Hearts and Minds

Real-Life Cardiotoxicity With Clozapine in Psychosis

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Abstract:

Background: Schizophrenia has a 1% prevalence in the population; 30% of these patients are treatment refractory. Clozapine is the only drug licensed to treat treatment refractory psychosis, but concerns about potential adverse effects result in only a proportion of eligible patients being treated. Although a well-documented neutropenia risk is mitigated by routine blood testing, cardiac toxicity is a commonly cited reason to discontinue clozapine treatment. However, there is little data on the real-life cardiac outcomes in those receiving clozapine treatment.

Methods: Retrospective review of electrocardiogram, echocardiogram, and clinical outcomes in 39 inpatients with treatment-refractory schizophrenia, treated with clozapine and other antipsychotic medication, referred for cardiologic opinion.

Results: Commonest reasons for referral were development of left ventricular (LV) impairment or sinus tachycardia with normal LV function. Patients were reviewed by a range of cardiologists, receiving varied interventions.

Median LV ejection fraction in the clozapine group was normal (52%). Serial echocardiograms demonstrated that clozapine-treated patients with LV impairment had no change in LV ejection fraction over a 4-month follow-up. Left ventricular ejection fraction did not differ between patients treated with clozapine and other antipsychotics. However, over an 11-year follow-up period, 48% of patients had discontinued clozapine treatment.

Conclusions: This naturalistic study demonstrates that clozapine is not associated with significant cardiac mortality or morbidity. There is a real need for multidisciplinary working between specialist cardiologists and psychiatrists caring for these complex patients to facilitate optimal long-term physical and mental health outcomes.

Key Words: clozapine, cardiomyopathy, myocarditis, cardiotoxicity
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Clozapine is the most effective antipsychotic for treatment-resistant schizophrenia; however, it is significantly underused due to various cardiac side effects, namely, sinus tachycardia, myocarditis, and cardiomyopathy. Sinus tachycardia is thought to be a benign process, occurring in 25%; however, myocarditis and cardiomyopathy, although carrying a significantly lower incidence, incur significantly elevated mortality.2,3 Fears surrounding such potential adverse outcomes are reflected in the data which show that 30% of eligible patients were not being offered the clozapine, whereas 57% were offered 3 or more different agents before commencing clozapine.4–6

The BNF states that clozapine should be used with caution in those with preexisting cardiac disease and should not be considered in those with severe cardiac compromise; this excludes a significant proportion of patients, given their established cardiac risk factor burden. Further, clozapine is frequently discontinued prematurely at the first sign of either cardiotoxicity or its other well-known side effect, agranulocytosis.

It is clear, therefore, that there is considerable difficulty in commencing and maintaining therapy with clozapine; however, there has been no large-scale study of clozapine cardiotoxicity nor has there been a prospective study of the effects of clozapine in those with established cardiac disease.

Given that clozapine is the only evidence-based treatment licensed in refractory schizophrenia, we sought to review outcomes in the cohort of patients on clozapine referred for cardiac review within our academic health sciences center. This “clozapine-treated” group was compared with a second group of patients with acute psychosis also referred for cardiac review but were taking other antipsychotic agents.

METHODS

We undertook a retrospective study of all patients admitted to our national mental health unit and referred, as inpatients, for cardiology review during the past 9 years. This was done via a data-mining search with the terms “schizophrenia,” “clozapine,” “antipsychotic,” “cardiomyopathy,” “myocarditis,” “tachycardia” on cardiology clinic letters collated on our electronic system. Patient demographics were recorded, in addition to start and stop dates of clozapine and dose. Cardiac data at the time of review was noted, specifically, measurements of echocardiographic (left ventricular [LV] ejection fraction) and electrographic indices (QRS duration, QTc interval, heart rate [HR]) were recorded. Mortality status (and cause of death) was obtained at the time of follow-up (date of search).

Results were analyzed using Student t test, Mann-Whitney U, Kruskal-Wallis, and 1-way ANOVAs as necessary. Linear regression analysis was also undertaken to determine correlative data.

RESULTS

Total Cohort

For 9 years at our institution, clozapine was started on 883 inpatients; 27 (0.3%) were referred for cardiology review. A further 12 inpatients on other antipsychotic agents were also referred for
cardiology opinion. Mean age for the total cohort was 46 ± 13 years; 31% (12) were women; of those being treated with clozapine, 16 (59%) were referred specifically for tachycardia. Total follow-up time from start of the drug to review of clinic and cardiac data was 10.8 ± 5.8 years.

