ISMP Adverse Drug Reactions

Risk Factors for Androgen Deficiency with Daily Opioid Use

Co-trimoxazole and Sudden Cardiac Death in Patients Receiving ACE Inhibitors

Clindamycin-Induced Myelosuppression

Apixaban-Induced Diffuse Alveolar Hemorrhage

DRESS Syndrome Induced by Allopurinol

*Michael A. Mancano, PharmD**

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.

RISK FACTORS FOR ANDROGEN DEFICIENCY WITH DAILY OPIOID USE

It is known that low testosterone or androgen deficiency is a consequence of chronic opioid use. Multiple studies have shown that androgen deficiency occurs frequently in men who use opioids daily, and this effect can happen quickly and can be profound. Although the effects can be severe, they are usually reversible if the opioid medication is discontinued. Androgen deficiency has serious health consequences by causing muscle loss, fatigue, loss of libido, erectile dysfunction, decreased bone density, osteoporosis, and increased bone fracture risk. Androgen deficiency may also be involved in the development of cardiovascular disease.

A retrospective cohort study was undertaken to evaluate the risk factors for androgen deficiency in men who received daily opioid treatment for chronic noncancer pain. The cohort consisted of 1,585 men, within the Kaiser Permanente Northern California (KPNC) health system, between 18 and 80 years of age who received chronic daily opioids. Patients received any one of the following opioids: codeine, hydrocodone, hydromorphone, fentanyl, methadone, long-acting morphine, or oxycodone in long-acting or short-acting formulations. The researchers converted all dosages of opioids to a morphine standardized equivalent (MSE) dosage to allow for easy comparison between various opioid medications. Of the

*Chair and Clinical Professor, Department of Pharmacy Practice, Temple University School of Pharmacy, Philadelphia, Pennsylvania; Clinical Advisor, Institute for Safe Medication Practices, Horsham, Pennsylvania

1,585 men in the study, 616 chronically utilized long-acting opioids and 969 utilized short-acting opioids.

The median MSE daily dose was 60 mg in androgen-deficient men and 40 mg daily in men who were not androgen deficient. Men receiving long-acting opioids had 3.39 times the odds of having androgen deficiency than men exclusively receiving short-acting opioids while controlling for MSE. The authors also noted that the dosage of the opioid had a greater effect in men taking short-acting opioids than in men receiving long-acting opioids. The authors evaluated the study participants for the components of metabolic syndrome (obesity, diabetes, hypertension, and hyperlipidemia); they noted that men having 2 or 3 metabolic syndrome-associated conditions and an age of 50 years old and older also had an increased risk of androgen deficiency.

The authors postulated a possible explanation for the inverse relationship related to testosterone levels in men receiving long- and short-acting opioids. The authors state, "Serum drug levels may be responsible for the increased incidence of androgen deficiency in men receiving long-acting-opioids. Because testosterone is produced in men in response to pulsatile secretion of gonadotropin-releasing hormone (GnRH) and then luteinizing hormone (LH), is possible that a serum drug level exists above which these pulses are less frequent or the amplitude of these pulses is inadequate to maintain normal testosterone." In addition, short-acting opiates have serum levels that rise and fall several times daily; short-acting opiates may halt testosterone production during peak opiate levels and they may allow testosterone production during trough opioid levels.

Based on their findings, the authors summarize that the duration of action was strongly associated with androgen deficiency even when accounting for or eliminating comorbidities such as obesity, diabetes, hypertension, and hyperlipidemia. MSE daily dose plays a role, but it seems to be more strongly associated with androgen deficiency among men who use exclusively short-acting opiates.

Rubinstein A, Carpenter DM. Elucidating risk factors for androgen deficiency associated with daily opioid use. *Am J Med.* 2014;127(12):1195-1201.

CO-TRIMOXAZOLE AND SUDDEN CARDIAC DEATH IN PATIENTS RECEIVING ACE INHIBITORS

Although it is known that co-trimoxazole can cause significant hyperkalemia, the researchers in this study chose to focus on a population that could be at

increased risk from the effects of hyperkalemia. These patients are 66 years of age and older and are receiving concomitant angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), because these medications can cause hyperkalemia.

