJ, Beckett GJ, Ratcliffe WA and Toft AD. Combination of potassium iodide and propranolol in preparation of patients with Graves' disease for thyroid surgery. N Engl J Med, 302: 883-885, 1980.

[9]. Hamilton WF, Forrest AL, Gunn A, Peden NR and Feely J. Beta-adrenoceptor blockade and anaesthesia for thyroidectomy. Anaesthesia, 39: 335-342, 1984.

[10]. Santiveri X, Mansilla R, Pardina B, Navarro J, Alvarez JC and Castillo J. Ephedrine shortens the onset of action of rocuronium but not atracurium. Rev Esp Anestesiol Reanim, 50: 176-1781, 2003.

[11]. Sandker GW, Weert B, Olinga P, Wolters H, Slooff MJ, Meijer DK and Groothuis GM. Characterization of transport in isolated human hepatocytes. A study with the bile acid taurocholic acid, the uncharged ouabain and the organic cations vecuronium and rocuronium. Biochem Pharmacol, 47: 2193–2200, 1994.

[12]. Proost JH, Roggeveld J, Wierda JM and Meijer DK. Relationship between chemical structure and physicochemical properties of series of bulky organic cations and their hepatic uptake and biliary excretion rates. J Pharmacol Exp Ther, 282: 715–726, 1997.

[13]. Schwarz LR and Watkins JB 3rd. Uptake of taurocholate, a vecuronium-like organic cation, ORG 9426, and ouabain into carcinogen-induced diploid and polyploid hepatocytes obtained by centrifugal elutriation. Biochem Pharmacol, 43: 1195–1201, 1992.

[14]. Smit JW, Duin E, Steen H, Oosting R, Roggeveld J and Meijer DK. Interactions between P-glycoprotein substrates and other cationic drugs at the hepatic excretory level. Br J Pharmacol, 123: 361–370, 1998.

[15]. Khuenl-Brady K, Castagnoli KP, Canfell PC, Caldwell JE, Agoston S and Miller RD. The neuromuscular blocking effects and pharmacokinetics of ORG 9426 and ORG 9616 in the cat. Anesthesiology, 72: 669–674, 1990.

[16]. Heier T, Caldwell JE, Sessler DI and Miller RD. Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans. Anesthesiology, 74: 815–819, 1991.

[17]. Caldwell JE, Heier T, Wright PM, Caldwell

JE, Heier T, Wright PM, et al. Temperature-dependent pharmacokinetics and pharmacodynamics of vecuronium. Anesthesiology, 92: 84–93, 2000.

[18]. Eriksson M, Rubenfeld S, Garber AJ and Kohler PO. Propranolol does not prevent thyroid storm. N Engl J Med, 296: 263-264, 1977.

[19]. Loan PB, Connolly FM, Mirakhur RK, Kumar N and Farling P. Neuromuscular effects of rocuronium in patients receiving beta-adrenoreceptor blocking, calcium entry blocking and anticonvulsant drugs. Br J Anaesth, 78: 90-91, 1997.

[20]. Puhringer FK, Khuenl-Brady KS and Mitterschiffthaler G. Rocuronium bromide: time-course of action in underweight, normal weight, overweight and obese patients. Eur J Anaesthesiol Suppl, 11: 107-110, 1995.