TACHYPHYLAXIS TO CISATRACURIUM

- Case Reports and Literature Review -

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Abstract

Nondepolarizing neuromuscular blocking agents (NNMBAs) are commonly used in the intensive care unit (ICU), mainly to facilitate mechanical ventilation in critically ill patients who are not responding to sedatives and analgesics alone. Tachyphylaxis, also referred to as resistance, may develop during long-term infusion of NNMBAs. Several case reports of tachyphylaxis to NNMBAs have been reported.

Although the definite mechanisms of tachyphylaxis to NNMBAs are not clear, several pharmacodynamic and pharmacokinetic changes have been described with the development of resistance. Tachyphylaxis to NNMBAs is associated with adverse outcomes including inadequate ventilation, increased risk of dose-dependent side effects, and increased drug costs. Patients who develop tachyphylaxis to one NNMBA should be treated with another NNMBA if neuromuscular blockade (NMB) is still indicated. We report three cases of tachyphylaxis to cisatracurium in a surgical intensive care unit (SICU): one in patient with acute respiratory distress syndrome (ARDS) and the other two with traumatic brain injury (TBI).

Key words: Tachyphylaxis, cisatracurium, neuromuscular blocking agents, critically ill, intensive care unit.

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Introduction

Nondepolarizing neuromuscular blocking agents (NNMBAs) are commonly administered to Intensive Care Unit (ICU) patients who require neuromuscular blockade (NMB). The use of NNMBAs in the ICU may be associated with a diversity of well-known side effects including prolonged recovery from NMB[1-5], acute quadriplegic myopathy syndrome (AQMS)[6,7], myositis ossificans, and tachyphylaxis[8-10].

We report three cases of tachyphylaxis to cisatracurium, in a Surgical Intensive Care Unit (SICU), at a University Hospital, and we review the literature.

Case Reports

Patient 1

A 55-year-old, 80 kg male patient, known case of a positive HIV test and hypertension, underwent a laparoscopic left adrenalectomy for aldosteronoma.

On postoperative day 3, he developed bilateral nosocomial pneumonia complicated by septic shock, acute renal failure, and severe Acute Respiratory Distress Syndrome (ARDS).

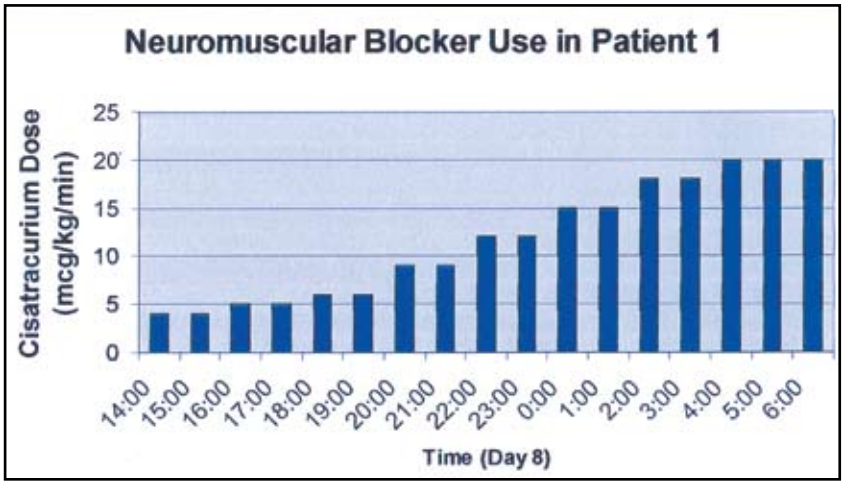
The patient was transferred to the SICU where he was intubated and mechanically ventilated for acute respiratory failure. He received broad spectrum antibiotics, fluids and vasopressors for septic shock, stress dose steroids (hydrocortisone 100 mg IV every 8 hours) for adrenal insufficiency, and renal replacement therapy (RRT) by continuous veno-venous hemodialysis (CVVHD) for acute renal failure (ARF). The ventilatory support included FiO_2 titration to maintain a PaO_2 ≥55 to 60 mmHg and/of oxygen saturation by pulse oximetry (SpO_2) ≥88 to 90%. Pressure control ventilation (PCV) to keep plateau pressure (Pp) ≤30 cm H_2O, and/or peak airway pressure (PAP) ≤40 cm H_2O with a tidal volume of 6 ml/kg of ideal body weight and a positive end-expiratory pressure (PEEP) determined by the pressure volume curve (Pflex)[11]. He required an FiO_2 of 1.0 and