The researchers evaluated 17 years of data from the Ontario drug benefit database. They also utilized a variety of patient databases to obtain hospital admission and death data. In their primary analysis, they examined the likelihood of sudden death within 7 days of an outpatient prescription for co-trimoxazole, ciprofloxacin, norfloxacin, nitrofurantoin, or amoxicillin in patients receiving concomitant ACE inhibitors or ARBs. In a secondary analysis, they evaluated the likelihood of sudden death within 14 days of receiving one of the above listed antibiotics.

Their findings indicate that co-trimoxazole was associated with a significantly increased risk of sudden death within 7 days. This risk was assumed to be due to co-trimoxazole-induced hyperkalemia. The authors also noted an increased risk in patients receiving ciprofloxacin, which may be due to its QT interval prolongation properties. However, norfloxacin, nitrofurantoin, and amoxicillin were not associated with an increase in sudden death. When evaluating the 14-day data, the authors found that only co-trimoxazole was associated with an increased risk of sudden death. Nitrofurantoin was associated with a decreased risk of sudden death in the 7-day analysis but not in the 14-day analysis.

Co-trimoxazole-induced hyperkalemia can occur quickly and can cause life-threatening arrhythmias, especially among patients receiving ACE inhibitors or ARBs. The authors' previous research (Antoniou T, et al) indicated a 7-fold increased risk of hospital admission with hyperkalemia following co-trimoxazole treatment with no risk demonstrated with alternative antibiotics.

The study has limited generalizability to younger patients, because the population was at least 66 years old. The researchers utilized administrative hospital data in their analysis, so they did not have access to serum potassium or serum creatinine values. They were also unable to reliably determine the dose of co-trimoxazole administered. Even with these limitations, they warn that it would be clinically appropriate to choose an alternative antibiotic or limit the dose and duration of co-trimoxazole treatment in older patients receiving ACE inhibitors or ARBs. They also recommend close monitoring of serum potassium in susceptible patients if co-trimoxazole is administered.

Fralick M, Macdonald EM, Gomes T, et al. Co-trimoxazole and sudden cardiac death in patients receiving inhibitors of renin-angiotensin system: Population based study. *BMJ*. 2014;349:g6196.

Antoniou T, Gomes T, Juurlink DN, et al. Trimethoprim-sulfamethoxazole-induced hyperkalemia in patients receiving inhibitors of the renin-angiotensin system: A population-based study. *Arch Intern Med*. 2010;170:1045-1049.

CLINDAMYCIN-INDUCED MYELOSUPPRESSION

A 22-year-old Hispanic male had been treated 1 month prior for a cough and tonsillitis with amoxicillin 500 mg daily for 7 days and acetaminophen. The patient improved but continued to have a cough, which was controlled with as-needed use of ambroxol (a mucolytic not available in the United States) and clenbuterol (a β_2 agonist not available in the United States). Three weeks after the above treatment, the patient experienced anal pain and a new tonsillar infection with a very frequent nonproductive cough and a fever of 39°C (102.2°F). The patient was admitted to the American British Cowdray Hospital in Mexico. Four days prior to admission, the patient had received 1800 mg daily of clindamycin.

On admission, the patient had a fever of 38.6°C (101.5°F), heart rate of 97 bpm, respiratory rate of 20 breaths/min, and blood pressure of 124/68 mm Hg. He was conscious and cooperative and in overall good condition. He had laryngeal edema and hypertrophy of the tonsils with purulent discharge. His laboratory results revealed a normal red blood cell count, intense leukopenia, and developing thrombocytopenia. His erythrocyte sedimentation rate (ESR) was 45 mm/h (reference, 0-20 mm/h) and C-reactive protein was 12.2 mg/dL (reference, 0-0.3 mg/dL), with normal liver and coagulation studies. The patient's anal pain was revealed to be a hemorrhoid thrombosis and an anal fissure that were resected without incident.

