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Evaluation of the Safety of Clozapine Use in Patients with Benign Neutropenia

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Abstract

Objective—Determine if clozapine can be safely utilized in a population of psychiatric patients with current or a history of benign neutropenia.

Method—A single-center, retrospective chart review was conducted in an inpatient psychiatric hospital. Patients included had benign neutropenia prior to receiving clozapine and received clozapine using modified monitoring guidelines. All available laboratory values for absolute neutrophil count (ANC) before clozapine initiation and during treatment were evaluated. The primary endpoint was the difference in ANC after initiation of clozapine compared to before clozapine treatment.

Results—A total of 26 patients were reviewed. Mean age was 34 years at clozapine initiation. The majority were African-American (73%), with more males than females (73% vs. 27%). The mean lowest ANC value was not significantly different after clozapine initiation compared to before (1.5 and 1.4×10^3 cells/mm³, respectively; $p=0.22$). There were no cases of agranulocytosis

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(ANC $<0.5 \times 10^3$ cells/mm³) and no patients were discontinued for falling below limits set by modified guidelines. There were fewer occurrences of mild neutropenia (ANC $<2.0 \times 10^3$ cells/mm³) after clozapine initiation than before (16% and 31.4%, respectively; $p < 0.001$). There were also fewer occurrences of moderate neutropenia (ANC $<1.5 \times 10^3$ cells/mm³) with 2.1% after clozapine and 13.3% before ($p < 0.001$). Occurrence of ANC $<1.0 \times 10^3$ cells/mm³ did not differ (0.4% before, 0.3% after, $p = 0.79$).

Conclusion—Twenty-six patients with benign neutropenia were safely treated with clozapine. Their pre-clozapine neutropenia did not predict increased risk for agranulocytosis with clozapine. Patients had significantly fewer episodes of mild and moderate neutropenia after receiving clozapine compared to before.

Keywords

clozapine; benign ethnic neutropenia; neutropenia

Introduction

It has been estimated that 35% to 40% of all patients with schizophrenia should be considered for a trial of clozapine.¹ However, in the U.S. only four to five percent of patients with schizophrenia ever receive clozapine. While the superior and unique efficacy of clozapine has been repeatedly supported by the literature, the frequency of clozapine use remains low.² Antipsychotic polypharmacy, which has virtually no support in the literature, is now used more frequently than clozapine.^{3–5}

There are numerous reasons why clozapine is not more broadly used. Patient reluctance may be a factor, although artful education, motivation, and persuasion by the treating psychiatrist are skills that can and should be developed and patients are actually more willing to take clozapine than physicians realize.^{6,7} Reluctance by clinicians to prescribe clozapine may also play a role.^{8,9} Some of this stems from the challenge of coordinating laboratory, pharmacy, and clinic visits and the extra time required to monitor laboratory results.¹⁰ The fractured nature of community care amplifies these challenges. Clinician reluctance also stems from clozapine's medical risks, especially agranulocytosis.⁸

The estimated agranulocytosis incidence with clozapine treatment is less than 1%,¹¹ and FDA-mandated complete blood count (CBC) monitoring guidelines¹² have been effective in preventing agranulocytosis. In a recent study from Australia, a review of national adverse events data revealed 141 cases of agranulocytosis due to clozapine during 1993 – 2011. Of these 141 cases, there were only four deaths. Because the death rate among those with agranulocytosis was so low, the authors concluded that early detection and clozapine withdrawal was unlikely to prevent many deaths due to clozapine-induced agranulocytosis. However, they estimated that without current monitoring, approximately 28 cases of agranulocytosis would occur per year.¹³ Unfortunately, the apparent inflexibility of the FDA guidelines has created a significant impediment to the broader use of clozapine, especially in patients of African and Middle Eastern descent, who may manifest “Benign Ethnic Neutropenia” (BEN). This condition may be explained by a genetic polymorphism which affects the expression of the Duffy antigen on red blood cells. Homozygotes for this

polymorphism do not express the Duffy antigen. Consequently, they are at lower risk of contracting malaria. For unclear reasons, homozygotes as a group also have an average ANC that is roughly 1.5×10^3 cells/mm³ less than groups of heterozygotes or non-carriers, without any evidence of immunocompromise.^{3,14,15} By chance, a significant number of these individuals normally have circulating ANC values that fall into a “neutropenic” range as defined by norms created by study of European descent patients. In a large cross-sectional study of 25,222 participants, Hsieh et al¹⁶ reported that 4.5% of African-American participants had an ANC of less than 1.5×10^3 cells/mm³ versus only 0.79% of European Americans. This finding has been replicated in other studies as well.^{14,15} The incidence of BEN is estimated to be up to 25–40% of those of African descent outside of the U.S.^{17,18} Despite having lower baseline white blood cell and neutrophil counts, these individuals appear to be at no greater risk of developing agranulocytosis or infection than those without BEN.^{19–21} These data support the development of more flexible CBC monitoring guidelines for clozapine.

