Invest Clin 65(4): 470 - 475, 2024 https://doi.org/10.54817/IC.v65n4a08

Severe necrotic colitis in an adolescent with polypharmacy and high clozapine doses according to his ancestry.

Trino Baptista[1,2,3], José de Leon[4,5], Antonio Guizar[2,6] and Laura Evia[2]

[1]Departamento de Fisiología, Facultad de Medicina, Universidad de Los Andes, Mérida, Venezuela.
[2]Clínica NeuroORIGEN, Queretaro, México.
[3]Facultad de Medicina, Universidad Anahuac Queretaro, Queretaro, México.
[4]Mental Health Research Center at Eastern State Hospital, Lexington, KY, USA.
[5]Biomedical Research Centre in Mental Health Net (CIBERSAM), Santiago Apostol Hospital, University of the Basque Country, Vitoria, Spain.
[6]Universidad Americana de Europa (UNADE), Spain.

Keywords: clozapine; constipation; colitis; ethnicity; polypharmacy.

Abstract. The antipsychotic drug Clozapine (CLZ) is approved for treatment-resistant schizophrenia and reduction in the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder. However, it is increasingly used in psychiatry and neurology worldwide in numerous off-label conditions. Clozapine is associated with diverse side effects which require careful monitoring in its use for prevention and treatment. The quality of CLZ use and pharmacovigilance varies considerably among Latin American countries. CLZ-induced gastrointestinal hypomotility (CIGH) is a relevant clinical problem, ranging from innocuous constipation to lethal necrotic colitis. Thus, optimal prevention, early detection, and treatment of CIGH deserves considerable attention. We describe here the case of a 15-year-old Mexican boy diagnosed with Oppositional Defiant- and Attention-Deficit/Hyperactivity Disorder who developed severe necrotic colitis after nine months of CLZ treatment, leading to permanent ileostomy. We ascribed this unfortunate outcome to careless polypharmacy that did not consider drug-related antimuscarinic activity, deficient clinical monitoring, and lack of attention to ethnicity concerning drug dosing. This case is of educational value for the mental health team in order to promote the proper use of CLZ, which may be life-saving in patients with severe mental disorders.

Corresponding author: Trino Baptista. Departamento de Fisiología, Facultad de Medicina, Universidad de Los Andes, Mérida, Venezuela. E-mail: trinobaptista@gmail.com

Severa colitis necrotizante en un adolescente con polifarmacia y dosis elevada de clozapina con relación a su origen étnico.

Invest Clin 2024; 65 (4): 470 – 475

Palabras clave: clozapina; colitis; constipación; etnicidad; polifarmacia.

Resumen. El antipsicótico Clozapina (CLZ) está aprobado en el tratamiento de la esquizofrenia resistente y para reducir el riesgo suicida en esta condición y en el trastorno esquizoafectivo. Sin embargo, su uso no aprobado en psiquiatría y neurología ha aumentado recientemente en todo el mundo. La CLZ se asocia a diversos efectos indeseables, los cuales ameritan monitorización cuidadosa para su prevención y tratamiento. La hipomotilidad gastrointestinal (HMGI) asociada al uso de Clozapina (CLZ), es un problema clínico relevante que se manifiesta desde un nivel de constipación inocua hasta colitis necrotizante letal. En consecuencia, la prevención óptima, detección temprana y el tratamiento de la HMGI amerita atención considerable. Presentamos el caso de un adolescente mexicano de 15 años con los diagnósticos de Trastornos Oposicionista-Desafiante y Déficit de Atención con Hiperactividad, que desarrolló colitis necrotizante severa que condujo a ileostomía permanente luego de 9 meses de tratamiento con CLZ. Atribuimos este cuadro clínico al uso inadecuado de polifarmacia en donde no se valoró adecuadamente al efecto antimuscarínico de los medicamentos, y al desconocimiento del impacto de grupo étnico en la dosificación de la CLZ. Este caso clínico es de valor educativo para el equipo de salud mental, con el fin de promover el uso adecuado de la CLZ, que puede ser una medida vital en pacientes con enfermedades mentales severas.

Received: 02-09-2024 Accepted: 07-11-2024

INTRODUCTION

The atypical antipsychotic drug Clozapine (CLZ) was synthesized in 1958. However, it was not until the years 1990-92 that the Food and Drug Administration (FDA) approved its use in the United States (US) for treatment-resistant schizophrenia (TRS) and the extension of the label for the reduction in the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder. These are the only label indications for CLZ use in the whole field of psychiatry [1].

