ISMP Adverse Drug Reactions

Ziprosidone-Induced Transient Agranulocytosis

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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.

ZIPRASIDONE-INDUCED TRANSIENT AGRANULOCYTOSIS

A 45-year-old African American male came to the emergency department with complaints of shortness of breath, lower extremity edema, and increased blood pressure. The patient had a history of schizophrenia, diabetes mellitus, hypertension, and stage 4 chronic kidney disease. The patient had been refusing hemodialysis for several months. His medication history included amlodipine, hydralazine, furosemide, insulin glargine, calcitriol, albuterol, and ziprasidone (*Geodon*) 80 mg twice daily. Although the patient had been refusing his hemodialysis sessions, he was taking his medication regularly as prescribed. On presentation, the patient's blood pressure was 211/116 mm Hg and his labs revealed a creatinine of 12.5 mg/dL, white blood cell count (WBC) $5.0 \times 10^3/\mu\text{L}$, absolute neutrophil count (ANC) 2,600 c/mm^3 , red blood cell count $3.34 \times 10^{12}/\text{L}$ (male normal value, 4.3-5.9 x

$10^{12}/\text{L}$), hemoglobin 8.5 g/dL (male normal value, 13.2-17.5 g/dL), and hematocrit 20% (male normal value, 39%-49%).

The patient was admitted to the hospital, and all of his outpatient medications were continued. The patient agreed to receive hemodialysis; it was restarted 3 times weekly, and the patient's symptoms improved with treatment. Approximately 18 kg of fluid was removed from the patient during 2 weeks of hemodialysis sessions. At that time, the patient developed a severe neutropenia with an ANC of 200 c/mm^3 and a WBC of $1.4 \times 10^3/\mu\text{L}$. Ziprasidone was discontinued and the patient's ANC and WBC returned to normal in 5 days. Because the patient had benefited greatly from ziprasidone, a rechallenge was initiated. The patient underwent a gradual titration from ziprasidone 20 mg twice daily up to 80 mg twice daily with no ill effect on his WBC or ANC. The patient was discharged.

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Six months after the prior admission, the patient was again admitted with the same symptoms due to his refusal to receive hemodialysis. The patient was again initiated on hemodialysis, and he again developed a severe neutropenia that resolved with the discontinuation of ziprasidone. The patient was slowly titrated up to ziprasidone 80 mg twice daily with no hematologic complications. The patient was admitted to the hospital for a third time under the same circumstances, however the medical team decreased the patient's ziprasidone to 40 mg twice daily before hemodialysis was initiated. The patient did not develop neutropenia after his hemodialysis was initiated as he had on prior admissions. The patient's ziprasidone was titrated up to 80 mg twice daily with no issues. All of the patient's concomitant medications remained the same through all 3 of his admissions.

The authors note that there is no recommendation for a dosage adjustment for ziprasidone in a patient receiving hemodialysis due to chronic kidney disease. Ziprasidone has 2 primary inactive metabolites, ziprasidone sulphoxide and ziprasidone sulphone, that are both excreted in the urine. In addition, ziprasidone is 99% protein bound and is not removed by hemodialysis. The authors theorize that the initiation of hemodialysis acutely increases the serum concentration of ziprasidone, with potential toxicity caused by a rapid decrease in the patient's fluid volume. They suggest a sharp increase in ziprasidone blood levels may lead to transient agranulocytosis in patients started on hemodialysis. To avoid this adverse effect, the authors recommend that the dose of ziprasidone should be decreased prior to the initiation of hemodialysis. The ziprasidone dose can then be slowly titrated to a therapeutic dose once the patient is medically stable. They call for more research to be directed to address this issue.

Iskandar JW, Vance JE, Kablinger, et al. Transient agranulocytosis associated with ziprasidone in a 45-year-old man on hemodialysis. *J Clin Psychopharmacol*. 2015;35(3):347-348.

DELAYED ONSET OF CARDIAC ADVERSE EFFECTS WITH FINGOLIMOD

A 51-year-old female with multiple sclerosis was started on fingolimod (*Gilenya*) therapy. Prior to the initiation of therapy, her baseline EKG demonstrated a normal sinus rhythm with a resting heart rate of 58 to 68 bpm. The patient was then given her first dose of fingolimod 0.5 mg and was observed for the recommended 6-hour cardiac monitoring interval. During monitoring, the patient had palpitations

without any other symptoms. She then developed a Mobitz Type 1 (Wenckebach) second-degree atrioventricular (AV) block with a ventricular rate between 43 and 68 bpm. The AV block and decreased ventricular rate continued to the end of the 6-hour cardiac monitoring period. The patient was sent to the emergency department (ED) for further evaluation.

