A Comparative Study on the Dose and Mode of Administration of Rocuronium During Cardiac Surgery Under Cardiopulmonary Bypass

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Background **---** Studies regarding the pharmacokinetics of muscle relaxants for cardiopulmonary bypass (CPB) abound but are conflicting. The available dose regimen does not guarantee adequate muscle relaxation. This study aims to determine the optimum rocuronium dose and mode of administration to maintain an adequate degree of muscular relaxation during CPB among adult patients.

Methods **---** This is a randomized controlled open label trial involving patients undergoing cardiac surgery. Eighty (80) subjects were randomly assigned to four treatment groups. For Group A, intubating dose was given at 0.6 mg/kg and maintenance by infusion. For Group B, intubating dose was given at 0.6 mg/kg andmaintenance by bolus. For Group C, intubating dose was given at 0.9 mg/kg and maintenance by infusion. For Group D, intubating dose was given at 0.9 mg/kg and maintenance by bolus. Maintenance dose was started when TOF count was >2. Onset and duration of action of the intubating dose and the total maintenance dose requirement were noted. All other aspects of anesthesia care followed the standard protocol.

Results **---** Subjects were homogenously distributed according to age (p-value =0.134), gender (p-value = 0.415), body mass index (p-value =0.636), type of surgery (p-value =0.191), and presence or absence of diabetes (pvalue 0.131) and hypertension (0.07). Rocuronium at 0.9mg/kg had faster onset (3.74 ± 2.99 min) compared to that given at 0.6mg/kg (6.28 ± 2.58 min). The two dosages did not differ in duration of action. Maintenance dose by bolus decreases the requirement to 2.64±0.821 mcg/kg/min compared to that by infusion given at 3.09 ± 1.12 mcg/kg/min.

Conclusion **---** For cardiac surgery under cardiopulmonary bypass, rocuronium at 0.9 mg/kg had a faster onset on action and maintenance dose by bolus decreases the requirements compared to that by infusion.

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Key Words: Rocuronium ■ Cardiopulmonary Bypass ■ Dosing ■ Muscle Relaxants

Neuromuscular relaxation is as important in cardiopulmonary bypass as in any other thoracic procedure under general anesthesia.[1] It is for this reason that anesthesiologists prefer to be on the safe side by giving more relaxant than needed than have the patient move during the critical open heart and vascular surgical procedures.

The clinical practice in the Philippine Heart Center is to give muscle relaxant infusions during long open heart procedures by giving one third of the intubating dose. For rocuronium with the intubating dose of 0.6 to 0.9 mg/kg and duration of 30 minutes, requiring 2 top-up doses per hour,[2-5] the usual computation is: Dose (mL/hr) = Wt x 0.6 x 1/3 x 2 + Concentration of preparation. Alterrnatively it can be given at 5 to 15mcg/kg/minute.[6] The advances in neuromuscular monitoring make it safer for anesthesiologists to adjust the dose without compromising relaxation and surgical ease. However, scarcity of data with regards to the optimum dose of muscle relaxants remains, especially in cardiovascular surgeries.

Smeulders et al in 1995[7] suggested that cardiopulmonary bypass decreases requirements for neuromuscular blockers because of numerous reasons. Cooling influences nerve conduction in the mobilization of acetylcho-

First Place, Oral Presentation 18th PHC Annual Research Paper Competition held on February 23, 2010 at Philippine Heart Center, *Correspondence to* ***Dr. Melissa Morala,*** Division of CV Anesthesia. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

line from the nerve vesicles, as well as modifying cholinergic receptors Cholinesterase enzyme activity is temperature dependent. This decrease in mobilization of acetylcholine is the most important effect of cooling.

