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Clozapine-associated myocarditis and cardiomyopathy: Epidemiology, clinical picture, risk factors, and management

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SUMMARY

Clozapine (CLZ) is the first-choice drug in the treatment of resistant schizophrenia but is also non-labeled used in dementia, bipolar disorder, severe anxiety, autism, and abnormal movement disorders, among many others. Clozapine's use is limited by clinically-relevant side effects such as neutropenia, myocarditis, cardiomyopathy, gastrointestinal hypomotility, and pneumonia. Heart dysfunction, particularly myocarditis, while lower than 0.1-1 % per year, imposes a serious health risk. Myocarditis occurs during the first few weeks of treatment, particularly at high CLZ doses. Patients report fever, resting tachycardia, chest discomfort, and eosinophilia, but it may be asymptomatic. Treatment involves CLZ withdrawal (but maybe reinstated later on) and standard treatment, such as steroids and heart/lung support. Clinicians should routinely conduct a brief clinical and laboratory examinations in the first 10-30 days of CLZ treatment, including heart auscultation, blood-cell count, electrocardiogram, C-reactive protein, and troponin-C. In general, CLZ should be started at low doses, but this is controversial. Cardiomyopathy may be undetected for a long time and manifest as heart insufficiency. Given the important role of CLZ in the psychiatric and neurological armamentarium, clinicians are advised to become familiar with these side effects and diagnostic protocols.

Key words: *Antipsychotic drugs, frequency, heart disease, schizophrenia.*

RESUMEN

La clozapina (CLZ) es el fármaco de primera elección en el tratamiento de la esquizofrenia resistente, pero también se usa en la demencia, el trastorno bipolar, la ansiedad severa, el autismo y los trastornos anormales del movimiento, entre muchos otros. El uso de clozapina está limitado por sus efectos secundarios clínicamente relevantes, como neutropenia, miocarditis, cardiomiopatía, hipomotilidad gastrointestinal y neumonía. La disfunción cardíaca, particularmente la miocarditis, aunque es inferior al 0.1-1% por año, impone un grave riesgo para la salud. La miocarditis ocurre durante las primeras semanas de tratamiento, particularmente a altas dosis de CLZ. Los pacientes informan fiebre, taquicardia en reposo, molestias en el pecho y eosinofilia, pero puede ser asintomática. El tratamiento implica la retirada de la CLZ (pero tal vez se restablezca más adelante) y el tratamiento estándar, como los esteroides y el apoyo cardíaco/pulmonar. Los médicos deben realizar rutinariamente breves exámenes clínicos y de laboratorio en los primeros 10-30 días de tratamiento con CLZ, incluida la auscultación cardíaca, el recuento de células sanguíneas, el electrocardiograma, la proteína C reactiva y la troponina-C. En general, CLZ debe iniciarse en dosis bajas, pero esto es controvertido. La cardiomiopatía puede no detectarse durante mucho tiempo y manifestarse como insuficiencia cardíaca.

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Dado el importante papel de CLZ en el arsenal psiquiátrico y neurológico, se aconseja a los médicos que se familiaricen con estos efectos secundarios y protocolos de diagnóstico.

Palabras clave: *Fármacos antipsicóticos, frecuencia, enfermedad cardíaca, esquizofrenia.*

INTRODUCTION

Clozapine (CLZ) is an atypical antipsychotic drug of the dibenzodiazepine group. It is considered the agent of choice for treatment-resistant schizophrenia (1) but it is out-of-label used in subjects with dementia, autism, bipolar disorder, suicidality, and severe anxiety. As an example, the well-informed use of CLZ is a central issue in the treatment success of Venezuelan institutions such as the Center for Attention for People with Schizophrenia and their Family in Maracaibo, Zulia state (CATESFAM).

While highly effective, CLZ administration requires careful monitoring, since it is associated with the following potentially lethal side effects (frequency in parenthesis): neutropenia (3.8 %) (2), agranulocytosis (1 %) (3), gastrointestinal hypomotility (up to 80 %) (4-6), seizures (6 %), metabolic syndrome (up to 40 %) (7), pneumonia (1.9 %) (8) and heart disorders such as myocarditis (0.3-3 %) and cardiomyopathy (0.01-0.1 %) (9). Less severe, while common unintended CLZ effects include dry mouth or excessive salivation, headache, blurred vision, and abnormal movements. CLZ-treated patients thus, require careful monitoring of signs and symptoms which may be often ostensible but frequently enough they are silent and insidious, such as gastrointestinal hypomotility as an example (4-6).

In this narrative review, we will focus on myocarditis and cardiomyopathy which are topics where our research group has conducted empirical studies in Venezuela.

CLZ-associated myocarditis was first described in 1999 (10) but several years elapsed until its complete recognition as an important clinical problem. These heart diseases may be observed during treatment with other antipsychotic drugs, but at a much lower frequency than with CLZ (9).

Clinical picture, risk factors, and pathogenesis

An agreement exists that CLZ treatment-associated myocarditis may evolve to cardiomyopathy after several years.

