



Effect of levetiracetam on rocuronium duration in patients undergoing cerebrovascular surgery

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Background: It has long been held that antiepileptics reduce the duration of action, and increase the requirement for, neuromuscular blocking agents. However, levetiracetam, a relatively novel antiepileptic agent, possesses different pharmacokinetic properties to other, conventional antiepileptics, such that its effect on neuromuscular blocking agents might also differ. The purpose of this retrospective study is to investigate the effect of levetiracetam on the clinical duration of rocuronium.

Methods: In this study, the duration of neuromuscular blockade induced by rocuronium was compared between control and levetiracetam-receiving groups. The data were retrieved from one of our previous studies.

Results: The control and levetiracetam groups comprised 16 and 13 patients, respectively, all of whom underwent cerebrovascular surgery. Subjects received supplementary rocuronium (0.15 mg/kg) whenever the train-of-four count reached 2 during surgery. The interval between supplementary rocuronium (0.15 mg/kg) injections was significantly longer in the levetiracetam vs. control group (50 and 39 minutes, respectively; $P = 0.036$).

Conclusions: The present results challenge the convention that antiepileptics decrease the duration of action of neuromuscular blockers, thereby alerting clinicians to the possibility of prolonged neuromuscular blockade in patients taking levetiracetam. Anesthetic management should encompass careful neuromuscular monitoring in such patients.

Keywords: Anticonvulsants; Neuromuscular blockade; Neuromuscular nondepolarizing agents.

INTRODUCTION

Epilepsy is the most common serious neurological disorder, affecting between 1% and 2% of the general population [1,2]. Patients with epilepsy should take their regular anti-epileptic drugs on the morning of surgery [3]. Moreover, the perioperative prophylactic use of antiepileptics is pervasive in neurosurgery, even for patients without underlying epilepsy, despite being controversial [4,5]. Therefore, anesthesiologist should be aware of interactions between antiepileptic and

anesthetic agents. Antiepileptics, including carbamazepine and phenytoin, are generally believed to attenuate the clinical effects of neuromuscular blocking agents, including rocuronium [6]. However, levetiracetam, a relatively new anti-epileptic, has pharmacokinetic characteristics different from those of other long-standing antiepileptics [7]. Accordingly, its effect on neuromuscular blocking agents might also differ. Levetiracetam is regarded as a useful adjunct in refractory epilepsy; its use is currently widespread among neurosurgical and epileptic patients scheduled for anesthesia [1]. In addi-

tion, the preoperative prophylactic use of levetiracetam to prevent seizures following neurosurgery in patients without underlying epilepsy has been proved effective and safe [8,9], indicating the importance of anesthesiologists being acquainted with interactions between levetiracetam and anesthetic medications. This study compared the duration of the clinical effect of rocuronium during craniotomy surgery in patients pretreated with levetiracetam with a control group.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB no. B-1312/230-109). The data were retrospectively collected from our previous double-blind randomized controlled trial [10], which was also approved by the Institutional Review Board of Seoul National University Bundang Hospital and registered at ClinicalTrials.gov (ID: NCT01460563). All the data of the present study were collected from the previous study [10], but the two studies differ in the primary outcomes and study objective.

In the levetiracetam group, levetiracetam at 500 mg intravenous (IV) was administered in the evening on the day before surgery, and “on call” to the operating room (total dose 1,000 mg). The control group were not treated with any anti-epileptics. The control and levetiracetam groups were treated equally, as per the following study protocol of our previous study [10].

Written informed consent was provided by all participants (age range, 18–65 years; American Society of Anesthesiologists physical status classification I–II) scheduled for elective aneurysm clipping or superficial temporal artery-middle cerebral artery anastomosis via craniotomy. The exclusion criteria were as follows: body mass index of < 18.5 or > 24.9 kg/m²; neuromuscular, renal, cardiovascular or hepatic insufficiency; a Glasgow Coma Scale score of < 15 ; allergy to any study drug; medications influencing the action of non-depolarizing muscle relaxants (including corticosteroids, aminoglycosides, and furosemide); breast-feeding; pregnancy; preoperative epilepsy, and previous use of antiepileptic drug including levetiracetam. No participant was taking any antiepileptic medication other than levetiracetam.

