Brief Report

Residual neuromuscular blockade after cardiac surgery: pancuronium *vs* rocuronium

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Purpose: To determine the incidence of residual neuromuscular blockade after cardiac surgery in patients receiving either rocuronium or pancuronium for muscle relaxation.

Methods: In a prospective, controlled, double-blind study, 20 patients undergoing coronary artery bypass were randomized to receive either rocuronium (n = 10) or pancuronium (n = 10) during surgery. Anaesthesia was induced with sufentanil, benzodiazepine and propofol or ketamine, and maintained with air/O_2/sufentanil/isoflurane. Neuromuscular blockade was induced with 0.1 ml·kg^{-1} from blinded syringes containing rocuronium (6 mg·ml^{-1}) (Group R) or pancuronium (1 mg·ml^{-1}) (Group P). Relaxants were administered according to clinical criteria and reversal agents were not given. After surgery, neuromuscular transmission was assessed by train-of-four stimulation of the ulnar nerve/adductor pollicis EMG (Datex Relaxograph). Mean values from three trains of stimuli were recorded and repeated 30 min later if TOF ratio was < 0.7. Time to extubation was recorded.

Results: On arrival in the ICU, nine of 10 patients in group R but only three of 10 patients in group P demonstrated four visible responses ($P < 0.05$). Mean TOF ratio in group P, 0.03 ± 0.05, was less than in group R, 0.68 ± 0.34 ($P < 0.001$). All patients in group P and 4 of 10 patients in group R had TOF ratio < 0.7 ($P = 0.01$). Time to extubation in group P (median 18, range 6–48 hr) was not statistically different from that in group R (14, 5–44 hr).

Conclusion: Residual neuromuscular block, TOF ratio < 0.7, is common after cardiac surgery but the incidence is less when pancuronium is replaced by rocuronium.

Objectif : Comparer après une chirurgie cardiaque l'incidence de la curarisation résiduelle secondaire au rocuronium avec celle du pancuronium.

Méthodes : Cette étude prospective, contrôlée et en double insu regroupait 20 patients opérés pour une chirurgie de revascularisation coronaire. Les patients étaient répartis aléatoirement pour recevoir soit rocuronium (n = 10) soit pancuronium (n = 10) pendant la chirurgie. L'anesthésie était induite au sufentanil, benzodiazépine et propofol ou kétamine et entretenue avec air/O_2/sufentanil/isoflurane. La curarisation était induite à l'aveugle avec 0,1 ml·kg^{-1} provenant de seringues contenant du rocuronium (6 mg·ml^{-1}) (Groupe R) ou pancuronium (1 mg·ml^{-1}) (Groupe P). On administrait les relaxants conformément aux critères cliniques et on n'utilisait pas d'antagonistes. Après la chirurgie, la transmission neuromusculaire nerf cubital-adducteur du pouce était évaluée avec la stimulation électromyographique au train-de-quatre (TOF : Datex Relaxograph). La valeur moyenne de trois trains de stimulations était enregistrée et répétée 30 min plus tard si la valeur du TOF était < 0,7. Le délai de l'extubation était noté.

Résultats : À l'arrivée à l'unité de soins intensifs, neuf des dix patients du groupe R mais seulement trois du groupe P avait quatre réponses visibles ($P < 0,05$). Le rapport TOF moyen du groupe P, 0,03 ± 0,05 était inférieur à celui du groupe R, 0,68 ± 0,34 ($P < 0,001$). Tous les patients du groupe P et quatre des dix patients du groupe R avait un rapport TOF < 0,7 ($P = 0,001$). Le délai d'extubation dans le groupe P (médiane 18, écart 6–48 h) ne différait pas statistiquement de celui du groupe R (14, 5–44 h).

Conclusion : La curarisation résiduelle définie comme un rapport TOF < 0,7, est fréquente après une chirurgie cardiaque mais son incidence est moindre quand le rocuronium remplace le pancuronium.

