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Heart shock secondary to the use of clozapine

Jorge Andrés Ojeda Villota [1,*], Guillermo David Barros Bohorquez [1], Leonardo José Mier Martínez [2], Lina Marcela Álvarez Vides [3], Martha Lucia Beltran Avilez [2], Andrés Felipe Salas Ramírez [4], John Edinson Pérez Ortega [5] and Guillermo Contento Suescun [6]

[1] *Internist, Universidad Metropolitana de Barranquilla, Colombia.*
[2] *General Physician, Universidad de Sucre, Colombia.*
[3] *General Physician, Universidad Del Sinú, Montería, Colombia.*
[4] *General Physician, Fundación Universitaria Juan N. Corpas, Bogotá, Colombia.*
[5] *General Physician, Universidad Autónoma de Bucaramanga, Colombia.*
[6] *General Physician, Universidad de Boyacá, Colombia.*

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Abstract

Clozapine is an exceptionally effective antipsychotic and is approved only for use in refractory schizophrenia due to its adverse effects, including neutropenia, agranulocytosis, seizures, metabolic syndrome, and myocarditis. Cardiogenic shock represents a pathophysiological state where the heart is unable to maintain effective cardiac output (CO) in relation to the metabolic demands of the body, when it is derived from the use of clozapine it is an indirect complication, which occurs secondary to myocarditis due to hypersensitivity to said drug or also other myocardial conditions, myocarditis is an acute inflammatory disorder whose etiology is associated with an infectious process or mediated by an immune response either by drugs or toxins.

Keywords: Clozapine; Cardiogenic Shock; Myocarditis; Drug

1. Introduction

Clozapine is an atypical antipsychotic drug approved by the FDA for refractory schizophrenia, it acts as an antagonist of the serotonin 5-HT2A receptor subunit, it is currently established as the most effective drug due to its multiple benefits, such as decreased risk of suicide, tardive dyskinesia, fewer relapses, improvement in symptoms of depression, anxiety, and negative cognitive factors associated with schizophrenia [1]. However, it is not the drug of first choice, this is due to the adverse reactions, which it has evidenced in different studies, within them Agranulocytosis, cardiovascular affectations, seizures, metabolic syndrome, pulmonary embolism, among others have been described [1,2].

The cardiovascular (CV) adverse events that have been found are rare with an approximate incidence of 0.2% - 3%, these include fulminant myocarditis, dilated cardiomyopathy, and cardiogenic shock [2]. Myocarditis is the inflammation of the heart muscle that causes tissue death, this can be caused by infections, toxins, cardio toxic drugs, systemic disorders and even most of the time it is idiopathic, when it is secondary to drugs it is called hypersensitivity myocarditis, If not diagnosed in time, it can be lethal, causing cardiogenic shock, this being a state where cardiac output is insufficient to perfuse and oxygenate the tissues, which triggers signs of tissue hypo perfusion and capillary congestion, regardless of whether there is adequate intravascular volume status [3].

* Corresponding author: Jorge Andrés Ojeda Villota
Internist, Universidad Metropolitana de Barranquilla, Colombia.

2. Methodology

This is a study aimed at a narrative review, it was carried out through the selection of original articles, a review of available research, written in English and / or Spanish, through recognized databases such as PubMed, scielo, science direct, Wiley, plos one. Regardless of its year of publication, using the search terms cardiogenic shock, clozapine, fulminant myocarditis. A search criterion was not established for a defined language, however, all articles containing the corresponding information and of great importance for conducting our review were selected.

3. Results

Myocarditis (MC) is an acute inflammatory process whose etiology is associated with an infectious process or mediated by an immune response either by drugs or toxins [4]. The clinical manifestations vary widely, ranging from mild or asymptomatic symptoms to fulminant myocarditis, which is the most severe form, this is defined as an acute and severe inflammation of the myocardium that produces cardiogenic shock, histologically characterized by myocytic necrosis and edema, diagnosis of this is based on laboratory tests CK, troponins and electrocardiogram images, transthoracic echocardiogram, as such a specific test is not available. In recent years, MRI has become the noninvasive method of choice, although cardiac biopsies remain the first method of choice [5].

When myocarditis caused by toxins or drugs, such as clozapine, is called hypersensitivity myocarditis, the exact Mechanism of its production is unknown, one of the most accepted hypotheses is IgE-mediated type I hypersensitivity, this is a Autoimmune reaction at the cardiac level usually related to a drug that has been recently prescribed. It is characterized by the presence of an acute skin rash, fever, peripheral eosinophilia and abnormalities in the ECG [6,7]. Histologically, it is characterized by the presence of an interstitial infiltrate with prominent eosinophils [8,9,10].

