

Complete resistance after maximal dose of rocuronium

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ABSTRACT

Rocuronium is a non-depolarizing neuromuscular blocking agent (NDNMBA), employed in the clinic as an adjunct to general anesthesia to facilitate tracheal intubation rapid sequence, and to provide skeletal muscle relaxation during surgery. Many cases of resistance to neuromuscular blocking agents (NMBAs) have been anecdotally reported. There are specific pathologic states, such as upper motor neuron lesions, severe thermal injuries, liver disease, renal failure, disuse atrophy, all of which show an increased resistance to the effects of nondepolarizing muscle relaxants. Also concurrent drug therapy can alter the efficacy of NMBAs such as some classes of antibiotics, furosemide, β receptor agonists, phosphodiesterase inhibitors, calcium antagonists, respiratory stimulants but also ketamine, propofol and barbiturates at high concentrations. In this scenario we describe an unusual case of 20-years-old man who showed a complete resistance to rocuronium maybe due to a glucocorticoids concomitant therapy.

Key words: Drug therapeutic failure, glucocorticoids, neuromuscular block, rocuronium

INTRODUCTION

Rocuronium is a non-depolarizing neuromuscular blocking agent (NDNMBA), employed in the clinic as an adjunct to general anesthesia, to facilitate rapid sequence tracheal intubation and to provide skeletal muscle relaxation during surgery. Resistance to the

neuromuscular effects of NDNMBAs has been reported following burns, immobilization, denervation, and infectious diseases.^[1] This resistance can be manifested either as a delayed onset of the effect, an incomplete neuromuscular block despite an effective dose, or a rapid recovery from paralysis.^[1] Many pharmacokinetic and pharmacodynamic factors and/or drug interactions can potentially contribute to this resistance. We report an unusual case of complete resistance to rocuronium in a 20-year-old patient undergoing renal biopsy, wherein, a neuromuscular block has been achieved by subsequent administration of cisatracurium.

To our knowledge, this is the first case of complete resistance to a double dose of an aminosteroid nondepolarizing muscle relaxant, but not to benzylisoquinolinium.

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CASE REPORT

A 20-year-old man, with height - 177 cm, weight - 78.4 kg, and body mass index (BMI) - 24.9, was scheduled for renal biopsy as part of a diagnostic protocol for undefined glomerulonephritis, with a nephrotic syndrome. He was hypertensive and thalassaemic, with hepatosplenomegaly, and was allergic to latex. The patient took oral prednisone therapy (30 mg/day), which lasted 140 days, and received the last dose (5 mg) two months before the scheduled surgery. Preoperative laboratory testing showed low hemoglobin levels (8.6 g/dl) and a low serum protein concentration (4.3 g/dl) with hypoalbuminemia (2.7 g/dl).

After receiving desensitizing therapy (betamethasone 4 mg twice a day) and ciprofloxacin (200 mg) intravenous (IV) for one day, the patient was admitted to the Operating Room and was premedicated with IV of midazolam (1 mg), fentanyl (0.05 mg), and atropine (0.7 mg). Intraoperative monitoring included an electrocardiogram (ECG), noninvasive blood pressure, pulse oximetry, end-tidal CO₂, and neuromuscular blockade monitoring. The intravenous catheter and arterial blood pressure monitor were placed on the contralateral arm for neuromuscular monitoring. Neuromuscular monitoring was performed by acceleromyography (M-NMT's transducer; MechanoSensor; Datex-Ohmeda). Electrodes were placed at the ulnar nerve on the volar side of the wrist. After three minutes of preoxygenation, anesthesia was induced with propofol (200 mg) and continuous remifentanyl (0.11 mcg/kg/minute). Just before the administration of rocuronium (0.6 mg/kg), the calibration of train-of-four (TOF) twitch height was performed. Three minutes later any depression of twitch height was observed (TOF-R >0.9) and the patient seemed to be partially awake without clinical signs of muscle relaxation. Additional doses of propofol (200 mg) and rocuronium (50 mg) from different batches were injected over ten minutes, but no depression in the twitch response was noted over the next seven minutes. An oral airway was inserted and the patient was ventilated by mask with sevoflurane (end-tidal concentration 2%) in oxygen (FiO₂ 0.5).

