Case in Point

Suspected Clozapine-Induced Cardiomyopathy and Heart Failure With Reduced Ejection Fraction

Daniel Patuszynski, PharmD; and Patricia M. Applegate, MD

An increased awareness of the adverse effects associated with clozapine can help physicians quickly diagnose this rare and potentially fatal condition.

Clozapine is an atypical antipsychotic that is usually reserved for use in patients with treatment-resistant schizophrenia or schizoaffective disorder with suicidality. Due to the risk of severe neutropenia, clozapine is available only through a restricted Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program, which requires provider certification, patient enrollment and adherence with absolute neutrophil count (ANC) testing and monitoring, and dispensing pharmacy certification.[1] In addition, clozapine (Clozaril) prescribing information contains a boxed warning for potentially fatal cardiomyopathy. One recently published study from Australia demonstrated a 4.65% incidence of cardiomyopathy in patients started on clozapine, which is much higher than the incidence provided by national drug surveillance programs.[2-4] An increased awareness is needed among health care professionals, including physicians, pharmacists, and nurses, about this serious fatal condition.

Dr. Patuszynski is a clinical pharmacy specialist in cardiology at the VA Loma Linda Healthcare System. **Dr. Applegate** is a staff cardiologist at the VA Northern California Healthcare System and an associate professor of medicine/cardiology at the University of California, Davis School of Medicine.

Clozapine-induced cardiomyopathy is a diagnosis of exclusion that requires the absence of other etiologies of cardiac dysfunction (ie, coronary artery disease, hypertension, valvular disease, congenital heart disease, etc). Diagnosing a clozapine-related cardiomyopathy may be a long and laborious task. Patients with cardiomyopathy may present with many nonspecific signs and symptoms, such as fatigue, dyspnea, edema, and/or nausea and vomiting, which are present in other diseases; therefore, multiple encounters and lab tests may be needed until a cardiac source is implicated. The exact mechanism is unknown; however, Chow and colleagues believe that clozapine is a direct toxin of the myocardium.[5-7]

CASE PRESENTATION

A 30-year-old woman with a history of asthma, hypothyroidism (euthyroid with supplementation), posttraumatic stress disorder, and schizoaffective disorder was started on clozapine due to major depression and increased suicidal ideation despite previous treatment with several other antipsychotic agents. Clozapine was gradually titrated to a dose of 150 mg twice a day during an inpatient psychiatric admission. Prior to starting clozapine, this patient had been admitted to the psychiatry unit 11 times within the prior 2 years. After initiating and titrating clozapine over 4 months, her psychiatric symptoms markedly improved.

More than 4 years after the initiation of clozapine and after various treatments for multiple symptoms (Sidebar), the patient was diagnosed with heart failure (HF) with a reduced ejection fraction (EF) of 10% to 15%. She was referred to the cardiology HF clinic. Her dose of clozapine 150 mg at bedtime was discontinued after a discussion with psychiatry. She had a negative workup for other HF etiologies and was started on HF medications that included carvedilol, losartan, and spironolactone. After discontinuation of clozapine, her psychiatric symptoms worsened, and she was admitted to the psychiatry unit twice within a year. Two months after clozapine was

discontinued, a repeat echocardiogram (ECHO) was obtained and was essentially unchanged. A chest X-ray (CXR) obtained 4 months after clozapine discontinuation demonstrated a normalized cardio-mediastinal silhouette. A third ECHO was ordered during her second psychiatric admission, which was 11 months after clozapine discontinuation; this revealed an improved left ventricular EF (LVEF) of 30% to 35% and resolution of left ventricular (LV) dilation.

This patient's clinical course led to an extensive chart review that investigated whether there may have been earlier signs and symptoms of HF or cardiomyopathy. It was discovered that the initial HF signs and symptoms were likely present for about 1 year before the diagnosis was made and after having been on clozapine for about 40 months (Videos of the patient's ECHO before and after clozapine discontinuation available at www.fedprac.com).

DISCUSSION

In retrospect, this patient likely had HF for many months prior to the official diagnosis; however, given this patient's young age, prior history of asthma, respiratory disorders, underlying severe psychiatric disease, and confounding symptoms, it is easy to understand why the diagnosis was initially overlooked and delayed.

This patient did not have significant lower extremity edema, but she reported nausea, vomiting, and weight loss. Typical patients with HF exhibit edema and weight gain unless they experience cardiac cachexia. It is not clear whether this patient had a coexisting gastrointestinal (GI) disorder or whether the GI symptoms were secondary to cardiac cachexia. Additionally, weight gain and metabolic syndrome have been documented with clozapine therapy.

It is interesting that a repeat ECHO within 2 months of clozapine discontinuation did not show an improvement, whereas a CXR at 4 months showed a normal cardiac silhouette, and an ECHO at 11 months showed an improvement in EF and normalization of LV size while on appropriate HF medications. It would have been interesting if an ECHO had been completed at 4 months to correspond with the time when the CXR normalized.

