Prolonged (more than ten hours) neuromuscular blockade after cardiac surgery: report of two cases

[Un blocage neuromusculaire prolongé (plus de dix heures) après une intervention en cardiochirurgie : présentation de deux cas]

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Purpose: We examine two cases of prolonged neuromuscular blockade (NMB) after cardiac surgery. To the best of our knowledge, these are the first reported cases of complete paralysis lasting more than ten hours after surgery.

Clinical features: We attribute the extended durations of NMB (more than ten hours) to high doses of NMB drugs in combination with magnesium sulphate and moderate renal failure. Advanced age, hepatic disease, aminoglycoside exposure, hypocalcemia, and possible interaction between rocuronium and pancuronium may have played minor roles.

Conclusion: We should avoid administering large doses of NMB agents, even in the context of planned postoperative ventilation. If NMB is not monitored intraoperatively in patients who are at risk of prolonged NMB, then train-of-four response should be measured in the intensive care unit. Adequate sedation should be provided until proper recovery of neuromuscular function is documented.

Objectif : Présenter deux cas de blocage neuromusculaire prolongé (BNM) après une intervention cardiaque. Selon nos connaissances, c'est la première publication de cas de paralysie complète qui dure plus de dix heures après l'opération.

Éléments cliniques : Nous croyons que la durée prolongée du BNM (plus de dix heures) est le résultat de fortes doses de médicaments de BNM combinées au sulfate de magnésium et à une insuffisance rénale modérée. L'âge avancé, la maladie hépatique, l'exposition aux aminoglycosides, l'hypocalcémie et une interaction possible entre le rocuronium et le pancuronium peuvent avoir joué des rôles mineurs.

Conclusion : Nous devons éviter d'administrer de fortes doses d'agents de BNM, même quand une ventilation postopératoire planifiée. Si le BNM n'est pas surveillé chez les patients à risque de BNM pro-

longé, la réponse en train-de-quatre doit alors être mesurée à l'unité des soins intensifs. Une sédation adéquate doit être donnée jusqu'à ce qu'une reprise convenable de la fonction neuromusculaire soit prouvée.

WE examine two cases of prolonged neuromuscular blockade (NMB) after cardiac surgery. We attribute the extended durations of complete paralysis (more than ten hours) to high doses of NMB drugs in combination with magnesium sulphate and moderate renal failure.

Case 1

A 67-yr-old woman was referred to the anesthesia service for prolonged NMB after mitral valve replacement.

The patient had been transferred to our hospital for surgical treatment of bacterial endocarditis and critical mitral stenosis. The patient was treated initially for two weeks with ampicillin and gentamicin and one week of ampicillin alone. Her past medical history included rheumatic mitral valve stenosis (with previous commissurotomy), pulmonary hypertension and chronic atrial fibrillation. Height and weight were 165 cm and 63 kg. Laboratory investigations revealed anemia, hypokalemia, and mild pre-renal failure (Table I). Preoperative medications included furosemide, digoxin, ramipril, *iv* heparin, flurazepam, ampicillin, and potassium chloride.

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No funding.

Accepted for publication March 22, 2004.

Revision accepted September 13, 2004.

The patient underwent a redo mitral valve replacement during a five-hour procedure. Anesthesia was induced with midazolam (8 mg), sufentanil (100 µg) and pancuronium (10 mg = 0.16 mg·kg⁻¹) and was maintained with an infusion of midazolam (10 mg), sufentanil (250 µg) and pancuronium (5 mg = 0.016 mg·kg⁻¹·hr⁻¹). Thus, a total of 15 mg of pancuronium was given. Extra pancuronium boluses were not administered after induction and the infusion was completed at the intensive care unit (ICU) transfer. No anticholinesterase agent was given. Hypothermic (32°C) cardiopulmonary bypass (CPB) was used. The cross clamp time was 52 min and total perfusion time 91 min. The patient received 3000 mL crystalloid solution, 500 mL pentastarch, and 6 U packed red blood cells. The patient was weaned off CPB with low-dose norepinephrine and milrinone. Heparin (36000 U) was reversed with protamine (500 mg). Magnesium sulphate (2.5 g) was administered 2.5 hr before ICU transfer. The only other drugs given to the patient were vancomycin (1.5 g), furosemide (40 g), mannitol (30 g) remifentanyl (500 µg), and morphine (10 mg). Urine output during the procedure was 400 mL and blood loss was 1800 mL.