Clozapine myocarditis (MCC) was described by Killian in 1999, it occurs in approximately 0.015% to 0.18% of patients medicated with this drug, the presentation of this adverse effect is rare, independent of the dose and life threatening Therefore, it is important to make an early diagnosis and establish a rapid management due to the associated morbidity and mortality. In some cases it may appear temporarily and mildly, the evidenced symptoms may be associated with the effects of the drug titration [11]. It is reported that 80% of CCM cases present within the first 4 weeks of treatment, and it is estimated that up to 90% may occur within the first 8 weeks [12].

Possible risk factors associated with the development of said disease due to the use of clozapine have been described in different literatures, among them we can mention the progressive and forceful adjustment of the dose, metabolic alterations, such as weight gain, use of illicit substances, joint administration of drugs from the same pharmacological group or drugs that have evidence of being cardio toxic such as some antibacterials, cisapride, thyroxine, ranitidine, cyclophosphamide, lithium, phenothiazine's, valproate and antidepressants (amitriptyline, imipramine and desipramine), therefore these Patients should be strictly monitored in case of myocarditis. (Figure 1) [13].

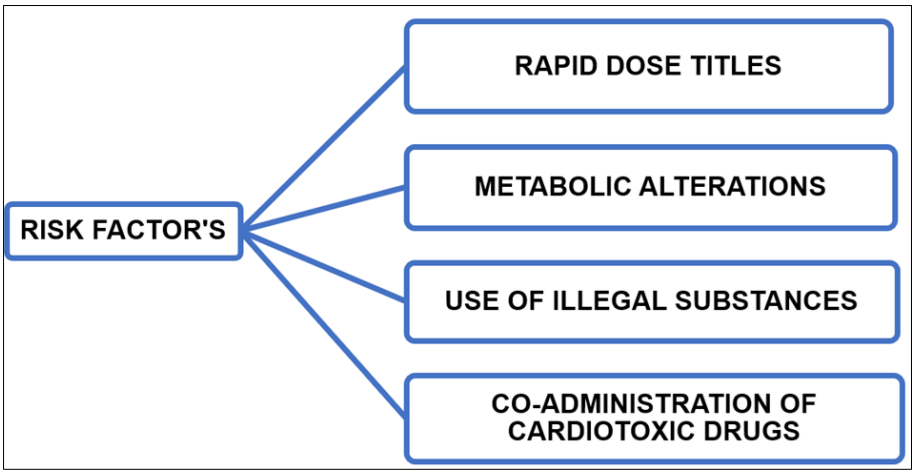

Figure 1 Risk factors for CCM

The clinical presentation of MCC in adults can be very wide, it can range from a subclinical presentation to fulminant heart failure, it is very common to find that it presents as a flu picture consisting of asthenia, feverish peaks, myalgia's and arthralgia's, dizziness, nasal congestion and sensations of "itchy throat", dyspnoea, at the same time there are also symptoms such as persistent tachycardia at rest, palpitations, chest pain, syncope, arrhythmias and hypotension. In the paraclinical there are also findings such as eosinophilia, increased LDH, CPK and troponin, nonspecific changes in the ECG, but none of these is pathognomonic for the condition, so in some cases the disease is underestimated or not identified [14].

The management of CCM must usually apply empirical measures and pharmacological treatment in order to improve the functioning of the heart muscle and reduce the risk of heart failure, drugs such as diuretics, beta-blockers and ACE inhibitors, corticosteroids are used. Diuretics work by decreasing fluid overload and the subsequent progression of heart failure [15]. Beta-blockers can improve ventricular function, limit further worsening of heart failure, and reduce mortality risks in patients with myocarditis. Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (ARBs) are also a treatment option for heart failure due to myocarditis [16]. On the other hand, clozapine should be discontinued, taking into account the risk of relapse to psychosis symptoms, and switching to another class of antipsychotics [17].

It is important to know the characteristics of this pathology to carry out an early detection of clozapine-related myocarditis in patients medicated with it, since early diagnosis improves clinical outcome and reduces mortality from CCM, since nonspecific symptoms may occur unnoticed and generally ends in cardiogenic shock, this being one of the most common complications in CCM without an adequate approach [18].

