ISMP Adverse Drug Reactions

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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.

METHIMAZOLE-INDUCED CHRONIC ARTHRITIS

A 40-year-old female presented to her physician with a 5-year history of right elbow pain and swelling and a 7-year history of intermittent bilateral knee swelling and pain. Examination revealed a thin White female with normal vital signs, mild exophthalmos, and an unremarkable general examination. Her musculoskeletal examination revealed a moderately swollen, warm, and markedly tender right elbow with limited range of motion as well as bilateral knee effusions. No other joint abnormalities were detected.

Upon further questioning, she revealed a history of Graves disease that occurred 8 years ago. She was diagnosed with Graves disease shortly after an

uneventful full-term pregnancy when she experienced palpitations, sweating, weight loss, fatigue, tremors, and exophthalmos. She was initiated on methimazole (*Tapazole*) 10 mg twice daily and then tapered after several months to 10 mg daily. After a few months of therapy, she began to experience intermittent arthralgias in the right elbow and both knees and her methimazole dose was decreased to 5 mg daily. The patient's pain became persistent and occurred on a daily basis; over the last 5 years, her right elbow swelling became chronic, persistent, and progressively severe.

The patient had been evaluated by a rheumatologist 3 years after her symptoms began, and she was

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diagnosed with seronegative rheumatoid arthritis. The rheumatologist evaluated samples of her synovial fluid, and they revealed 26,000 leukocytes/mL. She was started on sulfasalazine and then subsequently on methotrexate for treatment of her seronegative rheumatoid arthritis. Over the next several years, she was seen by orthopedic specialists who treated her with repetitive intra-articular corticosteroid injections and eventually recommended a right-elbow synovectomy and arthroscopic debridement of the right knee. Laboratory tests revealed a positive antinuclear antibody (ANA) 1:80 titer, negative rheumatoid factor, negative Lyme serology, and thyroid function tests within the normal reference range. Arthrocentesis of the right elbow was attempted with ultrasound guidance, but no synovial fluid could be aspirated. The ultrasound revealed synovial thickening, and Doppler analysis suggested significant inflammation. An MRI of the right elbow 5 years after methimazole was initiated revealed exuberant proliferative synovitis with reactive marrow edema and an inability to fully extend the joint.

Methimazole was discontinued with close monitoring of thyroid function. Within 2 weeks of methimazole discontinuation, the patient's elbow symptoms diminished with progressive and complete resolution of swelling. Additionally, her knee pain and swelling resolved. Six weeks after methimazole discontinuation, the patient's elbow appeared normal with full range of motion and both knees were entirely normal. A repeat ANA was 1:80, and a repeat MRI revealed a significant reduction in the volume of synovitis and resolution of the reactive marrow pattern with full elbow extension. At this stage, the patient remained totally asymptomatic, and thyroid function testing to date has remained normal.

The authors point out that the occurrence of antithyroid arthritis syndrome is underappreciated as a possible side effect of antithyroid therapy. They warn that arthralgia can be the first presenting symptom of a systemic vasculitic disorder, and therefore clinicians should be alert to recognize this potential rheumatologic adverse effect of antithyroid medication. The authors reviewed an additional 19 cases of antithyroid-induced arthritis published in the literature between 1969 and 2011. In reviewing these cases, it is evident that initial symptoms may range from arthralgias to inflammatory arthropathies manifesting as monoarthritis, episodic migratory polyarthritis, or most commonly polyarthritis. The adverse effects usually begin within weeks of antithyroid

medication initiation but may take up to 36 months to begin in some patients. The duration of the adverse effect is generally a short time before the drug is withdrawn. Once the drug is withdrawn, a prompt resolution of symptoms is observed. They also noted in a case series of over 500 patients receiving antithyroid medications that the second most common noted adverse effect was rheumatic symptoms, which occurred in 1.6% of patients.

The authors warn that it is important to diligently search for an etiologic agent when a patient presents with seronegative rheumatoid arthritis.

Gruber CN, Finzel K, Gruber BL. A case of methimazole-induced chronic arthritis masquerading as seronegative rheumatoid arthritis. *J Clin Rheumatol*. 2014;20:229-232.

BILATERAL GYNECOMASTIA ASSOCIATED WITH THE COMBINATION OF METHYLPHENIDATE AND PAROXETINE

A 10-year-old male was diagnosed with attention deficit hyperactivity disorder (ADHD) and social phobia and was initiated on methylphenidate (MPH) (*Concerta*) 18 mg daily and paroxetine (*Paxil*) 10 mg daily. After 2 months of treatment, his symptoms of each condition showed moderate improvement and the medications were well tolerated by the patient. At this time, his dosage of MPH was increased to 36 mg daily and his paroxetine dosage was increased to 20 mg daily. The patient remained on this regimen for 1 year and demonstrated further improvement in symptoms and tolerated the medications well. At 1 year, the patient began to develop some tolerance to his MPH and his dosage was increased to 54 mg daily. Six months after this dosage increase, the patient was evaluated for bilateral gynecomastia that had developed over the previous several months. The patient had no pain, tenderness, or galactorrhea, but the gynecomastia was psychologically, physically, and socially disturbing for him.

