Clozapine Treatment in a Patient with a Persistently Low Neutrophil Count

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Key Words: Schizophrenia, Clozapine, Side Effects

Introduction

Clozapine is an atypical antipsychotic that is effective for treatment-resistant schizophrenia (1). Despite its therapeutic advantages, clozapine has many safety risks associated with its use. Agranulocytosis with clozapine is known to occur most commonly within the first four to six months of treatment. Approximately 0.8% of clozapine–treated patients are reported to develop agranulocytosis (absolute neutrophil count [ANC] <500 cells/mm^3), while 2.9% are reported to develop neutropenia (ANC <2,000 cells/mm^3) (2, 3). In patients for whom the ANC falls below 1,500 cells/mm^3, there is a need to interrupt clozapine treatment. When the ANC falls below 1,000 cells/mm^3, patients are not eligible for a clozapine rechallenge (4). Development of neutropenia may be a sign of impending agranulocytosis, but not all neutropenic patients will progress to agranulocytosis. Since there are few effective treatment options for patients with treatment-resistant schizophrenia, the guidelines for hematologic monitoring may prevent some patients from access to this uniquely effective drug. We report a case of clozapine treatment in a patient with a persistently low ANC for which the etiology is unclear.

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Submitted: Aug 21, 2007; Revised: Aug 22, 2007;
Accepted: Aug 22, 2007

Case Report

The patient is a sixty-year-old white male residing in a supervised group home with a long history of schizophrenia and multiple antipsychotic treatment trials. The patient had clozapine treatment started in September 2000 due to persistent delusions and suboptimal psychosocial functioning while receiving concurrent risperidone and olanzapine therapy. Other concurrent medications at that time included clonazepam, divalproex, gemfibrozil, glyburide, metformin, and rosiglitazone. At the time of clozapine treatment initiation, the patient's baseline white blood cell count (WBC)/ANC level was 4.2 cells/mm^3/1.8 cells/mm^3, but the patient had an historical ANC of 1,400 cells/mm^3 measured in December 1999. The patient was treated with up to 400 mg/day of clozapine for nearly six continuous years.

During clozapine treatment, the patient had seventy ANC values that were below 2,000 cells/mm^3; 10% of these values were below 1,500 cells/mm^3. Overall, measured ANCs ranged from 1,150 to 6,810 cells/mm^3. During this same time period, the patient did not develop an abnormal platelet or eosinophil count. Other than the occasional cold, at no time did the patient develop any signs or symptoms of any other infection. During the six years of clozapine treatment, a hematologist was consulted twice. In each instance, the treat-

ment team was informed that while close monitoring was important, this patient's clozapine treatment could be maintained as long as measured ANCs were above 1,000 cells/mm^3 (this appears to be the lower limit for which phagocytic function is sufficient to prevent infection) (5). In February 2006, the patient had an ANC of 1,150 cells/mm^3; this finding resulted in a clozapine taper and discontinuation that was completed by June 2006 -- the patient was switched to ziprasidone.

Within the ensuing two months, the patient required an inpatient hospitalization because of suboptimal ziprasidone effectiveness. During this period, the patient's ANC remained low, with a nadir of 1,530 cells/mm^3, and ranged from 1,530 to 4,270 cells/mm^3 while off clozapine. Ziprasidone treatment was followed by treatment with haloperidol, risperidone, and divalproex without response. After a third consultation with hematology, it was determined that clozapine could be re-initiated once the neutropenia resolved. Clozapine treatment was re-initiated one day after a dose of granulocyte colony stimulating factor (G-CSF) was given; the patient's mental status has since improved dramatically. The WBC/ANC level prior to the G-CSF dose was 3.3 and 1.9 cells/mm^3, respectively; this peaked at 18.4 and 15.5 cells/mm^3, respectively, one day after G–CSF 480 mcg was administered. As the patient continued on clozapine 425 mg/day, his ANC remained as before, with a post-discharge nadir of 1,130 cells/mm^3, and has ranged from 1,130 to 4,160 cells/mm^3. Presently, the treatment team is adhering to routine monitoring (every one to two weeks as indicated by protocol) of this patient's WBC/ANC, and continuing clozapine unless the patient's ANC falls below 1,000 cells/mm^3.

Approximately 0.8% of clozapine-treated patients are reported to develop agranulocytosis (absolute neutrophil count [ANC] <500 cells/mm^3), while 2.9% are reported to develop neutropenia (ANC <2,000 cells/mm^3).

Discussion

Potential causes of neutropenia include, but are not limited to, chemical exposure, infection, neoplastic/autoimmune processes, and/or treatment with myelotoxic drug(s). Our patient was concurrently receiving medications prior to (and during his treatment with) clozapine, which have been reported to cause either neutropenia or agranulocytosis. Abnormal WBC findings have been reported for valproic acid (6), olanzapine (7), risperidone (8), ziprasidone (9), rosiglitazone (10), and glyburide (11). Each of these medications was either discontinued permanently, or temporarily, during the patient's clozapine treatment--despite this, there were no changes in the WBC/ANC patterns that were measured for this patient.

In addition to the above causes of neutropenia, there is also a phenomenon associated with clozapine known as morning pseudoneutropenia, where the morning neutrophil count is low, but sampling at another time of the day reveals a normal neutrophil count (12, 13).

In cases where neutropenia develops, it may be advisable to use granulocyte colony stimulating factor to elevate the neutrophil count so that the patient may remain on clozapine.

There are two cases (14, 15) of maintained clozapine treatment despite an episode of neutropenia (ANC <1,500 cells/mm^3), but this is the first case that describes the continuation of clozapine treatment during multiple episodes of neutropenia. One report (14) describes a patient with schizophrenia who was able to continue clozapine treatment during a neutropenic episode while receiving myelosuppressive chemotherapy for testicular cancer.

Since clozapine is uniquely effective for patients with treatment-resistant schizophrenia, development of neutropenia may leave the patient and clinician without other effective treatment options. In these cases it may be necessary to reinitiate clozapine. Unfortunately, 38% of patients will experience a second, and frequently more severe, blood dyscrasia upon re-initiation (16). In cases where neutropenia develops, it may be advisable to use G-CSF to elevate the neutrophil count so that the patient may remain on clozapine. There is some evidence (17-19) that this is an effective strategy in carefully selected patients.

Conclusion

We believe that attribution of the low ANC in our patient is unlikely to be clozapine-related. Prior to initiating clozapine, the patient had a low ANC. This may be an indication of the patient's phenotype with respect to white blood cell production. Also, the patient's low white blood cell count persisted despite multiple medication changes, including the discontinuation of clozapine. The decision to continue treatment with clozapine was supported by the patient's known responsiveness to clozapine, the ability to closely monitor for signs and symptoms of infection, the availability of G-CSF, and the hematologist's recommendation to continue unless the patient's ANC dropped below 1,000 cells/mm^3. Patients with low baseline neutrophil counts may be able to continue closely monitored clozapine treatment without developing agranulocytosis.

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