

Clozapine Induced Ischaemic Colitis and Gastrointestinal Necrosis Requiring Surgical Treatment: A Mini Review

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Introduction

Clozapine is an atypical antipsychotic used in the management of treatment-resistant schizophrenia. Numerous clinical trials, including randomized double-blind clinical trials and large cohort studies, have revealed that clozapine is more effective than any other antipsychotic drugs. It has been around since the 1960s and was withdrawn from use after an association with neutropenia (incidence 3%) and agranulocytosis (0.8%) was made. The pivotal study by Kane et al. in the 1980s proved that clozapine was more effective than conventional antipsychotics and it was reintroduced in the UK with compulsory haematological monitoring [1,2].

Studies have shown that 30% of patients who have previously been refractory to treatment improve significantly after 6 weeks' treatment with clozapine and up to 60% respond after one year. Although claims are made for the efficacy of clozapine in negative symptomatology, clinical gains in this area are much less marked. Clozapine treatment reduces suicidality and the data are sufficient for specific labeling for this indication in the USA. Clozapine has also a unique side-effect profile in that it has been associated with an extremely low incidence of extrapyramidal side-effects (EPSEs) and is not to cause precipitate tardive dyskinesia (TD). Many of the adverse effects of clozapine are dose-dependent and associated with speed titration [3] (**Tables 1 and 2**). However, the same studies have also shown that this drug has several adverse gastrointestinal effects such as acute necrotizing enterocolitis (ANE). Commonly the clozapine cause gastrointestinal hypomotility and Ogilvie syndrome (acute pseudo-obstruction caused by a disturbed balance in the autonomic regulation of intestinal motility) is described after clozapine usage [4,5].

The occurrence of seizures appears to be dose-related and can be managed by reduction in clozapine dosage. Clozapine-induced necrotizing colitis has been described in the literature and the anticholinergic activity is believed to be the cause. Intestinal necrosis is a partial or total necrosis of the small or large bowel with a mucosal starting point and consecutively transmural progression. Current pathophysiological of necrotizing enterocolitis can be related to three possible mechanisms:

a) Small intestine obstruction leading to distension, necrosis, perforation or sepsis [6]. The condition that increased intraluminal pressure reduces perfusion and causing ischaemia.

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Colonic distension may result in perforation, especially if the small intestine diameter exceeds 12 cm. The mortality rate for pseudo-obstruction may be as high as 50% if it progresses to ischemic necrosis and perforation.

- b) Aspiration from inhalation of feculent vomitus or dysphagia;
- c) Fecal stasis leading to translocation of luminal bacteria across

Table 1 Clozapine – common adverse effects.

Adverse effect	Time course
Sedation	First few months May persist, but usually wears off
Hypersalivation	First few months May persist but usually wears off Often very troublesome at night
Constipation	Usually persists
Hypotension	First 4 week
Hypertension	First 4 week Sometime longer
Tachycardia	First 4 week, but sometimes persists
Weight gain	Usually during the first year of treatment
Fever	First 3 weeks
Seizures	May occur at any time
Nausea	First 6 weeks
Nocturnal enuresis	May occur at any time
Neutropenia/agranulocytosis	First 18 weeks (but may occur at any time)

Table 2 Clozapine – uncommon or unusual adverse effects reported since its relaunch in 1990.

Adverse effect	Comment
Agranulocytosis/neutropenia	Occasional reports of apparent clozapine-related blood dyscrasia even after 1 year of treatment
Delirium	Reported to be fairly common, but rarely seen in practice if dose is titrated slowly and plasma level determinations are used
Eosinophilia	Reasonably common but significance unclear. Some suggestion that eosinophilia predicts neutropenia but this is disputed. May be associated with colitis and related symptoms
Heat stroke	Occasional case reported. May be mistaken for (Neuroleptic malignant syndrome (NMS)
Hepatic failure/enzyme abnormalities	Benign changes in LFTs are common (up to 50% of patients) but worth monitoring because of the very small risk of fulminant hepatic failure
	Rash may be associated with clozapine-related hepatitis
Pancreatitis	Rare reports of asymptomatic and symptomatic pancreatitis sometime associated with eosinophilia
	Some authors recommend monitoring serum amylase
Pneumonia	Very rarely results from saliva aspiration
	Infections in general may be more common in those on clozapine
	Note that respiratory infections may give rise to elevated clozapine levels. (Possible an artifact: smoking usually ceases during an infection)
Thrombocytopenia	Few data but apparently fairly common
	Probably transient and clinically unimportant
Vasculitis	One report in the literature in which patient developed confluent erythematous rash on lower limbs

the epithelial barrier, triggering an exaggerated and damaging local inflammatory response. The initial symptomatology, less than 24 hours, is represented by functional digestive signs such as abdominal pain, vomiting, nausea with or without emesis, diarrhea.

