Isr J Psychiatry Relat Sci Vol 44 No. 1 (2007) 54–56

Clozapine-Induced Eosinophilia and Switch to Quetiapine in a Patient with Chronic Schizophrenia with Suicidal Tendencies

Patricia Zipris, MD,[1,2] Yuval Melamed, MD, MHA,[1,2] Abraham Weizman, MD,[3] and Avi Bleich, MD, MPH[1,2]

[1] *Lev Hasharon Mental Health Center, Netanya, Israel*

[2] *Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel*

[3] *Laboratory of Biological Psychiatry, Felsenstein Medical Research Center, and Research Unit, Geha Psychiatric Hospital, Petah Tikva, and Sackler Faculty of Medicine, Tel Aviv University, Israel*

Abstract: Clozapine has proven effective in reducing morbidity and suicidality in chronic non-remitting patients with schizophrenia. Occasionally, despite good therapeutic response, clozapine must be stopped due to dangerous side effects such as agranulocytosis. Drug-induced eosinophilia is a non-dose-dependent side effect of clozapine. In cases of mild increments of eosinophils and if the patient is asymptomatic, there is no need to make an immediate decision. However, if the increment is severe and producing symptoms, withdrawing the probable causative drug is warranted. There is a possible association between eosinophilia and myocarditis, a life-threatening condition. The efficacy of corticosteroid therapy in the treatment of eosinophilia has not been clearly established. We present a case report where switching from clozapine to quetiapine maintained the improvement in clinical status, after remittance of eosinophilia.

Introduction

Patients with non-remitting schizophrenia, with partial response to neuroleptic treatment, are at higher risk for suicide. Clozapine has proven to be effective, reducing overall morbidity and suicidality in this population (1). Clozapine is also the treatment of choice for patients who fail to respond to adequate trials of one or more conventional antipsychotics and two atypical antipsychotics (Expert Consensus Guidelines and Algorithms) (2).

In some cases, however, despite good therapeutic response, clozapine therapy must be stopped due to dangerous side effects including agranulocytosis, seizures and diabetes (3).

There is a possible association between eosinophilia and myocarditis, a life-threatening condition. The efficacy of corticosteroid therapy in the treatment of eosinophilia has not been clearly established (4) since there are no placebo controlled trials assessing their effectiveness. There is no consensus regarding doses, but they generally tend to be high. Some patients may require long-term treatment, because of the possibility of relapse.

We report on a patient with chronic schizophrenia with a history of suicide attempts, who revealed improvement in positive and negative symptoms following initiation of clozapine treatment, but who subsequently developed non-dose-dependent eosinophilia.

Case Report

J. is a Latin American man, 28 years old, who was diagnosed with schizoaffective disorder according to DSM-IV criteria. Throughout the 14-year duration of his illness, J. received adequate trials of various first and second generation antipsychotic agents, including combination pharmacotherapy and augmentation with classic and novel mood stabilizers.

He was hospitalized repeatedly in public and private institutions in the United States and in Mexico because of serious suicide attempts and aggressive behavior. During various hospitalizations and in spite of compliance with medical treatment, he never achieved a stable and clear remission of his psychotic

Address for Correspondence: Dr. Patricia Zipris, Lev Hasharon Mental Health Center, POB 90000, Netanya 42100, Israel. E-mail: pzipris@lev-hasharon.co.il

symptoms. Thus, he was unable to participate in community-based rehabilitation programs.

In July 2004, J. was admitted to an open ward at Lev-Hasharon Mental Health Center, in Israel. His treatment prior to admission was olanzapine 20 mg/day, clonazepam 2 mg/day, lamotrigine 200 mg/day and venlafaxine extended-release 75 mg/day. At admission he had suicidal thoughts and was very agitated, with a score of 93 on the Positive and Negative Syndrome Scale.

Considering his long history of non-response to adequate trials of typical and atypical antipsychotic agents, absence of criteria for bipolar disorder or major depression, and prominent negative symptoms he was diagnosed as suffering from chronic schizophrenia. Because of psychotic agitation and suicidal thoughts, clozapine treatment was initiated.

Before beginning clozapine therapy, blood tests were normal. The patient received an initial dose of 25 mg/day, which was gradually increased to 150 mg/day. His mental condition gradually improved, he was less suicidal, became active in the ward and his PANSS score reduced to 56. An ECG revealed sinus tachycardia of 120 to 140 per minute, with no changes in blood pressure and without fever. Weekly blood tests showed eosinophils increased from normal values of 600 per mm3 to 1,200 per mm3 and finally 1,500 per mm3.

His mental condition notably improved and he gradually achieved a complete remission, with improvement in negative symptoms. Due to his satisfactory therapeutic response to clozapine treatment, the clozapine dosage was gradually reduced, but the eosinophilia proved to be non-dose-dependent. Because of the possible association between eosinophilia and myocarditis, a life-threatening condition, the patient underwent a cardiological examination including echocardiography that was normal.

After two weeks of reduced dosages of clozapine with no decrease of eosinophils, we concluded that the patient had developed an allergic reaction to clozapine and the medication was discontinued.

Considering the pharmacodynamic profile similarity between clozapine and quetiapine, clozapine was switched to quetiapine, beginning with 100mg/day, and up-titrated to 400mg/day in a period of 15 days. During the first few days of the switch to quetiapine treatment, the patient exhibited instability and partial relapse of psychotic symptoms, probably due to the gradual decrease of the dosage of clozapine parallel to the gradual up-titration of quetiapine, but he ultimately achieved a complete remission with quetiapine 400 mg/day. Despite the similar pharmacodynamic profile with clozapine, and the possibility that quetiapine may then cause similar hematologic disturbances, J. developed no side effects. His heart rate normalized and eosinophils gradually began to decline to the normal range. J. was then discharged and returned to his home country.

