Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i4.5776

CLOZAPINE INDUCED BLOOD DYSCRASIA IN PAKISTAN: A RETROSPECTIVE STUDY

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Abstract

Background: Clozapine is atypical antipsychotic particularly good at reducing the symptoms of schizophrenia, such as delusions and apathy. Despite being highly effective, the use of clozapine is limited due to the risk of blood disorders, known as blood dyscrasias. The objectives of the study were to determine how frequently clozapine-induced blood dyscrasia occur within study population, & outcomes associated with clozapine induced blood dyscrasia.

Methods: Medical data of patients was retrospectively reviewed in mentioned time period. Before data collection, ethical approval was taken from Ethical Review Committee. The study excluded all OPD patients. Data collection was done using a pre-tested questionnaire that was adapted from a previous study. The sampling technique was non-probability convenience. The data was complied with proper coding in Microsoft Excel and then further analyzed in Statistical Package for Social Sciences for Windows (SPSS) version 29

Results: A total of 86 patients files were reviewed who were taking clozapine with or without other medicines. During the study period 23 patients (27%) developed blood dyscrasia. Out of which 64% were females. Majority of dyscrasia events happened in first three months (58%), followed by six months (31%), nine months (10%) and twelve months (1%). Among patients who developed blood dyscrasia most of the patients were diagnosed with with Scizophrenia and Bipolar Affective Disorder BAD (n =18, 67 %) followed by schizophrenia alone, BAD alone, drug induced psychosis, and schizophrenia plus agoraphobia. Out of 23 patients who developed blood dyscrasia 78% (n=18) patients were prescribed other medicines concomitantly with clozapine. The most commonly used drug was risperidone. Patients were also using valproate, and amlodipine/valsartan for the treatment of Epilepsy and Hypertension respectively. Majority (70%) adverse events were agranulocytosis.

Conclusion: Study emphasizes the critical need for diligent monitoring, especially in the early phases of clozapine treatment. Further research is needed to explore determinants for incidence and

strategies for reducing the incidence of blood dyscrasia in patients taking clozapine. Future research should aim to identify predictive markers for these adverse effects to enhance patient safety and treatment efficacy.

KEY WORDS: Clozapine, Blood Dyscrasia, Adverse Events, Agranulocytosis, Schizophrenia

INTRODUCTION

Clozapine was first discovered in 1958 and became the initial drug of its kind—known as an atypical antipsychotic—introduced for clinical use in Europe in 1971. Its use was stopped abruptly in 1975 because it was linked to severe blood disorders that caused deaths in some patients in Finland.[1] After a critical study in 1988 showed that clozapine was very effective for patients with schizophrenia who did not respond to other treatments, it was reintroduced in 1989. However, this time, strict blood testing was required to monitor for safety.[2]

Despite being highly effective, the use of clozapine is limited due to the risk of blood disorders, known as blood dyscrasias. Regular blood tests are necessary to safely use clozapine because of these risks.[3,4,5,6] Clozapine is particularly good at reducing the symptoms of schizophrenia, such as delusions and apathy. It also helps prevent suicidal thoughts, causes fewer movement-related side effects (Extrapyramidal Symptoms-EPS) than other antipsychotics, and does not increase a hormone called prolactin, which can cause other side effects.[7,8,9]

Blood disorders associated with clozapine, like agranulocytosis (a severe decrease in white blood cells) and neutropenia (a decrease in a specific type of white blood cell), are well-documented.[10,11,12] There are three levels of severity: mild leukopenia, where white blood cell counts drop slightly to less than 3.06109 per liter but neutrophil counts are normal, occurs in 0.19% of patients; moderate neutropenia, where neutrophil counts drop to between 0.56 x 10^9 and 1.56109 per liter, occurs in 1.5-2.9% of patients and typically recovers quickly (2-8 days) when clozapine is stopped; severe neutropenia or agranulocytosis, where neutrophil counts are below 0.56109 per liter, occurs in 0.78% of patients and usually lasts 14-21 days.[13,14,15,16,17]

The risk of developing these severe conditions is highest during the first 18 weeks of treatment and significantly decreases after one year, with the risk of agranulocytosis dropping to 0.07% in the second year.[13]

Research also shows that Asian individuals face a 2.4 times higher risk of developing agranulocytosis compared to White individuals. This indicates a need for careful monitoring and possibly different treatment strategies for different ethnic groups to safely use clozapine[16] and dispensation of medicine with prescription only.[18]

The rationale for studying "Clozapine Induced Blood Dyscrasia" is rooted in the necessity to monitor the severe side effects associated with clozapine. Understanding the incidence, severity, and contributing factors to these adverse effects is critical for enhancing patient safety and optimizing therapeutic outcomes.

