Rocuronium-Induced Dilated Nonreactive Pupils in a Patient With Coronavirus Disease 2019: A Case Report

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We report the clinical case of a patient with coronavirus disease 2019 (COVID-19) who had recently undergone neurosurgery and presented with dilated nonreactive pupils during continuous rocuronium infusion, which was reversible with the suspension of the drug. Both the neurosurgical procedure and possible disruption of the blood–brain barrier due to COVID-19 infection may have led to the action of rocuronium in the central nervous system (CNS). Thus, clinicians must remember that neuromuscular blocking agents (NMBAs) can cause dilated nonreactive pupils in patients with COVID-19. (A&A Practice. 2021;15:e01491.)

GLOSSARY

ARDS = acute respiratory distress syndrome; **BBB** = blood brain barrier; **CNS** = central nervous system; **COVID-19** = coronavirus disease 2019; **CT** = computed tomography; **F_{IO_2}** = fraction of inspired oxygen; **ICU** = intensive care unit; **NMBA** = neuromuscular blocking agent; **POD** = postoperative day; **S_{O_2}** = oxygen saturation

The coronavirus disease 2019 (COVID-19) pandemic has brought a new scenario to intensive care units (ICUs) around the world. Every day, large numbers of patients require mechanical ventilation due to respiratory failure, and many of these patients develop severe hypoxemia, with a Pa_{O_2}/fraction of inspired oxygen (F_{IO_2}) ratio < 150. These patients often require neuromuscular blocking agents (NMBAs) to facilitate mechanical ventilation and pronation.

Deep sedation impairs the neurological examination, and, especially in ICU patients, alterations in pupil size and reactivity call attention to the possibility of a severe cerebrovascular event such as an ischemic or hemorrhagic stroke or venous sinus thrombosis. This presentation is particularly important during the current pandemic, as COVID-19 is associated with a high rate of cerebral thrombotic and hemorrhagic events.[1–3] In the present report, we discuss a patient with COVID-19 with dilated nonreactive pupils and respiratory failure who was receiving mechanical ventilation under deep sedation with a continuous infusion of NMBA. Written informed consent for publication was obtained from the patient's family.

CASE DESCRIPTION

A 34-year-old woman with a medical history of obesity (body mass index = 32 kg/m^2) and hypothyroidism underwent resection of a high-grade glioma in the right frontal region. On postoperative day (POD) 30, she was admitted to the ICU for respiratory failure due to COVID-19. At the time of admission, the patient did not have neurological deficits on a physical examination. During the first 4 days of hospitalization, the patient required invasive mechanical ventilation. Following endotracheal intubation and the institution of mechanical ventilation, the patient was sedated with midazolam and fentanyl and did not have any pupillary changes. Five days after intubation, the patient's ventilatory parameters improved, sedation was withdrawn, and the trachea was successfully extubated. However, on the seventh day of hospitalization, the patient's respiratory condition worsened, the trachea was reintubated, and the patient was mechanically ventilated. Sedation was started with midazolam 6 µg/kg/min, fentanyl 0.02 µg/kg/min, and rocuronium 11 µg/kg/min. The patient had a Pa_{O_2}/F_{IO_2} ratio of 98 and was placed in a prone position to treat severe acute respiratory distress syndrome (ARDS). She received meropenem and linezolid. The depth of neuromuscular relaxation was monitored by observation of clinical signs. Clinical assessments included the observation of skeletal muscle movement, signs of ventilatory efforts, ventilator asynchrony, elevated peak airway pressures, and inspiratory triggering of the ventilator.[4]

After 12 hours in the prone position, the patient developed dilated nonreactive pupils and was placed in the supine position. Head computed tomography (CT) did not show any acute changes in the central nervous system (CNS). She had findings compatible with previous resection of the brain tumor 1 month earlier. CT angiography did not reveal an obstruction of cerebral vessels. Laboratory tests produced the following values: sodium 140 mEq/L, urea 14 mg/dL, glucose 85 mg/dL, pH 7.49, P_{O_2} 114 mm Hg, P_{CO_2} 43 mm Hg, bicarbonate 32 mEq/L, oxygen saturation (S_{O_2})

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Written consent was obtained.

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100%, and lactate 1.0 mmol/L. The blood pressure and axillary temperature were normal. The electroencephalogram showed brain bioelectric activity >2 μV, no reaction to exogenous stimuli, and compatibility with residual clinical electroactivity. The sedation and NMBA were suspended, and after 9 hours, the patient began to show nonspecific movement of the upper limbs in response to painful stimuli, but she continued to have nonreactive pupils. After 12 hours without NMBA or sedation, the pupillary size and reactivity normalized, and the patient started to interact with the examiner. Her Glasgow coma scale score was 15.

