Delayed Rocuronium Onset in a Patient Taking Levetiracetam for Epilepsy: A Case Report

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Emerging evidence suggests that many conventional anticonvulsants, such as carbamazepine, phenytoin, and valproic acid, could cause cross-resistance to nondepolarizing muscle relaxants. However, there are few reports describing the interactions between levetiracetam and rocuronium. This case report describes the delayed onset of rocuronium in an adult patient with intractable epilepsy on long-term levetiracetam therapy. A 33-year-old man was scheduled for extraction of third molars and restorative dental treatment. His daily levetiracetam was continued preoperatively, and after a slow mask induction, rocuronium (20 mg; 0.66 mg/kg) was administered. Muscle relaxation was monitored by train-of-four (TOF) stimulation using the adductor muscle of the thumb. However, it took more than 9 minutes to finally obtain a TOF count of 0. This case report highlights that patients with intractable epilepsy taking levetiracetam may have resistance to rocuronium and should be carefully monitored to avoid harm triggered by prematurely initiated intubation maneuvers.

Key Words: Neuromuscular blockers; Muscle relaxant; Rocuronium; Anticonvulsant; Resistance; Intractable epilepsy; Levetiracetam.

Many drugs can impact nondepolarizing muscle relaxants (NDMRs), leading to prolonged or enhanced neuromuscular blockade. Long-term use of antiepileptic drugs (AEDs) such as carbamazepine, phenytoin, and valproic acid has been reported to be associated with resistance to both the aminosteroidal (eg, rocuronium, vecuronium) and benzylisoquinolinium (eg, atracurium, cisatracurium) NDMRs.[1–10] Reports on the effects of newer AEDs (eg, lamotrigine, levetiracetam) on rocuronium are scarce and may not be well recognized.

Herein, we report a case of delayed rocuronium onset during general anesthesia in a patient on long-term anticonvulsant therapy because of intractable epilepsy. Written consent was obtained from the patient's legal guardian to publish the details of this case report.

CASE PRESENTATION

A 33-year-old man (height, 150 cm [59 in]; weight, 30 kg; body mass index, 13.3 kg/m^2) was scheduled for extraction of all 4 third molars and restorative treatment for dental caries. He was delivered at 37 weeks gestation with no perinatal abnormalities. However, 3 days after delivery, he contracted bacterial meningitis and suffered hydrocephalus which led to intractable epilepsy and intellectual disability, thereby hampering communication. Using the Oshima classification for patients with severe motor and intellectual disabilities, he was graded division 4 (very severe).[11]

Because of his history of status epilepticus, levetiracetam (1800 mg, twice a day) had been prescribed for over 10 years as his daily antiepileptic medication along with diazepam suppositories (10 mg) for emergent use in the event of unabated seizures. Despite his medications, epileptic seizures occurred often (ie, once a week) leading up to the week before hospital admission. He needed full-time assistance for the activities of daily living and utilized a wheelchair for transportation. The patient had no known drug allergies and no relevant family history.

Preoperatively, an anterior-posterior (AP) chest radiograph demonstrated severe scoliosis and a 12-lead electrocardiography revealed right-axis deviation. Routine preoperative blood tests were not obtained because of his uncooperative nature and therefore were planned to follow induction of general anesthesia.

The following risk factors for difficulty with mask ventilation were identified: male, beard, thick neck, and Mallampati class IV. Regarding difficult tracheal intubation

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risk factors, poor cervical spine mobility and difficulty with mouth opening were detected. Airway management was expected to be challenging because of tracheal deviation and his bent posture, which were observed at the preoperative assessment (Figure 1A and B). The patient was deemed an American Society of Anesthesiologists physical status class 3.