PEEP of 15 cm H_2O. To facilitate his mechanical ventilation, he was deeply sedated to a Riker sedation scale[12] (Sedation-Agitation Scale: SAS) score of 1 with continuous infusions of propofol titrated between 50 to 100 mcg/kg/min, lorazepam at 25 mcg/kg/hr, and fentanyl at 2 mcg/kg/hr, and pharmacologically paralyzed with cisatracurium titrated between 0.5 to 4 mcg/kg/min (0.03 to 0.24 mcg/kg/hr) to maintain at least 1 to 2 visible twitches out of four by train-of-four (TOF) nerve stimulator monitoring.

On day 8 of NMB (eighth day of ICU admission), he had several episodes of oxygen desaturation which were attributed to inadequate NMB manifested clinically by shivering, coughing and dyssynchronization with the ventilator (very high peak airway pressures) and electrophysiologically by responding with four visible twitches to TOF stimulation. He required a gradual increase in the FiO_2 from 0.5 to 1.0, and multiple boluses of propofol, lorazepam, fentanyl and cisatracurium for over-breathing on ventilator. The maximum infusion rate of cisatracurium had to be gradually increased by fivefold from 4 to 20 mcg/kg/min (0.24 to 1.2 mcg/kg/hr) (Fig. 1).

Fig 1

Two additional boluses of 10 mg IV of cisatracurium could not achieve



the targeted degree of NMB. The patient was judged to have developed tachyphylaxis to cisatracurium. A single bolus of rocuronium of 50 mg

(0.625 mg/kg) IV was given and rapid clinical and electrophysiologic responses were observed (no agitation or shivering and TOF of 0/4). The patient could be easily ventilated with the previous ventilatory settings generating the same tidal volume, and this oxygen saturation (SpO_2) improved to 100%. The cisatracurium infusion was discontinued and replaced with a rocuronium infusion of 5 to 15 mcg/kg/min (0.3 to 0.9 mg/kg/hr) for 24 hours. To avoid the well-known side effects of the aminosteroidal NNMBAs, and because of potential increased costs, the rocuronium was discontinued and the cisatracurium was resumed, at the usual dose with good response, until the need for NMB was considered unnecessary. A percutaneous dilatational tracheotomy (PDT) was performed for prolonged intubation and he was weaned from mechanical ventilation. The patient recovered from his septic shock, renal failure and ARDS; and he was discharge from the SICU.

Patient 2

A 19-year-old, 61 kg female patient was involved in a motor vehicle accident (MVA) and sustained severe traumatic brain injury (TBI). Her severe TBI was managed, including intubation and mechanical ventilation, following the guidelines from the Brain Trauma Foundation (BTF)[13]. An intraventricular catheter was placed for intracranial pressure (ICP) monitoring and cerebrospinal fluid (CSF) drainage as indicated. Phenytoin (loading dose of 18 mg/kg IV followed by 100 mg IV every 8 hours for one week) was prescribed for early post-traumatic seizure prophylaxis[13]. In the absence of a correctable cause such as hypoxemia, hypotension, hypercarbia, or fever, she had a sustained intracranial hypertension (ICP >20 mmHg). All interventions to lower the ICP had failed including positioning head-of-bed to 30 degrees, deep sedation to a Riker (SAS)[12] score of 1, multiple boluses of 100 ml hypertonic saline solution (HSS) 7.5% over 15 minutes and mannitol 0.5 gm/kg IV over 15 minutes, and acute hyperventilation.