The significance of this research lies in its potential to improve public health outcomes. Clozapine, despite its risks, is a pivotal treatment option for patients who do not respond to other antipsychotic medications. By identifying risk factors and frequency of blood dyscrasias associated with its use, the study can inform clinical guidelines and monitoring protocols. This could lead to reduced rates of hospitalization and mortality among patients taking clozapine, thereby enhancing both the safety and efficacy of treatment regimes.

The objectives of the study were to determine how frequently clozapine-induced blood dyscrasia occur within study population, as well as the patient characteristics and outcomes associated with clozapine induced blood dyscrasia.

METHODS

This study was conducted from January 2022 to March 2023 in public psychiatric hospital. Medical data of patients was retrospectively reviewed in mentioned time period. Before data collection, ethical approval was taken from Ethical Review Committee. The study excluded all OPD patients.

As this type of study was not done in proposed population so we assumed a prevalence of 12.5% and a margin of error of 5%, resulting in a sample size of 86 patients who are taking clozapine. The sample size was calculated by using Cochrane's formula.[19]
Data collection was done using a pre-tested questionnaire that was adapted from a previous study.[20] The sampling technique was non-probability convenience. The data was complied with proper coding in Microsoft Excel and then further analyzed in Statistical Package for Social Sciences for Windows (SPSS) version 29.

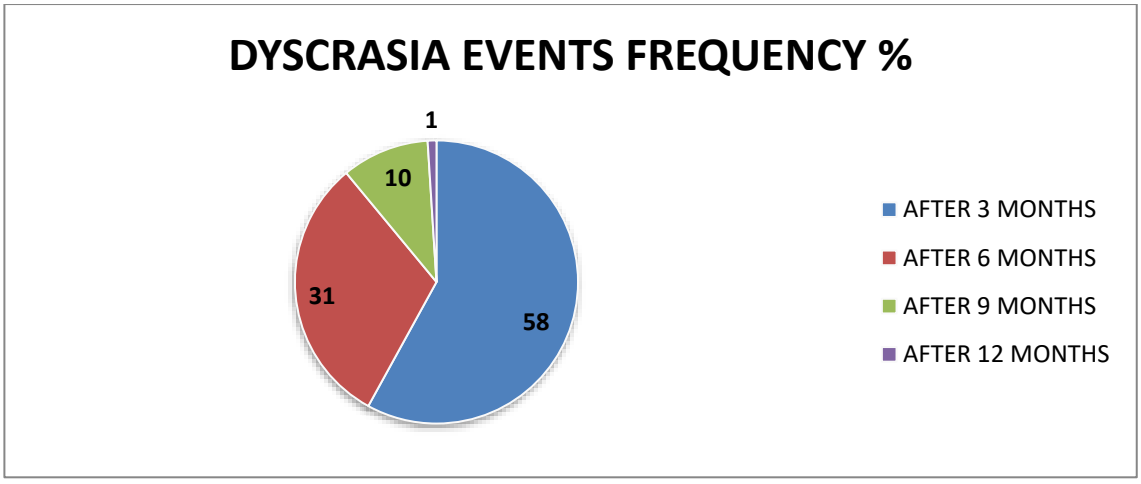
RESULTS:
A total of 86 patients files were reviewed who were taking clozapine with or without other medicines. Out of 86, we got no refusal, resulting in a refusal rate of 0% or a response rate of 100%. Patient gender characteristics show that 87% (n=75) were male and 13% (n=11) were females. Mean age of patients was 35, with the standard deviation of 1.92, indicating minimal variation in age.
The following table (Table 1) indicates response rate and demographic characteristics

Table-1 Response rate and demographic characteristics

CHARACTERISTICS	VARIABLES	PERCENTAGE
Response Rate	Response	100%
	Refusal	0%
Gender	Male	87%
	Female	13%

	N	MEAN AGE±SD
Age	86	35±1.92

During the study period 23 patients (27%) developed blood dyscrasia. Out of which 7 (64%) were females and 16 were male (18%). Thus female patients were in majority among them who developed blood dyscrasia. The mean age of patients developing blood dyscrasia was 38. The mean age of patients who did not develop blood dyscrasias was 31.
As for as the duration of events is concerned, majority of dyscrasia events happened in first three months (58%), followed by six months (31%), nine months (10%) and twelve months (1%).