The aim of this study was to reviewer retrospectively all cases of ischaemic colitis and intestinal necrosis related to clozapine required an urgent surgical treatment registered in the Pharmacovigilance Database up to January 1997 to day.

Methods

We searched in the pharmacovigilance database all cases of ischaemic colitis and gastrointestinal necrosis related to clozapine between 1997 and December 2014. We analyzed retrospectively

all clozapine case reports of ischemic colitis and gastrointestinal necrosis underwent to surgical procedure and all case reports of several digestive complications clozapine-related resolved with conservative treatment (**Table 3**) [7-18]. A literature search was performed using the databases PubMed (1950-2014), EMBASE (1980-2014), and Scopus, MEDLINE, EMBASE and SCOPUS were searching using the term such as: ischemic colitis, colon ischemia, bowel ischemia, intestinal necrosis, colon perforation, bowel perforation, clozapine.

Discussion

The clozapine has been shown to have a better efficacy and side-effects profile over other typical and atypical antipsychotic drug. The risk of causing agranulocytosis is well established and estimated to be 1%, a reason responsible for its initial withdrawal from the market before its reintroduction. Several case studies have shown various life-threatening side effects of clozapine, ranging from haematological (agranulocytosis), cardiac (cardiomyopathies, pericarditis), nervous (seizure), metabolic (diabetes, dyslipidaemia, liver failure) and gastrointestinal complications [19-21]. A review of the mortality effect of clozapine showed that it lowers the mortality rate in severe schizophrenia by decreasing suicide rates, while the mortality rate for less common causes of death, such as pulmonary embolism and cardiac failure is higher [22]. Reported gastrointestinal side effects of clozapine are oesophagitis, constipation and bowel ischemia [23,24]. Constipation is a very common complication occurring in 14% to 60% of patients [25-34]. Less well recognized is clozapine's potential to impair motility throughout the gastrointestinal system causing dysphagia, ileus, intestinal obstruction, bowel ischemia and megacolon.

The possible mechanisms by which clozapine cause ischemic colitis and gastrointestinal necrosis are reported by Palmer et al. [5]. They hypothesize three possible mechanism can have a fatal outcome: The first possible mechanism is an untreated bowel obstruction or pseudo obstruction leading to distension, necrosis, perforation or sepsis. Colonic distension may result in perforation especially if the bowel diameter exceeds 12 cm. The mortality rate for pseudo-obstruction may be as high as 50% if it progresses to ischemic necrosis and perforation [35]. The second possible mechanism is the aspiration from inhalation of feculent vomitus or dysphagia and finally another possible mechanism is represented by the fecal stasis leading to infection. Peyrière et al. reported that 24 out of 36 patients treated with clozapine were undergone to surgical operation, 9 patients from ischemic colitis and 15 from necrotizing colitis [1]. The mortality rate among the patients who underwent surgery was 25% (6 patients died).

In the analysis of 102 cases Palmer et al., 28 patients died (27.5%), 42 recovered (41.2%) and in 32 cases (31.4%) the outcome was unknown [5]. The large number of death may indicate difficult or delayed diagnosis or rapid decompensation. It is very important for clinicians to know that these symptoms may be these of an ischemic colitis or gastrointestinal necrosis related to the treatment of psychiatric disease. In the literature the population was young, 47% of the whole population and 64% of the death being under 40 years-old. Risk factors for digestive complications

Table 3 Summary of Case Reports Published of ischaemic colitis and gastrointestinal necrosis clozapine related.