In the ED, the patient's palpitations continued and EKG revealed a junctional tachycardia with a rate of 83 bpm. Junctional tachycardia has not been reported with fingolimod administration. While in the ED, the patient's heart rate slowed and a repeat EKG revealed a Mobitz Type 1 AV block with a ventricular rate of 63 bpm. The patient was then admitted to hospital for additional monitoring. Approximately 11.5 hours after fingolimod was administered, the patient experienced worsening palpitations with lightheadedness, dizziness, and a near syncopal episode. Cardiac monitoring continued to show a Mobitz Type 1 AV block with a decreased ventricular rate of 38 bpm. Atropine was administered, and the patient's symptoms resolved. A repeat EKG revealed sinus rhythm with 56 bpm and no AV block. The next day, the patient had a sinus rhythm of 54 bpm and a first-degree AV block. The patient was stable and discharged that day.

The authors point out, "The most common serious adverse event observed in clinical trials with fingolimod was symptomatic bradycardia." First- and second-degree heart block occurred 1.2% and 0.7%, respectively, in clinical trials. In explaining the reason their patient may have experienced such a prolonged cardiac dysfunction, the authors stated, "In pharmacokinetic studies, a single oral dose of fingolimod caused a dramatic rise in plasma concentrations over the first 6 hours followed by slower plasma elevations, which peaked in 12 to 36 hours with a median of 28 hours." Therefore the patient's delayed cardiac effects may be due to a prolonged time to peak plasma concentration even though she had normal renal and hepatic function. The authors recommend that extended cardiac monitoring may be needed in selected patients.

Rosini JM, Rajasimhan S, Fellows SE, et al. Delayed cardiac dysrhythmias after fingolimod administration. *Am J Emerg Med*. 2015;33:987.e1-987.e3.

TELMISARTAN-INDUCED MYOTOXICITY

A 49-year-old male physician was receiving olmesartan 20 mg every 12 hours, metoprolol 50 mg daily, and torsemide 5 mg daily for the treatment of his hypertension. During a follow-up visit, the patient's

blood pressure was elevated and his medications were changed to telmisartan (*Micardis*) 80 daily, chlorthalidone 12.5 mg daily, bisoprolol 5 mg daily, and amlodipine 5 mg daily. The patient's blood pressure was well controlled on his new 4-drug regimen. Six weeks after the initiation of his new regimen, the patient complained of malaise, low-grade fever, and muscle pain. Complete blood count (CBC) and basic metabolic panel were all within normal limits, however creatinine kinase (normal value for males, 55-170 U/L) was 1,022 U/L. The patient did not have a history of statin use, vigorous exercise, smoking, or alcohol intake. The patient was treated symptomatically for his muscle pain, but his pain increased and the following week he developed muscle weakness.

As the patient's condition worsened, his thyroid stimulating hormone, T4, T3, and electrolytes were evaluated to rule out other possible medical causes but they were all within normal limits. His creatinine kinase level had risen to 1,650 U/L. Because no obvious pathology was detected, the patient's antihypertensive medications were suspected as the cause of his myopathy. His recently initiated antihypertensive regimen of telmisartan, chlorthalidone, bisoprolol, and amlodipine was discontinued, and his prior regimen of olmesartan, metoprolol, and torsemide was reinitiated. Five days after the reinitiation of the prior regimen, the patient's symptoms began to improve and his creatinine kinase level decreased to 322 U/L. After 15 days, the patient had completely recovered, and his creatinine kinase had returned to within normal limits with a blood pressure of 160/90 mm Hg.

The patient is a physician, and he decided to rechallenge himself by replacing olmesartan and torsemide with telmisartan 80 mg daily and chlorthalidone 12.5 mg daily; he continued to take his metoprolol as prescribed. On the third day after his regimen adjustment, the patient began to experience muscle pain. He immediately switched back to his original regimen of olmesartan and torsemide, and his muscle pain resolved within 48 hours. The patient remained stable on the regimen of olmesartan, metoprolol, and torsemide for the next 2 months, after which the patient rechallenged himself by replacing torsemide with chlorthalidone 12.5 mg daily. The patient did not have symptoms of myotoxicity and his creatinine kinase level was 199 U/L after 2 months of chlorthalidone, olmesartan, and metoprolol. The patient was finally maintained on a daily 4-drug regimen of olmesartan 20 mg, chlorthalidone 12.5 mg, bisoprolol 5 mg,

and amlodipine 5 mg for more than 7 months. He experienced good blood pressure control without any signs of myotoxicity.

The authors state that angiotensin II can cause muscle atrophy through inhibition of protein synthesis and augmentation of proteasome activity. Myopathy has been reported with ACE inhibitors due to their effect on angiotensin II concentrations, but the myotoxicity in this case could not be attributed only to telmisartan's effect on angiotensin II because olmesartan did not cause the patient to have muscle pain.

The authors point out that "some ARBs have an off-target action on peroxisome proliferator-activated receptor- γ (PPAR- γ) and have been found to increase insulin sensitivity in the skeletal muscle. Telmisartan and irbesartan induce transcriptional activity of PPAR- γ at therapeutic levels, while losartan affects PPAR- γ at a high concentration, and other ARBs such as eprosartan, olmesartan and valsartan, do not have any effect on PPAR- γ activity." Increased activity of PPAR- γ has been associated with myalgia and rhabdomyolysis. A second factor that is important is lipophilicity, because it will enable a drug to cross cell membranes and lipophilic drugs have greater affinity for PPAR- γ . Telmisartan is highly lipophilic, whereas olmesartan is the least lipophilic. The authors theorize that the differences in lipophilicity and activation of the PPAR- γ receptor may be the reason for the development of a myotoxic reaction with telmisartan but not with olmesartan.

