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Risk Factors for Neutropenia in Clozapine-Treated Children and Adolescents with Childhood-Onset Schizophrenia

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Abstract

Objective: The purpose of this study was to retrospectively analyze rates of neutropenia and risk factors for neutropenia in hospitalized children and adolescents treated with clozapine.

Methods: A retrospective chart review was conducted for all patients who received clozapine at any time during a hospitalization at the National Institute of Mental Health (NIMH) between 1990 and 2011. All patients satisfied screening criteria for the NIMH childhood-onset schizophrenia study, including onset of psychosis before the age of 13 years. Absolute neutrophil count (ANC) values recorded during inpatient hospitalization were extracted for 87 eligible patients with a mean age of 13.35 ± 2.46 years at hospitalization and a mean length of stay of 117 ± 43 days.

Results: Mild neutropenia only (lowest ANC $< 2000/mm^3$ but $>1500/mm^3$) was observed in 27 (31%) patients and moderate neutropenia (any ANC $< 1500/mm^3$) was observed in 17 (20%) patients. There were no cases of agranulocytosis or severe infection. Significant risk factors for mild neutropenia compared with no hematologic adverse effects (HAEs) were male gender ($p = 0.012$) and younger age ($p < 0.001$). Male gender was also a significant risk factor for moderate neutropenia compared with no HAEs ($p = 0.003$). If a child of African American ethnicity developed neutropenia during hospitalization at all that child was significantly more likely to develop moderate neutropenia than mild neutropenia only ($p = 0.017$). African American boys had the highest rate of moderate neutropenia at 47%. Sixteen of the 17 patients exhibiting moderate neutropenia were successfully treated with clozapine by the time of discharge; 8 of these 16 required adjunctive lithium carbonate administration to maintain ANC $> 2000/mm^3$.

Conclusions: Our study shows that the rates of neutropenia in clozapine-treated children and adolescents are considerably higher than in the adult population. Younger age, African American ethnicity, and male gender were significant risk factors. These are also risk factors for benign neutropenia in healthy children and adolescents. Despite these high rates of neutropenia, all but one of the patients with neutropenia during hospitalization were successfully discharged on clozapine.

Introduction

Clozapine is an atypical antipsychotic with a unique clinical profile. It has been shown to be superior to both first and second-generation antipsychotics in the alleviation of positive and negative symptoms in adults with refractory schizophrenia (Wahlbeck et al. 2000; McEvoy et al. 2006). This result has been replicated in the child and adolescent population (Kumra et al. 2008; Fraguas et al. 2010). Double blind head-to-head comparisons in treatment-resistant patients with childhood-onset schizophrenia have shown clozapine to be superior to both haloperidol and olanzapine (Kumra et al. 1996; Shaw et al. 2006; Kumra et al. 2008). Clozapine treatment also leads to a reduction in aggressive behavior in children, allowing them to be discharged into less restrictive settings (Kranzler et al. 2005).

Unfortunately, the use of clozapine is limited by its potential for serious adverse effects, the most concerning of which is agranulocytosis, usually defined as a fall in the absolute neutrophil count (ANC) to $<500/mm^3$. The mechanism by which clozapine leads to a drop in white blood cell (WBC) count is still unknown. It is also unclear why the risk of agranulocytosis appears to decrease exponentially over time, and why some patients treated with clozapine develop a transient neutropenia, usually defined as an ANC $<1500/mm^3$, without progression to agranulocytosis. The risk factors for clozapine-induced agranulocytosis are different from those for clozapine-induced neutropenia (Alvir et al. 1993; Munro et al. 1999) and it has been suggested that they are caused by distinct mechanisms (Gerson 1993). It appears that both neutrophil precursors and mature peripheral neutrophils may be affected in agranulocytosis,

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whereas neutropenia may involve only the peripheral neutrophils (Flanagan and Dunk 2008).

