British Journal of Anaesthesia **99 (4):** 514–17 (2007)
doi:10.1093/bja/aem213 Advance Access publication August 3, 2007

BJA

Case Report

Prolonged residual paralysis after a single intubating dose of rocuronium

C. Claudius*, H. Karacan and J. Viby-Mogensen

Department of Anaesthesia and Intensive Care, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark

**Corresponding author: Department of Anaesthesia and Intensive Care 4231, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. E-mail: casperclaudius@dadlnet.dk*

It is often argued that neuromuscular monitoring is unnecessary when only one dose of an intermediate-acting neuromuscular blocking agent is given. This case report documents that it may take more than 3.5 h before it is possible to antagonize a block caused by a normal dose of rocuronium (0.6 mg kg^{-1}). Possible causes of the extremely prolonged duration of action are discussed, as is the importance of quantitative neuromuscular monitoring.

Br J Anaesth 2007; **99**: 514–17

Keywords: neuromuscular block, recovery; monitoring, neuromuscular function; neuromuscular block, rocuronium

More than 25 yr ago, it was documented that postoperative residual curarization (PORC) was frequent in patients given long-acting neuromuscular blocking agents.[1] Later studies have confirmed this finding even with intermediate-acting neuromuscular blocking agents.[2–5] Still it is a myth that PORC can be avoided if only one single intubating dose of an intermediate-acting neuromuscular blocking agent is given, and the surgical procedure is longer than 1–1.5 h.[6] We report a case of severe residual blockade of more than 3 h after a normal single intubating dose of rocuronium.

Case report

The patient was an 84-yr-old woman (height 159 cm, weight 50 kg, ASA III) undergoing hysterectomy and bilateral salpingo-oophorectomy. She suffered from no other known illness and received no medication. Preoperative laboratory investigations (normal range) showed a haemoglobin level of 9.3 g dl^{-1} (11.3–16.1), alanine aminotransferase 52 U $litre^{-1}$ (10–45), aspartate aminotransferase 64 U $litre^{-1}$ (15–35), alkaline phosphatase 288 U $litre^{-1}$ (35–105), lactate dehydrogenase 225 U $litre^{-1}$ (115–255), bilirubin 11 μmol $litre^{-1}$ (4–22), and creatinine 40 μmol $litre^{-1}$ (50–88).

Before anaesthesia, an epidural catheter was placed at the T11–12 junction. Anaesthesia was induced with alfentanil 1 mg and thiopental 125 mg. After induction, routine monitoring of neuromuscular block with train-of-four (TOF) stimulation of the left ulnar nerve at the wrist and recording of the response of the thumb was performed using acceleromyography (AMG) (TOF-Watch®, Organon NV, The Netherlands). The default stimulation current of 50 mA was used, and calibration of the twitch height performed using the built-in calibration of the TOF-Watch®. Rocuronium 0.6 mg kg^{-1} was injected and the trachea intubated. No supplemental doses were given during surgery. Anaesthesia was maintained with sevoflurane (end-tidal concentration 0.8–1%) in oxygen ($F_{I_{O_2}}$ 0.4–0.6). The oesophageal temperature was measured and kept above 32°C. A bolus dose of bupivacaine 0.5%, 6 ml was administered epidurally before incision, and during surgery, infusion of bupivacaine 0.25% with morphine 50 μg ml^{-1}, 4 ml h^{-1} was given. Cefuroxime 1.5 g and metronidazole 1 g were administered i.v. During the procedure, the patient had a blood loss of approximately 200 ml and received 1 unit of packed red blood cells, 1700 ml of crystalloids, and 500 ml of colloids.

