

# Myopathy, residual effect of rocuronium, or both? A possible ritonavir–rocuronium interaction interfering weaning from mechanical ventilation in a patient with COVID-19 pneumonia

## Introduction

Non-depolarizing neuromuscular blocking agents (NMBAs) are frequently administered to critically ill patients to facilitate invasive mechanical ventilation. The main drawback of using NMBA is the potential for aggravating Intensive Care Unit (ICU) acquired muscle weakness,<sup>[1]</sup> which, in turn, interferes with the weaning process.<sup>[2]</sup>

In addition to the well-known pharmacodynamic interactions, aminosteroidal NMBAs may be subjected to pharmacokinetic interactions as they undergo some degree of metabolism. Rocuronium undergoes renal excretion, but it has been shown to be a substrate for CYP3A4 enzymes.<sup>[3]</sup> Therefore, drugs inducing CYP3A4-enzyme activity such as carbamazepine are expected to decrease the relaxant effect of rocuronium, as it has been reported.<sup>[3]</sup> On the contrary, drugs strongly inhibiting CYP3A4-enzyme activity such as ritonavir have the potential of prolonging the muscle relaxant effect of rocuronium, although this myopathy–mimicking interaction has not been reported yet.

## Case Report

We describe the case of a 54-year-old, obese (90 kg, BMI 35 kg/m<sup>2</sup>), female patient who was admitted with COVID-19 pneumonia. According to the hospital COVID protocol, she was treated with lopinavir/ritonavir 400 mg/100 mg BID for 10 days, in addition to high dose dexamethasone for 10 days (20 mg/d for 5 days and 10 mg/d for 5 more days), and a variety of other drugs not expected to be involved in any pharmacodynamic or pharmacokinetic interaction with rocuronium nor ritonavir.

Due to the worsening of her respiratory condition, she was admitted to our COVID-19 pandemic-over-dimensioned

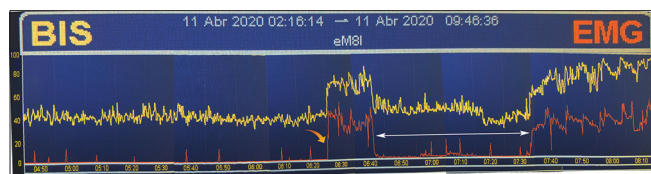
Postsurgical Intensive Care Unit (PICU) 5 days later. She required invasive mechanical ventilation (volume control), and this could be provided by an anesthetic ventilator (Dräger Primus) because of shortage of ICU ventilators. BIS-guided high dosages of sedatives were required (midazolam-fentanyl first and then propofol-remifentanyl, according to the clinical condition), but continuous infusion of NMBAs (specifically cisatracurium) was also required to tackle severe patient-ventilator asynchrony. Neuromuscular function could not be monitored because of shortage of devices in the PICU.

The hospital had a drug shortage of cisatracurium 4 days later also, and as an alternative treatment, rocuronium was prescribed (on day 9, still on ritonavir treatment) 0.5 mg/Kg/h for 4 days. By then, cisatracurium was procured and restarted.

Apart from a transient mild renal insufficiency associated to an infectious process (creatinine value increased from 0.75 mg/dL to 1.16 mg/dL, and then returned to baseline value after 3 days, which happened 6 days before extubation), the overall clinical progression was good, including improvement in X-ray infiltrates; sedatives were low-dosed, and cisatracurium was discontinued with a plan to extubate.

Under usual weaning ventilatory parameters (10cmH<sub>2</sub>O of pressure support, 5cmH<sub>2</sub>O of continuous positive airway pressure, FiO<sub>2</sub> 0.5), her spontaneous respiratory pattern was very irregular (tachypnea around 25–30 rpm, tidal volumes ranging from 330 to 500 mL). Extubation was dismissed and low-dose sedatives were reintroduced (dexmedetomidine-remifentanyl). At this time, we also considered a tracheostomy to hasten the weaning process.