Agranulocytosis in clozapine-treated patients was initially observed during an outbreak in Finland in 1975 when there were 16 cases of agranulocytosis and eight fatalities secondary to infection (Amsler et al. 1977). Because of this outbreak and the deaths resulting from it, clozapine was withdrawn from the United States market in 1975, but it was then reintroduced in 1989 with strict monitoring requirements (Hippius 1989; Crilly 2007). Clozapine is reserved for patients who fail to respond to standard antipsychotic treatment, and the medication is only available through a distribution system that requires monitoring of WBC count and ANC. Current United States Food and Drug Administration (FDA) requirements include a baseline WBC >3500/mm^3 and ANC >2000/mm^3 before clozapine therapy can be initiated. Hematologic monitoring is required weekly for the first 6 months. The frequency then decreases to every 2 weeks and subsequently to every 4 weeks the longer the patient stays on the medication, but it is always at least every 4 weeks. If mild leukopenia or mild neutropenia (defined as WBC <3500/mm^3 or ANC <2000/mm^3) is detected, then the frequency of monitoring increases to twice weekly blood draws. If moderate leukopenia or moderate neutropenia (defined as WBC <3000/mm^3 or ANC <1500/mm^3) is detected, it is recommended that therapy be interrupted. The specific requirement for reporting an ANC with every WBC is relatively new, having been only introduced in 2003.

The monitoring system in the United Kingdom and Ireland also requires measurement of both WBC and ANC, but it uses different ranges for patients with benign ethnic neutropenia (BEN) than for the general population. BEN can be defined as ''the occurrence of neutropenia, defined by normative data in white populations, in individuals of other ethnic groups who are otherwise healthy and who do not have repeated or severe infections'' (Rajagopal 2005). According to United Kingdom guidelines, immediate cessation of clozapine is only required when WBC falls <2500/mm^3 or ANC falls <1000/mm^3 in a patient with BEN, an ANC threshold that is 500/mm^3 lower than the general population (Rajagopal 2005). In order to be treated under these modified criteria, the patient must be registered with the Clozaril Patient Monitoring Service (CPMS) as a patient with BEN, which requires a letter from the patient's psychiatrist in consultation with a hematologist. A review of clozapine-treated patients in a London hospital suggests that failure to register black patients as having BEN may lead to much higher rates of discontinuation in the black population, and subsequently worse outcomes in these patients (Whiskey et al. 2011). In the United States there are no such accommodations for ethnicity in blood count reference ranges. There are also no FDA guidelines for clozapine use in pediatric patients. A case report from a United States hospital illustrates how this lack of recognition of BEN may lead to unnecessary blood draws and discontinuation of clozapine in black children (Blackman 2008).

In adults, the risk of neutropenia (defined as ANC <1500/mm^3) in the first year of clozapine treatment is ~3%, whereas the risk of agranulocytosis is ~0.8% (Alvir et al. 1993; Atkin et al. 1996; Copolov et al. 1998; Kang et al. 2006). In adults taking clozapine, increasing age is a risk factor for agranulocytosis, whereas *decreasing* age is a risk factor for neutropenia (Munro et al. 1999). In adults, female gender and Asian ethnicity have also been identified as risk factors for developing agranulocytosis, whereas African ethnicity is a clear risk factor for neutropenia (Alvir et al. 1993; Munro et al. 1999). Although African and some Middle Eastern ethnic groups have been shown to have a higher incidence of BEN, it has been shown that more Caucasians develop clozapine-induced agranulocytosis (Kelly et al. 2007).

