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Case Report: Resistance to Neuromuscular Blockade and the Benefits of Quantitative Monitoring

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ABSTRACT

Neuromuscular blockade (NMB) monitoring is essential in modern anesthetic practice, particularly for optimizing the administration of blocking agents and their reversal agents. We present the case of a 54-year-old female patient with a history of chronic carbamazepine use and monoplegia, who underwent a laparoscopic cholecystectomy. Despite the administration of standard and additional doses of rocuronium, significant resistance to NMB was observed, along with difficulty maintaining the surgical field, as confirmed by quantitative monitoring. The patient showed rapid recovery from the blockade without the need for reversal agents, highlighting the crucial role of continuous monitoring in intraoperative decision-making. This case underscores the importance of considering factors such as anticonvulsant use and neurological disorders in NMB response and emphasizes the impact of quantitative monitoring in resource-limited settings to enhance perioperative safety and outcomes.

KEYWORDS: neuromuscular blockade, neuromuscular blockers, anticonvulsants, monoplegia, rocuronium, carbamazepine.

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I. INTRODUCTION

Neuromuscular blockade (NMB) monitoring has been emphasized as a key recommendation in recent guidelines on anesthesia and perioperative care (1-4). This approach is particularly relevant in discussions about the benefits of deep blockade, complications associated with residual neuromuscular blockade, the costs of reversal agents, and the availability of monitoring technologies in resource-limited settings.

Its use allows for a quantitative assessment of response to neuromuscular blockers, which is essential not only for the appropriate administration of reversal agents but also for adjusting the depth of blockade according to the patient's needs (2, 5-9). Various studies have demonstrated that factors such as upper motor neuron conditions, denervation, prolonged immobilization, and the use of anticonvulsants—particularly phenytoin and carbamazepine—can alter the response to NMB (10-13), which must be considered in clinical practice.

In this article, we present and analyze a clinical case in which both chronic carbamazepine use and the presence of monoplegia led to resistance to NMB . This phenomenon was confirmed through quantitative monitoring of blockade depth using a mechanosensor in Train-of-Four (TOF) mode via ulnar nerve stimulation on the contralateral side to the plegia. Despite the administration of additional doses of neuromuscular blockers, the use of reversal agents was not required due to the quick recovery seen in the continuous NMB monitoring, highlighting the importance of this tool in real-time clinical decision-making.

II. CLINICAL CASE

We present the case of a 54-year-old female patient, 155 cm tall and weighing 73.5 kg, diagnosed with symptomatic cholelithiasis and scheduled for elective laparoscopic cholecystectomy under general anesthesia. Her medical history is notable for sequelae of childhood meningitis, including symptomatic focal epilepsy diagnosed 53 years ago and treated for the past 10 years with carbamazepine (400 mg – 200 mg – 400 mg per day). Additionally, the patient has monoplegia of the extensor muscles of the left forearm and wrist (C7 and C8 regions), diagnosed 53 years ago as of central origin. She also has a history of ductal carcinoma in situ of the right breast, treated with radical mastectomy two years ago, and is currently on maintenance therapy with tamoxifen 20 mg/day. Preoperative laboratory tests and evaluation results were within normal parameters, with no contraindications for the surgical procedure.

A. Anesthesia Induction

Once preoperative conditions were verified, anesthesia was induced using propofol 150 mg (2 mg/kg), midazolam 1 mg (0.01 mg/kg), fentanyl 150 mcg (2 mcg/kg), and rocuronium 40 mg (0.6 mg/kg) intravenously. NMB monitoring was performed using the CARESCAPE B450 monitor integrated into the Datex Ohmeda S/5 Avance anesthesia machine with a General Electric E-NMT module. A mechanosensor was placed on the right hand, contralateral to the paralyzed region, with electrodes positioned along the ulnar nerve pathway, as shown in Figure 1. Automatic calibration of supramaximal stimulus was performed during induction, establishing a current of 50 mA and an amplitude of 0.2 ms. Measurements were programmed every 60 seconds in TOF mode.

Figure 1. NMB monitoring.