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AFTER non-cardiac surgery, residual neuromuscular block, defined as train-of-four (TOF) ratio < 0.7 on arrival in the PACU, occurs in 25–40 % of patients after the use of long-acting relaxants, such as pancuronium and *d*-tubocurarine.[1–4] The incidence is reduced to less than 10% after the use of intermediate-acting agents such as atracurium, vecuronium[4,5] or the short-acting drug mivacurium.[6]

During cardiac surgery pancuronium is the most commonly used neuromuscular relaxant because its cardiovascular stimulating effects counteract the bradycardia associated with high-dose opioid anaesthesia.[7] The block is seldom reversed because the patients' lungs are usually ventilated postoperatively until cardiovascular parameters are stable.[8] Cost containment measures in health care have encouraged earlier tracheal extubation and discontinuation of postoperative mechanical ventilation by the use of lower doses of opioids and balanced general anaesthesia to facilitate "fast tracking" of postoperative cardiac patients.[9,10] However, residual neuromuscular block may delay early extubation and resumption of spontaneous respiration.

Rocuronium is an intermediate acting neuromuscular blocking agent that does not appear to be associated[11] with the occasional severe bradycardia that has been reported with the use of vecuronium during cardiac surgery.[12]

The purpose of this study was to determine the frequency of residual neuromuscular block after cardiac surgery. Two groups of 10 patients were studied in whom the only difference in management was the replacement of pancuronium with rocuronium to provide muscle relaxation. Residual block, identified on arrival in the ICU using electromyography, was defined as a TOF ratio <0.7, because such values are associated with reduced inspiratory force[13] and impaired ventilatory response to hypoxia.[14]

Methods

Subjects

After Ethics Committee approval and written informed consent, 20 patients scheduled for elective aortocoronary bypass surgery were studied. Exclusion criteria included patients receiving drugs known to interfere with neuromuscular activity, severe renal or hepatic disease, preexisting neuromuscular or neurological disease.

Intra-operative monitoring

Routine monitoring included 5-lead ECG, pulse oximeter, end-tidal capnograph, nasopharyngeal temperature, direct radial artery blood pressure, central venous and pulmonary artery pressures. Skin temperature over the thumb was monitored during surgery and in the ICU. Neuromuscular block was not monitored during surgery.

Anaesthesia and neuromuscular blockade

Anaesthesia was induced with sufentanil (50–350 μg) and a benzodiazepine [midazolam (2–5 mg) or diazepam (2–5 mg)] with the addition of propofol (60 mg, 1 patient) or ketamine (50 mg, 1 patient) and maintained with increments of sufentanil (25–150 μg) and/or benzodiazepines (midazolam or diazepam 1–5 mg), supplemented with isoflurane (up to 1% end-tidal) in oxygen enriched air. Morphine (3–30 mg *iv*) was administered toward the end of surgery, and isoflurane was discontinued at least 30 min before the completion of surgery.

Before induction of anaesthesia, patients were randomised, using randomisation tables, to receive either pancuronium or rocuronium which was supplied in blinded syringes containing 10 ml of approximately equipotent concentrations of each drug (pancuronium 1 $mg \cdot ml^{-1}$: rocuronium 6 $mg \cdot ml^{-1}$). Neuromuscular relaxation was induced by administration of 0.1 $ml \cdot kg^{-1}$ of the neuromuscular blocking drug and maintained with 1–2 ml increments according to clinical need (movement, attempts to breathe). Neuromuscular monitoring was not used during anaesthesia and the neuromuscular block was not reversed before arrival in ICU. Doses and times of all agents given were recorded, as well as the duration of CPB and surgery, intra-operative central and peripheral temperatures, fluid balance and haematocrit. The conduct of anaesthesia, including dosing of muscle relaxants, was at the discretion of the anaesthetist.

Surgery and CPB

Cardiopulmonary bypass was conducted using moderate hypothermia (28°C) followed by warming to a pulmonary artery temperature of approximately 36°C.

Neuromuscular monitoring in ICU

Upon arrival in the ICU, neuromuscular activity was measured electromyographically, by a blinded investigator, using train-of-four stimulation of the ulnar nerve at the wrist and recording over the adductor pollicis muscle (Datex Relaxograph). Three measurements were obtained for each patient and an average value determined. The measurements were repeated 30 min later if TOF ratio was <0.7. Clinical assessments of weakness (purposeful movement, hand grip, head lift) were made at the time of EMG testing.

Statistical analysis

Statistical analyses were performed using the NCSS computer programme, version 5.03. Categorical variables were analysed for between group differences using Fisher's exact test, with some categories combined when necessary. Normally distributed continuous variables were analysed using unpaired t tests with Bonferroni's correction for repeated measurements. The remaining continuous variables were analysed using Mann-Whitney tests. A P value of <0.05 was considered to indicate statistically significant differences.