After 24 hours of mechanical ventilation without sedatives or NMBA, the patient's respiratory exchange worsened, with a Pao_2/Fio_2 ratio <150, and patient–ventilator asynchrony recurred. Sedation was restarted with midazolam 6 μg/kg/min and fentanyl 0.02 μg/kg/min. A rocuronium infusion of 11 μg/kg/min was restarted as the patient–ventilator asynchrony persisted. On the tenth day of hospitalization with a continuous infusion of midazolam and fentanyl and 12 hours after rocuronium resumption, the patient again developed dilated nonreactive pupils. This pupillary alteration remained throughout the period in which rocuronium was continuously infused.

On the 17th day of hospitalization, the patient underwent tracheostomy, and the NMBA was suspended. Twelve hours after rocuronium was suspended, the pupils returned to a standard size and reactivity. Over the next several days, the patient remained sedated without NMBA and mechanically ventilated, and the pupils remained reactive. However, the patient's ventilatory condition worsened, with severe hypoxemia (So_2 <80%), and she died 27 days after hospitalization.

DISCUSSION

We describe a patient with COVID-19 who had a recent history of a neurosurgical procedure and developed dilated nonreactive pupils induced by a continuous infusion of rocuronium, which was completely reversed after drug withdrawal. A pupillary alteration in a patient with severe COVID-19 on mechanical ventilation requires imaging to clarify the patient's neurological status. CT can be challenging to perform given the need to transport the patient outside the ICU on mechanical ventilation. Rocuronium is an intermediate-acting NMBA that acts primarily as a competitive antagonist on postsynaptic nicotinic acetylcholine receptors at the motor end plate, presenting a fast onset and intermediate duration.[5] Because of its ionized state and low liposolubility, in normal circumstances, rocuronium does not cross the blood brain barrier (BBB) and does not act on the autonomic ganglia.[6,7]

Dilated nonreactive pupils secondary to administration of NMBAs have been reported in patients with sepsis and are attributed to the breakdown of the BBB due to the intense inflammatory state.[8] There is also a report of a neonate (10 days old) who had dilated nonreactive pupils secondary to the use of NMBA, which was attributed to immaturity of the BBB.[9] In addition, intrathecal NMBA administration induces autonomic dysfunction, cholinergic block, and seizures in rats.[6,10,11] Together, this evidence suggests that in patients with an impaired BBB, rocuronium can reach the CNS and cause dilated nonreactive pupils.

Our patient developed dilated nonreactive pupils twice in response to a continuous infusion of rocuronium, which was reversed when the infusion stopped. We speculate that changes in the BBB induced by the inflammatory and oxidative stress related to COVID-19 infection allowed the action of rocuronium on nicotinic receptors in the CNS and disturbed cholinergic signal transduction, resulting in the paralytic mydriasis observed in our patient.[10,12] Experimental data from newborn knockout mice have shown that the lack of α3 neuronal nicotinic acetylcholine receptors, which are widely expressed in autonomic ganglia and in some parts of the brain, induces dilated ocular pupils that do not contract in response to light. Thus, this congenital alteration reflects altered innervation of the ciliary body that controls contraction and dilation of the pupil, impairing parasympathetic input and leading to mydriasis.[13] This study may provide evidence that nicotinic receptors in the CNS are also involved in controlling pupil motility and that rocuronium, a nicotinic receptor antagonist, may have caused mydriasis via this mechanism in our patient.

COVID-19 infection induces an inflammatory process in the CNS mediated by a direct action of the virus or a systemic inflammatory reaction. Meningitis and encephalitis secondary to COVID-19 have been reported.[14] A large number of inflammatory mediators in brain tissue can lead to breakdown of the BBB, which could have allowed rocuronium to enter the brain in our patient. However, considering that not all septic patients with COVID-19 receiving a continuous NMBA infusion present nonreactive dilated pupils, we speculate that our patient's recent neurosurgery may have directly contributed to the BBB disruption, facilitating the passage of rocuronium into the CNS.

The present report illustrates a case of rocuronium-induced dilated nonreactive pupils in a patient with COVID-19 infection that has not previously been described in the literature. An awareness of this side effect of NMBA during the COVID-19 pandemic may avoid the need for a series of tests to investigate neurological events.

DISCLOSURES

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