Leukopenia Induced by Quetiapine in a Patient with History of Clozapine-induced Leukopenia

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Objective: Many antipsychotic medications can cause hematological abnormalities. Quetiapine is a dibenzothiazepine derivative similar to clozapine, an antipsychotic agent which has the highest risk of causing blood dyscrasias. A case of quetiapine-induced leukopenia is described here in a patient who had a previous history of leukopenia induced by clozapine. Case Report: A 34-year-old Taiwanese woman patient with schizophrenia had a history of clozapine-induced leukopenia. She developed leukopenia again after her receiving quetiapine treatment. After quetiapine was discontinued, her white blood count was increased to a normal range. Conclusion: Physicians should be cautious of having potential hematological abnormalities before prescribing leukopenia-causing drugs, especially in patients with a history of drug-induced leukopenia.

Key words: clozapine, quetiapine, leukopenia, blood dyscrasia


Introduction

Many antipsychotic medications can cause hematological abnormalities such as eosinophilia, leukopenia, leukocytosis, and agranulocytosis. Among all antipsychotic medications, clozapine is the most well-known drug of causing hematologic abnormalities. Clozapine has the highest leukopenia risk, which has also been observed in risperidone, olanzapine, and quetiapine. Similar to clozapine, quetiapine is a dibenzothiazepine derivative in chemical structure. Quetiapine is characterized by high 5-HT₂ related to DA₂ receptor affinity. In this case report, a patient with a previous history of clozapine-induced leukopenia is presented with quetiapine-induced leukopenia.

Case Report

A 34-year-old Taiwanese female patient first diagnosed with schizophrenia at age 29 years, had received haloperidol, amisulpride, risperidone and flupentixol injection for the first few years after the diagnosis. Due to poor drug compliance, she was admitted to the psychiatric ward several times

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for the treatment of acute exacerbations of psychotic symptoms including persecutory delusions, auditory hallucinations as well as self-harming and destructive behavior. Her white blood counts were ranged from 3,490 cells/μL to 6,900 cells/μL during those hospitalizations. Two years before this admission, she received clozapine. Her drug compliance was improved and white blood counts were checked regularly. After her psychotic symptoms were stabilized, the patient had received the maintenance clozapine dosage at 300 mg HS for about one year. She developed side effects of hypersalivation and sedation during the first few months of clozapine use. About six months ago, her white blood count was dropped to 2,330 cells/μL. Although she did not show clinical symptoms of leukopenia except for a low white blood count, patient’s clozapine was discontinued immediately and switched to olanzapine. She did not show up for the follow up clinic appointments after her medication change.

Two weeks before her appointment, the patient was admitted to our hospital, because she was found to have locked herself up in her room and cut her wrists in response to auditory hallucinations and persecutory delusions. But she was admitted to a psychiatric ward of another hospital. On the day of admission, her white blood count was 7,600 cells/μL. She was then treated with quetiapine 200 mg/day and haloperidol 5 mg/day. But the drug response was poor and she experienced severe Parkinsonian symptoms including hand tremors, bradykinesia and rigidity. She was later referred to our inpatient service by her family. On the day of admission to our hospital, the results of her physical examination and laboratories were normal except for bilateral wounds of her wrists and a white blood count being 8,200 cells/μL. We discontinued haloperidol and titrated quetiapine to 200 mg BID. After her admission, she received trihexyphenidyl hydrochloride 10 mg BID, and flunitrazepam 3 mg HS for extrapyramidal side effects and insomnia, respectively. On day 13 of admission, we rechecked her white blood count because of poor wound healing; her white blood cell count was 3,400 cells/μL. On day 20 of admission, her Parkinsonian symptoms, psychotic symptoms, and wound healing were improved, and she was discharged with a white blood count of 2,900 cells/μL. Quetiapine was discontinued, and her antipsychotic agent was switched to ziprasidone 120 mg/day. The hematologist also suspected that leukopenia was caused by quetiapine, and suggested further observation.

Our patient was suggested for outpatient follow up because of the absence of infection. But she continued to have poor insight and returned to our clinic only once. She had poor drug compliance and also had irregular outpatient follow-ups at the clinic at other hospitals. Her ziprasidone was switched to olanzapine 20 mg/day during outpatient clinic follow ups at another hospital. Two months after discharge, her white blood count was increased to 3,900 cells/μL. Four months later, she was readmitted to a psychiatric ward because of recurrent psychotic symptoms after her having been free from any antipsychotic drug. Her white blood count was 6,900 cells/μL which was within normal range.