A recent study found the incidence of neutropenia to be higher in clozapine-treated children and adolescents (16%) than in adults (3%), with a significant correlation between younger age and increasing risk (Gerbino-Rosen et al. 2005). This study did not find a similar correlation between agranulocytosis and age in children. In addition, there is evidence that children metabolize clozapine differently than do adults (Frazier et al. 2003), which may lead to differences in how the medication interacts with bone marrow and peripheral neutrophils. Because of these studies, there is concern that indiscriminately applying the adult FDA guidelines for clozapine to children may lead to unnecessarily frequent blood draws and unnecessary discontinuation of the medication in a large number of children who would benefit from the medication. Stopping clozapine treatment in these patients has significant consequences, including rebound psychosis, which tends to be more severe in children to begin with. Furthermore, in many cases, switching to an alternative antipsychotic after clozapine is discontinued does not lead to resolution of neutropenia (Flynn et al. 1997; Benedetti et al. 1999; Teter et al. 2000; Cosar et al. 2011).

Neutropenia in the course of clozapine treatment can clearly arise because of factors not directly related to clozapine. These include BEN, coexisting medical conditions, other medications, and medication interactions with clozapine (Esposito et al. 2005). There is also a pronounced circadian variation in the ANC, with a greater likelihood of neutropenia if blood is drawn earlier in the morning (McKee et al. 2011). An additional complicating factor in the monitoring and management of neutropenia in children taking clozapine is that the average ANC for people <18 years of age has been shown to be significantly lower at baseline than it is for adults. A number of reports have established differences in normal ANC range depending upon age and ethnic background, and these have shown that baseline neutrophil counts are lowest among male black children than in any other demographic group studied (Neser 1968; Caramihai et al. 1975; Rana et al. 1985; Hsieh et al. 2007). One study showed that the incidence of benign neutropenia (defined as an absolute neutrophil count <1500/mm^3 in a healthy individual) in African American participants between 12 and 14 years of age was as high as 10.5%, with 1.6% of participants in this demographic group demonstrating an ANC of <1000/mm^3 (Hsieh et al. 2007).

The two principal methods that have been used in the treatment or prevention of clozapine-related neutropenia are adjunctive treatment with lithium carbonate and use of the cytokines granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Esposito et al. 2005; Whiskey and Taylor 2007). The cost of long-term treatment with G-CSF or GM-CSF is prohibitively expensive; therefore, the majority of studies have used the lithium carbonate approach. Many reports, including some in children, describe positive outcomes, and patients for whom clozapine was the medication of last resort were able to continue clozapine treatment without recurrent neutropenia or significant lithium toxicity (Sporn et al. 2003; Bender et al. 2004; Mattai et al. 2009). There is some concern among other authors that lithium may not prevent agranulocytosis and may in fact mask impending agranulocytosis (Gerson et al. 1991; Valevski et al. 1993).

Identifying risk factors for the development of neutropenia in clozapine-treated children may help understand the mechanism by which the medication causes a drop in ANC. It may also help to inform monitoring practices for children receiving the medication. In this descriptive study we retrospectively evaluated the incidence

of low ANC in hospitalized children and adolescents with childhood-onset schizophrenia (COS) who were receiving clozapine. COS is a rare form of the adult-onset disorder and it has a severe, chronic, and, typically, treatment-resistant course (Nicolson and Rapoport 1999). In our experience at NIMH, most COS patients are eventually treated with clozapine, which remains the treatment of last resort in these patients (Gogtay and Rapoport 2008). We focused on correlations among age, gender, and ethnicity with the development of mild neutropenia (ANC <2000/mm^3, when FDA guidelines recommend an increase in monitoring frequency) or the development of moderate neutropenia (ANC <1500/mm^3, when the FDA guidelines recommend an interruption in therapy), to address which patients are likely to have increased monitoring or discontinuation of clozapine treatment under the current FDA guidelines.

