Fatalities Associated With Clozapine-Related Constipation and Bowel Obstruction: A Literature Review and Two Case Reports

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Background: Constipation is an exceedingly common side effect of treatment with clozapine. In rare cases, this side effect has resulted in fatal complications. Objective: The authors review the literature on fatal complications of clozapine-related constipation and bowel obstruction. Method: The authors provide two new case reports of patients who died of similar causes. Results: There were seven reports of deaths from clozapine-related bowel obstruction in the literature, with the most common mechanisms of death being severe impaction leading either to feculent vomiting or bowel necrosis. Discussion: The discussion outlines potential mechanisms and management of clozapine-related constipation.

Clozapine is regarded by many psychiatrists as “the most efficacious, but most dangerous,” antipsychotic. In terms of its risks, agranulocytosis and myocarditis are recognized as potentially life-threatening side-effects. A less frequent source of morbidity and mortality is related to the tendency for clozapine to impair gastrointestinal motility. Reports of fatalities associated with this phenomenon have been accumulating. In this article, we review the literature on severe constipation and intestinal obstruction leading to fatality in patients taking clozapine. We also offer two new case reports of patients who died of similar causes.

Although the Clozaril monograph reports an incidence of constipation of 14%, the rate may be higher in patients with concomitant inactivity and with the use of other constipating medications. The monograph states that “probably on account of its anticholinergic properties, clozapine has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction, and paralytic ileus. On rare occasions, these cases have been fatal.” Higher estimates of constipation have been reported in the psychiatric literature. Liebermann et al. suggested an occurrence of constipation of 33.3% in acute treatment with clozapine and 22.8% in maintenance treatment. Hayes and Gibler reported a 60% prevalence of constipation with clozapine use in their patient population.

To date, there have been seven reported deaths related to gastrointestinal complications from clozapine use; the most common cause of death was severe impaction leading either to feculent vomiting or bowel necrosis (Table 1). Hayes and Gibler reported the death of a 29-year-old man from aspiration of vomitus secondary to constipation and bowel obstruction. Theret et al. reported the fatality of a 31-year-old woman who had been administered clozapine (300 mg daily for 5 weeks). She died of shock, with pulmonary edema and had severe fecal impaction, with a greatly distended colon. Drew and Herdson reported the

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death of a 49-year-old man from pulmonary edema secondary to inhalation of feculent vomitus. Shammi and Remington described a fatal case of necrotizing colitis in a 36-year-old man on clozapine. Levin et al. reported the case of a 43-year-old man who died of refractory shock and progressive multi-system organ failure after a total colectomy and ileostomy for large bowel obstruction with necrosis. More recently, Townsend and Curtis reported

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Case Reports

the death of an apparently healthy 20-year-old man treated with clozapine who presented with abdominal pain and died of bowel ischemia within 2 days of the first complaint of constipation, without any previously reported abdominal symptoms. The rapid progression of symptoms in this case is especially alarming. Finally, in March 2007, Roussneau and Charbonneau\textsuperscript{10} reported the case of a 61-year-old woman on clozapine who presented with stomach cramps and died 2 weeks later of septic shock after colonic perforation.

Case Report \#1

“Mr. M” was a 61-year-old man with chronic, disorganized schizophrenia and intellectual deficits. He had been on clozapine for 7 years. His medications were clozapine (300 mg twice daily), lamotrigine (100 mg twice daily), flurazepam (15 mg at bedtime), procyclidine (5 mg twice daily), and oxybutynin (5 mg twice daily). The latter two were prescribed to treat prominent sialorrhea, but their anticholinergic effects probably contributed to the severity of Mr. M’s constipation. He had suffered from constipation intermittently over the previous 12 years and had been on a high-fiber diet, psyllium, docusate sodium, and glycerin suppositories before his hospitalization and death.

