

Death From Clozapine-Induced Constipation

Case Report and Literature Review

TOMER T. LEVIN, M.B.B.S.
JONATHAN BARRETT, M.B.B.S.
ALAN MENDELOWITZ, M.D.

Clozapine is commonly used in the therapy of patients with treatment-resistant schizophrenia and schizophrenia with prominent negative symptoms. Constipation occurs in 14% of patients receiving clozapine and is believed to be an anticholinergic side effect.¹ A recent edition of the Australian Adverse Drug Reactions Bulletin² highlighted the common nature of this side effect. However, this is not a trivial side effect. Of the 15 cases of serious constipation reported in Australia, 4 involved fecal impaction, 2 involved subacute bowel obstruction, 1 involved rectal prolapse requiring ileostomy, and there was 1 fatality secondary to inhalation of feculent vomitus.

The aforementioned fatality, described by Drew and Herdson,³ occurred in a 49-year-old man with paranoid schizophrenia who was treated with clozapine (500 mg/day) for 2 years. He died unexpectedly in a psychiatric ward. Postmortem examination revealed severe pulmonary edema secondary to inhalation of feculent vomitus. Extensive, severe fecal impaction was found, involving the entire large bowel with feculent fluid extending all the way to the stomach. There was also evidence of reflux esophagitis. Of note, in the month before his death, the patient had complained of intermittent nausea, vomiting, indigestion, and chest pain, but had complained of constipation only once, 11 days before his death.

Hayes and Gibler⁴ described a similar death in a 29-year-old man receiving clozapine (up to a dose of 400 mg/day) for 36 days, who also died of aspiration of vomitus secondary to constipation and bowel obstruction.

A French report⁵ of 30 cases of clozapine-induced constipation documented three cases of intestinal obstruction that required surgical laparotomy. One of the cases was fatal.

A further case of a 36-year-old man treated with clozapine (600 mg/day) for 4 months was documented by Shammi and Remington.⁶ Their patient had previously

documented constipation and upper gastrointestinal complaints. He presented with nausea and an acute abdomen, and laparotomy revealed a grossly dilated colon. Autopsy showed marked dilation and necrosis of the entire large bowel.

More recently, Freudenreich and Goff⁷ described a 49-year-old man who developed colon perforation and feculent peritonitis 6 weeks after commencing clozapine (400 mg/day). The patient had complained of constipation, but did not receive treatment. He required an emergency hemicolectomy and perioperatively sustained a dense cerebrovascular accident.

We describe a further death secondary to clozapine-induced constipation and fecal impaction. We believe this is the fifth fatality described in the literature. The ramifications of this complication for patients receiving clozapine are discussed.

Case Report

Mr. C. is a 43-year-old man who was admitted to the hospital with an acute abdomen and hypotension. He had a history of chronic paranoid schizophrenia of 20 years' duration, which had been treated with clozapine (750 mg/day) for the past 6 years before his admission. Mr. C. was also receiving medroxyprogesterone acetate (Depo-Provera) for aberrant sexual behavior and valproate sodium (1,200 mg/day) as augmentation for his antipsychotic medication. He had a history of ulcerative esophagitis and previously treated syphilis. At the time of ad-

Received October 16, 2001; accepted October 16, 2001. From the Department of Consultation Liaison Psychiatry, Long Island Jewish Medical Center, New Hyde Park, NY. Address correspondence and reprint requests to Dr. Levin, Department of Consultation Liaison Psychiatry, Long Island Jewish Medical Center, 270-05 76th Ave, New Hyde Park, NY 11040. E-mail: tlevin@lij.edu

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mission, Mr. C. resided in a community mental health facility and was treated under an involuntary community treatment order.

Six months before admission, Mr. C. underwent gastroscopy and abdominal computed tomography for investigation of vomiting and epigastric pain. The gastroscopy revealed ulcerative esophagitis, and the computed tomography results were reported as "normal apart from constipation." He was subsequently prescribed omeprazole 20 mg/day and psyllium 1 tsp. bid).

One month before admission, he saw his local doctor with complaints of vomiting and abdominal pain, and the dose of omeprazole was doubled.

On the morning of his admission, he was found to be unwell, complaining of abdominal pain with feculent vomiting, and was subsequently transferred to the hospital by ambulance.

On admission to the hospital, Mr. C. was conscious but confused, with cyanosis, tachycardia, tachypnea, and an unrecordable blood pressure. Examination otherwise revealed a distended, rigid abdomen with generalized peritonitis. He was intubated and resuscitated.

Emergency laparotomy revealed a large-bowel obstruction secondary to severe fecal impaction affecting the entire colon, especially the rectosigmoid junction. The colon, although macroscopically intact, was grossly distended with patchy hemorrhage and necrosis. Histologic examination later confirmed severe ischemic changes and toxic dilation.

Because of the sheer fecal bulk, a manual decompression was carried out before a total colectomy and ileostomy were performed.

Despite maximal treatment in an intensive care unit, Mr. C. died 3 weeks later with refractory septic shock and progressive multisystem organ failure.

