Lithium to Allow Clozapine Prescribing in Benign Ethnic Neutropenia

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Introduction

Clozapine is the gold standard antipsychotic for treatment-resistant schizophrenia. As life-threatening agranulocytosis occurs in approximately 1% of patients treated with clozapine (1, 2), regular monitoring of white blood cell (WBC) and absolute neutrophil counts (ANC) is mandated. Clozapine can only be prescribed if certain hematological parameters are met. If granulocytopenia occurs during treatment, clozapine must be interrupted or, in the case of agranulocytosis, discontinued. The cutoff values for the treatment decisions are based on normative values from white populations (3). These population-based values pose a problem for people of African descent as up to 50% have benign ethnic neutropenia (BEN) (3). This is a condition in which a low ANC is maintained in healthy individuals without evidence of negative consequences such as increased risk of infections (3, 4). We describe the case of an African immigrant with treatment-resistant schizophrenia who was successfully treated in the United States with clozapine despite having BEN. Lithium was used to increase his ANC in a dose-dependent manner so clozapine could be administered according to U.S. guidelines.

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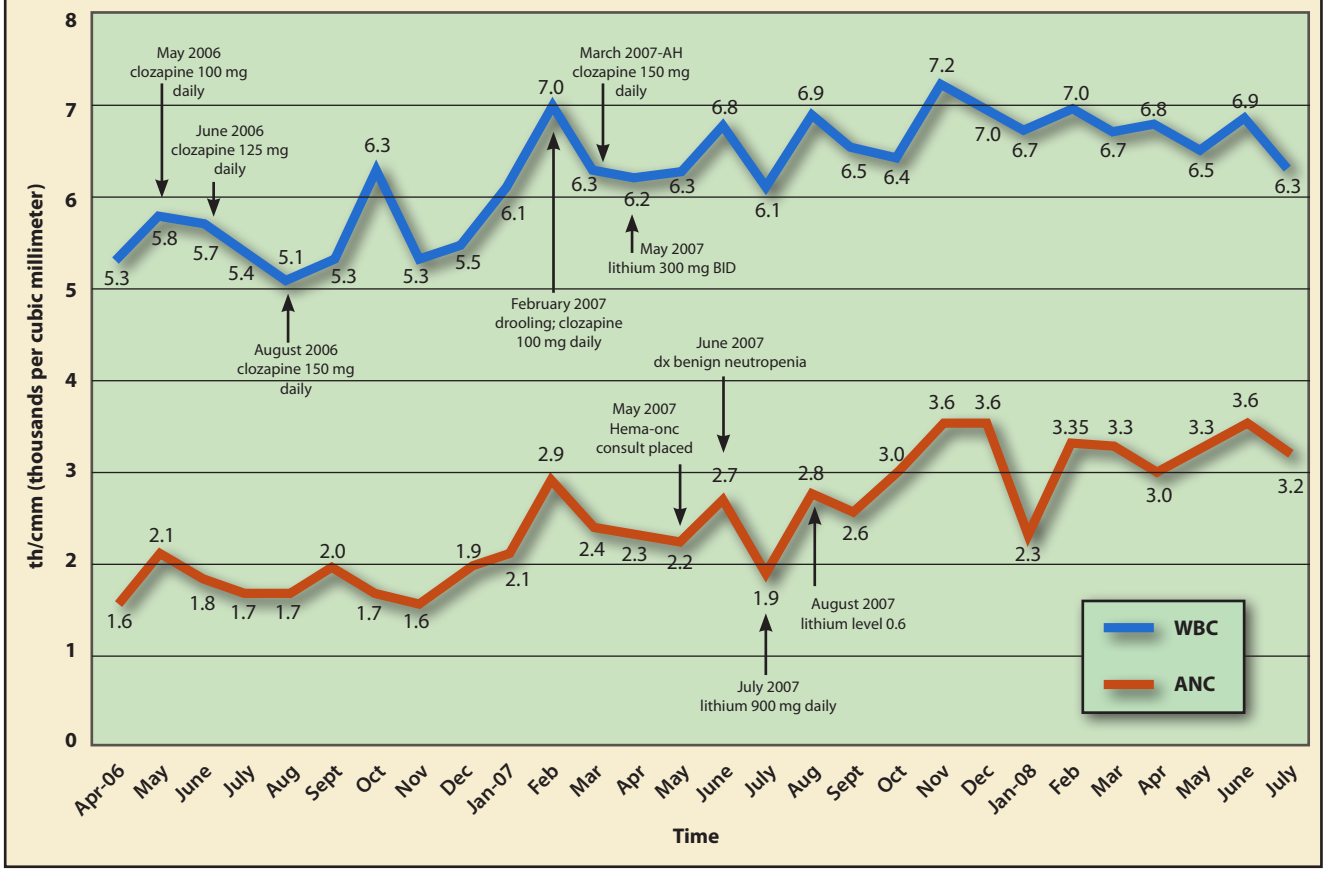
Case Report

Mr. A was a 40-year-old man who was born in Western Africa and raised in the U.S. In his twenties, he developed paranoid schizophrenia, complicated by incessant, insulting auditory hallucinations that told him he was worthless and would never be successful. Antipsychotic trials over the decades have included haloperidol, perphenazine, fluphenazine, olanzapine, quetiapine and ziprazidone, none of which ever successfully eliminated the voices. Early in his treatment, clozapine was considered but not pursued secondary to his chronically low WBC and ANC (an average of 4.1 mm^3 and 1.3 mm^3, respectively). Despite his significant psychopathology and constant hallucinations, his functioning has often been good and he held jobs and even published some books.

