Predictive Value of Eosinophilia for Neutropenia During Clozapine Treatment

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Background: Myelotoxicity continues to hinder the widespread use of clozapine in the United States. It has been theorized that eosinophilia predicts later agranulocytosis and that agranulocytosis occurs due to an immunologic mechanism. Our study compares the rates of these dyscrasias in clozapine-treated patients and a control group.

Method: Forty-one patients taking clozapine and 29 patients taking haloperidol were monitored for a period of 6 months. Rates of eosinophilia and neutropenia were compared between the two treatment groups.

Results: Treatment-emergent eosinophilia occurred frequently in both haloperidol- and clozapine-treated patients. No significant difference was seen between groups in the incidence of eosinophilia and neutropenia.

Conclusion: We find no statistical difference between the rates of eosinophilia or neutropenia in haloperidol- and clozapine-treated patients. This study does not support the use of eosinophilia as a reliable predictor of neutropenia.

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Clozapine is an effective medication in treatment-resistant schizophrenia. It has the additional benefit of inducing fewer extrapyramidal symptoms (EPS) than conventional antipsychotics. Unfortunately, clozapine-induced agranulocytosis occurs in approximately 1% to 2% of clozapine-treated cases.[1–3] Other blood dyscrasias have also been hypothetically associated with clozapine. This study investigates the possible relationship of leukocyte-associated blood dyscrasias, i.e., eosinophilia and neutropenia, in clozapine-treated patients.

Calculated incidence rates for clozapine-induced eosinophilia have varied in the literature. Of these reports, only a minority compare the incidence rate with that in a control group. Banov et al.[4] found a 14% incidence of eosinophilia among 118 clozapine-treated patients, Gerlach et al.[3] found eosinophilia in 41% of 54, and most recently, Hummer et al.[5] reported eosinophilia in 57% of 61. Other sources state much lower incidence rates: 1.0% in the Physicians' Desk Reference (PDR)[2] or even 0.2%.[6] Fleischhacker and colleagues[7] attribute clinical significance to eosinophilia, proposing that it may be an immunologic signal predicting neutropenia.

Neutropenia may predict a more serious condition if the low neutrophil levels continue to fall, resulting in potentially lethal agranulocytosis. Clozapine-induced neutropenia rates range from 2.8% in Hummer and colleagues' 1996 observations[5] to 4% in the PDR,[2] to 10.2% in Peacock and Gerlach,[8] to 22% in an earlier study by Hummer and colleagues.[9] Clinicians should recognize the patterns of moderate neutropenia to more correctly gauge safe clozapine treatment. Additionally, if Fleischhacker and others' assertion is correct, eosinophilia levels may provide early warning signs for the detection of neutropenia.

Our study examines this reported relationship between eosinophilia and subsequent neutropenia in clozapine-treated patients and compares the rates of these blood dyscrasias with those in a control group of haloperidol-treated patients.

METHOD

This is a retrospective study of data drawn from a multicenter double-blind study comparing the long-term safety of clozapine relative to haloperidol. All patients were receiving a first-time trial of clozapine (N = 41). As a control group, haloperidol patients were drawn from the

Table 1. Demographics*

Variable	Clozapine (N = 41)	Haloperidol (N = 29)
Age (y), mean	44	44
Sex		
Male	29 (71%)	21 (72%)
Female	12 (29%)	8 (28%)
Ethnicity		
African-American	8 (20%)	5 (17%)
Asian	2 (5%)	2 (7%)
Hispanic	4 (10%)	3 (10%)
Caucasian	27 (66%)	19 (66%)

*Percentages may not sum to 100 due to rounding.

Table 2. Rates of Blood Dyscrasias

Dyscrasia	Clozapine (N = 41)	Haloperidol (N = 29)
Neutropenia	3 (7%)	2 (7%)
Eosinophilia	13 (32%)	9 (31%)

same population (N = 29). Thirteen of the clozapine-treated patients were clinically treated patients followed for the same length of time as the double-blind study participants.