Because of hemodilution, there is an initial decrease in free drug concentration. However, because of associated decrease in albumin concentration during cardiopulmonary bypass, free concentration of neuromuscular blockers partially bound to albumin may actually increase.[2,4,7]

Hypothermia during cardiopulmonary bypass may also inhibit hepatic clearance of steroidal neuromuscular blockers including rocuronium hence their action may be prolonged.[7]

The studies by Gueret et al in 2004[1] and Cammu et al in 2007[8] suggested that the single bolus dose of atracurium and cisatracurium given during induction together with maintenance of adequate level of anesthesia were enough to provide adequate surgical conditions. No unwanted patient movement or diaphragmatic contractions were noted.

Contradicting studies by Coddens et al in 2000,[2] Boussemaere et al in 2005,[9] and Mirinejad in 2007[10] demonstrated no statistical significance in dose requirement of neuromuscular blockers before, during and after bypass. Giving a high intubation dose of cisatracurium will not ensure adequate muscle relaxation throughout the surgery.[9]

In clinical practice, rocuronium is a popular preference among anesthesiologists because of the following advantages: (1) faster onset of action (dose dependent)[5] (2) excellent intubating conditions[11] and (3) decreased incidence of postoperative residual muscle paralysis.[13,14]

In general anesthesia, Halothane used with rocuronium given as infusion provides greater stability of drug concentration and prevents occurrence of both inadequate and excessive drug effects. Controlled infusions titrated to effect minimize transfer of drug to compartments other than the effect compartment.[4]

Because rocuronium lacks active metabolites, drug elimination depends only on distribution among compartments and excretion by the liver and kidneys. Pharmacokinetic parameters (volume of distribution at steady state, plasma clearance and elimination half life) in rocuronium given as infusion were similar to those after a large single bolus.[5] However in another study,[3] patients given incremental boluses required lower doses of rocuronium to maintain adequate muscle relaxation (6.4 ± 2.3 mcg/kg/hr) compared to those given by infusion (9.9 ± 1.3 mcg/kg/hr).

Most recommendations for Train of Four (TOF) monitoring suggest drug titration to one or two twitches. Although a TOF of three twitches generally corresponds to an 80% muscular blockade, the resultant muscular weakness was sufficient to assure patient-ventilator synchrony and lower airway pressures and to optimize oxygen delivery in most patients.[14] The acceleromyographic TOF performed better than double-burst stimulation or 100 Hz tetanus having a sensitivity of 70% (95% CI, 54-86%), specificity 88% (95% CI, 67-100%), negative predictive value 47% (95% CI, 23-71%) and positive predictive value 95% (95% CI, 86-100%).[15]

This study aimed to determine the optimum dose and mode of administration of rocuronium to maintain adequate muscle relaxation during cardiopulmonary bypass among adult patients.

Methodology

This is a randomized controlled open label trial conducted at the Cardiovascular Operating Room, Department of Anesthesiology, Philippine Heart Center from August 2008 to May 2009. Institutional Review Board approval was obtained prior to the initiation of the study and written informed consent was obtained from all subjects included in the study.

All consecutive adult patients (18 to 55 years old) undergoing cardiovascular surgery under cardiopulmonary bypass were recruited for this

study. Excluded were those with contraindications to rocuronium, those with impaired liver and renal function, those with short surgical procedure (less than 3 hours), and those with no consent.

Patients who fit the inclusion criteria were randomly assigned to four treatment groups (A, B, C and D) using the table of random numbers. The standard conduct for induction and maintenance of anesthesia was followed. For uniformity, induction of all patients was done using midazolam, fentanyl and sevoflurane. For Group A, intubating dose was given at 0.6 mg/kg and maintenance dose by infusion. For Group B, intubating dose was given at 0.6mg/kg and maintenance dose by bolus. For Group C, intubating dose was given at 0.9 mg/kg and maintenance dose by infusion. For Group D, intubating dose was given at 0.9mg/kg and maintenance dose by bolus. After giving the intuba-ting dose, the time elapsed to achieve a Train of Four (TOF) Count of 2 was recorded as the onset of action in minutes. The time elapsed from the intubating dose of rocuronium to the time of recovery from neuromuscular blockade (Train of Four Count >2) was recorded as the duration of action in minutes.