After induction and a pharmacological latency of 5 minutes, a TOF ratio of 0.4 was observed. At 7 minutes, the TOF ratio dropped to only 0.3; however, orotracheal intubation was performed without complications on the first attempt, with adequate glottic visualization using direct laryngoscopy, classified as Cormack-Lehane grade I. A 7.0 mm endotracheal tube was inserted to a depth of 19 cm, with a cuff inflated to 4 cc. Proper placement was confirmed via capnography and symmetrical ventilation. Ventilation was initiated in volume control mode with a tidal volume (Vt) of 350 ml, respiratory rate (RR) of 12 bpm, PEEP of 5 cm H2O, a flow rate of 2 l/min, and an FiO2 of 40%. Peak pressures ranged from 16-22 mmHg. Ephedrine 10 mg IV was administered to correct hypotension following anesthetic induction. Maintenance anesthesia was provided with sevoflurane at CAM of 0.7-0.9, with 2.0 Vol %, and fentanyl in intermittent boluses every 50 minutes. Adjunct medications included dexamethasone 4 mg IV, ketorolac 60 mg IV, omeprazole 20 mg IV, and paracetamol 1 g IV.

B. Procedure

Adequate analgesia was maintained, defined by the absence of sympathetic reflex responses on monitoring. The surgeon used the Hasson technique to establish pneumoperitoneum and access the abdominal cavity. During this phase, bradycardia at 40 bpm occurred without hemodynamic compromise, treated with atropine 0.8 mg IV, with an adequate response. The surgeon reported a poor surgical field and palpable rigidity of the rectus abdominis muscles, prompting the administration of an additional dose of rocuronium 10 mg IV, 20 minutes after induction. Despite this, NMB monitoring continued to show a minimal TOF ratio of 0.2. During the intervention, perivesicular abdominal adhesion syndrome was detected, leading the surgical team to convert to open surgery.

Twenty-five minutes after the last dose of neuromuscular blocker, following the abdominal opening, the surgeon again noted rigidity of the rectus abdominis muscles and a reduced surgical field. Monitoring showed an apparent onset of recovery, with a TOF ratio of 0.3. Another dose of rocuronium 10 mg IV was given, but the TOF ratio remained at a minimum of 0.2, as shown in Figure 2. The procedure proceeded without further incidents and was completed as a subtotal cholecystectomy. Recovery began 25 minutes after the last neuromuscular blocker dose, reaching a TOF ratio of 0.8 at 60 minutes and 0.9 at 75 minutes, as shown in Figure 3. Despite this quick recovery, the surgeon did not report difficulties in completing the procedure.

Figure 2. Resistance to NMB despite subsequent doses.

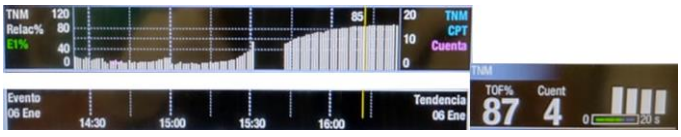

Figure 3. Accelerated and Complete recovery of NMB

C. Extubation and end of the case

Extubation was performed 140 minutes after anesthesia induction without the need for reversal agents, and with adequate ventilatory dynamics, was uneventful, and the patient was transferred stably to the post-anesthesia care unit (PACU) with an Aldrete score of 9/10, RAAS -1, and ENA 1/10. No anesthetic recovery events occurred, and the patient was later transferred to the ward with an Aldrete score of 10/10, ENA

3/10, and RAAS 0, without signs of recurarization or immediate respiratory complications.

III. DISCUSSION

Resistance to NMB and its accelerated recovery are documented phenomena in patients with spinal cord injuries, upper motor neuron lesions, prolonged immobility, and those using anticonvulsant medications (12). These events have been reported in the literature, particularly with the use of phenytoin, carbamazepine, and phenobarbital (14-20). Resistance to aminosteroid non-depolarizing neuromuscular blockers, such as vecuronium and rocuronium, has been highlighted in several publications involving patients with either or both of these conditions (14-25).

Tempelhoff R. et al. (14) described resistance in patients undergoing anticonvulsant therapy, even with benzylisoquinolinium-type non-depolarizing blockers such as atracurium. However, these findings were later debated by the results of studies conducted by Spacek (18, 19). In the case of rocuronium, Spacek (18) observed a reduced recovery time in patients using carbamazepine, with a 25-75% T1 recovery index of approximately 10.9 ± 4.6 minutes. This differs from our case, in which recovery took 18 minutes. Additionally, the time required to achieve a blockade greater than 95% of the recorded baseline amplitude was 2.8 ± 1.2 minutes in that study, significantly shorter than the 7 minutes required in our patient to achieve significant blockade. Despite a cumulative dose of 0.8 mg/kg of rocuronium, deep blockade was not achieved in our case.

Soriano et al. (19) evaluated the onset and recovery times of rocuronium in children receiving anticonvulsant therapy with phenytoin, carbamazepine, or both for more than one month. They found a significant shortening of the recovery time, with a T1 recovery index of 4.8 minutes, and a non-significant delay in the onset of action of 1.4 minutes. These findings partially align with our observations.