Methods

Subjects

COS patients were admitted to the Pediatric Behavioral Health unit of the NIMH between 1990 and 2011. Prior to admission, patients underwent a thorough screening by physicians and mental health professionals on the research team. Eligibility criteria included age between 6 and 18 years at first admission, onset of psychosis before age 13, absence of serious medical conditions, and pre-psychotic intelligence quotient (IQ) >70. In most cases, diagnosis was confirmed after a complete medication washout and a medication-free observation for up to 3 weeks. Patients who were admitted from 2003 onwards were only started on clozapine therapy if they had an ANC >2000/mm^3. Prior to 2003, patients only required a WBC of >3500/mm^3 for initiation of the medication. The general approach used for dosing and titration of clozapine has been described previously (Gogtay and Rapoport 2008). After starting clozapine, patients were carefully monitored for adverse effects, including complete blood count with differential at least once a week. If blood counts were observed to drop, the frequency of blood testing was increased for closer monitoring according to the FDA guidelines at the time of hospitalization, or more often, if deemed necessary by the treating physician. Clozapine treatment was interrupted at the discretion of the treating physician for WBC counts of <2000/mm^3 (prior to 2003) or ANC of <1500/mm^3 (from 2003 onwards). Patients for whom discontinuation of clozapine was necessary because of low ANC were re-challenged after recovery of ANC to >2000, often with the use of adjunctive lithium carbonate. For more information on use of lithium carbonate for this purpose please see previous publications (Sporn et al. 2003; Mattai et al. 2009).

Data acquisition

A retrospective chart review was undertaken for patients who had been diagnosed with COS or childhood-onset schizoaffective disorder and had been treated with clozapine at any point during an inpatient admission at the NIMH. Medical records were reviewed using the National Institutes of Health (NIH) Clinical Center's computerized Clinical Research Information System (CRIS), and both scanned and hard copies of archived paper records. Admission notes, discharge summaries, hematologic data, and medication administration records were used to abstract the following information: dates of admission and discharge for the earliest hospitalization during which the patient received clozapine, birth date, gender, ethnicity, admission medications with doses, discharge medications with doses, all ANC measurements during NIH hospitalization, and medication regimen at the patient's latest follow up evaluation.

Sample selection

Ninety-two charts of children treated with clozapine while hospitalized at the NIMH were identified. Of these, 87 charts were selected for analysis. Five charts were excluded because they did not contain complete records of ANC measurements during hospitalization.

Data analysis

The minimum ANC recorded during hospitalization was determined for each patient. At the time of admission, 83 of the 87 patients were either on clozapine or another antipsychotic, all of which are known to be associated with neutropenia to some degree. For this reason, we were not able to report meaningful baseline ANC values. Significant risk factors for mild neutropenia were determined by comparing the group of patients who had all measured ANC values >2000/mm^3 with those who had any recorded value <2000/mm^3. Similarly, analysis of risk factors for moderate neutropenia compared the group of patients who had all measured ANC values >1500/mm^3 with those who had any recorded value <1500/mm^3. Therefore, the group of patients who satisfied criteria for moderate neutropenia was a subset of the group of patients who satisfied criteria for mild neutropenia. Statistical analysis of gender and ethnicity used the χ^2 test, and analysis of age, clozapine dose, and length of hospital stay used independent two sample t-tests with equal variance. All reported p-values are two-tailed. All statistical analyses were conducted using version 18.0 of PASW Statistics (now IBM SPSS Statistics). The threshold for statistical significance was $p < 0.05$.

This study was approved by the NIMH Institutional Review Board (IRB) and informed consents and assents were obtained by the parents/legal guardians of the patients and patients themselves, respectively.

Results

Sample characteristics

The primary diagnoses at the time of last contact included schizophrenia ($n = 85$) and schizoaffective disorder ($n = 2$). All patients had onset of psychotic symptoms before13 years of age. Twenty-eight patients were identified as African American in their chart, 48 as white, four as Asian, one as Native American, and 7 as multiple race or unknown. Fifty of the patients were male and 37 were female. The mean age at admission was 13.35 ± 2.46 years (range 6.73–19.06). The mean length of stay in the hospital was 117 ± 43 days (range 21–205). Seventeen patients were taking clozapine on admission, and three of these patients were not discharged on it. Reasons for this included inability to maintain adequate ANC after two inpatient trials of clozapine ($n = 1$), entry into an open trial of olanzapine during admission ($n = 1$), and adequate relief from symptoms with risperidone ($n = 1$). For the 84 patients who were discharged on clozapine, the mean discharge dose was 349 ± 135 mg/day (range 75–825).

