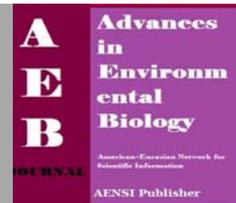




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Evaluating Complete Blood Count Alterations in Patients Treated with Clozapine in Psychiatric Hospitals of Shiraz

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ABSTRACT

Background: Clozapine is a complex psychopharmacological drug with two main side effects; agranulocytosis and seizure. We aimed to assess the CBC alterations in patients being treated with clozapine at psychiatric hospitals of Shiraz, southern Iran. **Methods:** This retrospective study was done for the first time at Hafez, Ibn-e-Sina, and Professor Mohareri Hospitals, Shiraz, southern Iran. The medical records of 192 admitted patients including data regarding the patients' age, sex, educational status, marital status, diagnosis, and complete blood counts (CBCs) before drug prescription were analyzed. CBCs were checked weekly for six months at the centers laboratory after clozapine administration. The incidence of blood complications related to clozapine including granulocytopenia (neutropenia and agranulocytosis) and leukopenia were evaluated. Moreover, the relationship between the patients' age and sex and the prevalence of these complications was assessed. **Results:** 3.12%, 2.6%, and 0.52% of the patients experienced neutropenia, leukopenia, and agranulocytosis with no mortalities. The prevalence of granulocytosis was similar in both sexes and significantly higher in the 36-40 year-old age group ($P < 0.019$). **Conclusion:** The prevalence of neutropenia and agranulocytosis in the studied population conformed to that of other similar studies. The frequent monitoring of blood indices in patients under treatment with clozapine reduces their risk of developing agranulocytosis.

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INTRODUCTION

Psychiatric and mental disorders are among the main causes of occupational disability, academic failure, family conflicts and divorce, incorrect personal and social relations, and addiction. Many of these social problems can be prevented through the timely diagnosis and treatment of mental disorders. Studies have shown that 10-20% of the population in different societies suffer from a type of mental disorder. About 1% of the population of all societies suffers from schizophrenia. In Iran, 700 000 people have schizophrenia, of which only 150 thousands receive adequate treatment [1]. Addiction is a psychiatric disorder that leads to other mental disorders so that about 70-90% of addicts simultaneously suffer from other mental disorders such as depression and anxiety [1]. Schizophrenia is a psychotic disorder with unknown etiology and different manifestations. Although schizophrenia is not a cognitive disorder, it leads to cognitive complications in objective thinking and data processing. The signs of schizophrenia have a negative effect on the individual's thinking, emotions, behavior, and social and occupational performances. This illness is usually chronic with prodromal, active, and residual stages. The prodromal and residual types present with mild active symptoms such as strange beliefs and thoughts, inefficiency in caring of one's self, and problems in interpersonal relationships [2].

Recently, a new generation of antipsychotic drug named dopamine and serotonin antagonists has entered the market. These drugs have been effective on the positive and negative symptoms of schizophrenia and cause fewer side effects. Since these drugs are known as the most important selective drugs for treating schizophrenia they are named as second generation drugs [3]. The first known drug from this group is clozapine [3]. In 1975, clozapine entered Finland and following reports about clozapine-induced agranulocytosis and related mortality and morbidity in Finland and other countries, it was collected from the market [4]. Since then however, clozapine has been used widely among patients, not only reduces their positive symptoms, but also effects the

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negative symptoms of their illness and improve late onset dyskinesia which might be due to the drug's effect on serotonin receptors [5]. Clozapine has a high tendency towards receptor 5-HT₂ and less tendency towards receptor d₂ [6]. In patients with schizophrenia, clozapine reduces aggressiveness, suicide, and drug abuse. Moreover, it improves symptoms in schizoaffective patients and patients with psychotic depression, obsession, borderline personality disorder, and mood disorders who are resistant to treatment as well as patients with neurological illness such as Parkinson's disease [3].

Among new generation drugs, clozapine has the highest treatment effect but with serious hematologic side effects [5]. Agranulocytosis and seizure are two serious side effects of Clozapine that limit its use as the first line of treatment [7]. Agranulocytosis is a serious and potent consequence of using neuroleptics and has been reported in 1-2% of patients treated with clozapine compared with 0.04-0.5% for standard neuroleptics [8]. In recent years, the prevalence of agranulocytosis has been reduced with frequent blood tests [9]. Considering the latest declaration of the Food and Drug Association of America, WBC as well as neutrophil counts should be monitored before and during therapy with Clozapine [1]. The better understanding of mental disorders in recent years has increased the use of specialized psychotropic drugs that affect the mood, anxiety level, and sleep [10]. Therefore, these drugs and their possible side effects should be further studied and psychiatrists have always prescribed them with caution. Since Clozapine has specific effects on the number of blood cells, we aimed to assess the CBC alterations in patients being treated with clozapine at psychiatric hospitals of Shiraz, southern Iran.

MATERIALS AND METHODS

This retrospective study was done for the first time at Hafez, Ibn-e-Sina, and Professor Moharreri Hospitals, Shiraz, southern Iran. The medical records of 192 admitted patients on Clozapine including data regarding the patients' age, sex, educational status, marital status, diagnosis, CBC before drug prescription, and CBCs were evaluated weekly for six months at the centers of laboratory were analyzed. The incidence of blood complications related to Clozapine including granulocytopenia (neutropenia and agranulocytosis) and leukopenia were evaluated. Moreover, the relationship between the patients' age and sex and the prevalence of these complications were assessed.