We planned for outpatient surgery rather than inpatient because of his difficulty adapting to different environments. The day of surgery, he took his usual dose of levetiracetam more than 2 hours before the induction of general anesthesia. He had fasted appropriately for more than 8 hours, and no other premedication was administered. Upon arrival to the operating room and application of the standard anesthesia monitors, including a muscle-relaxation monitor (NMT module, Philips; Figure 2A), his blood pressure was 95/70 mm Hg, pulse was 66 beats/min, and oxygen saturation was 97% at room air. Preoxygenation (6 L/min) was started, followed by a slow mask induction with sevoflurane (3%) that was started gradually and mixed with oxygen. After loss of consciousness, venous access was established in the left upper arm using a 22-gauge intravenous (IV) cannula. Boluses of fentanyl (50 μg) and rocuronium (20 mg; 0.66 mg/kg) were administered. Muscle relaxation was monitored using the train-of-four (TOF) test and the adductor muscle of the thumb (Figure 2B). Spontaneous ventilation was maintained and assisted mask ventilation was easy, so we opted to wait for a TOF of 0 using the muscle-relaxation monitor. However, it took over 9 minutes to obtain a TOF of 0.

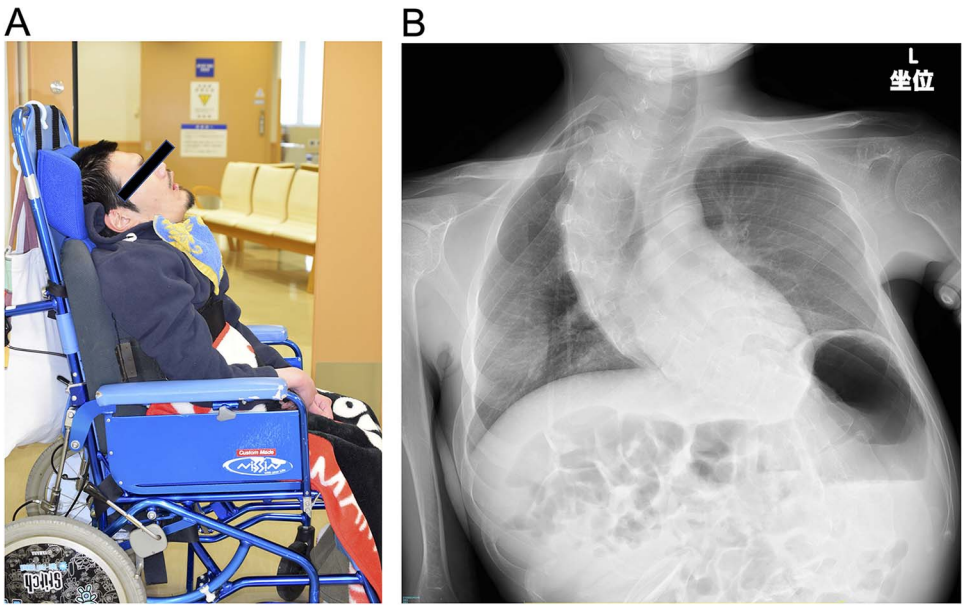
After sufficient muscle paralysis was confirmed, a video laryngoscope (McGRATH Mac, Medtronic) was employed, which produced a Cormack-Lehane grade 2 view. A flexible, wire-reinforced, endotracheal tube (internal diameter 7.0 mm) with a cuff (Shiley spiral tube, Covidien Japan) was used for the oral intubation. Adverse airway reflexes were not observed during the intubation. General anesthesia was maintained with oxygen (0.5 L/min), air (0.5 L/min), desflurane (4.5%), and a continuous infusion of remifentanil (0.2 μg/kg/min).

Rocuronium was not readministered during the dental procedure, and the patient's neuromuscular status prior to reversal at the end of the case was almost fully recovered with a TOF of 4 at 87%. However, sugammadex (200 mg) was administered preventively, and, after confirmation of adequate spontaneous breathing with airway patency, he was extubated. The duration of the dental procedure was 1 hour and 22 minutes. The duration of anesthesia was 3 hours and 2 minutes. The venous blood sample taken during the case showed hypoalbuminemia (3.1 g/dL; normal range, 4.1-5.1 g/dL), although his liver enzyme levels and serum Ca^{2+} were all on the low end of normal. The patient was discharged without complications on postoperative day 1.