The demographics of both the clozapine (N = 41) and the haloperidol control groups (N = 29) appear on Table 1. Analysis of variance (ANOVA) of age and chi-square tests of sex, race, and study site failed to reveal any significant demographic differences.

Blood tests were performed weekly for a 6-month period. Incidence rates of both eosinophilia and neutropenia were calculated for the clozapine-treated group and the haloperidol-treated group. Incidence rates in the two groups were compared using chi-square analysis.[10] Chi-square without continuity correction remains robust even when marginals are small.[11] We define eosinophilia as an absolute eosinophil level in excess of 500 cells per cubic millimeter.[12] Neutropenia is defined by an absolute neutrophil count below 2000 cells per cubic millimeter.[9] Eosinophil and neutrophil levels were obtained using a five-part automated differential of the white blood count (WBC) level.

RESULTS

Of the 41 clozapine-treated patients, 13 manifested eosinophilia and 3 developed neutropenia. Three of the 41 clozapine patients had sustained baseline eosinophilia. Of the 3 clozapine-treated subjects who had eosinophilia at baseline, 1 experienced a clinically significant improvement, 1 developed progressive eosinophilia, and 1 remained essentially unchanged. None of the clozapine patients developed both eosinophilia and neutropenia (see Table 2).

In comparison, of the 29 haloperidol control subjects, 9 developed eosinophilia and 2 developed neutropenia. While 1 of these patients exhibited symptoms of both eosinophilia and neutropenia, the symptoms of neutropenia preceded eosinophilia by 3 weeks. One of the 9 haloperidol subjects who developed eosinophilia also had baseline eosinophilia. This subject experienced no change in his clinical status during the haloperidol treatment phase. We observed no significant difference in the rates of eosinophilia between clozapine-treated and haloperidol-treated patients ($\chi^2 = 0.004$, df = 1, p = N.S.). There were also no significant differences in the rates of neutropenia between the two treatment groups ($\chi^2 = 0.004$, df = 1, p = N.S.).

No significant differences were found in the rates of eosinophilia between women and men ($\chi^2 = 1.70$, df = 1, p = .19), between study sites ($\chi^2 = 4.54$, df = 2, p = .10), among ethnic groups, ($\chi^2 = 0.17$, df = 3, p = .98), or in variances of age, (F = 1.4, p = .24). In short, we found that eosinophilia did not predict neutropenia.

DISCUSSION

It appears that eosinophilia is a fairly common dyscrasia in both clozapine- and haloperidol-treated patients. The incidence rate we observed for clozapine-induced eosinophilia (32%) lies in the range of values described in the literature. Although the rate for clozapine-induced eosinophilia appeared slightly higher than that for haloperidol-induced eosinophilia, the rates in the two drug groups were extremely close and not significantly different.

The high variability of the rates reported in the literature for clozapine-induced eosinophilia and neutropenia can be attributed to four factors: small sample sizes, differences in patient pools, varied trial lengths, and inconsistencies in the definition of this dyscrasia. Estimates of average or typical rates can be obtained by meta-analysis, but trial lengths and hematologic definitions must be kept constant. Trial lengths for clozapine studies range from 6 weeks to 1 year, with short-term trials more common than long-term. Since our experience indicates that blood abnormalities can appear as late as the fourth month of treatment, we recommend a standard trial length of at least 6 months.

Most of our patients who experienced eosinophilia did so in the first 6 weeks of treatment. These results agree with those of Banov et al.,[4] which describe the same general time frame for the first incidence of eosinophilia. In contrast to Banov, we did not find a disproportionate number of women who developed eosinophilia: a total of 4 female subjects developed eosinophilia, of whom 1 had the dyscrasia at baseline. The Fleischhacker hypothesis suggested that eosinophil and neutrophil levels may be negatively correlated due to the inhibitory effect of eosinophils on bone-marrow formation of neutrophils.[13] Our data do not support this hypothesis.

Drug names: clozapine (Clozaril), haloperidol (Haldol and others).

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