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*Original Article*

# The relationship between the target effective site concentration of rocuronium and the degree of recovery from neuromuscular blockade in elderly patients

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**Abstract:** Objective: To study the relationship between the target effective site concentration (Ce) of rocuronium and the degree of recovery from neuromuscular blockade in elderly patients. Methods: 50 elderly patients (ASA grade II) scheduled for selective surgical procedure under general anaesthesia were randomly divided into two groups, A and B, with 25 cases in each group. The Ce of rocuronium for intubation was 3 $\mu g \cdot ml^{-1}$ in both groups, and the Ce during operation were 0.8 and 1.0 $\mu g \cdot ml^{-1}$ in group A and B, respectively. When target controlled infusion of rocuronium was stopped, without the administration of reversal agents for neuromuscular blockade, the relationship between Ce and the first twitch height ($T_1$) was studied by regression analysis. Results: There was a significant linear relationship between Ce and $T_1$, and there was no statistical difference in regression coefficient and interception between group A and B ($P>0.05$). Conclusion: The degree of recovery from neuromuscular blockade could be judged by the target effective site concentration of rocuronium at the time of reversal from neuromuscular blockade in the elderly patients.

**Keywords:** Rocuronium, neuromuscular blockade, geriatrics, pharmacodynamics

## Introduction

There is an incidence of higher residual effect of muscle relaxation in elderly patients, and this effect can lead to hypoxia and increase mortality rate. Although we can overcome these malpractice by NMT monitoring, but it also has many drawbacks, such as there are more influencing factors and preparation is tedious and time-consuming. The target controlled infusion (TCI) technology can group pharmacokinetic parameters and computer technology, and can calculate drug's theoretical target effective site concentration (Ce) by describing the process of drug's access to the effective site [1]. There is an approximate relation between the effects of the muscle relaxant and Ce, so we can judge the degree of recovery of neuromuscular blockade by Ce.

Rocuronium, an intermediate, acting on muscle relaxant with a faster onset of action, has the pharmacokinetic (PK) properties that is suitable for continuous infusions [2]. Wierda et al. [3, 4] determined the relationships between PKs and pharmacokinetic-pharmacodynamic (PK-PD) of rocuronium and calculated the concentration in the effect compartment associated with a 50% drug effect (EC50) in adults, children, and infants by using the Sheiner model and the Hill equation [5, 6].

The aim of this study was to study their relationship between the Ce of rocuronium and the degree of recovery from neuromuscular blockade to analyze the feasibility of judging the degree of recovery from neuromuscular blockade by TCI of rocuronium Ce without NMT monitoring in elderly patients.

## Methods

### *Patients*

This study was approved by the institutional Medical Ethics Committee of the First Affiliated Hosptial of Zhengzhou University, and informed consent was obtained from patients. A total of 50 elderly patients (65-80 yr, ASA status I or II,

**Table 1.** Patient characteristic

| | Group A (n = 25) | Group B (n = 25) |
|---|---|---|
| Age (yr) | 69.7 ± 4.3 | 70.1 ± 5.0 |
| Weight (kg) | 62.0 ± 6.2 | 60.2 ± 6.5 |
| Height (cm) | 162.5 ± 4.5 | 161.1 ± 5.5 |
| Sex (M/F) | 12/13 | 13/12 |
| ASA physical status (I/II) | 5/20 | 4/21 |
| Duration of TCI (time) | 105.9 ± 14.6 | 109.8 ± 10.2 |

undergoing elective surgery under general anaesthesia) were selected for the study. Those with BMI above 30 $kg \cdot m^{-2}$, those with a history of neuromuscular disease, malignant hyperthermia, or renal or hepatic dysfunction, and those taking medication which had potential interference with neuromuscular transmission were excluded.

*Anaesthesia*

Patients were randomized into two groups, group A and group B, with 25 patients each. According to pretrial results, the Ce of rocuronium for intubation was 3 $\mu g \cdot ml^{-1}$ in both the groups, and the Ce during operation were 0.8 and 1.0 $\mu g \cdot ml^{-1}$ in group A and B, respectively. Patients were randomly assigned to one of the two groups by a physician who was not involved in the patient's care, using numbered sealed envelopes. All drugs were prepared by an independent anaesthetist who was not involved in the study.

None the patients were premedicated. A peripheral IV cannula was placed in the same arm used for neuromuscular transmission assessments. Standard monitoring included electrocardiogram (ECG), pulse oximetry, noninvasive blood pressure, capnography, and core body and peripheral skin temperature.