Numerous case reports in the literature describe the successful use of clozapine in patients with BEN.^{22–24} Recognizing the inappropriateness of applying Caucasian-based CBC monitoring guidelines to patients of African descent, the United Kingdom has adopted modified monitoring guidelines for subjects with BEN (Table 1).²⁵ However, the U.S. currently has not modified clozapine monitoring rules to adapt to the different needs of these patients. In the Maryland public mental health inpatient setting, we have the ability to request for individualized modified clozapine monitoring parameters on a case-by-case basis. These individualized “waivers” are approved by the patient, treating physician, clinical pharmacist, and clinical director of the hospital and the State of Maryland Clozapine Authorization and Monitoring Program (CAMP). The purpose of this study was to determine if clozapine can be safely utilized in a population of psychiatric patients with benign neutropenia prior to treatment with clozapine. To our knowledge, this will be the first study to evaluate a larger group of patients and to incorporate statistical comparisons of blood counts before and after clozapine.

Method

The current report is a case series based on retrospective chart reviews conducted at a single hospital and research center. The study population consisted of patients with treatment resistant psychotic disorders and benign neutropenia prior to receiving clozapine who received clozapine using modified monitoring guidelines. The modified monitoring guidelines were individualized based on each patient’s ANC history and gave a list of specified ANC values and corresponding actions required based on the value. Although most were developed before the UK guidelines were revised, they were similar to these guidelines where the thresholds for the green, amber, and red alerts were dropped by approximately 500 cells/mm³.

The primary outcome was the difference in ANC values after initiation of clozapine compared to those values before clozapine initiation. Secondary outcomes included within-participant fluctuations in ANC and patient outcomes on clozapine.

Data collected on each patient included age at clozapine initiation, sex, race/ethnicity, stabilized clozapine dose, ANC values, and patient outcome at the time of data collection. All ANC values available from hospital records before or after initiation of clozapine were used to compute within-patient summary statistics (mean, SD, minimum, etc.), with the exception that any ANC values obtained while the patient was receiving concomitant lithium treatment were excluded due to the potential elevation in WBC and ANC values. Data were collected retrospectively from clinical hospital records between July 2014 and December 2014 with all patients having their period of treatment between 2001 and 2014. Data were analyzed with Microsoft Excel and SAS. Analyses included descriptive statistics, paired student's t-test for pre/post clozapine average within-patient mean ANC values, and sign test for before/after changes in within-patient ANC standard deviations.

This data collection examining clozapine use was IRB approved as a retrospective review of existing records with a waiver of informed consent from both the University of Maryland and the Maryland Department of Health and Mental Hygiene Institutional Review Boards.

Results

Records were reviewed for 26 patients with a mean age of 34 years at clozapine initiation (range 20–56 years), including 19 males (73%) and seven females (27%). Nineteen (73%) patients identified as African-American while seven identified as Caucasian (27%).

Clozapine Characteristics

The mean stabilized dose of clozapine was 456 mg (range 50–900 mg). Patient laboratory values were reviewed before starting on clozapine for a median of 230 days (range 33–5259 days) and followed after initiating clozapine for a median of 364 days (range 28–399 days). There was a non-significant trend toward greater variability in ANC values after initiating clozapine with a median within-patient standard deviation of 0.75×10^3 cells/mm³ compared to 0.54×10^3 cells/mm³ pre-clozapine ($p = 0.052$). The mean of the lowest within-patient ANC values was not significantly different after clozapine initiation ($1.5 \pm 0.37 \times 10^3$ cells/mm³) compared to the pre-clozapine period ($1.4 \pm 0.33 \times 10^3$ cells/mm³) ($p = 0.224$) (Figure 1). The average of within-patient mean ANC values was significantly higher after clozapine initiation ($2.63 \pm 0.50 \times 10^3$ cells/mm³) compared to before ($2.13 \pm 0.51 \times 10^3$ cells/mm³) ($p < 0.001$). There were no cases of agranulocytosis ($ANC < 0.5 \times 10^3$ cells/mm³) and no patients were discontinued for falling below their waiver parameters.

