Monga V, et al., J Clin Stud Med Case Rep 2015, 2: 020
DOI: 10.24966/CSMC-8801/100020

HSOA Journal of
Clinical Studies and Medical Case Reports

Case Report

Clozapine Induced Ileus - A Case Report

Kellie Nelson, Varun Monga*, Ashish Sharma and Thomas Blunt

Department of Psychiatry, University of Nebraska Medicine Center, Omaha, Nebraska, USA

Abstract

Clozapine is the antipsychotic of choice in treatment resistant schizophrenia due to better efficacy and decreasing the suicide risks in patients. Clozapine induced serious side effects such as neutropenia, agranulocytosis and cardiomyopathy are given high importance but side effects such as bowel obstruction and paralytic ileus are often overlooked. We report a case of clozapine induced ileus.

Introduction

Clozapine is an atypical antipsychotic that has been effective in treatment-resistant schizophrenia, decreasing the suicide risk in schizophrenic disorders and decreasing aggressiveness in psychotic patients [1]. Of particular note, the drug has been associated with low rates of extra pyramidal side effects and a significant decrease of dyskinetic movements in patients with tardive dyskinesia [1]. The drug, however, is often used as a last resort due to a vast array of serious side effects. Bowel obstructions, paralytic ileus, colonic perforations or bowel necrosis are often overlooked side effects that could possibly be fatal [1].

Case Presentation

A 67-year-old Caucasian male presented to the Emergency Department (ED) for abdominal distention and black emesis. The patient had worsening abdominal distension that started a day before his arrival. His last bowel movement was two days before his arrival at the ED. The patient had a known history of schizoaffective disorder, hypertension, Gastroesophageal Reflex Disease (GERD) and constipation. He was being treated daily with 300 mg of clozapine and three doses of valproic acid: 500 mg in the morning, 1000 mg at noon and another 1000 mg at night to control his delusions and mood swings related to his schizoaffective disorder. The patient had been followed by a member of the psychiatric faculty of the institution for six years. The patient, previously, could verbalize that he had been on the clozapine for seven years and endorsed several failed antipsychotic

***Corresponding author:** Varun Monga, Department of Psychiatry, University of Nebraska Medicine Center, Omaha, Nebraska, USA, Tel: +1 4025171315; Fax: +1 4025526247; E-mail: monga.varun81@gmail.com

Citation: Nelson K, Monga V, Sharma A, Blunt T (2015) Clozapine Induced Ileus - A Case Report. J Clin Stud Med Case Rep 2: 020.

Received: April 17, 2015; **Accepted:** July 23, 2015; **Published:** August 06, 2015

During the review of systems, he endorsed vomiting, abdominal pain, constipation and abdominal distension. He additionally denied chest pain, shortness of breath, fevers or chills. When conducting the physical exam, he was found to be tachycardic and had abdominal distension without a palpable mass. He experienced mild tenderness to palpation in the suprapubic area and bilateral lower quadrants. The patient did not exhibit rebound or guarding.

In the ED, a Nasogastric tube (NG tube) was attempted until the patient aspirated gastrointestinal contents and developed respiratory distress, which resulted in emergent intubation for respiratory support as well as further airway protection. A supine abdominal x-ray was taken which showed multiple air-filled dilated loops of large and small bowel throughout abdomen. Additionally, the radiologist did not visualize or identify pneumatosis intestinalis or pneumoperitoneum on the image. The radiologist concluded this was consistent with an adynamic ileus and less likely a distal colonic obstruction. The patient was subsequently admitted to the Intensive Care Unit (ICU) and an NG tube insertion was successfully placed for suctioning purposes and the patient was put on bowel rest. After his admittance to the hospital, the patient would have no further episodes of emesis. When the patient was admitted, he was additionally taken off all his home medications except for his valproic acid. The patient was placed on a bowel medication regimen, which included polyethylene glycol, lactulose and magnesium hydroxide. On the fourth day of his hospitalization, the patient began to have bowel movements again and began to pass flatus. The patient was subsequently extubated on the sixth day of hospitalization and the NG tube was removed but he was continued on bowel rest and relied on total parenteral nutrition of metabolic support. He was also started on quetiapine 50 milligrams, on his sixth day of his hospitalization, to help with management of his schizoaffective disorder. This was due to Naranjo et al., adverse drug reaction score of four [2].

The patient, however, continued to have chronic colonic dilation, despite the passage of bowel movements, as visualized on serial abdominal x-rays, which did not respond to the conservative management. Therefore, on his fourteenth day of hospitalization, the patient received two milligrams of neostigmine intravenously to which he responded appropriately as visualized on subsequent abdominal x-rays with decreased gastrointestinal distension. On the patient's 18th day of hospitalization, he was found to have QT prolongation and thus, the decision to discontinue quetiapine and initiate with aripiprazole five milligrams orally daily was made. The patient was ultimately discharged on hospital day 23, on aripiprazole five milligrams at night and his previous home regimen of valproic acid as detailed above. Since discharge, the patient's aripiprazole has been titrated up over a four month time period to 20 mg daily due to an escalation of grandiose, disruptive behavior.