Results

The total duration of anaesthesia and surgery was approximately seven hours. No differences were found between the groups in any measured variable (Tables I, II) except for neuromuscular data (Table III).

On arrival in ICU, residual neuromuscular block was present in both groups. After pancuronium, all 10 patients had TOF ratios of <0.7 compared with 4 of 10 patients after rocuronium ($P = 0.01$). Thirty minutes later, TOF was <0.7 in all group P and in three group R patients ($P = 0.003$). In group P, only three patients had four responses to TOF stimulation at both testing times compared with nine in group R ($P = 0.02$). After pancuronium, severe residual weakness was present seven hours after the last dose whereas residual block after rocuronium occurred only up to two hours after last dosing (Figure). There were no differences in spontaneous or purposeful movement, or shivering at the times of testing. The time from arrival in ICU to tracheal extubation, of the pancuronium group, median 18 (6–48) hr was not significantly different from that in the rocuronium group, median 14 (5–44) (Table III).

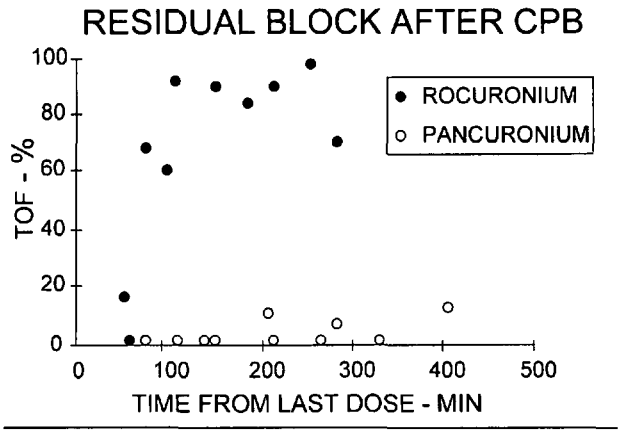

FIGURE Residual block and time from last dose of pancuronium or rocuronium.

Discussion

This study demonstrates that, after the use of pancuronium or rocuronium during anaesthesia for coronary artery bypass graft surgery, considerable residual neuromuscular blockade may persist. On arrival in ICU, all patients in the pancuronium group failed to achieve a TOF ratio >70% and, in 5/10 patients a profound block remained even though the median time

TABLE I Demographic data

	Pancuronium (n=10)	*Rocuronium (n=10)*
Age (yr)	65 (50–76)	69 (48–74)
Weight (kg)	75 ± 9	77 ± 15
Sex	M=7 F=3	M=7 F=3
Medical status		
-ASA -III	5	6
-IV	5	4
-Angina NYHA Class 3	5	8
Class 4	5	2
-Ejection fraction (%)	57 ± 11.3	53.7 ± 9.5
-LVEDP (mmHg)	16 ± 5	20 ± 6
-Creatinine ($mg \cdot dl^{-1}$)	89 (64–146)	96 (65–120)

Values expressed as median (Range) or mean ± SD.

TABLE II Surgical details

		Pancuronium	*Rocuronium*
CPB time	min	170 ± 45	168 ± 36
Cross-clamp	min	115 ± 43	114 ± 33
Temp °C	Initial	36.0 (35.6–36.3)	36.5 (35.7–37.3)
	CPB minimum	27.8 (26.5–32.0)	27.9 (26.2–35.0)
	Final	36.0 ± 0.8	36.0 ± 0.5
Duration anaesth	hr	7.0 ± 1.5	6.7 ± 1.5

Mean values ± SD or median (range). CPB - cardiopulmonary bypass. Oesophageal temperature (Temp) at the beginning (init) and end (final) of, and minimal value during, CPB.

