Case in Point

Steroid-Induced Myopathy and Associated Postoperative Complications

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The authors report a case of an elderly man with a bladder tumor who underwent a cystoscopy with general anesthesia. At the conclusion of the procedure, the patient was in a weakened state and had to be reintubated and supported on mechanical ventilation. The patient was ultimately diagnosed with steroid-induced myopathy exacerbated by the use of a neuromuscular blocking agent.

The field of anesthesiology has witnessed an abundance of technical advances in recent years. These advances, specifically involving pharmacology and awareness of drug-drug interactions, are helpful to clinicians. In addition, pharmacists have provided excellent guidance to clinicians and providers, helping them identify potential complications for patients who are at risk for weakness after extubation, especially in an elderly population with many comorbidities. There are several common reasons for postoperative complications in regards to weakness, including incomplete reversal with neuromuscular blocking agents (NMBAs), bronchospasm and fatigue due to comorbidities and age, and medication interactions.

A literature search for steroid-induced myopathy and hypothalamic-pituitary-adrenal (HPA) suppression caused by steroids returned a great number of studies, but most articles were published decades ago. Furthermore, there is extensive research about steroid-induced myopathy in the critical care perioperative patient, but rarely does it encompass surgical patients. Although the interaction with NMBAs is well-known, especially in critical care patients, there is significantly less published data about treatment and supportive care in postoperative patients. More recent trials were performed in laboratories. These trials attempted to explain the underlying mechanism of the adverse effects (AEs) related to steroid-induced myopathy.

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CASE REPORT

A 76-year-old African American bilateral amputee presented with gross hematuria. In 2009, the patient had a cystoscopy, which revealed malignant bladder tumors. The patient had a long history of noncompliance and acted against medical advice discharges. Several attempts to get the patient to surgery in 2009 failed due to the patient's poor compliance and comorbidities. The patient resided in an extended-care facility, where care and medications were continuously monitored. The patient's past medical history was significant for bilateral above the knee amputations, malignant bladder neoplasms, chronic obstructive pulmonary disease (COPD), osteoarthritis, type 2 diabetes, gastroesophageal reflux disorder, dyslipidemia, hypertension, and frequent urinary tract infections. The patient continued to smoke and had a 56 pack-year history; alcohol use was discontinued in 2004. The patient also had a surgical history of bilateral femoral popliteal bypass vein grafts, multiple cystoscopies, multiple transurethral bladder tumor resections, and history of percutaneous transluminal coronary angioplasty with 2 stents placed in 2009. The patient had no known drug allergies. Medications upon presentation included tramadol, lisinopril, amlodipine, sulfamethoxazole/trimethoprim, albuterol/ipratropium metered-dose inhaler, simvastatin, glipizide, and metformin. The patient also received a steroid taper in August 2010, to be completed over 12 days. The taper was as follows: prednisone 40 mg daily for 3 days, then 30 mg daily for 3 days, then 20 mg daily for 3 days, and finally, 10 mg daily for 3 days.

On the morning of surgery in August 2010, the patient was afebrile with stable vitals. An electrocardiogram (EKG) showed sinus rhythm with inferior and anterolateral ischemia, which was unchanged from the previous EKG. The only significant change in the laboratory values at the time of surgery was the prostate specific antigen at 84.54 ng/mL; all other laboratory values were within normal limits. Since the patient was on sulfamethoxazole/trimethoprim and lisinopril, it is important to note that preoperatively, the patient's serum creatinine (SCr) level was 1.1 mg/dL and the potassium level was 5.3 mmol/L.

The patient had no indications of renal dysfunction, although the potassium level was at the upper limit of normal. It's important to note that the patient's sodium level was 135 mmol/L both pre- and postoperatively. The patient was classified as an American Society of Anesthesiologist (ASA) Class 4 patient. The patient was taken to the operating room, and standard ASA monitors (EKG, blood pressure [BP], oxygen saturation by pulse oximeter, and temperature probe) were attached. In the supine position, the patient was preoxygenated, and general anesthesia was induced. The IV induction included midazolam 2 mg, lidocaine 100 mg, fentanyl 100 mg, propofol 100 mg, and succinylcholine 100 mg. The intubation was atraumatic and uneventful with an endotracheal tube 8.0 mm internal diameter being secured at 21 cm at the lips. The patient was placed in the lithotomy position and the train of four (TOF) was 2 of 4. The patient was given vecuronium 3 mg, hydrocortisone 100 mg (equivalent to 25 mg of prednisone), and ceftriaxone 1 g. Over the next 6 hours of surgery, the patient received a total of vecuronium 10 mg. The estimated blood loss during the surgery was about 250 cc. A total of 2,500 cc of lactated ringers was administered during the procedure. The patient's urine output was unable to be accessed as a cystoscope was inserted in the urethra.