However, CLZ use in psychiatry and neurology has significantly increased in the last twenty years for off-label indications such as dementia-related behavioral disorders, bipolar disorders, anxiety, autism spectrum, suicidality, drug use in psychosis, borderline personality, and neurological patients with movement disorders and/or psychosis [1]. While there are now available treatments more specific for these neurological disorders, they are not readily accessible in Latin American countries, and numerous neurologists still use off-label CLZ at low doses as adjunctive therapy, in general benefiting from CLZ-alleviating effects on anxiety and insomnia.

This trend is also due to the increasing understanding of CLZ pharmacokinetics, drug interactions, the role of ethnicity, genes, and adverse drug reactions (ADRs) [2,3].

CLZ has numerous ADRs, such as pneumonia, agranulocytosis, metabolic syndrome,

orthostatic hypotension, bradycardia, syncope, seizures, myocarditis, cardiomyopathy, mitral valve incompetence, hepatotoxicity, pancreatitis, sialorrhea, cancer, and gastrointestinal hypomotility (CIGH) [1]. The proper use of CLZ, thus, request for an *ad hoc* mental health team training, ideally including drug-serum monitoring, since many of those ADRs correlate with the drug blood levels. Latin American countries considerably differ in CLZ-ADR monitoring, pharmacovigilance, and related research quality. In Venezuela, there was even a recent CLZ shortage, and it is now provided without any mandatory regular blood monitoring, as suggested by experts [4,5].

The CIGH disorders range from mild constipation to severe and often lethal gut obstruction and necrosis, such as we describe in the following case.

CASE PRESENTATION

The mother's patient signed an informed consent for publishing this case. On Day 1, T.B., examined a 15-year-old Mexican non-smoking boy with severe restlessness, insomnia, and verbal and physical violence towards his mother and pets. He was of Indigenous American ethnicity with limited economic resources. At 12 years of age, he was diagnosed with severe Oppositional Defiant Disorder and Attention-Deficit/Hyperactivity Disorder and required a one-month hospitalization in a public institution. He was prescribed lithium carbonate (900 mg/day), methylphenidate (18 mg/day) and risperidone (up to 8 mg/day), this last agent being the only antipsychotic drug recommended for those disorders [6]. His irregular outcome led to poor school adaptation.

In the first interview, he exhibited an intelligence in the lower limit of normality, irritability, extreme restlessness (running in and out of the office) and a quarrelsome attitude toward his mother, who had Type II Bipolar Disorder with good insight.

Clozapine, 6.25 mg at bedtime, was started off-label (day 1). Therapeutic drug monitoring was unavailable. The slow titration was based on standard clinical tolerance and weekly serum C-reactive protein (CRP). The dose was slowly increased to 100 mg in three weeks, resulting in only a minimal improvement in sleep.

After no significant improvement, the family placed the patient in a short-term psychiatric inpatient unit for three weeks, with no participation of the previous treating psychiatrists (days 31 to days 52). He was prescribed six psychiatric drugs: CLZ 300 mg/day (100 mg three times a day), olanzapine 20 mg/day (10 mg twice a day), quetiapine 200 mg/day (100 mg twice a day), sodium valproate 1500 mg/day (500 mg three times a day), lamotrigine 50 mg/day (25 mg twice a day), and diazepam 20 mg/day (10 mg twice a day). Propranolol was added for suspected akathisia 40 mg/day (20 mg twice a day). The white blood cell (WBC) count remained normal, but no other laboratory tests were completed. Worried by the combination of three antipsychotics with antimuscarinic activity, TB constantly insisted, by phone, on monitoring for constipation but was told that disrupting behavior interfered with that. He prescribed preventive daily lactulose at bedtime.

After three weeks of minimal improvement (day 53), the patient was transferred to an outpatient facility without continuous medical or nursing monitoring. Approximately six months on CLZ (day 180), the patient started to complain of abdominal discomfort, and after two weeks, he was transferred to a hospital (day 194), where he was diagnosed with sepsis, renal failure, and severe gastrointestinal obstruction. The emergency surgery revealed massive dry fecal content and necrotic colon and led to a colon removal except for a small sigmoid portion with permanent ileostomy. After surgery, zuclopentixol, 20 mg every 3 weeks, levetiracetam 1000 mg/day (500 mg twice

a day), and oral clonazepam 2 mg/day at bedtime were prescribed. On the phone, the family informed TB they wanted to restart CLZ administration, but contact was lost afterwards.

DISCUSSION

The term CLZ-associated CIGH has been used to describe an extensive set of possible complications in the digestive system[7,8]. The World Health Organization (WHO) pharmacovigilance database receives reports on adverse drug reactions (ADRs). On July 19, 2019, CIGH was the fifth cause of fatal outcomes in CLZ patients, with 326 fatal outcomes associated with 2814 cases of constipation, toxic megacolon, and/or paralytic ileus [2,3]. CIGH develops [7,8] gradually during CLZ treatment, but up to 50% of patients may be unaware while gastrointestinal motility is objectively decreased [9,10].