**Clozapine Treated Patients—Whole Group**

Twenty-seven (69%) of the total patients referred for review were being treated with clozapine. Mean age at review was 43 ± 12 years, and 33% were women (n = 9; Table 1). Median LV ejection fraction (LVEF) was 52% (interquartile range [IQR], 44–55) and median HR was 98 bpm (IQR, 85–114; Table 1).

There was no significant relationship between age and LVEF (P = 0.99), age and QRS duration (P = 0.16), age and HR (P = 0.73), or age and QTc interval (P = 0.16). Further, we found no significant relationship between time on clozapine and LVEF at review (P = 0.85) or time on clozapine and QRS duration (P = 0.22).

**Clozapine Treatment and Development of Tachycardia**

Sixteen (59%) patients being treated with clozapine were referred to cardiology due to the development of a tachycardia. This was a sinus tachycardia in all cases; no arrhythmias were documented at any time point during follow-up in this group. Mean age of this cohort was 44 ± 13 years and 5 were women. Left ventricular ejection fraction was normal (55% IQR, 52–59), as were all electrical intervals (Table 1 below). Mean HR was 103 bpm (IQR, 94–116; Table 1).

There was no significant relationship between time on clozapine and HR (P = 0.15) or time on clozapine and QTc (P = 0.16). We also found no significant difference in HR in those with and without symptomatic palpitation (P = 0.49).

After review by cardiology, rate controlling medication was started in 44%: β-blocker (n = 5) and ivabradine (n = 2). However, there was no significant difference in HR in those whose rate controlling medication was started (101 ± 10 bpm) and those who are not (110 ± 14 bpm; P = 0.22). Forty percent of symptomatic and 45% of asymptomatic patients were treated.

In total, 17 cardiologists were involved in decisions relating to patient management (mean visits, 3.75 per patient). At the time of follow-up, 4 (25%) patients had discontinued clozapine, with a time to discontinuation of 28 ± 31 months after review. Reasons for discontinuation were neutropenia (1), poor compliance (1), patient choice/refusal (2). One patient died in this group, and the cause of death was recorded as a suspected suicide.

**Clozapine “Cardiomyopathy” Group**

Eleven (41%) patients treated with clozapine were referred due to possible development of heart failure/myocarditis or cardiomyopathy. These 11 patients had a median LVEF of 38% (IQR, 36–52) at first review; QRSd and QTc were within normal limits 90 ms (IQR, 88–98) and 431 ms (IQR, 416–440). There was no significant relationship between time on clozapine and ejection fraction in this group (r = –0.1, P = 0.78).

Follow-up time for this group was 11.6 ± 7 years. During this time, 8 patients discontinued clozapine—5 were diagnosed with myocarditis (only one confirmed with endomyocardial biopsy), and 3 were diagnosed with cardiomyopathy. Three patients died with causes of death as (1) occlusion of descending aorta, (2) subarachnoid hemorrhage, and (3) intestinal pseudo-obstruction (the latter 2 patients were still on clozapine at the time of death). Eighteen different cardiologists were involved in the management of this patient group; cardiac medication used included: 82% bisoprolol (9), 82% ace inhibitor (9), 27% mineralocorticoid receptor antagonist (3).

**Clozapine Group Comparison**

There was no significant difference in age (P = 0.49), sex, QRS duration (P = 0.74), or QTc interval (P = 0.56) in those developing a tachycardia or symptoms and signs of heart failure. Left ventricular ejection fraction was significantly lower in the clozapine “cardiomyopathy” group (38% vs 55%; P < 0.001), and HR was significantly higher in the clozapine tachycardia group (103 bpm vs 83 bpm; P = 0.002).

Those with LV impairment tended to be seen earlier than those who developed tachycardia; however, this did not reach statistical significance with a median time to review of 4.7 years versus 7.2 years (P = 0.24). Patients in the former group were far more likely to have clozapine discontinued compared with those in the tachycardia group (P = 0.027) and clozapine tended to be discontinued sooner after referral in the clozapine cardiomyopathy group compared with the clozapine tachycardia group (median time, 0.3 vs 2.3 years; P = 0.065).

