Hematological Adverse Events in Clozapine-Treated Children and Adolescents

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ABSTRACT

Objective: To retrospectively examine rates of hematological adverse events (HAEs) in psychiatrically ill, hospitalized children treated with clozapine. **Method:** Clozapine treatment was administered in an open-label fashion using a flexible titration schedule, and data from weekly complete blood counts was obtained. The rate of neutropenia and agranulocytosis (HAEs) development was determined for 172 eligible patients (mean age at clozapine initiation, 15.03 ± 2.13 years) with a median observation period of 8 months. **Results:** Neutropenia (absolute neutrophil count <1,500/mm^3) developed in 23 (13%) patients and agranulocytosis (absolute neutrophil count <500/mm^3) in one (0.6%) patient. The cumulative probability of developing an initial HAE at 1 year of clozapine treatment was 16.1% (95% confidence interval 9.7%–22.5%). Eleven (48%) of 24 patients who developed an HAE were successfully rechallenged on clozapine. Eight (5%) of 172 patients from this sample eventually discontinued clozapine because of an HAE (one agranulocytosis, seven neutropenia). **Conclusions:** The occurrence of HAEs is a significant risk associated with the administration of clozapine. However, in this sample, few children actually discontinued therapy because of an HAE and the incidence of agranulocytosis does not appear higher than what has been reported in the adult literature. *J. Am. Acad. Child Adolesc. Psychiatry,* 2005;44(10): 1024–1031. **Key Words:** neutropenia, agranulocytosis, clozapine.

Clozapine is an atypical antipsychotic primarily used to treat patients with schizophrenia and other psychotic disorders that are resistant or intolerant to other antipsychotic medications. It remains the only antipsychotic medication shown to have superior efficacy as compared with first-generation antipsychotic medications for both positive and negative symptoms of schizophrenia in adolescents with treatment-refractory schizophrenia (Kumra et al., 1996), similar to what has been reported in clinical studies of adults with treatment-refractory schizophrenia (Leucht et al., 2003). Despite the wide range of benefits associated with clozapine treatment, clozapine use has been reserved for treatment-resistant children and adolescents because of its greater propensity to cause serious hematological adverse events (HAEs; i.e., agranulocytosis), as compared with other first- and second-generation antipsychotic medications (Findling and McNamara, 2004; Pappadopulos et al., 2003).

In adult studies, the incidence of clozapine-induced agranulocytosis has been consistently estimated to be about 0.8% at 1 year (Alvir et al., 1993; Atkin et al., 1996; Copolov et al., 1998). In comparison, the incidence of clozapine-induced neutropenia in adult patients has

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been reported to vary from 2.3% (Atkin et al., 1996) to 22% (Hummer et al., 1994) at 1 year, although the latter study implemented a more liberal definition of neutropenia (e.g., absolute neutrophil count <2,000) than is commonly used.

In this descriptive study, we retrospectively evaluated the incidence of clozapine-induced neutropenia/agranulocytosis in 172 severely ill, hospitalized children and adolescents. Because of the concern that the rate of clozapine-induced neutropenia may be higher in children as compared with adults (Sporn et al., 2003), it is important to examine children being treated in naturalistic settings to provide better estimates of the potential risks for adverse hematological side effects for children and adolescents who require long-term clozapine treatment. We hypothesized that we would see a higher rate of neutropenia in this pediatric group as compared to the adult literature (Hummer et al., 1994; Kumra et al., 1996). Also, we focused on the time course about when HAEs occurred and the response of subjects to being rechallenged on clozapine after developing an initial HAE.

METHOD

Subjects

The following criteria were applied to include or exclude subjects from the study cohort: (1) initiated on clozapine at Bronx Children's Psychiatric Center (BCPC) as an inpatient and (2) treatment resistance. The New York State Office of Mental Health defines treatment resistance as a history of failed treatment with at least two antipsychotics in at least two chemical classes in clinically appropriate doses based on age and weight as judged by the clinician. Failure of treatment is defined as continued necessity of hospital level of care secondary to potential for self-harm, harm to others, or inability to care for self. At the time of the medication switch to clozapine, all of the patients were acutely ill and their clinical status in terms of psychosis, affective instability, and/or aggression necessitated a change in their medication regimen. As part of good clinical practice, a patient would not be treated with clozapine if the patient had a medical contraindication to clozapine initiation such as a history of drug-induced agranulocytosis or a bone marrow disorder.

Procedures

A retrospective chart review was undertaken of consecutively admitted treatment-resistant patients to BCPC, a long-term chronic care facility, between June 1992 and May 2004. All of the patients received carefully monitored, open-label inpatient trials of clozapine for the first time, and each patient was prospectively observed in a standard drug-monitoring program for clozapine in which there were weekly regular assessments of white blood cell counts (WBCs) and differential WBCs, consistent with recommendations from the New York Office of Mental Health (OMH; Finnerty et al., 2002). In addition, compliance with treatment recommendations from OMH by treating physicians and the incidence of adverse events and relationship to clozapine treatment were assessed at monthly Pharmacy and Therapeutic Committee meetings chaired by a pharmacist (L.N.) and a board-certified child and adolescent psychiatrist (H.K.). For the purpose of this analysis, information abstracted from subjects' medical records included primary diagnosis, date of birth, sex, pretreatment, and weekly WBCs and absolute neutrophil counts (ANCs), dose of clozapine administered, and adjunctive medications.

Sample Selection

One hundred eighty-two charts of children and adolescents treated with clozapine at Bronx Children's Psychiatric Center were identified. Of these, 172 charts were selected for evaluation. The reasons for excluding the 10 charts were as follows: four initiated clozapine at a hospital other than BCPC, five charts were not available for review, and one was excluded because this patient had been treated with clozapine for only 1 day and then had been transferred to another hospital.

Assessment of Hematological Side Effects

Because of mandatory blood monitoring, children and adolescents treated with clozapine were closely observed and adverse drug reactions were carefully reported, making it unlikely that a serious adverse drug reaction or HAE would remain unrecognized. The ANCs were reviewed for each subject while taking clozapine by two research assistants (D.F., D.A.T.) under the supervision of a board-certified child and adolescent psychiatrist (S.K.). Neutropenia was defined as an ANC between 500 and <1,500/mm^3. Agranulocytosis was defined as an ANC that dropped below 500/mm^3. There are no specified criteria provided by OMH for a rechallenge with clozapine so that the decision is made by the individual physician on a case-by-case basis.

The incidence of these adverse hematological side effects was then verified with the monthly minutes of the Pharmacy and Therapeutics Committee. Where other explanations (e.g., infections, concomitant therapy) were thought to be more likely the cause of these HAEs, as judged by a review of the medical record by the senior author (S.K.) and as reflected in the minutes of the Pharmacy and Therapeutics Committee, they were not considered ''cases'' in the sense of clozapine-related side effects.

Twenty-nine (16.9%) of the 172 patients were identified as having an ANC reaching ≤1,500/mm^3. Five of these patients did not stop clozapine because a repeated blood sample revealed a safe ANC. These patients were not included in the final total number of patients who developed a clozapine-induced HAE (n = 24).

Data Analyses

Statistical analyses of demographic characteristics used the χ^2 test or Fisher exact test for categorical variables, and two sample t tests for continuous variables. Because this was a naturalistic study, survival analysis was undertaken because subject accrual continued throughout the observation period and there were varying durations of follow-up. Survival analysis methods were applied to the two ''time until event'' variables: first episode of neutropenia/agranulocytosis and second episode of neutropenia. To estimate the cumulative probability of developing an initial HAE at 1 year of clozapine