CASE REPORT

Clozapine-Induced Fatal Bowel Ischaemia  
- A Neglected Side Effect?  

Razak NA\textsuperscript{1,2}, Mohd Nor F\textsuperscript{1}, Shafie MS\textsuperscript{1}, Hwang IS\textsuperscript{1}  

\textsuperscript{1}Department of Pathology, Universiti Kebangsaan Malaysia Medical Centre,  
Jalan Yaacob Latif, Bandar Tun Razak, Cheras, 56000 Kuala Lumpur, Malaysia  
\textsuperscript{2}National Defense University of Malaysia, Kem Sungai Besi, 57000 Kuala Lumpur, Malaysia  

Abstract  
There have been previous reported deaths due to clozapine-induced constipation. In all these cases, patients have experienced prior abdominal symptoms over a period of weeks or months. Clozapine is an anti-psychotic drug, and it is widely used for treatment of schizophrenia. The important side-effects of clozapine include postural hypotension, weight gain, tachycardia, cardiomyopathy, cardiomyositis, seizures, hypersalivation and agranulocytosis. However, constipation induced by clozapine need to be addressed since it may cause fatal consequences. Constipation associated with clozapine is thought to be mediated by the drug's pronounced dose-dependent cholinergic and serotonergic antagonism. Hence, a clozapine-induced rapidly fatal bowel ischaemia is the highlight of this report and this risky side-effect should be aware by the psychiatrist or physician before commencing the treatment.  

Keywords: Fatal Bowel Ischaemia, Clozapine, Constipation  

Introduction  
Clozapine is an anti-psychotic drug, and it is widely used for treatment of schizophrenia. The important side-effects of clozapine include postural hypotension, weight gain, tachycardia, cardiomyopathy, cardiomyositis, seizures, hypersalivation and agranulocytosis. However, constipation induced by clozapine need to be addressed since it may cause fatal consequences. The Sandoz (Sandoz Pharmaceutical Corporation, East Hanover, NJ) package insert recorded 14% prevalence rate [1]. Lieberman \textit{et al.} (1994) found constipation with clozapine in 33.3\% of cases during acute treatment and 22.8\% during maintenance treatment [2]. Hayes and Gibler (1995) found 60\% prevalence rate of constipation in the evaluation of clozapine [1]. Clozapine-induced constipation was believed due to its anti-cholinergic effects.  

Levin \textit{et al.} (2002) reported death in a patient receiving clozapine (750 mg/day) for the past six years, who had gastroscopy six months before his admission for investigation of vomiting and epigastric pain.
Drew et al. (1997) reported two patients on clozapine 500 mg/day for two years and 400 mg/day for 36 days, respectively, who died as a consequence of inhalation of faeculent vomitus subsequent to constipation and bowel obstruction [1,4].

Freudenreich and Goff (2000) documented a patient on clozapine 400 mg/day for six weeks, who developed perforation of colon and peritonitis requiring hemicolecotomy, which was sustained perioperatively following a dense cerebrovascular accident [5]. Shammi and Remington (1997) described a death, where a patient on clozapine 600 mg/day for four months presented with constipation and acute abdomen. Laparotomy revealed a grossly dilated colon [6]. Autopsy revealed evidence of necrosis and dilation of the entire large intestine.

Although some of the patients might present with mild symptoms and insignificant findings, in this case report, it had caused death. Therefore, this should be alarming to the medical practitioner to be cautious. Patient should be well-advised before commencing medication. Hence, this case is a death reported in a patient, who developed fatal intestinal obstruction while on treatment with clozapine.

**Case Report**

A 43-year-old gentleman was diagnosed with paranoid schizophrenia for 23 years, and was on clozapine 600mg/day since then. He complained of sudden onset of colicky abdominal pain and nausea prior to his death. The caretaker gave some traditional medications to relieve his pain, and he was found dead a few hours later. Previously, he had constipation for few days, but did not seek for treatment. Autopsy revealed a moderately built adult male with no external injuries. The abdomen was distended and soft. No palpable mass or skin changes were found.

The abdominal cavity showed the whole intestines were distended till the colon. The small intestines and large intestines were dusky in colour and infarcted, however no area of gangrene was noted. The mesentery was normal. No ascites was found. On opening the intestines, the intestines were distended by moderate to hard faeces, but no mass, tumour, volvulus or intussusceptions were found. Other organs were unremarkable. Laboratory investigations such as septic workout, electrolytes and cardiac markers were not significant. He had impacted faeces, which had pressed against the bowel wall causing ischaemia and infarction of the bowel.

**Discussion**

This case demonstrates that death can occur in a rapid course from constipation. In this case, it was probably induced by clozapine. Constipation can be further compounded by the administration of other pharmacologic agents, which may interact with or potentiate the effects of other medical or environmental factors promoting slowed bowel motility.

Death from constipation and subsequent bowel infarction are relatively common in elderly patients, and infarction causes a far more rapid and dangerous deterioration than does intestinal obstruction. There are a number of case reports linking clozapine with constipation, and at least seven published cases of death secondary to clozapine-induced constipation resulting in frank bowel necrosis, paralytic ileus, gastric outlet obstruction, colonic perforation with fecal peritonitis, with fatal aspiration of feculent vomitus as a result of bowel obstruction.
obstruction, postoperative ileus or eosinophilic colitis [6,7]. Constipation associated with clozapine is thought to be mediated by the drugs' pronounced dose-dependent cholinergic and serotonergic antagonism [8,9].

Patients taking clozapine should be aware of any abdominal pain, constipation, faeculant vomitus, and distended abdomen as signs and symptoms of possible complications of clozapine use. However, these signs and symptoms are non-specific. When prescribing Clozapine to the patient, the doctor should advise on regular physical monitoring, appropriate and timely use of laxatives, and early intervention in constipated patients before life-threatening disease develops. Prophylaxis may include high fiber diet, adequate fluid intake, especially if hypersalivation is also a problem, and exercise.

Conclusion

Clozapine-induced gastrointestinal hypomotility may lead to paralytic ileus, faecal impaction, aspiration of vomit, necrotizing colitis, and/or intestinal perforation. Pathologists and others who involved in the investigation of clozapine-associated deaths should know that clozapine is toxic to people, who are intolerance to the drug. Psychiatrists need to be alert to the medical emergencies, which can occur in the context of clozapine treatment, and also need to make other clinicians, who may have contact with their patients be aware of these complications.

References


**Corresponding Author**
Nadiawati Abdul Razak, MBBS
Forensic Pathology Trainee, Department of Pathology
Universiti Kebangsaan Malaysia Medical Centre
Jalan Yaacob Latif, Bandar Tun Razak, Cheras
56000 Kuala Lumpur, Malaysia
**Tel:** (006) (03) 91455369
**Fax:** (006) (03) 91311673

**Email:** drnadiawati@yahoo.com