At the conclusion of the surgery, the TOF was 1 of 4, so the NMBA was reversed with neostigmine 5 mg and glycopyrrolate 0.8 mg. The patient was extubated with the patient taking tidal volumes of 400 cc to 425 cc. However, 12 minutes after the extubation, the patient's oxygen saturation decreased to 84%. The decision was made to reintubate the patient with IV lidocaine 100 mg, IV propofol 100 mg, and IV succinylcholine 100 mg. On reintubation, the patient's tidal volumes were found to be 175 cc to 225 cc. The oxygen saturation by pulse oximeter and tidal volumes subsequently improved to 94% and 450 cc, respectively.

The intubated, monitored patient was transported to the surgical intensive care unit (SICU) and continued on mechanical ventilation. After transfer, an electrolyte panel showed all values within normal limits except for an elevated potassium level of 6.9 mmol/L and a slightly low bicarbonate level of 21 mmol/L. During this time, the patient's BP was about 70/50. The attending ordered an IV normal saline bolus of 500 cc, which was repeated twice (total = 1,500 cc), 2 units of packed red blood cells, and IV sodium bicarbonate. Following this, the patient's BP increased to about 120/70 and remained at goal. The potassium resolved within 2 hours to within normal limits without further elevations. Intravenous hydrocortisone 100 mg every 6 hours was also ordered. Ultimately, after 4 doses of IV hydrocortisone and 28 hours of postoperative ventilation, the patient was extubated without further complication.

DISCUSSION

Steroid-induced myopathy and HPA suppression are known concerns for patients receiving high-dose or long-term steroids. To further explore the association, a PubMed literature search was performed using the following keywords: vecuronium, NMBAs, myopathy, muscle atrophy, glucocorticoids, steroid-induced myopathy, and perioperative steroids. The results confirm that steroids are known to promote catabolism and proteolysis, which potentiates myopathy.[1,2] Based on this review, this effect is dose related and is commonly associated with daily doses of more than 40 mg to 60 mg of prednisone.[3] Although the time to onset is unknown, cases of muscle weakness associated with steroid use have been seen within 2 weeks of administration of steroids at the previously mentioned doses.[3] The exact mechanism of this myopathy is unknown, but there are 3 possible pathways. The first is associated with the glucocorticoids' activation of the ubiquitin-dependent proteolytic system. The activation of this system suppresses Akt1, which signals for protein kinase activity.[4,5] Ultimately, muscle breakdown activity is increased.[4,5] This system is further activated by sepsis, severe systemic illness, and polyneuropathy.[6]

The second mechanism is related to glucocorticoids' inhibition of glycolytic activity, which increases intramuscular glycogen concentrations.[7] This will impair carbohydrate metabolism, ultimately increasing muscle atrophy.[2,7] Last, glucocorticoids inhibit protein synthesis, resulting in a net increase of myofibrillar and protein degradation.[1,2] Eventually, there is a loss of thick filaments of the skeletal muscle.[1,2] This loss is thought to

be exacerbated by the concomitant use of steroids and NMBAs.[8] Data published by Larsson and colleagues showed that surgical denervation of skeletal muscles combined with high-dose steroids cause thick filament loss and myopathy.[8] This loss is shown to be worse in combination than with each agent alone.[8]

Most studies about steroid use and the long-term administration of NMBAs report atrophy and myopathy of the muscles in the extremities. However, there are more recent studies showing atrophy of the diaphragm muscle associated with NMBAs.[9,10] Several trials have shown that diaphragm immobilization in rats for as little as 18 hours resulted in a decrease in diaphragmatic force, muscle atrophy, and an increase in ubiquitin-proteasome proteolytic activity.[9,10] It is important to note that the effect on the ubiquitin-proteasome proteolytic activity is also thought to be affected by steroid use. Levine and colleagues published preliminary data in 2008 suggesting that these findings may also be applicable to humans.[11]

Another potential effect of steroids, which could possibly increase difficulty in extubation, is the HPA suppression. Due to suppression of this pathway by exogenous steroids, during surgery adrenal insufficiency results because of the inability to respond to the stimulus to release cortisol.[12] Furthermore, prostacyclin production is inhibited in the vascular endothelium, causing a decrease in vascular tone.[13] Signs of this impairment include vasodilation and hypotension.[13]

