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Dilated Nonreactive Pupils Secondary to Neuromuscular Blockade

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THE nondepolarizing neuromuscular blocking (NMB) agents do not readily cross the intact blood–brain barrier (BBB).[1,2] However, when introduced into the central nervous system (CNS), NMB drugs and some metabolites are known to be pharmacologically active. Cholinergic depression, autonomic dysfunction, neuronal excitotoxicity, seizures, and neuronal death have been reported.[3–6] With the exception of the atracurium metabolite, laudanosine, evidence suggests that these effects are mediated by neuronal nicotinic acetylcholine receptors within the CNS.[4]

In the critically ill patient population, disruption of the BBB may be present.[7–10] In addition, prolonged high concentrations of NMB drug may accompany continuous administration. The combination of BBB disruption and high drug concentrations may produce central effects by these agents.

Short-term administration of NMB agents has been shown to have no effect on pupil size in healthy anesthetized patients.[11] We report three cases in which dilated, nonreactive pupils were time- and dose-dependently associated with the prolonged use of atracurium or vecuronium and return of pupil reactivity was temporally associated with discontinuation of the respective NMB agent. These pupil changes were not associated with administration or discontinuation of any other pharmacological agent.

These cases represent 12.5% (3/24) of all patients ad-

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Key words: Atracurium; mydriasis; neuromuscular blocking agents; pupillary light reflex; vecuronium bromide.

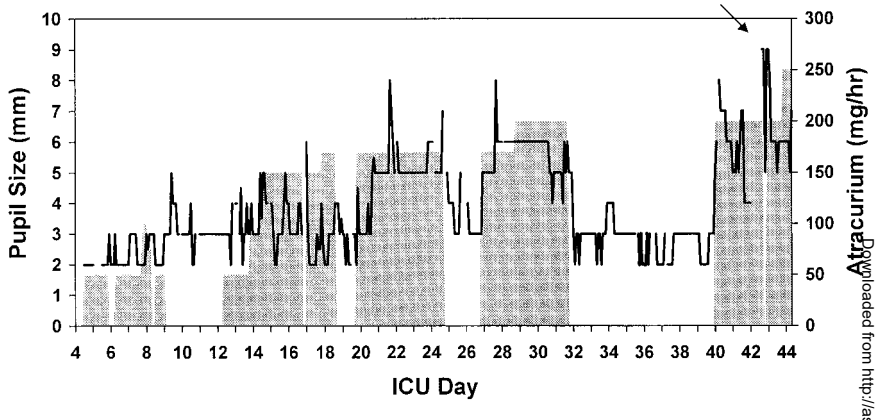

Fig. 1. Relation between pupil size and atracurium infusion rates over time for patient 1. Left *y*-axis (thick black line): pupil size assessment performed every 2 h. Right *y*-axis (gray-shading): atracurium infusion rate. *x*-Axis: time in intensive care unit (ICU) days. If no assessment was recorded for the 2 h time period, no pupil size was plotted (depicted as a break in the line). The arrow indicates the point at which pupils became dilated and nonreactive.

mitted to a pediatric oncology intensive care unit (ICU) during the same time period who received continuous NMB infusions for ≥3 days, and 27% (3 of 11) of patients who required escalating infusion rates. Data were abstracted retrospectively from the medical record and included diagnoses, demographics, NMB agent dosing, pupil size, concurrent medication dosing, vital signs, pertinent laboratory values, neuroimaging studies, and autopsy results (if available). Pupil size and reactivity was assessed by nursing staff according to unit protocol using a standardized gauge and recorded on the nursing flowsheet. Neuromuscular blockade was monitored by physical examination and, at times, by peripheral nerve stimulator.

Case Reports

Case 1

A 20-yr-old, 60 kg, man was admitted to the ICU 9 days after allogeneic bone marrow transplant for relapsed acute myelogenous leukemia. The ICU course was remarkable for prolonged mechanical ventilation (adult respiratory distress syndrome and Aspergillus pneumonia), pressor-dependent septic shock, dialysis-dependent renal failure, and severe cholestatic jaundice (direct bilirubin 25 mg/dl) secondary to graft versus host disease. The patient was continuously sedated with a combination of an opioid (fentanyl, morphine) and a benzodiazepine (midazolam) infusion. Atracurium was administered for 632 h in doses of 0.58 to 2.83 mg · kg^{-1} · h^{-1}. On day 43 of his intensive care admission, he was noted to have dilated (9 mm) and nonreactive pupils (fig. 1). In view of a recurrent pattern of mydriasis associated with atracurium (ICU days 21, 24, 27, and 40; fig. 1), the infusion was discontinued. Within 2 h, the pupils decreased to 5 mm and were reactive. There was no interruption of his infusions of opioids or pressors at times of pupil dilation and bolus administration of opioids given in response to pupil dilation had no effect on pupil size. Other medications that may have affected pupil size included oral naloxone, and intermittent doses of pentobarbital, lorazepam, meperidine, diphenhydramine, and hydroxyzine, but no changes in the administration of these drugs occurred during the periods of pupillary changes. The patient died on ICU day 45 secondary to progressive lung disease. Postmortem examination revealed no central nervous system abnormalities.