Neuromuscular transmission monitoring was complied with GCRP (good clinical research practice) [7, 8], using TOF-WatchR SX (Organon) NMT monitor. After induction, but before administration of the neuromuscular blocking agent, the TOF-WatchR SX NMT monitor was calibrated using its automatic start-up-procedure, and then applied 0.1 Hz single twitch stimulation. Following injection of the relaxant when maximal neuromuscular blockade was obtained, we switched to TOF stimulation assessed at 15 sec intervals by stimulation of ulnar nerve with four rectangular impulses at 2 Hz, duration 0.2 ms and supramaximal current. The evoked muscle response of adductor pollicis muscle was monitored with accelerometry with a sensor attached to the distal phalanx of the pollex. The forearm was immobilized in supination on a splint and original hand adaptor (Organon) was interposed between pollex and index finger. All data reflecting the effect of neuromuscular blockade were transferred into the PC via optical cable (Organon). TOF-Watch SX Monitor software v. 2.2 INT (Organon) was used to display the NMT values on the screen and was stored for further processing.

Following preoxygenation, anesthesia was induced with 0.1 $mg \cdot kg^{-1}$ midazolam and 5 $\mu g \cdot kg^{-1}$ fentanil in all patients. After establishment of stable neuromuscular response for at least 5 min, 3 $\mu g \cdot ml^{-1}$ rocuronium in a 20-mL syringe was given to all the patients using a TCI syringe driver (TCI-I, Szenohradszkay mode; Beijing sIgo high-tech development CO, China) to reach a theoretical Ce. After the first twitch height (T1) was less than or equal to 5%, direct laryngoscopy was initiated followed by tracheal intubation. The intubation was always performed by an experienced anaesthetist, using endotracheal tubes. Anesthesia maintenance comprised of continuous i.v. infusion of 6-12 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol and 0.1-0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil as required. No inhalation anesthetics were used. The core body temperature was maintained between 36°C and 37°C using a warming mattress. The arm used for monitoring the neuromuscular transmission was protected from heat loss with cotton towels.

*Indicatrices of assessment*

1. Onset time = Time interval from the completion of the intravenous injection of the relaxant to maximal T1 depression.

2. Intubating condition was assessed using the score recommended by the 1994 Copenhagen Consensus Conference on Good Clinical Research Practice in Pharmacodynamic Studies of Neuromuscular Blocking agents [9]. Intubation criteria include four variables: jaw relaxation and resistance to laryngoscopy, the position and movement of vocal cords, the movement of the limbs, and coughing reflux. Each of these variables was rated as excellent, good, or poor. Intubating conditions were considered excellent if all variables were excellent, good if all variables were good or excellent, and poor if any of the variable was poor.

**Table 2.** Intubating conditions

| | Onset time (s) | Ce of rocuronium at the moment of intubation (μg/ml$^{-1}$) | Intubating conditions according to the Copenhagen score. | | |
|---|---|---|---|---|---|
| | | | Excellent | Good | Poor |
| Group A (n = 25) | 111 ± 13 | 1.95 ± 0.12 | 15 | 10 | 0 |
| Group B (n = 25) | 106 ± 15 | 1.97 ± 0.11 | 16 | 9 | 0 |

**Table 3.** Rocuronium dosage and muscle strength recovery

| | Group A (n = 25) | Group B (n = 25) |
|---|---|---|
| The amount of Rocuronium used (mg) | 89.3 ± 12.1 | 107.5 ± 15.2* |
| Rocuronium dosage in per unit time (μg/kg$^{-1}$/min$^{-1}$) | 17.6 ± 1.8 | 22.4 ± 2.4* |
| Satisfactory rate of muscle relaxation | 100% | 100% |
| Recovery time to 25% of T1 (min) | 20.6 ± 3.5 | 27.0 ± 6.1* |
| Recovery index (min) | 20.2 ± 3.7 | 22.4 ± 4.2 |
| Ce of T1 restore to 25% (μg/ml$^{-1}$) | 0.24 ± 0.03 | 0.21 ± 0.04 |

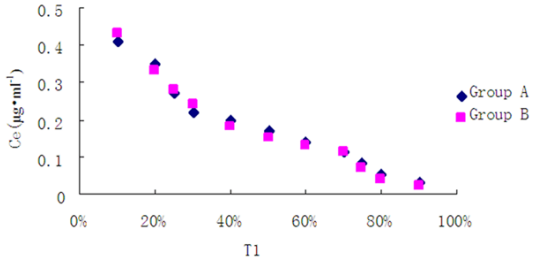


**Figure 1.** Relationships between Ce and T1 in both the groups at the time of recovery from muscle relaxation were studied by linear regression analysis. The Ce of rocuronium for intubation was 3 μg·ml$^{-1}$ in both the groups, and the Ce during operation were 0.8 and 1.0 μg·ml$^{-1}$ in group A and B, respectively. Regression equation: $Y_A$ = -0.4944XA+0.4517 (r = -0.9095), $Y_B$ = -0.4667XB+0.4747 (r = -0.8998).

3. Degree of Perioperative neuromuscular block. T1≤10% was considered as satisfactory muscle relaxation and T1>10% was considered to be unsatisfactory.

