

Prolonged Weakness After Infusion of Atracurium in Two Intensive Care Unit Patients

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Administration of neuromuscular blocking (NMB) drugs to patients in the intensive care unit (ICU) is used to facilitate mechanical ventilation, control intracranial hypertension, eliminate shivering, decrease oxygen consumption, and facilitate diagnostic procedures and studies (1,2). In the United States, the steroid-based NMB drugs, vecuronium and pancuronium, are most frequently selected for ICU administration (1,2). However, numerous reports suggest that prolonged administration of these drugs to ICU patients may result in sustained weakness, persisting days to weeks after withdrawal of the drug (3–5). Three features are common to these reports: 1) the prolonged, usually continuous infusion of steroid-based NMB agents, most often without peripheral nerve twitch monitoring, 2) concurrent administration of drugs which may alter neuromuscular transmission such as aminoglycoside antibiotics, calcium-channel blockers, magnesium, and especially high-dose corticosteroids, and 3) end-organ dysfunction such as significant renal failure (3–11).

Because of concern about administration of steroid-based NMB drugs in patients receiving concurrent exogenous corticosteroids, recommended strategies include the use of routine peripheral nerve twitch monitoring and the selection of neuromuscular blocking agents with an alternative (nonsteroid) pharmacologic structure (12). Atracurium, an intermediate-acting benzylisoquinolinium compound, is structurally unrelated to the aminosteroid NMB agents (13). Introduced in 1983, atracurium is a unique NMB drug that undergoes ester hydrolysis and Hofmann elimination (independent of hepatic or renal function) to laudanosine and monoacrylate metabolites (13), which are inactive at the neuromuscular junction.

Therefore, atracurium should be eliminated from plasma despite hepatic or renal dysfunction. However, we recently observed prolonged, severe muscle weakness in two mechanically ventilated patients treated for extended periods with atracurium and corticosteroids. Neither patient had clinically significant hepatic or renal dysfunction. No clearly identified alternative etiology for the prolonged muscle weakness could be established. Thus, we believe that both the aminosteroid and the benzylisoquinolinium NMB drugs (such as atracurium) may be implicated in the ICU phenomenon of prolonged muscle weakness after NMB drug infusion.

Case Reports

Case 1

A 38-yr-old man was found to be pancytopenic when evaluated for skeletal pain. He had a history of a left testicular seminoma 3 yr prior to admission. Treatment at that time consisted of a radical orchiectomy and postoperative pelvic radiotherapy (22.5 Gy), and no recurrent testicular cancer was observed in followup. A bone marrow examination on the current admission revealed acute myelocytic leukemia. Mild disseminated intravascular coagulation was present. The patient had no evidence of neuromuscular, hepatic, or renal disease or dysfunction.

Transretinoic acid (100 mg daily) was begun with dexamethasone (2 mg every 6 h) to induce remission, and heparin and ϵ -aminocaproic acid were administered to treat disseminated intravascular coagulation. The patient experienced fever and rigors on the fourth hospital day, and ticarcillin and tobramycin were administered. Vancomycin and amphotericin B were begun on the fifth hospital day when high fever and rigors persisted, and fever gradually subsided. Red blood cell and platelet transfusions were frequently administered. On the eighth day the patient experienced increasing respiratory distress, was transferred to the ICU, and required continuous positive airway pressure (mask CPAP) to maintain adequate oxygenation. A chest radiograph showed bilateral, fluffy alveolar infiltrates. Dexamethasone was increased to 4 mg every 6 h. The patient's respiratory rate increased to 42 breaths/min, and P_{aO_2} was 86 mm Hg (11.5 kPa) while breathing 100% oxygen.

