Irish Journal of Psychological Medicine, (2021), **38**, 227–231. doi:10.1017/ipm.2018.6

Continuing clozapine treatment after a diagnosis of cardiomyopathy

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A patient in a medium secure psychiatric unit with a 19-year history of treatment-resistant schizophrenia and violence whose mental illness only responded to clozapine, was noted to have a sustained tachycardia. Echocardiography revealed mild biventricular cardiomyopathy. The patient was not significantly affected by this. Initial recommendation from Cardiology was to consider discontinuation of clozapine. It was decided, however, that the risk of worsening psychosis and resultant violence outweighed the risk of the patient's relatively mild cardiomyopathy. The patient was commenced on ramipril, and later bisoprolol. The patient no longer requires treatment in a medium secure unit and has remained on clozapine with follow-up from cardiology.

Received 15 May 2017; Revised 9 January 2018; Accepted 22 March 2018; First published online 09 May 2018

Key words: Cardiomyopathy, clozapine, forensics, schizophrenia.

Introduction

Clozapine is the most effective antipsychotic for treatment-resistant schizophrenia. It reduces aggression more effectively than other antipsychotics (Krakowski *et al.* 2006), and there is evidence that patients with schizophrenia taking clozapine are more likely to live independently and to be in employment compared to those taking other medications (Wheeler *et al.* 2009). Clozapine has also been associated with reduced suicidal behaviour compared with olanzapine (Meltzer *et al.* 2003). However, its use is limited by the risk of significant adverse effects. One of the most serious of these is the association with cardiomyopathy.

The summary of product characteristics states that patients with clozapine-induced cardiomyopathy should discontinue clozapine and not be re-exposed to it (Electronic Medicines Compendium, 2016). Ongoing use of clozapine in patients with cardiomyopathy is therefore strictly off-licence. There is a significant risk in continuing clozapine in patients who experience adverse cardiovascular reactions to the medication, however, many patients with schizophrenia are on clozapine because no other antipsychotic has adequately controlled their mental illness (Alawami *et al.* 2012). One study showed that 80% of patients withdrawn from clozapine for medical reasons developed a psychotic relapse (Conley, 1998).

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Clearly, cardiomyopathy is an illness which can have a significant impact on the quality of a patient's life; however, so can schizophrenia. In this case, the patient's quality of life was not impaired by cardiomyopathy, but it had been adversely affected when not taking clozapine due to untreated psychotic symptoms. Therefore this case demonstrates that with careful risk–benefit analysis and close monitoring by cardiology, treatment with clozapine may be able to continue to the benefit of the patient following a diagnosis of cardiomyopathy.

Case presentation

The patient is a 42-year-old man with type two diabetes mellitus who, by the age of 21 had an established diagnosis of paranoid schizophrenia. The patient also has a significant history of assault associated with episodes where he had been mentally unwell. He had commenced clozapine in October 1997. Before this, he had been on many different antipsychotics including trifluoperazine, thioridazine, flupenthixol depot, zuclopenthixol depot and olanzapine. There have been longstanding concerns about the patient's inconsistent adherence to medication which had a negative effect on his mental health, even if very few tablets were missed. He was thus provided with input from support staff to promote his adherence to treatment. Whilst adhering to clozapine treatment, the patient was able to sustain living in the community.

In November 2013, the patient expressed a desire to try an alternative medication for unclear reasons. The patient started Olanzapine 20 mg instead for 3 days but

then wished to stop as it was doing 'nothing'. At the same time, his mental health deteriorated with evidence of hostility, agitation, poor self-care, overvalued ideas and delusions leading to informal admission to an open general adult psychiatric ward. He continued to refuse olanzapine, and despite alternatives such as haloperidol and aripiprazole antipsychotics being prescribed, the patient continued to deteriorate and assaulted a fellow patient leading to detention under the Mental Health Act, and transfer to an intensive psychiatric care unit (IPCU). Therefore, the impression was of clozapine being the one medication that could treat the patient's symptoms, and so it was recommenced. However, the patient remained ambivalent about continuing it and was only partially adherent to it. His condition continued to worsen culminating in further assaults on the IPCU and precipitating a transfer to medium security in February 2014. It was considered at the time that the further decline in his mental health had been due to non-adherence to clozapine.