The uneventful laparotomy was completed after 1.5 h (2 h after induction). At this time, there was no reaction to TOF stimulation. To ensure against malfunction of the acceleromyograph or the acceleration transducer, another acceleromyograph (TOF-Watch® SX) was placed contralaterally above the ulnar nerve at the wrist and the response of the thumb and temperature of the thenar transferred to a computer program (TOF-Watch® SX Monitor). The peripheral temperature was kept above 32°C. The stimulation current was manually set to 60 mA. The level of neuromuscular block was evaluated using the post-tetanic count (PTC) method (5 s of 50 Hz tetanic stimulation followed

3 s later by 1 Hz single stimulation)[7] and TOF. There was no response to the TOF stimulation, but the PTC was 8, indicating deep neuromuscular block, 140 min after the rocuronium administration. To accelerate recovery, sevoflurane was turned off, and anaesthesia maintained with supplementary doses of propofol 10 mg, in total 230 mg. A Cerebral State Monitor™ (Danmeter A/S, Denmark) was placed to ensure sufficient anaesthesia (Cerebral State Index 40–60) and minimize the risk of awareness.

The first response to TOF stimulation (T1) was recorded 193 min after the intubating dose of rocuronium. The second response (T2) appeared 25 min later (215 min after injection of rocuronium). At this time, reversal was performed with neostigmine (0.05 mg kg^{-1}) plus atropin (0.02 mg kg^{-1}). Sufficient recovery (TOF ratio >0.9) was reached 8 min later, and the trachea was extubated when the patient was awake. On arrival at the post-anaesthetic care unit (PACU; 265 min after injection of rocuronium), clinical tests of residual block (head/leg lift >5 s, handgrip >5 s, tongue depressor test, and presence of diplopia) were performed. The patient showed no signs or symptoms of residual paralysis. Figure 1 shows the sequence of events and the degree of block after rocuronium 0.6 mg kg^{-1}.

Discussion

The two main messages of this case report are: first, PORC cannot be excluded with certainty although only one normal dose of an intermediate-acting neuromuscular blocking agent has been given for tracheal intubation. Secondly, it demonstrates the value of objective neuromuscular monitoring in diagnosis and treatment of PORC.

Several factors may have contributed to the prolonged duration of action of rocuronium in this patient. First, the patient was 84 yr old, and the duration of action of rocuronium is prolonged in elderly patients.[8–11] Baykara and colleagues[8] found the time to first response to TOF to be 60.8 min in elderly patients, when compared with 48.8 min in young patients receiving rocuronium 1 mg kg^{-1}. Secondly, the variation in duration of action of rocuronium is huge. Arain and colleagues[9] examined the time from injection of rocuronium 0.6 mg kg^{-1} to the return of T1 of TOF to 25% of control twitch height in the elderly and found a median time of 63 min, but a range from 33 to 119 min. With the PTC method, it is possible to evaluate the level of deep block. The number of PTCs correlates well with the time to first response to TOF.[12] When the post-tetanic responses were recorded for the first time in this patient, the PTC was 8. Judging from the normal relationship between number of PTCs and time to first TOF response (T1) for rocuronium, reappearance of T1 in the TOF response was expected after 8 min, at most.[13] However, in this patient it took 53 min! This again demonstrates the huge variability in response to neuromuscular blocking agents, at least partly explained by differences in distribution and elimination.[11] Thirdly, the elimination of rocuronium is mainly due to biliary excretion,[14] and liver cirrhosis may prolong the duration of action of steroid-based neuromuscular blocking agents. Our patient had moderately elevated values of alanine aminotransferase, aspartate aminotransferase and of alkaline phosphatase, and we cannot exclude the possibility that this had an influence on the reaction to rocuronium. We do, however, consider it unlikely that this is the sole explanation. Fourthly, the sensitivity to neuromuscular blocking agents is higher in females than in males. Xue and colleagues[15] found the mean total duration (90% recovery) after rocuronium 0.4 mg kg^{-1} to be 46.8 min in females compared with only 33.6 min in males. Fifthly and lastly, anaesthesia in this patient was maintained with sevoflurane. The neuromuscular blocking effect of rocuronium is enhanced by inhalation anaesthetics, for example, sevoflurane. Recovery of a rocuronium block during sevoflurane anaesthesia is therefore markedly slower than recovery during a total i.v. anaesthesia. Thus, Lowry and colleagues[16] found that the time to TOF ratio 0.8 after rocuronium 0.6 mg kg^{-1} was

