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Letters to the Editor

Anesthetic Concerns in a Patient With Addison Disease

To the Editor:

Adrenal glands normally produce glucocorticoids, mineralocorticoids, and androgens. Glucocorticoids affect the metabolism of carbohydrates, fats, and proteins and are important in mediating the response to fasting and stress, whereas mineralocorticoids are essential for electrolyte and fluid balance.[1] Adrenal insufficiency, resulting in the inadequate production of one or more of these hormones, can be primary, secondary, or tertiary. The inability of the adrenal glands to produce an adequate amount of hormones despite normal or increased adrenocorticotropin hormone (ACTH) levels is known as primary adrenal insufficiency. In secondary adrenal insufficiency, caused by insufficient ACTH production by the pituitary gland, aldosterone secretion is maintained and the fluid and electrolyte disturbances are less marked. Tertiary adrenal insufficiency, on the other hand, is associated with insufficient corticotrophin-releasing hormone (CRH) production by the hypothalamus.[1]

Primary adrenal insufficiency, also known as Addison disease, is associated with adrenal cortical destruction and results in inadequate secretion of adrenal cortical hormones.[2] It is a rare endocrine disorder with an incidence of 0.8 cases per 100,000 population. The role of cortisol, the main hormone affected in Addison disease, in coping with stressful situations such as surgical stress is well known. Such situations can prove to be a major threat to life in persons with undiagnosed and untreated primary adrenal insufficiency.[3]

A 36-year-old female weighing 79 kg reported to our hospital with a chief complaint of nonunion of a right-sided femur shaft fracture. Surgery to place hardware with bone grafting was scheduled. Her Addison disease had been diagnosed 17 years earlier, and she took regular steroid supplements: oral prednisolone 5 mg once per day. Her preoperative laboratory results and baseline vital parameters were within normal limits, and she had no previous episodes of orthostatic hypotension. The night before the scheduled surgery, the patient received intravenous (IV) normal saline 2 mL/kg/h to maintain adequate hydration. Tablet prednisolone of 5 mg was continued until the morning of surgery.

On the day of the surgery, the patient's heart rate, electrophysiology, blood pressure, and oxygen saturation were monitored in the operating room. Injection hydrocortisone 100 mg IV was given preoperatively, followed by an infusion of 4 mg/h. Combined spinal-epidural anesthesia used 15 mg of 0.5% heavy bupivacaine in the subarachnoid space and an epidural test dose of 3 mL of 2% xylocaine with adrenaline. The patient was positioned with padding applied to all pressure points.

During the 3-hour surgery, she lost approximately 800-900 mL of blood and received 1.5 L of lactated Ringer's solution, 0.5 L of hydroxyethyl starch in sodium chloride, and 1 unit of packed red blood cells. Intraoperatively, the patient also received 70 mg of 0.5% bupivacaine epidurally. Her intraoperative course was uneventful, with no episodes of significant hypotension or electrolyte disturbances. Postoperative analgesia was an epidural infusion of 0.125% bupivacaine with 2 μg/mL fentanyl at 6 mL/h for 48 hours. Injection hydrocortisone infusion of 4 mg/h was continued on postoperative day 1. Hydrocortisone 50 mg IV every 8 hours followed on postoperative days 2 and 3. The dose was tapered to 25 mg IV every 8 hours on postoperative days 4 and 5. Thereafter, the patient began oral steroids and was discharged from the hospital on postoperative day 7.

Addison disease is commonly caused by the autoimmune destruction of the adrenal gland and tuberculous adrenalitis. Both cortisol and aldosterone levels are deficient in Addison disease, leading to weakness, dehydration, and the inability to maintain adequate blood pressure or respond to stress. Its symptoms are vague and nonspecific, with 25% of cases recognized only during periods of stress such as infection, trauma, or surgery. The disease is diagnosed mainly based on cortisol and ACTH levels along with ACTH stimulation tests (eg, the Synacthen test). Treatment includes lifelong hormonal replacement therapy.[3-5]

Anesthetic management of patients with Addison disease is challenging and fraught with difficulties. Patients with unsuspected Addison disease who present for surgery may develop Addisonian crisis during the perioperative period, the clinical manifestations of which vary from mild, nonspecific constitutional symptoms to the presence of profound shock unresponsive to vasopressor therapy. Alternatively, patients on chronic steroid supplementation may have systemic manifestations of long-term steroid therapy, including hypertension, skin atrophy, myopathy, arthritis, osteoporosis, coronary artery disease, secondary diabetes mellitus, suppressed immune response, and impaired wound healing.[5] Thus, to manage these patients, the anesthesiologist must

take a complete history and perform a detailed general and systemic physical examination. In addition, special care and vigilance are needed during transport, positioning, and administration of regional anesthesia. Patients taking exogenous steroids may have inadequate reserves to meet the demands of perioperative stress. Various recommendations exist regarding perioperative steroid supplementation.[2,4-6]