For Group A and C, the maintenance infusion of rocuronium was started at 10 mcg/kg/min and titrated to the lowest level that will maintain aTOF count of 2 or lower. For Group B and D, initial bolus dose was started at 10 mcg/kg/min and titrated to the lowest level that will maintain a TOF of 2 or lower.

Appendix A details the guidelines for intraoperative TOF monitoring that was used in the study. Surface electrodes were placed on the skin over the ulnar nerve. Four supramaximal impulses of 0.2ms in duration every 0.5 seconds were done using TOF-Watch® nerve stimulator (Organon®, Oss, The Netherlands).

All cases included in this study were comanaged by the principal investigator. All other aspects of anesthetic management for cardiopulmonary bypass were maintained according to the usual protocol.

Assuming a difference of 3.5 ± 2.3 mcg/kg/hr in total dose requirement by mode of administration at alpha of 0.05 and ß=0.20, the computed sample size is 20 per group. The basis for the assumed difference was the result of the paper of Khuenl-Brady K.S. et al. wherein the total dose required to maintain adequate muscle relaxation by infusion was 9.9 ± 1.3 mcg/kg/hr while that given by intermittent bolus was 6.4 ± 2.3mcg/kg/hr.[3]

Results

Table 1 shows the baseline characteristics of the subjects. There were 80 subjects included in the study. They were homogenously distributed according to age, gender and body mass index. Most of them underwent coronary artery bypass graft surgery. Twenty subjects were diabetic and 16 subjects were hypertensive.

Table 2 shows the onset and duration of action of rocuronium given IV bolus. The onset of action of 0.9 mg/kg was earlier than that of 0.6 mg/kg (3.74 min. vs. 6.28 min) and the duration of action was longer (70.61 min. vs. 64.42 min).

Table 3 shows the maintenance dose requirement of rocuronium according to the mode of administration. It is noteworthy that giving rocuronium via bolus needs a lower maintenance dose requirement compared with giving via infusion. (2.64 mcg/kg/min vs. 3.09 mcg/kg/min.)

Discussion

For cardiac surgery, rocuronium has a faster onset and longer duration of action when given at 0.9mg/kg bolus, and requires a lower maintenance dose if it is given via bolus instead of infusion.

Analysis of Variance (ANOVA) showed that rocuronium when given at 0.9mg/kg in cardiac surgery has a faster onset than when given at 0.6mg/kg (p-value 0.000). It is however slower than what is shown by data from general surgical procdures

Table 1. Baseline Characteristics of subjects undergoing cardiac surgery according to intubation dose and mode of administration of Rocuronium (PHC, 2010)

Characteristics	Intubating Dose 0.6mg/kg		Intubating Dose 0.9mg/kg		p-value
	Infusion n=20	Bolus n=20	Infusion n=20	Bolus n=20	
Mean Age (mean ± SD)	50.4 ± 17.7	48.0 ± 13.1	50.2 ± 17.3	40 ± 14.1	0.134
Gender					
Male	15	11	15	12	0.415
Female	5	9	5	8	
Body Mass Index					0.636
Underweight	0	0	3	3	
Normal	14	12	13	10	
Overweight	5	6	3	5	
Obese	1	2	1	2	
Markedly Obese	0	0	0	0	
Type of Surgery					0.191
Ischemic	9	14	5	5	
Valvular	6	4	9	9	
Congenital	2	2	1	3	
Combined	1	0	3	1	
Cardiac Tumors	2	0	2	2	
Diabetes Mellitus	5	7	2	2	0.131
Hypertension	4	9	5	2	0.07

Table 2. Onset and duration of action of rocuronium (minutes) given IV bolus for intubation (PHC, 2010)

Dose	0.6mg/kg		0.9mg/kg		p-value
	Mean	SD	Mean	SD	
Onset of action (min)	6.28	2.58	3.74	2.99	0.000
Duration of action (min)	64.42	41.71	70.61.	35.34	0.483

Table 3. Total maintenance dose requirement of rocuronium (mcg/kg/min) for cardiac surgery according to mode of administration (PHC, 2010)

Treatment Group	Maintenance Dose Requirement (mcg/kg/min)		p-value
	Mean	SD	
Infusion	3.09	1.12	0.045
Bolus	2.64	0.821	

where rocuronium given at 0.9 mg/kg was able to produce adequate muscle relaxation for intubation in 1 minute.