Preventive laxatives and careful use of agents with antimuscarinic properties are recommended at the start of CLZ treatment [7,8].

This is a case of severe, almost lethal colonic necrosis in a young man. CLZ and its metabolite norclozapine have high antimuscarinic activity, which reduces gastrointestinal motility [11].

During the first month of treatment under T.B. control, a carefully slow CLZ titration, including CRP monitoring, was conducted since he had Indigenous American ethnicity following a recent guideline [2]. Later, the complications probably happened by a combination of at least three significant factors:

1. Lack of proper bowel monitoring. First, at home, it happened due to the constant hostility between the patient and his relatives. In the unsupervised outpatient facility, medical assessment happened only after two weeks of severe constipation and abdominal pain.

2. High doses of CLZ and polypharmacy. After one month on CLZ with poor response, another consultant psychiatrist tried to manage the challenging behavior in the hospital by increasing CLZ to 300 mg/day, and adding valproate (1.500 mg/day), quetiapine (200 mg/day) and olanzapine (20 mg/day). In retrospect, this was an unwise decision due to a lack of drug serum levels and clinical monitoring. The CLZ dose (300 mg/day) was higher than the 225 mg/day recommended for male non-smokers among patients of Indigenous American ancestry [2].

In this regard, our research group has defined six personalized schedules for inpatients: 1) ancestry from Asia or the original people from the Americas with lower metabolism (obesity or valproate) needing minimum therapeutic dosages of 75–150 mg/day, 2) ancestry from Asia or the original people from the Americas with average metabolism needing 175–300 mg/day, 3) European/Western Asian ancestry with lower metabolism (obesity or valproate) needing 100–200 mg/day, 4) European/Western Asian ancestry with average metabolism needing 250–400 mg/day, 5) in the U.S. with ancestries other than from Asia or the original people from the Americas with lower clozapine metabolism (obesity or valproate) needing 150–300 mg/day, and 6) in the U.S. with ancestries other than from Asia or the original people from the Americas with average clozapine metabolism needing 300–600 mg/day.2.

Moreover, olanzapine is also mainly metabolized by the cytochrome P450 1A2 (CYP1A2) like CLZ [2,3], and due to the patient's ancestry, he was expected also to have higher plasma olanzapine concentration. As CIGH is a dose-dependent adverse reaction, which is more appropriately defined as concentration-dependent, the patient probably dis-

played very high serum antimuscarinic activity by high plasma concentrations of CLZ and norclozapine and from the additions from the plasma concentrations of olanzapine and quetiapine [11]. Valproate can inhibit CLZ and olanzapine, particularly in early treatment [2]. CIGH complications such as ileum and necrosis result from a complex set of antimuscarinic-induced hypomotility and inflammation. The associated inflammation probably inhibited CYP1A2 and caused significant increases in CLZ and olanzapine concentrations and possibly milder quetiapine concentrations [3].

These pharmacokinetic issues request for blood level CLZ and norclozapine monitoring. Unfortunately, Chile is the only Latin American country where public mental health facilities provide such monitoring in sections of Psychiatric Institutions designed as 'CLZ clinics' [4].

3. Whereas the indication of CLZ in children and adolescents with schizophrenia is well established [12], that is not the case for CLZ off-label indications, such as the present case. Among other potential factors, CLZ might display a heterogeneous and unexpected side effect profile, which are not necessarily explained by ancestry or its pharmacological properties [13].

CONCLUSIONS

The use of CLZ in psychiatry and neurology is rapidly increasing, mostly as off-label indications. Thus, the proper monitoring and treatment of diverse, potentially lethal CLZ-related ADRs, besides neutropenia, is mandatory. This case shows how CIGH may lead to almost lethal consequences, and it could have been prevented by taking into account the complex pharmacokinetic and pharmacodynamic properties of CLZ and the other drugs used in this case, ethnicity, monitoring constipation's severity and proper use of laxatives [2,7,8,10].

Psychiatric educators play a crucial role in training all mental health members on these issues in a CLZ-treated patient. This is particularly important in Venezuela, where there are no current mandatory guidelines for CLZ use in psychiatry and neurology. Hence, we recommend improving the knowledge about CLZ pharmacokinetics and drug interactions and using it as monotherapy when possible.

ACKNOWLEDGEMENTS

The authors thank the patient's family for authorizing this publication.