On day 1 of his hospitalization, the patient's leukopenia continued, his thrombocytopenia worsened, and his hematocrit decreased to 36.2% (reference male, 39%-49%). The following laboratory studies were drawn and were all negative or normal: vitamin B12, folic acid, beta-2-microglobulin, antinuclear antibody, venereal disease research laboratory test, heterophile antibodies, HIV 1 and 2, anti-toxoplasma, rubella, cytomegalovirus, herpes simplex virus 1 and 2, parvovirus B19, hepatitis serology, tonsil cultures, and blood cultures. The patient continued to exhibit progressive pancytopenia. A bone marrow biopsy and aspiration was undertaken

and demonstrated frank pancytopenia and injury to hematopoietic tissue.

After the patient's surgical procedure, he received metronidazole 500 mg every 8 hours for 8 days, meropenem 1 g every 8 hours for 6 days, and amikacin 500 mg every 12 hours for 6 days. He received fluconazole 100 mg every 12 hours with oral nystatin as prophylactic therapy for 5 days. Based on his bone marrow study results, the patient was started on pegfilgrastim 6 mg.

On the fourth day of his hospital stay, the patient's blood counts showed increased hematocrit to 44%, increased absolute leukocytes and granulocytes, and further diminished platelet counts, however he did not exhibit bleeding or purpura. On the seventh day, his platelet count began to increase. The patient was discharged on day 13. On discharge, he had a mild leukocytosis and neutrophilia and normal platelets and hematocrit. After 3 months of follow-up, the patient was found to have no abnormalities in his blood cell counts.

The authors point out that even though clindamycin is known to have been associated with anemia, neutropenia, and thrombocytopenia, pancytopenia had not previously been observed and was the result from direct injury of the hematopoietic cells. This was evident from their decreased numbers, morphological alterations, and interference with their differentiation in the bone marrow. The patient's pancytopenia recovered with withdrawal of clindamycin and administration of pegfilgrastim. They concluded that the patient's pancytopenia "may be the result of an idiosyncratic reaction, understood as a mixture of allergic and immunological phenomena caused by the clindamycin and perhaps facilitated by the infectious process that led to its use."

Morales MP, Carvallo APT, Espinosa KAB, et al. A young man with myelosuppression caused by clindamycin: A case report. *J Med Case Rep*. 2014;8:7.

APIXABAN-INDUCED DIFFUSE ALVEOLAR HEMORRHAGE

A 79-year-old female presented with syncope and hypoglycemia. She also exhibited black tarry stools in the weeks prior to admission and progressively worsening shortness of breath and dry cough in the previous 3 days. She did not have chest pain, hemoptysis, orthopnea, peripheral edema, fever, nausea, or vomiting. The patient's medical history included atrial fibrillation, diabetes, chronic hypoxia for which she required 3 L of continuous oxygen,

and 2 gastrointestinal (GI) bleeds while receiving individual warfarin and dabigatran therapy. The patient had recently been placed on apixaban (*Elquis*) 5 mg twice daily by her cardiologist. The patient had stopped taking all anticoagulants for 3 months prior to the initiation of apixaban.

A CT scan of the patient's chest showed diffuse bilateral infiltrates with ground-glass opacities. Her labs revealed a normal white blood cell count, low hemoglobin of 7.3 g/L (reference, female 11.5-16 g/dL) down from 10.3 g/dL a month earlier, and all common markers of autoimmune disease were negative. The patient's dyspnea did not improve with diuretic therapy, however it did worsen her renal function. Her oxygen requirement also escalated rapidly. The patient then had an esophagogastroduodenoscopy (EGD), which did not reveal a significant amount of blood in her upper GI tract. A bronchoscopy was conducted, and a large amount of dark blood was visualized in the trachea and lower airways. An echocardiogram was performed and revealed a normal ejection fraction, mild valvular abnormalities, and mild pulmonary hypertension. Ultimately the diagnosis of diffuse alveolar hemorrhage (DAH) secondary to apixaban therapy was established, which is a persistent or recurrent pulmonary hemorrhage.

The authors point out that although DAH is rare, it has been associated with antithrombotic and antiplatelet therapy however not with apixaban. The patient had initiated apixaban therapy 2 weeks prior to her admission after a 3-month period not receiving an anticoagulant. They recommend that DAH should be considered in patients presenting with diffuse pulmonary infiltrates who are receiving anticoagulant therapy.

Gabrilovich MI, Buxton DE, Lukins DM, et al. Diffuse alveolar hemorrhage secondary to apixaban administration. *Chest*. 2014;146(3):e115-e116.