TABLE III Neuromuscular data

		Pancuronium	*Rocuronium*
Total dose	$mg \cdot kg^{-1}$	0.18 (0.13–0.28)	1.14 (0.6–1.62)
	$ml \cdot kg^{-1}$	0.18 (0.13–0.28)	0.19 (0.1–0.27)
Last dose	min	208 (70–405)	120 (55–285)
TOF count	initial	1.5 (0–4)	4 (0–4)
	repeat	2.0 (0–4)	4 (0–4)
TOF ratio	initial	0.03 ± 0.05	0.68 ± 0.34†
	repeat	0.04 ± 0.06	0.71 ± 0.35†
TOF <0.7	initial	10/10	4/10*
	repeat	10/10	3/10*
Temp °C	core	35.7 ± 0.5	36.0 ± 0.6
	skin	30.0 ± 1.8	31.0 ± 1.6
Time to extubation	hr	18 (6–48)	14 (5–44)

Values expressed as mean ± SD or median (range). Time from last dose of relaxant until initial (init) neuromuscular evaluation in ICU
*$P < 0.05$, †$P < 0.001$ pancuronium *vs* rocuronium

from the last dose until testing was 208 (79–405) min. The best TOF ratios in this group were only 0.06, 0.11 and 0.12. In patients receiving rocuronium, the majority, 7/10, showed spontaneous recovery from neuromuscular blockade within 30 min of arrival in ICU without anticholinesterase antagonism of block and with a median time from the last dose of 146 (55–285) min. These data suggest that excessive doses of both relaxants were used in these patients. Also, under the conditions of the study, both pancuronium and rocuronium behaved as long-acting relaxants. There was no difference in the amount (volume and equipotent dose) of drug used in each group and current costing indicates that the price per ampoule of the two agents, in this institution, is similar.

The incidence of residual neuromuscular block after long, intermediate and short-acing neuromuscular relaxants has been well described in the non cardiac patient.[1-6] However, this has not been emphasised in the setting of cardiac anaesthesia because mechanical ventilation is usually continued for several hours after surgery. Residual neuromuscular blockade has not previously been considered an indication for postoperative mechanical ventilation in this group of patients although prolonged muscle weakness may occur following cardiac surgery.[15] Neuromuscular blockade is prolonged and recovery is delayed from maintenance doses of pancuronium,[16] atracurium[17] and rocuronium[18] under conditions of hypothermic cardiopulmonary bypass. However,the extent of residual block has not been assessed previously. Smeulers *et al.* demonstrated prolonged duration of action and delayed recovery of rocuronium during hypothermic CPB with decreased requirements upon rewarming: evidence of residual block was not sought.[19]

After cardiac surgery many factors affect the decision for tracheal extubation. In the current concern for early extubation and discharge from ICU after CABG surgery the role of residual neuromuscular blockade requires attention. Clinical use of muscle relaxants with regard to dose, monitoring, choice of agent, and reversal needs to be re-examined in patients undergoing cardiac surgery. However, the very long bypass times, approximately three hours, and the long duration of anaesthesia, almost seven hours, in the patients included in this study make it unlikely that they would have been considered for "fast-tracking."

The use of pancuronium for cardiac anaesthesia has been implicated in episodes of myocardial ischaemia related to tachycardia,[20] whilst the use of vecuronium has been associated with episodes of bradycardia and asystole.[12] Rocuronium produces haemodynamic stability at induction of anaesthesia,[11] possesses similar pharmacokinetic behaviour as vecuronium,[19] and has a rapid onset[21] and recovery profile.[18]

The median time to extubation in patients given rocuronium was 14 (5–44) hr and after pancuronium was 18 (6–48) hr. The difference is not statistically significant. Post hoc power analysis suggests that in a study of this size there is insufficient power to conclude that there is no difference in time to extubation when these two drugs are compared, and that a larger sample size is necessary. The present study had a power of 40% to detect a 50% difference in extubation times). We calculate that, to achieve a power of 80% and an α value of 0.05, it would be necessary to study 25 patients in each group.

In conclusion, this study demonstrated that residual block after cardiac surgery is common. Although the incidence was greater after pancuronium and the rate of recovery was more rapid after rocuronium, both relaxants were probably used in excessive doses. Current emphasis towards early extubation and spontaneous respiration after cardiac surgery ("fast tracking") necessitates re-evaluation of the use of muscle relaxants. Excessive doses may be avoided with the use of neuromuscular monitoring: the choice of drugs could be made according to their rate of recovery, and consideration might be given to the use of reversal agents to prevent residual neuromuscular block.

References

1 *Viby-Mogensen J, Jørgensen BC, Ørding H.* Residual curarization in the recovery room. Anesthesiology 1979; 50: 539–41.