4. Time duration of TCI, and the amount of rocuronium used.

5. Recovery time to 25% of T1 = Time interval from TCI stoppage to 75% recovery of T1 (T1 = 75%); Recovery index = Time interval from the end of clinical duration (T1 = 25%) to 75% recovery of T1 (T1 = 75%).

6. Ce of rocuronium at the moment of intubation, and the time points when T1 returned to 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75% 80%, 90% of neuromuscular blockade recovery after surgery.

*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 17.0). Sex distribution, ASA physical status and the degree of perioperative neuromuscular block were compared using Chi-square test between the two groups, and the Intubating conditions were compared using Wilcoxon rank sum test. The relationship between Ce and T1 was studied by linear regression analysis. 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

*Patient characteristic*

There were no differences between the two groups with respect to age, weight, height, sex distribution, ASA physical status, or intraoperative variables, such as duration of TCI (*P*>0.05) (**Table 1**).

*Ease of intubation*

There were no significant difference between the two groups on onset time and Ce of rocuronium at the moment of intubation (*P*>0.05). The number of patients presenting excellent or good intubating conditions was similar between two groups (*P*>0.05) (**Table 2**).

*Rocuronium dosage, degree of perioperative neuromuscular blockade and recovery of muscle strength*

The amount of rocuronium used, dosage in per unit time and recovery time at 25% of T1 were greater in group B than in group A (*P*<0.05).

There were no significant difference in the satisfactory rate of muscle relaxation, recovery index and Ce of rocuronium at the time of 25% of T1 between two groups ($P$>0.05) (**Table 3**).

*Relationship between Ce and T1 at the time of recovery from muscle relaxation*

The value of T1 at the time of recovery from neuromuscular blockade was regarded as independent variable (X), and the average proportional Ce of rocuronium was regarded as dependent variable (Y). The relationship between Ce and T1 in both the groups were studied by linear regression analysis (**Figure 1**).

Regression equation:

$Y_A$ = -0.4944XA+0.4517 (r = -0.9095)

$Y_B$ = -0.4667XB+0.4747 (r = -0.8998)

There were no significant difference in regression coefficient and interception between two regression equations, and there was a significant negative correlation between Ce and T1. When T1 was restored to 25%, the Ce were 0.26 ± 0.07 μg·ml$^{-1}$ and 0.25 ± 0.09 μg·ml$^{-1}$ in Group A and B, respectively, according to the regression equation. There were no significant difference between them ($P$>0.05), and corresponded to the results of descriptive statistics (**Table 3**, Group A: 0.24 ± 0.03; Group B: 0.21 ± 0.04) ($P$>0.05).

## Discussion

The elderly patients are a special group, as the effect of muscle relaxants is extended and the rate of postoperative residual muscle relaxation increased due to the physiological aging of organs. The muscle-monitoring system TOF can overcome these drawbacks, but its method can not be tolerated by sober patients. In addition, the cost of expensive equipments and cumbersome time-consuming preparation restrict its clinical use. TCI technology based on pharmacokinetics-pharmacodynamics theory, can calculate the theoretical Ce by embedded pharmacokinetic parameters. As the close Ce-effect relationship, we can judge the degree of neuromuscular blockade through the observation of Ce.

However, there are more influencing factors affecting the Ce, which sometimes can lead to the data distortion. In this experiment, the influencing factors of muscle-monitoring system and TCI are controlled, such as calibration time, skin temperature, large or rapid infusion [10] and so on. As these ensure that the group conditions is consistent, accurate and give reliable test results, so this minimizes the manhandling and other factors influence on the experimental results.

The number of patients presenting excellent or good intubating conditions and satisfactory rate of muscle relaxation were similar between the two groups A and B, in this experiment. But there were greater amount of rocuronium used and longer postoperative recovery time in group B than in group A. So considering saving medication and shortening postoperative recovery time, group A is a more rational treatment with satisfactory muscle relaxant.

When the TCI was stopped, the relationship between Ce and T1 was studied by linear regression analysis. In this experiment, there were no significant differences in regression coefficient and interception between two regression equations. There was a good, more fixed linear relationship between Ce and T1, and this relationship would not have a significant impact, whether anaesthesia was maintained by 0.8 μg·ml$^{-1}$ Ce or 1.0 μg·ml$^{-1}$ Ce. All these results suggested that we could generally judge the recovery of muscle relaxants through the Ce observation.

In summary, in elderly patients, TCI administration programme induced by setting rocuronium Ce to 3 μg·ml$^{-1}$ and maintained by 0.8 μg·ml$^{-1}$ Ce was more reasonable. After the TCI was stopped, there was a good, more fixed linear relationship between Ce and T1. When Ce falled to 0.2~0.3 μg·ml$^{-1}$ and T1 restored to about 25 percent, we might consider the reversal of muscle relaxation. Therefore, we can generally judge the recovery of muscle relaxants through the Ce observation in the absence of monitoring muscle relaxants.

## Disclosure of conflict of interest

None.

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