Case 2

A 17-yr-old, 50-kg, adolescent girl was admitted to the ICU for respiratory failure secondary to diffuse alveolar hemorrhage and myocardial dysfunction 26 days after allogeneic bone marrow transplant for chronic myelogenous leukemia. Her course was complicated by Grade IV graft versus host disease of skin and liver (bilirubin 5.1 mg/dl), renal failure (blood urea nitrogen 106 mg/dl and creatinine 3.9 mg/dl), and septic shock, requiring mechanical ventilation and continuous inotropic support. At all times the patient was heavily sedated with a combination of an opioid (hydromorphone, fentanyl) and a benzodiazepine (midazolam) infusion. Atracurium was administered for 88 h in doses of 0.5 to 2.6 mg · kg^{-1} · h^{-1} with increasing doses required to maintain neuromuscular blockade. On ICU day 3 she was noted to have dilated (7 mm) nonreactive pupils (fig. 2). At that time, she was hypothermic with a core body temperature of 32.8°C. She was hyperventilated and treated with thiopental and mannitol with no change in pupil size. Emergent computed tomography of the head revealed no evidence of hemorrhage, edema, or mass effect. With external warming and discontinuation of her atracurium, her core temperature returned to 36.6°C and her pupils decreased in size to 4 mm and became reactive. On ICU day 13, atracurium was restarted for worsening pulmonary hemorrhage. She remained on atracurium with progressive increase in pupil size until she died 2 days later (fig. 2). Other medications that may have affected pupil size included dobutamine, norepinephrine, and epinephrine infusions, and occasional intermittent doses of thiopental, meperidine, and diphenhydramine, but no changes in the administration of these drugs occurred during the periods of pupillary changes.

Case 3

An 8-yr-old, 30 kg, girl was admitted to the ICU in respiratory distress 113 days after allogeneic bone marrow transplant for acute myelogenous leukemia. She required prolonged mechanical ventilation for

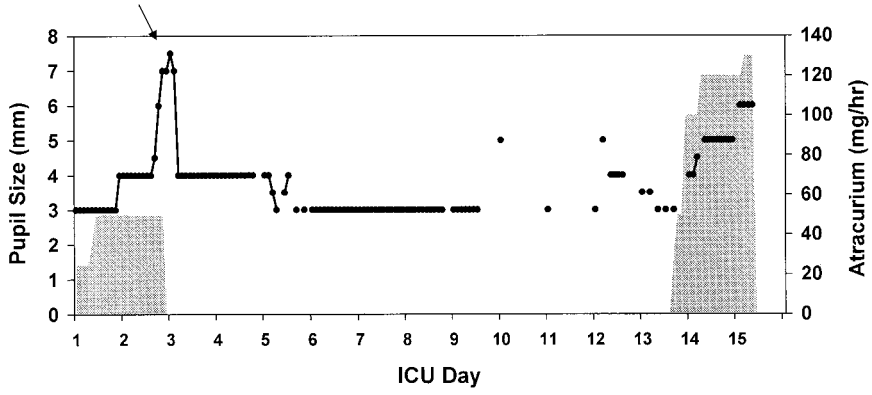

Fig. 2. Relation between pupil size and atracurium infusion rates over time for patient 2. Left *y*-axis (thick black line): pupil size assessment performed every 2 h. Right *y*-axis (gray-shading): atracurium infusion rate. *x*-Axis: time in intensive care unit (ICU) days. The arrow indicates the point at which pupils became dilated and nonreactive.