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Oxygenation progressively deteriorated, and succinylcholine 100 mg and etomidate 10 mg were administered to facilitate tracheal intubation and mechanical ventilation on the 10th day of hospitalization. After intubation, an atracurium bolus (50 mg) was given, followed by constant infusion of atracurium at $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Peripheral nerve twitch monitoring of the adductor pollicis brevis muscle was checked every 2–4 h, and the atracurium infusion rate adjusted to maintain one to two twitches in the train-of-four response. The cough reflex (noted during suctioning) was continually present. Atracurium infusion rates averaged $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ but ranged from 6.6 to $20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. The patient received a total of 13,958 mg of atracurium over a period of 8 days. Oxygenation gradually improved, and the atracurium infusion was discontinued on the 18th day. Creatine kinase (CK) was 585 U/L (normal 0–200) on the 13th hospital day. CK isoenzymes confirmed skeletal muscle origin. Despite clearing of the infiltrates on chest radiographs and significantly improved oxygenation, the trachea could not be extubated. The patient was alert but had diffuse, profound skeletal muscle weakness and was unable to lift his arms or legs above the surface of the hospital bed. Tobramycin was discontinued, and infusion of calcium gluconate did not reverse the severe weakness. The dexamethasone was decreased to 1.5 mg every 12 h. No positive blood cultures were obtained nor any site of focal infection identified. The trachea was successfully extubated on the 36th hospital day (2 wk after discontinuation of the atracurium infusion), but he remained profoundly weak.

Neurologic examination revealed intact cranial nerve function and intact peripheral pain and touch sensation. Profound proximal and moderate distal motor weakness were clinically evident. Electromyographic studies revealed severe proximal and distal myopathic changes without fasciculations, and evidence of regeneration. Nerve conduction studies demonstrated a mixed axonal and demyelinating motor neuropathy. There was no decrement with repetitive 2-Hz nerve stimulation and no evidence for a neuromuscular transmission defect. The patient's strength gradually improved, but he could not yet ambulate when discharged to a chronic care facility on the 60th hospital day.

Case 2

A 25-yr-old female patient was transferred to our institution 1 wk after developing hemoptysis and hematuria. High doses of methylprednisolone (750 mg/d) and cyclophosphamide (40 mg/d) were administered, and plasmapheresis was instituted 3 days prior to transfer. Goodpasture's syndrome was diagnosed by renal biopsy and positive antiglomerular basement antibody in serum. Massive alveolar hemorrhage occurred shortly after admission to our ICU, causing respiratory failure which necessitated endotracheal intubation and mechanical ventilation. Intravenous etomidate (10 mg), midazolam (2 mg), and vecuronium (10 mg) were given at the time of endotracheal intubation. After neuromuscular function returned, an atracurium infusion was begun to facilitate adequate mechanical ventilation. The atracurium infusion rate ranged from $7 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to a maximum of $14 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, titrated by the adductor pollicis twitch response to peripheral nerve stimulation. Sedation and analgesia were maintained with midazolam and morphine sulfate infusions.

The patient's hospital course while intubated was complicated by a left pneumothorax requiring tube thoracostomy,

pneumonia, and *Serratia marcescens* sepsis. After atracurium (total of 6572 mg over 6 days) was discontinued, her cough reflex and minimal spontaneous movements returned within hours. Profound, diffuse weakness was still present after tapering of sedatives and analgesics. Though the patient was capable of moving her head and eyes, upper and lower facial muscle weakness and incomplete horizontal and vertical eye movements were noted. Muscle wasting and decreased muscle mass were evident distally in all extremities. Weakness was also more prominent distally; strength in the upper and lower extremities was 2+/5. Diffuse tremor was observed. Electromyographic study revealed normal conduction velocities, no fasciculations, but small amplitude polyphasic motor unit potentials, consistent with a myopathic process or early reinnervation of a neuropathic process. Deep tendon reflexes were brisk (3+), equal, and not pathologic. Sensory function was normal. Sensory nerve conduction was completely normal with preservation of sensory evoked potential amplitudes. Repetitive 3-Hz and 24-Hz stimulation of the ulnar nerve demonstrated no decrement in response. CK and aldolase were normal at this time. An electroencephalogram and magnetic resonance scan of the head were normal. Neurology consultation concluded that these changes were consistent with postparalysis syndrome. Owing to progressive improvement in strength, a skeletal muscle biopsy was not obtained (patient refusal). The patient was weaned from mechanical ventilation with the trachea extubated on Hospital Day 37, discharged from the ICU on Day 40, and released from the hospital 58 days following admission. She required several additional weeks of rehabilitation and physical therapy to regain normal motor strength.

