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ISMP Adverse Drug Reactions

Ciprofloxacin-Induced Syndrome of Inappropriate Antidiuretic Hormone

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Complex Regional Pain Syndrome After Tetanus Toxoid Injection

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The purpose of this feature is to heighten awareness of specific adverse drug reactions (ADRs), discuss methods of prevention, and promote reporting of ADRs to the US Food and Drug Administration's (FDA's) MedWatch program (800-FDA-1088). If you have reported an interesting, preventable ADR to MedWatch, please consider sharing the account with our readers. Write to Dr. Mancano at ISMP, 200 Lakeside Drive, Suite 200, Horsham, PA 19044 (phone: 215-707-4936; e-mail: mmancano@temple.edu). Your report will be published anonymously unless otherwise requested. This feature is provided by the Institute for Safe Medication Practices (ISMP) in cooperation with the FDA's MedWatch program and Temple University School of Pharmacy. ISMP is an FDA MedWatch partner.

CIPROFLOXACIN-INDUCED SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE

A 68-year-old Caucasian woman was seen in the emergency department (ED) in 2008 reporting slight fatigue, nausea, and vomiting. The patient's past medical history included hypertension, hypercholesterolemia, atrial fibrillation, and gastroesophageal reflex disease (GERD). Her home medications included diltiazem, warfarin, atorvastatin, esomeprazole, and losartan. Her medications had been at their current dosages for the past 6 months. She had been treated for a sinus infection with amoxicillin/clavulanate approximately 2 weeks prior to her ED visit, but she did not tolerate the medication well. On her return visit to her physician, it was discovered she had a urinary tract infection. Her physician then prescribed ciprofloxacin 500 mg twice daily and discontinued her amoxicillin/clavulanate. The patient's lab results in the ER were significant for the following: sodium 104 mEq/L (reference range, 135-147 mEq/L), serum osmolality 221 mOsm/kg (reference range, 275-299 mOsm/kg), urine osmolality 236 mOsm/kg (reference range, 50-1200 mOsm/kg), blood urea nitrogen (BUN) 16 mg/dL (reference range, 7-20 mg/dL), and creatinine 0.49 mg/dL (reference range, 0.6-1.4 mg/dL).

The patient's ciprofloxacin was discontinued upon admission, because the patient did not exhibit any current signs of infection. The medical team decided to correct her serum sodium by approximately 10 mEq/L during the first 24 hours and by 18 mEq/L in the first 48 hours. This approach was

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undertaken to prevent central pontine myelinolysis (CPM), which can occur due to rapid correction of hyponatremia. CPM is brain cell dysfunction caused by the destruction of the myelin sheath covering nerve cells in the middle of the brainstem. The destruction of the myelin sheath that covers nerve cells prevents signals from being properly transmitted from one nerve to another. The patient's sodium was increased; by day 8 of her hospital stay, her sodium was 133 mEq/L and she was discharged.

The patient, now 72 years of age, returned to her physician in 2012 with complaints of dysuria. After a urinalysis, she was diagnosed with a urinary tract infection. She was prescribed ciprofloxacin 500 mg twice daily. Three days later, she returned to her physician complaining of symptoms similar to her last hyponatremic episode: general fatigue and feeling slower than usual. She requested that her physician check her sodium. She was called with the result the next morning and instructed to go to the ED because her sodium was 108 mEq/L. The patient reported that she had been feeling weaker since she was started on ciprofloxacin and had been getting progressively weaker. When she was examined, she was noted to have slowed speech but she was alert and oriented. Her chronic medications remained the same from her prior admission 4 years earlier with the addition of hydrochlorothiazide and sotalol.

On admission, her laboratory results were sodium 109 mEq/L, serum osmolality 222 mOsm/kg, urine osmolality 251 mOsm/kg, BUN 8 mg/dL, and creatinine 0.51 mg/dL. Because the patient had symptomatic hyponatremia, she was started on 3% NaCl at 30 mL/h. After about 50 minutes, her sodium was found to be correcting too quickly, and there were again concerns of CPM. The patient was only in the hospital for 3 days and was discharged with a sodium level of 133 mEq/L.

