Two case studies of clozapine-induced myocarditis

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There is currently limited knowledge about which side-effects patients will experience from clozapine. In this article, the authors describe two cases of patients who developed myocarditis during the initiation period of clozapine. The cases also illustrate the difficulty in diagnosing clozapine-induced myocarditis due to the non-specific nature of the symptoms.

Clozapine is a valuable drug in the treatment of refractory schizophrenia. In our practice of working in forensic rehabilitation the effect of clozapine in improving the lives of patients with enduring, debilitating and treatment-resistant conditions is invaluable. However, we have encountered some problems with serious unwanted effects – our case reports describe a need for extra vigilance when commencing clozapine.

Unwanted effects associated with clozapine are well known. Since clozapine’s introduction in 1961, the main concerns have been about agranulocytosis. Constipation can also become life-threatening, and lead to potentially fatal bowel obstruction. In the last 10 years there has been an increasing focus on the cardiotoxicity associated with anti-psychotic treatment, illustrated by QTc prolongation on the ECG. Although clozapine has a mild effect on QTc prolongation, it can also have a directly toxic effect on myocardial tissue, causing myocarditis. Kilian et al first described this association in 1999. This can be potentially fatal, perhaps with a risk of 1 per 1000 patients, and be very difficult to detect clinically.

The estimated incidence of this side-effect in clozapine-treated populations is variable. Some studies have estimated it to be as high as 8.5%. Other studies have suggested that as many as 66% of the patients treated with clozapine develop some findings consistent with myocarditis, but these are non-specific. Haas et al estimated the incidence of myocarditis in clozapine-treated patients to be between 0.7% and 1.2%. Since many patients are either undiagnosed or unreported, and symptoms can be very vague, it is difficult to assess the precise incidence. Mortality rates as high as 50% have been associated with clozapine-induced myocarditis, a delayed diagnosis resulting in poorer outcomes. A high index of clinical suspicion is needed to detect these cases, and to ensure that adequate medical treatment is provided. However, prompt diagnosis, discontinuation of clozapine, and supportive treatment can lead to spontaneous resolution with no lasting complications.

The pathophysiology of clozapine cardiotoxicity remains unclear. It probably has an auto-immune mechanism. Killian et al have suggested a type I immunoglobulin E (IgE)-mediated hypersensitivity reaction. This is an immediate type of allergic reaction in which the clozapine molecule, or metabolite of it, acts as a direct allergen, stimulating B-lymphocytes to produce IgE. This then stimulates mast cells to release histamine, leukotrienes and prostaglandins, which can then damage cardiac tissue.

There are likely to be slower immunological responses also, mediated through cytokines (also products of leukocyte extravasation). These too, are pro-inflammatory substances, and can have general effects on catecholamine release. Cytokine expression has been shown to depress myocardial contractility directly and may have a role in myocardial apoptosis. Some studies have also shown an increase in nitric oxide (NO) via NO synthase associated with circulating cytokines. This has a direct impact on myocardial cells, inducing negative inotropism and myocardial damage. Clozapine is also known to increase serum catecholamine levels. Cocaine shares this effect and has been shown to exacerbate viral myocarditis, suggesting a role for catecholamine in the development of the disorder.

Genetic and ethnic variations in drug metabolism have been an area of recent research interest. Clozapine is metabolised by the cytochrome P450 1A2 system, encoded by the CYP1A2 gene. Variation in this gene coding is known to be associated with either fast or slow metabolism of clozapine. Blockade of calcium-dependent ion channels and low serum selenium levels may also be relevant. These are likely to be areas for further research.

This article describes two cases of men who developed myocarditis during the initiation period of clozapine. This is likely to be the high-risk time, particularly given the immunological models concerning the pathology.

Case 1
The patient was a 31-year-old man of mixed ethnicity with a long-standing...
diagnosis of paranoid schizophrenia dating back to 2004. He had had several psychiatric admissions, including a previous admission to the medium secure forensic unit. He had a long history of offending behaviour, poor engagement with his treatment teams and erratic compliance with medication. His treatment in the past included a wide range of antipsychotic medication.