Laboratory analysis of the patient's liver, thyroid function, renal function, electrolytes, complete blood count, prolactin, testosterone, estrogen, luteinizing hormone, follicle stimulating hormone, and cortisol levels were all within normal limits. The patient denied using any other medicinal or herbal substances or eating any unusual foods. The patient's MPH and paroxetine were discontinued, however no significant improvement of his gynecomastia was seen after 7 months of not receiving MPH or paroxetine. Over the 7 months, he had gained 13 kg; he was 63 kg with a BMI of 24.9. His prolactin, estrogen, and

testosterone levels remained within normal limits. The patient's parents refused any surgical operation for managing the gynecomastia as they expected it to resolve on its own. The patient was advised to increase his physical activities and was referred to a dietician for weight management. The patient's ADHD symptoms returned, and he was referred to an academic support program; however his social phobia symptoms did not return.

This patient demonstrated prepubertal gynecomastia, which is characterized by the presence of palpable unilateral or bilateral breast tissue in boys without other signs of sexual maturation. The authors mention that Ensaf et al reported a case in 2012 of a 6-year-old boy who had been receiving MPH 10 mg daily since the age of 4 who was diagnosed with unilateral gynecomastia with ongoing progression. This patient was managed with subcutaneous mastectomy at the age of 12.

The exact physiologic mechanisms by which MPH can cause gynecomastia are unknown. However inhibition of dopaminergic neurotransmission by selective serotonin reuptake inhibitors (SSRIs) could be related to several adverse events such as hyperprolactinemia, extrapyramidal symptoms, sexual and cognitive dysfunction, galactorrhea, mammary hypertrophy, and rare cases of gynecomastia. The authors report there have been a number of case reports in the literature of SSRI-induced gynecomastia. Therefore the concomitant use of MPH and paroxetine could play a role in the patient's gynecomastia. The authors surmise that both medications may have potentiated their effects to cause gynecomastia in this patient. Despite being rare, gynecomastia may develop during MPH and/or paroxetine treatment in children, and this adverse effect can be psychologically, physically, and socially disturbing to them.

Coskun M, Adak I, Akaltun I. Bilateral gynecomastia in a pre-adolescent boy while under treatment with methylphenidate and paroxetine. *J Clin Psychopharm.* 2014;34(4):537-538.

Ensaf F, Edelbauer M, Wechselberger G. Unilateral gynecomastia in a prepubertal boy. *Eur J Pediatr.* 2012;171:197.

ADRENAL SUPPRESSION AND CUSHINGOID FEATURES WITH INHALED FLUTICASONE

A 61-year-old woman was admitted to the hospital for treatment of a pulmonary embolism. During her hospital stay, she was noted to have cushingoid clinical features. An 8:00 a.m. morning cortisol was ordered, and it was found to be suppressed at 2 nmol/L (reference range, 138-690 nmol/L). The

patient was referred for outpatient follow-up of adrenal insufficiency. A medical history revealed that she had received fluticasone 250 mcg/salmeterol 50 mcg (*Advair*) 2 puffs inhaled twice daily and inhaled albuterol for breakthrough symptoms for the last 11 years for the treatment of asthma. The patient reported feeling increased fatigue and dyspnea, and she had several large ecchymoses on her extremities. The patient did not have any evidence of hyperpigmentation, and her blood pressure was 130/82 mm Hg. Her laboratory results yielded a sodium of 147 mmol/L (reference range, 134-144 mmol/L), a potassium level of 3.6 mmol/L (reference range, 3.5-5.5 mmol/L), and a low adrenocorticotrophic hormone (ACTH) level of 0.01 pmol/L (reference range, 2-26.2 pmol/L). A 24-hour urine cortisol collection subsequently demonstrated an undetectable level of cortisol. A 1 mcg ACTH stimulation test was abnormal, with cortisol levels of 23 nmol/L (expected >650 nmol/L) at peak, indicating an inadequate response.

Based on the available evidence, the patient was diagnosed with central adrenal insufficiency, and corticosteroid replacement therapy was initiated as hydrocortisone 20 mg 3 times daily. Two months later at her follow-up visit, she was noted to have gained 8 kg with continued fatigue, leg weakness, dyspnea, and extremity bruising. She also had new onset hypertension of 147/90 mm Hg. The patient's fluticasone was immediately discontinued, and ciclesonide 80 mcg/daily was initiated and continued for 3 months. Oral hydrocortisone was slowly tapered over the next 8 months and her bruising, fatigue, and weakness slowly resolved over this same period. After 8 months, repeat cortisol levels and ACTH stimulation tests all were normal, which indicated that the patient's hypothalamic-pituitary-adrenal axis had been restored.

The authors report that recent literature demonstrates a dose-dependent relationship between inhaled corticosteroid and adrenal suppression in adults, which is seen primarily with inhaled fluticasone administration. The authors warn that clinicians should have an increased awareness that systemic absorption of commonly prescribed corticosteroids can occur even at established therapeutic doses. The lowest effective dose of inhaled steroids should be administered to avoid these effects.

