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# Clozapine, fluoxetine, and benztropine-associated ileus: Case report

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## ABSTRACT

Gastrointestinal complications of anticholinergic medications are prevalent, potentially life-threatening, and could be more actively prevented. We present a case report of an ileus that required surgical intervention and developed in the context of clozapine, benztropine, and fluoxetine use. The case exemplifies the potential anticholinergic toxicities of clozapine and benztropine as well as possible pharmacokinetic interactions between fluoxetine, clozapine, and benztropine. We discuss ways to minimize the likelihood of anticholinergic complications with these medications.

## CASE REPORT

A 50-year-old schizophrenic man presented with diffuse abdominal pain radiating to his flanks, cramping, green emesis, and no bowel movements for three days. Outpatient medications included clozapine 200 mg q AM and 400 mg qhs, benztropine 2 mg bid, and fluoxetine 20 mg q AM. He had a history of smoking one and one-half packs of cigarettes daily for 35 years. His abdomen was tender in the right lower quadrant and was distended and tympanic; bowel sounds were hypoactive. Dilated large bowel loops were visible in abdominal plain film and dilated proximal bowel was noted on CT scan. His treatment team was unable to resolve the small bowel obstruction through bowel rest and decompression. Therefore, exploratory laparotomy was performed. Surgery revealed a massively dilated jejunum with a clear transition point to decompressed distal bowel; no mechanical source of obstruction was identified.

He remained off his medications until post-op day 2, at which time he was re-started on fluoxetine 20 mg q AM and benztropine 2 mg bid. Clozapine 200 mg q AM and 400 mg qhs was re-started on post-op day 6. On post-op day 12, the Psychiatric Psychosomatic Medicine (PSM) Service evaluated the patient. The PSM Service noted the possibilities of a pharmacokinetic clozapine-fluoxetine drug interaction (inhibition of clozapine metabolism by

concurrent fluoxetine) and/or a pharmacodynamic clozapine-benztropine drug interaction (both agents have significant anticholinergic effects) causing or exacerbating the ileus through an anticholinergic mechanism. Recommendations to discontinue clozapine and benztropine then to start quetiapine 200 mg q AM and 400 mg qhs were implemented. Serum clozapine levels were not available. On post-op day 15, the patient reported relief of abdominal pain and had reduced abdominal distension. He was transferred to a psychiatric facility.

## DISCUSSION

Clozapine is an atypical antipsychotic that is an antagonist at numerous receptors: it is anti-serotonergic (5-HT<sub>2</sub>, 5-HT<sub>3</sub>), anti-alpha 1 adrenergic, antihistaminic (H<sub>1</sub>), and antimuscarinic. Its potent preferential blockade of dopamine D<sub>1</sub> and D<sub>4</sub> receptors are likely significant contributors to its antipsychotic effects (1). Clozapine produces a dose-dependent increase in anticholinergic activity and is primarily hepatically metabolized by P450 1A2 with additional secondary pathways (2). If used concurrently with clozapine, fluoxetine and fluvoxamine increase the risk of developing anticholinergic effects; these medications increase clozapine levels by 50% and three- to four-fold, respectively, due to inhibition of P450 1A2, 2C9/19, 2D6, and 3A4. Caffeine consumption may increase clozapine levels (by inhibiting P450 1A2), while smoking may decrease clozapine levels (by induction of P450 1A2) (3).

Gastrointestinal effects associated with clozapine include constipation, gastric outlet obstruction, prolonged postoperative ileus, and peritonitis with bowel perforation; fatalities have been reported (1, 4-10). The prevalence of developing intestinal side effects, ranging from constipation to bowel perforation, while taking clozapine has been reported as high as 33% (5-7).

The significant anticholinergic effects of benztropine, commonly prescribed for EPS, may be especially important when added to the anticholinergic effects of clozapine. There have been reported cases of intestinal dysmotility attributed to benztropine alone as the primary anticholinergic agent (11-13). Minzenberg et al. have produced a useful table of the relative anticholinergic potencies of various psychotropic agents (14). Their table includes both a “pharmacological index” (based on published in vitro studies of muscarinic antagonism) and a “clinical index” (based on clinician ratings of anticholinergic side effects). For both indices, benztropine is given a value of 1. Clozapine is among the most anticholinergic of the atypical antipsychotics; it has a “pharmacological

index” of 8 mg clozapine as the anticholinergic equivalent of 1 mg benztropine and a “clinical index” of 85 mg clozapine as the anticholinergic equivalent of 1 mg benztropine (14). Using the table of Minzenberg et al., we find that our patient initially had a combined anticholinergic effect totaling 79 benztropine equivalents by the “pharmacological index” and 11 by the “clinical index”; after clozapine and benztropine were discontinued and quetiapine was started, the patient received only 0.8 benztropine equivalents by the “pharmacological index” and 2.6 by the “clinical index” (14).

Long-term, treatment-refractory psychiatric inpatients have additional risk factors for developing an ileus. One factor is the compounding effect of a long history of high-dose antipsychotic medication that leads to reduced bowel motility. A second factor is the reduction of daily physical activity levels among patients living in long-term inpatient psychiatric facilities. At the Atascadero State Hospital in California, for instance, where 60% of patients on clozapine were found to have constipation, the staff implemented the Clozapine Constipation Protocol in 1995 (8). The protocol involves abdominal imaging and physical assessment prior to starting the medication, slow dosage increases (maximum of 100mg/day each week), daily documentation of bowel and dietary habits, and input from a dietitian who encourages a high-fiber diet, adequate fluid intake, and regular physical exercise. Most of the patients on clozapine receive a stool softener or a bulk-forming laxative, and some are prescribed bethanechol. Taking these measures resulted in a significant decline in both the prevalence of constipation and the number of patients transferred to the medical unit for the treatment of clozapine-induced gastrointestinal dysmotility (8).

We offer the following five suggestions to avoid adverse bowel events in patients on clozapine and/or benztropine: 1) increased surveillance for bowel dysfunction in patient receiving the medications 2) proactive management of early bowel dysmotility to prevent serious outcomes 3) avoidance of both pharmacodynamic and pharmacokinetic drug-drug interactions that increase anticholinergic effects of clozapine (specific avoidance of fluoxetine, fluvoxamine, or benztropine with clozapine) 4) use of alternative atypical antipsychotic medications with lower degrees of anticholinergic activity in patients at higher risk of bowel dysmotility and 5) avoidance of benztropine in patients who have had clinical signs of decreased intestinal motility. When clozapine is necessary despite a history of clozapine-induced ileus (e.g. in patients who are resistant to other medications), clinicians may try the following after the patient has fully recovered gastrointestinal motility:

1) restart clozapine at a lower dose while continuing to avoid fluoxetine, fluvoxamine, and benztropine; or 2) cautiously increase the clozapine dose while continuing to avoid these other agents. When possible, monitoring of serum clozapine levels may help.

## SOURCE INFORMATION

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