When he had not had a bowel movement for 3 days, developed a distended abdomen, and complained of abdominal pain, bisacodyl suppositories and an enema were prescribed. He received two suppositories and prune juice and had a bowel movement, but his abdomen appeared increasingly distended, and so he was brought to the hospital. He was found to have a hard, distended abdomen, with no bowel sounds. An abdominal CT scan revealed severe fecal impaction, with edematous rectal mucosa and acute-on-chronic constipation. His caregiver reported that he vomited while a nasogastric tube was being inserted. The suction liquid from the nasogastric tube was reported to be feculent. A few days later, pneumonia was diagnosed, and he was started on intravenous antibiotics. After several days of treatment with multiple enemas and manual disimpaction, he had a bowel movement, and his abdomen was soft. However, he continued to spike fevers and was found to be bacteremic 4 days after admission. White blood cell and neutrophil counts were $34.6 \times 10^9/L$ and $32 \times 10^9/L$ respectively (normal range, white cells: 4.0–11.0; neutrophils: 1.8–7.5). Ten days after admission, he was found unresponsive and pronounced dead, with the primary causes being pneumonia and overwhelming sepsis, apparently from aspiration of feculent vomitus.

Case Report \#2

“Mr. Z” was a 63-year-old man with schizophrenia who had been hospitalized on a psychiatric inpatient unit before his death. He was refractory to a combination of conventional and atypical antipsychotics. He refused electroconvulsive therapy and was started on clozapine (50 mg daily), which was increased over 7 days (to 400 mg daily). On Day 9, the dosage was reduced (to 300 mg daily) because of sialorrhea and myoclonic jerks. On Day 14, the clozapine was increased again (to 400 mg daily). He was also taking glyburide (2.5 mg every morning and 5 mg at bedtime) and levothyroxine (0.075 mg daily).

On Day 16, he reported not having had a bowel movement for several days, and docusate sodium was prescribed. The next morning, he was found collapsed in the bathroom with a clearly distended abdomen. He was transferred to the intensive care unit, intubated, and volume resuscitated. CT of the abdomen demonstrated near-complete collapse of the inferior vena cava from pressure in the abdominal cavity and distension of both the small and large bowel, with his rectum and sigmoid severely impacted with stool. He deteriorated rapidly, having developed very high intra-abdominal pressure felt to be due to a type of “abdominal compartment syndrome,” possibly secondary to the severely dilated loops of bowel. He was then taken emergently to the OR for decompression of a large-bowel obstruction. Peri-operatively, he developed multi-system organ failure from prolonged hypotension, resulting in his death.

Discussion

Although the mechanism of clozapine’s effect on intestinal motility is unknown, it is generally believed to be decreased peristalsis resulting from anticholinergic side effects. Less recognized is the possible contribution that serotonin antagonism could play in peristaltic slowing among patients taking clozapine. Clozapine is known to antagonize serotonin receptors centrally, one of which is 5-HT\textsubscript{3}.\textsuperscript{11} 5HT\textsubscript{3} antagonism in the gastrointestinal tract is known to cause constipation. For example, constipation is
a common side effect of ondansetron, a 5-HT₃ antagonist used for chemotherapy-induced nausea.¹² Housing approximately 95% of the body’s serotonin receptors,¹³ the gastrointestinal tract may be quite susceptible to the effects of serotonin antagonism. It is conceivable that clozapine may affect 5HT₄ receptors and 5-HT₃ receptors peripherally, resulting in impaired motility and contributing to the severity of constipation and bowel obstruction seen in some patients. Serotonin agonists such as tegaserod (which was used to treat constipation in irritable bowel syndrome, but is currently off the market) may erode (which was used to treat constipation in irritable bowel syndrome, but is currently off the market) may be helpful. Psyllium and other bulking agents may not be the best choice in slow-transit constipation,¹⁰ which we believe is the type presented by clozapine patients. Last, we advise patients that if they experience severe constipation with abdominal pain or vomiting, they should seek care immediately.

Constipation is an exceedingly common side effect of clozapine, and, in rare cases, can lead to fatal complications. Although the mechanism for decreased peristalsis in patients on clozapine is generally believed to be an anticholinergic effect, consideration should also be given to the possibility that clozapine could antagonize serotoninergic receptors in the gut and that serotonin agonists may play a role in treatment. It is recommended that patients on clozapine be monitored closely for gastrointestinal side effects, and efforts should be made to minimize the concomitant use of agents with the potential to impair peristalsis. Further study is warranted to determine patient risk factors and the frequency of severe consequences in clozapine-related constipation and bowel obstruction.

References

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