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 titration 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 immunological 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 150mg/kg plus saline solution and III: clozapine 150mg/kg in a 40% ethyl alcohol solution) studied after 4h. They described the myocardium of the rats receiving clozapine as having hypereosinophilic areas. The second and third studies, completed after 24h, 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

Funding
None.

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

Acknowledgements
The authors thank Lorraine Maw, M.A., at the Mental Health Research Center at Eastern State Hospital, Lexington, KY, USA, for editorial assistance.

References
1. Vesterby A, Pedersen JH, Kaempe B, Thomsen NJ. Pludselig dad under behandling med klozapin (Leponex) [Sudden death during treatment with clozapine (Leponex)]. Ugeskr Laeger. 1980;142:170-1 [Article in Danish].
2. Meeker JE, Herrmann PW, Som CW, Reynolds PC. Clozapine tissue concentrations following an apparent suici-


Oleg O. Kirilochev a,∗, Carlos De las Cuevas b, Jose de Leon c,d,e.

a Department of Clinical Pharmacology, Astrakhan State Medical University, Astrakhan, Russian Federation

b Department of Internal Medicine, Dermatology and Psychiatry, School of Medicine, and Instituto Universitario de Neurociencia (IUNE), University of La Laguna, Canary Islands, Spain

c Mental Health Research Center, Eastern State Hospital, Lexington, KY, USA
d Psychiatry and Neurosciences Research Group (CTS-549), Institute of Neurosciences, University of Granada, Granada, Spain
e Biomedical Research Centre in Mental Health Net (CIBERSAM), Santiago Apostol Hospital, University of the Basque Country, Vitoria, Spain.

∗ Corresponding author.
E-mail address: kirilochev@gmail.com (O.O. Kirilochev).

https://doi.org/10.1016/j.rpsm.2021.09.001 1888-9891 / © 2021 SEP y SEPB. Published by Elsevier España, S.L.U. All rights reserved.