CLOZAPINE INDUCED 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 refractory schizophrenic patients. This dibenzodiazepine derivative was discovered 35 years ago, but its introduction 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 USA[3] and UK,[4] it was licensed in the early 1990s for two main reasons:

- It is highly effective in treating patients with schizophrenia who do not respond to conventional neuroleptics; and
- The induced neutropenia and agranulocytosis 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 epidemiologic studies have been undertaken in order to obtain an accurate estimate of the incidence of clozapine-induced blood dyscrasias. Surveillance reports from different countries have shown that the risk of agranulocytosis 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.]

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According to the recommended guidelines by Novartis, neutropenia in the range of a white blood cell count less than 3000 per mm^3, or an absolute neutrophil count (ANC) less than 1500 per mm^3, is classified as being in the 'red-alert zone' during clozapine treatment. If a patient's blood test result falls into this zone, immediate discontinuation of clozapine is recommended and reinstitution is prohibited. However, in some patients, it is not entirely feasible to implement this standard guideline because of the lack of effective alternatives to clozapine treatment. However, there is some evidence in the literature that while the guidelines for the prevention 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 differentiate between benign neutropenia and that leading to fatal agranulocytosis.

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

MATERIAL AND METHODS

The medical records of 917 patients with a diagnosis 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 centres, mostly teaching hospitals and district headquarter hospitals. According to the Novartis Guidelines, every consultant have to record the diagnosis and other relevant 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 mm^3 or an absolute neutrophil count (ANC) more than 1500 per mm^3 only than the treatment was initiated. In the first 18 weeks of treatment 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 mm^3 or an ANC less than 1500 per mm^3 is found , is classified as being in the 'red-alert zone'. If a patient's blood test result falls into this zone, clozapine was discontinued immediately, 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 version-10.0. Frequency and percentages were computed to present clinical characteristics and neutropenia. Discrete 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 applied to compare these variables between groups of patients with and without neutropenia. Continuous variables were compared using the Students t-test Pearson's correlation was computed to assess correlation between ANC and duration of clozapine induction. Statistical significance 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 treatment in these patients was 6.0 years that was significantly higher than the median duration of 1 year for those patients 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 (225.91 – 280.41)	262 ± 67.94 (213.4 – 310.6)	0.073

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. Median dose (mg) of Clozapine induced neutropenia patients was higher (200 vs. 150, $p = 0.262$) however statistically 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 limitations have been imposed on clozapine administration to schizophrenic patients due to the potential development of neutropenia and agranulocytosis, which occurs in a small subset of patients. A clozapine analogue, DMP developed by Dupont-Pharma for the treatment of schizophrenia also exhibited similar problem. In a 3-month toxicity study in dogs, DMP 406 produced dose dependent, reversible hematological abnormalities resembling those seen in patients.[14]

It has been reported that Neutropenia or agranulocytosis 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 schizophrenia 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 agranulocytosis 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 treatment 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 correlation ($r = -0.046$) was observed between ANC and duration of clozapine induction.

Treatment with clozapine for a year results in neutropenia 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 different mechanisms (Gerson, 1994). It is possible that apoptosis may play a role in the pathogenesis of both forms of toxicity. With regard to clozapine agranulocytosis, 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 experiments, 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 objection to the hypothesis that antibody mediated damage is

responsible for the observed neutropenia: agranulocytosis 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-exposure 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 observed in cases of aminopyrine- induced agranulocytosis on second exposure. If clozapine or clozapine metabolites 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 consistent 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 sulphamethoxazole[18] 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 agranulocytosis would be delayed for a month or more after initiation of clozapine therapy.[19]

Declaration of conflict of interests:

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REFERENCES

1. Anderman B, Griffith RW. Clozapine-induced agranulocytosis: a situation report up to August 1976. Eur J Clin Pharmacol 1977; 11: 199-201.
2. Griffith RW, Saameli K. Clozapine and agranulocytosis. Lancet 1975; 2: 657.
3. Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JI, Schaaf JA. Clozapine induced agranulocytosis: incidence and risk factors in the United States. N Engl J Med 1993; 329: 162-7.
4. Atkin K, Kendall F, Gould D, Freeman H, Liberman J, S'Sullivan D. Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. Br J Psychiat 1996; 169: 483-8.
5. Dev VJ, Krupp P. Adverse event profile and safety of Clozapine. Rev Contem Pharmacother 1995; 6: 197-208.
6. Honigfeld G. Effects of the Clozapine national registry system on incidence of deaths related to agranulocytosis. Psychiatric Services 1996; 47: 52-6.
7. Honigfeld G, Arellano F, Sethi J, Bianchini A,Schein J. Reducing Clozapine-related morbidity and mortality: 5 years of experience with the clozaril national registry. J Clin Psychiatry 1998; 59 : 3-7.
8. Mendelowitz AJ, Gerson SL, Alvir JJ, Lieberman JA. Clozapine-induced agranulocytosis. Risk factors, monitoring and management. CNS Drugs 1995; 4: 412-21.
9. Pirmohamed M, Park K. Mechanism of clozapineinduced agranulocytosis. Current status of researchand implications for drug development. CNS Drugs 1997; 7: 139-58.
10. Rosenheck R, Cramer J, Xu W, Thomas J, Henderson W, Frisman L, et al. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. N Engl J Med 1997; 337: 809-15.
11. Deliliers GL. Blood dyscrasias in clozapine-treated patients in Italy. Haematologica 2000; 85: 233-7.
12. Ahn YM, Jeong SH, Jang HS, Koo YJ, Kang UG, Lee KY, Kim YS. Experience of maintaining Clozapine medication in patients with 'red-alert zone' neutropenia: long-term follow-up results. Int Clin Psychopharmacol 2004;19: 97-101.
13. Lorenz M, Evering W E, Provencher A, Blue J T, Lewis H B, Hazelette J et al. Atypical Antipsychotic-Induced Neutropenia in Dogs. Toxicology and Applied Pharmacology 1999; 155: 227-36
14. Hummer M, Kurz M, Barnas C, Aria A, Fleischhacker WW. Clozapine-induced transient white blood count disorders. J Clin Psychiat 1994; 55:429-32.
15. Guest I, Sokoluk B, MacCrimmon J, Uetrecht J. Examination of possible toxic and immune mechanisms of Clozapine-induced agranulocytosis. Toxicology 1998;131: 53-65.
16. Safferman, AZ, Lieberman JA., Alvir JMJ, Howard A. Rechallenge in Clozapine-induced agranulocytosis. Lancet 1992; 339: 1296-7.
17. Irvine AE, French A, Daly A, Ranaghan L, Morris TCM.. Drug-induced neutropenia due to direct effects on CFU-C-Ten years of culture experience. Eur J Haematol 1994; 52: 21-7.
18. Williams DP, Pirmohamed M, Naisbitt DJ, Uetrecht JP, Park BK. Induction of Metabolism-Dependent and –Independent Neutrophil Apoptosis by Clozapine. Molecular Pharmacol 2000; 58: 207-16.