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# CLOZAPINE INDUCED

ORIGINAL ARTICLE

# NEUTROPENIA IN PATIENTS

SUFFERING FROM SCHIZOPHRENIA : A MULTI CENTRE AUDIT

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## ABSTRACT

**Objective:** To determine the frequency of clozapine induced neutropenia and its associated clinical features among the patients suffering from schizophrenia.

**Design:** Cross sectional, comparative

**Place and duration of study:** The study is based on the blood count reports from various centres in Pakistan using Clozapine during a period 1992-2005.

**Subjects and Methods:** The medical records of 917 patients with a diagnosis of schizophrenia, aged 18 years and above were reviewed. Patient’s profile was evaluated consisting of gender, dose of clozapine, duration of treatment and complete blood count (CBC) findings including white blood cell (WBC) count or absolute neutrophil count (ANC), before starting the treatment. The case records showing WBC count below 3000 and ANC count less than 500 were identified and details of the clinical and sociodemographic variables were recorded on a proforma.

**Results:** Thirty eight patients (4.1%) developed clozapine induced neutropenia. Median duration of clozapine treatment in these patients was 6.0 years that was significantly higher than Median = 1 year of those patients who did not develope neutropenia (p < 0.001). An inverse correlation (r = -0.046) was observed between ANC and duration of clozapine induction. Median dose (mg) of clozapine induced neutropenia patients was higher (200 vs. 150, p = 0.262), however statistically insignificant.

**Conclusion:** The incidence of clozapine induced neutropenia of our study is comparable with that of worldwide reported incidence. Prolongation of treatment also increase the incidence.

**Key words:** Schizophrenia, Clozapine, Neutropenia.

## INTRODUCTION

Clozapine is a dibenzodiazepine derivative that is more valuable than standard neuroleptic drugs in refrac- tory schizophrenic patients. This dibenzodiazepine de- rivative was discovered 35 years ago, but its introduc- tion in some countries was delayed by its susceptibility to cause blood dyscrasias. Its use was restricted in the mid-1970s because it induced agranulocytosis.1,2 In the USA3 and UK,4 it was licensed in the early 1990s for two main reasons:

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* It is highly effective in treating patients with schizophrenia who do not respond to con- ventional neuroleptics; and
* The induced neutropenia and agranulocyto- sis appear to develop slowly and are easily detected by means of regular hematologic monitoring.

This means that the cytopenias are reversible if the treatment is promptly discontinued. Over the last fifteen years, different reports have clearly demonstrated that agranulocytosis and neutropenia can be easily prevented by means of strict hematologic surveillance.

Over the last ten years, a large number of epide- miologic studies have been undertaken in order to ob- tain an accurate estimate of the incidence of clozapine- induced blood dyscrasias. Surveillance reports from dif- ferent countries have shown that the risk of agranulocy- tosis and neutropenia is respectively 0.38% and 1.5-2.9%; as a result of hematologic monitoring, these rates decrease significantly after the first year of treatment, as does the risk of death due to secondary complications.3-11.

According to the recommended guidelines by Novartis, neutropenia in the range of a white blood cell count less than 3000 per mm3, or an absolute neutrophil count (ANC) less than 1500 per mm3, is classified as being in the ‘red-alert zone’ during clozapine treatment. If a patient’s blood test result falls into this zone, imme- diate discontinuation of clozapine is recommended and reinstitution is prohibited. However, in some patients, it is not entirely feasible to implement this standard guide- line because of the lack of effective alternatives to clozapine treatment. However, there is some evidence in the literature that while the guidelines for the preven- tion of agranulocytosis should be generally followed, it may be that judicious continuation of clozapine treatment is less risk-prone than previously considered in selected cases where only a few feasible alternatives to clozapine are available.12 Moreover, there is an apparent necessity to develop new measures or methods that can differenti- ate between benign neutropenia and that leading to fa- tal agranulocytosis.

Although clozapine has been liscenced for use in Pakistan over the last 15 years , the hematologic abnor- malities associated with its use have not been studied. The present study aimed at determining the frequency of clozapine induced neutropenia among the patients suf- fering from schizophrenia.