Incidents of Laboratory Values Below Cutoffs

According to the thresholds specified in current (as of 2015) FDA guidelines¹², there were approximately half as many incidences of mild neutropenia ($ANC < 2.0 \times 10^3$ cells/mm³) after clozapine initiation than before ($p < 0.001$), as well as less than one-sixth as many incidences of moderate neutropenia ($ANC < 1.5 \times 10^3$ cells/mm³) after clozapine initiation ($p < 0.001$) (Figure 2). The percentage of blood tests with $ANC < 1.0 \times 10^3$ cells/mm³ did not differ after clozapine (0.3%) compared to pre-clozapine (0.4%) ($p = 0.795$), and there were no cases meeting FDA guidelines for “agranulocytosis” ($ANC < 0.5 \times 10^3$ cells/mm³).

According to the individualized modified monitoring guidelines that were used for each patient, there were significantly fewer incidences of ANC values requiring twice weekly monitoring after clozapine (1.8%) compared to before clozapine (4.2%) ($p < 0.04$) (Figure 3). There were also significantly fewer incidences of ANC values requiring temporary discontinuation with 0.0% after clozapine and 1.9% before clozapine ($p < 0.001$). The percentage of blood tests requiring permanent discontinuation did not differ after clozapine (0.1%) compared to pre-clozapine (0.5%) ($p = 0.36$).

Patient Outcomes on Clozapine

At the time of the data collection in this report, 14 of the 26 patients were successfully discharged on clozapine (Figure 4). Eight patients remained hospitalized and continued to receive clozapine. Of the remainder, one patient eloped from a general hospital on clozapine, one was discontinued due to refusal of laboratory work, and two patients were discontinued due to thrombocytopenia. Of these two patients, the first was thrombocytopenic pre-clozapine and no change in platelets was seen with the addition of clozapine, but the medication was discontinued per physician decision. The second patient had normal platelet values pre-clozapine. With the addition of clozapine, this patient had a steady decline in platelets to a minimum of 93×10^3 cells/ μ L. After clozapine was discontinued, the platelet count improved, but did not recover to baseline when he was discharged four months after clozapine discontinuation. It is unknown if the patient had any medical consequences due to the thrombocytopenia or if other causes were identified. Of note, seven patients (26.9%) of the 26 evaluated had their individualized modified monitoring guidelines discontinued and successfully remain to date on clozapine using manufacturer monitoring guidelines.

Discussion

In this study of psychiatric patients with benign neutropenia pre-clozapine, treatment with clozapine did not increase the risk of agranulocytosis. There were significantly fewer incidents of mild and moderate neutropenia after addition of clozapine compared to laboratory values before clozapine initiation. Compared to pre-clozapine ANC values, patients had significantly fewer incidents of ANC values requiring twice weekly CBC's and temporary discontinuation as outlined in the patients' individual modified monitoring parameters after clozapine treatment. Furthermore, the average of within-patient mean ANC values increased significantly after clozapine initiation, with no difference in the average of within patient minimum ANC values. Based on this small population, clozapine appears to be a safe treatment option in these patients. This is supported by the existing literature which contains a few case reports of patients with Benign Ethnic Neutropenia. Blackman²³ described a case of a 19-year old male with a robust response to clozapine therapy. However, his frequently fluctuating ANC values necessitated once to twice weekly blood draws. Others have described cases of patients who responded well to clozapine, but the medication was discontinued due to low WBC and ANC values. These patients were started on medications (lithium^{26,27} and granulocyte colony stimulating factor²²) in order to augment their WBC and ANC values, which allowed for continued use of clozapine. It is unfortunate that these patients and possibly others like them are exposed to unnecessary, potentially harmful medications in order to meet current guidelines for use of clozapine.

In this study, two patients (7.7%) discontinued clozapine due to thrombocytopenia. Although one of these patients had low platelet count pre-clozapine, the other can potentially be attributed to the addition of clozapine. The literature contains a few case reports and studies reporting the incidence of thrombocytopenia associated with clozapine up to a maximum of 17.8% of cases.^{28–30} The current U.S. clozapine labeling lists the incidence of thrombocytopenia as less than 1%, although Canadian labeling recommends discontinuation if platelets fall below 50,000/mm³.³¹ Based on our findings, we recommend that clinicians include platelet count with regular CBC monitoring in patients with benign neutropenia.