Various studies report the incidence of adrenal insufficiency to be about 0.01% in urologic surgical procedures.[14] Patients are considered at risk if they received doses of prednisone 20 mg or more (or the equivalent) for more than 5 days prior to titration.[12] Recovery of axis function depends on the length of therapy and dosage before tapering.[15] For example, studies showed that patients receiving a dose of prednisone 20 mg or more for 1 year to 10 years saw the resolution of adrenal insufficiency within 1 month.[15] Studies further showed that shorter courses recover more rapidly; one study showed that a patient treated for 5 days recovered within 5 days.[16]

Current guidelines on perioperative steroid use are still somewhat controversial due to the potential AEs of steroids. Currently, the recommendations for perioperative steroid use consider the type of surgery and the length of surgery when deciding on the dose and duration of the steroid.[17,18] The cortisol secretory rate in response to general anesthesia and surgery rarely exceeds 200 mg per day.[17,18] For minor surgical stress, the suggested glucocorticoid target is 25 mg of hydrocortisone preoperatively with the patient resuming his or her usual therapy on postoperative day 1.[17,18] Most patients have normalized circulating cortisol concentrations within 24 to 48 hours postsurgery; thus, there are no data showing that patients will need more glucocorticoid coverage than that required by the surgical stress.[17] Furthermore, for patients with complications postoperatively, the recommendations are to provide glucocorticoid coverage appropriate for the postoperative stressor.[17]

Recent articles recommend testing for this suppression prior to surgery in patients who may be at risk based on their history of steroid use.[12,17] Studies have suggested that the 2 laboratory studies to use are the cortisol test and the adrenocorticotrophic hormone (ACTH) test.[12,17] Preprocedural cortisol levels are thought not to be reliable, because some patients with low levels have normal ACTH stimulation results.[12,17] This can result in unnecessary perioperative use of steroids, which is associated with a decrease in wound healing postoperatively.[12] Adrenocorticotrophic hormone tests assess adrenocortical function preoperatively but do not show outcomes.[12,17] Overall, the evidence for testing of HPA suppression is conflicting, yet testing is still recommended by most authors.

Although this patient is elderly and had lung disease, the patient's previous surgeries did not have this same complication. Furthermore, the time of symptom onset in regards to the reversal with the NMBA was greater than the half-life of the NMBA and greater than the time needed for appropriate reversal with neostigmine and glycopyrrolate. This led to the detailed discussion about a potential drug-drug interaction with steroids and NMBA in regard to muscle atrophy, which was potentially worsened by HPA suppression. Most likely this patient's case was complicated by the more severe AEs of a recent prednisone use.

In this patient, muscle myopathy and possibly atrophy were most likely present due to the high-dose steroids used for COPD exacerbations. Although the steroid treatments were short-term, this patient had a long history of intermittent therapy with prednisone and methylprednisolone. It is possible that inactivity induced by NMBAs for his procedure worsened the potentially already fragile state of the diaphragm muscle, thus creating the need for further respiratory support. His symptoms during initial extubation were consistent with the pathologic process of muscle atrophy associated with both NMBAs and steroids as reported in the literature. The patient's

renal function was stable based on the SCr level, so it is more likely that the elevated potassium level was a sudden increase. The elevated potassium level and hypotension experienced in the SICU are consistent with HPA suppression due to steroid use. It is possible that the elevated potassium level could exacerbate the muscle weakness created from steroid use and then NMBA. Because the patient's sodium level was within normal limits preoperatively, Addison's disease and Cushing's disease can be ruled out.

Furthermore, it is important to note the recent warnings and updated dosing and safety information published in 2011 about a drug-drug interaction between amlodipine and simvastatin. Per updated labeling, simvastatin doses should be limited to 20 mg when taking concomitant amlodipine due to an interaction causing an increased risk for myalgia and rhabdomyolysis.[19] Most data about myalgia showed an association with pain in the extremities, specifically legs, and patients with rhabdomyolysis have some degree of renal dysfunction.[19] This patient's renal function was stable, and there was no documentation pertaining to myalgia in the patient's extremities. Although the use of succinylcholine could increase the patient's risk for rhabdomyolysis, the updated labeling information does not comment on diaphragmatic muscle.

CONCLUSION

The current recommendations on steroid-induced myopathy include perioperative steroid administration, which occurred in this patient. Unfortunately, although the medication and dose preoperatively were within the current guidelines, it did not provide appropriate coverage to prevent anesthetic complications or reintubation. More research is needed to support the use of HPA suppression testing. It may lead to a correlation of the extent of suppression with other serious AEs of steroids, such as myopathy. Furthermore, a multidisciplinary team proved to be crucial in the diagnosis and treatment of this patient, especially in regards to drug-drug interactions. Finally, this case supports providers performing thorough medication reconciliations with patients, which is already the standard of care. It is imperative that providers are aware of potentially serious outcomes associated with drug-drug interactions, such as those involving a combination of NMBAs with steroids. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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