His current admission began in November 2012, following the deterioration of his mental state. He was initially treated with amisulpride on a psychiatric general ward. He was moved to the psychiatric intensive care unit (PICU) after he seriously assaulted a member of nursing staff and later transferred to a medium secure forensic psychiatric unit in April 2013, following ongoing concerns about his level of risk.

Because of the patient’s ongoing psychotic beliefs, despite at least two trials of different antipsychotic drugs over long periods, he was offered a trial of clozapine. The baseline tests were done and all were normal. His baseline pulse rate was 82 beats per minute (bpm) (see Figure 1) and blood pressure (BP) 123/73 mmHg.

Seven days after the beginning of the start-up titration, he complained of feeling tired and started to experience significant sedation; a slower titration regime was agreed. On the 14th day of titration, his pulse was 114 bpm, with a normal BP reading. He complained subjectively of palpitations and a feeling of panic. An ECG was performed, showing a sinus rate of 99 bpm with no abnormalities (see Figure 2).

The following day, he reported not feeling well and complained of headache; his pulse was recorded as 112 bpm, with a temperature of 37°C, and BP 136/89 mmHg. He was prescribed paracetamol for symptomatic relief. A day later (over the weekend) he stopped playing pool on the ward, as was his usual habit, stating that he felt too tired. He complained of ‘flu-like symptoms’ – a blocked nose, a sore throat and headache – this seemed like an emerging viral infection.

His flu-like symptoms continued over the weekend – his observations were normal apart from a slight tachycardia. He complained of night sweats, but was afebrile. On the Monday following the weekend he was seen by his team. He looked unwell; his skin complexion looked greyish, and he complained of a sore throat, blocked nose, a headache and anxiety. By this time, his pulse was 112 bpm, and temperature 37.5°C. Given the abnormal observations, his C-reactive protein (CRP), troponin levels, full blood count and clozapine levels were checked (this was done on the 18th day of clozapine titration). The results were abnormal: his serum troponin was high at 0.11 μg/L (three times above the normal 0.01–0.04 μg/L), as well as CRP of 87 mg/L (the normal level is below 10 mg/L).

Serum troponin level is a highly sensitive and specific biomarker for myocardial damage. The possibility of clozapine-induced myocarditis was considered. He was transferred to the medical ward and his clozapine was immediately stopped. Further investigations, after the clozapine was stopped, showed a normal ECG, normal chest X-ray, negative blood cultures, normal echocardiogram. His troponin levels return to a normal limit of 0.02 and CRP fell to 63 mg/L.

Following two days of investigations on a medical ward the patient was discharged to the psychiatric ward.
Further discussion with the cardiology team suggested the possibility of clozapine-related myocarditis. His antipsychotic medication was switched back to depot, and his physical health returned to normal.

**Case 2**

The patient was a 27-year-old man of mixed ethnicity who developed signs of a psychotic illness around six years earlier in the context of sustained cannabis misuse since his late teens. He developed persecutory and grandiose delusions, and delusions of reference. He had been admitted to hospital six times in the following four years, usually detained under the Mental Health Act. By 2012, he had been diagnosed with schizophrenia.

The patient’s admission to forensic services in July 2014 was due to deterioration of his mental state following medication noncompliance leading to violent behaviour. He was acutely psychotic when he was transferred to the local medium secure unit from prison. Although these later resolved in response to antipsychotic medication, Mr A still demonstrated significant negative symptoms of schizophrenia, which persisted after his transfer to a low security unit in February 2016. In view of the continuing tremor in his leg, which was felt to be related to his depot antipsychotic, the patient agreed to switch to clozapine, after the usual preliminary investigations – his baseline pulse rate was 87 bpm and BP normal. The baseline ECG was normal (see Figure 3) with a heart rate of 86 bpm. Mr A commenced a standard clozapine titration in April 2016.

On the 13th day of his clozapine titration the patient developed a tachycardia (see Figure 4) with pulse of 150 bpm; his temperature began to spike (with temperature of 40°C) and his BP dropped to 90/55mmHg. He complained of vomiting, nausea and diarrhoea.