**TABLE 1.** Demographics, Cardiac Variables, and P Values

|                    | Other Antipsychotics Group (n = 12) | Clozapine Cardiomyopathy Group (n = 11) | Clozapine Tachycardia Group (n = 16) | Clozapine Total Group (n = 27) | Whole Group (n = 39) | P*  |
|--------------------|-------------------------------------|----------------------------------------|-------------------------------------|-----------------------------|---------------------|-----|
| Age, y             | 56 ± 9 (P = 0.02)†                  | 44 ± 13                                | 40 ± 13                             | 43 ± 12                     | 0.49                | 46 ± 13 |
| Sex (% female)     | 3 (25%)                             | 4 (36%)                                | 5 (31%)                             | 9 (33%)                     | */—                 | 12 (31%) |
| Time on drug at review: median (IQR), y | 4.2 (1.6–9.7) (P = 0.35)†            | 4.7 (0.3–7.3)                          | 7.2 (1.3–10)                        | 4.8 (0.8–8.5)              | 0.24                | 4.8 (0.8–8.5) |
| HR: median (IQR), bpm | 75 (67–96) (P = 0.63)†              | 83 (76–90)                             | 103 (94–116)                        | 98 (85–114)                 | 0.002*              | 92 (79–106) |
| QRS duration: median (IQR), ms     | 95 (90–117) (P = 0.09)†              | 90 (88–98)                             | 90 (85–96)                         | 90 (86–96)                  | 0.74                | 90 (88–99) |
| QTc interval: median (IQR), ms      | 451 (422–502) (P = 0.14)†            | 431 (416–453)                          | 432 (418–453)                      | 434 (418–458)              | 0.56                | 437 (418–460) |
| LVEF median (IQR), %               | 31 (27–43) (P = 0.26)†              | 38 (36–52)                             | 55 (52–59)                         | 52 (44–55)                 | <0.001*              | 46 (36–55)   |
| Clozapine discontinued | —                                  | 8 (73%)                                | 4 (25%)                             | 13 (48%)                    | 0.027*              | —  |

*Comparison between the clozapine cardiomyopathy and tachycardia groups.
†Comparison between clozapine cardiomyopathy and other antipsychotics group.
Nonclozapine Antipsychotic Treatment

Twelve patients being treated with an antipsychotic other than clozapine were referred for review during the same period. Average age was 56 ± 9 years, and 25% (3) were women. Median HR was 75 bpm (IQR, 67–96), QRS duration of 95 ms (IQR, 90–117), QTc interval of 451 ms (IQR, 422–502), and LVEF 31% (IQR, 27–43).

This cohort was treated with antipsychotic medication for 4.2 (1.6–9.7) years until initial cardiology review. At follow-up, only 8 were being treated with the same antipsychotic; 4 had discontinued their original antipsychotic. Only one of these was secondary to a suspected cardiac side effect (risperidone). The remainder comprised risperidone (n = 2) and olanzapine (n = 1) and these agents were changed for noncardiac reasons. One patient died in this group with cause of death recorded as heart failure (this patient was on risperidone).

All patients with reduced LVEF were treated with at least 2 prognostic heart failure medications. Diagnoses comprised ischemic cardiomyopathy (n = 4), dilated cardiomyopathy (DCM) secondary to hypertension (n = 3), DCM secondary to valvular disease (n = 2), DCM related to chemotherapy (n = 1), and DCM with possible viral cause (n = 1). Sixteen cardiologists managed this group of patients.

Comparison Clozapine Versus Other Antipsychotics: Reduced LVEF

There was a significant difference in age at cardiology review with those on clozapine being younger than those not taking this drug (44 ± 13 years vs 56 ± 9 years; P = 0.02). There was no significant difference between length of time on drug at review between the two groups (P = 0.35). There were otherwise no significant differences in LVEF, HR, QRS duration, or QTc interval between the 2 groups.

Serial Echocardiogram Data in the Clozapine Cardiomyopathy Group and Nonclozapine Antipsychotics

In total, 7 patients in both groups (14) had serial echocardiograms during their drug treatment. Patients on nonclozapine antipsychotics had echocardiograms over a longer duration of time (28 ± 25 months vs 4 ± 3 months; P = 0.029) compared with those on clozapine.

