A successful re-trial after clozapine myopericarditis

K Sarathy[1], C Alexopoulos[2]

Abstract

Clozapine-induced myopericarditis is a well-described adverse drug reaction. Clozapine is also the most efficacious agent in refractory schizophrenia. We report a case of a patient who was successfully re-trialled on clozapine two years after developing myopericarditis, after which multiple lines of alternative treatment failed. We propose a protocol for safely attempting a re-trial of clozapine in such cases.

Keywords: clozapine, myopericarditis, re-trial

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Correspondence to:
K Sarathy
Port Macquarie Base Hospital
Port Macquarie
NSW
Australia

Email:
kiran.sarathy@unsw.edu.au

A 29-year-old man with a history of schizophrenia presented to our emergency department with acute psychosis manifesting as visual and auditory hallucinations associated with paranoid delusions and persecutory thoughts. He had been on treatment with monthly paliperidone 100 mg depot and had had recurrent lengthy admissions for previous episodes of psychosis. He had a history of polysubstance abuse and smoking. Clinical examination was normal apart from the mental state examination which was consistent with a relapse of schizophrenia, with a high risk of aggression and misadventure.

He was commenced on clozapine with monitoring as per local protocol. On day 16 of treatment he developed fever and tachycardia and shortly afterwards reported chest pain. His clinical examination remained unchanged; however, routine investigations revealed elevated troponin I, raised C-reactive protein (CRP) (Figure 1) and 12-lead ECG revealed dynamic T-Wave inversion in V5–V6 and leads I and aVL. Clozapine was discontinued and the patient was transferred to the Coronary Care Unit for management of presumed clozapine-induced myopericarditis. A CT coronary angiogram showed a calcium score of 0 with no significant coronary disease. Transthoracic echocardiography (TTE) revealed normal left ventricular size and function, no significant valvular pathology and no pericardial effusion. Inflammatory markers and cardiac enzymes were monitored until all had normalised. In the interim, the patient was managed with alternative antipsychotics. He required multiple lengthy admissions due to poorly controlled schizophrenia over the next two years, reflecting the relative efficacy of clozapine in this setting.[1]

Two years later, after the patient had been hospitalised for three months following another admission for an exacerbation of schizophrenia, our department was consulted regarding the feasibility of re-trialling clozapine as all other antipsychotic treatment options had been exhausted.

Baseline investigations including ECG, TTE, troponin, CKMB, brain natriuretic peptide, full blood count, erythrocyte sedimentation rate, and CRP were repeated. A protocol for monitoring was implemented that included daily clinical assessment, ECG and blood tests for the first two weeks, with a fortnightly TTE. Consent was obtained after explaining the risks and benefits to both the patient and family. Clozapine was commenced at a dose of 6.25 mg and increased in increments of 6.25 mg every week for the first four weeks. Following this, the dose was increased in increments of 12.5 mg weekly until a target dose of 300 mg was reached with adequate clinical effect. At two weeks of re-trial, frequency of blood tests was reduced to twice weekly; at four weeks this was reduced to weekly. At this time, monthly TTE was implemented. The patient remained an inpatient in the psychiatry ward for the first three months with ongoing monthly cardiology follow up for the next four months after discharge.

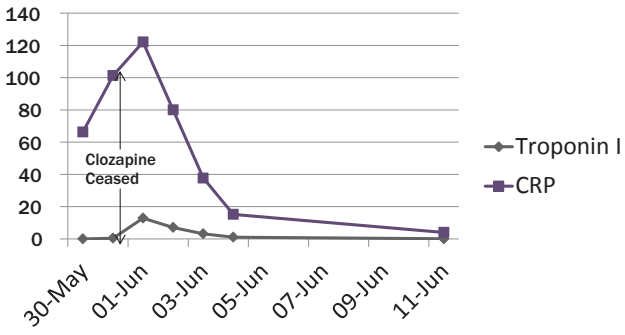
The rationale behind the design of our monitoring regime and dose titration was based on published data suggesting a peak incidence of myopericarditis at two to three weeks after initiation of clozapine.[2] Cardiac MRI was not available in our regional centre but would otherwise have been utilised as an adjunct in diagnosis.

At six months after commencement of the re-challenge, there has been no clinical, biochemical, or echocardiographic evidence of recurrent myopericarditis.

Clozapine is an atypical antipsychotic, specifically a tricyclic dibenzodiazepine. It is a highly efficacious treatment in refractory schizophrenia; indeed it has been shown to reduce mortality in schizophrenia via a reduction in suicide.[3] However, its use is limited by a side effect profile that includes cardiotoxicity. Clozapine myopericarditis was first described over 15 years ago and has an incidence of approximately 1%.[2]

[1]Cardiology Advanced Trainee; [2]Consultant Cardiologist, Port Macquarie Base Hospital, Port Macquarie, NSW, Australia

Figure 1 High sensitivity tropinin I and C-reactive protein levels over time from initial treatment with clozapine



A number of possible pathophysiological mechanisms has been proposed including an IgE-mediated hypersensitivity, a type 3 allergic reaction (though selective cardiac end organ damage makes this less likely), catecholamine-mediated ventricular dysfunction (akin to Takostubo's cardiomyopathy) and a direct toxic effect on the heart with associated inflammatory infiltrate.[1] Additionally, myopericarditis seems to exist on a spectrum of clozapine-related adverse drug reactions that ranges from tachycardia and pericarditis (without myocardial involvement) to severe cardiomyopathy and sudden cardiac death. It is worth noting that the incidence does not appear to be dose-dependent.[4]

The natural history of this process typically involves a heart rate rise of 10–20 beats per minute within the first 10–19 days after initiation of clozapine, though this may be unrelated to the development of myocarditis. After approximately day 20, the onset of generalised cardiorespiratory symptoms with an elevation of the CRP is generally noted with an associated worsening of the tachycardia. From about day 25 onwards, an elevation of the serum troponin (> 2 the upper limit of normal), the CRP (> 100 mg/L), and left ventricular impairment on echocardiography is seen.[5]

Our case highlights the feasibility of, and offers a protocol for, clozapine re-challenge, and adds to the limited number of published cases demonstrating that prior clozapine-induced myopericarditis is not an absolute contraindication to a re-challenge of clozapine treatment in selected cases.[5,6]

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