Total intravenous anesthesia was maintained with target-controlled infusion of propofol, titrated to maintain a bispec-

tral index value of between 40 and 60. If mean arterial pressure or heart rate was at $< 80\%$, or $> 120\%$, of baseline values, remifentanyl was first titrated, with propofol subsequently titrated if necessary.

Neuromuscular monitoring was conducted according to accepted clinical research practices [11]. Two pediatric surface electrodes were placed 4 cm apart over the cleansed skin along the ulnar nerve, on the side without either an intravascular line or blood pressure cuff. The four fingers and forearm were immobilized, and the position of the acceleration transducer was secured by placing the thumb in a hand adapter (Organon Ltd., Ireland). Using a train-of-four (TOF) Watch SX[®] (Organon Ltd.), following several 2-Hz TOF stimulations (stimulus duration = 200 μ s, square-wave) and 50-Hz tetanus for 5 seconds, calibration (implanted mode 2) and stable TOF responses ($< 5\%$ deviation for 2 minutes) were recorded in sequence, followed by 2-Hz TOF every 15 seconds.

Subsequently, rocuronium (0.6 mg/kg, IV) was administered for tracheal intubation. Intraoperative monitoring included electrocardiogram, blood pressure (radial artery cannulation) and central venous pressure measurement, and urinary output. Supplementary rocuronium (0.15 mg/kg) was administered whenever the TOF count reached 2 during surgery. The total rocuronium dose and the intervals between supplementary rocuronium (0.15 mg/kg) injections were also recorded.

Ventilation was maintained with 50% oxygen in air and with an end-tidal CO₂ of between 35 and 40 mmHg. Drug preparation, anesthetic care, and collection, measurement and analysis of data were performed by doctors, nurses, and research assistants, all of whom were blinded to the study conditions.

In our previous study [10], informed consents and data were collected from levetiracetam users as well, but they were subsequently excluded from data analysis, because of suspicion that levetiracetam might affect the action of rocuronium. The approval, from the Institutional Review Board, to use the previous study data retrospectively was subsequently granted (IRB no: B-1312/230-109). Therefore, we analyzed the data of the control (published) and levetiracetam groups (unpublished) from the same previous study [10].

Statistical analysis

The primary outcome was interval between supplementary rocuronium (0.15 mg/kg) injections. Total dose of rocuronium was also compared. Data are expressed as numbers of patients (%), means \pm SD, or medians (interquartile range; for skewed data). Student's *t*-test was used to compare total dose of rocuronium, the interval between rocuronium injections, and the doses of propofol and remifentanyl, respectively. The Mann-Whitney *U* or Kruskal-Wallis test was substituted for the *t*-test in instances of skewed data. Statistical analyses were performed with the PASW Statistics software package (version 17.0.2, SPSS Inc., USA). A value of $P < 0.05$ was taken to indicate statistical significance.

RESULTS

The control and levetiracetam groups comprised 16 and 13 patients, respectively. Demographic data are presented in Table 1.

Total dose of rocuronium was not significantly different between the groups (0.33 ± 0.12 [control] vs. 0.27 ± 0.07

Table 1. Patient and Surgery Characteristics

Characteristic	Control (n = 16)	Levetiracetam (n = 13)
Age (yr)	53 (18–65)	52 (20–65)
Gender (M/F)	7 (44)/9 (56)	6 (46)/7 (54)
Body weight (kg)	58.2 \pm 6.2	61.4 \pm 9.1
Height (cm)	159.7 \pm 6.7	161.4 \pm 6.6
Body mass index (kg/m ²)	22.9 \pm 2.1	23.6 \pm 2.9
ASA (I/II)	7 (44)/9 (56)	5 (38)/8 (62)
Operation		
Aneurysm clipping	11 (69)	10 (77)
MCA-STA*	5 (31)	3 (23)
Diagnosis		
Aneurysm	11 (69)	10 (77)
Moyamoya disease	2 (12)	2 (15)
Artery stenosis [†]	3 (19)	1 (8)
Surgeon (J.B./C.O.) [‡]	7 (44)/9 (56)	7 (54)/6 (46)
Anesthesia time (min)	337 \pm 102	347 \pm 110
Operation time (min)	263 \pm 102	282 \pm 111
Blood loss (ml)	340 (178–575)	305 (255–575)

