A Case of Clozapine-induced Fatal Bowel Infarction after More Than a 13-year Treatment

Clozapine is a second-generation (atypical) antipsychotic agent, commonly prescribed for patients with treatment-refractory schizophrenia [1]. Clozapine has a wide range of side effects, such as agranulocytosis, seizures, sialorrhea, constipation, weight gain, and hypotension. Among them, constipation is a common side effect of clozapine, and up to 60% of patients treated with clozapine experience constipation [1, 2]. Constipation can progress to distention and necrosis of the bowel following with peritonitis and sepsis, which revealed fatal outcome of clozapine-induced constipation [1, 3, 4].

Many reports exist in describing life-threatening gastrointestinal hypomotility caused by clozapine. Case reports about clozapine-induced bowel infarction mostly focus on treatment of clozapine less than five years [3, 5-7]. Here, we now present a 58-year-old female patient who experienced sudden death due to bowel infarction and sepsis after a 13 years of clozapine treatment.

The Case Report

A 58-year-old female patient was diagnosed as schizoaffective disorder at the age of 17 years, and she presented herself with self-talking and disturbing behavior, somatic delusion, and ideas of references, more talkative, labile mood, and decreased sleep time. The patient had medical history of diabetes mellitus and hyperlipidemia. Her previous medical treatment history before admission to our hospital was unknown. At the age of 45 years, she was admitted to our hospital, and she had received clozapine 200–300 mg/day for 13 years. Before the age of 56 years, she was prescribed risperidone or olanzapine for only a few months in combination with clozapine due to relapsed psychotic symptoms.

On top of having her daily clozapine 275 mg, the patient received chlorpromazine 200 mg, sodium valproate 500-700 mg and biperiden 2 mg due to vivid persecutory delusion and somatic complaints. During the 13-year treatment course, medications for managing of constipation had included sennoside, and/or magnesium accompanied with clozapine usage. She had no ileus history throughout the previous 13 years.

At the age of 58 years, the patient complained of poor appetite and stomachache in the morning. She also complained of fatigue and difficulty of passing stool. She had worsened hypotension, tachycardia, and hypoxia. She was then transferred to a general hospital at night because of unstable vital signs. Later, she was admitted to the intensive care unit one day later due to diagnosis of septic shock. Soon after admission to the intensive care unit, she died of septic shock. The results of the pathological postmortem examination confirmed that she died of bowel infarction.

Comment

Many psychotropic drugs and nonpsychiatric medications are strongly anticholinergic and cause constipation. In this patient, the most likely cause of bowel infarction was clozapine [8].

The mechanism of clozapine-induced constipation is not completely understood but is thought to be combination of anticholinergic activity, sedation due to histamine H1 receptor antagonism resulting in inactivity, and antagonism at 5-HT3 receptors [9]. The clozapine-induced constipation may cause intestinal occlusion, paralytic ileus, and death [1, 10]. Patients with schizophrenia might be at higher risk of ileus due to less exercise, poor diet, as well as common use of antipsychotics and anticholinergics. The insensitivity of pain, impaired expression of pain due to negative symptoms, and formal thought disorder can lead to worsened ileus and fatal consequences. Her psychiatric symptoms were controlled with clozapine. Difficulty in passing stool was her persistent side effect. Many of the adverse effects of clozapine are dose-dependent and associated with speed of titration [11]. Flanagan and Ball reviewed mortality of gastrointestinal hypomotility cases for postmortem clozapine concentration and suggested that clozapine toxicity is the cause of death and that constipation tends to be more common and severe at the beginning of therapy [12].

Palmer et al. [5] reported cases of serious clozapine-induced gastrointestinal hypomotility (CIGH) and found that 28 patients have fatal outcomes and 14 of them die eventually. The investigators found that 20% of patients develop serious CIGH within the first month of treatment, 36.3% of them within the first four months, and over 50% of them occur within the first year of treatment. A cross-sectional study revealed that clozapine caused marked gastrointestinal hypomotility, and colonic motility tends to happen regardless of clozapine dose and duration of treatment [13]. A previous report has described fatal bowel infarction after a one-week clozapine treatment [7]. But our patient in this case report provided an example of clozapine-induced fatal bowel infarction after the 13-year clozapine treatment.

The patient in our case report brings out an issue that the treatment of clozapine more than a decade can also cause fatal bowel infarction. The current American Psychiatric Association (APA) practice guideline [14] has noted that gastrointestinal hypomotility side effect of clozapine can be severe. It suggests stool softener, osmotic laxative, or stimulant laxative for treatment. The patient should obtain urgent medical care if experiencing constipation that is severe or does not resolve. Besides treatment of constipation, enhanced monitoring of CIGH is clearly needed to reduce
the likelihood of constipation-related fatality [9]. The APA guideline has suggested daily food and fluid charts and use of stool charts during the titration phase and the first period of clozapine treatment.

Based on this case report, we suggest that the preventive evaluation for constipation can be managed not only during early treatment of clozapine but also regularly with the entire clozapine treatment course. (This case report was approved by the institution review board of Yuli Hospital, Ministry of Health and Welfare, for publication [protocol number = YLH-IRB-10902, date of approval = May 28, 2020]. No written informed consent from the patient was obtained for the purpose of publication because this report was written after the patient passed away).

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Conflicts of Interest
The authors disclose no conflicts of interest related to this study.

References

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