The Mental Health Drug Bulletin

Clozapine-induced gastrointestinal hypomotility

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Introduction

Clozapine remains the 'gold standard' in the treatment of schizophrenia, with its superiority well established in terms of mental health outcomes, quality of life, and life expectancy. However, these advantages come at a cost, with an array of problematic adverse effects.[1]

Agranulocytosis and myocarditis are the most recognised potentially life-threatening conditions and have established monitoring protocols in place to reduce the risk of misadventure.

Less well recognised is clozapine's ability to impair motility throughout the gastrointestinal (GI) system. This adverse effect spectrum is known as 'clozapine-induced gastrointestinal hypomotility' (CIGH) and is one of the most common (and serious) adverse effects.[2] It is defined as an acquired state of delayed transit through the GI tract (i.e. transit time greater than 2 standard deviations above the mean) resulting from the medication's pharmacological action on the enteric nervous system.[2] Its manifestations can vary from nausea, oesophageal reflux and constipation to potentially severe and life threatening complications such as ileus, intestinal obstruction or pseudo-obstruction, bowel ischaemia and megacolon.[1]

In 2016 a study was published comparing transit times of clozapine with other antipsychotics including aripiprazole, olanzapine, risperidone, paliperidone, zuclopenthixol and haloperidol. The mean transit time was four times longer for patients taking clozapine compared to patients on other antipsychotics.[3]

Why is this important?

CIGH is very common, and deaths associated with it now far exceed those from agranulocytosis.[1,2,4]

Although the seriousness of CIGH and the need for timely diagnosis have been made clear, the literature has dedicated relatively little attention to this phenomenon. CIGH should be considered in all patients receiving clozapine who have a change in their normal bowel habits.

Mechanism of action

The mechanism of action is not completely understood but is thought to be a combination of clozapine's anticholinergic and antihistaminergic properties. This is further complicated by antagonism at serotonin receptors, which is known to slow GI transit time.[5]

It has also been suggested that anti-serotonergic effects of clozapine reduce nociception from the bowel leading to reduced symptoms and signs of distress resulting in diagnostic delay.[2]

Risk Factors
Co-prescription of anticholinergic medication
Obesity
Low-fibre diet
Dehydration from reduced fluid intake and exacerbated by hypersalivation
Higher clozapine dose/plasma level (consider the effect of interacting drugs or stopping smoking)
Medical condition such as diabetes, hypothyroidism and Parkinson's disease
Younger males may be less likely to disclose constipation
Concurrent febrile illness and fever
Co-prescription of pain modulation medications e.g. anticonvulsants
Serious mental illness may possibly reduce pain sensitivity
Bowel surgery and the post-operative period
History of constipation
Poor understanding of normal bowel function

Table 1 - Possible risk factors for developing clozapine induced constipation/CIGH[2,5]

Risk Factors

Unfortunately there has been no consistent relationship demonstrated between age, dose, or duration of treatment and the onset of life-threatening CIGH.[2,5] Table 1 contains possible risk factors although it appears anyone on clozapine may develop serious CIGH.

Prevalence

CIGH is very common. Between 50-80% of clozapine-treated patients have unambiguous objective evidence of CIGH in colonic transit studies and all regions of the colon are affected.[1]

A large study published by Every-Palmer and Ellis in 2017 reviewed all reports of serious CIGH submitted to the Therapeutic Goods Administration (TGA) and New Zealand Pharmacovigilance Centre between 1992–2013. A total of 43,132 people commenced clozapine over the study period. One hundred and sixty were reported as having serious GI hypomotility with clozapine the suspected cause (37/10,000 clozapine users). Of these, 66.3% were male, age range was 17-76 years, clozapine dose ranged from 25-1000mg (mean 439mg/day) and median duration of clozapine treatment was 2.5 years. Few had received laxatives. At least 29 patients died (7/10,000 clozapine users), a reported case fatality rate of 18%.[1] This reported prevalence is likely an underestimation of true prevalence as the data rely on voluntary reporting and serious or fatal adverse drug reactions are more likely to be reported, which may account for the high case fatality rate.