Subsequently, Soriano et al. (20) published a study in which they measured plasma concentrations of vecuronium and its metabolites after a 0.15 mg/kg dose. They observed an accelerated clearance of vecuronium in patients on chronic phenytoin and carbamazepine therapy, reflected in a recovery index of 12.5 minutes for phenytoin and 10.6 minutes for carbamazepine, compared to 21.8 minutes in the control group. This study found no relationship between the carbamazepine dose and the acceleration of clearance. Although they achieved complete neuromuscular blockade, their findings are consistent with our case regarding accelerated recovery.

In patients with cerebral palsy, Moorthy et al. (21) evaluated the response to 0.1 mg/kg of vecuronium using electromyography in children with spastic paralysis, finding an accelerated recovery time, approximately 50% shorter than in children without paralysis. Hepaguslar (22) analyzed the onset and recovery times of NMB in patients with cerebral palsy, with and without anticonvulsant use. The study found a non-significant prolongation of the onset time by 35 seconds and a shortened recovery index of 11 minutes for cerebral palsy alone and up to 5 minutes in patients with both cerebral palsy and anticonvulsant use. The author concluded that cerebral palsy induces resistance to aminosteroid NMBs and that the combined use of anticonvulsants potentiates this effect, reducing blockade duration by up to 70%. In their study, two patients with cerebral palsy and anticonvulsant use failed to achieve deep blockade, similar to what occurred in our case.

Regarding the pathophysiology, Robinson K.G. et al. (23) studied the abnormal distribution of basal lamina components in the neuromuscular junction of patients with cerebral palsy, highlighting alterations in laminin β2 and acetylcholinesterase distribution. Lee S. et al. (24) demonstrated overexpression and abnormal distribution of acetylcholine receptors in muscle tissue, correlating the degree of motor dysfunction with higher rocuronium requirements—up to 1.6 times more than in controls—regardless of anticonvulsant use. Additionally, they observed an additive effect between both conditions, as seen in our patient.

Soriano et al. (25) reviewed the pharmacodynamics and pharmacokinetics of anticonvulsant-induced resistance, highlighting cytochrome P450 induction (CYP2C and CYP3A), the production of immature acetylcholine receptors with lower affinity for blocking agents, the increased proportion of acetylcholine receptors leading to higher blocking agent requirements, and the induction of α1-acid glycoprotein, reducing the fraction of free active drug.

The findings in our patient are consistent with those reported in the literature regarding NMB resistance and accelerated recovery, likely attributable to monoplegia of presumed central origin and chronic carbamazepine use. The absence of deep blockade may explain the perceived surgical difficulty, aligning with reports on the benefits of deep NMB in delicate surgeries such as abdominal laparoscopy (5-9).

The availability of quantitative NMB monitoring is limited, and most referenced studies utilize electromyography for this purpose. However, the utility of mechanosensors is supported by clinical guidelines, and the effect of resistance has been evaluated in studies using mechanosensors (22,24), similar to the one used for monitoring our patient. Familiarity with its proper use allowed us to avoid the administration of reversal agents at the end of surgery, despite the subsequent doses of neuromuscular blockers. This supports guideline recommendations for NMB management, as well as the clinical benefits and cost reduction associated with the use of this type of monitoring.

IV. CONCLUSIONS

Quantitative monitoring of the depth of NMB is confirmed as an essential tool in the administration of neuromuscular blocking agents, particularly in patients with conditions that affect their response to these drugs, such as chronic anticonvulsant use or the presence of paralysis. This case highlights the importance of considering these variables to optimize both anesthetic safety and surgical outcomes,

especially in procedures where deep NMB is recommended, such as abdominal laparoscopic surgery.

Developing specific recommendations for the use of neuromuscular blocking agents in patients with neurological disorders or undergoing anticonvulsant treatment could be beneficial, given the variability in clinical effects resulting from altered pharmacodynamics and pharmacokinetics in these populations. Studies are required to evaluate the dosing protocol for rapid sequence intubation with rocuronium in this type of patients due to the risk of delayed onset of action or resistance, as well as the risk of an insufficient effect. This case reinforces the importance of anesthesiologists being familiar with NMB monitoring, including the proper interpretation of the train-of-four (TOF) ratio and T1 amplitude, enabling individualized dosing of neuromuscular blocking agents.

Finally, the experience in this case highlights the clinical and economic value of quantitative NMB monitoring, facilitating a safer and more efficient management of this critical component of general anesthesia. It underscores the importance of implementing NMB monitoring in all settings where neuromuscular blocking agents are used, as a means to optimize patient safety and promote the rational use of reversal agents.

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