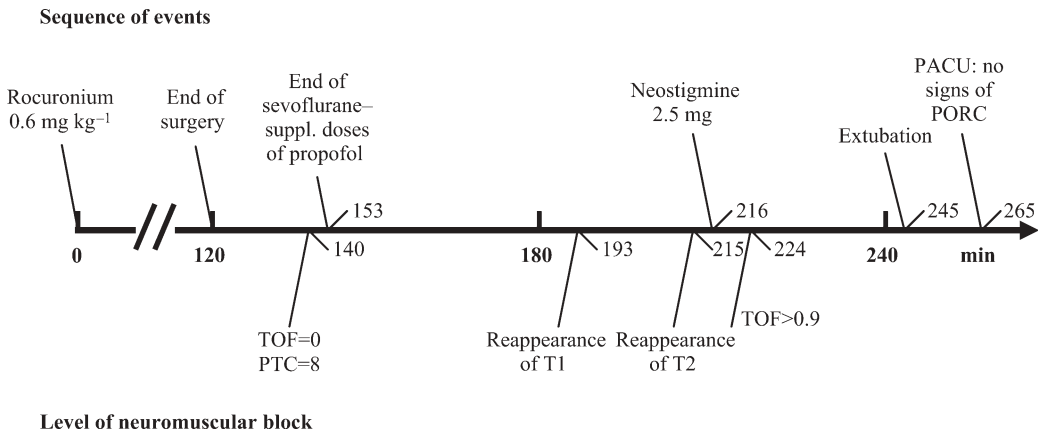

Fig 1 Events and degree of block after rocuronium 0.6 mg kg^{-1}. Numbers at the timeline indicate minutes after injection of rocuronium. (TOF, train-of-four; PTC, post-tetanic count; T1, first twitch in the TOF response; T2, second twitch in the TOF response, PACU, post-anaesthetic care unit.)

103 min in a group of patients receiving sevoflurane, compared with only 62 min in patients anaesthetized with propofol.

All in all, the most probable explanation of the prolonged response seen in this elderly patient is a genetically increased sensitivity to rocuronium, in combination with advanced age, decreased liver function, female gender, and the administration of sevoflurane.

Although there is good evidence that quantitative neuromuscular monitoring will decrease the risk of residual paralysis,[4 17] many clinicians still do not monitor routinely in daily practice. A recent study from Baillard and colleagues[18] showed that though the nurse anaesthetists at their department had received continuous information on the risk of residual paralysis for approximately 10 yr and apparatus for neuromuscular monitoring were available in every operating room, 40% of the patients were still not monitored. A Danish study[6] showed similar results. Only 43% of the clinicians used neuromuscular monitoring whenever a neuromuscular blocking agent was administered. For the clinicians who never or infrequently used neuromuscular monitoring, the main argument for not doing so was that only one intubating dose of the neuromuscular blocker was administered. However, Debaene and colleagues[19] found that of 526 patients receiving only one intubating dose of an intermediate-acting neuromuscular blocking agent, 37% had a TOF ratio of <0.9 (the threshold for excluding clinically significant residual curarization) in the PACU 2 h or more after the administration. In a recent meta-analysis of neuromuscular monitoring and PORC, Naguib and colleagues[20] could not demonstrate that the use of an intraoperative neuromuscular function monitor decreased the incidence of PORC. However, as can be seen from our letter to the Editor[21] as a response to the paper, we disagree with their conclusion. If the literature is evaluated according to generally accepted standards for evidence-based medicine,[22 23] there is insufficient evidence to confirm or deny that subjective neuromuscular monitoring decreases the incidence of PORC, whereas there is good evidence that objective neuromuscular monitoring with AMG decreases the incidence of PORC. Therefore, we support the notion recently expressed in an editorial in *Anesthesiology*: '... objective neuromuscular monitoring is an evidence-based practice and should consequently be used whenever a nondepolarizing neuromuscular blocking agent is administered'.[24]