suspected pulmonary graft versus host disease, adult respiratory distress syndrome, and pulmonary hemorrhage. Other complications included hemorrhagic cystitis with uremia (blood urea nitrogen 153 mg/dl, creatinine 2.8 mg/dl) and hypertension, septic shock, pericardial effusion requiring a pericardial window, hyponatremia (sodium 116 mg/dl), and upper gastrointestinal bleeding. Throughout her ICU course, she was sedated with a combination of opioid, benzodiazepine, and barbiturate infusions. Vecuronium was started 5 days after intubation and was administered intermittently for 808 h, with doses of 0.1–0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ (fig. 3). Late in her ICU course, her pupils were noted to be dilated and sluggishly reactive. On ICU day 54, the pupils were noted to be 6 mm and nonreactive. Head computed tomography revealed no evidence of edema, mass effect, or hemorrhage, and serum sodium was normal. Additional opioid boluses had no effect on pupil size. During the next 2 days her pupils remained dilated and nonreactive at which point neuromuscular blockade was discontinued. Within 12 hours of discontinuation of vecuronium, her pupils decreased in size and became reactive. Other medications that may have affected pupil size included dopamine and dobutamine infusions, and occasional intermittent doses of meperidine and diphenhydramine, but no changes in the administration of these drugs occurred during the periods of pupillary changes. The patient died approximately 2 weeks later from progressive pulmonary disease. Postmortem examination revealed diffuse cerebral cortical atrophy, consistent with previous neuroimaging findings.

Discussion

These cases suggest that atracurium and vecuronium may cause mydriasis and ultimately, nonreactive pupils in patients receiving prolonged high-dose infusions. The argument for a causal relation is strengthened by the fact that mydriasis was both reversible and reproducible when NMB agents were stopped and restarted (figs. 1, 2, 3; bold line). No other concurrent medications could be temporally linked to pupil size. Evidence that the NMB agents may cross the BBB and disrupt central cholinergic transmission could explain these observations.[3–6] All patients were bone marrow transplant recipients, received prolonged NMB agent infusions, required escalating doses, had multisystem organ dysfunction, and had conditions or treatments known to disrupt the BBB.

Neuromuscular blocking agents must cross the BBB to act centrally. Matteo demonstrated that d-tubocurarine penetrates the BBB with short-term use and that this passage appeared dependent on the serum-cerebrospinal fluid (CSF) gradient.[12] Consequently, with long-term

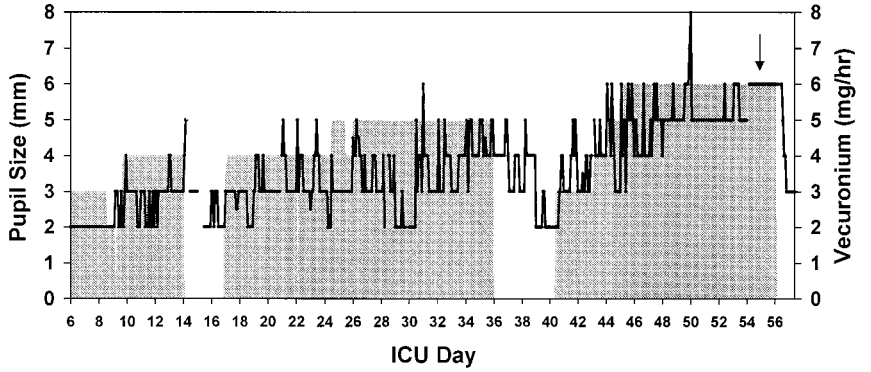

Fig. 3. Relation between pupil size and vecuronium infusion rates over time for patient 3. Left *y*-axis (thick black line): pupil size assessment performed every 2 h. Right *y*-axis (gray-shading): vecuronium infusion rate. *x*-Axis: time in intensive care unit (ICU) days. The arrow indicates the point at which pupils became dilated and nonreactive.

administration, NMB agents may continue to penetrate the BBB as long as a serum-CSF gradient exists. Atracurium, vecuronium and their respective metabolites have also been recovered in the CSF of patients.[3,4,13] In the critical care setting, inflammatory and oxidative stress are known to disrupt the BBB.[7,8] In the oncology patient population, radiation and chemotherapy can disrupt the BBB.[9,10] In addition, possible tolerance with long-term administration of vecuronium may explain the higher doses required to maintain NMB (figs. 1, 2, 3; gray).[14] The combination of prolonged high dose administration and BBB disruption may result in CNS concentrations that produce central effects.

The molecular pharmacology of central cholinergic neurotransmission is complex and poorly understood. Neuronal nicotinic acetylcholine receptors differ from their neuromuscular junction counterparts in that their heteromeric composition varies widely with combinations of multiple subunits (eight α and three β subunits identified) and they are more permeable to calcium.[1,2,15] Multiple subtypes with differing pharmacological activities have been identified in the brain as well as the autonomic ganglia and mediate both sympathetic and parasympathetic neurotransmission.[1,2,15] Many cholinergic agonists and antagonists have paradoxical central effects depending on the agent, concentration, and receptor subtype.[1,2,15] When introduced into the CNS, NMB agents also exhibit apparent paradoxical activity with both agonist and antagonist activity, as well as both excitation and depression.[3,4,6] In summary, the NMB agents are pharmacologically active when present in the CNS, and produce disruption of cholinergic signal transduction. Mydriasis may therefore represent such central effects.