Subjects who developed neutropenia

From the 87 patients included in our analysis, 27 (31%) met criteria for mild neutropenia only, defined as lowest ANC between 1500/mm^3 and 2000/mm^3 during hospitalization. The average

ANC at first diagnosis of neutropenia in these patients was 1757/mm^3 with a standard deviation of 149/mm^3. Seventeen (20%) patients met criteria for moderate neutropenia, defined as any ANC <1500/mm^3 during hospitalization. The average ANC at first diagnosis of moderate neutropenia was 1360/mm^3 with a standard deviation of 160/mm3. Characteristics of the groups of patients who met criteria for mild and moderate neutropenia are presented in Table 1. Patients who met criteria for mild neutropenia differed significantly from those who did not have any hematologic adverse events (HAEs) in gender ($\chi^2 = 6.313$, $p = 0.012$) and age at hospitalization ($t = 3.711$, $p < 0.001$), with boys and younger children more likely to develop mild neutropenia. Patients who met criteria for moderate neutropenia differed significantly from those who did not have any HAEs in gender ($\chi^2 = 8.945$, $p = 0.003$), with boys more likely to develop moderate neutropenia. Patients who met criteria for moderate neutropenia differed significantly from those who only developed mild neutropenia in ethnicity ($\chi^2 = 5.698$, $p = 0.017$) with African Americans more likely to have moderate neutropenia. African American boys were the demographic group with the highest rates of moderate neutropenia at 47% (7 out of 15).

We conducted pairwise comparisons of groups to look for confounding between variables. There was no significant difference in age between boys and girls ($t = 0.869$, $p = 0.387$), no significant difference in age between African Americans and non-African Americans ($t = 0.583$, $p = 0.562$), and no significant association between gender and ethnicity ($\chi^2 = 0.059$, $p = 0.808$). Development of neither mild nor moderate neutropenia was significantly associated with discharge dose of clozapine or length of stay in the hospital.

One patient met criteria for severe neutropenia during hospitalization with the lowest measured ANC value of 950/mm^3. This patient was severely neutropenic (defined as ANC <1000/mm^3) on admission before clozapine was started. The patient was started on lithium before beginning clozapine and was subsequently able to tolerate the medication. There were no recorded cases of agranulocytosis, and no incidences of serious infection.

Seven of the 17 patients with moderate neutropenia were admitted after 2003, and, therefore, had clozapine held in accordance with FDA guidelines. All patients who were successfully re-challenged received adjunctive lithium to keep their ANC above threshold. The one patient who failed re-challenge had clozapine initially held for an ANC of 1102. The patient then failed a re-challenge, unable to continue the medication because of a second drop in ANC <1500. Adjunctive lithium carbonate was not tried in this patient during hospitalization. The patient was, however, able to maintain adequate ANC values with adjunctive lithium treatment when this strategy was tried during a third trial of clozapine 9 years after discharge (at age 25).

Lithium carbonate administration

Ten of the 84 patients treated with clozapine were started on adjunctive lithium carbonate. Seven of these were started on lithium carbonate after the development of moderate neutropenia, two after the development of mild neutropenia, and one patient was started on lithium carbonate with a low normal ANC because of known episodes of neutropenia prior to hospitalization. None of these patients had any incidences of neutropenia after being started on lithium.

