INVESTIGATION ARTICLE

Clozapine-Induced Myocarditis: A review and Screening protocol.

Miocarditis inducida por Clozapina: Revisión y protocolo de Screening.

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ABSTRACT:
Although Clozapine is the gold standard treatment in resistant-schizophrenia, severe or even life-threatening adverse effects must be taked into account. Early myocarditis, a severe but unusual cardiovascular effect, can appear in the first 4-6 weeks of initiation. Incidence rates of myocarditis are about 0,015-0,188% around the world, being more elevated in Australia. Aethiology is unknown, suggesting Ig E mediated hipersensibility, hiperaeosinophilia and hiperadrenergy. Echocardiography seems to be one of the most helpful tools for diagnosing myocarditis. Endomyocardial biopsy is definitive, but not usually available. A role for cardiac magnetic resonance imaging (MRI) also has been proposed (findings of inflammation). In order to make an early diagnosis, several screening-criteria, considering clinical and laboratory ones, have been proposed: aeosinophylia, creatininkinase, C Reactive Proteine, troponin, and EKG. If we suspected clozapine-induced myocarditis, the drug must be removed and support medical treatment must be indicated.

Keywords: *Resistant-Schizophrenia. Clozapine. Myocarditis. Echocardiography.*

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INTRODUCTION

Clozapine is an atypical neuroleptic drug of the dibenzodiazepine family recognized by the scientific community as highly effective in psychotic spectrum disorders, especially refractory schizophrenia, for patients who have not responded to or tolerated at least two adequate trials of standard antipsychotics[1,2] Furthermore, this psychotropic drug has the ability to significantly reduce the risk of suicide in schizophrenia.[3].

Despite the beneficial effects of clozapine, its use is relatively restricted by the occasional potentially serious undesirable effects: agranulocytosis, hepatotoxicity, epileptic seizures and cardiovascular effects (4).

Among the adverse cardiovascular effects, clozapine has been associated with: tachycardia (in at least 10% of patients treated with it), increases or decreases in blood pressure, cardiogenic syncope, and alterations in the electrocardiographic tracing (with a estimated incidence of 1%). Early myocarditis and late cardiomyopathy are rare, but life-threatening, and are severe cardiovascular effects that require prompt therapeutic measures[5-8].

The actual prevalence figures of clozapine-induced myocarditis are not known, and there is an international disparity in the figures provided, with higher rates found in Australia than those reported in other places in the world[5,9,10]. Possibly the cardiovascular effects induced by clozapine are not completely documented in the scientific literature, because the nature of the signs present in patients are not specific, and also due to the lack of routine medical diagnosis and the lack of underlying pathophysiological mechanisms in cases of myocarditis and cardiomyopathy[7,11-13]. There are also no standardized criteria for monitoring cardiac complications associated with clozapine.

The objective of this work is to review the published data on epidemiology, the diagnosis, possible risk and protective factors and therapeutic measures to be established, concluding with a proposal for a monitoring protocol for the prevention and early diagnosis of clozapine-induced myocarditis (CIM). It is also intended that this protocol be a useful tool for clinicians.

METHODOLOGY:

A bibliographic search was carried out in the MEDLINE and EMBASE (Elsevier) databases, using the descriptors "clozapine" AND "myocarditis" until May 2017. Of the total of 148 articles obtained, and after their evaluation, those that included the object of the research were manually selected.

Myocarditis associated to clozapine

History

The first documented case of MIC dates back to 1980, presumably due to an overdose [14]. In the following decade, attention to the myocarditis-clozapine association increased, particularly in Anglo-Sphere countries such as the United Kingdom, Australia and New Zealand[7,15]. An investigation from 1999 strongly supported the relation between myocarditis and the initiation of clozapine treatment in 15 patients, with a mortality rate of 30%[16].

The causal association with clozapine was later supported by Coulter et al in 2001(17), using cases documented in the World Health Organization adverse drug reactions database. As these authors point out, it was possible that the indication for clozapine itself was related to a high risk of developing myocarditis, or that clozapine was an "innocent bystander," with no etiological relationship with myocarditis. Both monitoring of agranulocytosis and careful titration of clozapine at the beginning of the regimen have potentially led to a lower number of MIC diagnoses. The WHO recorded 231 documented cases of myocarditis and cardiomyopathy with clozapine. Only 89 of them were being treated with other antipsychotics. The analysis of the cases found a significant association involving only clozapine.

