Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

able prognosis. However, further studies are needed to better understand the mechanism.

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Disclosure of interest

The authors declare that they have no competing interest.

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Douja Hamdi[a], Mouna Korbi[a,*,b], Dhouha Sahnoun[c], Mohamed Mehdi Boussaada[d], Randa Said El Mabrouk[a], Hichem Belhadjali[a,b], Amel Chaabane[c], Jameleddine Zili[a,b]

[a] *Dermatology Department, Fattouma Bourguiba University Hospital, University of Monastir, 5000 Monastir, Tunisia*
[b] *Research laboratory LR20SP03A, University of Monastir, 5000 Monastir, Tunisia*
[c] *Pharmacology Department, Fattouma Bourguiba University Hospital, University of Monastir, 5000 Monastir, Tunisia*
[d] *Cardiology Department, Fattouma Bourguiba University Hospital, University of Monastir, 5000 Monastir, Tunisia*

* Corresponding author.
E-mail address: korbimouna68@gmail.com (M. Korbi)

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Adverse drug reactions associated with ivermectin use for COVID-19 reported in the World Health Organization's pharmacovigilance database

Keywords Ivermectin; Pharmacovigilance; COVID-19

Abbreviations

ADRs	adverse drug reactions
COVID-19	coronavirus disease 2019
PT	preferred terms
WHO	World Health Organization

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, numerous drugs have been proposed for the management of the infection. Among them, ivermectin has been the subject of many scientific studies evaluating its potential antiviral efficacy. Despite the fact that it has never been proven that ivermectin can be effective in the management of COVID-19 [1,2], North American and European tabloids as well as some public health policies began to mention it as a potential anti-COVID-19 treatment in May 2020 which led to its off-label use in several countries [3].

In 2021, a correspondence by Temple et al. showed an increasing number of calls regarding ivermectin exposure related to COVID-19 at a Poison Center in Oregon, USA [4]. Ivermectin has already been studied for its safety in various indications. It is well known that the use of ivermectin in individuals highly infected with loaisis, a parasitic disease endemic in Central Africa, may cause severe neurological adverse drug reactions (ADRs) [5,6]. In 2018, Chandler at al. reported 28 cases of serious neurological adverse events after the administration of ivermectin where loaisis infection was not reported [7]. In 2021, through an analysis of the World Health Organization (WHO) pharmacovigilance database, the occurrence of serious neurological adverse reactions was highlighted in areas where loiasis was not endemic [8].

We reviewed all ADRs reported with ivermectin and recorded in VigiBase®, the World Health Organization's ADRs database.

We highlighted a considerable increase in ivermectine-related reports since May 2020 (758 reports in 2018, 542 reports in 2019, 1418 reports in 2020 and 1252 reports in 2021).

From May 1st 2020 to December 21, 2021, a total of 1777 cases were reported with ivermectin specifying an indication for COVID-19. Gastrointestinal and neurological effects were the most reported. Among 53 cases considered as serious, the most frequently reported concerned neurologic disorders (11 cases including 1 encephalitis, 1 coma and 1 death), respiratory disorders (8 cases including 2 deaths), gastrointestinal disorders (8 cases including 1 death) and cardiac disorders (5 cases including 2 deaths by cardiac arrest). Four overdoses were reported and were mostly associated with neurologic disorders. Among these 4 cases, 2 were life threatening and 1 caused/prolonged a

Table 1 Characteristics of serious cases reported with ivermectin as single suspect.

Characteristics	Reported cases ($n = 35$)
Sex ratio (M/F)	1.5
Age (median [minimum, maximum])	51 [13,79]
Reporting region (n, %)	
North America	13 (37.1%)
Europe	9 (25.7%)
Asia	7 (20.0%)
Latin America	6 (17.1%)
Seriousness criterion (n, %)[a]	
Death	6 (17.1%)
Life threatening	9 (25.7%)
Disabling/incapacitating	2 (5.7%)
Hospitalization	16 (45.7%)
Other important condition	18 (51.4%)
System organ class [SOC] (n, %) [b]	
Nervous system disorders	10 (28.6%)
Injury, poisoning, procedural complications	9 (25.7%)
General disorders and administration site conditions	8 (22.9%)
Investigations	7 (20.0%)
Gastrointestinal disorders	7 (20.0%)
Respiratory, thoracic, mediastinal disorders	7 (10.4%)
Infections and infestations	6 (17.1%)
Skin and subcutaneous tissue disorders	4 (11.4%)
Psychiatric disorders	4 (11.4%)
Metabolism and nutrition disorders	3 (8.6%)
Cardiac disorders	3 (8.6%)
Eye disorders	2 (5.7%)
Ear and labyrinth disorders	2 (5.7%)
Musculoskeletal, connectives tissues disorders	2 (5.7%)
Vascular disorders	1 (2.9%)
Social circumstances	1 (2.9%)

[a] Each case can correspond to multiple seriousness criteria.
[b] Each case can correspond to 1 or more SOCs.

hospitalization. Table 1 summarizes characteristics of the 35 serious cases (including 6 deaths) where ivermectin was reported as the single suspect. The most reported preferred terms (PT) among those cases were: overdose, use of product in an unapproved indication, abdominal pain, pruritus and vomiting.

Among the 6 deaths, 4 were male and 2 were female, 1 patient was 20-years-old, 4 were between 50- and 80-years-old, and 1 patient was of unknown age. For 3 cases, death was the only term reported. The other 3 cases report the following PTs:

- confusional state, septic shock and digestive disorders;
- abnormal state sensation and acute respiratory distress syndrome;
- cardiac arrest, serious myasthenia and nervous system disorder.