In addition to deep sedation to a Riker score of 1 with fentanyl and propofol, cisatracurium was prescribed to lower the ICP[14] and to

prevent shivering from induced, therapeutic mild hypothermia (T° 32 to 34 C°). The cisatracurium dose was titrated between 0.5 to 4 mcg/kg/min (0.03 to 0.24 mg/kg/hr) to maintain a least 1 to 2 visible twitches out of four by TOF nerve stimulator monitoring. On day 2 of NMB (third day of ICU admission), and despite fourfold gradual increase of the maximum infusion dose of cisatracurium up to 16 mcg/kg/min (1 mg/kg/hr) (Fig. 2), she had inadequate NMB manifested clinically by shivering, coughing, dyssynchronization with the ventilator, increased ICP, and electrophysiologic response of four visible twitches to TOF stimulation.

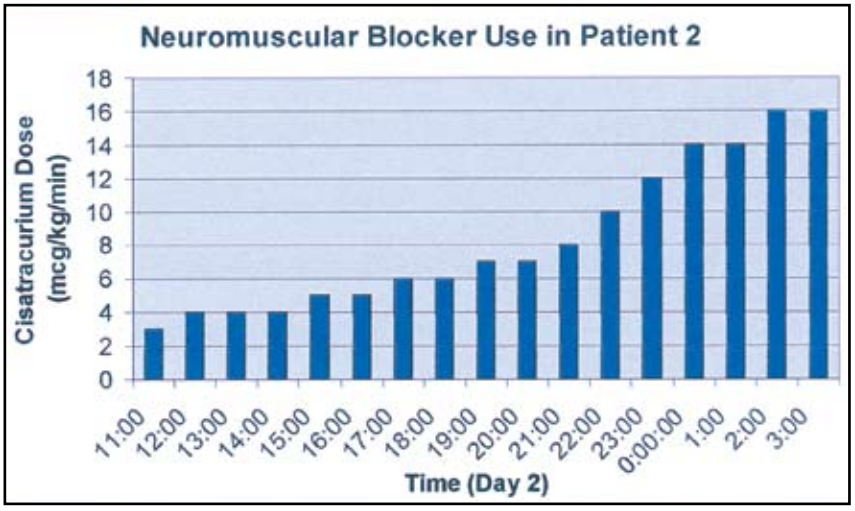


Fig 2

Two additional boluses of 10 mg IV of cisatracurium could not achieve the targeted degree of NMB. Tachyphylaxis to cisatracurium was suspected. A single bolus of rocuronium of 50 mg (0.8 mg/kg) IV was given and rapid clinical and electrophysiologic responses were observed (no agitation, shivering, or dyssynchronization with the ventilator, lowering of ICP and TOF of 0/4). The cisatracurium infusion was discontinued, and the NMB was maintained with rocuronium intermittent boluses for 24 hours until NMB was considered unnecessary. The patient was

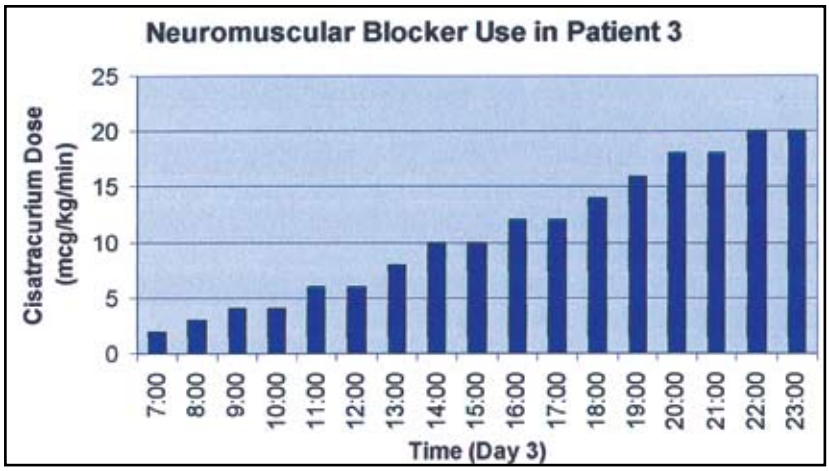
kept sedated and ventilated until her neurological conditions improved clinically and radiologically (CT of brain). A PDT was performed on day 10 for airway protection, and next day she was weaned from mechanical ventilation. After completing a 24-hour period of tracheal mask breathing she was discharged from the ICU with a Glasgow Outcome Score (GOS) of 4.

