Potentiation of a Neuromuscular Blocking Agent Postoperatively by a Polypeptide Class Antibiotic: A Case Report

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Abstract

During multiple surgical procedures, neuromuscular blocking agents (NMBAs) are administered as part of a general anesthetic to provide muscle relaxation. Examples of commonly administered NMBAs are succinylcholine, rocuronium, vecuronium, and cisatracurium. Administration of other medications during the surgical procedure can cause unexpected interactions, such as affecting the action of the NMBAs. The polypeptide class of antibiotics has been identified as one group of antibiotics that can potentiate NMBAs when administered during the perioperative period. Although the incidence of antibiotic-induced neuromuscular blockade is rare, it is important to be aware of this medication interaction and to know how to manage this potential complication. This report presents one such case with a review of the literature.

INTRODUCTION

Neuromuscular blocking agents (NMBAs) are administered as part of a general anesthetic to provide muscle relaxation during surgical procedures. Examples of commonly administered NMBAs are succinylcholine, rocuronium, vecuronium, and cisatracurium. Other medications administered during the surgical procedure may interact with NMBAs.[1-12] For example, some antibiotics are known to potentiate the effects of NMBAs. Antibiotics are also commonly administered to surgical patients during the perioperative period as a prophylactic measure for postoperative surgical wound infections or are given intraoperatively as part of continued treatment or for a newly identified infection risk. Although most antibiotics work by altering the membrane permeability of bacterial cells, they can also affect the neuromuscular junction by causing neuromuscular blockade.[1-13]

The polypeptide class of antibiotics has been identified as one group of antibiotics that can potentiate NMBAs when administered during the perioperative period.[1-12] This classification of antibiotics is thought to act at 2 independent locations of the neuromuscular junction.[1,2,4,10,12] Presynaptically, polypeptide antibiotics reduce the release of acetylcholine. Additionally, polypeptide antibiotics inhibit the acetylcholine from reaching its specific receptor postsynaptically. This potentiating action of polypeptide antibiotics may make it challenging to reverse a neuromuscular block.

Although a specific medication or therapy to fully reverse antibiotic-induced neuromuscular blockade has not yet been discovered, researchers have attempted to reverse the neuromuscular blockade produced from the combination of polypeptide antibiotics and NMBAs with calcium chloride and anticholinesterase medications.[1,3,4,7-13] These attempts have been shown to be inadequate and may only temporarily reverse the block or may adversely prolong the duration of the block.[1,3,4,7-13] Time and ventilatory support are the only proven treatment for full recovery of neuromuscular blockade prolonged by this interaction.[1-13] Although the incidence of antibiotic-induced neuromuscular blockade is rare, it is important to be aware of this medication interaction and to know how to manage this potential complication.[8] This report presents one such case with a review of the literature.

CASE REPORT

A 45-year-old, 152-cm, 121-kg woman was admitted for an emergent laparoscopic appendectomy. The patient had abdominal pain for approximately 2 days prior to admission but had attributed the pain to her menstrual cycle. The patient denied any previous surgeries or procedures. Her past medical history was significant for benign essential hypertension, but she was not taking any prescribed medications for this condition. Recent and relevant laboratory data included a white blood cell count of 18.32 x 100/L. This laboratory value was elevated and was consistent with the diagnosis of appendicitis.

The patient's physical status was scored as American Society of Anesthesiologists (ASA) IIE related to the following conditions: chronic hypertension, body mass index greater than 40 kg/m^2, and scheduled for an emergent surgery. A Mallampati score of 3 and a thyromental distance of 3 finger breadths were noted during assessment of the airway with the patient in the upright and sitting position. Range of motion capabilities were assessed and determined to be nonrestrictive. The patient was complaining of abdominal pain with nausea and vomiting. On the basis of the patient's current condition, a general anesthetic with an endotracheal tube utilizing a rapid-sequence induction was determined to be the best anesthetic plan. In the preoperative area, metronidazole 500 mg and piperacillin-tazobactam 4.5 g were administered intravenously to help mitigate any potential infection risk associated with the patient's ruptured appendix. Morphine sulfate 5 mg was also administered intravenously to the patient prior to surgery to assist with pain relief. The patient was given 1 L of Lactated Ringers IV prior to induction to increase intravascular fluid volume and to help to prevent hypotension during induction. Before leaving the preoperative area, the patient received famotidine 40 mg to reduce gastrointestinal pH.