Values are presented as mean (range), number (%), mean \pm SD or median (interquartile range) (for non-normal distributions). ASA: American Society of Anesthesiologists physical status classification. *Superficial temporal artery-middle cerebral artery anastomosis. [†]Cerebral artery stenosis of non-Moyamoya origin. [‡]J.B. and C.O. are the initial letters of the surgeons' names.

[levetiracetam] mg/kg/h; $P = 0.075$; Table 2). However, the levetiracetam group required a significantly longer interval between supplementary rocuronium (0.15 mg/kg) injections compared with controls (50 ± 14 vs. 39 ± 13 minutes, respectively; $P = 0.036$; Table 2).

DISCUSSION

In this study, patients pretreated with levetiracetam were characterized by delayed recovery from rocuronium-induced neuromuscular blockade. This could have been due to interactions between levetiracetam and rocuronium, because both agents are probable substrates of P-glycoprotein [12–14]. P-glycoprotein is a transmembrane drug efflux pump that transports various drugs (i.e., substrates of P-glycoprotein which readily bind to P-glycoprotein) across the cell membrane [15], thereby excreting its substrates into bile, the gastrointestinal tract, and urine, and playing an important role in drug elimination [13]. P-glycoprotein also facilitates excretion of rocuronium [14], and might also transport levetiracetam [12,16]. P-glycoprotein substrates might competitively inhibit the P-glycoprotein-mediated transport of other drugs [17]. In the same context, levetiracetam inhibits efflux of rhodamine 123, a P-glycoprotein substrate [18], and thus could hinder the P-glycoprotein-mediated excretion of rocuronium, thereby leading to prolonged neuromuscular blockade. In view of previous findings suggesting that vecuronium is a P-glycoprotein substrate, and that decreases in P-glycoprotein activity result in reduced elimination of vecuronium [13,19], 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 novel antiepileptic, and thus its interaction with anesthetic

Table 2. Dose of Rocuronium and Anesthetics

Parameter	Control (n = 16)	Levetiracetam (n = 13)	P value
Total Roc dose (mg/kg/h)	0.33 \pm 0.12	0.27 \pm 0.07	0.075
Roc injections interval (min)	39 \pm 13	50 \pm 14	0.036
Propofol (mg/kg/h)	8.9 \pm 1.8	8.5 \pm 1.8	0.498
Remifentanyl (μ g/kg/min)	0.073 \pm 0.037	0.086 \pm 0.032	0.325

Values are presented as means \pm SD. Student's *t*-test was used. Roc: rocuronium. Roc injections interval, the interval between supplementary rocuronium (0.15 mg/kg) injections.

agents has rarely been assessed, unlike other antiepileptics such as phenytoin, carbamazepine, and valproic acid [6,10,20–23].

Phenytoin is also a P-glycoprotein substrate [12], but, in contrast to levetiracetam, its chronic administration might reduce the duration of action of neuromuscular blocking agents, including rocuronium [20,23]. A possible explanation here is that phenytoin induces cytochrome P450 isoenzymes, which could facilitate the elimination of non-depolarizing neuromuscular blocking agents [20]. In addition, phenytoin increases plasma α 1-acid glycoprotein, leading to decreased free, unbound forms of neuromuscular blocking agent with the potential to exert their effects at neuromuscular junctions [20]. In contrast, levetiracetam neither induces cytochrome P450 isoenzymes, nor alters the protein binding of other drugs, unlike other antiepileptics [7]. The different pharmacokinetic characteristics of levetiracetam, compared with other antiepileptics, 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 [24]. In this study, chronic use of anticonvulsants including levetiracetam was excluded. Therefore, chronic use of levetiracetam needs to be studied as well to elucidate the effect of levetiracetam on neuromuscular blocking agents.