Long-term follow-up

Fifty of the 84 patients who were discharged on clozapine had accessible information from a follow-up visit after their hospital

TABLE 1. SAMPLE CHARACTERISTICS FOR CLOZAPINE-TREATED CHILDREN HOSPITALIZED AT THE NATIONAL INSTITUTES OF HEALTH CLINICAL CENTER ($N = 87$)

	Mild neutropenia only compared with no HAEs							*Moderate neutropenia compared with no HAEs*							*Mild neutropenia only compared with moderate neutropenia*						
	Lowest ANC ≥*2000* (n=*43*)		*Lowest 1500*≤*ANC* <*2000* (n=*27*)		df	*Test statistic*	p	*Lowest ANC* ≥*2000* (n=*43*)		*Lowest ANC* <*1500* (n=*17*)		df	*Test statistic*	p	*Lowest 1500* ≤*ANC*<*2000* (n=*27*)		*Lowest ANC* <*1500* (n=*17*)		df	*Test statistic*	p
	Mean	*SD*	*Mean*	*SD*				*Mean*	*SD*	*Mean*	*SD*				*Mean*	*SD*	*Mean*	*SD*			
Gender																					
Male	17		19		1	6.313	0.012[a]	17		14		1		0.003[a]	19		14		1	0.799	0.371[a]
Female	26		8					26		3			8.945		8		3				
Ethnicity																					
African American	13		5		1	1.191		13		9		1			5		9		1	5.698	
Not African American	30		22				0.275[a]	30		8			2.705	0.100[a]	22		8				0.017[a]
	Mean	*SD*	*Mean*	*SD*				*Mean*	*SD*	*Mean*	*SD*				*Mean*	*SD*	*Mean*	*SD*			
Age at NIH hospitalization (yr)	14.17	2.00	12.17	2.48	68	3.711	<.001[b]	14.17	2.00	13.14	2.82	58	1.585	0.118[b]	12.17	2.48	13.14	2.82	42	1.206	0.235[b]
Dose at discharge (mg/day)	342	152	350	135	66	0.241	0.811[b]	342	152	364	89	55	0.548	0.586[b]	350	135	364	89	41	0.357	0.723[b]
Length of stay (days)	114.1	44.7	114.7	46.7	63	0.049	0.961[b]	114.1	44.7	126	30.6	55	1.018	0.313[b]	114.7	46.6	126.8	30.6	36	0.890	0.380[b]

[a] χ^2 test.
[b] Independent-samples *t*-test.
HAE, hematologic adverse effect; ANC, absolute neutrophil count.

admission. The mean time between hospitalization and the most recent follow up visit was 5.9 ± 3.8 years (range 1.1–20.8). Of these 50 patients, 45 were on clozapine at most recent follow up and 5 were not. Reasons for discontinuation of clozapine included low blood counts ($n = 1$), seizures ($n = 1$), sedation and concentration problems ($n = 1$), poor symptom control ($n = 1$), and entry into an open label study of olanzapine at the NIMH ($n = 1$). The patient with low blood counts leading to discontinuation of clozapine by the patient's outpatient psychiatrist did not have mild or moderate neutropenia while hospitalized at the NIMH.

Discussion

In this study, there were surprisingly high rates of moderate neutropenia at 20%. This rate of moderate neutropenia is considerably higher than the cumulative 1 year incidence found in adult studies (3%), despite the fact that our patients were observed for < 1 year on average. This is also higher than the incidence in the study by Gerbino-Rosen et al. (2005), which showed a 1 year cumulative incidence of 16.1% in children and adolescents, although that study looked at patients of an older average age (15 years). Despite these high rates of neutropenia in our patients, there were no incidences of agranulocytosis or serious infection, in either those who were continued on the medication despite neutropenia (prior to 2003), or those in whom the medication was stopped and a re-challenge attempted (after 2003). Also notable is the fact that all but 1 of the 17 patients with moderate neutropenia during hospitalization were able to be safely discharged on clozapine. This is consistent with recent reports suggesting that careful re-challenge can be safely considered in clozapine-treated patients who develop neutropenia (Manu et al. 2012).

