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A systematic review of clozapine-induced myocarditis

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ABSTRACT

Background: Clozapine is an atypical antipsychotic that is beneficial to some patients who failed to have an adequate clinical response to other antipsychotic drugs. Its clinical use is limited due to several potentially fatal adverse reactions including myocarditis. Careful monitoring of patients on clozapine is required.
Methods: We conducted a systematic review of the literature on myocarditis associated with clozapine therapy. The search engines used to identify cases were MEDLINE, EMBASE, PsycINFO and Cochrane reviews. The references included in the manuscripts reviewed were searched to identify additional reports.
Results: We identified a total of 3347 articles that addressed the cardiac complications of clozapine. Of these, 82 articles detailed cases of clozapine-induced myocarditis. The median age of patients and dose of clozapine at presentation was 30 years and 250 mg/day respectively. Symptoms and signs of myocarditis developed in 87% of patients within the first month of treatment. Clinical presentation included: shortness of breath (67%), fever (67%) and tachycardia (58%). Cardiac markers were elevated in 87% of the 54 cases that reported these markers. Global ventricular dysfunction was the predominant echocardiogram finding (57%).
Conclusions: Patients on clozapine require routine monitoring for symptoms and signs of myocarditis during the first three months of therapy. This adverse drug reaction is difficult to diagnose due the non-specific nature of the symptoms and signs. Alternate causes of myocarditis should be ruled out before attributing the myocarditis to clozapine.

1. Introduction

Schizophrenia is a debilitating psychiatric disorder with a poorly understood multifactorial aetiology that affects 1% of the world's adult population [1]. Those affected often have impaired mental and cognitive functions, which limits their ability to engage in relationships and meaningful work. Symptoms are both acute and chronic in nature, typically present late in adolescence and contribute to the variable course of the illness over a lifetime [2]. Schizophrenia is associated with a significant increased mortality risk (2–3 fold) and the mortality gap between people with schizophrenia and those without has been increasing over past decades [3]. According to the World Health Organization, it is one of the top 10 illnesses leading to disability [4].

Clozapine is a uniquely effective atypical antipsychotic indicated for treatment-resistant schizophrenia. It is the only medication used to manage the symptoms of schizophrenia that reduces death from suicide [5]. In one study of 66,000 patients, patients on clozapine had a mortality rate significantly lower than patients on any other antipsychotic medication [6]. There is also consistent evidence demonstrating that clozapine reduces aggression, is associated with fewer psychiatric inpatient admissions and higher levels of independent living and employment compared with any other therapy [7]. In addition, clozapine is well tolerated by patients who have long-term extrapyramidal side effects from other antipsychotic drugs, as it does not cause the distressing abnormal involuntary movements associated with typical antipsychotic medications. However, clozapine use is also associated with significant medical and surgical risks and as a consequence, it is not currently a first-line therapy. Careful management of patients who are taking this drug is required and cardiac specialists are frequently asked to provide input on the assessment and management of these side effects. For some patients clozapine is the only effective agent; stopping clozapine can consign a patient to a lifetime of uncontrolled hallucinations, disorganised thinking, apathy and significantly increased risk of suicide and death. Alternate causes for myocarditis should be considered before discontinuing the medication clozapine.

Some of the adverse effects associated with clozapine that present during initiation are reasonably explained by its diverse pharmacological profile and are sometimes managed by slower titration, dose reduction and close monitoring. Agranulocytosis is perhaps the most well-known

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and potentially fatal adverse reaction to clozapine. Without careful monitoring, there is a 1–2% incidence of clozapine-induced agranulocytosis [8]. For this reason, all patients worldwide initiating clozapine must undergo mandatory standardised haematological monitoring.

Myocarditis and cardiomyopathy are both rare side-effects associated with clozapine use. Like agranulocytosis, the underlying mechanism(s) are unknown despite the fact that the first case report of clozapine-induced myocarditis appeared in the literature over 30 years ago [9]. A type 1 drug hypersensitivity reaction has been proposed given its early presentation in clozapine treatment [10]. This may be due to clozapine itself or due to the formation of a cardiotoxic metabolite of clozapine via altered metabolism, which damages cardiac protein and attracts inflammatory infiltrates. However, there has only been one study investigating the underlying mechanism(s) and this has been done in a murine model; it is not known if this also occurs in the human heart [11]. The cardiac complications of clozapine have been under-investigated because psychiatrists primarily prescribe the drug.

2. Methods

We conducted a systematic review of the literature on the cardiotoxic side effects of clozapine using the following search engines: MEDLINE, EMBASE, PsycINFO and Cochrane reviews. The search string for MEDLINE, EMBASE, PsycINFO included: {clozapine [subject heading] or clozapine or clozapril or leponex or clopine (keyword)} and {adverse effect* or adverse reaction* or adverse drug reaction* or side effect* or contraindication* or toxicit* [keyword]} AND {cardio* or cardiac* or myocard* or heart [keyword]} or {heart [subject heading]}. Manuscript references were individually searched for relevant articles. The search was completed in September 2016. Articles were also identified by reviewing the references of relevant papers, asking colleagues at academic conferences and at university hospitals.

