

LETTERS TO THE EDITOR

A fatal case of ischemic colitis during clozapine administration

Rev Bras Psiquiatr. 2014;36:358
doi:10.1590/1516-4446-2014-1402

Clozapine (CLZ) is the antipsychotic drug of choice in refractory schizophrenia, but is under-prescribed because of concerns about its safety.¹ Gastrointestinal hypomotility is an often unrecognized side effect of CLZ,² and there is a scarcity of studies about this complication in South America.

A 28-year-old man was admitted with severe abdominal pain and distention, fever (39°C), and a white blood cell count of 24,500/mm³ (55% neutrophils). After 12 hours of antibiotic therapy, a laparotomy was performed. The large bowel was severely dilated, with approximately 10 pounds of compacted stools and small areas of focal necrosis in the transverse colon; no colonic resection was carried out. Abdominal pain and distention improved, but after 36 hours, the patient developed severe dyspnea and died, probably due to septic lung thromboembolism. Postmortem examination was not performed.

At age 26, the patient had been diagnosed with an unspecified bipolar disorder and prescribed quetiapine (900 mg/day), oxcarbazepine (1,200 mg/day), and clonazepam (6 mg/day). After 2 years of partial response, a diagnosis of schizoaffective disorder was suggested. CLZ (50 mg/day) was started in November 2013 and increased to 500 mg/day by the end of December, augmented with 6 mg of paliperidone, and the patient showed considerable clinical improvement. Oxcarbazepine and paliperidone were tapered off, and as of early January 2014, the patient's treatment regimen consisted of CLZ 500 mg/day and clonazepam 2 mg/day. In February 2014, the CLZ dose was reduced to 200 mg/day; the gastrointestinal complication occurred 2 weeks thereafter.

Constipation develops in 25.2-60% of patients under prolonged CLZ treatment.³⁻⁵ Life-threatening consequences include ileus, fecal impaction, and bowel obstruction, ischemia, necrosis, and perforation. The incidence of gastrointestinal hypomotility during CLZ administration is 4-8 per 1,000, but according to case report data, mortality in complicated constipation is higher with CLZ than with other antipsychotic drugs, reaching 27.5%.^{3,4} Data from the Danish registry system report ileus in 0.8% of CLZ-treated subjects, with a fatality rate of 15%.⁵

Gastrointestinal hypomotility in antipsychotic therapy is probably related to anticholinergic, antiserotonergic, and antihistamine effects,⁴ and its frequency with other

antipsychotic drugs is as follows: zotepine (39.3%), clozapine (21.3%), haloperidol (14.6%), risperidone (12%), amisulpride (11.7%), sertindole (10.8%), placebo (10.4%), olanzapine (9.8%), ziprasidone (9.6%), quetiapine (7.6%), aripiprazole (5%), risperidone (D) 4.8%.⁴

This case is relevant for the following reasons:

- 1) The clinical response to CLZ-treatment was excellent;
- 2) Previous administration of quetiapine could be heuristically suggested as a predisposing factor;
- 3) The patient had no pretreatment history of constipation and no gastrointestinal discomfort until the onset of symptoms. It is unclear whether an altered pain threshold related to both the mental disorder and the adverse effects of treatment could impair early gastrointestinal symptom recognition by patients and relatives.

This case also underlines the need for formal prevention and careful monitoring of gastrointestinal function in CLZ-treated subjects. Patients and their relatives must learn how to recognize early symptoms of bowel inflammation and/or obstruction. The preventive use of laxatives during CLZ administration has been suggested, but further studies are needed to determine their efficiency. Finally, additional research should be conducted to identify individual factors that predispose to gastrointestinal hypomotility.

Trino Baptista

Department of Physiology, Medical School, Universidad de Los Andes, Mérida, Venezuela

Submitted Mar 15 2014, accepted Mar 24 2014.

Acknowledgments

The author thanks Françoise Salager-Meyer for her editorial assistance.

Disclosure

The author reports no conflicts of interest.

References

- 1 Agid O, Foussias G, Singh S, Remington G. Where to position clozapine: re-examining the evidence. *Can J Psychiatry*. 2010; 55:677-84.
- 2 Flanagan RJ, Ball RY. Gastrointestinal hypomotility: An under-recognized life-threatening adverse effect of clozapine. *Forensic Sci Int*. 2011;206:e31-6.
- 3 Cohen D, Bogers JP, van Dijk D, Bakker B, Schulte PF. Beyond white blood cell monitoring: screening in the initial phase of clozapine therapy. *J Clin Psychiatry*. 2012;73:1307-12.
- 4 De Hert M, Hudyana H, Dockx L, Bernagie C, Sweers K, Tack J, et al. Second-generation antipsychotics and constipation: a review of the literature. *Eur Psychiatry*. 2011;26:34-44.
- 5 Nielsen J, Meyer JM. Risk factors for ileus in patients with schizophrenia. *Schizophr Bull*. 2012;38:592-8.