2 *Lennmarken C, Löfström JB.* Partial curarization in the postoperative period. Acta Anaesthesiol Scand 1984; 28: 260–2.

3 *Beemer GH, Rozental P.* Postoperative neuromuscular function. Anaesth Intensive Care 1986; 14: 41–5.

4 *Bevan DR, Smith CE, Donati F.* Postoperative neuromuscular blockade: a comparison between atracurium, vecuronium, and pancuronium. Anesthesiology 1988; 69: 272–6.

5 *Andersen BN. Madsen JV, Schurizek BA, Juhl B.* Residual curarization: a comparative study of atracurium and pancuronium. Acta Anaesthesiol Scand 1988; 32: 79–81.

6 *Bevan DR, Kahwaji R, Ansermino JM, et al.* Residual block after mivacurium with or without edrophonium reversal in adults and children. Anesthesiology 1996; 84: 362–7.

7 *Liu W, Bidwai AV, Stanley TH, Isern-Amaral J.* Cardiovascular dynamics after large doses of fentanyl and fentanyl plus N_2O in the dog. Anesth Analg 1976; 55: 168–72.

8 *Thomson IR, MacAdams CL, Hudson RJ, Rosenbloom M.* Drug interactions with sufentanil. Hemodynamic effects of premedication and muscle relaxants. Anesthesiology 1992; 76: 922–9.
9 *Mounsey JP, Griffith MJ, Heaviside DW, Brown AH, Reid DS.* Determinants of the length of stay in intensive care and in hospital after coronary artery surgery. Br Heart J 1995; 73: 92–8.
10 *Karski JM.* Practical aspects of early extubation in cardiac surgery. J Cardiothorac Vasc Anesth 1995; 9 (Suppl 1): 30–3.
11 *Nitschmann P, Oberkoglere W, Hertsig M, Schwarz S.* Comparison of haemodynamic effects of rocuronium bromide with those of vecuronium in patients undergoing CABG surgery. Eur J Anaesthesiol 1994; 9(Suppl): 113–5.
12 *Starr NJ, Sethna DH, Estafanous FG.* Bradycardia and asystole following the rapid administration of sufentanil with vecuronium. Anesthesiology 1986; 64: 521–3.
13 *Ali HH, Wilson RS, Savarese JJ, Kitz RJ.* The effect of tubocurarine on indirectly elicited train- of-four muscle response and respiratory measurement in humans. Br J Anaesth 1975; 47: 570–4.
14 *Eriksson LI, Sato M, Severinghaus JW.* Effect of a vecuronium-induced partial neuromuscular block on hypoxic ventilatory response. Anesthesiology 1993; 78: 693–9.
15 *Buzello W, Schluermann D, Schindler M, Spillner G.* Hypothermic cardiopulmonary bypass and neuromuscular blockade by pancuronium and vecuronium. Anesthesiology 1985; 62: 201–4.
16 *D'Hollander AA, Duvaldestin P, Henzel D, Nevelseen M, Bomblet JP.* Variations in pancuronium requirement, plasma concentration and urinary excretion induced by cardiopulmonary bypass with hypothermia. Anesthesiology 1983; 58: 505–9.
17 *Flynn PJ, Hughes R, Walton B.* Use of atracurium in cardiac surgery involving cardiopulmonary bypass induced with hypothermia. Br J Anaesth 1984; 56: 962–72.
18 *Hudson ME, Rothfield KP, Tullock WC, Firestone LL.* Duration of effect and spontaneous recovery characteristics after repeated doses of rocuronium in patients undergoing cardiopulmonary bypass. Anesth Analg 1996; 82: S192.
19 *Smeulers NJ, Wierda JM, van den Broek L, Gallandat Huet RC, Hennis PJ.* Effects of hypothermic cardiopulmonary bypass on the pharmacodynamics and pharmacokinetics of rocuronium. J Cardiothorac Vasc Anesth 1995; 9: 700–5.
20 *Thomson IR, Putnins CL.* Adverse effects of pancuronium during high-dose fentanyl anesthesia for coronary artery bypass grafting. Anesthesiology 1985; 62: 708–13.
21 *Bartkowski RR, Witkowski TA, Azad S, Lessin J, Marr A.* Rocuronium onset of action: a comparison with atracurium and vecuronium. Anesth Analg 1993; 77: 574–8.