Among patients who developed blood dyscrasia most of the patients were diagnosed with with Scizophrenia and Bipolar Affective Disorder BAD (n =18, 67 %) followed by schizophrenia alone,

BAD alone, drug induced psychosis, and schizophrenia plus agoraphobia. The following table (Table 2) indicates diagnosis wise dyscrasia.

Table-2 Diagnosis wise events

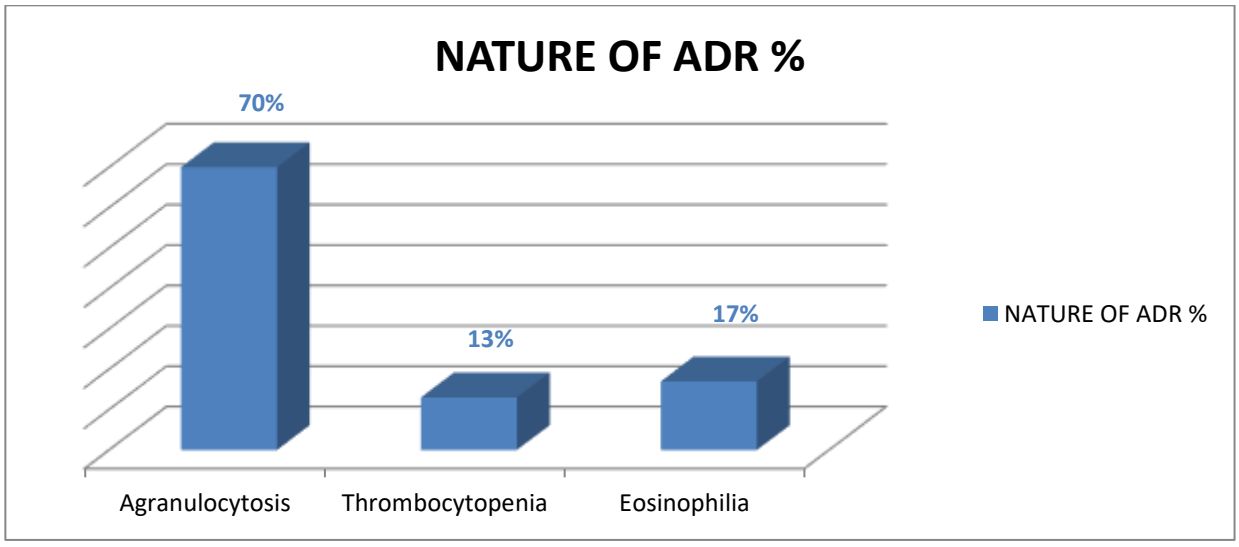
DIAGNOSIS	NUMBER	PERCENTAGE
Schizophrenia plus BAD	15	65%
Schizophrenia	4	17%
BAD	2	9%
Drug Induced Psychosis	1	4.5%
Schizophrenia plus Agoraphobia	1	4.5%

Out of 23 patients who developed blood dyscrasia 78% (n=18) patients were prescribed other medicines concomitantly with clozapine. The most commonly used drug was risperidone. Patients were also using valproate, and amlodipine/valsartan for the treatment of Epilepsy and Hypertension respectively. The following table (Table 3) indicates concomitant administration of medicines.

Table-3 Concomitant Administration of Medicines

MEDICINE	NUMBER	PERCENTAGE
Risperidone	9	39%
Estezine	5	22.5%
Olanzapine	4	17%
Valproate	4	17%
Amlodipine	1	4.5%

A total of 16 patients (70%) developed agranulocytosis, neutropenia and leukopenia combined. The mean age of patients developing such an event was 35 years. Severe agranulocytosis developed in three patients; two of them after 1 month of clozapine therapy which led to clozapine dis continuation in one patient, one patient after 1 years. Fortunately, there were no reported deaths among patients due to clozapine induced agranulocytosis, neutropenia or leukopenia.
Only three (13%) patients developed thrombocytopenia, with a mean age of 36 years, two of the three patients were females.
Eosinophilia developed in four patients (17%). The mean age of these patients was 35 years. Males were in majority (three male and one female) who developed eosinophilia.