While the CIGH prevalence was similar to other studies[2], it differs significantly from the clozapine prescribing information issued by regulators and pharmaceutical companies who report serious GI complications at rates of less than 1/10,000, almost a 40-fold difference. The current prescribing guidelines provide inadequate information on CIGH and this may be contributing to poor awareness and high associated morbidity and mortality.[1]

Prevention and Monitoring

Monitoring patients for constipation can be difficult and patients may not always disclose or be aware they are constipated. While important in assessing subjective distress, constipation symptoms are not sensitive in predicting hypomotility. This is consistent with many earlier reports where subjects had no prior complaints until serious pathology emerged.[3] Careful monitoring and assertive treatment for CIGH is strongly advocated but the evidence for how best to achieve this is still lacking. We suggest:

Prior to starting clozapine:

- Identify and treat pre-existing constipation and do not start clozapine until this has resolved
- Consider the use of prophylactic laxatives
- Warn patients and caregivers of the risks associated with constipation and provide written information
- Educate on the importance of adequate dietary fibre, fluid intake, and exercise for bowel health
- Review concurrent medication that can cause constipation e.g. anticholinergics, iron & calcium supplements, calcium channel blockers & opioids
- Take a GI history and perform an abdominal examination

Constipation can happen at any time during treatment so ongoing vigilance is required

During clozapine treatment:

- Slow titration of clozapine
- Reinforce advice regarding adequate dietary fibre, fluid intake, and exercise
- Stool charts should be used for all inpatients prescribed clozapine and use the Bristol Stool Chart to assist monitoring
- Enquire about bowel habits:
    - Daily for the first 4 weeks of clozapine treatment for hospital inpatients (minimum of weekly for community commencement patients)
    - At least weekly for hospital inpatients and patients on weekly full blood count (FBC) monitoring
    - At least every four weeks for patients on 4-weekly FBC monitoring in the community
    - *Be aware patients under-report constipation symptoms*

- Assertively treat any emerging constipation with a low threshold for further investigation
- Review the need for and dose of other medication that may be contributing to constipation
- Have a high index of suspicion for GI symptoms and 'red flags' (see Table 2) – *serious CIGH is a medical emergency*
- Monitor adherence to and correct administration of laxatives

Adopting the Rome III criteria for functional constipation (abbreviated version below) at the time of routine FBCs may assist in diagnosing chronic constipation and help prevent patient deaths.[2,5]

Ask the following - Does the patient experience?

1. Fewer than 3 bowel motions a week?
2. At least 1 of the following:
   - Straining at defaecation ≥25% of the time
   - Lumpy and/or hard stools ≥25% of the time
   - A sensation of incomplete bowel evacuation ≥25% of the time

Management of CIGH

If a patient acknowledges constipation, abdominal examination and timely treatment is essential.

- Moderate to severe abdominal pain (*although pain may be absent*)
- Abdominal distention
- Vomiting
- Overflow incontinence or bloody diarrhoea
- Absent or high-pitched bowel sounds
- Acute abdomen
- Haemodynamic instability
- Signs of sepsis

Table 2 – Warning signs of acute CIGH[5,6]

These suggest acute CIGH. A low threshold for referral to an emergency department is warranted as death can occur within hours.

A common finding is that diagnosis is often difficult and/or delayed; there have been reports of fatalities occurring only hours after symptoms first present, and this emphasises the urgency for prompt assessment and management.[5] Whereas a blood test can clearly indicate levels of white cells and neutrophils, it can be difficult to establish if a patient is constipated without an abdominal x-ray.

Recommendations for selecting a laxative

Docusate and Senna is recommended first line for treatment and prevention of CIGH (see Table 3).[7] Recent evidence suggests that the risks of chronic stimulant-laxative use have historically been overstated,[6] and long term use is now considered safe.[7]

First line	Stimulant and stool softener laxatives (e.g. Docusate and Senna) Initial dose - TWO tabs nocte[7] *If intestinal obstruction is excluded.*
Second line	Lactulose and polyethylene glycol (e.g. macrogol) are effective and could be considered as second-line options or in addition to the stimulant and softener combination if needed.[5] Initial dose - Lactulose 15-45ml daily[8] Macrogol sachet 1 sachet BD[7]

Table 3 - Recommendations for prophylaxis and management of CIGH [5,6,7]

Bulk forming laxatives (e.g. psyllium - Metamucil®, ispaghula husk - Fybogel®) should be avoided in slow transit constipation as there is a risk of faecal impaction and bowel obstruction.[5]

