

Atypical Digestive Disorders under Clozapine

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Abstract

Case Report

Clozapine is a key atypical antipsychotic used in treatment-resistant schizophrenia, but its gastrointestinal adverse effects are most often limited to constipation. This report describes a rare case of clozapine-induced diarrhea in a 44-year-old male hospitalized for resistant schizophrenia. Two weeks after initiating clozapine (400 mg/day), the patient developed profuse watery diarrhea with mild abdominal pain and leukocytosis, but without major inflammatory signs. Infectious and inflammatory causes were suspected, but diarrhea resolved quickly after clozapine withdrawal, suggesting a probable drug-related effect. The case emphasizes that, although rare, diarrhea can occur under clozapine treatment, possibly through immune-mediated or mucosal toxicity mechanisms. Clinicians should maintain a high index of suspicion and collaborate with gastroenterology for diagnosis, as early recognition can avoid unnecessary investigations and prolonged treatment interruption.

Keywords: Clozapine, Atypical antipsychotics, Diarrhea, Adverse drug reaction, Drug-induced diarrhea.

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INTRODUCTION

Clozapine, marketed under the name Leponex, is a reference atypical antipsychotic for the treatment of resistant forms of schizophrenia. Despite its proven clinical efficacy, its use remains limited due to a profile of potentially serious adverse effects, notably hematological, cardiovascular, and gastrointestinal. Among the latter, the most frequently reported digestive disorders are constipation—sometimes severe—potentially evolving into paralytic ileus or intestinal necrosis. In contrast, the occurrence of diarrhea under clozapine is a rarer, often underestimated, and poorly documented adverse event.

Recent clinical cases have nonetheless highlighted severe forms of diarrhea associated with eosinophilic colitis or microscopic colitis, occurring within the first weeks of treatment. These digestive manifestations can mimic infections or chronic inflammatory bowel diseases, making their identification difficult without a high level of clinical suspicion.

CLINICAL CASE

To illustrate this link, we report the case of a 44-year-old single male admitted to the men's psychiatric emergency ward at Ar-razi Hospital in Salé, for management of behavioral disturbances characterized by hetero-aggressiveness and soliloquy, with verbalization

of persecutory delusional ideas, in the context of treatment-resistant schizophrenia.

He has been followed in the psychiatry department of Ar-razi Hospital since 2015 for resistant schizophrenia. His personal history includes several psychiatric hospitalizations, a suicide attempt in a delusional context, and a family history of psychotic disorder (a cousin with psychosis).

The patient was hospitalized following an exacerbation of psychotic symptoms. On initial psychiatric examination, he presented with a persecutory delusional syndrome and predominantly auditory hallucinations. Physical examination was unremarkable. A complete biological workup and ECG were requested, both without abnormalities.

Due to the inefficacy of conventional antipsychotics during previous treatment courses, clozapine was prescribed after a normal pre-Leponex assessment.

After two weeks of treatment with clozapine titrated to 400 mg/day, the patient developed profuse, watery, non-bloody diarrhea, associated with diffuse abdominal pain. Clinical examination revealed a subfebrile state (37.8°C) without signs of dehydration or abdominal guarding. Blood tests showed elevated white

blood cells (WBC: $12.85 \times 10^9/L$) with marked neutrophilia (PNN: $8.91 \times 10^9/L$), without major inflammatory syndrome.

Given the persistence of digestive symptoms, a gastroenterology consultation was requested. The gastroenterologist suspected drug-induced colonic involvement and recommended colonoscopy with biopsies to rule out infectious, inflammatory, or eosinophilic colitis induced by clozapine. Meanwhile, a temporary discontinuation of the antipsychotic was advised.

The clinical course was marked by the progressive disappearance of diarrhea in the days following clozapine withdrawal, supporting the hypothesis of a drug-related digestive adverse effect.

DISCUSSION

Clozapine is widely recognized for its efficacy in the treatment of resistant schizophrenia. However, its safety profile requires strict monitoring due to numerous adverse effects, among which gastrointestinal events are often underestimated. While severe constipation and paralytic ileus are well documented, cases of diarrhea induced by clozapine are rare and poorly described in the literature.

In our case, the patient developed acute, non-bloody diarrhea two weeks after starting clozapine, with leukocytosis but no major biological inflammatory syndrome, suggesting a probable drug-induced effect. This timeline aligns with rare published cases. Aarons *et al.* reported eosinophilic colitis induced by clozapine, which resolved after discontinuation.

Possible mechanisms include immune-allergic pathways or type IV hypersensitivity, direct mucosal toxicity, or gut microbiota imbalance. Clozapine's anticholinergic effect is better known for causing constipation, but other gastrointestinal alterations remain possible.

The reversibility of symptoms after drug discontinuation supports a causal link, consistent with the Naranjo criteria (score ≥ 5). While severe constipation and ileus are well reported, diarrhea remains atypical and often overlooked in trials.

Colonoscopy, though delayed in this case, is crucial to exclude infectious causes (e.g., *Clostridium difficile*, CMV), chronic inflammatory bowel disease, or

microscopic colitis. Some biopsies in patients on clozapine have shown nonspecific inflammation or intraepithelial eosinophils.

This observation underscores the need to consider atypical digestive side effects in patients on clozapine, especially with unexplained acute diarrhea. Multidisciplinary collaboration between psychiatry and gastroenterology is essential for accurate diagnosis and to avoid prolonged discontinuation of a crucial psychiatric treatment.

CONCLUSION

Clozapine, though essential for resistant schizophrenia, can cause atypical gastrointestinal side effects such as diarrhea, still underreported. This case highlights the importance of considering drug-induced diarrhea in such contexts. Resolution after drug withdrawal supports the adverse drug reaction hypothesis. Psychiatrist–gastroenterologist collaboration is key for prompt diagnosis, appropriate management, and avoiding prolonged treatment interruption.

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