DISCUSSION

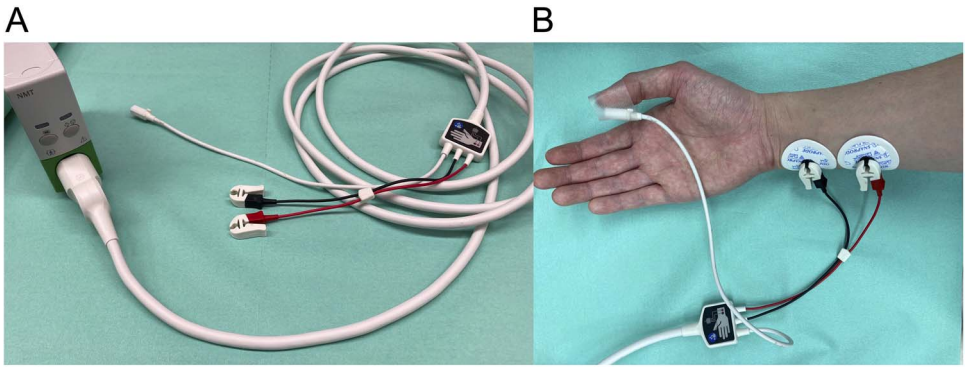
Intractable epilepsy can be associated with muscle weakness and impaired upper extremity coordination and dexterity. In general, rocuronium at 0.6 mg/kg should provide sufficient muscle relaxation for safe tracheal intubation approximately 2 minutes after IV administration.[12] However, in this case, it

Figure 1. Clinical Picture and Chest Radiograph of the Patient.



A, Side view of the patient. B, AP chest radiograph demonstrating significant scoliosis and tracheal deviation.

Figure 2. Muscle Relaxation Monitor.



A, NMT module with electrode clips and acceleration detection monitor. B, The acceleration detection monitor attached to the patient's thumb along with 2 electrodes used to stimulate the ulnar nerve.

took more than 9 minutes to obtain a TOF of 0. Intraoperative blood tests were performed to investigate whether the patient had any liver and/or kidney impairment due to long-term use of levetiracetam, but no abnormal values were found. Because Ca^{2+} levels can impact the effects of rocuronium, we checked his serum Ca^{2+} levels and found them to be within normal limits. The blood tests we obtained notably did not include Mg^{2+}, which can also impact muscle relaxation, so it remains unclear if that played a role.

Spontaneous ventilation was maintained while we were waiting for the TOF of 0, which was one of the clinical signs of the delayed paralysis onset we encountered. Although there was one report of delayed recovery from rocuronium-induced neuromuscular blockade in patients taking levetiracetam (1000 mg) acutely before operations,[13] there were few reports of long-term levetiracetam use (ie, over 10 years) that we were able to identify in the existing literature. Accumulation of findings in cases of long-term levetiracetam use is needed.

Anesthesiologists should assess neuromuscular function to avoid insufficient muscle relaxation, which can cause adduction or complete closure of the vocal cords (ie, laryngospasm) and a cough reflex during endotracheal intubation, endangering patient safety.[14–16] In such situation, the risks of a challenging intubation and vocal-cord injury due to glottis closure are high. Waiting patiently for the onset of sufficient muscle relaxation, as was done in this case, is important. Furthermore, adverse events (eg, glottis closure due to premature initiation of intubation) can be avoided by using a muscle-relaxation monitor, as was also done in this case. Careful assessment of the patient's neuromuscular status prior to intubation and throughout the surgical procedure, especially in patients with intractable epilepsy on long-term anticonvulsants like levetiracetam, is highly recommended because sufficient paralysis is essential for safe anesthesia management. The NMT monitor utilized in this study was approved as a medical device by the Japanese government and is widely used in daily clinical practice. We do not have any information on whether this device shows higher sensitivity vs traditional twitch monitors. Therefore, this device is anticipated to have the same sensitivity in detecting muscle relaxation as a traditional twitch monitor.

Deeper knowledge of drug interactions is becoming important, especially in anesthesiology and critical care. Emerging evidence suggests that AEDs such as phenytoin, carbamazepine, phenobarbital, and valproic acid can induce resistance to NDMRs like rocuronium. Delayed rocuronium onset has been reported in children taking the AEDs phenytoin and carbamazepine for a long time (eg, for more than 1 month).[17] However, few reports have described NDMR resistance in an adult taking AEDs for over 10 years.