The authors recommend that if patients develop myotoxicity due to an ARB, they can then be prescribed an ARB that lacks PPAR- γ -activating activity and low lipophilicity.

Barvaliya MJ, Naik VN, Shah AC, et al. Safety of olmesartan in a patient with telmisartan-induced myotoxicity: A case report. *Br J Clin Pharmacol*. 2015;79(6):1034-1036.

SEVERE DILATED CARDIOMYOPATHY INDUCED BY ADALIMUMAB AND USTEKINUMAB

A 57-year-old male who had utilized a variety of treatments for his psoriasis was started on anti-tumor necrosis factor (TNF) therapy with adalimumab (*Humira*) 40 mg subcutaneously every 15 days. He had a history of non-insulin-dependent diabetes mellitus, mild hypertension, and mild hypertensive heart disease with mild left ventricular hypertrophy and a stable ejection fraction of 65%, which was monitored annually. All of the patient's medical conditions were well managed with pharmacologic therapy.

After 8 months of adalimumab therapy, the patient presented to the ED complaining about general malaise, progressive dyspnea on minimal exertion, and a dry cough. He reported that the symptoms had been present for approximately 72 hours. Physical exam revealed pitting ankle edema and laboratory tests revealed a mild hypoxemia, mildly elevated troponin, and a negative d-dimer. An EKG showed sinus rhythm with signs of an increased size of the left chambers similar to previous results. An emergent CT scan ruled out a pulmonary embolism but revealed dilated coronary arteries and mediastinal lymph nodes. The patient was admitted to the hospital; adalimumab was stopped and intravenous diuretics were administered. An echocardiogram revealed dilated cardiomyopathy with a left ejection fraction (EF) of 23% with accompanying left atrial enlargement. The patient had a stress test that was inconclusive due to his functional limitation. The patient was given the possibility of inclusion in a heart transplant program. However, he quickly improved after 5 days of hospitalization and was discharged. The patient was not restarted on adalimumab, however his psoriasis worsened and was controlled with topical corticosteroids.

In the months that followed, the patient continued to improve and his EF increased to 39%. His left atrial enlargement persisted but had decreased. With the worsening of the patient's psoriasis even with topical corticosteroids, he was then started on methotrexate and sulfasalazine, which ultimately did not control his symptoms. Eight months after his prior admission, treatment with ustekinumab (*Stelara*) was started. The patient was to receive 45 mg at weeks 0 and 4 and then every 12 weeks thereafter. After the second dose of ustekinumab, the patient experienced progressive dyspnea and edema in his lower extremities, so he went to the ED for the second time. An EKG revealed atrial fibrillation with rapid ventricular response and left anterior hemiblock. The patient was admitted to the hospital and anticoagulation was started. Ustekinumab was discontinued and the patient was treated with beta-blockers and diuretics. An echocardiogram revealed

dilated cardiomyopathy and an EF of 23%. After this second event related to biological therapy for psoriasis, it was decided to withdraw all biological therapy in this patient. Since the second admission, the patient showed progressive improvement in cardiac symptoms to New York Heart Association class I. Four months after his discharge, the patient's EF was 45%. Since this time, the patient has not had another exacerbation of cardiac symptoms.

The authors investigated a possible mechanism for the patient's cardiac symptoms. Adalimumab is a recombinant human monoclonal anti-TNF antibody. They state that there has been an association between anti-TNF drugs and adverse cardiac events, but there is no pathophysiological explanation. There have been reports of cardiomyopathy with anti-TNF drugs; these agents are contraindicated in patients with heart failure and should be discontinued in patients who develop new or worsening heart failure.

The authors evaluated ustekinumab, which is a fully human monoclonal antibody to interleukin 12/23 (IL 12/23). They state that the cardiovascular effects of IL-12 and IL-23 are unclear. The cytokines induce the lymphocyte activation that produce interleukins. One of the interleukins produced is IL-17, which has uncertain vascular effects. It is thought that IL-17 stabilizes plaque, but it is suggested that IL-17 could induce proinflammatory effects. The authors state that there is no theory that explains the association between IL-12/IL-23 with the onset of cardiomyopathy and no literature that links ustekinumab with cardiomyopathy or heart failure.

The authors summarize, "Although this is an isolated case report, and its impact on daily clinical practice is unclear, we think it should be taken into consideration. Biological therapies should be carefully administered to patients with cardiac history. Further studies are needed to determine the real effect of these drugs in people with heart disease."

Membrillo de Novales FJ, Jimenez AA, Melendez LM, et al. Severe dilated cardiomyopathy induced by adalimumab and ustekinumab. *J Clin Rheumatol*. 2015;21(3):170-172. ■