In the operating room, a pulse oximeter probe, an automatic blood pressure cuff, and electrocardiogram pads were placed on the patient. Oxygen was delivered via a facemask at a rate of 10 L/min once the patient was appropriately positioned on the operating table. Vital signs were assessed and were within the patient's normal range. An intravenous induction was performed with fentanyl 100 mcg, lidocaine 50 mg, propofol 160 mg, succinylcholine 100 mg, and rocuronium 50 mg, while cricoid pressure was held, to assist with the rapid-sequence intubation. An endotracheal tube was smoothly and successfully inserted in one attempt under direct laryngoscopy. Cricoid pressure was released after correct endotracheal tube placement was confirmed by auscultating bilateral breath sounds. Desflurane was chosen as the maintenance anesthetic, with end-tidal concentrations maintained at 5.2%. Rocuronium 25 mg was given 4 minutes after induction, when 4 twitches were present, prior to incision to provide sufficient muscle relaxation. No further rocuronium was given. Controlled ventilation was maintained throughout the surgical procedure with ventilation settings of 600 mL for tidal volume and a respiratory rate of 13 breaths per minute. The end-tidal CO_2 reading was approximately 35 to 38 mm Hg throughout the procedure. Before the completion of surgery, a lavage of the peritoneum was performed with an irrigant containing polymyxin b and bacitracin. A total of 100 mcg of fentanyl was given for the entire surgical case.

Three out of 4 twitches at the patient's corrugator supercilii muscle were present upon assessment of train-of-four with a peripheral nerve stimulator at the end of the case. When the abdomen was no longer insufflated, neuromuscular blockade was reversed with a maximal dose of neostigmine (5 mg), along with glycopyrrolate (0.8 mg). The patient began spontaneously breathing within a few minutes of reversal at 12 breaths per minute with an unassisted tidal volume of 350 to 450 mL. Two doses of labetalol 5 mg were also administered intravenously upon emergence because the patient's blood pressure increased to 165/92 mm Hg. The patient was successfully extubated after confirming a 5-s head lift and after appropriate responses to verbal commands were performed. The entire anesthetic and surgical procedure were uneventful except for the treatment of hypertension during emergence from anesthesia.

Immediately after the patient was transferred to the hospital bed with full assist of the operating room staff, respiratory weakness was noted. Two-person assisted ventilation was initiated. The patient was responding to verbal commands and was able to move her upper and lower extremities with some weakness noted. However, she could not lift her extremities for more than 3 to 4 s. She could open her eyes but could not appropriately track movement. The anesthesiologist involved in the case was notified. Thirty minutes after extubation, naloxone 0.04 mg was administered intravenously to determine whether the noted respiratory weakness was due to excessive narcotics. However, no apparent change in respiratory rate or effort was seen. The end-tidal concentrations of desflurane were noted to be 0.0% at this time. Ten minutes after the initial naloxone dose, an additional dose of 0.08 mg was given intravenously. The patient continued to follow some commands appropriately, but was only able to exert a tidal volume of 30 mL when not assisted. Doxapram 40 mg was administered intravenously 5 minutes after the second dose of naloxone, followed by a second dose of 80 mg intravenously 10 minutes later. At this time the anesthesiologist went to discuss the current situation with the patient's husband to determine if any recreational drug use had occurred recently. The husband reported that the patient had smoked marijuana 2 days before the surgical date.

After the second dose of doxapram it was determined that the patient would require ventilator assistance and a size 4 laryngeal mask airway was successfully inserted. Although no additional anesthetic was administered before laryngeal mask airway insertion, the patient did not show any signs of discomfort or have any changes in vital signs upon device insertion. The patient's condition was reported to an intensive care unit registered nurse. Because an intensive care unit bed was not yet available, the laryngeal mask was removed and an endotracheal tube was inserted to better protect the patient's airway.

