Extremely prolonged neuromuscular block after cardiopulmonary resuscitation

AG Stegeman¹, A Oude Lansink¹, F Ismael¹, BM de Jong², MWN Nijsten¹

1 Department of Critical Care, University Medical Center Groningen, University of Groningen, The Netherlands
2 Department of Neurology, University Medical Center Groningen, University of Groningen, The Netherlands

Abstract - A young woman known with end-stage heart failure and renal and liver abnormalities underwent cardiopulmonary resuscitation. Seven hours after administration of 1.2mg/kg of rocuronium, acceleromyography still showed a complete neuromuscular block. After administration of rocuronium-antagonist sugammadex (16mg/kg), she could promptly move upon commands. Several of the published risk factors for block prolongation were present in our patient. To our knowledge, this is the first time that sugammadex reversed an extremely prolonged rocuronium-induced neuromuscular block. This case underscores the importance of recognizing neuromuscular failure. She had recently been admitted to the cardiology ward for screening for heart transplantation. During this admission mild liver function abnormalities were noted. Subsequently, a subcutaneous tunneled subclavian vein catheter was placed for long-term inotropic support with dobutamine. Liver function tests had normalized when the patient was discharged with a continuous dobutamine infusion at 2μg/kg/min. After one week she was readmitted to the coronary care unit (CCU) with malaise and suspected catheter-related infection that was treated by catheter replacement and administration of vancomycin. Despite conservative measures, her renal function deteriorated rapidly with an estimated glomerular filtration rate of 12 ml/min (creatinine 365 µmol/l) During the morning rounds on the CCU the patient collapsed whilst in the middle of a conversation. Immediate resuscitation (witnessed pulseless electrical activity) according to the resuscitation guidelines was started. The patient was intubated after administration of a single dose 1.2 mg/kg (100 mg) of the neuromuscular blocking (NMB) agent rocuronium to facilitate opening the mouth to release a strong bite. During the prolonged resuscitation (3 hours) the intra-arterial blood pressures were equal or higher than her normal pressure under isotropic support. A total of 10mg of adrenalin and 20 IU of vasopressin were administered. On admission to the ICU, the patient was unresponsive with dilated pupils and no light reflexes. She received continuous infusion of adrenalin, noradrenalin, dopamine and levosimendan for persisting cardiogenic shock. This severe haemodynamic instability was the main reason for not inducing therapeutic hypothermia. A continuous infusion of 4 gram magnesium sulphate per day was also started. Both on admission to the ICU and seven hours after the single dose of rocuronium, examination by two neurologists revealed a Glasgow Coma Score (GCS; eye-motor-verbal) of 1-1-tube with no brain stem reflexes. However, at seven hours after resuscitation she was able to trigger the ventilator, probably because the diaphragm recovers more rapidly from NMB activity than the ulnar nerve and thumb, and because only a slight contraction of the diaphragm is enough to trigger a ventilator.

Since renal insufficiency may prolong neuromuscular blockage even for rocuronium, acceleromyography (TOF-Watch® (Organon Teknika, Boxtel, Holland)) in a train-of-four (TOF) mode with the use of supramaximal stimuli (60mA) with a duration of 0.2ms at 2 Hz every 15s was obtained. It revealed a complete neuromuscular block (TOF-0) at several stimulation sites (ulnar, facial and tibial nerves). The device was checked for technical malfunction on the examiner’s ulnar nerve at a low mA output. Since it was unclear to what extent the neuromuscular block was contributing to the patient’s low GCS, a single dose of sugammadex 16mg/kg (dose for complete block reversal) was administered. Sugammadex antagonizes rocuronium by encapsulating the rocuronium molecule, after which the complex is excreted in the urine. If adequately dosed, sugammadex is capable of rapidly reversing a complete rocuronium-induced block, even in patients with end-stage renal failure [1,2].

Within 2 minutes of receiving the sugammadex, the patient became fully responsive with a GCS of 4-6-tube. We concluded that the patient had not experienced a true coma but had been paralyzed. The presence of cardiac failure, renal failure and knowledge of the pharmacokinetics of rocuronium provided the necessary clue for performing acceleromyography in this patient.
Continuous renal replacement therapy was started to improve the metabolic acidosis but had no beneficial effect on the patient’s haemodynamics. For rapid haemodynamic improvement, the patient was taken to the operating room and fitted with a left ventricular assist device (LVAD Levitronix®). However, lactic acidosis persisted, repeated ventricular tachycardia developed and her internal cardioverter defibrillator was triggered several times. On the next day, sustained and refractory ventricular fibrillation occurred as a result of which the LVAD output declined sharply. Later that day, and 22 hours after the cardiopulmonary resuscitation had been started, the patient died. Her death was probably due to right heart failure rendering the LVAD ineffective as reflected by progressive lactic acidosis.

Because this patient died, our Institutional Review Board has allowed publication of this case without informed consent having been obtained.

Discussion

The fact that our patient displayed a complete neuromuscular block seven hours after the administration of 1.2 mg/kg of rocuronium is probably due to several factors, including a low cardiac output. The patient’s apparent comatose state associated with this block was immediately reversed after administering sugammadex.

In the literature we found three cases that had a similar length of neuromuscular block prolongation [3,4]. However, these patients were all over 60 years of age and in one patient only was rocuronium the only neuromuscular blocker used. A case with a less extreme prolongation of blockage occurred with a dose of 0.6 mg/kg in an 84-year-old patient. In this case the T1 (first twitch 25% of maximal twitch height) response on TOF was obtained 193 minutes after the single intubation dose [5].