In the medium secure unit, he was initially managed in seclusion and remained floridly psychotic with evidence of thought disorder, and delusions of a grandiose and persecutory nature. The patient remained reluctant to recommence clozapine. With treatment with adequate doses of depot zuclopentixol decanoate and subsequently high-dose oral olanzapine, he could be managed out of seclusion but continued to be troubled by psychotic symptoms. Time off the ward required a two nurse escort and passes were regularly revoked due to deteriorations in the patient's mental state. In December 2014, the patient was persuaded to recommence clozapine treatment and showed a very positive and sustained response. The olanzapine was stopped, and he was not on any additional regular antipsychotics. His speech became more coherent, and while he continued to hold delusional beliefs, these had become less salient, and the associated distressing effects were greatly reduced. His escort level for passes was reduced from two nurses to one. As the patient continued to progress positively, some unescorted pass was subsequently introduced.

The patient had a history of tachycardia documented in his notes dating back to 2000. In December 2014, 8 days after starting clozapine, due to a tachycardia of over 130 beats per minute, the patient was commenced on atenolol. Clozapine escalation was stopped. An electrocardiogram (ECG) at that time showed only a sinus tachycardia and the patient was asymptomatic. C-reactive protein and troponin were taken 5 days later which were normal. A referral was made to Cardiology. The opinion from the cardiologist was that the tachycardia was likely driven by a combination of olanzapine and clozapine, and discontinuation of these drugs with a view to an alternative was suggested.

A response to this letter was written by his treating Forensic Psychiatrist which indicated that clozapine treatment was necessary as stopping would lead to deterioration in his mental health and subsequent increased risk of violence to others, deterioration in the quality of life and poor adherence to the management of diabetes. By this time, the patient was reporting palpitations and concerns about his cardiac health. A review at the clinic was therefore requested, and an out-patient two-dimensional echocardiography (ECHO) was organised in June 2015. This confirmed a mild-to-moderate degree of global left ventricular systolic impairment with a left ventricle which was mildly dilated in systole. The left ventricular diastolic diameter was 53 mm (normal 40–57 mm). The impression from the cardiologist was that the patient's relatively mild biventricular cardiomyopathy could well be driven by antipsychotic medication and was unlikely to be due to sustained sinus tachycardia. The cardiologist recommended that serious consideration should be given to discontinuing antipsychotic medication for a period of time if there were concerns with regards to his cardiovascular status. A chest X-ray in October 2015 did not show features of heart failure, and the patient's functioning was not affected by cardiomyopathy.

A response from the consultant forensic psychiatrist again stated that withdrawal of clozapine would almost certainly end the patient's progression back to his own accommodation in the community and would likely lead to him being detained in a medium secure unit on an open-ended basis. It was felt that due to the patient's illness, that he lacked the capacity to take part fully in treatment decisions, but he had always expressed a clear and consistent preference for living in his own house. There were further discussions with Cardiology regarding the difficult risk/benefit balance involved in stopping or continuing clozapine. It was agreed not to imminently stop clozapine. Ramipril was commenced. It was felt that atenolol was probably not required as there was by this time no concern regarding symptoms.

A nuclear medicine isotope scan, a cardiac multiple gated acquisition (MUGA), was requested to determine cardiac output. This scan involves injecting the isotope intravenously into the circulating blood. A gamma camera is then used to detect the amount of radiation-emitting blood passing through the heart at different stages of the cardiac cycle, and also the size and shape of the heart chambers. The gamma camera is linked to the ECG so that this information can be collected over a number of cardiac cycles so that the systolic and diastolic phases can be 'gated' and left ventricular ejection fraction (LVEF) can be calculated. The reference range for LVEF can vary dependent on the method but is usually >60% (Newby *et al.* 2010). MUGA scans are

https://doi.org/10.1017/ipm.2018.6 Published online by Cambridge University Press

