Cisatracurium in Acute Respiratory Distress Syndrome

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Introduction

Acute Respiratory Distress Syndrome (ARDS) is a condition characterized by damage to the alveoli and cytokine mediated inflammation, which results in the disruption of the lung endothelium and increased pulmonary edema.[1] This acute injury can result in the onset of hypoxemic respiratory failure which eventually manifests itself as multiple organ failure, pulmonary fibrosis, and pulmonary vascular destruction. Common causes include sepsis, aspiration, trauma, and pneumonia. The Berlin Definition, published in 2012, provides updated criteria for diagnosis and disease severity stratification.[2] For a diagnosis of ARDS according to this definition, the patient must experience an insulting injury or onset of hypoxemia worsening within one week, display bilateral opacities upon chest imaging, and the pulmonary edema cannot be attributed to congestive heart failure. A measure of the lung's ability to transfer inhaled oxygen to the blood stream, PaO_2/FiO_2, is used to categorize the severity of ARDS, with values of 201-300 termed mild, 101-200 moderate, and $\leq$ 100 severe. ARDS affects an estimated 190,000 patients annually in the United States, with mortality estimates ranging from 26-58%.[3-5]

Cisatracurium is an intermediate duration, non-depolarizing neuromuscular blocking agent (NMBA). It is an isomer of atracurium, which antagonizes the action of acetylcholine by competitively binding to cholinergic receptors on the motor end-plate and blocking neuromuscular transmission.[6] Cisatracurium undergoes Hofmann elimination, or non-enzymatic degradation at physiological pH and temperature, to inactive metabolites which are eliminated primarily by the liver and kidneys. Cisatracurium is indicated to relax skeletal muscles and facilitate tracheal intubation. It also can be used as an adjunct to either general anesthesia during surgery or sedation during mechanical ventilation in the intensive care unit. The two standard bolus doses of cisatracurium are 0.15 mg/kg and 0.2 mg/kg. This loading dose can be followed with a continuous infusion for maintenance, with clinical trial doses ranging from 0.5-10 mcg/kg/min, and the average maintenance dose of 3 mcg/kg/min.

Three studies, conducted by the same research team in France, have evaluated the use of cisatracurium in patients with ARDS.[7-9] The first two trials displayed an increase in oxygenation as measured by PaO_2/FiO_2 as well as a reduction in inflammatory markers IL-1, IL-6, and IL-8 associated with cisatracurium use.[7-8] These two trials indicated a trend toward decreased mortality associated with the infusion of cisatracurium. However, they did not meet

statistical significance and the studies were not powered to do so.

The third trial evaluated 90-day mortality associated with a 48-hour continuous infusion and found a non-significant trend toward reduced 90-day crude mortality, 31.6% in the cisatracurium group vs 40.7% in the placebo group ($p = 0.08$).[9] However, a statistically significant reduction was observed after adjustment for baseline PaO_2/FiO_2, plateau pressure, and the Simplified Acute Physiology II score. In a subgroup analysis, the more severe patients, characterized by a PaO_2/FiO_2 of less than 120, saw the most improvement with a statistically significant reduction in mortality.[9] A meta-analysis and systematic review conducted of these three articles concluded that compared to placebo, a 48-hour continuous cisatracurium infusion resulted in a statistically significant 28% relative risk reduction in hospital mortality.[10]

Case Report

A 60-year-old Caucasian male was brought to the emergency department via emergency medical services with a chief complaint of abdominal pain beginning three hours prior to arrival. Onset was one hour post-prandial and rated at 9/10 with no associated nausea or vomiting. The patient self-reported a history of peptic ulcer at age 16. He was not taking any prescription medications, but reported use of 10 ibuprofen 200 mg tablets every 2-3 days and 20-30 aspirin 325 mg tablets a week for back pain and "sinus problems". He also reported a history of smoking 2-3 cigars per day.

The physical examination was remarkable for hypoactive bowel sounds, diffuse abdominal tenderness, and guarding. An abdominal computed tomography (CT) scan revealed pneumoperitoneum consistent with perforated viscus. Exploratory laparotomy revealed a perforated duodenal ulcer which was repaired with a Graham patch (Omental patch).