## MATERIAL AND METHODS

The medical records of 917 patients with a diag- nosis of Schizophrenia who are currently on the data base of Novartis Pakistan were retrieved. All the patients age 18 years and above, taking clozapine during the period 1992 -2005, were included. These patients have been under the care of different psychiatrists in various cen- tres, mostly teaching hospitals and district headquarter hospitals. According to the Novartis Guidelines, every consultant have to record the diagnosis and other rel- evant clinical details before initiating clozapine Blood tests i.e. complete blood count (CBC) was done to check the white blood cell (WBC) count or absolute neutrophil count (ANC), before starting the treatment and if the WBC count was more than 3000 per mm3 or an absolute neu-

trophil count (ANC) more than 1500 per mm3 only than the treatment was initiated. In the first 18 weeks of treat- ment CBC was done weekly and clozapine was also given weekly. After 18 weeks CBC was done on monthly basis and clozapine was also given on monthly basis. During clozapine treatment whenever neutropenia in the range of a white blood cell count less than 3000 per mm3 or an ANC less than 1500 per mm3 is found , is classified as being in the ‘red-alert zone’. If a patient’s blood test re- sult falls into this zone, clozapine was discontinued im- mediately, as recommended by Novartis. All the relevant information was collected on a proforma designed for this purpose.

## STATISTICAL ANALYSIS:

Data analysis was performed through SPSS ver- sion-10.0. Frequency and percentages were computed to present clinical characteristics and neutropenia. Dis- crete variables including duration and dose of clozapine induction were presented by median (interquartile range); In view of high variation and heterogeneity in the data regarding duration and dose of clozapine and in order to control outliers (either very small or large observations), we presented the data by Median (Interquartile range) rather than Mean ± S.D. Mann Whitney U test was ap- plied to compare these variables between groups of pa- tients with and without neutropenia. Continuous variables were compared using the Students t-test Pearson’s cor- relation was computed to assess correlation between ANC and duration of clozapine induction. Statistical sig- nificance was taken at p < 0.05.

## RESULTS

We reviewed the records of 917 patients suffering from schizophrenia during this period. 640 (52.9%) were males and 277 (47.1%) were females (M: F = 1.13: 1). Incidence of clozapine induced neutropenia was 4.1% (n = 38 patients). Median duration of clozapine treat- ment in these patients was 6.0 years that was significantly higher than the median duration of 1 year for those pa- tients who did not developed neutropenia (p < 0.001). An inverse correlation (r = -0.046) (p= .16) was observed

Table-1

Duration of treatment, gender distribution and dose of Clozapine in patients with and without neutropenia.

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | Neutropenia (n = 38) | Without Neutropenia (n = 879) | p-value |
| Gender (M / F) | 28 / 10 | 612 / 267 | 0.594 |
| Duration of treatment (years)† | 6 (1 – 9.25)\* | 1 (<1 – 3) | 0.001 |
| Dose used (mg) † | 200 (100 – 300) | 150 (87.5 – 250) | 0.262 |

Key: † Median (Interquartile range), ‡ Mean ± SD (95% confidence interval of means),

\*Shows significantly greater at p < 0.001.

ANF = Absolute Neutrophil count, WBC = White blood cell count

Table-2

Comparison between male and female patients suffering from neutropenia (n=38).

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | Male | Female | p-value |
| Gender | 28 (73.7%) | 10 (26.3%) | 0.004 |
| Duration of treatment (years)† | 3.5 ( 1 – 3.5 ) | 10 ( 7.25 – 10 ) | 0.041 |
| Dose used (mg)† | 150 (100 – 250 ) | 250 ( 187 – 340 ) | 0.054 |
| Median ANC‡ | 5.6 ± 1.41 (5.09 – 6.18 ) | 5 ± 1.49 (3.93 – 6.06) | 0.640 |
| Lowest ANC |  |  |  |
| •1 0.0 | 21 (75%) | 10 (100%) | 0.156 |
| * 2 1.0 | 7 (25%) | 0 (0%) |  |
| WBC‡ | 8.55 ± 1.96 (7.79 – 9.31) | 8.10 ± 1.97 (6.69 – 9.51) | 0.530 |
| Platelet count‡ | 253.13 ± 70.10 | 262 ± 67.94 | 0.073 |
|  | (225.91 – 280.41) | (213.4 – 310.6 ) |  |

Key: † Median (Interquartile range), ‡ Mean ± SD (95% confidence interval of means),

\*Shows significantly greater at p < 0.001.