not commonly used in regular Cardiology practice as they have a relatively high radiation dose and measure only LVEF as a number. They are mainly used by Oncology to assess the effect of chemotherapy on left ventricular (LV) function on an intermittent basis. A MUGA scan was picked in this instance because it would be easier for the patient to tolerate than a cardiac magnetic resonance imaging scan and there was less demand for this test so it could be organised more quickly, whilst still giving a good objective indication of cardiac function. The ejection fraction with MUGA is more reproducible and less affected by patient shape, poor-quality images and inter-observer error than ECHO. It does, however, involve radiation (Personal Communication, Professor Uren, 9 October 2017). A selenium level, which can be associated with cardiomyopathy in patients on clozapine (Vaddadi *et al.* 2003), was taken which was within normal limits. As clozapine-induced cardiomyopathy is not felt to be dose-dependent (Alawami *et al.* 2012), the patient's clozapine dose was increased gradually to gain better control over the psychosis.

The cardiac MUGA in December 2015 showed that the LVEF was mildly impaired measuring 33% (normal range 40–70%). All professionals involved concurred that there was a difficult balancing act between cardiac risk and severe impairment of function and quality of life due to mental illness. The plan at that time was to repeat the MUGA on an annual basis to monitor the patient's cardiac function. A year was chosen as the interval on a purely arbitrary basis. Discussions were had with the Mental Welfare Commission, and a meeting was arranged with the next of kin. The patient remained on clozapine with no symptoms of cardiac impairment. Although he continued to have breakthrough psychotic symptoms, he was much more settled in presentation and was discharged from medium security to an open general adult ward in June 2016.

Initially, the patient overall remained physically and mentally stable on the open ward. An attempt was made in November 2016 to switch the patient to lurasidone. In less than 4 weeks, the medication had to be changed back to clozapine due to increasing aggression and worsening psychosis. The patient had a further interruption to his clozapine treatment in January 2017 when he started refusing it as he believed it was damaging him. This unfortunately culminated in a deterioration in mental state and a significant assault on another patient necessitating a transfer to IPCU. Shortly after transfer to IPCU, the patient agreed to recommence clozapine, his mental health and aggression improved thereafter, and he was able to recommence passes out to the community. He was accepted for transfer to the rehabilitation service in April 2017 as it was felt he was not stable enough for a direct discharge due to his delusional concerns for his safety at home. He remained an inpatient in IPCU whilst awaiting transfer.

The patient continued to be verbally threatening at times to staff and patients on the IPCU and assaulted another patient due to delusional ideation in June 2017 leading to the suspension of his passes. However, he remained stable enough to be transferred to the rehabilitation unit in July 2017 when a bed became available. He has been largely settled since transfer and engaging well with staff and treatment. The patient continues, however, to demonstrate psychotic symptoms. To this end, 10 mg aripiprazole was commenced at the end of August 2017 to augment clozapine treatment. He also intermittently becomes agitated, and there was a psychotically driven serious assault on a staff member when on a pass in the community in September 2017. There is the possibility of cannabis use which may have also contributed to the decline in mental state. The patient's presentation settled soon after the violent incident, he did not require a move to a higher level of security and has since had unescorted passes restarted. Following the assault, diazepam (which had been withdrawn) was restarted. His clozapine dose is currently 500 mg daily.

The patient has had ongoing tachycardia and has been commenced on bisoprolol 2.5 mg once daily as a result, but he has no other cardiac symptoms. In September 2017 he had a repeat ECHO and his ECHOs over the last 18 months were reviewed. He had two ECHOs whilst in the medium secure unit, and three after discharge from there. They showed that he had some reduction in his left ventricular function: he had left ventricular systolic dilatation and left ventricular end-diastolic diameter of 56 mm which is on the upper limit of normal. The resting tachycardia was considered to be currently a cardiovascular compensation for reduced cardiac output. The ramipril dose has been increased to 2.5 mg daily with advice to increase up to 10 mg daily as tolerated. The current plan is for the patient to be seen by Cardiology again in April 2018, and to have a repeat ECHO with LV strain measurement which is becoming a more sensitive measure of subtle LV dysfunction than MUGA and has the benefit of not involving radiation. The Cardiologist has stated that if the LVEF were to fall by 5% or more, that the antipsychotic should be altered.