**Discussion**

In this case report, we have shown that a patient with a history of leukopenia induced by clozapine, also experienced the same side effect with quetiapine. Her other medications included trihexyphenidyl hydrochloride and flunitrazepam. A chronologic relationship existed between leukopenia development and increased dose of quetiapine. Leukopenia only appeared when she was tak-
ing quetiapine, and her white blood cell count was normalized after its discontinuation. Thus, we believed no other medications besides quetiapine could have caused leukopenia.

Leukopenia is defined as a white blood count below 3,000 cells/μL. Severe leukopenia is a predisposing factor for infections, and its symptoms can include headache, malaise, and fever. Leukopenia may result from associated physical and emotional stimuli, infections, tumors as well as metabolic, endocrinological, hematological, and congenital disorders. In addition, many medications such as antipsychotic agents, antibiotics, anticonvulsants, antidepressants and immunosuppressive agents can also decrease the number of white blood cells. The rates of quetiapine-induced blood dyscrasias including leukopenia and agranulocytosis are 1% and < 1%, respectively.

The literature focusing on quetiapine-induced blood dyscrasia mechanisms is scarce. A PubMed search yielded only five other case reports of quetiapine-induced leukopenia. The dosages of quetiapine for those cases were at least 600 mg/day. There may be in vivo or in vitro dosage-related blood dyscrasia phenomenon which was induced by quetiapine [1]. Four of the dyscrasia cases included individuals taking quetiapine and valproate [2-5]. The leukopenia incidence caused by valproate itself is about 0.5%. Valproate acid can increase quetiapine plasma levels up to 77%. Thus, the causes of leukopenia in the above cases might be related to the increased quetiapine blood levels, individual drug hypersensitivity, the combination of valproate and quetiapine, or valproate itself. In our case, the dosage of quetiapine was only 400 mg/day, which was lower than the other reported cases; there was no correlation with valproate which might increase quetiapine plasma levels. Quetiapine has a similar structure and pharmacologic profile of clozapine. Both have high 5HT₂-receptor affinity related to DA₂ receptors; quetiapine and clozapine, or their metabolites, may also cause blood dyscrasias.

Clozapine is a second-generation (atypical) antipsychotic drug which is effective in the treatment-refractory schizophrenia. Its use is limited in some patients due to its side effects of blood dyscrasias (eosinophilia, neutropenia, leukopenia, leukocytosis, agranulocytosis) and seizure. The incidences of leukopenia and agranulocytosis induced by clozapine are 3% and 1%, respectively. The mechanisms how clozapine causes blood dyscrasia are still unknown.

The hypotheses of leukopenia include bone marrow suppression and/or peripheral destruction of the white blood cells. Clozapine is metabolized through the mediation of cytochrome P450 1A2 (CYP1A2) mainly into norclozapine, which is believed to be the primary cause of blood dyscrasia [6]. A dose-dependent toxicity exists for blood dyscrasia; the higher medication dosage may have higher risks for causing blood dyscrasia [1]. Besides drug-induced blood dyscrasia, there may be dose-independent hypersensitivity. Certain haplotypes of human leukocyte antigen genes [7], such as tumor necrosis factor microsatellites d3, b4 [8], variant genes of HSP 70 (heat-shock protein), and dihydronicotinamide riboside (NRH). Quinone oxidoreductase gene (NQO₂) polymorphisms may be also associated with clozapine-induced agranulocytosis [9]. Our patient had leukopenia induced after the use of clozapine for 18 months. To differentiate if the leukopenia is resulted from dose-dependent toxicity or dose-independent hypersensitivity is hard, because our patient had received a stable dosage of clozapine. Clozapine rechallenge would be more likely to develop blood dyscrasia if they have already had its history. In rechallenged patients, the subsequent blood dyscrasia occurred more rapidly, last-
Leukopenia Associated with Quetiapine

Leukopenia associated with quetiapine may develop longer and/or were more severe than the previous blood dyscrasia [10]. Our patient may be more sensitive to dibenzothiazepine-derived medications because leukopenia developed later with quetiapine use.

Unlike clozapine, quetiapine does not have any clinical guideline for monitoring blood counts during its use because the rate of quetiapine-induced blood dyscrasia is rare. Our case is the first report of a patient who developed leukopenia with quetiapine after developing leukopenia with clozapine previously. Therefore, physicians should be cautious of hematological abnormalities and inform patients about the possible risk of blood dyscrasia before using those drugs. This caution is especially important in patients who have a history of drug-induced blood dyscrasia. If such adverse effects are suspected, immediate discontinuation of the offending medication is suggested.

References