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Rocuronium action can be affected by hyperventilation: a case report and computational simulation

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Abstract

The neuromuscular blocking potency of rocuronium varies with respiratory pH changes, increasing at lower pH and decreasing at higher pH; thus, hyperventilation-induced respiratory alkalosis is expected to decrease the potency of rocuronium. We report a case of anesthetic management of modified electroconvulsive therapy (m-ECT) for a patient monitored with electromyography-based neuromuscular monitoring during two patterns of ventilation to elucidate their relationship and propose the possible mechanisms underlying the effects by computational simulations. *Case presentation*: The patient was a 25-year-old man with schizophrenia. In m-ECT, hyperventilation may be used to produce longer seizures. We compared the neuromuscular monitoring data recorded during hyperventilation and during normal ventilation while receiving the same dose of rocuronium. Despite receiving the same dose of rocuronium, the time required for the first twitch to decrease to 80% of the control value was delayed in hyperventilation compared to normal ventilation. *Conclusions*: This case report and computational simulation suggest that respiratory alkalosis might delay the action of rocuronium. It is necessary to consider the delayed action of rocuronium when hyperventilation is

performed.

Keywords: modified electroconvulsive therapy, rocuronium, muscle relaxant, neuromuscular blockade, respiratory alkalosis, pH

Background

Modified electroconvulsive therapy (m-ECT) is a biological treatment procedure involving a brief application of electrical stimulation to produce a generalized seizure [1]. Provocation of peristimulus hypocapnia by hyperventilation is linked to longer seizures [2], leading to the occurrence of respiratory alkalosis. The neuromuscular blocking potency of rocuronium varies with respiratory pH changes, increasing at lower pH and decreasing at higher pH in vitro [3]; thus, respiratory alkalosis is expected to decrease the potency of rocuronium. Although respiratory acidosis prolongs the duration of neuromuscular blockade with rocuronium in patients undergoing ventilation [4], the effects of respiratory alkalosis are unknown.

We report a case of anesthetic management of m-ECT for a patient monitored with electromyography-based neuromuscular monitoring during two patterns of ventilation to evaluate their relationship and elucidate the possible mechanisms underlying the effects by computational simulations.

Case presentation

A 25-year-old man, 50 kg in weight and 167 cm in height, was scheduled to undergo m-ECT twice a week for a total of 10 sessions due to the decreasing efficacy of his drug treatment for schizophrenia at Kansai Seishounen Sanatorium. The patient was not premedicated. An intravenous catheter was inserted into the forearm vein, and standard monitoring (electrocardiogram, noninvasive blood pressure, and pulse oximetry) was performed. The electromyography-based neuromuscular monitor (TetraGraph™; SENZIME, Uppsala, Sweden) was placed on the abductor digiti minimi muscle with stimulation of the ulnar nerve calibrated by Auto mode. After preoxygenation, general anesthesia was induced with propofol. After loss of consciousness, the patient was ventilated by mask, and a tourniquet was tied to the lower thigh with an inflating pressure of 300 mmHg. The neuromuscular monitor was calibrated, and a subsequent 2-Hz train-of-four (TOF) stimulation every 20 seconds was started. Ten seconds after TOF stimulation, rocuronium bromide (Eslax™, MSD, Tokyo, Japan) and a subsequent 10 ml saline flush were administered. At 150 seconds after rocuronium administration, the psychiatrist performed electrical stimulation.

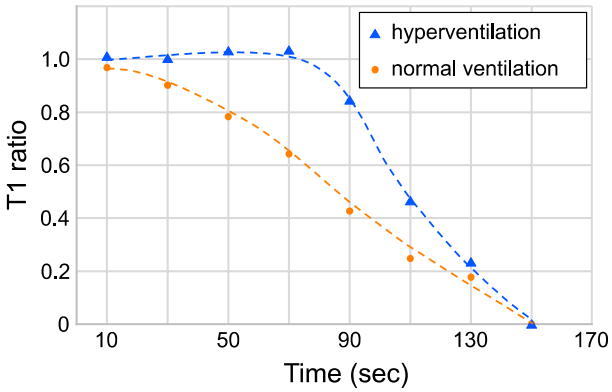
The ventilation rate was 8-10 times per minute with a target end-tidal carbon dioxide

partial pressure ($EtCO_2$) of 35 mmHg (normal ventilation). When hyperventilation was requested by the psychiatrist, deep breathing was encouraged from the time of preoxygenation, and the ventilation rate was 20-30 times per minute with a target $EtCO_2$ of 25 mmHg. Normal ventilation was administered up to the 9th session, but hyperventilation was administered during the 10th session based on the psychiatrist's request. Mask ventilation was uncomplicated, and the $EtCO_2$ waveform was normal.