Choice of laxative should also be based on the patient's previous response to certain agents in association with the required speed of action. Stimulant laxatives are usually the fastest acting (6-10 hours), whereas lactulose may take up to 72 hours of regular use to work.[5]

Why a prophylactic laxative should be initiated at commencement of clozapine treatment

Careful monitoring of bowel function and the use of prophylactic laxatives should be considered for all patients prescribed clozapine. This is because CIGH is more common than blood dyscrasias, mortality rates are higher and it can cause significant morbidity, largely due to bowel resection. Subjective complaints of constipation are unreliable in predicting objective hypomotility. In a large study of 102 cases of life-threatening CIGH, only 45% of patients reported constipation prior to the evolution of serious and sometimes fatal complications.[2]

A study conducted by Attart *et al* in 2019 suggested challenging the status quo of reserving laxative use for those patients with identified or reported clozapine-induced constipation.[6] Given the prevalence and the high mortality rates associated with this adverse effect, they were of the view that it is ethically sound to use prophylactic laxatives throughout the patient's entire treatment with clozapine, as CIGH can occur at any time. They recommended review of regular laxatives only if diarrhoea develops or a change in frequency of bowel habits necessitates their withdrawal.

- CIGH is common (50-80% of patients)
- Has potentially life-threatening consequences
- Can occur at any time
- Self-reported constipation is a poor predictor of objective hypomotility
- Clozapine-treated patients may not recognise or experience constipation in the same way as others due to changes in pain sensitivity or habituation and thus less likely to complain
- 'As required' laxatives are generally not requested or used by this cohort
- The risks of not treating far outweigh the benefits of the 'wait and treat' approach

Table 4: Key reasons for initiating prophylactic laxatives[1,3,6,7]

Other potential treatment options:

Cholinergic agents, such as bethanechol or donepezil have been suggested for CIGH.[5] Lubiprostone is licenced for constipation in the United Kingdom (only available under the special access scheme in Australia) and has been reported to be effective in obviating the need for other laxatives in a clozapine re-challenge following a severe case of CIGH.[5,6]

Conclusions

- **Serious CIGH is a potentially fatal medical emergency and early detection and assertive monitoring and treatment are essential to reduce mortality.**
- **Despite the prevalence and potential seriousness of CIGH, knowledge about prevention, identification, and management remains poor, even among those most familiar with clozapine.**
- **Bowel habits need to be monitored in all patients on clozapine.**
- **The use of prophylactic laxatives should be considered for all patients on clozapine.**
- **Extra vigilance is required when adding anticholinergics or other medication that can cause or worsen constipation and careful risk benefit analysis considered.**

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Appendix I - Case of a man who died in 2015 of suspected CIGH

Case
Mr X was a 35-year old man.
Diagnosis of chronic paranoid schizophrenia.
Two previous discontinued trials of clozapine: stopped firstly for non-adherence and then for neutropenia.

Medical History
Seizures (clozapine induced), hypertension, subclinical hypothyroidism, hepatitis C PCR +ve

Medications
Clozapine 600mg nocte (clozapine levels in previous 4/12 ranged from 738-458mcg/L and norclozapine levels 221/395mcg/L. Two weeks before he died his clozapine level was 458mcg/L, norclozapine 395mcg/L)
Levetiracetam 1250mg bd
Clonazepam 500microg mane, 750mcg nocte
Lithium carbonate SR 450mg bd
Movicol® 1 sachet daily
Levothyroxine 50microg mane
Hyoscine hydrobromide 300microg mane
Atropine 1% sublingual drops 2 drops bd
Perindopril 5mg mane

Clinical presentation
Mr X was diagnosed with constipation and started on macrogol sachets four months prior to his death and this was likely precipitated by the addition of sublingual atropine drops and hyoscine tablets 6-8 weeks earlier for severe hypersalivation. He then started refusing macrogol 2-3 weeks prior to his death.

Acute onset of symptoms included tachycardia, significant faecal incontinence followed by vomiting and aspiration of faeculent vomitus. Nil reported pain or fever. Death was within 7 hours of symptom onset.

Outcome
Mr X died 24 months after recommencing clozapine for the third time. Cause of death was reported as acute vomit aspiration in a man with acute large intestine obstruction (severe megacolon) and potential clozapine induced gastrointestinal hypomotility.

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