Patient 3

A 16-year-old, 60 kg female patient was transferred to our hospital several hours after a MVA in which she sustained severe traumatic brain injury (TBI). She was intubated and mechanically ventilated. The management of her severe TBI was consistent with the guidelines from the Brain Trauma Foundation (BTF)[13]. An intraventricular catheter was placed for ICP monitoring and CSF drainage as indicated. Phenytoin (loading dose of 18 mg/kg IV followed by 100 mg IV every 8 hours for one week) was prescribed for early post-traumatic seizure prophylaxis[13]. She had a sustained intracranial hypertention (ICP >20 mmHg) with no obvious or correctable cause such as hypoxemia, hypotension, hypercarbia, or fever. All measures to control the ICP have failed including positioning head-of-bed to 30 degrees, deep sedation to a Riker score of 1, multiple IV boluses of 100 ml hypertonic saline solution 7.5% over 15 minutes and 0.5 gm/kg mannitol over 15 minutes, and acute hyperventilation.

In addition to deep sedation to a Riker score of 1 with fentanyl and propofol, she required NMB with cisatracurium to lower the ICP and to prevent shivering from induced, therapeutic mild hypothermia (T° 32 to 34 C°). The cisatracurium dose was titrated between 0.5 to 4 mcg/kg/min (0.03 to 0.24 mg/kg/hr) to maintain at least 1 to 2 visible twitches out of four by TOF nerve stimulator monitoring. On day 3 of NMB (fourth day of ICU admission), and despite a fivefold gradual increase of the maximum infusion dose of cisatracurium up to 20 mcg/kg/min (1.2 mg/kg/hr) (Fig. 3), inadequate NMB was manifested clinically by shivering, coughing, dyssynchronization with the ventilator, increased ICP and electrophysiologic response with four visible twitches to TOF stimulation.

Fig. 3



Two additional boluses of 10 mg IV of cisatracurium could not achieve the targeted degree of NMB. Tachyphylaxis to cisatracurium was suspected. A single bolus of vecuronium of 6 mg (0.1 mg/kg) IV was given and rapid clinical and electrophysiologic responses were observed (no agitation, shivering, or dyssynchronization with the ventilator, lowering of ICP and TOF of 0/4). The cisatracurium infusion was discontinued and the NMB was maintained with vecuronium infusion titrated between 1 to 2.5 mcg/kg/min (0.06 to 0.15 mg/kg/hr) for 5 days until NMB was considered unnecessary. Despite aggressive management including barbiturate coma and bifrontal decompressive craniectomy, her neurological status did not improve. A PDT and a percutaneous endoscopic gastrostomy (PEG) were performed on day ten of ICU admission for prolonged ventilation and enteral feeding, respectively. In light of her grave prognosis, the family decided to withdraw support and start comfort care. The patient was weaned from the ventilator and transferred to the palliative care unit where she expired after 2 days.

Discussion

All three patients were critically ill and developed, at different times from initiation, a gradually increased requirement for infused cisatracurium.