Myocarditis may be acute or chronic and may show no symptoms, mild or severe ones. When mild, subjects may feel chest discomfort, tachycardia, and mild fever; when severe, fever increases and there is chest pain, fluid retention (edema), and fatigue, which is linked to heart insufficiency and may be lethal (11). Histology may show focal or diffuse myocardium inflammation (11). Cardiomyopathy generally involves extensively damaged myocardial areas that may run unnoticed for many years and show as progressive heart failure (11).

Markers of myocardium necrosis and inflammation include elevations in erythrocyte sedimentation rate and serum levels of creatine kinase, cardiac troponin, lactate dehydrogenase, alanine transaminase, aspartate transaminase, C-reactive protein (11). The electrocardiogram (EKG), which is a key diagnostic procedure generally, shows sinus tachycardia, T wave inversions, ST-segment elevation, low-voltage QRS segments, and arrhythmias such as atrial fibrillation, ventricular ectopic beats, and sinus or ventricular tachycardia. Echocardiographic findings in CLZ-associated myocarditis are unspecific and include asynergic ventricular areas, left ventricular hypertrophy, hyperrefractile myocardial areas, ventricular thrombi, and restrictive ventricular filling (11).

The risk of myocarditis is higher at the beginning of the CLZ treatment. In a review of 59 cases (12), it developed within the first three weeks of treatment in 54 % of the patients (range: 4-21 days), and 81 % within the first three months. By contrast, only one among those 59 cases developed myocarditis after prolonged treatment, 8 years in this particular report (13).

Cardiomyopathy may be silent for a long period. When symptomatic, the diagnosis requires a detailed medical history, symptoms, and signs of heart failure, multiple EKG findings such as T-wave inversion, ST-segment depression, and pathologic Q waves, and signs of dilated, hypertrophic (restrictive or not) ventricular morphology (11). These last features are

detected by echocardiography or heart magnetic resonance. Given its chronic and progressive course and the multiple risk factors that may be present in subjects with severe mental disorders, the etiological role of CLZ could be difficult to ascertain.

The risk factors for CLZ-associated myocarditis are fast titration after starting the treatment and concomitant use of valproate or serotonin reuptake inhibitors (14,15). While the risk of rapid titration is controversial (16,17), consensus exists for parsimonious dose increase when starting treatment (18).

Once myocarditis or cardiomyopathy was diagnosed, CLZ should be withdrawn along with standard cardiovascular treatments (steroids, diuretics, beta-blockers, and angiotensin converting enzyme inhibitors). Reinstallation of CLZ after recovery is often considered in severely-ill subjects, but myocarditis may recur as much in half of the patients (19-21). There is a paucity of studies about this issue, which awaits clarification.

Several hypotheses have been postulated for the mechanisms of CLZ-associated myocarditis: Ig-E mediated, type I immune reaction; direct effects of CLZ in the myocardium, and catecholamine-induced oxidative stress. However, no mechanisms have been definitively established (22-26).

Frequency

In a recent meta-analysis of 28 studies comprising 258 961 people, Siskind et al., 2020 (27) reported the following frequency values: for myocarditis, event rate = 0.7 % (95 % confidence interval [CI] = [0.3- 1.6]) and case fatality rate = 12.7 (95 % CI = [3.4-37.7]). The cardiomyopathy event rate was 0.6 % (95 % CI = [0.2- 2.3]) and case fatality rate = 7.8 % (95 % CI = [1.8- 28.5]).

In one study conducted in Mérida (Mérida state) and Maracaibo (Zulia state), our research group evaluated patients undergoing treatment either with CLZ (n = 125) or with other typical or atypical antipsychotic drugs (n = 59) for at least e consecutive months. The subjects were examined by a cardiologist who also recorded echocardiograms and electrocardiograms to diagnose cardiomyopathy. No case was detected (28).

In another observational study conducted in the above-mentioned cities, we transversally screened outpatients for myocarditis by comparing a CLZ group of 132 subjects, with a non-CLZ group taking other APs (n = 371) only, and in 21 CLZ-treated patients and 18 subjects treated with other APs who had been followed for more than one year (29,30). The diagnostic protocol consisted of heart and lung auscultation, white cell count, troponin C and creatine-kinase MB resting EKG and evaluation by a cardiologist when suspecting myocarditis. One single case was detected, which represents the frequency of myocarditis of 1.6 % during the first month of treatment.

The frequency of myocarditis is higher in Australia than in any other country (3 %). While a true high incidence has not been definitively discarded, it may be due to an efficient monitoring health system (30).

General discussion

Myocarditis and cardiomyopathy associated with CLZ treatment may be detected by the primary physician and/or psychiatrist. For myocarditis, we have proposed a realistic protocol to be implemented throughout the first month of treatment. It includes a heart-focused physical examination, EKG, white blood cell quantification (searching for eosinophilia), and troponin-c serum levels, this last one easily conducted in the physician's office (30). This protocol may aid in preserving the proper place of a life-saving drug for people with severe mental disorders.

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