Epidemiology

The actual incidence data of MIC are unknown. International figures stand between 0.015-0.188%[7], while Australian studies show much higher incidences[18]. These differences are due neither to greater susceptibility (genetic or environmental) nor to disparity in clozapine use (patient age or clozapine titration). A possible reason would be the underdiagnosis of this pathology outside of Australia. Within this country, the widespread use of cardiac monitoring guidelines and the high awareness of this existing relationship among psychiatrists, cardiologists

and pathologists would justify the rates found and the high effectiveness of pharmacovigilance systems[15].
Ronaldson, took into account previous publications of Australian studies, and estimated that the incidence of MIC would be around 3% (mean range between 1.1 and 5%) (7) An update of the article by Killian et al.[16] was published in 2007, reviewing the 116 cases of myocarditis in Australia documented between 1993 and 2003 [10]. The figures are higher than those of the rest of the world. This information showed percentages of myocarditis in 7-12 per 1000 patients who began receiving clozapine.

The time of myocarditis presenting during clozapine treatment varies, and in fact the distinction between early myocarditis and late cardiomyopathy is not always clear. A few cases of myocarditis have been diagnosed after several months of treatment[19], but most have been identified in the first two to three months after starting clozapine in previously healthy non-geriatric psychiatric patients [10,16,20–26]

Etiology
Its etiology is still uncertain, but some researchers such as De Beradis et al have recently summarized some theories. It has been suggested that MIC may be caused by a) Ig E-mediated hypersensitivity; b) hypereosinophilic syndrome causing cardiotoxicity through blockade of M2 cholinergic receptors; c) increased sympathetic adrenergic tone, as revealed by elevated plasma norepinephrine levels in patients treated with clozapine[8,16,27–29].

On the other hand, Devarajan [30] and Linnet[31] have postulated that deficiencies in cytochrome CYP450 1A2 and 1A3 may cause a decrease in the metabolism of clozapine in certain cohorts of patients, leading to lower levels. elevated plasma levels of clozapine exerting anticholinergic and therefore cardiotoxic effects. Deficiencies in isoenzymes 3A4, 2C19 and 2D6 have also been described.

Regarding the moment when MIC develops, either during the initial phase or in the maintenance phase, Freunderich[12] proposes two different etiological mechanisms: during the initial stage the mechanism may be due to a type I immunological phenomenon or an acute hypersensitivity mediated by IgE; and during maintenance, the etiological mechanism would correspond to a type III allergic reaction mediated by immune complexes or direct cardiotoxicity induced by clozapine.

Diagnosis
The general lack of knowledge about MIC sometimes has non-specific symptoms. Thus, symptoms may include tachycardia (with a heart rate greater than 100), shortened breathing or dyspnea, moderate fever, flu-like symptoms, nausea, dizziness, and rarely chest discomfort[15,32]. In some fatal cases, no clinical symptoms suggestive of cardiac dysfunction were documented prior to death[15]. Additionally, some features of MIC, including low-grade fever, tachycardia, fatigue, and eosinophilia, commonly occur when initial doses of clozapine are being increased. These symptoms are usually self-limiting and of little clinical significance [6].

Altered laboratory parameters found early in myocarditis include an increase in eosinophil counts and serum concentrations of inflammatory markers, especially C-reactive protein (CRP), troponins T and I, creatine kinase (CK-MB), B-type natriuretic peptide (BNP), terminal fragment of pro-BNP, and possibly also interleukin-6 (IL-6).) and tumor necrosis factor alpha (TNFa). Electrocardiographic abnormalities or arrhythmias may or may not appear [24,32–36].

Echocardiography, usually used in the presence of clinical or analytical signs or symptoms suggestive of myocarditis, can show left ventricular or biventricular dysfunction, as well as a reduction in the left ventricular ejection fraction. Multiple investigations recognize and support this procedure as one of the most useful for the diagnosis of myocarditis[19,23–25,33,34,36-38].

On the other hand, endomyocardial biopsy is widely considered one of the most defining means of diagnosis, showing eosinophilic inclusions in the myocardial tissue and cellular inflammatory infiltrates, with or without associated cardiomyocyte necrosis. However, an endomyocardial biopsy is usually avoided due to its risks and clinical limitations [26,39].

