

# FOR YOUR INFORMATION



## PHARMACY NEWSLETTER



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### Cardiovascular Toxicity with Clozapine Therapy

#### Introduction

Clozapine is a tricyclic dibenzodiazepine atypical antipsychotic that has been available in Canada since 1991. It is indicated for treatment-resistant schizophrenia and is effective in 30-60% of patients. The use of clozapine is limited by a risk of agranulocytosis, a potentially lethal adverse effect. Clozapine associated agranulocytosis occurs in about 1% of patients in the first year of treatment. As a result, many countries, including Canada, implemented compulsory registering and monitoring of patients on clozapine therapy. Clozapine may cause other adverse effects such as seizures, orthostatic hypertension, tachycardia and ECG changes.

*The term myocardial toxicity includes: myocarditis, cardiomyopathy, myocardial infarction, heart failure, mitral insufficiency, pericarditis and pericardial effusion.*

More recently, reports of myocardial toxicity related to clozapine use has received increased attention. Since these reports included fatalities, a “Dear Healthcare Professional” letter and a Public Advisory notice was distributed by Novartis, the manufacturer of Clozaril® (clozapine). Novartis revised its monograph to include more information on clozapine associated myocardial toxicity.

Most information on clozapine associated myocardial toxicity is gathered from case reports.

#### Myocarditis

##### Incidence

According to the “Dear Healthcare Professional” letter, the Novartis international pharmacovigilance database contains 213 reports of myocarditis out of an estimated 3,000,000 patient-years of exposure to clozapine (1/14000 patient years). Fatalities were reported in 50 of these cases. In Canada there have been 9 reported cases of myocarditis with 3 fatalities. In the American version “Dear Health Care Provider” letter, data was reported from four countries with Clozaril® national registries: the U.S., Canada, the U.K. and Australia. The lowest reported incidence of myocarditis was in the U.S. (5.0/100,000 patient-years), while Australia (96.6/100,000 patient-years) had the highest incidence. Canada and the U.K. reported 16.3 and 43.2 cases/100,000 patient-years respectively. The incidence of death was 2.3, 2.8, 11.5 and 32.2 cases/100,000 patient-years in Canada, the U.S., the U.K. and Australia respectively. Grenade et al estimated the incidence of fatal myocarditis in the U.S. during the first month of therapy to be 321 per million person-years of observation. This greatly exceeds the reported background rate of 4 per million per year.

##### Dose and Duration

In 85% of the reports, myocarditis occurred within the first two months of initiation of clozapine therapy. Most patients were prescribed doses between 200-500mg/day (within the recommended daily dose). Twenty-two percent were taking less than 300mg/day, indicating myocarditis occurred during dose titration.

## Age

This reaction appears to be independent of age. Forty percent of patients were between 19 to 30 years old and 34% were between 30 and 40 years of age.

## Cardiomyopathy

### Incidence

There are 178 cases of cardiomyopathy in the Novartis international pharmacovigilance database, 32 of which have been fatal. Cardiomyopathy was confirmed at autopsy in 7.9% of cases and by echocardiography in 36%. Diagnosis of cardiomyopathy was four times more frequent in men than women. Only 10% of patients were reported to be taking other antipsychotics. In 50% of the cases and 28% of the fatalities there was no other apparent cause of cardiomyopathy.

### Dose and Duration

Clozapine doses were within the recommended range. Sixty-five percent of the patients had a duration of treatment of more than 6 months.

## Age

The incidence of reported cardiomyopathy in patients 15-44 years of age was reported to be greater than in the general population. Eighty percent of the cases occurred in patients under the age of 50. The average age for individuals without other known associations for cardiomyopathy was 37.

*True incidence rates cannot be estimated by spontaneous adverse drug reaction reports due to underreporting. This may be illustrated by the large variation in myocarditis reported in the U.S., Canada, the U.K. and Australia. Definite causal relationships cannot be concluded by case reports, as confounding factors cannot be accounted for.*

## Signs and Symptoms

Patients that develop myocardial toxicity on clozapine therapy usually present with the following symptoms:

- persistent tachycardia at rest
- ST-T wave abnormalities or arrhythmias on EKG
- signs and symptoms of heart failure (e.g. chest pain, dyspnea, tachypnea, palpitations, peripheral edema)
- fatigue
- flu-like symptoms
- fever that is otherwise unexplained
- hypotension
- raised jugular-venous pressure

Cases of sudden death have occurred where patients exhibited no symptoms or mild symptoms and myocarditis was only diagnosed at autopsy. Autopsy identified myocardial infiltration with eosinophils as well as other immune mediators. Myocarditis with and without eosinophilia has been reported.

## Monitoring

If signs and symptoms of myocardial toxicity occur in patients on clozapine therapy, diagnostic evaluation for cardiovascular dysfunction should be conducted by a cardiologist. It is recommended that patients with a family history of heart failure should have a cardiac evaluation prior to clozapine therapy. Clozapine treatment is contraindicated in patients with severe cardiac disease. Cases of clozapine associated myocarditis have been documented in patients without previous cardiac history. This reaction appears to be as likely to occur in young

and older patients alike. Cardiovascular adverse effects not related to myocardial toxicity occurs on about one-third of clozapine treated patients. Tachycardia and hypotension can be induced by clozapine's anticholinergic and antiadrenergic effects. As well, the strong  $\alpha$ -antagonism of clozapine can cause orthostatic hypotension, reflex tachycardia and syncope. Decision on the continuation of clozapine therapy with the presentation of such symptoms is difficult, as these reactions may not be related to toxic effects of the drug on the heart.

### **Risk Factors**

Risk factors for developing myocarditis and cardiomyopathy are:

- immune response to infection
- alcohol
- other toxins
- other drugs (e.g. methyl dopa and sulphonamides)
- arteriosclerotic cardiovascular disease
- hypertension
- diabetes mellitus
- obesity

### **Mechanism**

The mechanism by which clozapine causes myocardial toxicity is unclear.

One hypothesis is that myocardial toxicity is an immunoglobulin E-mediated hypersensitivity (type I allergic) reaction. This is unlikely as other type I reactions (i.e. urticaria and anaphylaxis) rarely occur during clozapine therapy.

Another theory postulates that this reaction is due to a hypereosinophilic syndrome induced by clozapine. This explanation is more plausible as

eosinophilia has been associated with clozapine myocarditis. At autopsy, myocardial tissue has been shown to contain eosinophilic infiltrates. The majority of hypereosinophilic syndrome cases, regardless of etiology, have cardiac involvement. However, there have also been cases of myocarditis in clozapine patients without eosinophilia and myocardial eosinophilic infiltrates. Finally, it has been suggested that clozapine has a direct toxic effect on myocardial tissue.

### **Treatment**

Recovery from myocarditis is usually prompt with clozapine withdrawal. Supportive care with cardiac medications to improve the signs and symptoms of heart failure has been used. In two cases, severe heart failure resolved within a few days after cessation of clozapine and treatment with high doses of corticosteroids. Clozapine rechallenge is not recommended due to the seriousness of the reaction. There is a single case report where myocarditis did not recur with a clozapine rechallenge supported by close cardiac monitoring.

### **Conclusion**

Clozapine associated myocardial toxicity is rare but potentially fatal. More studies need to be conducted to help determine the actual incidence, possible risk factors and the mechanism of this reaction.

*Written by: Jenie Le, B.Sc. (Pharm), RCH Pharmacy Resident*

*Reviewed by: Debbie Thompson, (Pharm. D)*

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