There was a nonsignificant trend toward clozapine having less deterioration in LVEF per month compared with other antipsychotics (0.8 ± 1.4% vs 0.3 ± 0.8%; P = 0.09). Patients on nonclozapine antipsychotics were more likely to experience deterioration in ejection fraction during treatment 86% versus 14% (P = 0.004). In the 4 patients on clozapine that did have an echocardiogram before treatment, we find a mild mean LV impairment (51 ± 3%) which did not significantly deteriorate postclozapine treatment (mean, 54 ± 4%; P = 0.18).

DISCUSSION

Clozapine has been shown to reduce all-cause mortality, homelessness, and suicidality in treatment-resistant schizophrenia, as compared with other antipsychotics; however, anxiety regarding cardiotoxicity significantly limits its use.8 Our experience appears to contradict many of the concerns regarding its use; this study shows that clozapine is generally very safe, with an absence of any cardiac-related mortality during the follow-up period, and no evidence that longer duration of treatment correlated with deterioration in cardiac function, even in those with preceding LV impairment. Despite this, we also show that our cohort had a significant number of patients where clozapine was discontinued.

Our findings confirm that the cardiotoxic effects related to clozapine tend to fall into 2 distinct categories: a sinus tachycardia with preserved LV function, and a presentation with impairment of LV function without significant tachycardia. It is heartening that none of those in the tachycardia group developed cardiac disease during the follow-up period. Two patients in this group had borderline impaired ejection fraction at review; one had undergone previous cardiothoracic surgery to repair a flail mitral valve leaflet, and the other had suspected ischemic cardiomyopathy. Neither showed progression of LV impairment, and no other patient in this group developed this. Our findings would therefore support the literature that clozapine-associated tachycardia is benign; however, further prospective study is needed to assess the long-term benefits of masking tachycardia with rate-controlling drugs.

Tachycardia is also a recognized feature, albeit extremely nonspecific, of myocarditis. We found that 59% of referrals to the cardiology service with “tachycardia” were prompted due to a concern of myocarditis in the patient. Our study estimates an average incidence of clozapine myocarditis at 0.11%, less than the current estimates of the incidence (0.7–1.2%). The only definitive method for diagnosis myocarditis is through endomyocardial biopsy, which was only undertaken in one of our patients in the study. The clinical features of myocarditis are wide-ranging and nonspecific; however, tachycardia is not in its diagnostic criteria, and often complicates the initial dose titration of the drug. Ronaldson et al advocated for weekly C-reactive protein (CRP) and troponin monitoring in the first month of starting clozapine. CRP and troponin are both sensitive but nonspecific for myocarditis and would be excellent gatekeepers to echocardiography, especially in the first month of dose titration where myocarditis is most common; however, the usefulness of this screening method has not been assessed and does not form part of the standard practice.10,11

We find no significant correlation between duration on clozapine and LVEF, suggesting that clozapine does not cause a cumulative detrimental effect on cardiac function as supported by the study of Chow et al12 as outlined below. In those patients with LV systolic dysfunction already present at the time of cardiology review, we found no deterioration in cardiac function in the short term while remaining on clozapine. Baseline echocardiography is not routinely performed in our patients before starting clozapine, thus, it is difficult to be sure if LV systolic dysfunction predated—and was thus unrelated to—clozapine use: we should remember that this cohort of patients is at significant risk for other cardiovascular disease.

Other studies might suggest that long-term clozapine use is associated with a small decline in LV systolic function over time. Chow et al12 compared patients with schizophrenia receiving either clozapine (n = 100) or taking nonclozapine antipsychotics (n = 21) and 20 healthy, untreated, individuals over a 2-year period. They noted a reduced ejection fraction (EF) of approximately 3.9% in the clozapine group compared with the group taking other antipsychotics, and 6.5% compared with the healthy group. We feel that comparing those with schizophrenia and its incumbent cardiovascular risk profile to healthy individuals is fundamentally flawed and, further, a 4% difference between the groups is well within the established margin of reporting error for LVEF. Another group studied 38 patients on clozapine over a 12-month period and likewise found subclinical LV dysfunction in one third of treated patients with a 5% decline in EF during the course of the study. The authors in this latter group, however, ascribe LV dysfunction to an EF between 50% and 55%: many cardiologists would feel this is within the normal range, and as such, it is difficult to interpret the findings of this study. It is also very important to note that the major limitation in these studies is that the use of
prognostic heart failure medications was not described in the treatment or control groups; this would significantly affect LV function, but also change and recovery of such also.12,13

Other retrospective studies, namely, those conducted by Ronaldson et al7 and Haas et al,5 describe clinical features, biochemical, and echo findings of patients diagnosed with clozapine myocarditis.3,5 Our study is unique in that it provides additional insight into the management approaches adopted by clinicians, and a comparison with cardiac outcomes of nonclozapine antipsychotics, something that has not yet been described to our knowledge. Our study also has the longest follow-up period for these patients at 11 years, and data were obtained from the largest psychiatric research center in Europe.