The first patient received cisatracurium to facilitate mechanical ventilation for ARDS, and steroids to treat adrenal insufficiency. The other two received cisatracurium to help lowering intracranial pressure, in addition to phenytoin for prevention of early post-traumatic seizures. NMB was monitored clinically and electrophysiologically with TOF nerve stimulator monitoring. The dose of cisatracurium was titrated to obtain an adequate clinical response and to maintain a least 1 to 2 visible twitches out of four by TOF nerve stimulator monitoring.

Other probable explanations for the increased requirements of infused cisatracurium were ruled out. The cisatracurium was refrigerated until use, in refrigerators located in the Pharmacy. Our patients all received fresh infusions of cisatracurium which were prepared by personnel in the pharmacy and were changed at least every 12 hours. Cisatracurium was always infused with electronic pump via a dedicated port of a central venous catheter. Cisatracurium from the same lots was infused to different patients in the unit with adequate NMB at the usual doses. The additional boluses of cisatracurium were verified (name, expiry date) by two registered nurses before administration. The alternative NNMBAs (rocuronium, vecuronium) were administered via the same port through which cisatracurium was infused. There was no remarkable changeability in patient temperature or acid-base balance that might have explained the increased requirement.

NNMBAs are frequently administered to critically ill patients either as intermittent boluses or as continuous infusions. Although, there are no prospective, randomized, controlled trials enrolling patients, who are considered candidates for NMB to a NNMBA versus placebo, NNMBAs are recommended to be used as a last resort, only when all other means have failed to improve the clinical situation[14]. They are indicated in a select group of patients in a variety of situations[15-28]. The most common indications for long-term administration of NNMBAs are facilitation of mechanical ventilation, control of increased intracranial pressure (ICP), treatment of muscle spasms associated with tetanus, and decreasing oxygen consumption[1]. The prolonged use of NNMBAs in critically ill patients may

be associated with a diversity of side effects including prolonged recovery from NNMBAs[1-5], acute quadriplegic myopathy syndrome (AQMS)[6,7], myositis ossificans, rapidly evolving myopathy[1], acute myopathy of intensive care[3], and tachyphylaxis[8-10].

Tachyphylaxis, also commonly referred to as resistance to NNMBAs, is usually recognized by gradually increased dosage requirements over time to maintain adequate NMB. The dose of a NNMBA is adjusted by both clinical and electrophysiologic assessments of the depth of NMB. Clinical assessment is based on a subjective observation of skeletal muscle movement and respiratory effort. Electronic methods include detection of spontaneous ventilatory efforts and TOF peripheral nerve stimulator monitoring.

Although the precise mechanisms of tachyphylaxis are not clear, several pharmacodynamic and pharmacokinetic changes have been described with the development of resistance[29]. The pharmacodynamic changes include alterations in nicotinic acetylcholine receptor (nAChR) physiology or sensitivity, inhibition of serum cholinesterase activity, and interaction with plasma mediators. Alterations of nAChRs involve increased number and altered reactivity, a phenomenon referred to as up-regulation. This up-regulation causes an increased response to depolarizing NNMBAs but a decreased response (i.e., resistance) to NNMBAs because more receptors must be blocked. Several clinical situations have been associated with up-regulation of AChRs such as loss of nerve function (upper or lower motor neuron lesions)[30-32], stroke[33,34], Guillain-Barré syndrome[35], crush injury[36], thermal injury[37-41], muscle disuse due to immobilization[36,42], prolonged administration of NNMBA[43], and long-term therapy with phenytoin[44-47]. The increased number of nAChR is due to the formation, triggered by prolonged administration of a NNMBA[47-49], of immature (fetal) variant of nAChR in which a gamma subunit replaces the normal epsilon subunit. These immature nAChRs are distinguished by specific characteristics, and are different compared to mature nAChRs[36]. The immature nAChRs are not located only in the junctional area of the muscle endplate but are distributed across the entire membrane surface (i.e., junctional and

extrajunctional areas). Metabolically, immature nAChRs are unstable and short-lived (<24 hours). Lastly, immature nAChRs are more sensitive to agonists (depolarizing NMBA: Succinylcholine) and more resistant to competitive antagonists (NMBAs)[50,51]. The pharmacokinetic alterations of NNMBAs include changes in volume of distribution, protein binding, and clearance.

