



**Libyan International Medical University
Faculty of Basic Medical Science**



Clozapine Can Result in Serious Gastrointestinal Complications

Submitted by: - Sfai Aldeen Abdulla Seleem Mohammed , third year student, faculty of basic medical science, Libyan International Medical University.

Student number: - 1264

Supervisor: - Sarah Elmegerhi

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Summary (Abstract):-

Clozapine remains the 'gold standard' in treatment-resistant schizophrenia, with its superiority well established in terms of mental health outcomes, quality of life, and life expectancy. However, clozapine's advantages come at a cost, with an array of problematic adverse effects of which clozapine-induced gastrointestinal hypomotility (CIGH) is one of the most serious, albeit one that has received scant attention until the last decade.

Gastrointestinal adverse effects of clozapine are very common and include nausea, vomiting and constipation. Other troublesome unwanted effects include dry mouth and hypersalivation, which involve the autonomic nervous system. Constipation is a particularly common adverse effect that has been reported to occur in 14-60% of patients. The management of clozapine-induced constipation has been the subject of a past Drug Bulletin. Clozapine's association with constipation could be explained by its potent anticholinergic properties. Rarely, clozapine-induced constipation has led to serious complications including ileus, bowel obstruction and necrotising colitis. A review was conducted to determine what serious gastrointestinal adverse effects have been reported in the literature and these are discussed below.

Introduction:-

Clozapine is the preferred antipsychotic for treatment-resistant schizophrenia, but has significant adverse effects, including gastrointestinal hypomotility or 'slow gut', which may result in severe constipation, ileus, bowel obstruction, and even death. These gastrointestinal effects remain inadequately recognized.¹

Mechanism of Action:

- Blocks D2 & 5-HT_{2A} receptors.
- Receptor affinity profile: D₄ & α₁ > 5-HT_{2A} > D₂ & D₁ receptors.
- Also blocks M & H₁ receptors.
- And Clozapine's association with constipation could be explained by its potent anticholinergic properties that block acetylcholine from binding to its receptors on certain nerve cells. They inhibit actions called parasympathetic nerve impulses. These nerve impulses are responsible for involuntary muscle movements in the gastrointestinal tract, lungs, urinary tract, and other parts of your body.²

Discussion:- Case study

- 1- Faecal Impaction** There are three reported cases of death secondary to clozapine-induced constipation and faecal impaction. One case involved a 49 year old man who had been receiving clozapine for two years, who died of severe pulmonary oedema secondary to inhalation of feculent vomitus. Another case in a 43 year old man who had been treated with clozapine for six years, suffered a large-bowel obstruction secondary to faecal impaction. The patient died three weeks after presentation from refractory shock and progressive multi-system organ failure, despite maximal care. A further case involved a 29 year old man who had only been taking clozapine for 36 days. He died after aspiration of vomitus secondary to bowel obstruction.
- 2- Intestinal Obstruction/Occlusion** There is a French report of three cases of intestinal occlusion in clozapine treated patients, one of which was fatal. Another report describes two cases of clozapine-induced intestinal obstruction. One of these involved a 51 year old man with no past history of constipation, who had been taking clozapine for two months. He suffered from an intestinal obstruction, from which he fully recovered and

clozapine was recommenced. The other case involved a 35 year old woman who had been taking clozapine for four months when she developed abdominal symptoms. She was diagnosed with intestinal obstruction which resolved with treatment and clozapine was continued. An analysis of side effects in 7921 clozapine patients in China found the main overall side effects occurred in 600 patients. There were 8 patients from this 600 patient sample who had paralytic intestinal obstruction .

- 3- **Paralytic Ileus** There has been a case reported of postoperative paralytic ileus in a 42 year old man who had been taking clozapine for over a year . Throughout the 14 months of followup after surgery, the patient experienced no subsequent gastrointestinal tract symptoms.
- 4- **Colon Perforation and Peritonitis** A case of a perforated colon and peritonitis has been reported in a 49 year old man who had been treated with clozapine for six weeks. However, the patient had a long history of constipation prior to clozapine. He survived after a hemicolectomy and colostomy, though did suffer a massive cerebrovascular accident peri-operatively, resulting in dense hemiplegia.
- 5- **Gastric Outlet Obstruction** There has been a reported case of possible clozapine induced gastric outlet obstruction in a 35 year old man treated with clozapine. The patient recovered once clozapine was ceased and the authors suggest gastrointestinal medications should be instituted with caution in clozapine patients so as not to mask serious adverse effects.
- 6- **Necrotising/Ischaemic Colitis** A case involving a 36 year old man who developed necrotising colitis is reported. The patient had a history of upper gastrointestinal complaints and constipation prior to clozapine use and had been treated with clozapine for 4 months. Unfortunately the case had a fatal outcome, which the pathology report speculated was secondary to the anticholinergic effects of clozapine and/or benztropine³.

Conclusions:-

In conclusion, psychiatrists, general physicians and radiologists should be aware of the seriousness of clozapine-induced constipation and of the risk of progression to bowel occlusion (particularly, in those schizophrenics with a long history of high-dose antipsychotic treatment before clozapine therapy [which may have contributed to less bowel motility] and in those psychotic subjects with prolonged inpatient hospitalization [who are less likely to be active].

Reference:

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