It is thought that NDMR resistance associated with long-term antiepileptic therapy using conventional agents like carbamazepine, phenytoin, and valproic acid is due to 3 main factors operating alone or in combination: (1) induced hepatic drug metabolism, (2) increased protein binding of the NDMR, and (3) upregulation of acetylcholine receptors (AChRs).[18] These factors are discussed below.

Conventional AEDs such as carbamazepine, phenytoin, and valproic acid produce cytochrome P450 (CYP450) enzymatic induction, which can increase drug metabolism in the liver, leading to shorter duration of action.[19–21] Some reports have indicated that phenytoin increased alpha-1 glycoprotein (AAG) in human serum and rats.[22,23] Increased AAG blood levels promote plasma protein binding of cationic drugs, including all NDMRs (ie, the aminosteroids and benzylisoquinolines), which results in a decreased concentration of unbound, free drug capable of exerting its pharmacological effects (ie, paralysis), leading to delayed onset and shorter duration of action.[23–25] Decreased function of the neuromuscular junction with decreased receptor sensitivity and increased numbers of postsynaptic AChRs have been reported, which requires increased NDMR quantities

and can otherwise lead to delayed neuromuscular blockade onset.[26]

However, compared with other conventional antiepileptics, levetiracetam is an orally active drug with a unique profile. Its pharmacokinetics closely approximate the ideal characteristics expected of an AED: good bioavailability, rapid achievement of steady-state concentrations, linear and time-invariant kinetics, minimal protein binding, and minimal metabolism.

The major metabolic pathway of levetiracetam is not dependent on the hepatic CYP450 system, nor does it cause hepatic enzyme inhibition or induction. Sixty-six percent of an administered levetiracetam dose is eliminated unchanged in the urine; 24% is metabolized to an inactive metabolite that is detectable in the blood and excreted in the urine. Levetiracetam is not appreciably plasma protein–bound, nor does it affect the protein binding of other drugs. Thus, because of its minimal protein binding and lack of hepatic metabolism, the risk of drug interactions is very low.[27,28]

Regarding AAG, it is unclear whether levetiracetam elevates AAG in the same or similar ways as conventional AEDs. It has been reported, however, that AAG concentrations are higher in epileptic patients during periods of frequent seizures.[27] Therefore, it is possible that the patient in this report had elevated AAG levels secondary to his frequent seizures and that the resulting decrease in free, unbound rocuronium due to its binding with AAG may have attributed to the delayed onset of the muscle relaxant effects.

It is also unclear whether levetiracetam causes upregulation in AChRs similarly to phenytoin and carbamazepine.[30] However, previously published studies have demonstrated increased requirements for NDMRs after prolonged immobilization. Immobility is functionally comparable with denervation syndrome in that both result in muscle atrophy and AChR upregulation.[31] These could be associated with the delayed onset of rocuronium seen in this case. On the other hand, there is a report that fiber atrophy, but not changes in AChR expression, contributes to muscle dysfunction after immobilization.[26] Thus, the impact of immobilization remains unclear.

The possible impact of levetiracetam on the duration of action and recovery from rocuronium was unfortunately not examined in detail in this case. However, the TOF at the end of the operation (3 hours after rocuronium administration) was 87%, implying a slight residual muscle relaxant effect. A previous report has shown delayed recovery from rocuronium-induced neuromuscular blockade in patients taking levetiracetam.[13] However, this was a single-dose experiment; therefore, further investigation is necessary regarding NDMR recovery in cases of long-term levetiracetam use. Delayed recovery from rocuronium-induced neuromuscular blockade could be explained by interactions between levetiracetam and rocuronium because both agents are probable substrates of P-glycoprotein. P-glycoprotein is a transmembrane drug efflux pump that transports various drugs (ie, substrates that readily bind to P-glycoprotein) across the cell membrane, thereby excreting its substrates into bile, the gastrointestinal tract, and urine and playing an important role in drug elimination. It also facilitates excretion of rocuronium and might also transport levetiracetam. P-glycoprotein substrates might competitively inhibit the P-glycoprotein-mediated transport of other drugs. In the same context, levetiracetam inhibits efflux of rhodamine 123, a P-glycoprotein substrate, and thus could hinder the P-glycoprotein–mediated excretion of rocuronium, thereby leading to prolonged neuromuscular blockade. In view of previous findings that suggested vecuronium is a P-glycoprotein substrate and that decreases in P-glycoprotein activity resulted in reduced vecuronium elimination, a possible interaction between levetiracetam and neuromuscular blocking agents other than rocuronium cannot be discounted. However, this purported mechanism is speculative and requires further validation.