In our department, monitoring of neuromuscular block is routinely performed with AMG (TOF-Watch®). Although AMG cannot be used interchangeably with the 'gold standard' mechanomyography (MMG), it is more user-friendly in the daily clinic. As the AMG TOF-ratio is often 10% higher than that of MMG during recovery, it has been suggested to change the threshold for excluding PORC to an AMG TOF ratio>1.0.[25] However, in our patient, an AMG TOF ratio of 1.0 was reached within 1 min of a TOF ratio of 0.9.

As it is difficult and often impossible to exclude PORC using only clinical criteria,[26] sufficient recovery of neuromuscular function was documented in the operating room before tracheal extubation by the use of the TOF-Watch® SX. However, we also assessed the patient in the PACU and found no signs or symptoms of residual paralysis.

Objective monitoring has a good applicability, but demands frequent use. There are many myths and excuses for not using a nerve stimulator. The truth is, however, that there are no good reasons for not monitoring neuromuscular block, whenever a neuromuscular blocking agent is given.

Sugammadex represents a new approach for reversal of rocuronium and if this drug becomes commercially available, it may change our view on objective monitoring.[27] Sugammadex encapsulates rocuronium and can reverse even deep block in <2 min.[28] If sugammadex was available, most probably the neuromuscular block could have been antagonized at the end of the surgery. This would have saved the patient from 2 h of anaesthesia.

Conclusion

This case illustrates the importance of quantitative neuromuscular monitoring. Although neuromuscular blocking agents with intermediate duration of action have a relatively short total duration of action, the variation in response is huge, making objective neuromuscular monitoring necessary whenever the agents are administered. Several factors may contribute to a prolonged effect with the risk of residual paralysis, including genetically individual differences, age, organ dysfunction, female gender, and the use of inhalation anaesthesia.

References

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

2 Baillard C, Gehan G, Reboul-Marty J, Larmignat P, Samama CM, Cupa M. Residual curarization in the recovery room after vecuronium. Br J Anaesth 2000; **84**: 394–5

3 Hayes AH, Mirakhur RK, Breslin DS, Reid JE, McCourt KC. Postoperative residual block after intermediate-acting neuromuscular blocking drugs. Anaesthesia 2001; **56**: 312–8

4 Gatke MR, Viby-Mogensen J, Rosenstock C, Jensen FS, Skovgaard LT. Postoperative muscle paralysis after rocuronium: less residual block when acceleromyography is used. Acta Anaesthesiol Scand 2002; **46**: 207–13

5 Debaene B, Plaud B, Dilly MP, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. Anesthesiology 2003; **98**: 1042–8

6 Sorgenfrei IF, Viby-Mogensen J, Swiatek FA. Does evidence lead to a change in clinical practice? Danish anaesthetists' and nurse anesthetists' clinical practice and knowledge of postoperative residual curarization. Ugeskr Laeger 2005; **167**: 3878–82

7 Viby-Mogensen J, Howardy-Hansen P, Chraemmer-Jorgensen B, Ording H, Engbaek J, Nielsen A. Posttetanic count (PTC): a new method of evaluating an intense nondepolarizing neuromuscular blockade. Anesthesiology 1981; **55**: 458–61

8 Baykara N, Solak M, Toker K. Predicting recovery from deep neuromuscular block by rocuronium in the elderly. J Clin Anesth 2003; **15**: 328–33

9 Arain SR, Kern S, Ficke DJ, Ebert TJ. Variability of duration of action of neuromuscular-blocking drugs in elderly patients. Acta Anaesthesiol Scand 2005; **49**: 312–5