Option to awake the patient was discussed because TOF stimulation continued to evoke four equal twitches without fade (TOF-R >0.9) during the subsequent ten minutes. Finally, it was decided to attempt neuromuscular relaxation with a benzylisoquinolinium non-depolarizer compound, and cisatracurium (0.2 mg/kg) was injected. Train-of-four responses disappeared quickly (120 seconds) and completely and orotracheal intubation was easily performed. During general anesthesia (sevorane and remifentanyl) any movements or diaphragmatic contractions were noted. No additional cisatracurium was needed. The operation took approximately half an hour and was uneventful. At a TOF-R >0.9 the patient's trachea was safely extubated, without any airway complications,

using pharmacological reversal with neostigmine (2 mg), atropine (1 mg), and sugammadex (2 mg/kg). The postoperative course was uneventful.

DISCUSSION

We report the first case, to our knowledge, of complete resistance to a double dose of aminosteroid nondepolarizing muscle relaxant, but not to benzylisoquinolinium. All possible causes that could account for such unusual failure of effect of an aminosteroid muscle relaxant, such as, outdated rocuronium and/or improper storage conditions were carefully assessed before being excluded as the likely causes. We used the same batch of rocuronium for a variety of other procedures with normal therapeutic effects. There was no infiltration of the IV infusion at any time during the procedure. We placed the IV catheter and arterial blood pressure monitor on the contralateral arm for neuromuscular monitoring, to minimize any interference between these monitorings. We checked the correct placement of the stimulating electrodes along the ulnar nerve at the wrist during the procedure. The neuromuscular blockade monitor used was checked and found to be functioning adequately.

Many cases of resistance to neuromuscular blocking agents (NMBAs) have been anecdotally reported. There are specific pathological states, such as, upper motor neuron lesions, severe thermal injuries, liver disease, and disuse atrophy, all of which show an increased resistance to the effects of nondepolarizing muscle relaxants.^[2] Also concurrent drug therapy can change the efficacy of NMBAs.^[3] It is known that the possible interaction between NMBAs and other common drugs used in anesthesia can lead to a variability of their effect. The interaction can take place at various levels involving the transmission of an action potential in the motor nerve, the synthesis and release of acetylcholine, and the integrity of post synaptic receptors. Focusing on our patient's clinical and pharmacological history, we hypothesize that resistance to rocuronium may be on account of the patient's corticosteroid therapy. As we have just reported, the patient received two doses of betamethasone before the surgery and ended the prednisone long term therapy two months before. Data from the literature report that glucocorticoids are able to interact with neuromuscular transmission in different ways. They facilitate impulse generation at the end of the motor nerve axon. Additionally, glucocorticoids act:

- *presynaptically*, stimulating synthesis, spontaneous release, as well as stimulated the release of acetylcholine^[4]
- *postsynaptically*, with upregulation of the nicotinic acetylcholine receptor (nAChRs) with a genomic effect, in long-term treatments.^[5]

Resistance to aminosteroid NMBAs given in association with steroid therapy has been reported in several cases. In all of these

cases, the occurrence of resistance has been reported in terms of delayed onset time, incomplete neuromuscular block despite an effective dose or a rapid recovery from paralysis,^[1] however, no one has described the complete absence of curarization after administration, within the clinical range of therapy.