While waiting in the operating room for a bed to become available, the patient began to cough, purposefully reach for the endotracheal tube, and produced adequate tidal volumes. The patient was subsequently extubated. Within 5 of minutes of extubation, the patient once again began to have reduced tidal volumes. A nasal trumpet was inserted and two-person mask ventilation was initiated. The patient had spontaneous eye opening, with no tracking, but showed weakness when attempting to follow

verbal commands. The patient was re-intubated, started on a propofol drip, and was transported to the intensive care unit. Her vital signs remained stable during transport, and ventilation with 100% oxygen was assisted with a manual resuscitator. Ventilator settings in the intensive care unit were SIMV (synchronized intermittent-mandatory ventilation) with a minimum of 8 respirations per minute. Twenty minutes after arrival to the intensive care unit, the patient was extubated. The patient was able to effectively, spontaneously breathe without supplemental oxygen only 12 hours after being admitted to the intensive care unit. Twenty-four hours later, the patient was discharged home in stable condition without sequelae.

DISCUSSION

Antibiotics and NMBAs are often administered to patients undergoing surgery requiring muscle relaxation. Antibiotics can be administered by the anesthesia provider or by the surgeon. The type of antibiotic given varies depending on the type of surgery, the presence of infection, and the allergies of the patient undergoing the surgical procedure. The effects of different antibiotics on a cell membrane's permeability are relatively well understood. However, the effects of certain antibiotics at the neuromuscular junction are still being researched and may be unpredictable. Muscle relaxation during surgery can be achieved by using NMBAs such as rocuronium, succinylcholine, vecuronium, and pancuronium.

The patient in this case had a neuromuscular block initially produced by succinylcholine and then rocuronium. Blockade from the succinylcholine was ruled out when 4 twitches were noted prior to the second dose of rocuronium. The neuromuscular blockade may have been prolonged when the polymyxin and bacitracin irrigant was administered and then further enhanced with neostigmine. Before the reversal agents were administered to this patient, 3 out of 4 twitches for train-of-four were present, with sustained tetany that included fade. Polymyxin, when administered alone, can cause fade upon train-of-four assessment, but will not show depression during assessment of tetanus.[1,3,6,12] Also, 4 out of 4 twitches can be seen with 70% of cholinergic receptors blocked or occupied.[12]

Some antibiotics have been shown to augment nondepolarizing muscle relaxants by enhancing the neuromuscular block.[1-13] Polymyxins, along with other antibiotics, can have a synergistic effect on neuromuscular blockade produced by various muscle relaxants.[1,4,6-12] Polymyxins, bacitracin, and daptomycin are all examples of polypeptide antibiotics. Polymyxins have also been shown to cause muscle weakness when administered without any NMBA.[1-2,5-7,9-10,12]

Polymyxin affects the neuromuscular junction at both the presynaptic and the postsynaptic level. At the presynaptic level it decreases the amount of acetylcholine released.[1-6,12] At the postsynaptic level it blocks acetylcholine from entering specific receptor channels.[1-6,12] Each of these alterations at the neuromuscular junction has an effect on the action potentials in muscle tissue and nervous tissue. The polypeptide antibiotics affect the postsynaptic junction by noncompetitively antagonizing the acetylcholine-active channels on the endplate.[2,4-5,10,12] An additive effect occurs when polypeptide antibiotics are administered with an NMBA because the 2 types of drugs are acting on the same site. Thus, if the cholinergic receptors at the postsynaptic junction are occupied with the NMBA, the antibiotics can have a synergistic effect with the muscle relaxants by also being capable of affecting the presynaptic junction.[12]

Although the specific method of action by which polypeptide antibiotics affect acetylcholine release and their receptor channels is not completely known, some studies have compared the actions of this antibiotic class to the actions of magnesium.[2,4,12] At the neuromuscular junction, magnesium antagonizes calcium.[2,4,12] Calcium is necessary for acetylcholine to be released.[2,4,12] Therefore, magnesium inhibits the release of acetylcholine from the presynaptic junction.

A few studies have revealed that the ED_{50}, which is the dose that is effective in at least 50 percent of people, is significantly decreased when NMBAs are combined with certain antibiotics.[6,12] Therefore, if a polypeptide antibiotic and an NMBA are both required during the perioperative period, the anesthesia provider and the surgeon should discuss possibly decreasing the dosage of one of these drugs. Decreasing the dosage of the NMBA or the antibiotic will decrease the intensity of the block. Furthermore, it is important to recognize that polymyxin can not only potentiate the neuromuscular blockade produced by an NMBA but also cause some degree of neuromuscular blockade when administered alone.[1-2,5-7,9-10,12] Lindesmith et al[9] in 1968 discussed cases in which patients experienced symptoms of neuromuscular toxicity due to polypeptide antibiotics without being given any NMBA or other potentially neurotoxic antibiotics. The polypeptide antibiotics were administered intramuscularly to most of the patients.[9] Also, to prevent possible complications, polypeptide antibiotics and certain NMBAs should be used cautiously in patients with altered renal function or myasthenia gravis.[8] These patient populations are at higher risk for neurotoxicity and nephrotoxicity after polypeptide antibiotic administration.[8]