Discussion

Although constipation is a common and usually benign side effect of treatment with clozapine, this case highlights the consequences of undertreated or unrecognized, severe clozapine-associated constipation progressing to fatal bowel obstruction. This is perhaps the overriding and surprising message of this case: that clozapine-induced constipation can lead to death.

This case is remarkably similar to the four previously published cases reviewed above. Clinically, there seem to be two mechanisms whereby clozapine-induced constipation can have a fatal outcome. In the case presented and in that of Shammi and Remington⁶ outlined above, bowel obstruction led to distention and necrosis of the bowel and presented as an acute abdomen with a picture of sepsis. In the remaining two cases, death was secondary to inhalation of feculent vomitus.

Another common element is that diagnosis was often difficult or delayed. Symptoms were either nonspecific or

not appreciated as heralding a possibly fatal condition. There may be a number of reasons for this, which are considered briefly below.

Schizophrenic patients may have altered sensitivity to pain.⁸ This phenomenon may be particularly important in diagnosis of the acute abdomen because pain is usually the central feature.^{9,10} The precise degree of pain insensitivity is unclear. Neuroleptic and anticonvulsant medications may have sedative or pain-modulating effects, and this may be a confounding factor in medicated patients. It is noteworthy, however, that the syndrome of pain insensitivity was well described before neuroleptic drugs were introduced.¹¹

Another possibility is that pain perception is normal but that schizophrenic patients have difficulty expressing the pain that they feel.⁹ For example, the negative symptoms of schizophrenia may affect the expression of pain, and physicians may be misled by flattened affect and apathy into minimizing pain symptoms. Patients with a formal thought disorder may have difficulty in organizing their thoughts to express symptoms of pain. Paranoia may discourage physicians from thoroughly evaluating their patients. Guieu et al.¹² attempted to evaluate pain perception objectively using nociceptive reflex thresholds as an index of pain perception in neuroleptic-naïve patients. Although they found no differences between the patient and control groups, the serious methodologic flaw of not using uniform diagnostic criteria for schizophrenia casts doubt on their findings. For example, 4 of their group of 10 patients had simple schizophrenia, and 1 patient had been ill for only 2.4 months.

In the face of a florid psychotic illness, constipation may be trivialized as a minor side effect, acceptable in light of the difficulty of managing an acute psychosis. Moreover, the nature of the schizophrenic illness requires a team management approach. Consequently, the patient may first report constipation to a mental health worker who may not appreciate its implications. The psychiatrist is often the next in line to hear about the symptoms. The general physician or gastroenterologist, who has the expertise to deal with the diagnosis and management of constipation, may be involved only relatively late. Moreover, these same physicians, who easily investigate constipation in nonpsychiatric patients, may be challenged by the same symptom in psychotic patients. Often this seemingly simple problem will require a coordinated and intensive multidisciplinary approach. For example, administering enemas to the schizophrenic Mr. C., with his residual symptoms, lack of

insight and compliance, and aberrant sexual behaviors, could easily turn into a logistical nightmare.

Future attention should focus on both the pathophysiology and management of this condition. The pathophysiology of clozapine-induced constipation has always been assumed to be due to an anticholinergic side effect of the medication, but this has never been rigorously investigated. Cholinergic agents such as bethanechol or donepezil, for example, have never been systematically tested in a controlled manner for this condition. Diagnostic and treatment protocols for clozapine-induced constipation, therefore, must be developed and tested for both the inpatient and outpatient settings. For example, in an already severely constipated patient, a bulk-forming agent may theoretically worsen constipation, and perhaps an enema should be used first.

A logical strategy is to minimize the dose of clozapine. Measurement of serum clozapine levels may be helpful in this regard. If serum levels of clozapine are in the range of 500–700 ng/mL or greater, then the dose can be cautiously lowered. Serum levels lower than a threshold of 350 ng/mL are associated with a lack of clinical response.¹³ Another strategy may be to replace part of the clozapine dose with quetiapine, and thus use it as a clozapine-sparing agent. For example, the dose of clozapine could be reduced by 25%

by substituting 2 mg of quetiapine for every 1 mg of clozapine. Reinstein et al.¹⁴ used this strategy of combination clozapine–quetiapine therapy to improve glycemic control and reduce weight in patients previously treated with clozapine alone. There are, however, no reports of clozapine–quetiapine combination therapy for treating clozapine-induced constipation.

Although we have discussed this case specifically as it relates to clozapine, other commonly used psychiatric medications such as thioridazine, chlorpromazine, and benztropine, to name but a few, also present a large anticholinergic burden and may cause constipation.

In conclusion, psychiatrists, general physicians, radiologists, and consultation-liaison psychiatrists, in particular, should be aware of the seriousness of clozapine-induced constipation and of the risk of progression to bowel obstruction. Psychiatrists should actively enquire about symptoms of constipation in this group of patients and have a lowered threshold for investigation and treatment. A patient receiving clozapine and presenting with vomiting and abdominal pain against a background of constipation should raise immediate concern.

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