On ICU admission, the patient had slightly reactive pupils to light and no motor responses to painful stimuli. The patient was maintained on ventilatory support, warmed (34.4°C on arrival) and started on ampicillin (2 g Q 8 hr) and ticarcillin clavulanate (3.1 g Q 12 hr). In the first 12 postoperative hours, urine output was 305 mL, despite the administration of furosemide (120 mg).

On postoperative day (POD) 1 (12 hr after ICU admission), the patient was still completely unresponsive. No pain control or NMB drugs were given in the ICU. There were no deep-tendon, oculo-cephalic, or plantar reflexes. The pupils remained slightly reactive to light. The biochemical laboratory values were normal (Table I) and the cumulative urine output was 935 mL (305 + 630 mL) over 16 hr. The ICU staff consulted a neurologist, who agreed with the physical examination findings. A computed tomography (CT) scan of the head was ordered to rule out intracranial and/or brain-stem pathology and anesthesia was asked to rule out prolonged NMB from the muscle relaxants given the day before.

Ulnar nerve stimulation at the wrist [train-of-four – (TOF)] revealed no contraction of the adductor pollicis muscle 16 hr after arrival to the ICU, despite appropriate current (> 50 mA). Neostigmine (2.5 g) and glycopyrrolate (0.6 g) were given without change in the TOF response. A second dose produced a small muscle twitch. A propofol infusion was begun for sedation and the CT scan was cancelled.

By the end of POD 1 (24 hr after ICU admission), the patient had recovered full neurological function. Tracheal extubation took place on POD 2 and transfer to the ward on POD 4. No other episode of neurological impairment occurred. The patient did suffer moderate renal failure (Table I). Her serum creatinine and urea, normally 63 and 5.7, peaked at 177 and 11.4, respectively, around POD 2. Likewise, mild elevations in serum liver enzymes were noted. The patient was discharged home on POD 15.

To estimate the plasma and effect-site concentrations of pancuronium, we used the program Stanpump (S. L. Shafer, Stanford University, Stanford, CA, USA version November 1996, <http://anesthesia.stanford.edu/pkpd>), with the Rupp-kinetic set for the elderly. The simulation used a bolus of 10 mg followed by an infusion of 1 mg·hr⁻¹ for five hours. The predicted effect-site concentration of pancuronium on ICU arrival was 0.3 µg·mL⁻¹ (corresponding to 99% NMB). The concentrations associated with 50% (0.12 µg·mL⁻¹) and 1% (0.05 µg·mL⁻¹) blockade would have occurred at 2.8 and 6.3 hr after ICU admission, respectively.

Case 2

A 78-yr-old woman was diagnosed with possible prolonged NMB after quadruple coronary artery bypass plus aortic root and valve replacement.

The patient presented to hospital for an elective coronary angiogram for chest pain investigation. Her past medical history included coronary artery disease, hypertension, hypercholesterolemia, and diabetes mellitus type II. Her height and weight were 152 cm and 69 kg. Medications at admission included isosorbide mononitrate, omeprazole, nadolol, diltiazem XL, aspirin, and nitroglycerine spray.

