A Case Report of Clozapine-Induced Severe Gastrointestinal Hypomotility

To the Editor: Clozapine is an antipsychotic that exhibits a unique pharmacodynamic profile. It has a strong affinity for dopaminergic D_4 receptors, weak activity at D_2 receptors, and potent serotonergic, noradrenergic, histaminic, and muscarinic receptor antagonism.[1] Some of the side effects of clozapine, such as agranulocytosis,[2] are well recognized as life-threatening complications. We present a case in which constipation, a common and often considered nuisance side effect of clozapine, progressed to life-threatening proportions.

Case report. Mr A is a 50-year-old man with a long history of smoking, schizophrenia, and hypertension who was admitted to the hospital after presenting to the emergency department from a free-standing psychiatric hospital with concerns of abdominal distention, constipation, and altered mental status. The psychiatry service was consulted to manage the patient's psychiatric medications and delirium.

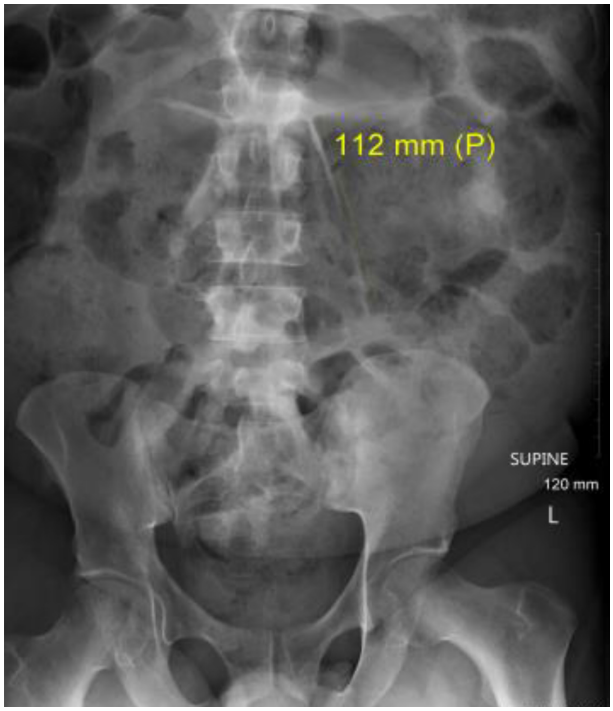
During his 4-day hospitalization at the psychiatric facility for psychotic decompensation, Mr A had continued to receive his scheduled home medications, which included clozapine 200 mg once in the afternoon and 400 mg at bedtime and once-daily dosages of solifenacin 5 mg, lisinopril 10 mg, omeprazole 20 mg, ferrous sulfate 325 mg, and valproate extended release 2,000 mg. In addition, he had received a total of 120 mg of olanzapine for psychosis and agitation over the 4 days prior to transfer.

In the emergency department, Mr A's vital signs were stable. Physical examination was notable for significant abdominal distension. Mental status evaluation displayed disorientation, behavioral disinhibition, and unintelligible speech. A kidney-ureter-bladder x-ray (KUB) demonstrated a large stool burden and a prominent 11-cm dilation of the transverse colon (Figure 1). Laboratory workup was fairly unremarkable outside of a mild hypernatremia (147 mmol/L), slightly decreased glomerular filtration rate (54 mL/min/1.73 m^2), and an elevated non-trough valproate level (18 mg/L). The hypernatremia and acute kidney injury resolved quickly with intravenous fluids, and the free-valproate level normalized (12 mg/L) with a decrease in valproate dose to 500 mg twice daily.

Plans to manage his partial ileus included decreasing the clozapine dose, minimizing exposure to other anticholinergic medications, discontinuing ferrous sulfate, obtaining a consultation with a gastroenterologist, and initiating an aggressive bowel care management regimen (polyethylene glycol, docusate sodium 50 mg and sennosides 8.6 mg [Senna-S], and bisacodyl). Despite these measures, Mr A continued to exhibit significant constipation and delirium. Asenapine was subsequently initiated because it has both minimal anticholinergic properties and antipsychotic efficacy. It was cross-titrated with a gradually decreasing clozapine dose. The patient's constipation eventually improved, and he was able to tolerate a general diet. With a reduction in his clozapine dosage and an asenapine dose of 15 mg twice daily, his delirium resolved and he exhibited minimal active symptoms of psychosis. He was subsequently transferred back to the psychiatric hospital on clozapine 50 mg daily (with a plan to gradually taper off completely), asenapine 15 mg twice daily, valproate 500 mg twice daily, polyethylene glycol 68 g three times daily, Senna-S 3 tablets twice daily, and bisacodyl 10 mg daily.

Constipation has been reported to be one of the most common side effects associated with clozapine, affecting 1 of every 3 patients taking the drug.[3] Clozapine's induction of gastrointestinal hypomotility, most likely a consequence of the medication's antagonist action on muscarinic and serotonergic receptors, has the potential to lead to significant medical complications. This patient's presentation may have been further exacerbated by elevated clozapine levels due to pharmacokinetic mechanisms secondary to the recent cessation of smoking and the coadministration of omeprazole. In addition, the chronic and acute administration of other medications commonly associated with constipation (ferrous sulfate, olanzapine, solifenacin) may have further increased the risk of gastrointestinal dysfunction in this patient.

Figure 1. Kidney-Ureter-Bowel X-Ray Highlighting Distended Transverse Colon Diameter



The recognition of clozapine's inherent properties to disrupt gastrointestinal motility coupled with the potential for drug interactions (pharmacokinetic and pharmacodynamic) requires clinical vigilance on the part of the consultation-liaison psychiatrist. This recognition may prevent the deleterious and commonly unappreciated adverse effect of clozapine-induced gastrointestinal dysmotilty and its associated morbidity and mortality.

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