



Case Report

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Prucalopride for the Treatment of Clozapine Induced Constipation: A Case Report



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Abstract

Clozapine is an atypical antipsychotic that is classically used for treatment resistant schizophrenia. Constipation is a commonly occurring side effect of clozapine but little research has been done on it and it is considered to be one that can cause significant distress. It is among the 4 most commonly complained about side effect in clozapine users with prevalence of up to 60%. In severe cases, intestinal obstruction and paralytic ileus can occur and these are potentially life threatening situations with 28 deaths among 102 schizophrenics who had been treated with clozapine being reported. These 2 case studies highlight the gravity of the problem but there is potentially a light at the end of the tunnel with the option of using prucalopride to treat clozapine induced constipation. The constipation did not respond to conventional means of treating it but both responded well to prucalopride regardless of whether it was for a patient who was just introduced to clozapine or if one has been on it for years. Prucalopride could be key to improving the quality of life as well as reducing mortality rates among clozapine patients.

Keywords: Constipation; Clozapine; Prucalopride; Treatment resistant schizophrenia

Introduction

Clozapine is an atypical antipsychotic that is classically used for treatment resistant schizophrenia. Its efficacy in treating treatment resistant patients has been proven [1]. However, Clozapine's remarkable therapeutic value comes at a high price. Many patients develop adverse effects from taking it and some of these effects are intolerable to the point of potential fatalities. Clozapine carries with it black box warnings for agranulocytosis; seizures; myocarditis and cardiomyopathy; other adverse cardiovascular side effects such as orthostatic hypotension, bradycardia and syncope and last but not least an increased mortality in dementia-related psychosis in the elderly. Of the less life threatening complications, constipation is perhaps the one that distressed patients the most. Constipation is a commonly occurring side effect but little research has been done on it [2-4]. It is among the 4 most commonly complained about side effect in clozapine users with prevalence of up to 60% [5-7]. In severe cases, intestinal obstruction and paralytic ileus can occur and these are potentially life threatening situations [6, 8-10]. In fact Palmer et al. [6] had described 28 deaths among 102 schizophrenics who had been treated with clozapine. If death results from clozapine induced constipation, it would be a tragedy as constipation is a condition that clinicians are in position to influence the outcome. According to De Hert et al. [2], mortality due to constipation could be potentially higher than

agranulocytosis and this makes it imperative that death should not be the end result once constipation occurs.

As we all know, constipation impacts significantly on quality of life especially when it becomes chronic making it difficult to treat [11,12]. What are the distressing symptoms of chronic constipation? The classical symptoms are [13]

- a) Straining during bowel movements
- b) Hard or lumpy stools
- c) Stool that cannot be passed
- d) Incomplete emptying during bowel movements
- e) Abdominal fullness or bloating
- f) Manual maneuvers such as digital evacuation being required
- g) Less than 3 bowel movements per week

In some studies, the rates of constipation among younger schizophrenic patients were found to be more than what were seen in the general population [14,15]. A study done to assess the prevalence and severity of constipation in patients on antipsychotics demonstrated that constipation was present in 36.3% of patients and medication was required in most cases

[16]. However, an estimated 50% of chronically constipated individuals are less than satisfied with the usage of laxatives during their attempts to relieve their constipation [11].

Due to the poverty of literature available regarding antipsychotics particularly clozapine induced constipation [16], the following are 2 cases of clozapine induced constipation that never responded to conventional intervention methods but responded to prucalopride with varying degrees of success.

Case Report 1

Miss LPK was a 49 years old Chinese lady who has been under follow-up for chronic schizophrenia for 30 years. She usually presented with distressing auditory hallucinations including commanding ones as well as persecutory and erotomanic delusions. She was never without symptoms despite being compliant to her medication at optimal dosages. She was switched to Olanzapine reaching a dose of 20mg a day. After initial improvement, she subsequently became worse again and had one day started wailing and banging her head on the wall at home in an attempt to get rid of the voices. She was admitted and was started on Clozapine and is now currently stable with only minimal residual symptoms. She also found a part time job in a bakery. Her main problem however, was constipation ever since clozapine was initiated. She only had 2-3 bowel movements per week and felt her abdomen to be bloated and uncomfortable most of the time. Conventional laxatives such as Liquid paraffin and bisacodyl did not influence her constipation in any way. She was initiated on prucalopride 2mg daily and after a month of treatment, her bowel movements had normalized and she had regular and satisfactory bowel evacuations since. The constipation remained regular even after she had stopped prucalopride after a month.

Case Report 2

Madam RJP was a 61 years old Indian lady with background history of undiagnosed schizophrenia for years as a result of her constant travels around the world. She had followed her then husband to Europe, Casablanca and the United States and finally returning home to Malaysia after she had a divorce. By then, she was already suffering from schizophrenia for years that was unrecognized and hence undiagnosed as her husband was never around much due to his work commitments. By the time she presented to psychiatric services, she was floridly psychotic with bizarre delusions such as having diamonds deposited in her rectum after Hitler had sodomized her. She was started on Risperidone 2mgbd and she gradually improved and regained a sense of normalcy. However, she started deteriorating after a year despite compliance to treatment and subsequently defaulting her medication after she became psychotic once more requiring admission again. She was stabilized with Olanzapine 15mg daily and was discharged well. Unfortunately, she became ill again after a year of treatment despite compliance to medication that was supervised by her sister. She was tried

on other medications and failed to respond to any of them and she remained psychotic. She was then started on clozapine that was titrated gradually up to 300mg daily and she went into remission. She was discharged well and started a part time job giving English tuition at home. She had constipation with clozapine for many years and even though Liquid Paraffin helped to ease her constipation minimally, she felt embarrassed by the staining of her clothes due to it. Other laxatives were not effective at all. By the time prucalopride became available locally, she has had constipation for many years manifesting as less than 2 bowel movements per week and each movement produced small quantities of hardened stools. She was started on 2mg daily of prucalopride and had shown favourable response to it. Her bowel frequency had increased to 4-5 times per week and the quantity and consistency of her stools were satisfactory as well. However, she required a maintenance dose of 1mg daily as she had tried stopping before and the constipation returned.

Conclusion

From the success experienced by the 2 patients in easing some of their troubles in an already troubled existence, there is at least hope that clozapine that is supposed to help them overcome their plethora of psychotic symptoms can be better tolerated in terms of constipation. It also appeared that prucalopride not only addresses constipation in newly treated clozapine patients as highlighted by the first case report, it also helps with patients who have had constipation after many years of clozapine exposure as per the second case. These 2 cases also provided vital information that treating clozapine induced constipation early and aggressively could influence the quality of life of a patient. How prucalopride works to relieve clozapine induced constipation is unknown since it is caused by blockade of Muscarinic 1 receptors and prucalopride works by specific activation of 5-HT₄ receptors by interacting with them in the gastrointestinal tract that results in acetylcholine release from enteric cholinergic neurons [17]. However, because of the enhanced gastrointestinal motility and mucosal secretion, this could be the mechanism that is responsible for ameliorating the constipation by stimulating the contraction of longitudinal muscles in the colon, leading to propulsion of the luminal contents.

There is a sizable literature on prucalopride in chronic constipation. Its efficacy in chronic constipation was never in doubt and has been demonstrated in a number of randomized, placebo-controlled trials, though not in clozapine-induced constipation. In addition, Prucalopride also has a favorable safety profile and has no apparent cardiac adverse effects such as QT interval prolongation [18,19].

It remains to be seen whether prucalopride will be effective for all patients with clozapine induced constipation but this discovery may open doors to look further into this distressing event for treatment resistant schizophrenics.

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