In general, for minor surgical procedures, IV hydrocortisone 25 mg intraoperatively is usually recommended. For major surgery, the commonly followed perioperative steroid regimen is IV hydrocortisone 75-150 mg intraoperatively or dexamethasone 0.75 mg preoperatively and 3 mg intraoperatively. In cases of increased stress and acute adrenal insufficiencies, patients may receive IV hydrocortisone 100 mg as a bolus dose followed by an infusion of 100-200 mg given over 24 hours (ie, approximately 4-8 mg/h). Some authors recommend postoperative hydrocortisone 50 mg every 8 hours for 24 hours followed by 25 mg every 8 hours for 24 hours, whereas others recommend hydrocortisone 50 mg every 8 hours for 3 days, followed by a normal dose on postoperative day 4.

Additionally, these patients often present with potassium derangement, requiring judicious perioperative fluid replacement. Adequate postoperative pain relief is also vital because increased stress from inadequate pain control can lead to crisis.

Although Addison disease is a rare disorder, people with the disease can lead normal active lives when properly treated and monitored with additional steroid supplementation during periods of stress. In the perioperative period, these patients require high supplemental doses of steroids. Vigilance in administering steroids and their judicious use may be key factors in the safe conduct of anesthesia in this group of patients.

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Ophthalmic Erythromycin Chronologically Linked to Acute Pancreatitis

To the Editor:

Although occurrences are rare, erythromycin has been reported to cause acute pancreatitis through both oral and intravenous routes.[1-4] A literature search indicates that acute pancreatitis has not been reported in patients receiving erythromycin via ophthalmic ointment.

An 86-year-old male with a history of bilateral corneal abrasions being treated with erythromycin ophthalmic ointment for 3 days presented to the emergency department with complaints of abdominal pain and nausea but no vomiting. Laboratory results were significant for elevated serum lipase, and a computed tomography (CT) scan of the abdomen found fat stranding around the head of the pancreas. Based on the patient's symptoms, CT scan findings, and elevated lipase level, the gastroenterology (GI) team diagnosed acute pancreatitis but was unable to identify any source other than erythromycin for the condition. Consequently, a presumptive diagnosis of erythromycin-induced acute pancreatitis was made. The patient improved with conservative and symptomatic treatment and was started on another ophthalmic antibiotic to treat his corneal abrasions.

Acute pancreatitis is generally caused by alcohol use or biliary tract stones. Our patient had no history of alcohol use, and a work-up was unremarkable for abdominal tumors or biliary tract pathology. Other etiologies—such as drugs, toxins, and insect bites—may be considered if a clear etiology of abdominal pain in the setting of elevated lipase levels is not evident. In reality, medications play a more important role in the development of acute pancreatitis than previously thought, and more than 120 drugs have been implicated as causing pancreatitis.[5]

The mechanism of the pathogenesis described by Tenenbein and Tenenbein[6] suggests a dose-related stimulation of motilin receptors (erythromycin working as an agonist), resulting in increased contraction of the GI tract, including the gallbladder and the

sphincter of Oddi. Contractions of the sphincter of Oddi cause the reflux of bile into the pancreas, resulting in pancreatitis.[6] Our patient developed acute pancreatitis after using erythromycin ophthalmic ointment. This preparation is known to have systemic absorption and to result in side effects similar to those caused by oral erythromycin preparations. We recommend maintaining a high index of suspicion in patients presenting with acute pancreatitis with recent initiation of erythromycin. Removal of the drug usually leads to the resolution of symptoms.

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Methotrexate-Induced Neurotoxicity: Getting the Word Out

To the Editor:

Methotrexate-induced neurotoxicity (MIN) can occur in patients receiving intrathecal methotrexate for the treatment of primary central nervous system lymphoma and hematologic malignancies. However, few case reports describe MIN following low-dose oral and subcutaneous administration, as typically used in treating rheumatology patients. We report 2 patients who displayed acute onset neurologic changes suggestive of MIN.