The calculated sample size that was expected for neutropenia and agranulocytosis was 156 patients under treatment with clozapine ($\alpha=0.05$, 2.5% accuracy). With respect to the longitudinal nature of the study and the drop out possibility during the follow-up period, a sample size of 192 patients was considered. After collecting and evaluating the patients' data, the frequency and percentage of the patients was assessed based on sex, weekly CBCs, and age groups and diagnosis considering sex. SPSS software, version 11.5, was used for data analysis. Chi-square test and Pearson's correlation coefficients were used as appropriated.

RESULT AND DISCUSSION

Results:

Of the 192 patients, 130 (67.7%) were men and 62 (32.3%) were women with a mean age of 31.6 years (range: 16-60 years) and notably 54 patients in the range of age 31-35 years used Clozapine frequently. Table 1 shows the frequency distribution of the patients according to age groups and sex. Most patients (82.8%) suffered from schizophrenia. Other diagnoses were as follows: bipolar disorder (7.8%), severe psychotic depression (6.3%), obsessive compulsive disorder (2.1%), severe Tardive dyskinesia (0.5%), and Parkinson's disease (0.5%). The frequency distribution of different complications based on the patients' sex is shown in table 2.

7 people experienced granulocytopenia and clozapine was discontinued for them. We did not find any significant difference between the men and women with respect to the prevalence of granulocytopenia or leukopenia ($P>0.05$). We found that no patient experienced granulocytopenia within the first 6 weeks, while 3 (43%) experienced granulocytopenia within the second and third six weeks, and only 1 (14%) patient experienced this side effect in the fourth six weeks of receiving clozapine ($P>0.05$).

Discussion:

67.7% of the men and 32.3% of the women used clozapine in this study. It seems that the reason for this increased percentage in men is the higher rate of resistance to other types of antipsychotics treatment among men with schizophrenia. Moreover, the prognosis of this disease is better in women than men and women need to use clozapine less than men. Patients who were 31-35 years old used clozapine more frequently and considering that the peak age for schizophrenia is around 25, we can conclude that they had had this disorder for a long time and since they were resistance to or could not tolerate other drugs, clozapine was prescribed for them.

Studies have shown that the serum of patients with clozapine-induced agranulocytosis is toxic for the multi-lobed leukocytes of healthy individuals [11]. Besides reducing WBC and neutrophils leading to agranulocytosis in 1-2% patients, clozapine does not have any other potent or permanent side effects. Studies have shown that the administration of clozapine should be discontinued if $WBC < 2000 \text{ mm}^2$ and granulocytes are less than 1000 mm^2 , and the patient should never receive clozapine thereafter. Moreover, the patient's CBC should be checked for 4 weeks after discontinuing clozapine [12]. However, if CBC is controlled, clozapine potent side effects would decrease. Women are more at risk of clozapine-induced agranulocytosis [12]. The prevalence of neutropenia, agranulocytosis, and leukopenia has been reported to be approximately the same and no significant difference was seen between these complications and sex [12].

It has been found that age is one of the risk factors for agranulocytosis (8). We found that 36-40 year-olds had the highest prevalence of granulocytopenia and hence it is important for psychiatrists to consider this when prescribing clozapine for patients in this age range compared with other age groups. Considering the positive and effective effects of clozapine for psychosis, prescribing this drug along with continuous CBC monitoring could be safe, especially for the first six months of treatment. Previous studies have shown that agranulocytosis is a dangerous complication of treatment with clozapine and could occur at any stage of treatment [12, 13]. Although the risk of agranulocytosis is higher during the first three months of treatment, the risk still exists in the first year of treatment. After one year treatment with clozapine the prevalence of agranulocytosis reduces to about 0.8% [14]. Therefore, weekly CBC monitoring can control this complication.

Table 1: Frequency and percentage of men and women in different age groups

Age groups	Men (n=130)		Women (n=62)		Total	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
16- 20	10	7.69	4	6.45	14	7.29
21- 25	27	20.76	9	14.52	36	18.75
26- 30	31	23.84	13	20.96	44	22.92
31- 35	35	26.93	19	30.64	54	28.12
36- 40	10	7.69	8	12.9	18	9.37
41- 45	9	6.93	2	3.23	11	5.73
46- 50	4	3.08	2	3.23	6	3.13
> 50	4	3.08	5	8.06	9	4.69

Table 2: Frequency distribution of the patients based on their diagnosis

Complication	Men		Women		Total	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Schizophrenia	116	89.23	43	69.3	159	82.8
Bipolar disorders	5	3.84	10	16.2	15	7.8
Severe psychotic depression	5	3.84	7	11.3	12	6.3
Obsessive compulsive disorder	2	1.54	2	3.2	4	2.1
Severe Tardive dyskinesia	1	0.77	0	0	1	0.5
Parkinson's disease	1	0.77	0	0	1	0.5

Table 3: Prevalence of granulocytopenia and leukopenia among the patients according to sex

Side effect	Men		Women		Total	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Neutropenia	4	3.07	2	3.22	6	3.12
Agranulocytosis	0	0	1	1.61	1	0.52
granulocytopenia	4	3.07	3	4.83	7	3.64
Leukopenia	3	2.3	2	3.22	5	2.6

Conclusion:

The frequent monitoring of blood indices in patients under treatment with clozapine reduces their risk of developing agranulocytosis. In patients with a lower risk of experiencing granulocytopenia, if CBC could be checked with longer intervals during initial treatment stages, the patients would have better compliance with this drug's treatment protocol.

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