The first patient in this study was treated in 2001, well before the phenomenon of BEN was described. Nineteen of the 26 patients in this study were self-identified African Americans, and it is reasonable to hypothesize that many of these patients had the genetic condition now referred to as Benign Ethnic Neutropenia. However, it is notable that seven of the patients identified as Caucasian, with no evidence of African or Middle Eastern heritage. It is unlikely that any of these individuals were homozygotes for the African dominant polymorphism, and astronomically unlikely that all of them were. It is more prudent to assume that there are multiple genetic or acquired conditions (e.g., post-chemotherapy) that predispose these patients to benign neutropenia. Thus, any suggestion that authorization for guideline modification be determined solely by confirmation of the Duffy Null state would only continue artificial barriers to a treatment that can be life-saving as well as life-changing.

Although other countries have more relaxed clozapine monitoring guidelines and some even have specifically modified guidelines for those with benign neutropenia, the FDA has yet to allow such modifications to the monitoring parameters in the United States. Based on current manufacturer guidelines, our patients would have been subjected to more frequent laboratory tests and may have had their access to clozapine restricted or denied. Modification of monitoring parameters, particularly in the population of patients with benign neutropenia, will lead to reduced frequency of blood draws and may lead to improved compliance, greater patient satisfaction, and more willingness to continue this potentially life-saving medication.

Limitations of the Study

This was a retrospective study so the process for how each patient was identified as having benign neutropenia was varied. No genetic markers were evaluated in this sample, so it is unknown if the patients carried the allele commonly seen in BEN. Furthermore, the findings in this small sample size may not be generalizable to a larger population. Nonetheless, this is the first systematic collection of a group of patients with benign neutropenia treated in the U.S. using modified monitoring guidelines.

Future Research

Our research group has recently been funded by the NIMH to study the safety and possible genetic biomarkers associated with clozapine in BEN patients. This study (NCT# 02404155) will be conducted in the U.S. and Nigeria and will be the first such study to prospectively treat patients with BEN. The study will be using modified guidelines that have been

approved by the FDA under an Investigational New Drug (IND) Application. Our hopes are that eventual changes will be made to U.S. guidelines and knowledge of BEN will become more widespread which may allow for many more patients to be safely treated with clozapine.

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Figure 1.
Mean of the Lowest and Overall Average Within-Patient ANC Values

Figure 2.
Percent of Laboratory Tests below FDA Cutoffs

Figure 3.

Percent of Laboratory Tests below Individualized Modified Monitoring Guidelines

Modified monitoring guidelines were individualized based on each patient's ANC history and gave a list of specified ANC values and corresponding actions required based on the value. All patients were monitored on a weekly basis, with a certain ANC value requiring twice weekly CBC's until ANC recovered to the specified value. There were further ANC values requiring temporary discontinuation and monitoring. These patients were able to be restarted on clozapine once the ANC increased to a predetermined value. Another specified ANC value required permanent discontinuation of clozapine without the chance for rechallenge.

Figure 4.
Patient Outcome on Clozapine

Table 1

Comparison of Current U.S. and U.K. Clozapine Monitoring Guidelines

Characteristic	United States (U.S.)	United Kingdom (U.K.) – Non-BEN subjects	United Kingdom (U.K.) – BEN subjects
CBC monitoring – weekly	First six months of therapy	First 18 weeks	
CBC monitoring – every two weeks	6–12 months of therapy	18 weeks through end of 12 months	
CBC monitoring – every four weeks	> 12 months of therapy	> 12 months of therapy	
Satisfactory result ¹	WBC 3.5 and ANC 2.0	WBC > 3.5 and ANC > 2.0	WBC > 3.0 and ANC > 1.5
Twice-weekly monitoring and continue therapy ²	WBC 3.0–3.5 and/or ANC 1.5–2.0	WBC 3.0–3.5 and/or ANC 1.5–2.0	WBC 2.5–3.0 and/or ANC 1.0–1.5
Temporary discontinuation and twice-weekly monitoring	WBC 2.0–3.0 and/or ANC 1.0–1.5	N/A	N/A
Permanent discontinuation ³	WBC < 2.0 and/or ANC < 1.0	WBC < 3.0 and/or ANC < 1.5	WBC < 2.5 and/or ANC < 1.0

BEN = Benign Ethnic Neutropenia

CBC = Complete Blood Count

WBC = White Blood Cell Count ($\times 10^3/\text{mm}^3$)ANC = Absolute Neutrophil Count ($\times 10^3/\text{mm}^3$)¹“Green alert” in the U.K.²“Amber alert” in the U.K.³“Red alert” in the U.K.