However, over the years, he has had periods where it was difficult for him to ignore the voices, and two years ago he was arrested after assaulting a stranger in response to the voices. Prior to the assault he had been switched from risperidone to aripiprazole and it was thought this may have contributed to his decompensation. The arrest led to a forensic hospitalization during which a clozapine trial was revisited. Given the escalation in his behavior as the result of his symptoms and because the patient continued to suffer, experiencing incessant hallucinations without reprieve,

Figure 1 Treatment with Lithium to Increase ANC



clozapine was initiated and titrated to 150 mg daily. His initial WBC and ANC were 4.9 mm^3 and 2.1 mm^3, respectively. Within two weeks, Mr. A reported less frequent and bothersome voices, as well as increased energy and concentration.

Approximately three weeks after initiation, his ANC was 1.8 mm^3 despite a WBC of 6.1 mm^3. There was concern the drop was related to clozapine and the dose was decreased to 100 mg daily. His reported ANC one week later was 2.1 mm^3. Given his chronically low WBC and recent drop in ANC, a hematology-oncology consult was obtained to rule out any underlying pathology. This consult resulted in a diagnosis of benign ethnic neutropenia (BEN). Mr. A was continued on clozapine at 100 mg daily, but after four months began to complain of increasing voices and the dose was returned to 150 mg daily. Over the next eight months, he was unable to tolerate any dose higher than 150 mg daily due to sedation. Throughout this period, his ANC was as low as 1.6 mm^3, with an average of 1.98 mm^3. Fourteen months into treatment, a decision was made to initiate lithium to stimulate granulocytosis primarily to allow for the eventual decrease in monitoring frequency and to avoid intermittent treatment interruptions or increased WBC monitoring as per U.S. guidelines. Lithium was initiated at 300 mg twice daily and increased to 900 mg daily after eight weeks. His average ANC, from the initiation of lithium to the present, is 2.8 mm^3. He has continued to report decreased symptoms, does not experience extrapyramidal side effects, is gainfully employed and has published another book since the initiation of clozapine. The addition of lithium has allowed the frequency of his blood work to decrease to every other week. (See Figure 1.)

Discussion

Clozapine is known to induce neutropenia in up to 2.8% of patients (18). While the etiology is not completely understood, myeloid cells are abundant and the neutropenia is thought to be secondary to a reduction in granulocyte and macrophage-colony stimulating factor (GM-CSF). In the much rarer case of clozapine-induced agranulocytosis, myeloid and myeloid precursor cells are not present, possibly as the result of an immunologically mediated response (17) or cytotoxic reaction that selectively affects these cells, leading to apoptosis (5). GM-CSF is a glycoprotein growth factor that stimulates precursor granulocyte and macrophage cells in the bone marrow to form mature colonies (19) and enhances mature neutrophil functioning (5). It can be given

to treat clozapine-induced neutropenia and has been shown to increase the time of recovery from clozapine-induced agranulocytosis. However, the treatment is cost prohibitive and invasive, requiring daily or weekly injections (7), thus limiting its use. The use of lithium to boost granulocyte count in cases of neutropenia, including clozapine-induced neutropenia, has been previously documented (2, 5-7). Lithium is thought to exert this effect by a combination of redistribution of marginated granulocytes and by stimulating granulocyte production (4). However, in this case, the patient's chronically low WBC and ANC were attributed to a common condition, BEN. Lithium increased the ANC in a dose-dependent manner: the average ANC during the 600 mg daily lithium dose was 2.5 mm^3, increasing to 3.2 mm^3 with a daily lithium dose of 900 mg and a lithium level of 0.6. The use of lithium allowed uncomplicated prescribing of clozapine, eventually lowering the blood monitoring frequency.

Added lithium treatment is not without risk, including the possibility of inadvertent lithium toxicity and, during long-term administration, kidney and thyroid damage. Lithium added to antipsychotics has been associated with serious extrapyramidal side effects (8, 9). Seizures have been reported after the addition of lithium to clozapine treatment (10). Clinicians must also remain aware of the fact that lithium does not prevent clozapine-induced agranulocytosis but might delay its detection (5, 11). Given the likely immunomediated or cytotoxic destruction of cells in the case of agranulocytosis, the myleostimulatory effects of lithium would eventually be overcome (11, 12). It is important to review the risks and benefits of added lithium treatment with all patients, as well as to closely monitor lithium levels, renal function and TSH in appropriate intervals.

Without lithium, our patient had to accept an unnecessary monitoring burden despite a nonpathological condition—a case of "treating numbers" instead of the patient. BEN puts patients at a disadvantage even if their baseline is normal since any fluctuation in ANC, whether caused by diurnal variation (13) or laboratory error (14) can put the patient inside the "danger zone" of low ANC. Our use of lithium allowed a patient with BEN to be treated with clozapine but we must question if this end justifies the means. Is it justified to demand potentially toxic lithium use for rather purely bureaucratic reasons? And, perhaps more importantly, is it fair to subject nonwhite ethnic groups to standards derived from white populations and create ethnic disparities? A chart review of 1,875 patients with schizophrenia found that significantly more African Americans than white patients discontinued clozapine due to leukopenia (15). Given the prevalence of BEN in this population, it is likely that a great number of these patients had their treatment interrupted or discontinued unnecessarily, as the U.S.'s normative standards for WBC and ANC measurements do not take into account ethnic differences (16). Withholding or stopping treatment for African/African Americans with normal physiology that does not fit guidelines based on largely white populations is not only unfair, but unnecessary. A low baseline WBC and African-American ethnicity are not predictors of future development of agranulocytosis (1). The Clozaril Patient Monitoring Service (CPMS) in the United Kingdom and Ireland has adopted a practice of considering a lower ANC cutoff for patients with benign ethnic neutropenia (1). The U.S. should follow suit to assure that all patients have equal access to the most effective treatments.

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