Clozapine-induced Gastrointestinal Hypomotility (CIGH): A Case Series and Pathomechanistic Review

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Background

- Clozapine is associated with well-known side effects, including agranulocytosis, seizures, and orthostasis, yet gastrointestinal effects such as constipation or intestinal obstruction are less often appreciated
- Consultation-liaison (CL) psychiatrists may under-appreciate the ubiquity of clozapine-induced gastrointestinal hypomotility (CIGH)
- Over 80% of patients on clozapine experience clinically-significant gastrointestinal slowing[1]
- Studies suggest over a quarter of patients on clozapine face GI-related mortality[2]

Pathomechanistic Review

- Delayed bowel transit is most associated with muscarinic (M_3) receptor antagonism

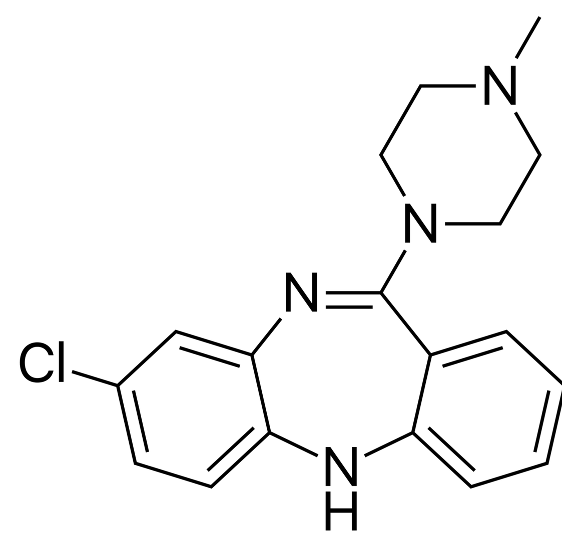

Figure 1. Structural formula for clozapine

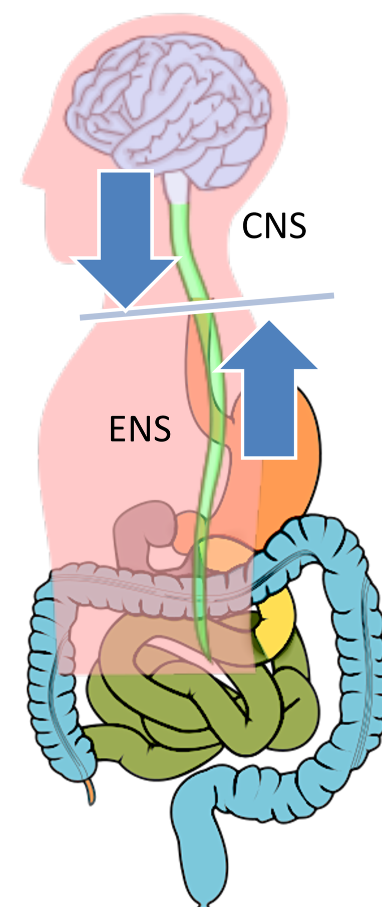

Figure 2. Relationship between central nervous system (CNS) and enteric nervous system (ENS)

- However, clozapine's unique antagonism on 5-HT receptors may contribute to hypomotility and reduced bowel nociception, in contrast with other second-generation antipsychotics
- Studies show that average colonic transit time in patients on clozapine is above 100 hours, whereas in non-clozapine controls transit time is under 24 hours[3]

Case Series

Case 1: 56-year-old male with schizoaffective disorder on clozapine 550mg at bedtime and benztropine 1mg twice a day was admitted for nausea and dizziness. Abdominal CT revealed partial small bowel obstruction (SBO); he was treated conservatively with nasogastric tube (NGT) decompression and laxatives. Clozapine was reduced to 200 mg at bedtime and benztropine was reduced to 0.5 twice a day, with gradual improvement in SBO.

Case 2: 50-year-old male with schizophrenia on clozapine 200mg at bedtime was admitted for abdominal pain for 2 days. Abdominal CT revealed closed loop obstruction of sigmoid bowel with incompetent ileocecal valve. Clozapine was discontinued. NGT decompression failed to relieve symptoms and patient required a sigmoidectomy and end colostomy creation

Case 3: 66-year-old male with schizophrenia on clozapine 400mg at bedtime was admitted for nausea, vomiting, and abdominal pain exacerbated by food intake. Abdominal CT revealed a SBO in the distal ileum. Clozapine was discontinued and the patient responded to intravenous fluids and NGT decompression.

Case 4: 43-year-old male with schizoaffective disorder on clozapine 500mg at bedtime presented with agitation and abdominal pain. Abdominal CT revealed massive fecal impaction with bilateral hydroureteronephrosis secondary to bladder compression by a massively distended sigmoid. Clozapine was initially reduced to 350mg at bedtime, but he continued to experience significant anticholinergic effects and repeat abdominal imaging showed potential development of SBO. Clozapine was discontinued entirely and conservative management followed, avoiding surgery, though he suffered from persistent urinary tract infections.

Risk Factors for CIGH

- Risk factors associated with CIGH based on studies of case series include: [4,5]
  - **Older age**
  - **Male gender**
  - Induction of treatment (first 4 months)
  - Co-prescription of constipating agents (anticholinergic/opiates)
  - Higher doses (serum >500 ng/mL)
  - Abrupt smoking cessation

Discussion

- Management of obstruction includes reduction of dose or cessation of clozapine[6]
- No clear guidelines on prevention of constipation/delayed gut motility currently exist
- Screening is not sufficient, as self-reported screening for constipation are not diagnostically sensitive likely due decreased nociperception and patient population[7]
- Prevention of constipation leading to obstruction is critical to prevent adverse outcomes
- Non-pharmacological interventions include high fiber diet, exercise and increased fluid intake
- Prophylactic laxative treatment has been studied in short term duration, with some recommendations for use of daily laxatives, including docusate, senna augmented by polyethylene glycol,[8] and newer studies suggesting role for prucalopride[9]

Conclusion

- CIGH is common, serious, and necessitates broader awareness amongst CL psychiatrists for improved management, detection and prevention

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