Clozapine and Constipation

Subjects: Others

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Clozapine is a highly protein-bound drug that is metabolized to norclozapine (desmethylclozapine) and other metabolites by the cytochrome P450 enzymes CYP1A2, CYP3A4, CYP2C19, and also with some effect from the enzymes CYP2C9 and CYP2D6. Each enzyme is more effective at different clozapine concentrations and has its own set of inducers and inhibitors, which makes plasma level monitoring and dose adjustments crucial in maintaining the drug's therapeutic value. Studies investigating the pharmacokinetic parameters of clozapine in patients with schizophrenia also echo this need for monitoring, as clozapine was shown to have a "wide interpatient variability" in the time it takes to reach peak plasma concentrations (1.1 to 3.6 h), elimination half-life (9.1 to 17.4 h), clearance (8.7 to 53.3 L/h), and volume of distribution (1.6 to 7.3 L/kg).

Keywords: clozapine ; treatment-resistant schizophrenia ; adverse effects ; constipation

1. Introduction

Schizophrenia is a complex disorder that leaves many patients debilitated and unable to function well in society without successful treatment. The majority of patients today respond well to typical or atypical antipsychotics, but approximately one-third of patients are considered treatment-resistant [1]. It is theorized that schizophrenia can be distinguished by subtypes, which might link differences in response to treatment with antipsychotics to certain genetic markers [2].

This response may indicate that treatment-resistant schizophrenia symptoms are driven by non-dopaminergic abnormalities [1]. A 2014 study using positron emission tomography (PET) scans found that individuals with treatment-resistant schizophrenia had no increased capacity for dopamine synthesis after antipsychotic treatment compared to those with disease responsive to antipsychotic treatment [3]. In a separate proton magnetic resonance spectroscopy study, it was also found that in patients with persistent psychosis, despite antipsychotic treatment, there were elevated glutamate levels in the anterior cingulate cortex compared to those who responded to antipsychotic treatment [3].

Similar to other second-generation antipsychotics, clozapine exhibits a greater ability to block serotonin 5-HT2A receptors than dopamine D2 receptors [4]. However, unlike some second-generation medications such as risperidone, clozapine weakly inhibits dopamine binding at D2 receptors and has a ten times greater affinity for the D4 receptors [4][5]. These binding properties of clozapine contribute to a lower incidence of extrapyramidal symptoms and a reduction of negative symptoms [5].

Studies investigating the pharmacokinetic parameters of clozapine in patients with schizophrenia also echo this need for monitoring, as clozapine was shown to have a "wide interpatient variability" in the time it takes to reach peak plasma concentrations (1.1 to 3.6 h), elimination half-life (9.1 to 17.4 h), clearance (8.7 to 53.3 L/h), and volume of distribution (1.6 to 7.3 L/kg) [6]. Moreover, clozapine exhibits a dose- and time-dependent effect on lowering the seizure threshold, and when compared to first-generation medications, it has a minimal or transient impact on increasing serum prolactin levels [6][7].

2. Clozapine Side Effects and Black Box Warnings

A study that investigated the prevalence of constipation in patients taking clozapine found a significant trend in the Bristol Stool Form and Constipation Assessment Scale (an increase in severity of constipation) with the use of clozapine. A positive correlation was found between the development of constipation with age, duration of treatment, and duration of illness [8]. The researchers found a higher incidence rate of constipation in clozapine patients, but this could be related to the fact that constipation was being directly investigated compared to previous studies that had been done. Further, patients in this study who received clozapine as a treatment were four times more likely to develop constipation [8]. Not

only was the prevalence in the clozapine group higher than the control (a group on a different antipsychotic medication), but they also had a higher severity of constipation. Additionally, the patients with constipation needed pharmacological intervention related to severity.

Additional research in Japan, where the use of clozapine was delayed related to apprehension of agranulocytosis development, showed that patients treated over a 12-week period had a highly significant improvement of their baseline Positive and Negative Syndrome Scale (PANSS) total score [9]. More specifically, patients' PANSS positive, negative, and general subscale scores improved. During this study, one patient developed ileus, and, in addition to two other patients that dropped out, they all recovered in three days after proper treatment. Constipation, along with other adverse effects such as insomnia, nausea/vomiting, and hypersalivation, were observed in 30% of the participants in this trial [9]. This is a significant number of participants, which provides sufficient reasoning to monitor constipation in patients on clozapine as a serious and life-threatening side effect if not caught early. This study shows the efficacy of the use of clozapine in treatment-resistant schizophrenia, and the importance of monitoring side effects, especially constipation.