Soltez *et al.* have reported that the administration of dexamethasone immediately before induction of anesthesia does not attenuate the rocuronium effect, but even if administered at a lower dose (0.3 mg/kg), two or three hours before induction, it can reduce the duration of the neuromuscular block.^[6]

A presynaptic cholinergic receptor binding interaction between steroids and neuromuscular blocking agents that have steroid derived molecular structures is one possible factor that may have brought about complete resistance.^[7] On the other hand, it has been suggested that rocuronium, as any other aminosteroid NMBA, acts predominantly at presynaptic receptor sites, whereas, cisatracurium, similar to other benzylisoquinoliniums, primarily a postjunctional receptor blockade,^[7] has a synergic effect when used in combination. Moreover, the patient's chronic glucocorticoid therapy, according to Maestroni and colleagues,^[5] induces an upregulation of native muscle nAChR in cultured human muscle, with a genomic effect. As reported elsewhere, upregulation of nAChRs in the skeletal muscle is associated with the development of resistance to NMBA. The same phenomenon occurs further to glucocorticoid exposure, both *in vivo* and in patients.^[5] To the best of our knowledge, we can only suppose that this upregulation was still present in our patient, although the therapy ended two months before the observed resistance, and it also occurred in patients with burns. Even in those patients there is an upregulation of nAChRs and it has been reported that recovery of neuromuscular function to preburn levels may take several months or even years after the burn injury.^[8]

Therefore, our case of complete resistance to the rocuronium effect could be on account of a double sided interference: Presynaptic and postsynaptic. Rocuronium action was reduced at the presynaptic junction (by betamethasone administered before the surgery), and despite its dose being doubled, it was not enough to determinate a significant effect on the postsynaptic increased receptors, with complete absence of clinical effects revealed, with any sort of twitch depression on acceleromyography. It has been found that in normal subjects 75% receptor occupancy by the antagonist is necessary before any effect can be seen, and at least 95% receptor occupancy is necessary for complete suppression of the twitch.^[9] We cannot exclude that the normal effect observed after cisatracurium administration was because of the synergic effect between rocuronium and cisatracurium. It would be interesting to know what would have happened if we had used the benzylisoquinolinium compound as a first choice.

It has also been reported in a retrospective clinical review performed by Parr and colleagues, that patients receiving long term pretreatment with betamethasone required, on an average, 75% more vecuronium;^[10] conversely, in our case it was doubled (100% more).

An additional factor that may contribute to the resistance is decreased acetylcholinesterase activity (AChE). Here, breakdown of acetylcholine (ACh) would be diminished increasing the levels of ACh at the neuromuscular joint.^[9] We did not have dosed AChE in our patient, but Kaplan *et al.* examined the effects of dexamethasone on the AChE activity and they found no significant influences.^[11]

Moreover, Liu and Dilger reported that mutations in both the ϵ - and δ -subunits of nAChR affected the inhibitory potency of rocuronium in the *in vitro* experiment, and we cannot exclude a similar condition in our case.^[12]

At the end of the procedure conventional reversal agents were used. As two kinds of NMBAs were administered in sequence, and one of these in a double dose, the postoperative residual curarization risk cannot be predicted. Therefore, we decided to administer sugammadex also as a rocuronium antidote.

CONCLUSION

To the best of our knowledge, this is the first case of complete resistance to a doubled dose of an aminosteroid nondepolarizing muscle relaxant, but not to benzylisoquinolinium, in a patient who received corticosteroid therapy before surgery. Therefore, the case described is an example of drug therapeutic failure (DTF) by pharmacodynamic interaction. The DTF is, to date, included within the wider definition of an adverse drug event given by the World Health Organization (WHO) and it is proposed as a peculiar type of adverse drug reaction designated as 'failure'.

For this reason pharmacovigilance post-marketing studies are key elements to monitor the safety and effectiveness of approved drugs.^[13-17] Therefore, pharmacovigilance post-marketing could also be a valid instrument to identify the reactions by interaction, such as those described, and to promote appropriate studies that may help to understand the underlying mechanisms.

REFERENCES

1. Fink H, Lupp A, Mayer B, Rosenbrock H, Metzger J, Martyn JA, *et al.* Systemic inflammation leads to resistance to atracurium without increasing membrane expression of acetylcholine receptors. *Anesthesiology* 2003;98:82-8.
2. Reddy P, Guzman A, Robalino J, Shevde K. Resistance to muscle relaxants in a patient receiving prolonged testosterone therapy. *Anesthesiology* 1989;70:871-3.