Tsoukas MA, Krishnamoorthy P, Richards BJ, et al. Adrenal suppression with cushingoid features from inhaled corticosteroid therapy in an adult asthmatic patient. *Am J Med.* 2014;127(5):e1-e2.

PULMONARY THROMBOEMBOLISM DUE TO PALIPERIDONE

The authors present 2 cases of pulmonary thromboembolism (PTE) induced by paliperidone (*Invega*). The first patient is a 28-year-old male who was admitted to the hospital with his first psychotic episode. Treatment was initiated with paliperidone 3 mg daily with a gradual increase to 9 mg daily. After 8 weeks of treatment, the patient was taken to the emergency room with complaints of respiratory pain and hemoptysis. On physical exam, he was noted to have dyspnea, tachypnea, and fever. Blood tests revealed an elevated C-reactive protein of 121 mg/L (reference range, <10 mg/L), fibrinogen 600 g/L (reference range, 2-4 g/L), and d-dimer 0.89 mg/L (reference range, <0.5 mg/L). The patient's liver function, renal function, and cardiac enzymes were within normal limits, however his prolactin level was elevated at 45 mg/dL (reference value, males 3-14 mg/dL). A CT scan revealed a PTE in the left lower lobe. Anticoagulant therapy was initiated immediately, and the patient promptly responded to therapy.

The second case occurred in a 40-year-old male who was treated with risperidone 8 mg daily for 3 years for a psychotic disorder. Six months prior to admission, the patient had been switched to paliperidone 6 mg daily due to complaints of drowsiness from risperidone. The patient presented to the emergency room with fever, irritability, and mild dyspnea over the preceding 4 days. Blood tests revealed an elevated C-reactive protein of 155 mg/L (reference range, <10 mg/L), fibrinogen 970 g/L (reference range, 2-4 g/L), and d-dimer 1.2 mg/L (reference range, <0.5 mg/L). The patient's liver function, renal function, cardiac enzymes, and prolactin level were within normal limits. A CT pulmonary angiography revealed a left lobar pulmonary artery thrombosis, regional consolidation, and atelectasis with infection in the left lower lobe and a small pleural effusion. Based on the findings, the patient was diagnosed with a PTE, was promptly treated, and recovered.

The 2 patients had no history of recent surgery or trauma, peripheral vascular disease, cancer, or cardiovascular diseases. The patients' physical activity and body mass index were both normal. The patient in case 1 never smoked and did not use illicit drugs or alcohol, whereas the second patient consumed 1 bottle of wine per week and 20 cigarettes a day. Both patients had a complete coagulopathy workup, including factor V Leiden, prothrombin deficiency, protein C and S deficiency, antiphospholipid antibodies, activated protein C resistance, elevated factor VIII, and hyperhomocysteinemia. All coagulopathy tests were unremarkable for both patients.

The first patient continued receiving heparin for 6 months and the second patient received heparin for 1 year. Neither patient had a thromboembolic episode during the follow-up period. Case 1 had his paliperidone discontinued, and he was initiated on aripiprazole 10 mg daily. Case 2 was monitored for 3 years, and his dose of paliperidone was tapered to 3 mg daily.

The authors reviewed the medical literature to date and point out that antipsychotic treatment has been linked to a higher risk of venous thromboembolism (VTE) in most studies. Typical and atypical antipsychotics have been associated with a higher risk of PTE, with the highest risk found with clozapine followed by ziprasidone, risperidone, and olanzapine. Although a definitive mechanism of antipsychotic-induced VTE has not been put forth, the authors suggest a possible theory. Atypical antipsychotic drugs have an affinity for the type 2A serotonin receptor (5HT_{2A}) that is greater than type 2 dopamine receptors. 5HT_{2A}-induced platelet aggregation might be affected in patients receiving olanzapine, risperidone, and clozapine. Platelet aggregation may be enhanced via 5HT_{2A} antagonism by second-generation antipsychotics or due to hyperhomocysteinemia. An additional theory suggests that hyperprolactinemia is an important novel risk factor for PTE in patients receiving antipsychotic medications and that the thrombogenic effect is caused by adenosine diphosphate-stimulated platelet activation. The plasma prolactin level of the patient in case 1 was elevated but the plasma prolactin level in the patient in case 2 was not elevated.

Based on their literature review, the authors point out that the biological mechanisms involved in the pathogenesis of antipsychotic-induced VTE are largely unknown. The authors discuss that several hypotheses have been suggested such as drug-induced sedation, obesity, increased levels of antiphospholipid antibodies, enhanced platelet aggregation, and hyperhomocysteinemia. The association with VTE may also be related to underlying risk factors in the psychotic patient, such as recently started antipsychotic therapy (within the past 3 to 12 months), higher doses of medication, concomitant multiple antipsychotic therapy, intravenous or intramuscular administration of drug, and use of second-generation antipsychotics, particularly clozapine. The authors warn that clinicians should consider antipsychotic drugs as a potential risk factor for VTE and PTE.

Sengul MCB, Kaya K, Yilmaz A, et al. Pulmonary thromboembolism due to paliperidone: Report of 2 cases. *Am J Emerg Med*. 2014;32:814.e1-814.e2. ■