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Review

A systematic review of clozapine induced cardiomyopathy

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ABSTRACT

Background: Clozapine is a unique anti-psychotic medication that is most effective in the treatment of refractory schizophrenia and reducing suicidality. Cardiomyopathy is among the side effects of this medication that limits its use. There are a number of case reports, case series and expert opinion papers discussing clozapine induced cardiomyopathy, but there is no evidence-based review of the subject to guide clinicians.
Methods: We undertook a systematic review of the literature on cardiomyopathy associated with clozapine. The primary systemic search was in MEDLINE but EMBASE, PsycINFO, and Cochrane were searched and manufacturers of clozapine were contacted for cases. Articles were then individually reviewed to find additional reports.
Results: We identified 17 articles detailing 26 individual cases and 11 additional articles without individual case data. The mean age at time of diagnosis was 33.5 years. The mean dose of clozapine on presentation was 360 mg. Symptoms developed at an average of 14.4 months after initiating clozapine. The clinical presentation was generally consistent with heart failure: including shortness of breath (60%) and palpitations (36%). Echocardiography at presentation showed dilated cardiomyopathy in 39% of cases and was not specified in other cases.
Conclusion: There should be a low threshold in performing echocardiography in suspected cases of clozapine induced cardiomyopathy. Clozapine should be withheld in the setting of cardiomyopathy without other explanation. There is limited data on the safety of drug re-challenge in clozapine induced cardiomyopathy. Re-challenge may be considered in carefully selected cases but close monitoring and frequent echocardiography are required.

1. Introduction

Approximately 1% of the world's adult population suffers from schizophrenia [1]. Clozapine is the most effective agent for the treatment of schizophrenia and is considered especially effective in patients with treatment-resistant schizophrenia [2–4]. It is also the only antipsychotic agent with a demonstrated significant reduction in suicidality (6-fold) for patients with schizophrenia and it usually produces few or no extrapyramidal symptoms (such as tardive dyskinesia or dystonias caused by typical antipsychotics) [5,6].

Unlike other antipsychotics, clozapine has been shown to be more effective at not only reducing the disturbing hallucinations and delusions that accompany this disease, but also treating the apathy and social withdrawal that make schizophrenia so debilitating [7]. Clozapine also has been shown to reduce aggression more effectively than other antipsychotics; in patients with a history of violence it allows them to re-engage safely with society and family after forensic and prison settings [8]. There is strong evidence that patients with schizophrenia on clozapine – despite being classified as treatment-resistant – are significantly more likely to live independently and to be employed when compared to other medications [9]. Finally, in a recent study of 66,681 patients followed over 11-years, patients on clozapine were shown to have the lowest overall mortality and fewest deaths due to ischemic heart disease as compared to the eight most commonly used typical and atypical antipsychotic agents [10].

Clozapine would appear to be the first choice agent for treating schizophrenia. Instead it is only initiated when patients have failed two or more other antipsychotic agents — on average 10 years after they began treatment for schizophrenia [11]. A Canadian study suggested that clozapine was 40% under-utilized in patients with treatment-resistant schizophrenia [12]. This is because there are significant adverse effects associated with clozapine, including: fatal agranulocytosis, toxic megacolon, and cardiotoxicity. The first two risks are well managed by the psychiatric community; the potential cardiotoxicity of clozapine is not well characterized.

Clozapine was introduced in 1975 and withdrawn from active marketing the same year after reports of agranulocytosis were released. It remained available and after the use of routine blood tests was shown to reduce the mortality risk of agranulocytosis and was re-introduced in the 1990s due to its superior efficacy. Notably it was during this black-out period that the first case of clozapine related cardiomyopathy was reported in 1986 [13].

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Both myocarditis and cardiomyopathy are difficult to detect clinically and often will appear to be more benign conditions until patients develop profound symptoms or are detected incidentally, such as in pre-operative evaluation. Both conditions are associated with severe morbidity and mortality that can require enormous resources from inpatient and outpatient cardiology services. Cardiologists are often consulted to offer opinions on potential cases of clozapine induced cardiotoxicity but there is little medical literature to assist them in providing expert opinions.

There is a risk of over-attributing clozapine as a source of cardiotoxicity and stopping this medication for which there often is no substitute in treatment-resistant schizophrenics might lead to an adverse outcome. However there is also a risk in continuing to use clozapine in patients suffering from adverse cardiovascular reactions to the medication.

2. Methods

We conducted a systematic review of the literature on the cardiac side effects of clozapine. The primary systematic search was in MEDLINE, EMBASE, PsycINFO and Cochrane reviews. Article references were then individually searched to find additional reports. Experts were surveyed and the manufacturers of clozapine were contacted to discover unpublished data.

The search string included: {clozapine/adverse effects [MESH] or clozapine/contraindications [MESH] or clozapine/toxicity [MESH] or clozapine (keyword)} AND {(keywords: card* or cardio* or cardiotox* or cardiac* or cardiomy* or myocard* or heart) or heart [MESH]}.