Discussion

A systematic review of patients rechallenged on clozapine after potentially life-threatening drug-related conditions found that 138 patients were rechallenged between 1972 and 2011 but none of them was rechallenged after cardiomyopathy (Alawami *et al.* 2012).

https://doi.org/10.1017/ipm.2018.6 Published online by Cambridge University Press

There is thus little evidence to inform clinicians in making the decision to proceed with off-licence use in these circumstances. The same review article suggested that rechallenge could be considered in carefully selected cases but that frequent monitoring including ECHO is necessary. Two review articles have recommended three monthly ECHOs to evaluate cardiac function in cases where it is decided that the benefits of continuing clozapine outweigh the risks in a patient who has developed cardiomyopathy (Merrill *et al.* 2005; Sawicke & Sturla, 2008). A decrease of 15% in LVEF from baseline to 45% or below has been suggested a criterion for discontinuation of treatment with clozapine in those with clozapine-induced cardiomyopathy to prevent further cardiac damage (Merrill *et al.* 2005).

There are four published case reports where clozapine has been discontinued after a diagnosis of cardiomyopathy, and then rechallenge attempted. Thus our case appears to be unique in the published literature as there was no withdrawal of clozapine after the diagnosis of cardiomyopathy. There are significant risks in continuing clozapine in such circumstances such as serious deterioration of cardiac function and potentially death due to heart failure. Indeed in two of the other cases, rechallenge was unsuccessful due to either recurrence of cardiomyopathy or lack of improvement of cardiac function; and clozapine was again withdrawn (Roh *et al.* 2006; Estefanos *et al.* 2013). However, in the two other case reports the patients maintained stable cardiac function after rechallenge (Floreani & Bastiampillai, 2008; Rostagno *et al.* 2008).

Due to the lack of evidence available to guide clinicians when considering off-licence clozapine use, case reports such as this one can be useful to assist clinicians considering whether rechallenge in cardiomyopathy should be attempted with an individual patient. The other advantages of case reports in such situations are that clozapine-induced cardiomyopathy is a rare condition, so more robust forms of studies (e.g. case-control, randomised controlled studies) are difficult to conduct, and due to the risk to the patients involved, would be considered unethical (Nissen & Wynn, 2014). Case reports allow the impact of an intervention on an individual patient to be explored; the decision to rechallenge with clozapine is one which must be made on an individual patient basis to allow appropriate weighing up of advantages and disadvantages. The weaknesses of case reports also need to be recognised and include: lack of ability to generalise, publication bias (in favour of those that show positive results), over interpretation (tendency for readers to generalise without due justification), emphasis on the rare, being produced retrospectively and lack of ability to repeat the study (Nissen & Wynn, 2014). As such, the results of this and other case reports should be interpreted with caution.

Conclusions

The summary of product characteristics for clozapine states that patients with clozapine-induced cardiomyopathy should discontinue clozapine and not be re-exposed to it (Electronic Medicines Compendium, 2016). Ongoing use of clozapine in patients with cardiomyopathy is therefore off-licence. However, clozapine is also the most effective pharmacological treatment for schizophrenia. It can be life-changing for some patients and alleviate their symptoms to such a degree that their care can be managed in the community which would not be possible on other antipsychotics. Therefore, in patients with severe schizophrenia who develop cardiomyopathy, careful consideration of the risks and benefits must be made in order to determine if clozapine treatment should be continued. Use of cardiac medications such as angiotensin-converting enzyme inhibitors and β-blockers have been used in this and other cases to attempt to prevent further cardiac injury if clozapine therapy is continued.

Acknowledgements

The authors would like to thank Professor Neal Uren, Consultant Cardiologist, New Royal Infirmary of Edinburgh, for his assistance with the cardiology aspects of this case report; Dr Debbie Mountain, Consultant Psychiatrist, Royal Edinburgh Hospital for her assistance in getting an update on the patient's clinical progress; Dr Lindsay Mizen, ST6 in Psychiatry of Intellectual Disability, Lothian Learning Disability Service, for her review and advice on the writing of the case report.

Conflicts of Interest

F.W., F.L., A.R. have no conflicts of interest to disclose.

Financial Support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that ethical approval for publication of this case report was not required by their local Ethics Committee. The patient gave written informed consent for the publication of this case report.

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