
CASE REPORT



Prolonged Neuromuscular Weakness Following Concurrent Administration of Non-depolarizing Skeletal Muscle Blockers and High Dose Corticosteroids

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INTRODUCTION

Nondepolarizing neuromuscular blockers (NMBs) such as pancuronium and vecuronium are being used with increasing frequency in intensive care settings to facilitate mechanical ventilation in critically ill patients.¹ Recently, prolonged neuromuscular weakness following the discontinuation of NMBs has been reported in patients concomitantly treated with high dose corticosteroids for status asthmaticus.²⁻⁷ We describe such a case of muscular weakness possibly due to the concomitant use of vecuronium and high doses of hydrocortisone and methylprednisolone and review the literature on this topic.

CASE

A 42 year-old female presented to hospital with chills and increasing shortness of breath over several hours which was unresponsive to aerosol bronchodilators. The patient had a long-standing history of asthma which had been managed using only as needed salbutamol.

Her past medical history consisted of dermatomyositis diagnosed six to

seven years prior which had been treated in the remote past with steroids and azathioprine for two to three years with complete remission. She had not received steroids nor immunosuppressive therapy in the last two years. Two years earlier, the patient had suffered from viral pneumonia and in the past had undergone a cholecystectomy and a tubal ligation.

Review of systems was remarkable only for respiratory complaints. The patient had no known drug allergies. She was a smoker and had a family history of diabetes mellitus as well as asthma.

On examination she was noted to be in respiratory distress with a blood pressure of 163/101 mmHg, heart rate of 144 beats per minute, respiratory rate of 30 breaths per minute, and a temperature of 37.8°C. Her skin was noted to be pale and white. Examination of her chest revealed decreased breath sounds bilaterally, diffuse wheezing with a prolonged expiratory phase, and expiratory rhonchi throughout. She was able to only speak two to three words at a time due to shortness of breath, and had indrawing accessory

muscles. Heart sounds were normal and the remainder of the physical examination showed normal periphery and abdomen.

Arterial blood gases were as follows: PO₂ 72 mmHg, PCO₂ 65 mmHg, pH 7.27 and HCO₃ 28 mmol/L. The white blood cell count was elevated (18.0 x10⁹/L) with a predominance of neutrophils.

The patient was initially treated with methylprednisolone 125mg intravenously (IV), combined with salbutamol and ipratropium bromide by inhalation. Despite these measures, the patient showed no improvement and PCO₂ remained elevated. Salbutamol was then started IV without improvement and the patient was subsequently intubated, sedated with midazolam, and transferred to ICU where she was paralyzed with vecuronium.

She was continued on salbutamol and ipratropium bromide by inhalation. Hydrocortisone 250mg IV q8h, and on day two changed to methylprednisolone 40mg IV q12h was administered for two days before being reduced to 40mg daily. Midazolam initiated at 4mg/hr, and

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vecuronium, initiated at 5mg/hr, were both administered as continuous infusions and were adjusted periodically according to clinical status. The vecuronium infusion was run for six hours after which it was discontinued, while the midazolam continued for two more days before being weaned off.

On day two, the patient's creatinine phosphokinase (CK) level was reported to be elevated at 1101 U/L with MM fraction of 1073. The white blood cell count rose to $33.4 \times 10^9/L$, pneumonia was suspected and erythromycin was added to the regimen. Over the next two days, respiratory status became stable but hypercarbia persisted.

On day five, the patient developed acute wheezing with PCO_2 increasing to 99mmHg. This was treated with IV salbutamol, reinstatement of the vecuronium, and continuation of assisted ventilation. Following this, the patient again stabilized.

The CK decreased over the next few days with values on days five, six, and seven being 431, 192, and 139 U/L, respectively.

After 10 days, the patient was successfully extubated and transferred to the chest medicine floor. She was not dyspneic and had no wheezes on auscultation but her PCO_2 remained elevated up to 55-60 mmHg. Her alpha-1 antitrypsin was normal. The patient complained of weakness and deltoid and hip flexion weakness was confirmed on examination. The possibility of reactivation of the patient's dermatomyositis was considered and a neurology consult was obtained. The motor findings were confirmed, whereas sensation, tone, and deep tendon reflexes were normal. The weakness was attributed to ICU deconditioning and mild steroid myopathy, and not to a recurrence of dermatomyositis.