After discontinuing sedatives 24 h later, the patient was fully awake and cooperative in spite of BIS values around 40–50 [Figure 1, before arrow down]. She gestured for the orotracheal tube to be removed because of intense discomfort sensation. However, her respiratory pattern was as irregular as the one previously described. Weakness was so severe that she was nearly unable to raise her hands, and the only spontaneous movements were turning head from one side to another; to remark, baseline EMG values in BIS were low and only isolated spikes appeared as a results of these head movements [Figure 1, before arrow down]. We suspected myopathy or residual curarization. In the absence of ionic disturbances and other pharmacodynamic drug interactions, the possibility of a ritonavir–rocuronium interaction was considered, even though



**Figure 1:** BIS-EMG values before and after sugammadex. Arrow down: sugammadex bolus. Horizontal arrow: period of transient recurarization

rocuronium had been discontinued 8 days ago. In view of this, a trial of sugammadex was started.

After a 200 mg bolus of sugammadex [Figure 1, arrow down], EMG value abruptly rose and she immediately regained strength enough to nearly achieve auto-extubation with her hands. Also, respiratory pattern turned regular (18–20 bpm, Vt 500 mL) in less than a minute. Extubation was smooth and successful. Revised 24 h later in retrospective, EMG pattern resembled transient recurarization starting 20 min after sugammadex and lasting for 1 h [Figure 1, horizontal arrow]; this episode had no repercussion in pulse oximetry and passed unnoticed in our overburdened unit. Permission to report the case was further obtained from the patient.

## Discussion

Ritonavir–rocuronium interaction should not have happened, as cisatracurium is the preferred NMBA for critical care patients<sup>[1]</sup>; the eventual reported interaction would have never happened if not for the shortage that occurred during the COVID-19 pandemic.<sup>[2]</sup>

In the observation reported, failure to achieve good extubation conditions in a myopathic patient (prolonged immobilization, high doses of dexamethasone) was suspected to be also because of residual curarization caused by rocuronium. Lacking neuromuscular monitoring precluded a definitive diagnosis, but presumptive diagnosis was strongly supported by three findings. First, EMG showed isolated spikes in response to the patient's head movements before sugammadex, and a similar pattern was found in an awake volunteer making movements while under incomplete neuromuscular block with rocuronium.<sup>[4]</sup> Second, the clinical and EMG responses elicited by sugammadex strongly mirrored that obtained in 10 awake volunteers under rocuronium blockade<sup>[4]</sup>; this was the most important finding. Additionally, EMG showed a pattern compatible with transient recurarization shortly after sugammadex.

By accepting that, rocuronium delayed effect was attributed to a pharmacokinetic interaction with ritonavir. Rocuronium was administered coincident with the maximal strong inhibitory effect ( $\approx 90\%$ ) of ritonavir on CYP3A4<sup>[5]</sup> which was able to

increase more than 20-fold the systemic exposure of CYP3A4 substrates administered after a single dose.<sup>[5]</sup> Considering that rocuronium was administered as a continuous infusion (accumulated dose of 4,460 mg) and that the inhibitory effect of ritonavir still remains as high as  $\approx 60\%$  3 days after its discontinuation,<sup>[5]</sup> the possibility exists for a residual rocuronium effect 8 days after its discontinuation.

## Conclusion

Physicians should always be aware of the risk for potential pharmacokinetic interactions caused by CYP3A4-inhibitors which are more commonly used in ICUs than ritonavir, such as macrolides for instance. Concerning specifically rocuronium, we recommend to make a sugammadex trial when residual curarization is suspected, especially when tracheostomy is being considered.

## Consent

The patient reported actually works as a nurse in our hospital. After discharge, she moved to another city (Ciudad Real, Spain) to go on recovery with her close relatives. We contacted her by phone to ask for permission and, as a health worker, she gently authorized us to send this brief report for publication. Approval from our Institutional Review Board has been also obtained on date May 28, 2020.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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None.

## Conflicts of interest

There are no conflicts of interest.

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