DISCUSSION

The results of this study provide a comprehensive overview of the demographics, incidence, and outcomes of blood dyscrasias among patients treated with clozapine, either alone or in combination

with other medications. Notably, the 100% response rate in our study ensured a robust dataset, devoid of potential biases associated with non-response.

The gender distribution in our study population consisted of females (13%), reflecting similar trends observed in the wider literature concerning schizophrenia and Bipolar Affective Disorder (BAD), where a higher prevalence among females is often reported.[21]

Despite the predominance of males (87%) in the overall study population, females represented a disproportionately high percentage of those who developed blood dyscrasias, which aligns with the finding of a systematic review conducted in 2019. [22] Overall, this finding suggests a potential gender-specific vulnerability to this side effect of clozapine treatment, which warrants further investigation.

The age analysis indicated a slight increase in the mean age of patients who developed blood dyscrasias (38 years) compared to those who did not (31 years). This age-related disparity suggests that older patients might be at a higher risk, which could guide clinicians in monitoring and management strategies.

A significant finding from our study was the high incidence of blood dyscrasias occurring within the first three months of therapy (58%), indicating the critical need for vigilant monitoring during this period. This early onset of blood dyscrasias aligns with existing recommendations for frequent blood monitoring in the initial stages of clozapine therapy. These findings are in contrast with the similar study conducted in Saudi Arabia.[20]

Regarding the types of psychiatric diagnoses associated with the development of blood dyscrasias, patients diagnosed with both Schizophrenia and BAD were most affected. This might suggest higher baseline vulnerability or an interaction effect between these conditions and clozapine's hematologic side effects. These findings align with the similar study conducted in Saudi Arabia.[20]

Concomitant medication use was prevalent among patients who developed blood dyscrasias, with risperidone being the most commonly used drug. This highlights the complexity of treating patients with multiple medications, which may contribute to or exacerbate side effects such as blood dyscrasias. Therefore, careful consideration must be given to the drug-drug interactions and cumulative side effect profiles in such patients. In contrast, a study published in 1996, shows risperidone is very safe drug to be prescribed in patients with clozapine induced blood dyscrasia.[23]

The specific hematological adverse effects observed, such as agranulocytosis, neutropenia, and leukopenia, predominantly occurred in 70% of the cases, with a severe form of agranulocytosis prompting discontinuation of clozapine in some cases. These findings underscore the severity of clozapine-induced hematological side effects, despite their well-documented efficacy in treating resistant schizophrenia and BAD.

Interestingly, thrombocytopenia and eosinophilia were less common but still significant, affecting 13% and 17% of the patients, respectively. The presence of these conditions further complicates the clinical management of patients under clozapine therapy, necessitating a comprehensive approach to monitoring and intervention. These findings align with the similar study conducted in 2020.[20]

Implications of the study includes thee 100% response rate suggests high cooperation enhancing the reliability of the findings, and gender wise (females are more prone) potential of clozapine induced blood dyscrasia. The temporal distribution of dyscrasia events underscores the importance of monitoring patients, especially during the initial months of treatment, and suggests a potential window for intensified surveillance. The predominance of certain diagnoses among patients developing blood dyscrasias suggests a possible association between specific mental health conditions and susceptibility to adverse effects of clozapine.

Limitations of the study includes the relatively small sample size of 86 patients limits the generalizability of findings and may not fully capture rare adverse events. The retrospective nature of the study may introduce bias or missing data, affecting the accuracy and reliability of the results. While the study identifies concomitant medications, it does not explore their potential interaction effects or dosage variations, which could influence the occurrence of adverse events. The absence of reported deaths due to clozapine-induced adverse effects may be subject to underreporting or incomplete data, potentially underestimating the severity of such events. Lastly, the dose specific

blood dyscrasia is not researched in this study, which opens the avenue for researchers to conduct the same in future.

CONCLUSION

Study emphasizes the critical need for diligent monitoring, especially in the early phases of clozapine treatment. Further research is needed to explore determinants for incidence and strategies for reducing the incidence of blood dyscrasia in patients taking clozapine. Future research should aim to identify predictive markers for these adverse effects to enhance patient safety and treatment efficacy.

Funding source:
Authors received no extramural funding for this research

Conflict of interest:
Nothing to declare.

Patient written informed consent for publication:
Not applicable

Ethical approval:
It was taken from the hospital review committee.

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