10 Bevan DR, Fiset P, Balendran P, Law-Min JC, Ratcliffe A, Donati F. Pharmacodynamic behaviour of rocuronium in the elderly. Can J Anaesth 1993; **40**: 127–32

11 Matteo RS, Ornstein E, Schwartz AE, Ostapkovich N, Stone JG. Pharmacokinetics and pharmacodynamics of rocuronium (Org 9426) in elderly surgical patients. Anesth Analg 1993; **77**: 1193–7

12 Viby-Mogensen J, Howardy-Hansen P, Chraemmer-Jorgensen B, Ording H, Engbaek J, Nielsen A. Posttetanic count (PTC): a new method of evaluating an intense nondepolarizing neuromuscular blockade. Anesthesiology 1981; **55**: 458–61

13 Schultz P, Ibsen M, Ostergaard D, Skovgaard LT. Onset and duration of action of rocuronium—from tracheal intubation, through intense block to complete recovery. Acta Anaesthesiol Scand 2001; **45**: 612–7

14 van Miert MM, Eastwood NB, Boyd AH, Parker CJ, Hunter JM. The pharmacokinetics and pharmacodynamics of rocuronium in patients with hepatic cirrhosis. Br J Clin Pharmacol 1997; **44**: 139–44

15 Xue FS, Tong SY, Liao X, Liu JH, An G, Luo LK. Dose–response and time course of effect of rocuronium in male and female anesthetized patients. Anesth Analg 1997; **85**: 667–71

16 Lowry DW, Mirakhur RK, McCarthy GJ, Carroll MT, McCourt KC. Neuromuscular effects of rocuronium during sevoflurane, isoflurane, and intravenous anesthesia. Anesth Analg 1998; **87**: 936–40

17 Mortensen CR, Berg H, el Mahdy A, Viby-Mogensen J. Perioperative monitoring of neuromuscular transmission using acceleromyography prevents residual neuromuscular block following pancuronium. Acta Anaesthesiol Scand 1995; **39**: 797–801

18 Baillard C, Clec'h C, Catineau J, *et al*. Postoperative residual neuromuscular block: a survey of management. Br J Anaesth 2005; **95**: 622–6

19 Debaene B, Plaud B, Dilly MP, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. Anesthesiology 2003; **98**: 1042–8

20 Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis. Br J Anaesth 2007; **98**: 302–16

21 Viby-Mogensen J, Claudius C, Eriksson LI. Neuromuscular monitoring and postoperative residual curarisation. Br J Anaesth 2007; **99**: 927–9

22 Eccles M, Freemantle N, Mason J. North of England evidence based guidelines development project: methods of developing guidelines for efficient drug use in primary care. Br Med J 1998; **316**: 1232–5

23 Pedersen T, Moller AM. How to use evidence-based medicine in anaesthesiology. Acta Anaesthesiol Scand 2001; **45**: 267–74

24 Eriksson LI. Evidence-based practice and neuromuscular monitoring: it's time for routine quantitative assessment. Anesthesiology 2003; **98**: 1037–9

25 Capron F, Alla F, Hottier C, Meistelman C, Fuchs-Buder T. Can acceleromyography detect low levels of residual paralysis? A probability approach to detect a mechanomyographic train-of-four ratio of 0.9. Anesthesiology 2004; **100**: 1119–24

26 Viby-Mogensen J. Postoperative residual curarization and evidence-based anaesthesia. Br J Anaesth 2000; **84**: 301–3

27 Hunter JM, Flockton EA. The doughnut and the hole: a new pharmacological concept for anaesthetists. Br J Anaesth 2006; **97**: 123–6

28 Sparr HJ, Vermeyen KM, Beaufort AM, *et al*. Early reversal of profound rocuronium-induced neuromuscular blockade by sugammadex in a randomized multicenter study: efficacy, safety, and pharmacokinetics. Anesthesiology 2007; **106**: 935–43