This patient had repeated occurrences of syndrome of inappropriate antidiuretic hormone (SIADH) following reexposure to ciprofloxacin. She was hyponatremic and hypotonic with her serum osmolality lower then her urine osmolality. However, the patient continued natriuresis with no edema and no signs of dehydration, and her BUN and creatinine were normal and were at her baseline on both admissions. The author evaluated this adverse event using the Naranjo scale; the event scored an 8, which indicated that the adverse event was probably caused by the patient's ciprofloxacin.

A review of the literature reveals 3 published cases of quinolone-induced SIADH (Yam FK et al, Adker D et al, and Mussig K et al), with 1 case involving ciprofloxacin and 2 cases involving moxifloxacin. The age range of the patients experiencing SIADH was between 66 and 73 years, leading one to suspect that elderly patients might be at higher risk for this adverse effect. The duration of quinolone exposure prior to SIADH ranged from 2 days to 1 week. The patients' sodium ranged from 104 to 113 mEq/L and serum osmolality ranged from 221 to 265 mOsm/kg.

The author theorized that the possible mechanism by which ciprofloxacin could cause SIADH is initially due to the fact that ciprofloxacin is lipophilic and can cross the blood-brain barrier. There have been in vitro data indicating that fluoroquinolones have the potential to bind to gamma aminobutyric acid and N-methyl-D-aspartate receptors, and stimulation of these receptors have been shown to play a role in antidiuretic hormone (ADH) synthesis and release. So the likely mechanism through which ciprofloxacin causes SIADH could be by stimulating the release of ADH from the central nervous system. Given the short half-life of ADH, removal of the offending agent can lead to a rapid drop in ADH levels.

Babar SM. SIADH associated with ciprofloxacin. *Ann Pharmacotherapy.* 2013;47(10):1359-1363.

Yam FK, Eraly SA. Syndrome of inappropriate antidiuretic hormone associated with moxifloxacin. *Am J Health Syst Pharm.* 2012;69:217-220.

Adler D, Voide C, Thorens JB, et al. SIADH consecutive to ciprofloxacin intake. *Eur J Intern Med.* 2004;15:463-464.

Mussig K, Schnauder G, Morike K. Severe and symptomatic hyponatremia after moxifloxacin intake. *Neth J Med.* 2009;67:197.

ANAPHYLACTIC SHOCK DUE TO THROMBOLYTIC ADMINISTRATION

In 2011, a 61-year-old female presented to the ED with an episode of acute-onset facial weakness, right hemisensory loss with deficits, and a National Institutes of Health (NIH) Stroke Scale score of 4. The patient was deemed appropriate for recombinant tissue plasminogen activator (r-tPA) and received standard dosing. Within 30 minutes of initiating r-tPA, the patient developed acute-onset hypotension with a systolic blood pressure (SBP) reaching as low as 44 mm Hg. Her extremities were hypoperfused with a cold and clammy appearance. The intravenous r-tPA was immediately discontinued, and aggressive fluid resuscitation was started along with the administration of diphenhydramine 50 mg intravenously (IV). The patient's SBP reached 120 mm Hg,

and she did not display allergic symptoms such as rash or oropharyngeal swelling. An emergency CT scan excluded an intracerebral hemorrhage, and her hemoglobin was unchanged from her baseline value of 18 g/dL. The patient had received *Omnipaque* iodinated contrast media as part of a CT angiogram and CT perfusion scan 60 minutes prior to her hypotensive episode. However, the patient had received contrast agents as part of a percutaneous coronary intervention previously without any documented adverse event. No further episodes of hypotension were noted during her hospital stay, and she was discharged without any residual neurological effects on hospital day 3.