We compared the patient's neuromuscular monitor data recorded during hyperventilation (10th session) and the most recent data recorded during normal ventilation (9th session) with the same dose of propofol (2 mg/kg) and rocuronium (0.4 mg/kg). The $EtCO_2$ immediately before stimulation was approximately 25 and 35 mmHg, respectively. The results are shown in Figure 1 and Table 1 (Supplementary file 1). The pulse width of the twitch and the current applied differed between the two sessions due to the Auto mode settings. We therefore compared the ratio of twitch responses to control responses rather than a simple comparison of twitch responses between the two ventilation conditions. Despite the use of the same dose of rocuronium, the T1 ratio decreased faster during normal ventilation than during hyperventilation. The time

required for the first twitch to decrease to 80% of the control value was approximately 50 seconds during normal ventilation and approximately 90 seconds during hyperventilation.

Fig. 1



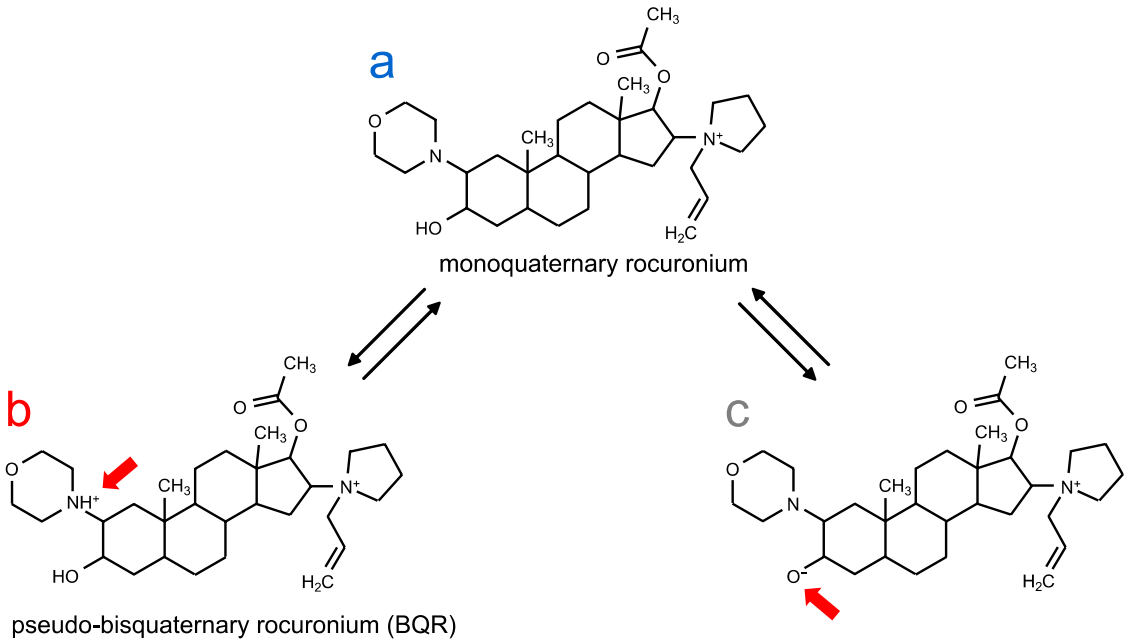
Changes in neuromuscular blockade over time. The vertical axis indicates the T1 ratio, which is obtained by calculating the value of T1 with the calibration value as 1, and the horizontal axis indicates the time after administration of rocuronium.

Discussion

The rocuronium molecule has a positively charged quaternary ammonium group and a noncharged tertiary amino group (Fig. 2a) and is termed a monoquaternary steroidal

compound. Ono et al. [5,6] speculated that low pH may contribute to a change in the tertiary amino group into a quaternary ammonium group by combining with a hydrogen ion (Fig. 2b); hence, rocuronium might change into a pseudo-bisquaternary steroidal compound (pseudo-bisquaternary rocuronium; BQR) at low pH. This change may increase the attraction of rocuronium to the acetylcholine binding position of the nicotinic acetylcholine receptor. Cation-π interactions with aromatic amino acids [7] and electrostatic interactions, e.g., with negatively charged acidic amino acids [8], the hydroxyl group of tyrosine [9], and carbonyl oxygen [10], are known binding modes of the positively charged ligands at this site, and the interacting amino acids differ depending on the muscle relaxants [11]. In the case of d-tubocurarine, its quaternary ammonium group has been shown to interact with the tyrosine of the acetylcholine receptor through cation-π interactions [12]. Therefore, if Ono's speculation is correct, the neuromuscular blocking potency of rocuronium increases at lower pH and decreases at higher pH, but there is no literature that examines the ionic changes of rocuronium with the change in pH.