Discussion

Clozapine is a controversial atypical antipsychotic, which has brought hope to many patients suffering the debilitating effects of treatment resistant schizophrenia. It has been shown to be superior to other antipsychotics for treating positive symptoms of schizophrenia and there is growing evidence that it is more effective

in treating negative symptoms than other first line antipsychotics [1]. However, the severe side effect profile of clozapine limits its use clinically. These side effects limit not only the use but also the rate of dosage increase. Much attention is given to clozapine's serious and potential fatal side effects of agranulocytosis, CNS depression, leukopenia, neutropenia, bone marrow suppression, cardiomyopathy and myocarditis. However, it is also important for physicians to be aware of clozapine's ability to cause gastrointestinal hypomobility that can lead to a paralytic ileus, ischemia or necrosis. In fact, it has recently been implied that fatalities due to constipation and its consequences could be greater than fatalities due to agranulocytosis induced by clozapine [1,3]. Palmer et al., in 2008, estimated the prevalence of clozapine gastrointestinal hypomotility to be 3 in 1,000 patients exposed to clozapine [4]. Additionally, Palmer et al., found a mortality rate of 27.5% among patients who used clozapine and subsequently developed gastrointestinal hypomotility [4].

Clozapine demonstrates high binding affinity for cortical dopamine D_4 receptors as well as significant serotonergic, adrenergic (α_1 and α_2), anti-cholinergic and histaminergic (H_1) antagonism [3]. Clozapine's high affinity for anti-cholinergic and serotonergic receptors is often implicated as the cause of constipation, ileus and ischemia [1]. Acetylcholine acts as an excitatory neurotransmitter on both intestinal smooth muscle cells and the Cajal cells of the intestinal tract [4]. The cajal cells play an integral role in the pacing of the smooth muscle contractions of the intestine [4]. Clozapine's antagonism of acetylcholine receptors inhibits smooth muscle contraction and delays intestinal transit time [4]. Clozapine has a greater potential for ileus and constipation than other anti-cholinergic medications because in addition to its strong anti-cholingeric properties, it also antagonizes serotonin receptors, which are critical to motor and secretory gastrointestinal function. Clozapine antagonizes 5-HT_2, 5-HT_3 and 5-HT_7 [3]. Of particular note, antagonism 5-HT_3 is implicated in slower colon transit time, decreased gastrocolic reflexes, increased colonic compliance and possible reduced intestinal sensitivity to distension [4]. Additionally, the risk of anti-muscarinic and anti-serotonergic side effects increases with clozapine dosage as demonstrated by De Leon et al., who found that plasma clozapine concentrations are good predictors of serum anti-muscarinic activity in patients taking doses of 300 mg/day or higher [5]. The current recommended dosing scheme is initiate the mediation at 12.5 milligrams once or twice daily and to increase as tolerated in increments of 25-50 mg daily to a target dose of 300-450 milligrams daily at the end of two weeks. After reaching this goal, the medication can continue to be titrated in increments less than 100 milligrams once weekly to a maximum total daily dose of 900 milligrams.

Patients with schizophrenia possess several risk factors for developing an ileus. In addition to their typical higher use of antipsychotics and anticholinergic drugs they have the increased likelihood of living a sedentary lifestyle as compared to the general population [1]. Other risk factors for an ileus include older age and female gender [1]. With these risk factors, physicians should initiate prevention of constipation and paralytic ileus in patients who begin taking clozapine. There is no current consensus on an accepted prevention regimen. One of the earlier prevention recommendations by Hayes and Gibler in 1995 offered one of the more comprehensive regimens of a physical and radiographic exam on initiation of clozapine. It included a daily nursing flow sheet on bowel habits and a dietician consult to ensure proper fiber and fluid intake as well as an avoidance of calcium [6]. Additionally, they recommended a slow rate of titration of no more than 25 milligrams a day [6]. More recent publications have encouraged physicians to emphasize exercise, increased fluid intake and higher fiber diets to prevent constipation [1]. For mild to moderate cases of constipation, stool softeners or laxatives should be used, while stimulant cathartics can be used in severe cases [1]. Additionally, there is evidence that orlistat, a natural inhibitor of pancreatic lipases which causes loose stools as a side effect, reduces clozapine associated constipation [1,7]. Despite the positive effects of orlistat, it is important to note that this drug is not FDA approved and is not financially covered by insurance companies.

Conclusion

It is important for physicians to be aware of the possible intestinal side effects that clozapine can directly cause due to it's muscarinic and serotonergic antagonism. Physicians should be proactive at preventing and monitoring possible bowel obstructions along with patient education about nutrition, supplementation and the warning signs of possible bowel obstructions.

References

1. Raja M, Raja S (2014) Clozapine Safety, 40 Years Later. Curr Drug Saf 9: 163-195.
2. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, et al. (1981) A Method for Estimating the Probability of Adverse Drug Reactions. Clin Pharmacol Ther 30: 239-245.
3. De Hert M, Hudyana H, Dockx L, Bernagie C, Sweers K, et al. (2011) Second-generation antipsychotics and constipation: a review of the literature. Eur Psychiatry 26: 33-44.
4. Palmer SE, McLean RM, Ellis PM, Harrison-Woolrych M (2008) Life-threatening clozapine-induced gastrointestinal hypomotility: an analysis of 102 cases. J Clin Psychiatry 69: 759-768.
5. de Leon J, Odom-White A, Josiassen RC, Diaz FJ, Cooper TB, et al. (2003) Serum antimuscarinic activity during clozapine treatment. J of Clin Psychopharmacol 23: 336-341.
6. Hayes G, Gibler B (1995) Clozapine-induced constipation. Am J Psychiatry 152: 298.
7. Kahl KG, Hagenah J, Zapf S, Trillenberg P, Klein C, et al. (2004) Botulinum toxin as an effective treatment of clozapine-induced hypersalivation. Psychopharmacoloy (Berl) 173: 229-230.