The first injection of the right coronary artery caused an aortic dissection, which did not progress. The angiogram showed three-vessel coronary artery disease and an ejection fraction of 60%. The patient underwent emergency cardiac surgery for 9.5 hr. Anesthesia was induced with midazolam (5 mg), sufentanil (75 µg) and rocuronium (50 mg = 0.72 mg·kg⁻¹). It was maintained with sevoflurane (0.5–1.0%) and an infusion of midazolam (15 mg) plus sufentanil (250 µg). A second dose of rocuronium (30 mg = 0.43 mg·kg⁻¹) was given six hours before ICU transfer. The patient also received three boluses of pancuronium: 5 mg (0.072 mg·kg⁻¹) 45 min after induction, 5 mg at the beginning of CPB, and then 2 mg (0.029 mg·kg⁻¹) five hours before ICU transfer. No anticholinesterase agent was given. Hypothermic (32°C) CPB was used. The cross-clamp

time was 196 min and total perfusion time 238 min. The patient received 1000 mL crystalloid solution, 750 mL pentastarch, 8 U packed red blood cells, 4 U fresh frozen plasma, 6 U platelets, and 6 U cryoprecipitate. At the end of CPB, the patient required cardiac pacing, an intra-aortic balloon pump (1:1), epinephrine ($10 \mu\text{g}\cdot\text{min}^{-1}$), norepinephrine ($17.5 \mu\text{g}\cdot\text{min}^{-1}$), and milrinone ($0.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Magnesium sulphate (2.5 g) was administered four hours before ICU transfer. The only other drugs given to the patient were vancomycin (1 g), furosemide (40 mg), mannitol (30 g), aprotinin (9450 mg), insulin ($2 \text{ U}\cdot\text{hr}^{-1}$) and calcium chloride (500 mg). At the end of the case, urine output was 1300 mL, blood loss was 3000 mL, and the cardiac index was $2.16 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^2$.

On ICU admission, the patient was unconscious and her pupils were equal and non-reactive to light. The patient was maintained on ventilatory support and warmed (35.3°C on arrival). No additional doses of NMB agents were administered in the ICU. On POD 0, the patient received vancomycin 1 g, famotidine 20 mg, amiodarone 150 mg, ticarcillin clavulanate 3.1 g TID, and furosemide 40 mg BID. Urine output was 250 mL in the first two postoperative hours.

On POD 1 (11.5 hr after ICU admission), the patient was still completely unresponsive. The urine output was 795 mL (1045 mL since ICU admission) in the first eight hours of POD 1 and 540 mL (1585 mL total) in the second eight hours. There were no deep-tendon, oculo-cephalic or plantar responses. The pupils were midsize, equal, and reactive to light. No contraction of the adductor pollicis muscle was elicited with ulnar nerve stimulation at the wrist, using both TOF and post-tetanic count. A trial of neostigmine (3.5 mg) and glycopyrrolate (0.7 mg) were given 13.5 hr after ICU arrival. The patient was able to obey commands 3.5 hr later. No further episodes of neurological impairment occurred. The patient remained on ventilatory support until POD 6. Transfer to the ward took place on POD 11 and discharge home on POD 20.

The Stanpump simulation for pancuronium used boluses at minute 45 (5 mg), 105 (5 mg), and 240 (2 mg). The pancuronium simulation predicted an effect-site concentration of $0.08 \mu\text{g}\cdot\text{mL}^{-1}$ (corresponding to 12% blockade) on ICU arrival. The 1% blockade concentration of $0.05 \mu\text{g}\cdot\text{mL}^{-1}$ would have occurred two hours after ICU transfer. A second simulation was done with rocuronium, using boluses at minute zero (50 mg) and 180 (30 mg). The rocuronium simulation yielded a predicted effect-site concentration of $0.02 \mu\text{g}\cdot\text{mL}^{-1}$ (corresponding to approximately 0% blockade)¹ on ICU arrival. The sim-

ulations did not account for the additive effects of combining pancuronium and rocuronium.

Discussion

Residual NMB after cardiac surgery is well-documented.²⁻⁴ Its occurrence is not surprising given the numerous predisposing factors associated with cardiac surgery: long-acting neuromuscular blocking agents, planned postoperative ventilation, magnesium sulphate, co-morbidities, advanced age, hypothermic CPB, volatile agents, acidosis, hypocalcemia, aminoglycosides, vancomycin, furosemide, mannitol, beta-blockers, and calcium channel blockers.⁵ To the best of our knowledge, however, these are the first reported cases of complete paralysis lasting more than ten hours after cardiac surgery.