Reversal of neuromuscular blockade caused by antibiotics is difficult, and attempts to reverse with calcium chloride and cholinesterases have not proven effective.[1,3-4,6-12] Although neostigmine is an acetylcholinesterase inhibitor, it can actually augment the neuromuscular blockade enhanced by polypeptide antibiotics.[6] Subclinical doses of acetylcholinesterase inhibitors may inadequately antagonize neuromuscular blockade and actually enhance the blockade at standard reversal dosages.[1,3,6,7] This insufficient antagonizing of the neuromuscular blockade by neostigmine is seen only when nondepolarizing muscle relaxants are utilized.[1,3-4,6-12] Conversely, no change in the neuromuscular blockade intensity is seen after neostigmine administration when a depolarizing muscle relaxant is utilized.[3,12] This difference is likely due to the NMBA structure when binding to cholinergic receptors on the postsynaptic junction of the neuromuscular junction.[3,7,12]

Another method of attempting to reverse this type of neuromuscular block is the administration of calcium chloride.[1,3,7,12] Calcium chloride has been shown to only temporarily improve the neuromuscular reversal.[1,3,7,12] Calcium levels that cause hypertension, tachycardia, and arrhythmias have been shown to not completely reverse this type of block.[3] This temporary reversal could be due to how polypeptide antibiotics affect the neuromuscular junction at 2 independent

levels.[1-6,12] Administering calcium chloride increases the release of acetylcholine at the presynaptic junction of the neuromuscular junction.[1,2,4,12] However, increased levels of calcium chloride do not affect the polypeptide antibiotic at the postsynaptic junction of the neuromuscular junction because the calcium chloride acts as a noncompetitive antagonist to acetylcholine at the acetylcholine-activated channels of the endplate.[3,7,12] Calcium chloride as a reversal, although partially effective, may not be the best choice because the patient is likely to experience muscle weakness again shortly after initial recovery.[13] Also, calcium chloride administration could antagonize the antibiotic's antibacterial effect.[13]

Whether an NMBA is administered in addition to a polypeptide antibiotic or administered alone, it is commonly recommended to administer a reversal agent for neuromuscular blockade caused by an NMBA.[14] Although immediate recovery from neuromuscular blockade caused by NMBAs is difficult to achieve, not administering a reversal agent after an NMBA can cause residual weakness.[14] Also, confirming the presence of at least one twitch with a neuromuscular twitch monitor is necessary before administering the reversal agent to prevent further residual weakness. Without at least one twitch, the patient is at risk for residual paralysis once the reversal agent is no longer at the neuromuscular junction.[14] The commonly used reversal therapy for nondepolarizing NMBAs is neostigmine. It is recommended that 0.04 to 0.07 mg/kg be administered to assist in the reversal of neuromuscular blockade, depending on the patient's train-of-four ratio.[14] The greater the number and intensity of twitches, the less the amount of reversal needed.[14] Another cause of residual paralysis could be from overdosing a reversal agent, such as neostigmine. Neostigmine acts by binding to the same receptor as the nondepolarizing neuromuscular blockers and would then cause further muscle weakness.[14]

Although it is standard treatment to administer reversal agents for patients who receive nondepolarizing NMBAs, it is also difficult to determine how much of the neuromuscular block is due to the nondepolarizing NMBA and how much is due to the polypeptide antibiotic. The known recovery time for a block caused by both, NMBAs and polypeptide antibiotics, or by only polypeptide antibiotics has yet to be discovered. The necessary recovery time can vary widely depending on the antibiotic and NMBA administered. Therefore, ventilation should be controlled in a patient who has received cyclic peptide antibiotics and muscle relaxants until standard requirements for extubation have been met and no signs of neuromuscular weakness are seen. These steps will decrease future unnecessary airway manipulation, irritation, and injury from re-intubations. Additionally, during this recovery period, no further additional doses of neostigmine should be administered to prevent further muscle weakness.

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