Dilated nonreactive pupils are commonly associated with profound CNS pathology. No patient had acute CNS pathology as determined by neuroimaging and by return of neurologic function with cessation of NMB. Hypothermia, sympathomimetic agents, anticholinergic agents, and increased endogenous sympathetic tone commonly cause dilated pupils but rarely to the extreme of pupil nonreactivity. Hypothermia unlikely accounted for the degree of dilated pupils experienced in patient 2 who had mydriasis again when her temperature was normal (fig. 2).[16] Each patient received medications known to influence pupil size, however, no changes in the administration of these drugs were coincident with the pupil changes. Mydriasis in patients receiving NMB agents is commonly interpreted as pain and treated empirically with administration of analgesia. Interestingly, additional opioid boluses administered in response to pupil dilation had no effect on pupil size. The possibility that central excitatory effects of laudanosine caused mydriasis was considered but would not explain the pupil findings in patient 3.[5] No other common pathophysiological mechanism to explain this phenomenon could be identified.

These cases were identified by the finding of dilated nonreactive pupils. Clearly, in these patients, mydriasis was not an all-or-nothing response but rather a continuum of drug effect that reached an extreme endpoint of dilated, nonreactive pupils. It is therefore possible that these reports describe an extreme end-point of a more widely present drug effect, which is easily obscured by the multiple factors affecting pupillary size and reactivity. These observations are supported by a strong temporal association, reproducibility, and plausible mechanisms by which NMB agents may cause mydriasis. If these agents are crossing the BBB, mydriasis in and of itself may not be as important as the fact that it may be an indicator of unappreciated CNS drug action. Central nervous system actions of NMB agents should therefore be considered in the differential diagnosis of dilated nonreactive pupils.

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Massive Hemoptysis after the Initiation of Positive Pressure Ventilation in a Patient with Pulmonary Tuberculosis

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RESPIRATORY tract hemorrhage in a patient with old pulmonary tuberculosis after positive pressure ventilation during general anesthesia is an unusual but often lethal complication. We describe a case of massive hemoptysis induced by positive pressure ventilation during general anesthesia. After successful resuscitation, the patient received an epidural anesthesia with spontaneous ventilation while undergoing low anterior resection for rectal cancer.

Case Report

A 78-yr-old 60-kg man was to undergo low anterior resection for rectal cancer. He had history of pulmonary tuberculosis for 20 yr. On physical examination, a partially collapsed right upper lobe and cavity were noted at chest roentgenogram. He had no history of abnormal hematologic data. Preoperative pulmonary function test showed to have mild chronic obstructive pulmonary disease with positive response to bronchodilators.

No premedication was administered. After the patient's arrival in the operating room, intravenous access was established. Induction of general anesthesia was accomplished with vecuronium bromide, fentanyl, and propofol. Tracheal intubation was facilitated by the administration of succinylcholine. Neuromuscular blockade was maintained with vecuronium bromide after induction. Anesthesia was maintained with $50\%N_2O/50\%O_2$. Mechanical ventilator settings were tidal volume of 600 ml and a respiratory frequency of 10 breaths per minute.

Shortly after beginning positive pressure ventilation, massive amounts of fresh blood were noted refluxing from the endotracheal tube. The patient's hemodynamic status deteriorated into pulseless electrical activity within minutes, and resuscitative efforts including chest compressions, intravenous epinephrine, and 1000 ml whole blood replacement were initiated. Then the patient was transported emergently to the angiographic room for embolization. After embolization of the bleeding right superior bronchial artery, the patient was returned to the operating room. The patient was extubated subsequently in the operating room and the surgical procedure was cancelled. The patient was transported to the intensive care unit for postoperative care and recovered without obvious neurologic sequelae. The postoperative chest roentgenogram showed total collapse of the right upper lobe with the typical air bronchogram sign and pneumonic consolidation change.

The patient was rescheduled to undergo surgery again 1 week later. After insertion of an intravenous catheter, he received 25 mg pethidine and 5 mg midazolam intravenously. With the patient in the left lateral knee-chest position, the epidural catheter was inserted at the L_2L_3 interspace with loss of resistance technique. Lidocaine 2% with 1:200,000 epinephrine was administered in incremental dose of 5 ml to a total of 40 ml. A surgical level of sensory anesthesia was obtained from T_4 to S_5.

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Key words: Centroneuraial blockade; pulmonary hemorrhage; suffocation.