On post-operative day (POD) 1, the patient displayed signs of sepsis (pulse 96, respiratory rate 25, white blood cell count 13.1 K/cm^3) and progressive hypoxemia. A chest x-ray demonstrated diffuse alveolar infiltrates. Attempts at non-invasive positive pressure ventilation failed and he was intubated subsequently on POD 2. At that time, the differential diagnosis included congestive heart failure and ARDS secondary to sepsis, gastric aspiration, and/or pneumonia. Normal echocardiogram and serum brain natriuretic peptide (BNP) excluded chronic heart failure. As a result, lung protective ventilation (tidal volume 6 mL per kilogram of predicted body weight and a plateau pressure of 30 cm of water or less) was initiated in accordance with the ARDS Network.[11]

Despite low tidal volume ventilation and empiric broad spectrum antibiotics on POD 3, the patient had a PaO_2/FiO_2 of 118, and the decision was made to initiate neuromuscular blockade to facilitate mechanical ventilation and improve oxygenation. The patient was sedated with midazolam and fentanyl to a Ramsey score of 6 and bolused with a 15 mg loading dose of cisatracurium, followed by a 37.5 mg per hour continuous infusion for 48 hours. Train of four (TOF) monitoring was conducted intermittently throughout the duration of neuromuscular blockade. His doses would have been 11.7 mg and 2.3 mg/hr, respectively, if the 77.7 kg patient had been bolused and a drip started based on the low end dosage given in the package insert.

The infusion was diluted to a concentration of 1 mg/mL, resulting in the total administration of 1,815 mg of cisatracurium in 1,815 mL of 0.9% sodium chloride. Five minutes prior to initiation of the cisatracurium infusion, a TOF

measurement at the wrist revealed 4/4 twitches. TOF measurements taken 15 minutes, 30 minutes, one hour, and two hours after initiation of the infusion all resulted in a TOF of 4/4 twitches. Monitoring of TOF's conducted at 8 hours and 18 hours after the initiation of the infusion both revealed 0/4 twitches, indicating the achievement of 100% neuromuscular blockade.

When it was clear that thorough neuromuscular blockade had been achieved, TOF measurements were stopped per the previous study protocol as well as the lack of dosage adjustments. The patient received fentanyl and midazolam throughout the duration of paralysis. Shortly after 48 hours, the cisatracurium infusion was discontinued and the patient began to recover full neuromuscular function slowly. Within two hours, the patient was able to open his eyes and follow commands to squeeze an examiner's hand. Roughly seven hours after the cessation of the infusion, the patient was neurologically intact. Figure 1 highlights the observed change in the patients PaO_2/FiO_2 associated with the cisatracurium infusion.

The patient was extubated on POD 9, four days after the cessation of the cisatracurium infusion. His hospital stay subsequently was complicated by *clostridium difficile* infection for which treatment with metronidazole was administered. The patient was discharged on POD 23 to a skilled nursing facility.