Neuroimaging (NMR) criteria would include two or more of the following indicators of myocardial inflammation [26,40–42]:
1. An increase in signal intensity on T2.
2. An increase in gadolinium uptake on T1-

Table 1. Diagnostic criteria of clozapine-associated myocarditis (23)
Appearance of new symptoms, such as palpitations, tachycardia, chest pain, and fever within the first 45 days after starting clozapine
Absence of other probable causes or history of heart disease
New signs of isolated cardiac dysfunction such as persistent tachycardia, third heart sound, basal pulmonary crackles, and peripheral edema with or without fever may suggest
At least one of the following diagnostic abnormalities: a) peripheral eosinophilia, b) elevated serum concentrations of troponin T or I, or CK-MB, c) electrocardiographic changes that may include ST segment decrease > 1 mm or T wave inversion, d) radiological findings of pulmonary congestion and heart failure, and e) evidence of left or right ventricular dysfunction, defined by echocardiographic criteria.
MRI evidence of myocarditis
Defining Histologic Findings in a Cardiac Tissue Biopsy

Table 2.- "OSUNA" PROTOCOL FOR SCREENING OF MYOCARDITIS ASSOCIATED WITH CLOZAPINE:

The monitoring protocol for early detection proposed by the Psychiatry Service of the Hospital de la Merced de Osuna (Seville) is based on previous proposals from other researches [12,33,38,66] adapted to our usual clinical practice and its viability in a public health service in our country. The cases in which echocardiography should be performed follow the previous indications proposed by Ronaldson in 2011 [33]: see Table 3.

	Clinical Exam	Hemogram	EKG	PCR	Troponins	Baseline
Echocardiogram	✓	✓	✓			According to Ronaldson criteria (see Table 3)
Week 1	✓	✓	✓	✓	✓	
Week 2	✓	✓		✓		
Week 3	✓	✓	✓	✓	✓	
Week 4	✓	✓		✓		
Week 8	✓	✓		✓	✓	

Table 3. Ronaldson criteria to perform an Echocardiography in case of suspected clozapine-induced myocarditis (33)

Performing an echocardiogram if at least 1 of the following criteria is met
Troponins >2x
PCR>100

weighted images.
3 At least one focal lesion showing delayed and non-ischemic uptake.

Finally, and as a diagnostic synthesis, we present in Table 1 the criteria that Ronaldson et al [23] propose for MIC.

Prognosis and treatment
In case of suspected MIC, drug withdrawal and supportive treatment constitute the fundamental therapeutic bases. The remission of symptoms after suspending treatment would help confirm the etiological hypothesis. A rapid recovery of left ventricular function is achieved after the withdrawal of clozapine, with significant improvement in the first 5 days even in severe cases.[43]. Documented cases of mortality due to MIC are between 10-30% of people with this condition[5,10,16,20].

The search for new therapeutic targets is based on the theory of an imbalance in the functioning of the autonomic nervous system, with a decrease in parasympathetic tone and an increase in sympathetic tone [44]. The action mechanism of clozapine includes potent peripheral and central muscarinic anticholinergic actions, as well as an alpha 1 and alpha 2 adrenergic receptors blockage. To date, various empirical pharmacological interventions have been used, which fundamentally include the use of corticosteroids, beta-adrenergic blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor antagonists (ARBs) [8,21,22,25,44–47].

Preventive measures: Risk factors and protective factorsfor Clozapine-induced myocarditis.
Rapid dose titration
In a study of cases and controls, Ronaldson and colleagues focused on the importance of rapid titration, concluding that each 250 mg of clozapine administered in the first nine days was associated with an Odds Ratio (OR) of 1.26. They also reported that a cumulative dose of 920 mg in the first nine days was associated with an OR of 2.31 (I.C. 0.98-5.48) in comparison with a cumulative dose of 500 mg.[48].
Chung et al reported that a titration rate of more than 50 mg/week was associated with an OR of 18.9 (I.C. 5.3-66.7)[49]

Concomitant Valproic acid Treatment
In the same case-control study, Ronaldson et al found that concomitant use of valproic acid resulted in an OR of 2.59 (I.C. 1.51-4.42) for the development of MIC. Chung et al found that valproic acid was also associated with an OR of 3.6 (I.C. 1.5-8.9) for the development of clozapine-induced fever [49]. Therefore, it is suggested that slow titration is more reasonable in patients taking valproic acid. (50,51)

Age
The study by Ronaldson et al reported that each following decade was associated with an OR of 1.31 (1.07-1.60) [48].

Captopril
In laboratory studies in rats, Abdel-Wahab et al [35] have shown that the administration of captopril with clozapine doses of 25 mg/kg/day attenuates the effects on the parameters of oxidative stress, nitric oxide and DNA degradation products (8-OHdG) in a dose-dependent manner, suggesting the authors that Captopril could have a protective role in the development of myocarditis.