In 2013, the patient again presented with an episode of right-sided hemiparesis, hemisensory loss, and an NIH Stroke Scale score of 3. The patient received a noncontrast CT scan and was determined to be an appropriate candidate for IV r-tPA. Because of the patient's prior reaction to r-tPA, she was premedicated with IV diphenhydramine 50 mg and hydrocortisone 100 mg. A 1 mg test dose of r-tPA was administered to the patient; no reaction was noted after several minutes, after which standard dose r-tPA was administered. After 40 minutes of IV r-tPA, the patient developed systemic hypotension with SBP values reaching 60 mm Hg. The r-tPA was discontinued and IV fluids and a single dose of 0.1 mg of IV epinephrine were administered with modest benefit. A continuous epinephrine infusion was initiated at 0.02 mcg/kg/min, and the patient's blood pressure reached normotensive. The patient remained in the hospital for 24 hours and was again discharged without any residual neurological deficits.

The authors queried the US Food and Drug Administration Adverse Event Reporting System (AERS) for information on other possible anaphylactic reactions to thrombolytic agents. They reviewed 924 adverse event cases over an 8-year period and acquired detailed individual safety reports of 33 cases in which allergic events were documented. Of the 33 cases, there were 12 adverse allergic reactions directly attributable to IV thrombolytics. The reports of allergic reactions included angioedema, facial swelling, urticaria, skin rash, cutaneous hypesthesia, hypotension, anaphylactic shock, and death. Of the 12 cases, 11 were related to the IV administration of alteplase and 1 with the administration of reteplase. In the remaining 21 cases, IV thrombolytics remained as possible secondary causes of the allergic reaction, but concomitantly administered medications made the relationship difficult to ascertain.

The authors theorized that IV thrombolytics may cause allergic reactions by various mechanisms. Histamine and bradykinin-related mechanisms are implicated in the development of allergic reactions. Recombinant tissue plasminogen activator can activate the complement system by elevating the levels of C4a, C3a, and C5a, resulting in mast cell degranulation and the release of histamine. Recombinant tissue plasminogen activator also generates plasmin that cleaves bradykinin from its precursor kininogen. Bradykinin has vasodilator properties and increases vascular permeability, which can result in angioedema. Anaphylactoid reactions or angioedema have been reported to occur in less than 0.02% of patients receiving r-tPA for acute myocardial infarction (MI). A higher incidence (up to 1.9%) of allergic reactions has been reported in patients receiving r-tPA for ischemic stroke.

The authors warn that although IV alteplase is identical to endogenous tPA, AERS data suggest that it is the most commonly reported cause of allergic reaction among currently utilized thrombolytics. They recommend that health care professionals have a greater awareness of the possible allergic adverse effects due to IV r-tPA, as this will allow for prompt recognition and treatment of this potentially serious adverse effect.

Zarar A, Khan AA, Adil MM, et al. Anaphylactic shock associated with intravenous thrombolytics. *Am J Emerg Med.* 2014;32:113.e3-113.e5.

HYDROXYCHLOROQUINE-INDUCED QT-INTERVAL PROLONGATION

A 41-year-old African American female was seen as an outpatient for recently diagnosed congestive heart failure (CHF) with systolic left ventricular dysfunction. The patient's past medical history also included hypertension and systemic lupus erythematosus (SLE) complicated by lupus nephritis and chronic kidney disease stage 5. The patient's inpatient echocardiogram revealed moderately reduced systolic function with an estimated ejection fraction of 35%. The patient admitted to several months of poor adherence to her prescribed medications, including hydroxychloroquine that had been prescribed 3 years earlier. Hydroxychloroquine was restarted after consulting with her rheumatologist.

One week later, the patient returned for a routine follow-up visit. At that time, she was completely asymptomatic with no palpitations, chest pain, syncope, or further episodes of dyspnea. The patient reported adherence to all of her medications, denied any alcohol or illicit drug use, and

stated that she was a lifelong nonsmoker. Her family history was negative for any cardiac or rheumatic diseases. A routine EKG revealed a normal sinus rhythm, left axis deviation, T-wave inversion, and significant prolongation of the QT and corrected QT (QTc) intervals of 586 and 614 ms, respectively. The normal QTc value for women is less than 450 ms.