Discussion

J. suffered from chronic schizophrenia with suicidal thoughts and was treated with clozapine. Soon after the initiation of clozapine, he developed drug-induced eosinophilia (peripheral blood eosinophil count greater than 600 per mm3). Hypereosinophilia is defined as a peripheral blood count greater than 1,500 per mm3. It is a common allergic manifestation of various drugs that usually disappears when the causative drug is discontinued. Eosinophilia is an allergic response that, without treatment, tends to affect the heart, lungs, skin, joints, gut and the central nervous system.

Shear (5) reported a case of pulmonary infiltrations with eosinophilia that became apparent three weeks after initiation of chlorpromazine treatment. Antidepressants are not commonly associated with eosinophilia, although there are a number of reports related to desipramine, imipramine and trazodone, and one case of eosinophilia-jaundice associated with amitriptyline (6, 7). Tryptophan, which was used as an antidepressant and a dietary supplement, has been implicated in a case of potentially fatal eosinophilia-myalgia syndrome (EMS) (8).

Anticonvulsants such as carbamazepine and phenytoin have been implicated in severe multisystem, potentially life threatening eosinophilic reactions with an incidence of 1/1,000 to 1/10,000.

The pharmacodynamic profile of quetiapine is similar to clozapine. Quetiapine is an antagonist at multiple neurotransmitter receptors in the brain: 5HT1A and 5HT2, dopamine D1 and D2, histamine H1 and adrenergic alfa 1, and it has no appreciable affinity at cholinergic muscarinic and benzodiaz-

epine receptors. It has been proposed that its antipsychotic activity is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonism.

Clozapine interferes with the binding of dopamine at D1, D2, D3 and D5 receptors, has a high affinity for the D4 receptor, and also acts as an antagonist at adrenergic, cholinergic, histaminergic and serotonergic receptors.

In clinical trials, clozapine has been associated with eosinophilia with an incidence of 13% (9), and quetiapine associated hematological disturbances similar to those associated with clozapine treatment have been noted in a few case reports (10, 11). It is not known whether eosinophilia is a reliable predictor of myocarditis, but clozapine is associated with an increased risk of myocarditis, especially during the first month of therapy. In patients who develop tachycardia at rest accompanied by other signs and symptoms of heart failure, the possibility of myocarditis, cardiomyopathy and/or other cardiovascular dysfunction must be considered. The drug's manufacturer reported 213 cases of myocarditis world over (including 50 deaths), during clozapine therapy, 85% of which developed during the first two months of therapy (12).

In our case, the eosinophils count began to increase during the first days of clozapine treatment and continued to climb. The principle associated symptom was a persistent sinus tachycardia of 120–140 per minute. Since the patient's mental condition remarkably improved for the first time in his life, the option of treating eosinophilia with corticosteroids was briefly considered. Though corticosteroids are often used, their role in the management of this condition is controversial (4). When eosinophilia develops, treatment usually consists of withdrawing the probable causative drug (4), in our case, clozapine.

Implications for Clinical Care

Our case report suggests that quetiapine, which exhibits pharmacologic similarity to clozapine may be a viable therapeutic option for clozapine-responders who developed adverse effects to clozapine treatment. However, due to the pharmacodynamic similarities between the agents, ongoing hematologic follow-up is necessary for quetiapine treated patients as well.

Acknowledgement

The authors thank Rena Kurs for assistance in preparation of the manuscript.

References

1. Meltzer H, Ikayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: Impact on risk-benefit assessment. Am J Psychiatry 1995;152:183–190.
2. Kane J, Leucht S, Carpenter D, Docherty JP. The Expert Consensus Guideline Series: Optimizing pharmacologic treatment of psychotic disorders. J Clin Psychiatry 2003;64 (Suppl. 12):1–97.
3. Miller DD. Review and management of clozapine side effects. J Clin Psychiatry 2000;61 (Suppl. 8):14–17.
4. Maidment I, Williams C. Drug-induced eosinophilia. Pharmaceutical J 2000;264:71–76.
5. Shear K. Chlorpromazine induced PIE syndrome. Am J Psychiatry 1978;135:492–493.
6. Amsterdam J. Lyfler's syndrome: An uncommon adverse reaction to imipramine. Int Clin Psychopharmacol 1986;1:260–262.
7. Salerno S, Strong J, Roth B, Sakata Y. Eosinophilic pneumonia and respiratory failure associated with a trazodone overdose. Am J Respir Crit Care Med 1995; 152:2170–2172.
8. Milburn D, Myers J. Tryptophan toxicity: A pharmacoepidemiologic review of eosinophilia myalgia syndrome DICP. Ann Pharmacother 1991;25: 1259–1262.
9. Chatterton R. Eosinophilia after commencement of clozapine treatment. Aust N Z Psychiatry 1997;31: 874–876.
10. Ruhe HG, Becker HE, Jessurun P, Marees CH, Heeringa M, Bermeulen HDB. Case report: Agranulocytosis and granulocytopenia associated with quetiapine. Acta Psychiatr Scand 2001;104:311.
11. Roesch-Ely D, Van Einsiedel R, Kathofer S, Schwaninger M, Weisbrod M. Myocarditis with quetiapine. Am J Psychiatry 2002;159:1607–1608.
12. Wooltorton E. Antipsychotic clozapine, myocarditis and cardiovascular toxicity. CMAJ 2002;166:1185–1186.