CASE REPORT

Clozapine-induced Constipation: A Case Report

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Abstract

Clozapine is an atypical antipsychotic medication, used primarily as the drug of choice in treatment resistant schizophrenic. Despite its considerable advantages, clozapine’s licence is restricted because of its potential to induce agranulocytosis. Hence, white blood cell count monitoring is mandatory in patients receiving clozapine treatment. A side effect of clozapine that has received relatively less attention is constipation, which is caused by the drug’s anticholinergic effect. This potentially serious problem can result in life-threatening bowel obstruction, ischemia, necrosis, perforation, and pulmonary aspiration. Despite this evidence, routine inquiry about constipation in clozapine treated patients is not emphasised in current clinical guidance. We report a case to highlight constipation as both a potentially serious side effect and as a factor, insufficiently recognised, in non-adherence to clozapine.

Keywords: Clozapine, Side Effects, Constipation, Non-adherence

Introduction

Clozapine is a tricyclic dibenzodiazepine derivative classified as an atypical antipsychotic. It is recommended in treatment resistant schizophrenia, defined as a lack of response to at least two antipsychotics after a trial of 6–8 weeks.\textsuperscript{1} Other advantages of the drug include a relatively low risk of extra pyramidal symptoms and an association with significantly reduced suicidal behaviour in patients with schizophrenia.\textsuperscript{2} Despite these added benefits in comparison to other antipsychotics, clozapine’s prescribing licence is restricted because of its potential to induce agranulocytosis. Before clozapine is prescribed, patients must be either refractory to or have experienced intolerable side-effects from at least two different antipsychotics. In addition, white blood cell count monitoring is mandatory in patients receiving clozapine treatment.\textsuperscript{3}

Other than agranulocytosis, important potential side effects of clozapine include seizure, myocarditis, diabetes, weight gain and metabolic syndrome.\textsuperscript{4} A side effect that has received relatively less attention, however, is constipation, which is caused by the anticholinergic effect of clozapine. This potentially serious problem can result in life-
threatening bowel obstruction, ischemia, necrosis, perforation, and pulmonary aspiration.\textsuperscript{5,6} Despite this evidence, routine inquiry about constipation in clozapine treated patients is not emphasised in current clinical guidance.\textsuperscript{3}

Here, we report the case of a patient receiving clozapine for treatment resistant schizophrenia who was persistently non-adherent due to constipation as a side-effect of the drug. We describe the consequent impacts on the course and outcome of the patient’s illness. We discuss the case in light of previous literature on the association between constipation and clozapine and address recommendations for changes in current guidance for clinicians prescribing this medication.

**Case Report**

A 24-year-old female was prescribed clozapine for treatment resistant schizophrenia, after separate trials of three antipsychotics and following a serious suicide attempt at the age of 18.

Premorbidly, the patient reported an unhappy childhood and interpersonal difficulties at school. She had been a quiet person and was socially isolated from peers. Complaints of being talked badly about by peers had apparently led to several transfers of school during her secondary school years. The patient had four inpatient psychiatric admissions in all since being diagnosed at 16 years old.

After commencing clozapine, the daily dose had been gradually titrated up to 250 mg. However the patient was not adherent and reduced the dosage to only 50 mg daily due to the side effect of constipation which she found distressing and unacceptable. She appeared not to have revealed this to the treatment team before experiencing a further relapse resulting in her third hospital admission. During this admission, and after she had revealed the reasons for her non-adherence, the patient was persuaded to take clozapine 50 mg BD which was supplemented with the depot anti-psychotic, flupenthixol 40 mg monthly by intramuscular injection. She had been maintained on this medication regime up to her fourth in-patient psychiatric admission. Besides that, laxatives were also prescribed during follow-ups in the clinic. However, the patient was not committed in taking the laxatives prescribed as she was afraid of the side effects that the medications might cause. During the fourth admission, the patient had residual paranoid delusions besides showing poor insight to her mental illness. However, she had experienced no auditory hallucinations since her previous admission.

In response to further questioning by the first author (TYW), the patient acknowledged that she had again failed to take her oral medication as prescribed in the period prior to her readmission. She revealed that this was because of the persistent problem of constipation. In an effort to minimise the constipation, she admitted that she had omitted the morning dose of clozapine and only took the nighttime dose.

Following this revelation, laxatives were subsequently prescribed again by the treating psychiatrist, and the patient was counselled well on her illness and the importance of taking medications as prescribed to prevent further relapse.

During the subsequent follow-up in the clinic few months later, the treating team decided to withdraw the monthly depot injection and establish the patient on clozapine monotherapy in view of her
improved adherence to clozapine which she was now taking at the prescribed dose of 125 mg daily. The current treatment plan is for a gradual increase in the dose of clozapine in order to achieve the drug’s optimal therapeutic effect on residual symptoms and functioning.

Discussion

We have described the case of a 24-year-old female with treatment resistant schizophrenia, and significant suicidal risk, who was persistently non-adherent to clozapine due to the side effect of constipation.

The patient’s history suggests that even the low dose of clozapine the patient found acceptable, was of some benefit in reducing the frequency of auditory hallucinations. It seems likely, therefore, that her residual paranoid delusions, which were clearly disabling, might have also responded if she had taken clozapine at the prescribed dose. The remediable side effect of constipation, therefore, through its negative impact on adherence, appears to have significantly undermined the potential benefits of the drug in terms of symptoms, functioning and lessening of the future risk of suicide.

The evidence arising from our case supports the previous literature suggesting that constipation associated with clozapine is insufficiently recognized and that screening guidelines should be modified to include routine screening questions regarding constipation in patients considered for or maintained on clozapine therapy.7

In addition, our case prompts consideration of the question of why clozapine associated constipation may be not be adequately recognised? In this, we suggest that both clinician and patient factors may contribute.

From the physician perspective, because of the restriction in the licensing of clozapine, it may be that clinicians are preoccupied with the need for close monitoring of clozapine’s more widely known haematological risks. It may be, also, that many are simply unaware that the frequency of constipation in clozapine treated patients is actually much higher than the frequency of agranulocytosis and the mortality is also higher at 15 %-27.5 %, compared to the mortality rate of 0.1 %-0.3 % for agranulocytosis.7

From the patient perspective a possible factor may be that some patients may not easily report the problem of constipation and be more inclined to attempt to deal with it themselves and without discussion with their prescribing doctor. This, in turn may be related to the personal nature of the side-effect and possible embarrassment associated with raising it with the prescribing physician. Further research could usefully explore these and other possible contributors.

Conclusions

This case highlights how important it is for clinicians to recognise and actively treat clozapine related constipation in order to lessen the risk of non-adherence, and increase the likelihood of exposure to the medication at a therapeutic dose. Hence, it is recommended that constipation be added to the screening guidelines of patients on clozapine therapy in this country. We recommend routine, sensitive questioning regarding (a) whether a patient considered for clozapine treatment has a previous history of chronic constipation and/or (b) is experiencing constipation since commencement of the drug.
References


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