There does not seem to be a high level of awareness regarding this potentially fatal diagnosis of cardiomyopathy related to the use of clozapine. A recent review of clozapine-induced cardiomyopathy by Alawami and colleagues revealed characteristics, including median age of diagnosis of 33.5 years, a mean daily dose of 360 mg (range 125-700 mg/d), average time of therapy until the development of symptoms 14.4 months (range between 3 weeks and 4 years), and the presence of ventricular dilation in 39%.[8] The most common symptoms on clinical presentation were shortness of breath (60%), palpitations (36%), cough (16%), fatigue (16%), and chest pain (8%).[8]

It is interesting that edema was not present in the patients studied in their review; this difference from the usual presentation of severe HF may lower clinical suspicion and makes diagnosing this type of cardiomyopathy more difficult. Alawami also noted that patients with an LVEF < 25% at the time of diagnosis tended to have a poorer prognosis with the highest risk of mortality and limited recovery. Fortunately, in this case, the patient's LVEF improved significantly, and it will be interesting to continue to monitor the patient for further improvement.

As a result of this case, the

Clinical Course Review

Month 0: Patient started on clozapine 150 mg twice a day.
Month 29: Patient presented to the emergency department (ED) with a cough and congestion for 4 days; chest X-ray (CXR) was unremarkable; she was treated for bronchitis.
Month 40: Patient presented to the ED with shortness of breath, particularly with exertion, chest congestion, productive cough, and chest pain. Vital signs were stable, physical exam was unremarkable. Cardiac markers were negative. The CXR was interpreted by a radiologist as possible cardiomegaly. She was diagnosed with bronchitis and discharged with an antibiotic.
Month 44: Patient had nausea and intermittent vomiting for 2 months, unassociated with food, with an accompanying 22 pound weight loss. An upper gastrointestinal (GI) barium air contrast study was obtained demonstrating barium pooling, suggesting poor esophageal motility.
Month 47: Patient presented to the walk-in clinic with worsening cough for 8 days and was prescribed azithromycin.
Month 48: First outpatient ECHO was ordered after the patient presented again to the ED with chest pain and shortness of breath for 2 days. At that time, the patient mentioned that a computerized tomography scan that had been done in month 44 as part of the gastrointestinal workup showed fluid in the lungs. Brain natriuretic peptide was markedly elevated.
Month 49: ECHO was completed and revealed an ejection fraction (EF) of 10% to 15% and left ventricular (LV) dilation; cardiology referral was made.
Month 51: Patient completed first outpatient cardiology visit after several no-show appointments; clozapine suspected as a possible etiology of cardiomyopathy.
Month 52: Clozapine stopped after a discussion with psychiatry.
Month 54: ECHO unchanged.
Month 56: CXR demonstrated a normalized cardio-mediastinal silhouette.
Month 63: Third ECHO showed an improved EF of 30% to 35% and resolution of LV dilation.

authors have performed a chart review on all patients prescribed clozapine at VA Loma Linda Healthcare System. Additionally, this case supports the implementation of better cardiomyopathy monitoring of all clozapine patients. It may be recommended to obtain a baseline CXR in all patients starting clozapine, conduct monthly cardiomyopathy symptom screening that coincides with ANC monitoring, and perform an ECHO immediately on any clinical suspicion of cardiomyopathy.

CONCLUSION

Better awareness and regular screening for signs and symptoms of HF may help prevent a delay in diagnosing a rare but serious and potentially fatal condition associated with clozapine. Chest X-rays demonstrating cardiomegaly can be helpful when the early diagnosis of HF is suspected and may be the first diagnostic imaging test to normalize after clozapine discontinuation.

Since clozapine is a REMS medication and all patients are scheduled for regular ANC follow-up, it would seem prudent that patients also should be screened for signs and symptoms of HF, including the new onset or worsening of baseline shortness of breath, palpitations, cough, fatigue, chest pain, edema, gastroparesis, and perhaps extreme weight loss. Once a physician suspects HF, an ECHO should be obtained immediately.

In addition to the clozapine boxed warning for cardiomyopathy, it would be helpful if the clozapine patient counseling information section had a specific warning that advises patients to contact their clinician if they develop the signs and symptoms of HF. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of Federal Practitioner, *Frontline Medical Communications Inc., the U.S. Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review the complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*

REFERENCES

1. Clozaril [package insert]. Rosemont, PA: HLS Therapeutics (USA), Inc; 2015.
2. Youssef DL, Narayanan P, Gill N. Incidence and risk factors for clozapine-induced myocarditis and cardiomyopathy at a regional mental health service in Australia. *Austalas Psychiatry*. 2016;24(2):176-180.
3. La Grenade L, Graham D, Trontell A. Myocarditis and cardiomyopathy associated with clozapine use in the United States. *N Eng J Med*. 2001;345(3): 224-225.
4. Kilian JG, Kerr K, Lawrence C, Celermajer DS. Myocarditis and cardiomyopathy associated with clozapine. *Lancet*. 1999;354(9193):1841-1845.
5. Chow V, Yeoh T, Ng AC, et al. Asymptomatic left ventricular dysfunction with long-term clozapine treatment for schizophrenia: a multicenter cross-sectional cohort study. *Open Heart* 2014;1(1):e000030.
6. Scelsa SN, Simpson DM, McQuistion HL, Fineman A, Ault K, Reichler B. Clozapine-induced myotoxicity in patients with chronic psychotic disorders. *Neurology*. 1996;47(6):1518-1523.
7. Reznik I, Volchek L, Mester R, et al. Myotoxicity and neurotoxicity during clozapine treatment. *Clin Neuropharmacol*. 2000;23(5):276-280.
8. Alawami A, Wasywich C, Cicovic A, Kenedi C. A systematic review of clozapine induced cardiomyopathy. *Int J Cardiol*. 2014;176(2):315-320.