Our experience is that the short- to medium-term outcome during therapy with clozapine is acceptable with no observable deterioration in LV function. Any potential decline in cardiac function with clozapine needs to be balanced against the beneficial effects of the drug on patients with treatment-resistant schizophrenia, which carries its own considerable morbidity and mortality. Effective prognostic medical therapy of LV dysfunction would be hoped to support the ongoing use of clozapine: This is something that facilitates ongoing cancer therapy with a similar agent that causes LV dysfunction, trastuzumab.14 For this reason, the authors advocate for referral and ongoing follow-up of these patients in specialist heart failure units.

During the 9 years that data were collected, 883 patients in total were started on clozapine in our Trust, approaching to 100 initiations per year. Despite this volume, there are no national clinical guidelines for the monitoring of cardiotoxicity in patients receiving clozapine; a starting point might be adapting those already in place for anticancer drugs; such as the afore-mentioned trastuzumab, used in breast cancer. Here, baseline echocardiograms are done followed by further studies at 4 and 8 months and on completion of treatment.14

Our study found 18 different cardiologists involved in the management of these patients, with wide ranging clinical decisions based on the preference and expertise of the individual cardiologist, most of whom were not heart failure specialists. There is a wealth of data to support the fact that any patient with LV dysfunction has less mortality under a specialist,15 and as such, we proposed that a dedicated team (including a heart failure specialist) should manage these patients, facilitating early review and ongoing dialogue with psychiatrists to enable continuation of clozapine and prevention of premature (unnecessary) discontinuation of it. Of the significant number of patients who had clozapine discontinued, it is entirely possible that some of might have been advised to continue had their care been under a specialist joint supervision and had there been structured guidelines in place. The lack of a cohesive coordinated approach to care in our study is emphasized by the finding that the group of patients receiving HR control drugs compared with those that did not had no significant difference in HR nor symptoms nor outcome.

Tendency to increased cardiac mortality in patients with schizophrenia is attributable at least in part to the adverse metabolic effects of antipsychotics, including weight gain, dyslipidemia, and diabetes.16 However, one of the largest population studies to date, the Fin11 trial, demonstrates that clozapine reduces all-cause mortality as compared with other antipsychotics.14 Of course, the better their mental health are treated, the better treated the cardiac problems tend to be. Most antipsychotics in common use have been associated with cardiotoxicity to varying degrees as described by Coulter et al, with the highest incidence attributed to clozapine use.17 However, a bias must be conferred to the fact that clozapine cardiotoxicity is much better described than cardiotoxicity associated with other antipsychotics. This bias is observed in our cohort of patients on nonclozapine antipsychotics where only 1 patient had cardiac side effect mentioned as a contributing factor to their impaired cardiac function, in contrast to clozapine, where it was considered the culprit in all patients, despite very similar cardiac risk factor profiles.

CONCLUSIONS

Clozapine use is relatively safe with very acceptable short- and medium-term data. Misconceptions and lack of specialist knowledge drive the early termination of its use and fears regarding what are often benign side effects. We advocate for the promotion of joint working between heart failure and psychiatric teams in multidisciplinary fashion.

Limitations

Although we are the largest mental health unit in the United Kingdom, the sample size presented here is relatively small. It is possible that this reflects the low, but true, incidence of clozapine cardiotoxicity; however, it is also possible that patients may have been missed due to referral to the emergency department instead of cardiology specifically. This is unlikely, however, as such patients would be expected to have been subsequently picked up by the cardiologists. It is also possible that subacute incidences of myocarditis were missed; however, we feel that this reflects the nature of myocarditis in that many healthy individuals will never present to medical services either. In our unit, we undertake CRP and troponin measurements on starting clozapine so it is unlikely that even subacute cases were missed.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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