This study challenges the long-standing belief that antiepileptics increase the requirement for neuromuscular blocking agents during surgery [6]. These results should also alert clinicians to the prolonged duration of neuromuscular blockade in levetiracetam-treated patients. Delayed recovery from neuromuscular blockade, precipitated by levetiracetam, can result in residual neuromuscular blockade during the early postoperative period, which can delay weaning from ventilatory support and increase the incidence of pulmonary aspiration, upper airway obstruction, hypoxemia, critical respiratory events, and the risk of mortality [25,26]. The incidence of postoperative residual neuromuscular blockade ranges between 9% and 88% [25]; levetiracetam use can be associated with increased risk. In addition, prolonged effects of neuromuscular blocking agents raise the issue of recurarization, following the administration of anticholinergics as reversal agents [27]. The level of anticholinergics at the neuromuscular junction decreases as they are metabolized and

redistributed, but rocuronium might remain, especially in levetiracetam-treated patients whose rocuronium elimination is suspected to be delayed. Reinstatement of neuromuscular blockade, following apparent reversal, places patients at risk of impaired ventilation and hypoxemia, which might be overlooked if monitoring is reduced following confirmation of adequate respiration and muscular tone. Recently, intraoperative neurophysiologic monitoring using somatosensory and motor evoked-potentials has been adopted to reduce the risk of neural injury; neuromuscular blockade should be modulated or reversed to achieve adequate monitoring [28,29]. In such cases, prolonged neuromuscular blockade in levetiracetam-treated patients can impede neurophysiologic monitoring. Anesthesiologists should therefore be conscious of potential delays in recovery from rocuronium use in patients taking levetiracetam. Guidance with neuromuscular monitoring devices for rocuronium supplementation, accurate timing of reversal, and weaning from ventilator support, are all warranted in these patients.

The clearly favorable pharmacokinetic profile of levetiracetam, compared with other, standard antiepileptics, and accumulating evidence pertaining to its utility as an adjunct to refractory epilepsy, has established that levetiracetam is a valuable antiepileptic [1,7]. Accordingly, it has been released to the market in over 50 countries [1]. In addition, levetiracetam can be administered preoperatively to patients without underlying epilepsy to prevent seizure following neurosurgery [8,9]. Therefore, during the pre-anesthetic evaluation, treatment with levetiracetam should be identified in patients taking antiepileptics or in neurosurgical patients, in light of its possible interaction with rocuronium.

We excluded patients with epilepsy from this study because P-glycoprotein expression could be increased in such individuals [30]. This is because P-glycoprotein facilitates rocuronium excretion, such that variably elevated P-glycoprotein levels in epilepsy might shorten the duration of action of rocuronium, which would represent a confounding variable.

A limitation of this study concerns its retrospective design. However, anesthetic management and data collection were equally controlled in both groups, and anesthetic caregivers and data collectors were blinded to the study aims. In addition, it has recently become difficult to prospectively investigate the effect of levetiracetam on muscle relaxants in clinical settings, because intraoperative neurophysiologic monitoring

is commonly used in neurosurgeries, which obligates restriction of muscle relaxants in order to achieve adequate monitoring. In neurosurgeries, levetiracetam can be prophylactically given to epilepsy-free patients [4,5]. However, it is usually used for epileptic patients with elevated P-glycoprotein [30], which can act as a confounding factor in pharmacodynamic studies of neuromuscular blocking agents. In this context, this study provides valuable data that cannot be readily collected in recent clinical settings. Another limitation is that this study was not powered to compare total rocuronium dose. It was lower in the levetiracetam group (0.27 ± 0.07 vs. 0.33 ± 0.12 mg/kg/h), but this study is not sufficient to detect its statistical significance.

Levetiracetam may delay recovery from neuromuscular blockade of rocuronium, which requires further study for definite conclusion. This can lead to serious morbidities; therefore, recognition of prolonged rocuronium duration and careful neuromuscular monitoring should be a prerequisite for patients taking levetiracetam.

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