Clozapine-induced gastrointestinal hypomotility: More than just constipation

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KEY WORDS

clozapine, constipation, side effect

CASE

A 60 y.o. male with longstanding paranoid schizophrenia was admitted from a local group home with abdominal pain and distention of several days in duration and vomiting for the previous 24 hours. He had been seen in the family practice clinic at this academic medical center on the day prior to admission for similar complaints and magnesium citrate was recommended. An abdominal plain film from that visit was consistent with ileus and moderate stool load. The patient was admitted to the emergency treatment center later that day with new-onset vomiting. He was sent home after three soap suds enemas with only minimal results.

The patient was initially admitted to the general surgery service after a CT scan showed profound pneumotosis and portal venous gas with moderate grade partial small bowel obstruction. The psychiatry consult service was contacted for recommendations on management of psychotropic medications given the patient's NPO status. The patient had been on clozapine 100 mg in the morning and 300 mg at bedtime and chlorpromazine 200 mg daily prior to admission with a bowel regimen of polyethylene glycol 3350 17 g daily and psyllium 3.4 g daily. The psychiatry consult team recommended to hold clozapine since it likely contributed to the partial small bowel obstruction and to consider holding chlorpromazine due to its anticholinergic effects. Despite these recommendations, the patient was given one dose of clozapine 300 mg PO at bedtime and five doses of chlorpromazine 25 mg IV four times daily. The patient developed symptoms consistent with delirium the next day and both clozapine and chlorpromazine were discontinued. Psychotic symptoms were managed with IV haloperidol for the next 5 days until the ileus resolved. During this time, the patient was transferred to the combined Internal Medicine-Psychiatry unit for further management.

Upon resolution of the ileus, the patient's thought process was disorganized and most of his speech could be described as word salad. The decision was made to retitrate clozapine as it was the only agent that had been modestly effective for this patient's psychosis. Outside records documented a history of treatment- refractory psychotic symptoms despite antipsychotic polypharmacy and adequate clozapine blood levels (700-800 ng/mL). Clozapine was titrated very slowly with an initial bowel regimen of polyethylene glycol 3350 17 g daily and close monitoring of bowel movements. The patient's psychiatric condition slowly stabilized, though he continued to have auditory and visual hallucinations at the time of discharge, nearly four months after his initial presentation. The patient was discharged to a state mental health institute on clozapine 150 mg in the morning and 300 mg at night with docusate 200 mg twice daily, calcium polycarbophil 625 mg daily, and polyethylene glycol 3350 17 g twice daily.

DISCUSSION

Constipation occurs commonly with clozapine and may affect as many as 50% of those treated.[1] Proposed mechanisms for gastrointestinal slowing with clozapine include its significant anticholinergic effects, as well as 5-HT_3 antagonism.[2,3] Acetylcholine is the primary excitatory neurotransmitter in the enteric nervous system and plays a role in regulating gastrointestinal motility. The anticholinergic effects of medications such as clozapine can lead to inhibition of gastrointestinal smooth muscle contraction and delay intestinal transit.[2] However, the anticholinergic effects of clozapine are insufficient to explain the risk of severe gastrointestinal hypomotility since this risk is higher with clozapine than with other medications that have similar anticholinergic properties. Antagonism at the 5-HT_3 receptor is also thought to contribute to gastrointestinal hypomotility with clozapine. Other medications with potent 5-HT_3 antagonism are known to slow bowel transit. This includes the 5-HT_3 inhibitor alosetron used for

management of severe diarrhea-predominant irritable bowel syndrome in women, which carries a black-box warning for serious complications of constipation.[2]

While constipation may be viewed as a minor drug side effect, clozapine has been associated with significant gastrointestinal hypomotility in numerous case reports, including some with fatal outcomes.[2] Severe fecal impaction leading to feculent vomiting or bowel necrosis is a commonly reported cause of death in these cases.[3] Almost 40% of reported cases of serious clozapine-induced gastrointestinal hypomotility occurred within the first 4 months of initiating treatment.[2] However, several cases of death related to clozapine-induced gastrointestinal hypomotility occurred years after initiation of clozapine, indicating that clinicians should remain vigilant for symptoms of constipation throughout the duration of clozapine therapy. Data reported to the U.S. Food and Drug Administration (FDA) indicate that the mortality rate from clozapine-induced gastrointestinal hypomotility is about three times higher than the mortality rate of agranulocytosis.[4]

Palmer and colleagues reviewed 102 cases of clozapine-induced gastrointestinal hypomotility and attempted to identify risk factors for serious gastrointestinal adverse drug reactions leading to hospitalization or death.[2] Proposed risk factors include higher clozapine doses, concomitant use of other anticholinergic medications (e.g. benztropine, chlorpromazine), and concomitant medical illness. Abdominal pain/distension and vomiting were reported even more commonly than constipation in case reports of severe gastrointestinal complications from clozapine.[2] Clozapine-treated patients should be educated to seek immediate medical attention if these symptoms occur.

As patients treated with clozapine are most often treatment refractory, clinicians may be more inclined to view constipation as an acceptable consequence of treatment.[5] The issue of constipation may seem particularly minor against the background of other potential severe side effects of clozapine, such as agranulocytosis, seizures, and myocarditis. Many clinicians do not recognize the potential danger of clozapine-induced constipation and gastrointestinal hypomotility. Underrecognition is highlighted in this case by the fact that the patient presented for medical treatment twice on the day prior to his hospital admission and was not referred for further workup. Psychiatric healthcare practitioners must recognize and monitor for constipation in patients treated with clozapine and educate other providers about the potential serious consequences of constipation in these patients.

While there are no established guidelines for prevention and management of clozapine-induced gastrointestinal hypomotility, practical recommendations guided by case reviews have been put forth. Recommended strategies for prevention include educating patients about the risk of constipation and avoiding concomitant medications that may slow GI transit time (e.g., anticholinergic agents, opiates). There is no clear consensus as to the best laxative to use when clozapine-induced constipation is identified. Some authors suggest senna and docusate,[2] while others recommend lactulose or polyethylene glycol 3350.[3] No matter which agent or combination of agents is chosen, close monitoring to ensure success of the selected bowel regimen is necessary. Another strategy for management of constipation may be to minimize the clozapine dose if possible, particularly if serum levels are 500-700 ng/mL.[5] For patients who present with symptoms indicating a potentially life-threatening gastrointestinal complication (e.g. abdominal pain with nausea in the context of constipation), urgent referral for treatment is warranted and clozapine should be temporarily discontinued.[2]

Constipation is a common side effect of clozapine, though in some cases severe constipation can progress to small bowel obstruction and even death. Patients receiving clozapine therapy should be regularly monitored for constipation and should be treated aggressively when constipation occurs.

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