ANF = Absolute Neutrophil count, WBC = White blood cell count

between ANC and duration of clozapine induction. Me- dian dose (mg) of Clozapine induced neutropenia pa- tients was higher (200 vs. 150, p = 0.262) however sta- tistically insignificant (Table-1).

Male predominance (73.7% vs. 26.3%) was found among 38 neutropenic patients (p = 0.004). Incidence of neutropenia in relation with duration of treatment was significantly higher in females than males (p = 0.041). Mean levels of ANC, WBC and platelet count were found insignificant between both genders (Table-2).

## DISCUSSION

Despite its clear therapeutic advantages, strict limi- tations have been imposed on clozapine administration to schizophrenic patients due to the potential develop- ment of neutropenia and agranulocytosis, which occurs in a small subset of patients. A clozapine analogue, DMP developed by Dupont-Pharma for the treatment of schizo- phrenia also exhibited similar problem. In a 3-month tox- icity study in dogs, DMP 406 produced dose dependent, reversible hematological abnormalities resembling those seen in patients.14

It has been reported that Neutropenia or agranu- locytosis with myeloid hypocellularity develops in a small subset (1 to 5%) of Clozapine-treated patients.14 In our 14 years’ experience of clozapine treatment of schizo- phrenia on 917 patients, incidence of clozapine induced neutropenia was 4.1% (n = 38 patients). However, the 0.9% incidence of clozapine-related neutropenia in Italy is much lower than the 2.9% reported in American and British patients;4 this difference is probably due to the fact that for Italian psychiatrists adhesion to the ICLOS

study is optional.6, 7 Furthermore, an important finding emerging from ICLOS and other epidemiologic studies is that the risk of developing neutropenia and agranulo- cytosis clearly exists during the first 18 weeks of therapy, but decreases significantly after the first year and is similar to that observed with some phenothiazines whose use is not associated with regular blood testing.3,4,9 In our retrospective analysis, median duration of clozapine treat- ment in these patients was 6.0 years that was significantly higher than Median = 1 year of those patients who did not developed neutropenia (p < 0.001). An inverse cor- relation (r = -0.046) was observed between ANC and duration of clozapine induction.

Treatment with clozapine for a year results in neu- tropenia in 1.5 to 2.9% of patients and agranulocytosis in 0.8% of patients. The mechanisms of both forms of neutrophil toxicity are unclear.11 It is has been suggested that the neutropenia and agranulocytosis are due to dif- ferent mechanisms (Gerson, 1994). It is possible that apoptosis may play a role in the pathogenesis of both forms of toxicity. With regard to clozapine agranulocyto- sis, it can be postulated that the cellular target will be a more committed neutrophil precursor, as well as mature peripheral PMNs, and for the neutropenia, In initial ex- periments, Guest et al found that the cells of two of three patients with a history of clozapine associated severe neutropenia exhibited a great sensitivity to the effects of clozapine oxidized by HOCl at low concentrations when compared to cells from normal controls or patients who had been treated with clozapine without experiencing neutropenia. The parent drug did not cause significant toxicity at the same concentrations.16 The main objec- tion to the hypothesis that antibody mediated damage is

responsible for the observed neutropenia: agranulocy- tosis is the time-course of the pathology, particularly upon re-exposure. Based upon published clinical studies (Safferman et al., 1992) and our own observations, the average duration between exposure to clozapine and agranulocytosis is 8–12 weeks upon first exposure and 6–12 weeks for the second exposure. The long lag time between reemergence of agranulocytosis upon re-expo- sure to clozapine is very difficult to reconcile with an amnestic antibody response, which would be expected to occur much faster and is in contrast to what is ob- served in cases of aminopyrine- induced agranulocyto- sis on second exposure. If clozapine or clozapine me- tabolites affected the neutrophil precursors, a drop in the number of neutrophils in the blood would be expected to occur 10–14 days later, which would not be consis- tent with the time course observed in CIA.17

An increased sensitivity of cells of some, but not all, patients has also been documented in neutropenia induced by other drugs, including chlorpromazine, carbamazepine and sulphamethoxazole18 Therefore, it is possible that clozapine-induced agranulocytosis is due to the toxicity of the reactive metabolite of clozapine and the idiosyncratic nature of the reaction could be due to differences in the sensitivity of neutrophil precursors; however, the increased sensitivity was not consistent and it is difficult to understand why the onset of agranulocy- tosis would be delayed for a month or more after initia- tion of clozapine therapy.19

**Declaration of conflict of interests:**

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