Is the reintroduction of Clozapine viable after an eposode of Myocarditis associated with it?
Reinstating clozapine treatment after associated myocarditis is generally not recommended. However, the decision essentially rests on the

SELF-ASSESSMENT QUESTIONNAIRE:

1.- Some of the rare but potentially serious undesirable effects of clozapine are:

a) Agranulocytosis.
b) Early myocarditis
c) Late cardiomyopathy.
d) Epileptic seizures.
e) All of the above

2.- Regarding the incidence and clinical presentation of Clozapine-induced Myocarditis (MIC) it is correct to say that:

a) There are higher rates in the rest of the world than in Australia.
b) The clinical signs and symptoms suggestive of MIC are specific.
c) Possibly if found over diagnosed.
d) It is rare, with international incidence rates of 0.015-0.0188%.
e) It appears after several months of treatment.

3.- The usual time between the initial use of clozapine and the appearance of myocarditis is:

a) 1-2 days.
b) It usually appears within the first 7 days.
c) It usually appears within the first 8-12 weeks.
d) It appears after several months of treatment.
e) It usually appears at any time during treatment, from days to years.

4.- Among the clinical criteria for suspected myocarditis, choose the incorrect one:

a) Low fever
b) Dyspnea
c) Thoracic discomfort.
d) Bradycardia.
e) Peripheral edemas.

5.- The clinical and laboratory diagnosis of MIC, includes all of the following except:

a) Tachycardia.
b) Hypereosinophilic syndrome
c) CK-MB Decrease
d) Troponins Increase
e) Increased CRP.

6.- The Ronaldson criteria states the obligation to perform an Echocardiography when:

a) Presence of tachycardia and Hypereosinophilic syndrome
b) There are EKG alterations.
c) There is an increase in CRP > 100 and troponins > 2x.
d) Blood count shows agranulocytosis.
e) All of the above

CORRECT ANSWERS:

1.- e) All of the above

Agranulocytosis, myocarditis, delayed cardiomyopathy, and seizures are all rare but serious adverse effects of clozapine. The most common undesirable effects of clozapine are sedation and hypersalivation.

2.- d) It is rare, with international incidence rates of 0.015-0.0188%.

In Australia, perhaps due to greater consideration when applying early screening techniques, higher incidence rates have been reported than in the rest of the world. The signs and symptoms suggestive of myocarditis are not specific, but rather non-specific (low-grade fever, general discomfort, tachycardia, dyspnea...). MIC is possibly under-diagnosed and never over-diagnosed since early screening tests are sometimes ignored in routine clinical practice. Finally, MIC usually appears within the first 8-12 weeks of starting treatment with clozapine, and not after months.

3.- c) It usually appears within the first 8-12 weeks.

The rest of the periods mentioned are incorrect.

4.- d) Bradycardia.

The clinical criteria for suspected MIC are non-specific and include all those mentioned in the rest of the options (low-grade fever, dyspnea on moderate exertion, chest discomfort, peripheral edema) and tachycardia, sometimes even a third heart sound.

5.- c) CK-MB Decrease

Clinical and laboratory data suggesting MIC includes tachycardia, hypereosinophilic syndrome, increased acute phase reactants such as CRP, and increased cardiac muscle enzymes such as CK-MB and troponin.

6.- c) PCR >100 y troponina > 2x increase.

According to the Ronaldson criteria, Echocardiography should be requested when CRP is >100 and there are more than double troponins. There is controversy about the greater or lesser use of Echocardiography as a cost-effective screening method in a large number of cases, since many of the clinical and laboratory alterations can occur at the beginning of treatment with clozapine, are nonspecific and sometimes irrelevant to the clinician. Thus, Ronaldson et al choose to point out the markers of myocardial inflammation (CRP) and cellular damage (troponin) as the most objective parameters to request an Echocardiography.

severity of the psychiatric pathology for which clozapine was initially administered, as well as the clinical value provided by the antipsychotic. If reintroduction is chosen, we have favorable data in the scientific literature, with a total of 17 cases of reinstitution of treatment and a 71% success rate [33,42,48,52–65]. If clozapine is reintroduced, it should be done when there has been a restoration of previous clinical and laboratory parameters and a lack of evidence for cardiac dysfunction. Reintroduction, under controlled conditions and initially in the hospital, should be performed with very low doses and very slowly titrated, with repeated and frequent evaluations of cardiac markers that have shown abnormal results during acute myocarditis.[40,53,56,57,59,61,62]. Finally, it should always be kept in mind that some cases of recurrence of myocarditis have been reported after reintroducing clozapine [24,56].

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