It is not excluded that these effects also reflect the lack of effectiveness of ivermectin in the management of COVID-19. These findings call for extreme caution when using ivermectin, especially since there is no current scientific evidence to support its use in the treatment of COVID-19.

Acknowledgements

Our study is based on the use of VigiBase®, a global pharmacovigilance database, with information from a variety of sources. The likelihood that the suspected adverse reaction is drug-related is not the same in all cases. The Uppsala Monitoring Centre has provided the data but the study results and conclusions are those of the authors and not necessarily those of the Uppsala Monitoring Centre, National Centers, or WHO.

Disclosure of interest

The authors declare that they have no competing interest.

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Jeremy T. Campillo[a,b,*], Jean-Luc Faillie[a,c]
[a] *Department of medical pharmacology and toxicology, CHU Montpellier, 34000 Montpellier, France*
[b] *UMI 233 TransVIHMI, Université de Montpellier, Institut de Recherche pour le Développement (IRD), INSERM Unité 1175, Montpellier, France*
[c] *IDESP-UMR UA11 Inserm, université de Montpellier, 34000 Montpellier, France*

* Corresponding author. Inserm unité 1175, UMI 233, institut de recherche pour le développement (IRD), université de Montpellier, 34000 Montpellier, France.
E-mail address: jeremy.campillo@ird.fr (J.T. Campillo)

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Clozapine associated myocarditis: A lesional mechanism suspected☆

Keywords Clozapine; Myocarditis; Antipsychotic; Cardiac; Adverse effect; Pharmacovigilance

Abbreviations

CRP	C-reactive protein
ECG	electrocardiogram

Introduction

Clozapine, discovered in the early 1970s, is the leading atypical antipsychotic. Several studies have demonstrated its efficacy and superiority to other antipsychotics [1]. However, clozapine has been incriminated in the genesis of several serious adverse drug reactions, particularly agranulocytosis. For this reason, this drug was withdrawn from the market at the beginning of the 1980s and finally put back for more restricted indications, essentially refractory schizophrenia [2]. Moreover, clozapine has been associated with cardiac adverse drug reaction, including cardiomyopathy and myocarditis [3].

Herein, we report a case of a male patient who experienced myocarditis under clozapine treatment with a favorable outcome after drug cessation, notified to the Chalbi Belkahia National Center of Pharmacovigilance on January 2020. (Registration number: 395/2020)

Case report

A 47-year-old patient with no history of heart disease, followed since 2004 for schizophrenia, was initially treated with fluphenazine decanoate 200 mg per month and haloperidol 25 mg per day. Due to refractory schizophrenia, he was started, in 2005, on clozapine 500 mg per day then 600 mg per day with good tolerance.

In 2011, the patient experienced palpitations with sinus tachycardia on the electrocardiogram (ECG). Cardiac echocardiography was normal. The decision was to decrease the daily dose to 400 mg per day and initiate acebutolol 200 mg. After that, the cardiac rhythm was back to normal.

In 2015, due to the patient's non-compliance, he was put back on fluphenazine decanoate 225 mg per month and haloperidol 25 mg per day. Between 2015 and 2020, the patient was lost to follow-up.

In 2020, he consulted again with severe psychiatric symptoms led by suicidal and aggressive behaviors. The decision was to put him back on clozapine 400 mg per day. After five weeks, the patient experienced chest pain, with a two mm-ST-segment elevation on the ECG. Biologically, he presented a hypereosinophilia of 633 cells/mm3; troponins and ultrasensitive C-reactive protein (CRP) were negative. Clozapine was discontinued. The outcome was favorable with no recurrence of chest pain normalization of the ECG and eosinophils number after 20 days.

Discussion

Incidence of clozapine-associated myocarditis is uncommon (<0.1 to 1%) but could be potentially serious [4]. In our report, myocarditis onset was five weeks. Analysis of cohort studies has found that 75% of clozapine-induced myocarditis reports occur within the first month [5]. Imputability score was C2S2 (possible) because of compatible delay and favorable outcome after drug withdrawal [6]. Diagnosis of clozapine-induced myocarditis was suspected based on the occurrence of chest pain with ST-elevation on ECG and hypereosinophilia. Our patient presented three diagnostic criteria of clozapine-induced myocarditis (clozapine-induced myocarditis is retained from 2 criteria) [3]. It should be noted that in our patient's case, cardiac MRI and endomyocardial biopsy were not performed, because of the negativity of troponins and CRP. Negativity of those biomarkers could be explained by the fact that were sampled too early. However, their elevation, although favourable to the diagnosis of myocarditis, is not constant. In fact, sensitivity of CRP in myocarditis diagnosis is only 50.1% [7]. Elevation of troponin in some studies would be more a sign of a permanent lesion of the myocardium, which is apparently not the case of our patient [7].

In our report, responsibility of clozapine was retained due to symptomatology improvement after drug discontinuation. The hypothesis of an IgE-mediated hypersensitivity mechanism has been suggested since there is no dose-dependent relationship [3]. However, in our patient's report, a lesional mechanism involving cardiac muscle's microtrauma due to previous exposure could be suspected since appearance of myocarditis several years after treatment onset. Indeed, the hypothesis of subclinical cardiac adverse drug reaction established during previous exposures may be presumed since the patient had an episode of sinus tachycardia during previous exposure to clozapine. Moreover, haloperidol and fluphenazine may have contributed to cardiac microtraumas since their association with cardiac toxicity [8,9].

Some authors recommended the administration of a specific treatment for clozapine-associated myocarditis with discontinuation and a switch to another class of antipsychotics to reduce mortality risk in patients [4]. Clozapine

☆ This case has been declared to the Chalbi Belkahia National Center of Pharmacovigilance on January 2020 under the registration number 395/2020.