Author	Nb cases	Medical and Psychiatric History	Clinical Presentation	Surgical Treatment and Outcome
Levin et al. [34]	1	chronic paranoid schizophrenia of 20 years' duration	abdominal pain	died before surgery
Townsend et al. [4]	1	long history of schizophrenia	abdominal pain + vomiting	died before surgery for bowel ischaemia (post-mortem examination)
Leong et al. [9]	1	chronic schizophrenia	abdominal distension + vomiting and diarrhea	right hemicolectomy without primary anastomosis
Peyrière et al.	38	schizophrenia in 14 pt another psychosis in 6 pt bipolar disorder in 3 pt mental retardation in 3 pt severe depression in 1 pt autism in 2 pt delirium in 1 pt psychopathic personality in 1 pt	abdominal pain + vomiting diarrhea	partial or total resection of the colon and/or small bowel in 24 pt (9 pt suffered from ischaemic colitis and 15 from necrotizing colitis)
Hibbard et al. [11]	2	schizophrenia	Constipation, tender abdomen, Hypotension and tachycardia	died for bowel necrosis before surgery
McKinnon et al. [12]	1	history of treatment-resistant schizoaffective disorder urinary incontinence with a permanent cystostomy	Abdominal pain + feculent vomiting	subtotal colectomy with intraoperative ileorectal anastomosis
Lavi et al.	1	schizophrenia of 40 years' duration	Tender abdomen + nausea + constipation	cecotomy and transverse colostomy
Hasan B. Alam et al.	1	Paranoid schizophrenia	Abdominal distension and shock	recovered with conservative treatment
Prieto et al. [14]	1	schizophrenia	nausea + constipation	no surgery
Fayad et al. [15]	1	schizophrenia	abdominal pain + vomiting	died before surgery (autopsy was not performed)
Park et al. [16]	1	Bipolar disorder + depression	abdominal pain	no surgery
Ikai et al. [17]	1	schizophrenia	abdominal distension + shock	laparotomy for perforation of large intestine
Shah et al. [18]	1	chronic schizophrenia	constipation, abdominal pain, vomiting	colonic resection with stoma Formation
SC et al.	1	chronic schizophrenia	nausea; abdominal pain	died before surgery 1 week after taking clozapine

in these young patients were infection HIV related, enteritis, obesity and gastrointestinal infection and metabolic disorders. Nausea tends to develop later in the course of treatment and affects 11% of patients. The pathophysiological basis is uncertain but may involve the anticholinergic effect of delayed gastric emptying. Constipation occur in 1 percent of patients treated with clozapine and can be severe.

Three deaths from severe ileus and obstipation have been reported [29-34] (**Table 4**). It is most likely due to the anticholinergic properties of clozapine and other medications with anticholinergic properties may exacerbate it. Because long term use of stimulant cathartics can result in degenerative changes in colonic muscles and nerves, short-term treatment is recommended. So, constipation in psychotic patient should be monitored because the risk for ischemic colitis is higher in patient with constipation [26]. The biological data is very poor in review of literature, nevertheless in the literature metabolic acidosis is considered as a factor of seriousness and early metabolic acidosis should incite the clinicians to be aware for visceral

intestinal complications (ischaemic or infectious). Three cases of gastrointestinal necrosis were reported in patients treated by clozapine [35-37].

A recent publication reports one case of acute necrotizing enterocolitis (ENA) induced by antipsychotics (quetiapine), were reported in the literature one case of neonatal delayed peristalsis after in-utero exposure to clozapine.

The mechanism for this syndrome probably is related to the anticholinergic effect of the clozapine associated with a substantial plasmatic concentration and possible increased half-life elimination. Finally we hypothesize that the high mortality rate related to severity of ischaemic colitis induced by clozapine in schizophrenic patient can be associated to altered sensitivity to pain and it can be responsible of delayed diagnosis and treatment.

Conclusions

The physicians should be suspicious when abdominal digestives symptoms are present with-out evidence of other predisposing

Table 4 Death due to clozapine associated gastrointestinal hypomotility.

Patient	Presentation	Reference
M, 29	Aspiration of vomit secondary to obstruction of the transverse colon	Hayes and Gibler [27]
F, 31	Large bowel obstruction with mucosal necrosis, pulmonary edema, and shock	Thèret et al.
M, 49	Intermittent indigestion, nausea, chest pain, and vomiting. Collapsed with pulmonary edema secondary to inhalation of feculent vomit	Drew and Herdson [31]
M, 36	Necrotizing colitis	Shammi and Remington [12]
M, 43	History of ulcerative esophagitis. Abdominal pain, feculent vomiting, and severe fecal impaction with large intestinal necrosis	Levin et al. [14]
M, 44	Found dead. Evidence of pulmonary edema, paralytic ileus, and gastroenteritis	Ferslew et al.
F, 47	Large bowel infarct	Flanagan et al.

factors and in future a multidisciplinary approach (psychiatrists, surgeons and radiologist) towards the overall management of

this complication and is key factor for a good outcome because an early diagnosis and early surgery can improve the chances of these patients.

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