He was transferred urgently to a medical ward, where he was admitted and treated initially for a suspected gastrointestinal infection complicated with generalised sepsis (white blood count 11.7 × 10⁹/L and neutrophils of 9.7 × 10⁹/L, CRP of 143mg/L). His troponins were not measured at this stage, as a diagnosis of clozapine-induced myocarditis had not been considered.

The patient’s clozapine titration was slowed down and he was started on an intensive course of intravenous antibiotics. However, his temperature continued to be high despite the antibiotic treatment. On the 17th day of clozapine treatment, the patient went into a dramatic tachyarrhythmia of 180 bpm and was transferred to the intensive care unit with diagnosis of cardiac failure. An echocardiogram showed impaired systolic function of the heart (with a left ventricular ejection fraction of 35–40%). He developed pulmonary oedema. Only at that point did the medical team raise concerns of myocarditis. Further investigations showed high creatinine kinase of 1982μ/L (10 times above normal), and a continued high troponin. His CRP assay continued to increase to 178mg/L.

The diagnosis was changed to myocarditis; clozapine, however, was stopped following consultation with the psychiatric team. He was treated on the cardiology ward (temporarily) with ACE inhibitors and beta-blockers. These were subsequently discontinued.
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References

Discussion
Both of these cases illustrate the difficulty in diagnosing clozapine-induced myocarditis, due to the vagueness and non-specific nature of the symptoms. Case 2 illustrates the dramatic sequelae of a delay in diagnosis. Troponin measurements were helpful in confirming the condition.

Both patients developed this condition during the initiation phase of their clozapine treatment. This may be a particularly high risk period. Mild fever, tachycardia, and fatigue are common during the start-up titration. Developing one or two symptoms during this period is very common indeed. Low-grade fever is thought to occur in up to 20% of the patients commencing treatment with clozapine and is considered a benign, self-limiting phenomenon. Isolated tachycardia is also very common in early stages of treatment and also could be benign.

It is the constellation of symptoms, coupled with a fever in this start-up period that seems to be key in aiding the clinical diagnosis. Tachycardia, flu-like symptoms, vomiting, dyspnoea, may all be present. Chest pain, normally alerting clinicians to a cardiac problem, may be completely absent. Other blood abnormalities such as the development of an eosinophilia, elevated cardiac enzyme levels, or ECG changes may help with the diagnosis. No single finding is pathognomonic. Even biopsy (following death) has limited sensitivity and specificity: the diagnosis is often guided by clinical evidence. Conclusion
Treatennent with clozapine, which can be highly beneficial, is not without its risks. We have limited knowledge currently about which patients will experience which side-effects from clozapine, or from the other drugs we prescribe. However, patients who develop more than one vague symptom, for example, tachycardia and fever, during the initial titration phase with clozapine must be considered to be at risk of having developed myocarditis. It is imperative that this condition is recognised, as it can develop into a life-threatening condition, but is completely reversible if clozapine is stopped.

ECG analysis, CRP and troponin assays help with the diagnosis. Both patients were transferred to medical units for supportive treatment and further investigation, but returned to psychiatric inpatient care when it was safe to do so. We have changed our practice to regular assays of serum troponins during the clozapine start-up period to help with the early recognition of this important condition.

After the development of life-threatening side-effects, clinical teams are left with the problem of what to do next in terms of medication for treatment-resistant patients. This is a great challenge, and may require careful discussion with the team pharmacist as to what might be helpful. There remains very limited evidence for combinations of antipsychotic treatments aside from clozapine. However, these sorts of options can be appropriate where trials of clozapine have been unsafe.

Declaration of interests
No conflicts of interest were declared.

The patient was discharged back to the psychiatric ward following two weeks of treatment on medical wards. Since that time he has been very settled. His vital signs have stabilised and his cardiac function, which was found to have been impaired, has improved. His schizophrenia is now treated with another atypical antipsychotic drug, which he is currently tolerating well.