Male gender was a significant risk factor for both mild and moderate neutropenia. To our knowledge this is the first time this has been reported in clozapine-treated children. This is also the youngest group of patients in whom the relationship between age and risk for neutropenia during clozapine treatment has been investigated. We found younger age to be a risk factor for mild neutropenia in our sample, but it was not a risk factor for moderate neutropenia, in contrast to the population studied by Gerbino-Rosen et al. (2005). If they developed neutropenia at all, African Americans were significantly more likely to develop moderate neutropenia, rather than mild neutropenia only.

Limitations

In this study, we do not have a comparison group of patients who were medication free, or taking another antipsychotic. These contrast groups are difficult to obtain as it is not easy to find medication free COS patients and general practice guidelines for other antipsychotics do not include obtaining routine complete blood count (CBC) values. We were not able to report meaningful baseline ANC values for our patients because the majority of them (83 of 87) were either on clozapine or another antipsychotic on admission, and all of these medications are known to induce neutropenia to some degree. However, all patients were required to have an ANC >2000 and WBC >3500 (after 2003) or only a WBC >3500 (prior to 2003) before the initiation of clozapine.

Although all included patients were treated with clozapine during their hospitalization, we did not have sufficient data to do a meaningful analysis of the trajectory of ANC values in neutropenic patients, or to correlate weekly dose changes in clozapine administration with changes in ANC. We did not restrict the use of concomitant non-antipsychotic medications. Therefore, reduced ANC values in our patients could be influenced by other factors than clozapine use.

There are other limitations of a retrospective study, such as lack of randomization to clozapine, and standardized titration schedules. Some patients were lost to follow-up after their hospitalization; therefore, it is possible that the rate of discontinuation after discharge because of neutropenia is underestimated. This study also looked at inpatient hospitalizations over a period of 20 years, during which the blood monitoring practices and management of clozapine-induced neutropenia have changed. Although a complete blood count with differential was obtained at least weekly from each patient on clozapine, in the 1990s total WBC values alone were used instead of ANC values to make decisions about discontinuing the medication, or increasing the frequency of blood monitoring. Therefore, patients admitted later on in the study were more likely to be started on lithium carbonate or taken off clozapine for ANC values <1500/mm^3. We decided to include these patients in the study because all but three patients had recorded ANC values <1500/mm^3 before any kind of intervention was initiated.

Clinical Significance

Clozapine remains the most effective medication for children and adolescents with severe, treatment-refractory schizophrenia or other psychotic illnesses that have not responded to first line antipsychotics. The purpose of regular monitoring is to become aware of falling blood counts, as a predictor of agranulocytosis. However, care must be taken in the interpretation of low ANCs in children. The characteristics that we found to be independent risk factors for neutropenia in clozapine-treated children – African American ethnicity, male gender, and younger age – are all risk factors for benign neutropenia seen in healthy children and adolescents. This suggests that the mechanism for clozapine-related neutropenia may be related to the risk for low baseline ANC.

We did not see any cases of agranulocytosis in our patients during hospitalization, or in the subset for which we have long-term follow-up data. However, if children shared the risk of 0.8% over 1 year, seen in large studies of adults, then we would not expect to see a case in our sample of 87 patients. Although the high rate of neutropenia seen in these children may be an effect of clozapine, there is no evidence yet to suggest it is related to impending agranulocytosis or an increased risk of infection. Therefore, it is possible that using guidelines based on adult studies leads to unnecessary monitoring and discontinuation of the medication in children for whom this is the medication of last resort. Further study of neutropenia in children treated with clozapine and benign neutropenia in healthy children would be useful to determine safe age- and ethnicity-adjusted ANC thresholds.

Disclosures

Drs. Maher, Tossell, Miller, Greenstein, Overman, Rapaport, and Gogtay and Mr. Tan, Mr. Weisinger, and Mr. Gochman had no conflicts of interest or financial ties to disclose.

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