3. Soriano SG, Sullivan LJ, Venkatakrishnan K, Greenblatt DJ, Martyn JA. Pharmacokinetics and pharmacodynamics of vecuronium in children receiving phenytoin or carbamazepine for chronic anticonvulsant therapy. *Br J Anaesth* 2001;86:223-9.
4. Soltész S, Mencke T, Stunz M, Diefenbach C, Ziegeler S, Molter GP. Attenuation of a rocuronium-induced neuromuscular block in patients receiving prednisolone. *Acta Anaesthesiol Scand* 2009;53:443-8.
5. Maestroni E, Lagostena L, Henning RH, Hertog AD, Nobile M. Functional aspects of dexamethasone upregulated nicotinic acetylcholine receptors in C2C12 myotubes. *Pharmacol Res* 1995;32:305-8.
6. Soltész S, Fraisl P, Noé KG, Hinkelbein J, Mellinghoff H, Mencke T. Dexamethasone decreases the duration of rocuronium-induced neuromuscular block: A randomised controlled study. *Eur J Anaesthesiol* 2014;31:417-22.
7. Robinson BJ, Lee E, Rees D, Purdie GL, Galletly DC. Betamethasone-induced resistance to neuromuscular blockade: A comparison of atracurium and vecuronium *in vitro*. *Anesth Analg* 1992;74:762-5.
8. Cronan T, Hammond J, Ward CG. The value of isokinetic exercise and testing in burn rehabilitation and determination of back-to-work status. *J Burn Care Rehabil* 1990;11:224-7.
9. Martyn JA, White DA, Gronert GA, Jaffe RS, Ward JM. Up-and-down regulation of skeletal muscle acetylcholine receptors. Effects on neuromuscular blockers. *Anesthesiology* 1992;76:822-43.
10. Parr SM, Galletly DC, Robinson BJ. Betamethasone-induced resistance to vecuronium: A potential problem in neurosurgery? *Anaesth Intensive Care* 1991;19:103-5.
11. Kaplan I, Blakely BT, Pavlath GK, Travis M, Blau HM. Steroids induce acetylcholine receptors on cultured human muscle: Implications for myasthenia gravis. *Proc Natl Acad Sci U S A* 1990;87:8100-4.
12. Liu M, Dilger JP. Site selectivity of competitive antagonists for the mouse adult muscle nicotinic acetylcholine receptor. *Mol Pharmacol* 2009;75:166-73.
13. Mazzitello C, Esposito S, De Francesco AE, Capuano A, Russo E, De Sarro G. Pharmacovigilance in Italy: An overview. *J Pharmacol Pharmacother* 2013;4 Suppl 1:S20-8.
14. Ruggiero S, Rafaniello C, Bravaccio C, Grimaldi G, Granato R, Pascotto A. Safety of attention-deficit/hyperactivity disorder medications in children: An intensive pharmacovigilance monitoring study. *J Child Adolesc Psychopharmacol* 2012;22:415-22.
15. Rafaniello C, Ianniello B, De Vizia M, Mercogliano A, Lettieri B, Rinaldi B, *et al.* Cardiorespiratory effects of change in posture after spinal anesthesia with hyperbaric bupivacaine. *Minerva Med* 2011;102:501-4.
16. Capuano A, Irpino A, Gallo M, Ferrante L, Illiano ML, Rinaldi B, *et al.* Regional surveillance of emergency-department visits for outpatient adverse drug events. *Eur J Clin Pharmacol* 2009;65:721-8.
17. Capuano A, Motola G, Russo F, Avolio A, Filippelli A, Rossi F, *et al.* Adverse drug events in two emergency departments in Naples, Italy: An observational study. *Pharmacol Res* 2004;50:631-6.

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