Levetiracetam is a relatively unique and somewhat newer AED, and thus its interaction with anesthetic agents has rarely been assessed, unlike other antiepileptics like phenytoin, carbamazepine, and valproic acid. Phenytoin is also a P-glycoprotein substrate, but, in contrast to levetiracetam, its chronic administration might reduce the duration of action of neuromuscular blocking agents, including rocuronium. A possible explanation is that phenytoin induces CYP450 isoenzymes, which could facilitate increased elimination of drugs that use CYP450 pathways. In addition, phenytoin increases plasma α1-acid glycoprotein, leading to decreased concentrations of free, unbound neuromuscular blocking agents with the potential to exert their effects at neuromuscular junctions. In contrast, levetiracetam neither induces CYP450 isoenzymes nor alters the protein binding of other drugs, unlike many of the other antiepileptics. The different pharmacokinetic characteristics of levetiracetam as compared with other AEDs might account for its different effects on neuromuscular blocking agents. Another explanation is that acute administration of antiepileptic agents may increase the clinical duration of neuromuscular blocking agents.[13] However, in this previous study, chronic use of anticonvulsants including levetiracetam was excluded. Therefore, chronic use of levetiracetam likely requires further investigation.

CONCLUSION

This case report suggests that patients with intractable epilepsy who are chronically taking levetiracetam may have resistance to rocuronium. Close assessment of neuromuscular function and reversal to ensure full return of function should be considered.

Conflict of Interest

The authors have no conflicts of interest relevant to the contents of this report.

