

A clozapine's uncharted voyage: Five years and a pandemic after the end of mandatory haematological notifications to the Spanish medicines agency



Un viaje desconocido para la clozapina: 5 años y una pandemia después del final de las notificaciones hematológicas obligatorias a la Agencia Española del Medicamento

Dear Editor,

Clozapine was synthesized in 1958. In 1972, it was first introduced in Switzerland, Austria, and Germany, and within the following years in 30 other countries. In September 1975 Idänpään-Heikkilä et al.¹ published a letter to *The Lancet* editor, describing a series of cases of Finnish patients suffering from serious blood dyscrasias, such as agranulocytosis, associated with the use of clozapine in mono or polytherapy. Due to this fact, Spain, as many other countries, withdrew clozapine from the market.

Nevertheless, given its efficacy in treatment-resistant schizophrenia, Spain reauthorised its prescription and dispensation in 1993, subject to precautionary measures. In order to prevent blood disorders, a haematological control protocol was established that ensured early detection of changes in the white blood cells count, allowing an immediate withdrawal before agranulocytosis. This protocol involved filling monitoring sheets that had to be sent regularly to the National Pharmacovigilance Service of the regulatory Spanish Medicines Agency (AEMPS). In addition, the doctor who prescribed the drug for the first time had to provide the patient with a booklet that had to be updated periodically, stating the frequency of haematological controls, dose to be administered and leukocyte counts. The booklet was signed by the prescriber. This national follow-up procedure also helped acquire a better understanding of other drug characteristics, such as therapeutic response, relapse prediction or other side effects.²

On October 4, 2017, the AEMPS published an informative note cancelling the obligation to submit the haematological results for patients undergoing treatment with drugs containing clozapine.³ The AEMPS delegated full responsibility on following the requirements established in the prescribing information sheet to the treating physicians. Although this note acknowledged that regular haematological controls had been effective in preventing agranulocytosis, it released physicians from notifying results to the AEMPS, which aimed to erase the bureaucratic burden that it entailed. However, it emphasised that clozapine still had to be considered a "special medical control" drug, with restrictions on its prescription, use and pharmaceutical dispensation. In 2011, Pons et al.⁴ had already considered the need to review this monitoring protocol due to the high cost for patients and health services, noting the increased risk of agranulocytosis the first six months from the start of treatment, but pointing out a significant risk reduction after the first year.

On December 5, 2019, a new Spanish Royal Decree repealed the identification of certain drugs, including cloza-

pine, with the "special medical control" label. This decision was based on the understanding that this drug classification had been superseded by Pharmacovigilance legislation.⁵ Three months later, the Spanish Government declares a national state of alarm to face the unprecedented health crisis caused by SARS-CoV-2.

This sequence of official repeals related to historical procedures on the follow-up of patients on clozapine in Spain, added to the urgent reorganisation of health services to cope with the outbreak of SARS-CoV-2, could affect patient access to mandatory haematological controls. In fact, possible changes in haematological monitoring during the beginning of the COVID-19 pandemic could have been extended or even perpetuated in some regions.

Bearing all this in mind and the fact that almost five years have passed since the end of mandatory leukocyte count notifications to the AEMPS, it seems appropriate to evaluate the current situation of these patients in Spain. For instance, it would be advisable to know the number of adverse reactions, hospital admissions and deaths related to haematological alterations during the last five years, as well as the different protocols developed locally and/or regionally for the haematological control of these patients. This would yield relevant information to determine if the current monitoring systems offer the same level of safety as the national procedure established before the AEMPS informative note in 2017, and if health services across the country have shown enough resilience to maintain haematological monitoring, according to the prescribing information sheet, during a health crisis such as the COVID-19 pandemic.

Conflicts of interest

None.

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Clozapine-induced myocarditis in Russia: Animal studies but no clinical studies



Miocarditis inducida por clozapina en Rusia: estudios animales pero no clínicos

Dear Editor:

In 1980, Vesterby et al.¹ published the first case of clozapine-induced myocarditis during an overdose. In 1990, after another case of clozapine-induced myocarditis during an overdose, Meeker et al.² described a case of eosinophilic myocarditis characterized by an infiltration of eosinophils. Eosinophilic myocarditis is the typical presentation of clozapine-induced myocarditis and is indicative of a drug hypersensitivity reaction.³

During the 1990s, the national drug agencies started paying attention to this clozapine adverse drug reaction (ADR).⁴ Vigibase, the database of the World Health Organization, receives data from the national drug agencies. In early 2021, a Vigibase search identified more than 3000 cases of clozapine-induced myocarditis associated with a 5% mortality rate (178/3572). Almost all the cases of myocarditis in clozapine patients appeared early in treatment with 84% (1309/1560) in the first month and another 5% (82/1560) in the second month, which is compatible with clozapine uptitration that was too rapid for the metabolism of that specific patient.⁴ The occasional cases of myocarditis following clozapine overdose have the same mechanism. In the Vigibase search, there were no reports of clozapine-induced myocarditis from the Russian drug agency.

Clozapine started being used in Russia in 1973. In a cross-sectional study on a governmental database, 51% (22,676/44,836) of outpatients with schizophrenia were taking clozapine.⁵ In 2010, Slyundin et al.⁶ reported that clozapine ranked first in drug intoxication in the forensic studies that occurred in Moscow during the period from 2003 to 2009.

Thus, we decided to do a systematic search of clozapine-induced myocarditis in the Russian scientific literature. On August 14, 2021, the first author, using clozapine as the key word, found 185 articles. After a careful review of all of them only 17 of them provided any reference to clozapine-induced myocarditis. Most of them were review articles. Babkina et al.⁷ mentioned the involvement of immuno-

logical mechanisms in clozapine-induced myocarditis. We found no articles describing clinical cases after overdoses or rapid titration, but we found three articles on animal studies⁸⁻¹⁰ modeling clozapine intoxications completed by the same research group. The first study⁸ included 14 Wistar male rats divided into 3 groups (I: saline solution, II: clozapine 150 mg/kg plus saline solution and III: clozapine 150 mg/kg in a 40% ethyl alcohol solution) studied after 4 h. They described the myocardium of the rats receiving clozapine as having hypereosinophilic areas. The second and third studies, completed after 24 h, described similar myocardial changes.^{9,10}

In summary, the limited Russian literature suggests that clozapine intoxication is a relevant problem in Russia and that Russian authors are aware of the risk of clozapine-induced myocarditis, but there is no clinical data on whether or not this ADR is frequent in Russia. Russian psychiatrists may need to be aware of this ADR and report it to the Russian drug agencies.¹¹ They also need to start publishing cases of clozapine-induced myocarditis in medical journals and consider the possibility that slow personalized titration may contribute to decreasing its incidence.¹²

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Conflict of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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