Dose-Dependent Clozapine-Induced Supraventricular Tachycardia

To the Editor: Clozapine is used in patients with treatment-resistant schizophrenia.[1–3] Agranulocytosis, myocarditis, and cardiomyopathy are potentially fatal side effects of clozapine, although the incidence is low.[4] Tachycardia occurs in approximately 25% of patients, with a mean increase of 10 to 15 bpm,[5] and appears to be related to vagal inhibition by the anticholinergic properties of clozapine.[6] Here, a case of dose-dependent supraventricular tachycardia in a schizophrenic patient taking clozapine is presented.

Case report. A 40-year-old Chinese woman was assessed in December 2011 by the emergency services department at a mental health institute. She presented with a 12-month history of irritability, hearing voices, and suspicions that strangers were plotting to kill her, that a bomb was planted in her apartment by terrorists, and that the media sent messages to her about the plot. Hospital admission was precipitated by disruptive behavior in public. There was no positive psychiatric family history and no history of previous psychiatric treatment.

The mental status examination revealed auditory hallucinations with paranoid, persecutory, and referential delusions. She was diagnosed with schizophrenia using *DSM-IV-TR* diagnostic criteria. The physical examination, basic investigations, and electrocardiogram (ECG) were normal. She was treated with the optimal dose and duration (4 weeks) of risperidone (6 mg) and olanzapine (25 mg), to which she showed a mild response, and was switched to clozapine 12.5 mg at night, which was increased by 12.5 mg every 4 days to 37.5 mg. She was also taking olanzapine 10 mg at this time, as it was being cross-titrated with clozapine. Two days after the increase of clozapine to 37.5 mg, she complained of palpitations. Her heart rate was 170 bpm, her blood pressure was 104/90 mm Hg, and an ECG showed supraventricular tachycardia. She was treated with intravenous adenosine bolus 6 mg and monitored every 15 minutes; an ECG was administered at 10, 20, and 30 minutes. The supraventricular tachycardia resolved 10 minutes after the adenosine bolus injection was given. She was kept under observation for 12 hours, and all antipsychotics were stopped during this time. The next day, only clozapine 25 mg was restarted and increased to 37.5 mg after 4 days. Her pulse was monitored twice a day. There was a repeat of the supraventricular tachycardia 2 days later with exactly the same symptoms. The pattern of treatment and response was the same as mentioned previously, although she was kept under observation for 48 hours.

The patient was fully monitored in the medical unit for cardiac functions including cardiac enzymes after she developed supraventricular tachycardia in both instances. ECG and pulse monitoring were done regularly. All test results were normal when she was transferred out of the medical unit. On clozapine 25 mg, she had no palpitations, and her pulse rate and ECG were normal. She was discharged from the hospital on clozapine 25 mg and olanzapine 10 mg, as it was not possible to increase the dose of clozapine. As she had shown some response to olanzapine, a combination of the 2 drugs was deemed an optimal option. No palpitations and a normal pulse were noted during follow-up. Her ECG was normal. The cardiac enzyme testing was repeated once after a period of 3 months, despite no symptoms, and was within normal limits. With therapy and medications, the psychotic symptoms have decreased, although not completely remitted. She has resumed work, and her functioning has improved.

Myocarditis, a risk of clozapine use, has been estimated at 0.015%–0.188%.[4,7–9] However, true risk is most likely higher, as according to a study,[10] only a minority of adverse medication-related events are diagnosed and reported. Retrospective studies[11,12] have found that as many as 66% of the patients treated with clozapine develop some findings consistent with myocarditis, like tachycardia, fever, chest pain, dyspnea, flu-like symptoms, eosinophilia, elevated cardiac enzyme levels, and ECG changes, although these are nonspecific. Although our patient did not develop a fever, she had shortness of breath, tachycardia, and ECG changes. Immediate treatment could be sought to reverse the symptoms while monitoring the pulse rate. A learning point from this case is that baseline ECG monitoring and regular pulse monitoring, especially when increasing the dose of clozapine, may help reduce risks of serious cardiac complications secondary to clozapine.

References

1. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45(9):789–796.
2. Meltzer HY, Kostacoglu A. Treatment-resistant schizophrenia. In: Lieberman J, Murray R, eds. *Comprehensive Care of Schizophrenia: A Textbook of Clinical Management*. London, UK: Martin Dunitz; 2001:181–203.
3. Miller A, McEvoy J, Jeste D, et al. Treatment of chronic schizophrenia. In: Lieberman J, Stroup TS, Perkins D, eds. *Textbook of Schizophrenia*. Washington, DC: The American Psychiatric Publishing; 2006:365–381.
4. Kilian JG, Kerr K, Lawrence C, et al. Myocarditis and cardiomyopathy associated with clozapine. *Lancet*. 1999;354(9193):1841–1845.
5. Safferman A, Lieberman JA, Kane JM, et al. Update on the clinical efficacy and side effects of clozapine. *Schizophr Bull*. 1991;17(2):247–261.
6. Rechlin T, Claus D, Weis M. Heart rate variability in schizophrenic patients and changes of autonomic heart rate parameters during treatment with clozapine. *Biol Psychiatry*. 1994;35(11):888–892.
7. Degner D, Bleich S, Grohmann R, et al. Myocarditis associated with clozapine treatment. *Aust N Z J Psychiatry*. 2000;34(5):880.
8. La Grenade L, Graham D, Trontell A. Myocarditis and cardiomyopathy associated with clozapine use in the United States. *N Engl J Med*. 2001;345(3):224–225.
9. Hägg S, Spigset O, Bate A, et al. Myocarditis related to clozapine treatment. *J Clin Psychopharmacol*. 2001;21(4):382–388.
10. Dukes MN. The importance of adverse reactions in drug regulation. *Drug Saf*. 1990;5(1):3–6.
11. Wehmeier PM, Schüler-Springorum M, Heiser P, et al. Chart review for potential features of myocarditis, pericarditis, and cardiomyopathy in children and adolescents treated with clozapine. *J Child Adolesc Psychopharmacol*. 2004;14(2):267–271.
12. Reinders J, Parsonage W, Lange D, et al. Clozapine-related myocarditis and cardiomyopathy in an Australian metropolitan psychiatric service. *Aust N Z J Psychiatry*. 2004;38(11–12):915–922.

Sutapa Basu, MD, DPM[a]
sutapack@yahoo.co.uk

[a]Institute of Mental Health, Buangkok Green Medical Park, View, Singapore

Potential conflicts of interest: None.

Funding/support: None.

Published online: June 30, 2016.

Prim Care Companion CNS Disord 2016;18(3):doi:10.4088/PCC.15l01867