The duration of action of a single bolus of rocuronium did not differ significantly whether it was given at 0.9mg/kg or 0.6mg/kg. It is longer than that which is shown in literature in noncardiac patients where rocuronium is expected to maintain adequate surgical relaxation (TOF count 2) in 30 minutes.

Pharmacokinetic and pharmacodynamic behavior of a single dose of rocuronium, such as that administered during intubation can be accounted for by the variables unique in the cardiac surgical patient including changes in cardiac output, decrease in muscle mass and increase in fat content, increase in volume of distribution, third space distribution, and decrease in plasma protein binding. These differences may be seen even in young adult patients with normal liver and renal function and in the

absence of hypothermia. However, this fairly homogenous sample demonstrated that a faster onset of action is achieved by increasing the intubation dose.

Due to temperature-related effects on the distrubution, elimination and physiology of the neuromuscular junction during cardiopulmonary bypass, the total maintenance dosages of rocuronium was below than what is recommended for general surgical procedures (5-15mcg/kg/min). There was a statistically significant decrease in total maintenance dose requirement when rocuronium is given by bolus than by infusion (p-value 0.45).

At present, there were no adverse drug reactions of rocuronium encountered during the study. However, there were three occasions of sudden diaphragmatic movement even with the TOF count of 2, which can be explained by the low negative predictive value of TOF (47%). During those times, rocuronium dose was increased as necessary.

Conclusion

Although there was a faster onset of action of rocuronium when given in 0.9mg/kg compared to 0.6mg/kg, there was no difference in the duration of action. Total maintenance dosage likewise showed significant decrease when rocuronium is given by bolus.

A multicenter study with serum determination of rocuronium during different phases of cardiopulmonary bypass (e.g. induction, maintenance, rewarming) will help in formulating a more accurate dose regimen for muscle relaxation.

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APPENDIX A

Guidelines for Intraoperative Train of Four (TOF) Monitoring

1. Train of Four (TOF) Monitoring shall be used for the evaluation of onset, duration of action and as a guide for dose adjustment for the bolus and infusion administration of the maintenance dose during cardiopulmonary bypass.

2. TOF monitoring shall be based on the following principles:

- Evaluation of the muscular response to supramaximal electrical stimulation of a peripheral motor nerve
- Reduction in response during constant stimulation reflects degree of neuromuscular blockade
- Electrical impulse should be supramaximal, monophasic and rectangular.optimal duration 0.2 ms
- Four (4) stimuli elicited every 0.5 secs, repeated every 15 secs
- Fading in the response is basis for evaluation
- TOF-ratio: amplitude 4th response/amplitude 1st response. TOF-R=1.0 before administration of muscle relaxant
- TOF count: the number of response for every 4 stimuli

3. The site of stimulation shall be the ulnar nerve or the facial nerve. And electrodes shall be placed as seen in the figure.

4. Evaluation of blockade shall be based on the following:

- Onset of Action of Rocuronium: "period of no response" after injection of Rocuronium (in minutes), no response to TOF or single twitches
- Surgical blockade: maintenance of 2 responses to TOF (4 stimulations)
  1 response = degree nm-blockade 90-95%
  4 responses = nm-blockade 60-85%
- Recovery from Rocuronium Blockade: 4th TOF response heralds recovery, good correlation with clinical signs. For uniformity, this shall be set at TOF-Count <3

5. Onset of action and duration of action (recovery) shall be recorded in minutes.

6. The optimum dosage of rocuronium used to achieve TOF Count of 2 during the maintenance period shall be recorded in mcg/kg/min.

Figure 1. Electrode placement for twitch monitoring of the (a) ulnar nerve muscle and (b) facial nerve muscle.

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