The dose and type of drugs used in the operating room are the primary determinants of NMB duration.⁶ The doses of neuromuscular blocking agents given to the patients were high. The first patient received 15 mg of pancuronium ($0.048 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$), while the second patient received 80 mg of rocuronium ($0.12 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$) and 12 mg of pancuronium ($0.018 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$). In the second patient, potentiation of neuromuscular activity between rocuronium and pancuronium may have occurred, but if so, the impact would have been low. Isobolographic analysis demonstrates an additive (and not synergistic) response between rocuronium and pancuronium.⁶ Therefore, even in the context of high steroidal NMB drug doses, the durations of NMB were considerably longer than predicted by pharmacokinetic and pharmacodynamic modeling. Furthermore, the actual drug concentrations may have been lower than predicted because the simulations did not include drug elimination by blood loss and drug dilution by CPB, *iv* fluids and blood products.

The drug that most likely increased the duration of muscle relaxation was magnesium sulphate. Both patients received 2.5 g of magnesium sulphate for its anti-arrhythmic properties. Increased levels of serum magnesium followed the timeframe during which the patients remained paralyzed (Tables I and II). Magnesium prolongs NMB by inhibiting the release of acetylcholine at the nerve terminal.⁷ In a study considering the effects of magnesium sulfate on NMB, Fuchs-Buder, *et al.*⁷ showed that recovery from vecuronium with neostigmine was decreased by 30% in obstetrical patients pretreated with magnesium sulphate. Similarly, in a case report by Kwan *et al.*,⁸ therapeutic serum magnesium levels in a woman with severe pre-eclampsia prolonged the effect of 1 mg of vecuronium to four hours. These findings are consis-

TABLE I Case 1 laboratory values

<i>Labs</i>	<i>Admission</i>	<i>Preop</i>	<i>POD 0</i>	<i>POD 1</i>	<i>POD 2</i>	<i>POD 3</i>
Hb (g·L ⁻¹)	89	82	101		89	
Hct (L·L ⁻¹)	0.27	0.25	0.29		0.27	
WBC (10 ⁹ ·L ⁻¹)	7.31	7.17	17.41		7.31	
Plts (10 ⁹ ·L ⁻¹)	89	164	77		189	
INR (0.8–1.20)	1.28	1.08	1.90	1.25	1.19	
PTT (27.0–40.9 sec)	56.9	43.3	74.8			
Na (mmol·L ⁻¹)	140	143	143			
K (mmol·L ⁻¹)	2.8	3.5	3.4			
Cl (mmol·L ⁻¹)	102	106	113			
HCO ₃ (mmol·L ⁻¹)	30	28	22.6			
Urea (mmol·L ⁻¹)	6.3	4.6	5.0	6.2	9.5	11.4
Creatinine (umol·L ⁻¹)	104	73	97	153	177	158
Glucose (mmol·L ⁻¹)	5.4	5.2	9.4	12.9	7.0	6.9
Mg (mmol·L ⁻¹)	0.83	2.26	1.71	1.39	1.25	0.96
Ca (mmol·L ⁻¹)	2.19	1.17				
PO ₄ (mmol·L ⁻¹)	0.89	1.31				
Albumin (g·L ⁻¹)			15			
Total bilirubin (umol·L ⁻¹)			22.20	32.37	15.66	12.9
AST (U·L ⁻¹)			120	161	108	77
Amylase (U·L ⁻¹)			145	807		454
pH			7.46			

POD = postoperative day; Hb = hemoglobin; Hct = hematocrit; WBC = white blood cells; Plts = platelets; INR = international normalized ratio; PTT = partial thromboplastin time.

tent with those published by Kussman *et al.*, who demonstrated increased durations of NMB in patients given magnesium sulphate before rocuronium⁹ and with those published by Pinard *et al.*, who showed prolonged NMB in cardiac surgery patients given magnesium sulphate and cisatracurium.¹⁰ Lastly, it is interesting to note that the patients' postoperative serum calcium levels were low. Since calcium has the potential to reverse the effect of magnesium at the nerve terminal, low serum calcium may be an additional contributory factor.¹¹

Renal function was probably the dominant patient factor that contributed to the long durations of NMB (Tables I and II). Although renal failure likely prolonged the effects of the NMB agents, it is difficult to imagine that moderate postoperative renal impairment explains complete paralysis lasting greater than ten hours. Increased age and mildly abnormal liver function are other patient factors that may have played limited roles.