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REFERENCES

1. Kumar CM, Lawler PG. Phenytoin-induced resistance to vecuronium. *Anaesthesia*. 1989;44(3):263–264.
2. Gough JD, Smith A, Wise CC. Phenytoin-induced resistance to vecuronium. *Anaesthesia*. 1989;44(6):520.
3. Tempelhoff R, Modica PA, Jellish WS, Spitznagel EL. Resistance to atracurium-induced neuromuscular blockade in patients with intractable seizure disorders treated with anticonvulsants. *Anesth Analg*. 1990;71:665–669.
4. Platt PR, Thackray NM. Phenytoin-induced resistance to vecuronium. *Anaesth Intensive Care*. 1993;21(2):185–191.
5. Spacek A, Neiger FX, Krenn CG, Hoerauf K, Kress HG. Rocuronium-induced neuromuscular block is affected by chronic carbamazepine therapy. *Anesthesiology*. 1999;90(1):109–112.
6. Koenig MH, Edwards LT. Cisatracurium-induced neuromuscular blockade in anticonvulsant treated neurosurgical patients. *J Neurosurg Anesthesiol*. 2000;12(4):314–318.
7. Hernández-Palazón J, Tortosa JA, Martínez-Lage JF, Pérez-Ayala M. Rocuronium-induced neuromuscular blockade is affected by chronic phenytoin therapy. *J Neurosurg Anesthesiol*. 2001;13(2):79–82.
8. Richard A, Girard F, Girard DC, et al. Cisatracurium-induced neuromuscular blockade is affected by chronic phenytoin or carbamazepine treatment in neurosurgical patients. *Anesth Analg*. 2005;100(2):538–544.
9. Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. *Epileptic Disord*. 2014;16:409–431.
10. Bloor M, Nandi R, Thomas M. Antiepileptic drugs and anesthesia. *Paediatr Anaesth*. 2017;27:248–250.
11. Oshima K. The fundamental problem of severe mentally and physically disabled person. Article in Japanese. *Kuoshuueisei*. 1971;35:648–655.
12. Kumar N, Rani D, Jain A. Evaluation of intubating conditions with rocuronium 0.6 mg/kg using train of four stimulation in elective surgery. *Indian J Anaesth*. 2022;66:S108–S114.
13. Jeon YJ, Kim MH. Effect of levetiracetam on rocuronium duration in patients undergoing cerebrovascular surgery. *Anesth Pain Med*. 2018;13(4):409–414.
14. Ghimouz A, Lentschener C, Goater P, Borne M, Esteve M. Adducted vocal cords relieved by neuromuscular blocking drug: a cause of impaired mechanical ventilation when using a laryngeal mask airway: two photographically documented cases. *J Clin Anesth*. 2014;26:668–670.
15. Kondo T, Izumi H, Kuroda M, Kitagawa M. Two cases of progressive vocal cord closure during desflurane-remifentanil anesthesia relieved after administration of propofol. *J Anesth*. 2013;27:791–792.
16. Kohno T, Ikoma M. Sudden vocal cord closure during general anesthesia using remifentanil. Article in Japanese. *Masui*. 2008;57:1213–1217.
17. Soriano SG, Kaus SJ, Sullivan LJ, Martyn JA. Onset and duration of action of rocuronium in children receiving chronic anticonvulsant therapy. *Paediatr Anaesth*. 2000;10:133–136.
18. Soriano SG, Martyn JA. Antiepileptic-induced resistance to neuromuscular blockers: mechanisms and clinical significance. *Clin Pharmacokinet*. 2004;43:71–81.
19. Anderson GD. A mechanistic approach to antiepileptic drug interactions. *Ann Pharmacother*. 1998;32:554–563.
20. Pirttiaho HI, Sotaniemi EA, Pelkonen RO, et al. Hepatic blood flow and drug metabolism in patients on enzyme-inducing anticonvulsants. *Eur J Clin Pharmacol*. 1982;22:441–445.
21. Soriano SG, Sullivan LJ, Venkatakrishnan K, et al. Pharmacokinetics and pharmacodynamics of vecuronium in children receiving phenytoin or carbamazepine for chronic anticonvulsant therapy. *Br J Anaesth*. 2001;86:223–229.
22. Bailey DN, Briggs JR. The binding of selected therapeutic drugs to human serum alpha-1 acid glycoprotein and to human serum albumin in vitro. *Ther Drug Monit*. 2004;26(1):40–43.
23. Kim CS, Arnold FJ, Itani MS, Martyn JA. Decreased sensitivity to metocurine during long-term phenytoin therapy may be attributable to protein binding and acetylcholine receptor changes. *Anesthesiology*. 1992;77(3):500–506.
24. Fink H, Luppa P, Mayer B, Rosenbrock H, et al. Systemic inflammation leads to resistance to atracurium without increasing membrane expression of acetylcholine receptors. *Anesthesiology*. 2003;98(1):82–88.
25. Fink H, Bogdanski R, Luppa P, Martyn JAJ, Blobner M. Nitric oxide is not a mediator of inflammation-induced resistance to atracurium. *Anesth Analg*. 2005;101(5):1362–1367.
26. Ibebunjo C, Martyn JA. Fiber atrophy, but not changes in acetylcholine receptor expression, contributes to the muscle dysfunction after immobilization. *Crit Care Med*. 1999;27:275–285.
27. Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. *Pharmacol Ther*. 2000;85:77–85.
28. Patsalos PN. Clinical pharmacokinetics of levetiracetam. *Clin Pharmacokinet*. 2012;43;707–724.
29. Morita K, Yamaji A. Changes in the concentration of serum alpha 1-acid glycoprotein in epileptic patients. *Eur J Clin Pharmacol*. 1994;46:137–142.
30. Jung KT, An TH. Updated review of resistance to neuromuscular blocking agents. *Anesth Pain Med*. 2018;13:122–127.
31. Ibebunjo C, Nosek MT, Itani MS, et al. Mechanisms for the paradoxical resistance to d-tubocurarine during immobilization-induced muscle atrophy. *J Pharmacol Exp Ther*. 1997;283:443–451.