Chronic Leukocytosis Associated with Clozapine Treatment

Michael A. Sopko [1], Charles F. Caley [2]

Abstract

Clozapine is an important second-generation antipsychotic that is reserved for patients with refractory schizophrenia. Unfortunately, clozapine is also associated with a number of adverse effects, with agranulocytosis being one of the chief concerns. Interestingly, patients who receive clozapine treatment may occasionally experience elevations in their total white blood cell count (WBC). In some of these patients, the leukocytosis may be persistent. We report the case of a patient with refractory schizophrenia who is treated with clozapine and who experienced chronic leukocytosis. A brief review of the literature addressing clozapine-associated leukocytosis follows the case report.

Key Words: Clozapine, Side Effects, Leukocytosis

Introduction

Clozapine is an atypical antipsychotic indicated for the management of treatment-resistant schizophrenia that carries a risk for several severe adverse effects (1). A long-standing barrier to clozapine treatment has been its risk for agranulocytosis and neutropenia necessitating regular hematological monitoring. Initially, it was feared that clozapine would cause a leukopenia rate of 2.8%, and an agranulocytosis rate of 1 to 2% (2). However, between 1990 to 1994, there were 99,502 patients registered with the Clozapine National Registry (CNR) and the incidence rates of agranulocytosis (ANC<500/mm^3) and leukopenia (WBC<3,000/mm^3) during this period were 0.38% (382 patients) and 2.95% (2,931 patients), respectively (2). Based on these results from the CNR, the U.S. Food and Drug Administration reduced the frequency of WBC monitoring after six months of treatment to every fourteen days instead of weekly (2).

In addition to agranulocytosis and neutropenia, clozapine also has been reported to be associated with other types of blood dyscrasias, including leukocytosis (3). The mechanism by which clozapine may cause leukocytosis is unknown, but increases in granulocyte colony-stimulating factor and tissue necrosis factor-alpha have been proposed (4-6).

Deliliers attempted to determine the incidence of various blood dyscrasias with clozapine, including leukocytosis, using the Italian Clozapine Monitoring System (ICLOS) (7). From the 2,404 patients analyzed in this system, the incidence of leukocytosis was reported to be 7.7%, and was more frequent in males than females (9% and 6.4%, respectively) (7). Hummer et al. performed a prospective analysis of a clozapine monitoring program to determine the incidence

[1] *Touro College of Pharmacy, New York, NY*
[2] *University of Connecticut School of Pharmacy, Storrs, CT*

Address for correspondence: Charles F. Caley, PharmD, BCPP, Institute of Living, Burlingame Center for Psychiatric Research and Education, 200 Retreat Avenue, Hartford, CT 06106
Phone: 860-545-7228; Fax: 860-545-7066; E-mail: c.caley@uconn.edu

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rates of various blood dyscrasias in sixty-eight patients taking clozapine (8). Of these, 40.9% developed leukocytosis which lasted an average of 1.3 weeks. One patient developed chronic leukocytosis, with WBC counts ranging between 11.1K cells/mm^3 to 15.6K cells/mm^3 over two years.

Chronic leukocytosis in the absence of infection or a medical condition has been reported in only a few cases with clozapine treatment. Trinidad et al. reported a case of a 41-year-old Caucasian male treated with clozapine for the stabilization of paranoid schizophrenia (9). A medical record review indicated a normal WBC count prior to the initiation of clozapine, with leukocytosis (15.4K cells/mm^3–24.4K cells/mm^3) manifesting shortly thereafter and lasting for a period of eight years. However, leukocytosis was not entirely attributed to clozapine in this case, since the patient was also on concurrent lithium therapy (9).

Popli et al. reported a case of a 50-year-old Caucasian male treated with clozapine for chronic schizophrenia (10). Pertinent medical history included a past head injury and a splenectomy at age seventeen secondary to a motor vehicle accident. Before clozapine treatment, the patient had a normal WBC count of 5.2K cells/mm^3 with a normal differential. After reaching a clozapine target dose of 350 mg/day, WBC counts fluctuated between 5.2K cells/mm^3 and 12.2K cells/mm^3. A WBC count of 15.6K cells/mm^3 was observed at week 16, without sore throat, rash, or flu-like symptoms. From week 16 to week 23, the patient presented with intermittent leukocytosis, ranging from normal to significantly elevated WBC counts (10).

Madhusoodanan et al. reported seven cases of chronic leukocytosis with clozapine (11). All patients were afebrile without any evidence of infection or other potential causes of increased WBCs (trauma, burns, etc.). All seven patients were males, and six patients had clozapine doses ≥450 mg/day. The highest peak WBC level reported for these seven patients was 19.8K cells/mm^3; leukocytosis for these patients has been reported for a duration of 2 to 5 years. The course for all patients was benign in nature, as there were no adverse effects associated with the leukocytosis. These authors also addressed chronic cigarette smoking and male gender as being possible leukocytosis risk factors (11).