The search was completed in May of 2014.

3. Results

We found 9935 articles that addressed clozapine on PubMed/MEDLINE, 25,818 on EMBASE and 6299 on PsycINFO. Out of those articles 523 on PubMed/MEDLINE, 396 on EMBASE and 347 on PsycINFO involved cardiac complications of the drug. In addition to that there were 17 further possible abstracts identified through Google, Google Scholar, textbooks, personal communications with pharmacists, researchers and clinicians and from citations.

In our review of the detailed case studies the mean age was 33.5 years with a range from 17 to 59 years. The majority of cases were male patients (76.9%). The ethnicity was poorly documented. Only 7 reports specified the ethnicity of afflicted patients, but this included a wide range, including Caucasian, Latin American, Chinese, Korean, Indian and Middle Eastern. The baseline characteristics are shown in Table 1. In a manufacturer adverse event database approximately 80% of clozapine-treated patients in whom cardiomyopathy was reported were less than 50 years of age [14].

4. Discussion

Our review of the 26 detailed case studies and 11 other relevant articles discussing epidemiology, pharmacovigilance database reporting, summated case series, mechanism and pathophysiology is summarized by section.

Table 1
Baseline characteristics of individual case reports of clozapine induced cardiomyopathy.

Mean age	33.5 years
Mean dose	360 mg
Clinical presentation	• Shortness of breath (60%) • Palpitations (36%) • Cough (16%) • Fatigue (16%) • Atypical symptoms (12%) • Chest pain (8%)
Average time for symptoms to develop	14.4 months
Echo findings	Reduced ejection fraction with a global dysfunction. Dilated cardiomyopathy specifically mentioned in 39% of individual case reports and 2/3 of manufacturer reports.

4.1. Diagnosis

In addition to the clinical assessment, the diagnosis was primarily made on the basis echocardiographic evidence of reduced ejection fraction. ECGs and blood tests including raised B-type natriuretic peptide levels were supportive but were not used as a method of diagnosis except in one case [15]. 2 cases were diagnosed on post-mortem examination [16,17]. Measurement of BNP to detect cardiac dysfunction in patients on antipsychotics has been studied and shows promise but there are no studies showing that it is cost-effective or diagnostically useful for the early detection of clozapine induced cardiomyopathy [18].

4.2. Disease frequency

According to national databases reporting adverse drug effects, the rate of cardiomyopathy in clozapine treated patients in the U.S. was 8.9 per 100,000 person-years [19]; if this were truly representative, the rate of clozapine-induced cardiomyopathy would be equivalent to the general population. The rate of clozapine-induced cardiomyopathy may even be much higher. It is unknown, but possible that the rate of drug-induced cardiomyopathy is underestimated due to lack of reporting or failure by mental health teams to recognize the symptoms and signs of cardiomyopathy. An Italian study suggested that >5% decrease in left ventricular (LV) ejection fraction occurred in one third of patients initiated on clozapine at one year follow-up [20]. Although our clinical experience includes several incidences where clozapine induced cardiomyopathy was referred to cardiology in the setting of incidentally noted reduced ejection fraction during preoperative evaluation, this has only been reported in two cases [21,22].

Previous studies have estimated that it occurs at a rate of 51.5 per 100,000 patient years or 1 case per 1000 on clozapine [23]. This is more than five times the estimated rate of cardiomyopathy in the U.S. general population derived from the 1999 National Hospital Discharge Survey data (9.7 per 100,000 person-years). International studies have suggested a rate in the general population of 7.5–10 per 100,000 patient years [24]. The incidence of clozapine induced cardiomyopathy ranges from 0.02% in the UK to 0.1% in Australia [23,25]. However this figure is based on active reports to regulatory agencies and it almost certainly represents a drastic under-reporting of actual cases. An analysis of the French PharmacoVigilance Database also confirmed a significantly elevated rate of clozapine induced cardiomyopathy, with 4 cases representing a reporting odds ratio of 11.5 (4.2–31 in the 95% confidence interval) [26].

4.3. Duration of treatment

The duration of treatment in the case studies we found was 14.4 months. This is considerably longer than the duration reported in the data abstracted from reports to the U.S. Food and Drug Administration (FDA) between 1989 and 1999 where the duration of treatment was 8 months for patients who survived and 10 months for patients who died from clozapine induced cardiomyopathy [19]. Other reports have suggested that the time to onset of clozapine-induced cardiomyopathy can vary between 3 weeks [27] and as long as 4 years [17]. Based on reports to national sentential event databases, most cases appear to occur within 6–9 months of initiation [16].

4.4. Dosing

Clozapine induced cardiomyopathy does not appear to be dose dependent [9]. In this review, the range of doses for patients with reported cardiomyopathy was 125 mg–700 mg, with a mean dose of 360 mg. In the U.S. FDA report from the 1990s, the median dose was 450 mg in patients who survived and 400 mg daily in patients who died from clozapine induced cardiomyopathy.