A cohort study, in Iceland, was done on patients diagnosed with schizophrenia and using clozapine for therapy to determine the prevalence of constipation and development of ileus in these patients. The results of the study found that there was a higher prevalence of constipation in schizophrenic patients on clozapine than what had been previously stated [10]. This discrepancy could be due to the length of study time, detection bias, or differences in diet and lifestyle in other studies that took place. The researchers recommended that the physicians increase their screening of constipation in patients taking clozapine in order to take appropriate action to reduce the risk of developing ileus. Monitoring should also be increased with patients on additional medications that can cause constipation, such as anticholinergics, opioids, and tricyclic antidepressants [10]. With the patients on clozapine plus the additionally previously stated drugs that reduce bowel movement, only half were receiving laxatives, while only 15.6% of those only on clozapine were given laxatives [10]. This data shows that the underuse of laxatives during clozapine treatment can lead to constipation, ileus, or discontinuation of the drug [10]. The researchers were also able to conclude based on their data that the prevalence of ileus is higher than that of agranulocytosis, which is typically monitored when compared to larger studies [10]. This further provides evidence that constipation should be on a physician's radar when treating a patient with clozapine.

Gastrointestinal hypomotility was further researched in a cross-sectional study with patients taking clozapine. The study found that gastrointestinal hypomotility is a highly significant problem in any patient taking clozapine with no regard to dose, gender, or treatment duration [11]. With that being said, in a previously mentioned study, a positive correlation was found between the development of constipation and age, duration of treatment, and duration of illness [8]. In this study, it was found that patients taking clozapine had a median colonic transit time of 104.5 h compared to the 23 h of the control group [11]. These results confirm that clozapine has a serious effect on gastrointestinal motility and bowel function. In order to better monitor the development of constipation, research has been done on different types of screenings for constipation. In one such study, a means to objectively identify and question whether or not a patient taking clozapine is affected by constipation was investigated. To develop an accurate and objective screening for constipation, the researchers decided to compare the sensitivity, specificity, and positive and negative predictive values of the patient-reported constipation (PRC) method and screening for Rome criteria—the standard for assessing constipation symptoms. Both the PRC method and Rome criteria screening were conducted by trained nurses. In order to determine the accuracy of each screening method, tests were done using a standardized radiopaque marker and wireless motility capsule to determine if the patient truly suffered from constipation. The results of the study showed that both screening methods had low sensitivity and therefore were not helpful in evaluating constipation symptoms [12]. Despite the low sensitivity of the screenings, patients on clozapine should still be monitored for constipation due to the severity of mortality and morbidity of the clozapine-induced gastrointestinal hypomobility [12].

3. Conclusions

Schizophrenia is a chronic disease requiring treatment to prevent disability and improve the lives of patients who suffer from this disorder. Antipsychotics are the mainstay of treatment, however, there is still a subsection of patients that may be seen as treatment-resistant. Clozapine has been seen as a good alternative for those who have failed treatment with other antipsychotics. This could be due to the fact that clozapine works on not just the dopamine system like first-generation antipsychotics, and not just the dopamine and serotonin dopamine system like second-generation antipsychotics. Indeed, clozapine also works on the glutamate system which could be the reason why it works better for those who are treatment-resistant; however, it also has anticholinergic properties which makes constipation a complication. Studies have shown that constipation is not a complication to be taken lightly, as it can cause an ileus and intestinal blockage leading to rupture and death. This complication has been shown in studies to be due to gastrointestinal

hypomobility. Although patients are screened by their physicians for agranulocytosis by weekly lab monitoring, constipation is also a complication that needs to be considered. Much like opioid-induced constipation, this complication can be reduced with the use of laxatives and reduction in the co-prescribing of anticholinergic therapies with clozapine.

Patients who have schizophrenia depend on the treatment of their psychotic symptoms to live as normal a life as possible. Both agranulocytosis and constipation are limiting side effects. The difference is that one is regularly screened for while the other may not be screened for by clinicians. It is important for clinicians to both recognize and treat/ prevent constipation, as treatment options may be limited for those who have failed treatment with other antipsychotics.

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