DISCUSSION

Several reports of continued paralysis following prolonged use of NMBs in asthmatics during mechanical ventilation have appeared in the literature.²⁻⁷ The patient in our case shares some of their common features.

In each case, the patient received high dose corticosteroids, most commonly hydrocortisone or methylprednisolone, concomitantly with a nondepolarizing NMB, either pancuronium or vecuronium. Upon discontinuation of mechanical ventilation and NMB therapy, patients experienced marked weakness of proximal and distal muscle groups in addition to respiratory muscle insufficiency which led to difficulty in weaning from the ventilator.⁷ Recovery of muscle strength tended to be complete within weeks to months. The serum CK levels in reported cases ranged from normal to up to 100 fold elevations indicating breakdown of muscle fibres.⁷ Consistent with this case, the CK levels in our patient were noted to be markedly elevated on the day following the administration of the steroids and vecuronium. Unfortunately baseline values were not available.

Critical care neuropathy was unlikely the cause of the weakness because of the absence of sensory changes and absence of sepsis and predisposing conditions such as multiple organ failure.^{8,9} Deconditioning, as suggested by neurology, was a possible etiologic factor but, by itself, could not explain the increased CK.² While dermatomyositis was also a concern this had not been active for several years prior to admission.

Both NMBs and corticosteroids have been associated with myopathy when given as single agents.¹⁰⁻¹³ However, many reports have involved patients who were receiving both of these agents suggesting that an

interaction between the two therapies was involved in the development of the myopathy.²⁻⁷

Animal models have been used in an effort to define the etiology of the interaction. Morphological examination of muscle biopsies from patients receiving high dose corticosteroids and NMBs demonstrate the loss of myosin which is similar to denervated animal models given high dose steroids.¹⁴ Denervation used in these models may mimic the disuse phenomena that occurs with NMBs. One study using denervated muscle fibre exposed to therapeutic dexamethasone doses demonstrated myosin loss within seven days.¹⁵ As well, regeneration of normal muscle function following reinnervation is delayed and similar to the clinical scenarios involving NMB and corticosteroids.

DuBois et al¹⁶ presented experimental data demonstrating that muscle denervation resulted in a rise in the number of glucocorticoid receptors in skeletal muscle cytosol within one day suggesting that the myopathy of muscle denervation may be amplified by corticosteroids.

However, there is not yet complete consensus on the interaction between NMBs and corticosteroids. This is likely due, in part, to the multiplicity of factors in the critical care environment which may influence the development of myopathy. Zochodne et al¹⁷ recently reported electrophysiologic findings in seven intensive care unit patients who developed an acute myopathy in association with the use of NMBs. Only some of those patients had received corticosteroids. This group suggested that the corticosteroid may act as a potentiating agent in the toxic effect triggered by NMBs.

Theoretically, all NMBs could produce these effects when combined with corticosteroids. However, the majority of reported cases have

involved pancuronium or vecuronium with only two cases to date being reported with atracurium.^{8,18,19} Whether this is due to the relatively limited use of atracurium in the critical care setting, chemical structural differences or differences in the clearance of parent drug or metabolites is unknown but requires further study.^{1,8}

As critically ill patients are often subjected to combination therapy with NMBs and high dose corticosteroids, measures should be taken to prevent and minimize this effect. In asthmatic patients, corticosteroids should be prescribed at the lowest effective dose, and NMBs added only if sedation and analgesia are contraindicated or unsuccessful in reducing patient agitation sufficiently to enable mechanical ventilation. Since the myopathy may be related to total dose of NMB, the lowest effective dose should be used.²⁰ This dose of NMB can be determined with the aid of a peripheral nerve stimulator if this technology is available.²¹ Minimizing the use of other medications which may have effects on neuromuscular function such as aminoglycosides, vancomycin, verapamil, quinidine, and inhalational anesthetics may be prudent.²² As well, monitoring serum CK concentrations may be helpful although the usefulness of CK elevation as an early injury marker has not been established.

Pharmacists should be aware of the potential for the development of a myopathy in patients receiving high dose corticosteroids and NMBs. ☒

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