Fig. 2

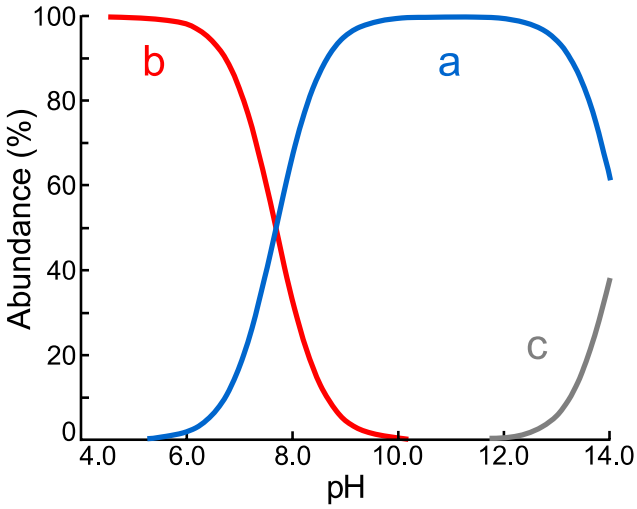


Main ionic species of rocuronium predicted by the Marvin sketch. **a** The structure of monoquaternary rocuronium. **b** The structure of pseudo-bisquaternary rocuronium (BQR). **c** The structure of rocuronium with a dissociated hydroxyl group.

We used Marvin sketch software version 21.9 (ChemAxon, https://chemaxon.com/) to estimate the acid dissociation constant (pKa) of rocuronium. This program is a broad and well-recognized pKa predictor [13], using the molecular structures as input and estimating pKa using an empirical statistic algorithm derived from large compound

collections with available experimental pKa data [14]. The chemical structure of rocuronium was analyzed at 310 K (37 °C). The results showed that the rocuronium molecule had two ionization centers, one in the tertiary amino group (pKa: 7.69) and the other in the hydroxyl group (pKa: 14.19). Thus, in the range of pH 0-14, it was revealed that there were three species in rocuronium (Fig. 2), which has not been reported in the past. The distribution chart showed that in the pH range of 5-10, the proportion of BQR increased as the pH decreased (Fig. 3). Detailed information is shown in Table 2 (Supplementary file 2). Although the chart generated a sigmoid curve, it showed a steep, almost linear change in the pH range of 6.8-8.6, indicating that the proportion of BQR was likely to change with even a slight change in pH (Fig. 3). Furthermore, since the ratio of BQR is approximately 66% at pH 7.4, which is the normal physiological pH, the proportion is likely to change whether the pH is high or low.

Fig. 3



The ionic species distribution chart of rocuronium predicted by the Marvin sketch. The symbols on the chart correspond to the ion symbols in Figure 2.

Although we did not measure the blood pH directly, $EtCO_2$ values are closely related to arterial partial pressure of carbon dioxide ($PaCO_2$) in patients without pulmonary disease [15]. Thus, it is reasonable to presume that hypocapnia by hyperventilation is associated with increased pH, according to the Henderson-Hasselbalch equation.

For the muscle relaxant to exert its action, the receptor occupancy rate must exceed the "margin of safety" [16]. Therefore, in the case of this patient, respiratory alkalosis due to hyperventilation decreased the proportion of BQR, a high-affinity rocuronium, and the

time for rocuronium's receptor occupancy to exceed the margin of safety was extended, which might have delayed the time required for the first twitch to decrease to 80% of the control value. Additionally, after approximately 130 seconds, the difference was no longer observed (Fig. 1), but this may be because rocuronium's actions reached a maximum value. There are various possible causes for the difference in action timing such as cardiac output [17], injection speed, injection methods, etc. However, our results are based on the same anesthesiologist performing anesthesia on the same patient at short intervals, administering the drugs at the precise timing determined by the m-ECT protocol, and administering a saline flush immediately after administering rocuronium. Therefore, the effect of these factors on the variation in action timing was likely extremely small. Further studies are needed to determine whether the effects of hyperventilation on rocuronium action are clinically relevant.

Conclusion

This case report and computational simulation suggest that respiratory alkalosis during hyperventilation might delay the action of rocuronium. Therefore, the delayed action of

rocuronium needs to be considered when hyperventilation is performed during m-ECT.

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Author contribution ST and DF collected data. ST and MS drafted the manuscript. NO and SM revised the manuscript for important intellectual content. All authors have read and approved the final version to be published.

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Data availability All data analyzed in this case report are included in this article and supplementary information files.

Code availability Not applicable.

Declarations

Conflict of interest The authors have no potential conflicts of interest to declare.

Ethical approval This case report was approved by the institutional ethics committee (Ethics Committee, Kobe University Graduate School of Medicine, Japan). Ethics approval was waived because this manuscript is a case report.

Consent for publication Written informed consent for publication was obtained from the patient.

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