Rocuronium is an NMB of the non-depolarizing steroid type. With regard to onset, it is the fastest non-depolarizing NMB [6]. At a dose of 1.2 mg/kg, its mean onset time is 55 sec (range 36-84 sec). Rocuronium is frequently used as an alternative to the depolarizing agent succinylcholine since it does not induce depolarizing block. A TOF ratio (T4/T1) of 75% is correlated with the response before the administration of the NMB defined as 100%. TOF is frequently used in the evaluation of non-depolarizing block. A TOF ratio (T4/T1) of 75% is correlated with clinical recovery.

Multiple causes for the extreme prolongation of the neuromuscular block after a single rapid sequence dose of rocuronium in our young female patient may have been relevant (Table 1). A high BMI may result in relatively high doses in patients with a low lean body mass. The variation in duration of action of rocuronium in a mixed clinical population is significant, depending on multiple patient factors. Female patients have longer block durations: after a dose of 0.4 mg/kg, time to recovery to 90% of maximal twitch height was 47 minutes in females compared to 34 minutes in male patients [9]. In elderly patients after a 0.6 mg/kg intubation dose, the duration to T1 ranged from 33 to 119 minutes [10]. However, in contrast to the previously mentioned cases, our patient was a young female.

The variability in block duration in young healthy patients is also considerable. The spontaneous recovery index of rocuronium versus cis-atracurium was assessed in young healthy adults under propofol anaesthesia, by measuring the time interval from T1-25% to TOF 90%. The variability of this index was twice as great for rocuronium compared to cis-atracurium [11].

The block duration of rocuronium is prolonged in patients with renal dysfunction. In young patients with propofol-based anaesthesia, block duration to T1 (25% height) of 0.6 mg/kg, rocuronium was 32.8 +/- 5.6 minutes in patients without renal failure versus 58.4 +/- 20.2 minutes for patients with renal failure [12]. This block prolongation in renal failure is accompanied by an even larger variability in recovery time. A recovery time of 88 minutes (range 45-150) was observed in patients with renal failure and compared to 54 minutes (range 35-78) in other patients [13].

Another factor that could prolong the neuromuscular blockage is liver dysfunction since rocuronium in healthy adults is mainly eliminated through the biliary excretion [14]. Our patient, however, had mild liver function abnormalities prior to blockage. Although her liver function normalized during dobutamine infusion, as was reflected by normalisation of laboratory values, after the resuscitation she had sustained heart failure. It is possible that the liver might not function properly in these circumstances. So, the contribution of liver dysfunction is a definite possibility here.

Several medications used in this patient might also contribute to NMB prolongation. Most patients receive magnesium

Table 1. Factors that may prolong the action of non-depolarizing relaxants such as rocuronium.

<table>
<thead>
<tr>
<th>Renal failure</th>
<th>Liver failure</th>
<th>Respiratory acidosis</th>
<th>Female sex, higher age</th>
<th>Neuromuscular diseases, (relatively) low muscle mass</th>
<th>Hypothermia</th>
<th>Hypokalemia, hypocalcemia, hyernatremia, hypermagnesemia</th>
</tr>
</thead>
</table>

AG Stegeman, A Oude Lansink, F Ismael, BM de Jong, MW Nijsten
In this case [17]. During the prolonged block our patient received magnesium resulting in a moderately elevated serum magnesium of 1.78 mmol/l. As antibiotic therapy for suspected catheter sepsis the patient had received vancomycin. Prolonged block after the use of vecuronium in patients receiving vancomycin has been described and the enhanced blocking effect provided by vancomycin may be partially independent of the NMB agent [17]. Other concomitant and known interacting medication (anticonvulsants, calcium blockers) were not used in this patient. This patient was normothermic and remained normothermic, both before and after resuscitation. The use of therapeutic hypothermia can lead to further block prolongation. So, if one decides to use therapeutic hypothermia it would be prudent to monitor neuromuscular block if NMB are used.

We think that in our patient several of the above mentioned factors added to the prolongation of the blockage. Since complete reversal was achieved with sugammadex, the vancomycin was not suspected to be the prime cause of the neuromuscular block in this case [17]. Low cardiac output has never been described as a reason for block prolongation, although it is an obvious cause when organ failure ensues. In this patient, renal failure was evident and some measure of liver failure was probably present as well. Rocuronium clearance from the neuromuscular junction might have been impaired by the systemic hypo-perfusion. This peripheral hypo-perfusion was likely to have existed in this patient with low output and progressive lactic acidosis with high dose adrenaline, noradrenaline and dopamine. In our opinion, the combination of low cardiac output together with organ dysfunction was the most likely cause for the extreme NMB prolongation.

Conclusion

Extreme prolongation of neuromuscular block after a single dose of rocuronium may be discovered more often if more patients who receive a neuromuscular blocker are checked for residual block. A low output state with pre-existing or new organ dysfunction may predispose an ICU patient for neuromuscular block prolongation. It is good practice to check for residual block in each comatose or sedated patient who has received a neuromuscular blocker before or during ICU admission, especially in the presence of risk factors for block prolongation. This is particularly relevant when tendon stretch reflexes are absent at neurological assessment in apparently comatose patients.

References

12. Kocabas S, Yedinciocuçu D, Askar FZ. The neuromuscular effects of 0.6mg/kg rocuronium in elderly and young adults with or without renal failure. Eur J Anesthesiol 2008;25:940-6.