We wish to report a case of chronic leukocytosis associated with clozapine treatment in an outpatient with a history of schizophrenia, paranoid type.

Case

Our patient (OP) is a 37-year-old Caucasian male with a history of treatment-refractory paranoid schizophrenia. The patient also has a diagnosis of obsessive-compulsive disorder (OCD), a history of substance abuse, and has had multiple psychiatric hospitalizations over the past thirteen years.

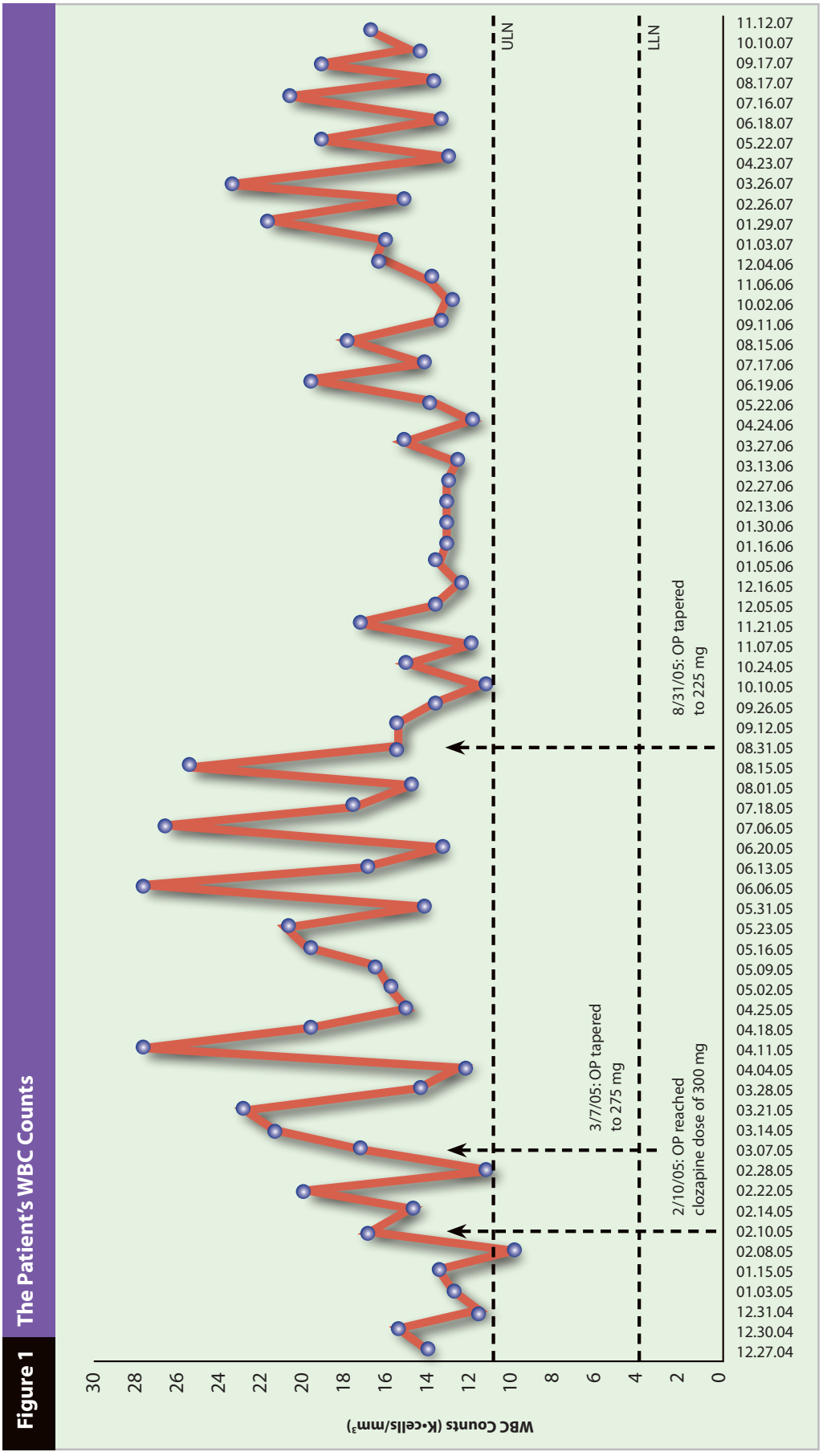
The patient was started on clozapine in December 2004. He was titrated to a target dose of 300 mg by February 2005. The core concurrent medications of OP's treatment regimen, since the initiation of clozapine, have been fluoxetine, clonazepam, disulfuram, esomeprazole and clomipramine. Other medications that OP has been treated with since clozapine initiation include: haloperidol, benztropine, lansoprazole, trazodone, zolpidem, and donepezil.