The first patient, a 57-year-old African-American female with a 1-year history of seropositive rheumatoid arthritis (RA), presented to the pulmonology clinic with increasing shortness of breath following recent treatment for bronchitis. During the appointment, she developed an intermittent headache, stuttering, and bilateral upper extremity action tremor. She rated the pain associated with the headache at 10/10 and reported recent paresthesias and tremor of the upper extremities. Methotrexate (15 mg orally per week) and adalimumab (40 mg per week) had been stopped 3 weeks prior to the current presentation because of acute bronchitis.

Neurologic consultation was obtained to assess her acute neurologic changes. Magnetic resonance imaging (MRI) of the brain with and without contrast was normal. Lumbar puncture revealed a raised opening pressure of 25 mmHg and yielded 3 mL of clear, straw-colored cerebrospinal fluid (CSF) containing 2 white blood cells per mm^3, 110 red blood cells per mm^3, and an elevated protein of 68 mg/dL. Neurology consultants suggested that the patient might have been experiencing MIN. As noted above, the patient's last methotrexate dose was 3 weeks before the onset of her neurologic changes. Rheumatology consultants agreed to further withhold methotrexate and adalimumab. One week following discharge, the patient reported that her headaches, stuttering, and tremor had spontaneously resolved.

The second patient was a 51-year-old African-American female with severe erosive deforming RA (rheumatoid factor and cyclic citrullinated peptide antibody positive) and systemic sclerosis. She reported stuttering since starting methotrexate. She initially received a dose of 7.5 mg weekly that was slowly increased to 25 mg weekly over the course of 2 years. Methotrexate was discontinued because of extreme fatigue. Although the stuttering improved after the cessation of methotrexate, it never completely resolved. She was referred to a neurologist for further investigation. However, testing did not reveal the cause of her stuttering. Lumbar puncture showed negative CSF oligoclonal bands. The CSF immunoglobulin G synthesis rate was 0. The angiotensin-converting enzyme level of the CSF was <4, the Venereal Disease Research Laboratory-CSF test was nonreactive, glucose was 58 mg/dL, protein was 17 mg/dL, and she had no red blood cells or white blood cells in the CSF. The patient also had a negative MRI of the brain as well as magnetic resonance angiography. Although drug-induced stuttering usually re-

solves following cessation of the offending medication, MIN could not be ruled out.

MIN is manifested by a variety of symptoms and signs. Cases of speech difficulty, including aphasia and dysarthria, have been reported in patients who received intrathecal methotrexate.[1,2] Patients receiving high-dose systemic intravenous therapy (8-9 g/m^2) developed behavioral disturbances and sensorimotor deficits indicative of encephalopathy.[3]

One case of neurotoxicity following subcutaneous methotrexate has been reported.[4] The patient experienced fluctuating dysarthria, dysmetria, and ataxia with concomitant pneumonitis that all spontaneously resolved after the cessation of methotrexate. Several cases have been reported in patients receiving low-dose oral methotrexate, with reversible symptoms such as word-finding difficulty, unilateral weakness, headaches, and leukoencephalopathy.[5-8]

While the pathogenesis of MIN remains elusive, 1 hypothesis suggests that the disruption of folate metabolism, causing homocysteine toxicity, is the cause of MIN.[9] Consequently, excessive excitation of N-methyl-D-aspartate (NMDA) receptors in the brain results in neurologic changes and seizure activity.[9] Few studies have measured serum and CSF levels of methotrexate in patients experiencing symptoms of neurotoxicity. However, when drug levels were measured, they were within normal limits.[3]

Thus far, there is no definitive treatment for MIN. Dextromethorphan has shown promise in a study involving 5 patients who experienced complete resolution of their symptoms.[10] Dextromethorphan, a noncompetitive antagonist of NMDA receptors, prevents excitation by excess homocysteine and its metabolites.

Because of the rarity of low-dose MIN, determining the risk factors involved is difficult. The majority of cases involved females, with only 1 male patient reported. This result may reflect the female predilection for autoimmune disease. The age of the patients ranged from 49-68 years. The cumulative dose does not appear to be a factor because of the wide range of doses and treatment durations. The case involving subcutaneous administration occurred after 6 weeks of treatment, a mere cumulative dose of 90 mg.[4] The case reports involving encephalopathy involved cumulative doses of 2,700-5,200 mg.[5,6] The 2 patients who died received cumulative methotrexate doses of 500 and 780 mg.[7,8]

The outcomes of MIN can range from complete resolution to death. Because of the paucity of studies surrounding this adverse drug reaction, elucidating risk factors that may predispose patients to MIN is difficult. Although this adverse effect is rare, clinicians should remember it when treating patients with methotrexate for rheumatologic disease.

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