3. Results

We identified 7436 articles that addressed clozapine on MEDLINE, 27,981 on EMBASE and 6971 on PsycINFO. Of these, 391 on MEDLINE, 2543 on EMBASE and 413 on PsycINFO involved cardiac complications of clozapine. This review identified at least 359 possible cases of clozapine-induced myocarditis through individual case reports, case series, summated case series, spontaneous pharmacovigilance reporting and reviews. A summary of these findings is outlined in Table 1.

The median age of clozapine treated patients who developed myocarditis was 30 years with a range from 16 to 77 years. Seventy-eight percent were male in cases where the sex of the patient was given. Ethnicity was only reported in 16 cases but was diverse including Caucasian, African-American, Filipino, Hispanic and Malaysian decent.

3.1. Diagnosis

In this review of the literature, diagnosis of clozapine-induced myocarditis was made in the majority of cases using a combination of symptoms, clinical findings, evidence of inflammation and evidence of cardiac involvement (Table 1). Clinical findings included, but were not limited to, either one or a combination of the following: fever, tachycardia, tachypnoea, hypotension, crepitations on lung auscultation, or clinically abnormal heart sounds. Evidence of inflammation included, but was not limited to, either one or a combination of the following: elevated C-reactive protein (CRP), white blood cells (including eosinophils) or an increased erythrocyte sedimentation rate (ESR). Finally, evidence of cardiac involvement included one or a combination of the following: elevated creatinine kinase (CK), creatinine kinase-myocardial band (CK-MB), troponin I, troponin T, B-type natriuretic peptide (BNP), an abnormal electrocardiogram (ECG), chest X-ray (CXR), echocardiogram (echo), cardiac MRI or *endo*-myocardial biopsy (including those taken at post-mortem). Additionally, there was one case of what was labelled cardiomyopathy [13], one case of polysersitis [21], and one case of pneumonitis [60] that the authors believed could be myocarditis related.

3.2. Disease frequency

Kilian et al., reported 23 cases of clozapine-induced myocarditis out of 8000 patients initiated on clozapine (0.28%) [10]. The incidence reported in the literature ranges from 0.015–8.5% [22,24,30,35,39,62]. The international database on adverse drug reactions run by the World Health Organization program for international drug monitoring reported 231 cases of combined clozapine-induced myocarditis and cardiomyopathy out of 24,730 patients on clozapine (0.93%) [84].

3.3. Duration of treatment

Analysis of these reports demonstrates that 87% of the 79 cases where time-specific data was available displayed symptoms within 30 days or less of treatment. All but four cases developed symptoms within the first 12 weeks of treatment. Approximately one-half of these patients developed symptoms and signs within the first 14 days. There are several reports of clozapine-induced myocarditis in patients taking clozapine for a year or more [24,39,43,73]. However, it is not known if these patients were re-titrating, or if other more common causes of myocarditis (e.g. viral) were ruled out.

3.4. Dosing

The dose at the onset of symptoms and signs was between 50 mg/day and 600 mg/day while the median was 250 mg/day in the 53 cases where patient-specific data was available. These findings are similar to the findings of several summated reports and reviews [22,30,39,43].

3.5. Presenting symptoms, signs and investigations

Patient-specific symptoms or lack thereof were reported in 76 cases. The most frequently reported symptoms included shortness of breath (32 of 76 cases, 42%), chest pain (28 of 76 cases, 37%), flu-like symptoms and/or feeling unwell (14 of 76 cases, 18%), cough (9 of 76 cases, 12%) and gastrointestinal discomfort including diarrhoea (8 of 76 cases, 11%). One patient was reported to be asymptomatic while one was reported to have no cardiac symptoms.

Patient-specific clinical findings on physical examination were reported in 62 cases. The most frequently reported findings were fever (42 of 62 cases, 67%), tachycardia (36 of 62 cases, 58%) hypotension (8 of 62 cases, 13%) and tachypnoea (5 of 62 cases, 8%). Additional clinical findings included crepitations on lung auscultation, rales or crackles (7 of 62 cases, 11%), and a S_3 and/or S_4 heart sound and/or gallop rhythm (9 of 62 cases, 10%). A pericardial rub and elevated jugular venous pressure was reported in two cases. A rash was reported in two cases.

Evidence of inflammation was noted in 44 patients where patient-specific information was available. An elevated CRP level was found in 23 of 44 cases (52%) and similarly an elevated peripheral blood eosinophil count was reported in 23 of 44 cases (52%). Elevated cardiac markers were reported 47 of 54 cases (87%). Troponin levels were elevated in 35 of the 54 cases (65%). An *endo*-myocardial biopsy was performed in three living patients confirming the diagnosis of myocarditis [31,42,74]. Of these three reported cases, one was predominantly eosinophilic and two were lymphocytic. In nearly all of deaths resulting from clozapine-induced myocarditis, cardiac histology revealed a predominately-eosinophilic infiltrate.

3.6. ECG, echo, CXR and cardiac MRI findings

Patient-specific ECG findings were reported in 62 cases. Sinus tachycardia was the most common ECG finding (23 of 62 cases, 37%). The next ECG abnormality by frequency was T-wave inversions (15 of 62 cases, 24%). Most reports noted this to be localised to the inferolateral