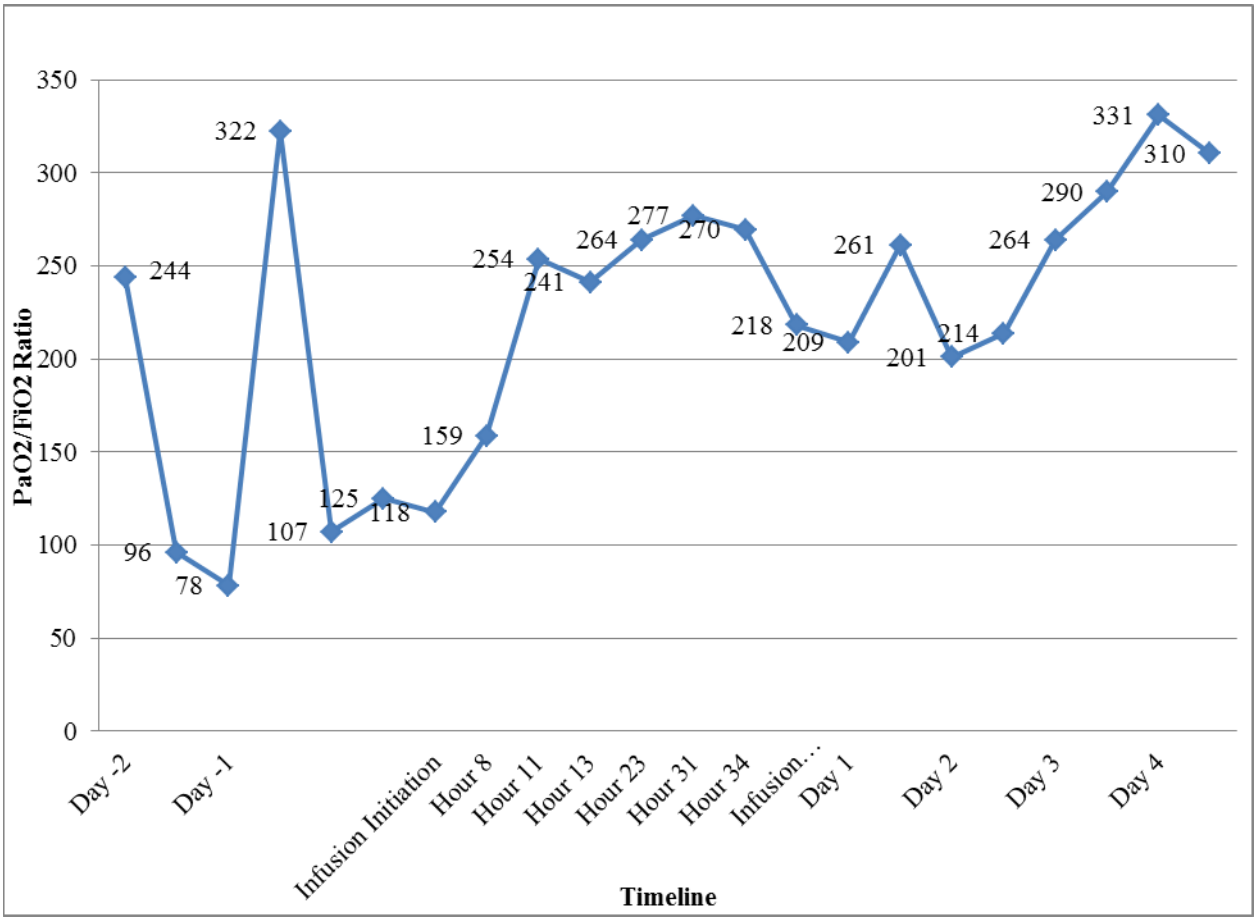

Figure 1. PaO2/FiO2 ratio.

Discussion

The dose of cisatracurium employed in this case was based on that used in the Papazian trial: a 15-mg bolus followed by a 37.5 mg per hour, 48-hour continuous infusion.[9] As displayed in Figure 1, the patient displayed rapid improvements in oxygenation corresponding with the cisatracurium administration. Improvement in the patient's PaO_2/FiO_2 of 100 (118 to 218) from infusion initiation to infusion termination were observed. Multiple measurements during the infusion also displayed even greater improvements in oxygenation than the final value obtained, with a peak value of 277. The cisatracurium infusion appeared to be a turning point toward clinical improvement in this patient. No other interventions such as prone positioning, inhaled nitric oxide, or epoprostenol were administered to the patient at any point during the treatment course. An outlier PaO_2/FiO_2 value was observed the day prior to cisatracurium initiation when a weaning trial was attempted. The post-cisatracurium period also consisted of continued improvement in oxygenation, despite the patient's overall complicated clinical picture.

Train of four monitoring via a peripheral nerve stimulator was used throughout the 48-hour period to assess neuromuscular blockade although it was not used to titrate the neuromuscular blocking agent. The Papazian study did not allow TOF monitoring to ensure proper blinding, however, in this case it was determined that TOF monitoring would be performed to assess effectiveness of neuromuscular blockade at set dose.[9] The patient's first four TOF measurements during the first two hours of the infusion displayed 4/4 twitches. This was an unexpected observation that is not explained readily. The TOF values obtained mid-infusion resulting in 0/4 twitches, suggested that neuromuscular blockade was effective. Prolonged blockade and muscle weakness are two primary concerns associated with NMBA infusion, however, this patient displayed no issues pertaining to either parameter. The patient regained motor function after cessation of the infusion and was considered neurologically normal within seven hours.

In the future, weight-based dosing titrated to a train of four response of 0/4 twitches could be considered to minimize cumulative exposure to cisatracurium and prevent possible adverse events associated with prolonged neuromuscular blockade or ICU acquired myopathies or polyneuropathies. Dose reductions could prove to be beneficial in terms of cost-savings due to medication acquisition costs and medication backorders due to drug shortages. To use this 77.7 kg patient as an example, his dosing range based on the standard administration rates would have been anywhere from 2.3 mg/hr to 46.6 mg/hr. The administered dose of 37.5 mg/hr, while in the dosage range, is on the higher end and positive outcomes may have been achievable with less medication. Diluting the concentration of the infusion to 1 mg/mL resulted in an increased volume administered, however, this was helpful in reducing confusion with regards to administration rates and dosing. With further practice and increased comfort, it may be preferable to administer this infusion undiluted, given that ARDS is an edematous disease state and conservative fluid administration is recommended.[12] This patient displayed a consistently positive fluid balance of +2,403 mL on the day of initiation, +1,152 mL during the first day, and +1,458 mL during the second day. For the treatment of this patient, just as in the cited studies, cisatracurium was utilized exclusively.[7-9] Future studies may be conducted to determine if the beneficial

effects observed are a result of an NMBA class effect or are exclusive to cisatracurium.

Conclusion

In summary, this case of a 60-year-old Caucasian male with ARDS was treated successfully with a 48-hour continuous infusion of cisatracurium, resulting in oxygenation improvement as measured by PaO_2/FiO_2. Cisatracurium may have resulted in recovery from ARDS and long-term survival. Based on these results coupled with the available literature, cisatracurium appears to be a safe and viable therapeutic option for patients with Acute Respiratory Distress Syndrome.[7-10]

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