When there is CCM or any other damage to myocardial tissue, acute heart failure is generated followed by cardiogenic shock, which physiologically manifests as a severe depression of contractility, which ends in a vicious cycle with decreased cardiac output, hypotension and perfusion altered coronary artery, which in turn further decreases contractility (TC) and cardiac output. These acute alterations generate diastolic deficiency and pulmonary congestion due to a poor adaptation of the vasculature to the pulmonary level. Establishing that cardiogenic shock is a deterioration of the circulatory system in general and not only of the left ventricle (LV) [19,20]. With left ventricular dysfunction, peripheral vascular resistance (PVR) is increased in order to improve perfusion. All this process generates exhaustion that is manifested in the stiffness of the walls, disturbance of the heart muscle and deterioration of the elastance at the ventricular level, which degenerates more global perfusion that in turn causes the release of catecholamine's and

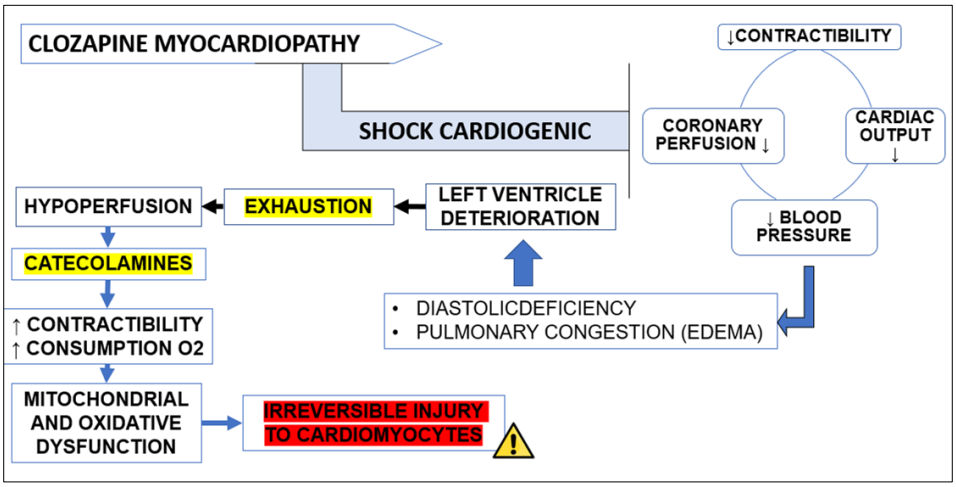

Figure 2 Pathophysiology of cardiogenic shock

Other pro-inflammatory substances (such as IL- 6, TNF, etc.), which increases contractility and oxygen consumption. All these responses are reflected at the cellular level and generate mitochondrial and oxidative disorders, which generates irreversible deterioration of cardiomyocytes [21]. (Figure 2) In certain cases, the pathophysiological processes may vary in different clinical presentations, where the peripheral vascular response may be inappropriate, indicating a systemic inflammatory syndrome with normal to low PVR due to increased nitric oxide release [22,23].

4. Discussion

In Australia between the years 1993-2003, 116 suspected cases of myocarditis secondary to the use of clozapine were followed, of which it was found that most of the patients developed the disease in approximately 17 days after the start of treatment, where 51, 8% was detected and management was performed, 14.7% had not undergone management as they were not identified, and 33.6% it is unknown what outcome they had or died from cardiogenic shock. Other studies have been published that establish that the use of clozapine is linked to an increased risk of sudden death, either due to myocarditis or dilated cardiomyopathy, which end in cardiogenic shock, on the other hand, it exposes the lack of research in this regard based on the fact that there have been cases of sudden death in a patient undergoing treatment with this drug and no in-depth study has been carried out. This same study documents the appearance of fever between days 14 and 21 after the start of clozapine, thus associating it with the appearance of myocarditis, it also establishes that age as a risk factor for this disease. Thus, many case studies have been carried out that document the appearance of said adverse effect that often goes unnoticed, which has a fatal consequence.

5. Conclusion

Clozapine-mediated cardiotoxicity is a rare adverse effect, but with high morbidity and mortality that often goes unrecognized due to various confounding factors. Cardiogenic shock derived from the use of clozapine is an indirect complication, which occurs secondary to myocarditis due to hypersensitivity to this drug, it can vary in presentation, as well as it is not well understood and is often underestimated due to its nonspecific symptoms. But be very vigilant, as fulminant myocarditis is an unusual complication with a rapidly progressive course resulting in severe heart failure followed by cardiogenic shock.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest.

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