Funding

None

Conflict of interest

None

Authors' ORCID number

- Trino Baptista (TB): 0000-0001-6839-4614
- Jose de Leon (JDL): 0000-0002-7756-2314
- Antonio Guizar (AG): 0009-0005-0661-0576
- Laura Evia (LE): 0000-0009-2527-698X

Author contribution

TB and JDL wrote the manuscript. TB was the former treating physician. AG and LE assisted TB in treating the patient and revised the manuscript.

REFERENCES

1. **Leung JG, de Leon J, Frye MA, Singh B, Cotes RO, McElroy SL.** The modernization of clozapine: a recapitulation of the past in the United States and the view forward. J. Clin. Psychopharmacol

2022; 42: 565–580. *doi.org/10.1097/ JCP. 0000000000001606.*

2. **de Leon J, Baptista T, Motuca M, Ruan CJ, Schoretsanitis G, De Las Cuevas C.** Promoting safer clozapine dosing in the Americas. Braz J Psychiatry 2022. 22; 363-365. *doi: 10.47626/1516-4446-2021-0041.*
3. **de Leon J.** Reflections on the complex history of the concept of clozapine-induced inflammation during titration. Psychiatr Danub 2022. 34: 411-421. *doi.org/ 10.24869/psyd.2022c.411.*
4. **Baptista T, Motuca M, Serrano A, Perez Lo Presti A, Fernandez-Arana A, Olmos I, Pabon A, Yepez JGA, Alejo Galarza GJ, Rivera Ramirez NM, Elkis H, Sanz EJ, De Las Cuevas C, de Leon J.** An expert review of clozapine in Latin American countries: Use, monitoring, and pharmacovigilance. Schizophr Res. 2024. 268. 60-65. *doi: 10. 1016/j.schres.2023.10.025.*
5. **Baptista T, Serrano A, Presti APL, Fernandez-Arana A, Elkis H, Motuca M, Olmos I, Schoretsanitis G.** Clozapine safety monitoring and related research in psychiatry and neurology in South America: A scoping review. Schizophr Res. 2024; 268: 29-33. *doi: 10.1016/j.schres.2023.07.029.*
6. **Pringsheim T, Hirsch L, Gardner D, Gorman DA**. The pharmacological management of oppositional behavior, conduct problems, and aggression in children and adolescents with attention-deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder: a systematic review and meta-analysis. Part 2: antipsychotics and traditional mood stabilizers. Can J Psychiatry 2015;60: 52-61. *doi: 10.1177/070674371506000203.*
7. **Every-Palmer S, McLean RM, Ellis PM, Harrison-Woolrych M.** Life-threatening clozapine-induced gastrointestinal hypomotility: an analysis of 102 cases. J Clin Psychiatry 2008. 69:759-768. *doi: 10.4088/jcp.v69n0509.*
8. **Every-Palmer S, Newton-Howes G, Clarke MJ.** Pharmacological treatment for antipsychotic-related constipation. Cochrane Database Syst Rev. 2017. 24:1(1):CDO11128. *doi: 10.1002/14651858.CD011128.*
9. **Baptista T, Carrizo E, Fernandez E, Connell L, Servigna M, Parra, A, Quintero J, Pabón A, Sandia I, Uzcáteguid E, Serrano A, Pirela N, Villarreal L.** Colonic transit diagnostic test shows significant gastrointestinal hypomotility in clozapine-treated patients in comparison with subjects treated with other antipsychotics. Schizophr Res. 2015. 166: 207-211. *doi: 10.1016/j. schres.2015.05.025*.
10. **Baptista T.** A fatal case of ischemic colitis during clozapine administration Rev Bras Psiquiatr. 2014;36:358. *doi. org/10.1590/1516-4446-2014-1402.*
11. **de Leon J, Odom-White A, Josiassen RC, Diaz FJ, Cooper TB, Simpson GM.** Serum antimuscarinic activity during clozapine treatment. J Clin Psychopharmacol 2003; 23:336-341. *doi:10.1097/01. jcp.0000085405.08426.73.*
12. **Correll CU, Arango C, Fagerlund B, Galderisi S, Kas MJ, Leucht S**. Identification and treatment of individuals with childhood-onset and early-onset schizophrenia. Eur Neuropsychopharmacol 2024; 82:57-71. *doi: 10.1016/j.euroneuro.2024.02.005.*
13. **Pringsheim T, Hirsch L, Gardner D, Gorman DA.** The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with attention-deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder: a systematic review and meta-analysis. Part 2: antipsychotics and traditional mood stabilizers. Can J Psychiatry 2015 60: 52-61. *doi: 10.1177/070674371506000203.*