In the first case, an aminoglycoside was administered, but then stopped one week before surgery. The effect of this drug was likely minimal. Aminoglycosides can produce a curare-like NMB in animals at serum concentration levels higher than those obtained with conventional dosing (1–2

mg·kg⁻¹ every eight hours).¹² According to Wong *et al.*, these blocks are rarely encountered clinically.¹²

In summary, the most likely cause of prolonged NMB was the combined use of magnesium sulphate with high doses of NMB in patients with moderate renal failure. The other factors (NMB agent potentiation, hypocalcemia, age, hepatic function) likely had minor effects. We should avoid administering large doses of NMB agents, even in the context of planned postoperative ventilation. Excessive doses of long-acting muscle relaxants may increase the duration of postoperative ventilation and lead to prolonged, undetected intraoperative awareness.¹³

Neuromuscular function is not routinely monitored during cardiac surgery,¹⁴ a trend that is probably influenced by planned postoperative ventilation and lack of access to the adductor pollicis muscle. TOF stimulation of the temporal branch of the facial nerve is a possible method to monitor NMB intraoperatively, but the risk of overdosing patients with muscle relaxants still exists. The orbicularis oculi is more resistant to non-depolarizing agents than the adductor pollicis and direct facial muscle stimulation can occur unintentionally around the eye.⁴ Alternative techniques, such as phonomyography,¹⁵ have been proposed for monitoring NMB during cardiac surgery,

TABLE II Case 2 laboratory values

Labs	Preop	POD 0	POD 1	POD 2	POD 3
Hb (g·L ⁻¹)	116	88	64-94		
Hct (L·L ⁻¹)	0.34	0.24			
WBC (10 ⁹ ·L ⁻¹)		16.4	9.8-15.8		
Plts (10 ⁹ ·L ⁻¹)	434	188	98-237		
INR (0.8-1.20)	1.07	2.0	1.4-1.6		
PTT (27.0-40.9 sec)	30.9	77.8	47-63		
Na (mmol·L ⁻¹)	141	149	147	137	
K (mmol·L ⁻¹)	4.6	4.0	3.2	3.9	
Cl (mmol·L ⁻¹)	111	111	111	107	
HCO ₃ (mmol·L ⁻¹)		27	28	23.9	24
Urea (mmol·L ⁻¹)	12.2	8.1	9.7	13.9	12.1
Creatinine (umol·L ⁻¹)	111	105	88	190	129
Glucose (mmol·L ⁻¹)	6.6	12.4	11.1	4.3	6.3
Mg (mmol·L ⁻¹)		1.8	1.27	0.90	1.30
Ca (mmol·L ⁻¹)			1.74	1.59	1.54
PO ₄ (mmol·L ⁻¹)		0.97	0.76	1.93	1.49
Albumin (g·L ⁻¹)		19	17	22	21
Total bilirubin (umol·L ⁻¹)		62.0	33.9	73.75	54.9
AST (U·L ⁻¹)			136	419	482
Amylase (U·L ⁻¹)		70	91	518	420
pH		7.46			

POD = postoperative day; Hb = hemoglobin; Hct = hematocrit; WBC = white blood cells; Plts = platelets; INR = international normalized ratio; PTT = partial thromboplastin time.

yet these techniques are not used widely. If NMB is not monitored intraoperatively in patients who are at risk of prolonged NMB,¹³ then TOF response should be measured in the ICU. Adequate sedation should be provided until proper recovery of neuromuscular function is documented.

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