In February 2005, the patient reported flu-like symptoms, with myalgias, arthralgias, and headaches being the most prominent. Blood concentrations measured a clozapine level of 837 ng/mL and a norclozapine level of 374 ng/mL. Because the patient was thought to possibly be a slow metabolizer, the clozapine dose was decreased to 275 mg/day. In August 2005, the dose was decreased further to 225 mg/day. Blood levels measured in February 2006, while OP was still taking 225 mg/day, indicated a significant reduction, with clozapine at 406 ng/mL and norclozapine at 232 ng/mL.

Since the introduction of clozapine, the patient has been observed to have a chronic leukocytosis. The WBC counts have ranged from 11.1K cells/mm^3 to 27.7K cells/mm^3, without any apparent medical condition or infection being the cause. Figure 1 illustrates OP's WBC counts during his clozapine treatment. Prior to the initiation of clozapine, OP's WBC counts had been either slightly elevated or within normal limits. The highest recorded WBC level before the start of clozapine was 14.6K cells/mm^3. During clozapine treatment, 54% of all measured WBCs were greater than 14.6K cells/mm^3 and 99% were greater than 11.0K cells/mm^3.

Multiple consultations have been made to determine the cause of the chronic leukocytosis. In February 2005, a consult was made to a physician who found no signs of infection. The following month, the patient was given an HIV antibody test, which was negative. Two weeks later, a Lyme antibody IgG/IgM screen was performed, and was also negative. In March 2005, a pulmonologist performed a complete sinus CT scan. OP's frontal, sphenoid, and maxillary sinuses were well aerated and clear. There was a patchy mucous in the ethmoids bilaterally, but this was not identified as a potential cause for chronic leukocytosis. In April 2005, OP was determined to have an acute upper respiratory infection (URI), with a body temperature of 99.8° F, chills, sinus congestion, and body aches. However, this URI cannot account for OP's chronic leukocytosis during the previous three months. In May 2005, OP had a myoglobin level of 604 ng/mL, with muscle aches of varying intensity. The patient was diagnosed with rhabdomyolysis, but the myoglobin level was 30 ng/mL upon follow-up. OP's pulmonary and abdominal CT scans were all negative in July 2005, and a dental examination was also negative for infection. An infectious disease special-

Figure 1 The Patient's WBC Counts



ULN=upper limit of normal; LLN=lower limit of normal

ist diagnosed OP with sinobronchial syndrome. However, it was determined that this was unlikely to account for the chronic elevation in the patient's WBCs. The patient reported being "exposed" to tuberculosis (TB) in 2002, resulting in treatment with antibiotics. Subsequent chest X-rays revealed that OP did not contract active TB.

Discussion

Reports of chronic leukocytosis with clozapine treatment have been limited to a few cases and one case series (9-11). While it appears to be rare, chronic leukocytosis associated with clozapine treatment may be occurring more frequently than previously believed. The mechanism by which this phenomenon occurs is unknown, but it is theorized that changes in G-CSF and TNF-α blood concentrations may be important (4, 5). Other potential causes include cigarette smoking, male gender, and medications (e.g., lithium).

In this patient, chronic leukocytosis developed after the implementation of clozapine to treat paranoid schizophrenia. Multiple consultations did not reveal evidence of any infection, or any other potential cause for the patient's chronic leukocytosis. Also, WBC levels above 14.6K cells/mm^3 were not seen prior to clozapine treatment, further implicating clozapine as a potential contributor to this finding. The likelihood that clozapine caused the chronic leukocytosis was determined to be "possible" based on a Naranjo ADR Probability Scale score of 3 (12).

Another potential cause of leukocytosis in OP could be the concomitant use of esomeprazole. The product labeling for esomeprazole indicates that the incidence of leukocytosis is less than 1% (13). OP was initiated on esomeprazole in February 2005, so its contribution to the leukocytosis cannot be easily dismissed. However, there are no known published case reports of chronic leukocytosis with esomeprazole. Also, the possibility of esomeprazole causing or contributing to OP's condition markedly reduced the Naranjo ADR Probability Scale score from 6 to 3, despite the clinical improbability of this interaction occurring (12).

Our case report appears to be most similar to the case reported by Trinidad et al. (9). Both patients had persistently elevated total WBC counts after the initiation of clozapine treatment, and both patients had peak WBC counts well above 20.0K cells/mm^3. The patient reported by Trinidad et al. had elevated WBC counts for eight years; our case has experienced elevated WBC counts for nearly four years. Three important differences between the two cases include: 1) our patient had WBC counts above the upper limit of normal prior to starting clozapine treatment; 2) there was one identified infection that our patient experienced; and, 3) our patient was not receiving concurrent lithium treatment.

Conclusions

We report the case of a clozapine-treated patient who has experienced chronic leukocytosis for nearly four years. Previously published reports have reported similar findings. Chronic leukocytosis, associated with clozapine treatment, appears to be a benign condition that has no detrimental effects. Clinicians who elect to use clozapine treatment for their patients should be aware that chronic leukocytosis may be associated with clozapine treatment. Additional work is needed in order to determine the true incidence of this blood dyscrasia and what the cause(s) are.

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