Discussion

Over 30 medical centers have reported prolonged weakness after the administration of steroid-based NMB drugs to ICU patients. We now report sustained weakness after administration of the benzylisoquinolinium NMB drug, atracurium, in two critically ill patients receiving concurrent corticosteroid therapy. There are no previous reports of persistent weakness (>12 h) after prolonged atracurium infusion and corticosteroids. Muscle biopsy was contraindicated in Patient 1 because of severe, sustained thrombocytopenia and in Patient 2 because of clinical improvement and patient refusal. Nonetheless, the manifestations of our patients were identical to previous reports of patients with weakness attributed to administration of the aminosteroid NMB agents, with or without coadministration of corticosteroids (7–10,12,14–16). Similarities include young ICU patients with prolonged exposure to NMB drugs, diffuse proximal and distal skeletal and respiratory muscle weakness persisting long after NMB drug withdrawal, a predominantly myopathic process on electromyography with nerve conduction and sensory function largely preserved, variable increases in serum creatine kinase concentration, and a slow clinical recovery.

Although myopathy has been described after extended administration of a NMB drug alone in neonates (17) or corticosteroids alone (15,18), the majority of reports describe concomitant drug therapy (NMB drugs and corticosteroids) (4-12,14-16). Thus, clinical weakness and myopathy may be caused by a drug interaction between corticosteroids and steroid-based NMB drugs, amplified by pharmacologic denervation. Although we are reporting the first prolonged weakness after infusion of atracurium and corticosteroids, the previous absence of such reports may reflect the more frequent use of vecuronium in ICU patients. There is speculation that the risk of prolonged weakness after an aminosteroid-NMB drug with concomitant corticosteroids is greater than the combination of benzyloquinolinium drugs and steroids (communication of FDA meeting, November 1992).

Patients with renal or hepatic dysfunction may be at increased risk for quadriplegia after NMB drugs (12). These drugs, administered by continuous infusion or intermittent bolus, may accumulate in these patients and produce persistent pharmacologic block at the neuromuscular junction (3). Ramsay et al. (16) propose that myopathy follows the administration of a "priming factor" (glucocorticoids, myotropic infections, sepsis) and a "triggering agent" (nondepolarizing NMB agent). We propose that these adverse drug events may be categorized into pharmacologic causes (accumulation of parent drug or drug metabolites at the neuromuscular junction) (3), physiologic causes (changes in acetylcholine receptor, affinity, or acetylcholine release) (19), and toxicologic causes (neuromyopathic injury to the muscle or nerve, usually associated with combined use of NMB drugs and corticosteroids) (16).

Finally, other causes of diffuse neuromuscular dysfunction must be considered in critically ill patients in the ICU. Drug-induced neurotoxicity, nutrition, toxins, demyelinating polyradiculoneuropathy (Guillain-Barré syndrome), or polyneuropathy of critical illness may cause diffuse skeletal muscle weakness in such patients (20,21). However, the polyneuropathy of critical illness is a combined sensorimotor neuropathy and tends to occur in elderly, extremely ill patients (20,21).

In summary, our report suggests that prolonged atracurium administration to patients receiving corticosteroids may result in protracted weakness similar to that previously observed with the aminosteroids, pancuronium and vecuronium. This occurred despite the use of peripheral nerve stimulation as a monitor. Our observations suggest that both pharmacologic classes of NMB drugs (aminosteroid and benzyloquinolinium), in the setting of concomitant corticosteroid administration, may lead to prolonged weakness and possibly myopathy. We urge caution in the use of NMB agents to facilitate mechanical ventilation in the ICU, particularly when corticosteroids are concurrently

administered, because current methods of nerve stimulation monitoring may not be able to prevent this complication. Neuromuscular block should be avoided if sedatives and analgesics can adequately facilitate mechanical ventilation.

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