A 31 year old white man was referred by his general practitioner to the cardiology outpatient department for investigation of a persistent sinus tachycardia. His only significant past medical history was of chronic schizophrenia for which he had been taking clozapine for six years. An electrocardiogram demonstrated sinus tachycardia, voltage criteria for left ventricular hypertrophy, and a prolonged QTc. Echocardiographic findings were consistent with a dilated cardiomyopathy. Serious cardiac complications of clozapine use are rare but have been reported previously. It is important to note that sinus tachycardia may be the only obvious clinical sign, and that complications can manifest months or even years (as in this case) after starting the drug. Patients on clozapine should be informed of potential cardiac symptoms and doctors should maintain a high degree of clinical suspicion throughout the duration of treatment.

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DISCUSSION

Clozapine is a dibenzodiazepine antipsychotic used in the treatment of resistant schizophrenia. Minor cardiovascular side effects, namely orthostatic hypotension and sinus tachycardia, are relatively common and have been previously described. There is also a well recognised 1% risk of agranulocytosis during the first year of treatment. Of great concern are the lesser reported serious and potentially fatal cardiac complications. In particular both myocarditis and dilated cardiomyopathy have been reported. To date the CSM has received 30 reports of cardiomyopathy and 40 cases of myocarditis associated with clozapine use. Killian et al presented 23 cases of myocarditis and cardiomyopathy temporally associated with this drug. Between 1989 and 1999 the United States Food and Drug Administration received reports of 28 cases of myocarditis (including 18 deaths) and 41 cases of cardiomyopathy (including 10 deaths) in patients receiving clozapine. Bayesian analysis as applied to the World Health Organisation drug monitoring database has demonstrated that clozapine is significantly more frequently reported in relation to myocarditis and cardiomyopathy than other drugs (including other antipsychotics). Interpretation of case reports is complicated by the often non-specific symptoms and signs of myocarditis and cardiomyopathy. ECG changes reported are also non-specific and include sinus tachycardia, T-wave inversion, prolonged QTc, and ST flattening/depression. It must be borne in mind that many of the cases reported have not had definitive evidence for their diagnoses.

It is, however, very likely that there is a causal link between clozapine and myocarditis/cardiomyopathy. Several cases have been associated with a peripheral and/or cardiac eosinophilia suggestive of an IgE-mediated hypersensitivity reaction. The greatest risk of cardiac involvement most commonly occurs

Abbreviations: CSM, Committee on Safety of Medicines; ECG, electrocardiogram; QTc, corrected QT interval
Summary points

- Cardiac complications of clozapine are rare but potentially fatal.
- Cardiac complications (especially cardiomyopathy) can occur months or even years after the introduction of clozapine treatment.
- Persistent sinus tachycardia may be the sole presenting sign and must not be assumed to be a benign side effect.
- A high degree of clinical suspicion must be maintained in patients on clozapine, and a low threshold for referral for cardiological assessment.

During the first month of use. Although as reported in this case, risk persists throughout its use. It is also likely that myocarditis typically presents earlier than cardiomyopathy.

In this case there was both subjective and objective evidence of improvement on withdrawal of clozapine. Although it is difficult to know the contribution of drug treatment, there have been reports of improvement on withdrawal of clozapine in both cardiomyopathy and myocarditis. In addition to standard supportive treatment for myocarditis and cardiomyopathy it has also been suggested that corticosteroids have a role.

In conclusion, clozapine associated myocarditis and cardiomyopathy are serious and potentially lethal complications. Patients should be informed of symptoms of cardiotoxicity. It is important that a high degree of clinical suspicion is maintained throughout the duration of clozapine therapy with a low threshold for referral to a cardiologist.


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Clozapine associated dilated cardiomyopathy

M A Tanner and W Culling

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