Due to her prolonged QTc, she was admitted directly to the coronary care unit. At that time, the decision was made to discontinue her hydroxychloroquine. A review of her outpatient medications did not suggest other potential causes of QT prolongation. The patient's outpatient regimen included calcitriol, carvedilol, ferrous sulfate, furosemide, a multivitamin, mycophenolic acid, nifedipine, sodium bicarbonate, and hydroxychloroquine. Furosemide was continued as an inpatient, but carvedilol was held to avoid bradycardia. During her admission, the dose of nifedipine was increased to achieve adequate blood pressure control. Serial EKGs revealed gradual shortening of the QTc interval. A nuclear stress test showed normal myocardial distribution of activity and no evidence of reversible ischemia. The patient remained asymptomatic.

The patient was discharged after a 3-day hospital stay with a wearable cardioverter defibrillator and instructed to follow up with her cardiologist in 1 week. An EKG performed 1 week after discharge demonstrated continued improvement in the QTc interval. At her 1-year follow-up visit, her QTc was relatively normal at 473 ms.

The authors point out that although rare, cardiac conduction abnormalities associated with hydroxychloroquine use include QRS-complex widening, QT-interval prolongation, torsades de pointes, and ventricular arrhythmias. The observed prolongation in QTc may have been multifactorial. Serological testing revealed positivity to anti-Ro/SSA antibodies, which have been associated with increased risk of QTc prolongation. This patient's QTc interval did not approach normal values until 1 year after complete discontinuation of hydroxychloroquine. This may be attributed to the long half-life of hydroxychloroquine potentiated by the patient's renal impairment.

Morgan ND, Patel SV, Dvorkina O. Suspected hydroxychloroquine-associated QT-interval prolongation in a patient with systemic lupus erythematosus. *J Clin Rheum.* 2013;19(5):286-288.

COMPLEX REGIONAL PAIN SYNDROME AFTER TETANUS TOXOID INJECTION

A 32-year-old right-handed male reported a 2-month history of pain and swelling of the right hand and forearm. The patient's symptoms were progressive and were associated with weakness and inability to use the affected extremity during his work as a carpenter. The patient had received a tetanus toxoid injection in his right upper arm after having stepped barefoot on an exposed nail. The patient's symptoms started approximately 16 hours after the tetanus toxoid injection. No other injections were given, but he recalled receiving an oral pain killer together with the vaccine. On examination, the patient's right hand and forearm were diffusely swollen and very sensitive to the touch. The affected side felt colder than the contralateral side and there was an early stage of flexion contractures of the fingers with atrophic skin changes in the palm as well as a weak right-hand grip. The patient was not known to suffer from any type of arthritis or connective tissue disorder. He was an ex-smoker, did not drink alcohol, and had no prior psychiatric history.

Routine blood, serology, venous duplex study, x-ray, and lymphoscintigraphy did not reveal any abnormalities. An MRI revealed diffuse edema of the subcutaneous compartment of the dorsum of the hand and forearm with no evidence of tenosynovitis or a fluid collection. Three-phase bone scintigraphy demonstrated slightly increased hyperemia in the right upper limb. On the subsequent delayed films, there was periarticular uptake in the right hand and elbow joints. These findings were highly supportive of the clinical impression of right-hand and forearm complex regional pain syndrome (CRPS) type I.

CRPS type I was formerly referred to as reflex sympathetic dystrophy. CRPS type I is an incompletely understood response of the body to an external stimulus, resulting in pain that usually is nonanatomic and disproportionate to the inciting event or expected healing response. Several potential inciting events were suggested, including a direct trauma to a limb such as surgery, fractures, crush injuries, and sprains. It can also result from undetermined causative process not necessarily involving the affected limb directly, such as that occurring following stroke, spinal cord injury, or even MI. Other inciting events reported in the literature range from paper cuts to ovarian cancer, dental extraction, venipuncture, shingles, and frostbite.

The patient was prescribed prednisolone 0.5 mg/kg/day, amitriptyline 25 mg at bedtime, and intensive right upper extremity physiotherapy. The patient showed remarkable improvement within 3 weeks following treatment. The dose of prednisolone was tapered off within 4 months. The patient was able to return to work as his right upper extremity was almost back to normal function.

Al-Nesf MA, Abdulaziz HM. Complex regional pain syndrome type I following tetanus toxoid injection. *J Clin Rheum.* 2014;20(1):49-50. ■