DRESS SYNDROME INDUCED BY ALLOPURINOL

A 39-year-old woman reported a history of fever, malaise, pharyngitis, and diffuse maculopapular rash on her body. She was admitted to the hospital and started on amoxicillin/clavulanate for a suspected upper respiratory infection. Five days after starting the antibiotic, she was seen by dermatology to evaluate her lingering rash. The patient's medical history was only significant for an appendectomy and a pituitary tumor operation 5 years earlier. She had been treated with allopurinol for the management of elevated uric acid levels. The allopurinol had been

initiated 7 week earlier, and she had developed a skin eruption that began on her trunk and upper limbs and gradually disseminated for a couple of days. Physical examination revealed a generalized maculopapular exanthema, some of them with edematous follicular accentuation, periorbital edema, and generalized lymphadenopathy. The patient was febrile with a temperature of 38.2°C (100.8°F).

Laboratory findings showed a white blood cell count of $14 \times 10^3/\mu\text{L}$ (reference, $4.1\text{-}10.9 \times 10^3/\mu\text{L}$) with 7.6% eosinophils (reference, 1%-3%). Liver function tests were abnormal with increased levels of aspartate aminotransferase 455 U/L (reference, 0-35 U/L), alanine aminotransferase 565 U/L (reference, 0-35 U/L), gamma-glutamyl transferase 532 U/L (reference, 0-50 U/L), and alkaline phosphatase 346 IU/L (reference, 30-120 U/L). There was an increase in serum creatinine 1.64 mg/dL (reference, 0.50-0.9 mg/dL) and urea 89 mg/dL (reference, 17-43 mg/dL) and decreased creatinine clearance 61.72 mL/min (reference, 85-125 mL/min). Blood cultures, urine and stool cultures, and nasal-throat swabs were negative for bacteria, protozoa, or helminthic eggs. Serologic tests including syphilis, Epstein-Barr virus, HIV, and hepatitis B and C, and antinuclear antibody were negative. Chest x-ray was normal. Echocardiography showed pericardial effusion 0.8 cm around the left ventricle, and abdominal sonography showed moderate hepatomegaly.

A skin biopsy was performed and it yielded mild acanthosis (diffuse epidermal hyperplasia) and leukocytoclastic vasculitis in the upper dermis. Leukocytoclastic vasculitis refers to vascular damage caused by nuclear debris from infiltrating neutrophils. The patient was diagnosed with drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. Allopurinol was immediately withdrawn and systemic prednisolone 75 mg daily and antihistamines were administered to the patient. The patient's clinical appearance and laboratory abnormalities began to improve. The dosage of corticosteroids was gradually tapered and stopped as the clinical and laboratory abnormalities resolved over 6 months in order to prevent a recurrence of the symptoms of the disease.

The authors summarize that with regard to DRESS, fever often up to 38°C to 40°C or rash is the first sign seen in 90% to 100% and 90% of cases of DRESS, respectively. The face, trunk, and upper extremities are initially affected and the eruption is usually macular erythema that becomes

confluent. Swelling of the face with a marked periorbital involvement is a warning to the diagnosis, occurring in about 25% of patients. Local or generalized lymphadenopathy is found in 70% to 75% of cases. Various hematologic abnormalities are observed including leukocytosis, eosinophilia, and atypical lymphocytes similar to mononucleosis. Liver involvement is the most common visceral manifestation, after the lymphadenopathy. Hepatitis with elevation of liver transaminases is found in 51% of cases. Renal involvement is also reported in patients. DRESS has a 10% to 20% mortality

and is characterized by a latency period ranging from 3 weeks to 3 months after the introduction of the offending drug. The syndrome is defined by the presence of fever, rash, eosinophilia, atypical lymphocytes, and multiorgan involvement.

The authors conclude that a correct and early diagnosis is necessary as DRESS syndrome is potentially associated with serious and sometimes fatal visceral involvement.

Kavala M, Karadag AS, Demir FT, et al. Drug rash with eosinophilia and systemic symptoms syndrome induced by allopurinol. *J Med Cases*. 2014;5(7):420-422. ■