Several case reports of tachyphylaxis to NNMBAs in critically ill patients have been published[8-10,52,53]. Coursin and colleagues[52] described two critically ill patients who developed progressive relative resistance to vecuronium following long-term infusion for ARDS. The patients required significant and steady increases in the infused dose of vecuronium (6-and 5-fold, respectively) to maintain adequate NMB for optimizing gas exchange.

Kelly et al.[53] described a patient who developed resistance to atracurium, but subsequently was adequately neuromuscularly blocked with a standard dose of pancuronium. One day 3 of NMB, the patient became unresponsive to atracurium as evidenced by excessive physical movement, increased peak airway pressures, and overbreathing assist control ventilation. Repeat boluses and increases in the atracurium infusion rate to a maximum of 1.27 mg/kg/hr (21.1 mcg/kg/min) failed to provide a desired clinical response. A bolus dose of pancuronium 0.15 mg/kg was administered and the constant infusion was then changed to pancuronium 0.078 mg/kg/hr (1.3 mcg/kg/min). Within minutes, decreased respirations, peak airway pressures, and agitation were noted. The authors concluded that the development of resistance to a specific NNMBA in the ICU does not necessarily imply cross-tolerance or resistance to alternative agents, and loss of respiratory control by one NNMBA may be overcome by changing agents.

Coursin and colleagues[8] reported four critically ill patients with marked tachyphylaxis to long-term infusions of atracurium (range, 0.96 mg/kg/hr to 2.4 mg/kg/hr, or 16 to 40 μg/kg/min). Patients were successfully blocked with doxacurium infusions (rates, 0.015 mg/kg/hr to 0.045 mg/kg/hr, or 2.25 to 0.75 μg/kg/min) and had adequate clinical response.

Tschida et al.[10] described a patient who developed tolerance to atracurium evidenced by TOF monitoring combined with clinical assessment. The atracurium requirement escalated from 0.31 to 1.8 mg/kg/hr (5 to 30 µg/kg/min) over 10 days. Despite a total atracurium loading dose of 1.4 mg/kg followed by an infusion rate titrated to 1.8 mg/kg/hr (30 mcg/kg/min), inadequate NMB persisted. Subsequently, the patient was successfully neuromuscularly blocked with a pancuronium infusion of 0.6 to 3 mg/kg/hr (10 to 50 µg/kg/min) for a period of five days.

Fish and Singletary[9] described a patient who developed resistance to atracurium during therapy for ARDS. Despite multiple loading doses and progressive increase of infusion rates up to 3.57 mg/kg/hr (60 µg/kg/min), he was inadequately neuromuscularly blocked as assessed by clinical and ventilatory parameters as well as TOF monitoring. Atracurium was discontinued and vecuronium infusions of 2.3 mg/kg/hr (38.3 mcg/kg/min) lastly produced adequate NMB for seven days. Tachyphylaxis then developed to vecuronium which prompted discontinuation of NNMBAs. Two days later, 3 mg/kg/hr (50 µg/kg/min) atracurium infusions were required with high-dose midazolam and fentanyl infusions to achieve adequate oxygenation and acceptable airway pressures; however, TOF monitoring showed unacceptable level of NMB. The authors concluded that cross-resistance among chemically dissimilar NNMBAs poses a difficult patient management problem and supports a pharmacodynamic basis of resistance to these agents.

Conclusion

Tachyphylaxis to NNMBAs might occur in critically ill patients who receive prolonged infusions, and should be suspected if there is an increased requirement of the infused NNMBA to maintain an adequate NMB. Tachyphylaxis to a NNMBA is managed by discontinuation of the implicated drug to avoid side effects and increased cost, and use of a different NNMBA if NMB is still indicated.

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