Case Report

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Neutropenia and Thrombocytopenia Induced By Quetiapine Monotherapy: A Case Report and Review of Literature

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ABSTRACT:

Neutropenia and thrombocytopenia induced by quetiapine monotherapy: a case report and review of literature

Antipsychotic drugs can cause neutropenia which can progress to life-threatening agranulocytosis. Clozapine is well-known for this side effect which is rare for other antipsychotics. Quetiapine is a newer atypical antipsychotic which shows similarities with clozapine in chemical structure. We present a rare case of neutropenia and thrombocytopenia induced by quetiapine monotherapy of 600 mg/day in a 69-year-old patient with the diagnosis of bipolar I disorder. Hematological adverse effects were resolved by the discontinuation of quetiapine treatment. Although monitoring blood counts during quetiapine use is not recommended, clinicians should be aware of this rare but hazardous side effect.

Keywords: Quetiapine, neutropenia, thrombocytopenia

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INTRODUCTION

Antipsychotic drugs, most notably clozapine, have a risk of causing neutropenia. Other antipsychotic drugs are less known to be associated with neutropenia[1,2]. Since monitoring of white blood cell (WBC) counts during treatment with other antipsychotics is not recommended, delayed diagnosis and severe complications may be observed[1]. Quetiapine fumarate is a dibenzodiazepine derivative with a chemical structure similar to clozapine and olanzapine. It has affinity for histamine, alpha-2 adrenergic autoreceptors, serotonin 5HT-2, and dopamine receptors[3]. Neutropenia (neutrophil count $<1.5x10^9$/L) and thrombocytopenia (platelet count$<150x10^9$/L) are very rare side-effects of quetiapine[4-7]. Hematological toxicity of quetiapine is more common when concomitant medication is involved[8]. In the current paper, a case of neutropenia and thrombocytopenia induced by quetiapine monotherapy is described along with relevant review of the literature.

CASE REPORT

A 69-year-old male patient with a previous diagnosis of bipolar I disorder (BD-I) was referred

with symptoms of decreased sleep, logorrhea and increased energy levels over the last two weeks. He had not been on medication for the previous 2 years. He had a history of poor drug compliance. He reported olanzapine induced weight gain, risperidone and aripiprazole related extra-pyramidal side effects and emesis associated with lithium therapy. The patient was hospitalized with a diagnosis of BD-I manic episode and due to low incidence of side effects he was started on quetiapine at 600 mg/day. He did not have a history of systemic diseases and his body mass index was within normal limits. On initial admission all hematological parameters were within normal ranges.

On the 20th day of treatment the patient's body temperature was 39ºC. Blood, urine and throat cultures, complete blood count, biochemistry including creatine phosphokinase and hepatitis panel were examined. Erythyrocyte sedimentation rate (ESR) was 42 (normal range 0-20) and the C-reactive protein value was 10.3 mg/dl (normal range <0.5), while other laboratory values were normal. There was no rigidity on neurological examination. Bilateral rales were detected on physical examination. With a preliminary diagnosis of pneumonia the patient was started on prophylactic intravenous 1 g ceftriaxone twice daily. No significant elevation was observed in respiratory system viral markers, and there was no growth in cultures. Fever persisted during ceftriaxone therapy. Four days later, leukocyte count decreased to 2.7x10^9/L (normal range: 4.8-10.8x10^9/L) and platelet count to 77x10^9/L (normal range: 130-400x10^9/L). Respiration rate was 40/min and oxygen saturation decreased to 84%. On consultation to infectious diseases department, the patient was suspected of having a viral pneumonia caused by a probable H1N1 virus which might have caused leukopenia and thrombocytopenia and specific blood tests were ordered to rule it out. Quetiapine therapy was discontinued and the patient was transferred to the intensive care department. On the 3rd day of monitoring in intensive care, blood cell counts returned to normal ranges. The patient was transferred to the psychiatry department and started on quetiapine at 200 mg/day, gradually increasing to 600 mg/day. The blood test for H1N1 virus was reported to be negative. Seven days after initiation of quetiapine therapy for the second time, leukocyte count was 1.1x10^9/L, neutrophil count 0.3x10^9/L and platelet count 111x10^9/L, while other laboratory findings were normal. At peripheral blood smear, neutrophil value was 21%, monocyte 14%, lymphocyte 65%, and reticulocyte 2%. Despite receiving filgrastim (G-CSF analogue) therapy for 5 days, leukocyte count decreased to 0.9x10^9/L and neutrophil count to 0.13x10^9/L. No monocytes, basophils or eosinophils were determined. Bone marrow biopsy revealed drug-induced myeloid suppression which was likely to be caused by quetiapine. Quetiapine therapy was discontinued and two days later, leukocyte count increased to 6.2x10^9/L, neutrophil count to 3.3x10^9/L and platelet count to 109x10^9/L. A final diagnosis of quetiapine-induced leuhopenia and thrombocytopenia was made and filgrastim therapy was discontinued and lithium 600 mg/day was initiated. Fourteen days after discontinuation of quetiapine, platelet count was measured to be 184x10^9/L. Lithium therapy was maintained at a dose of 1200 mg/day. All blood counts were normal at patient's discharge.

DISCUSSION

The literature search from 1998 to August 2015 through PubMed database using the keywords quetiapine, leukopenia, neutropenia, granulocytopenia and thrombocytopenia revealed 21 case reports (Table 1). This report describes a case of neutropenia and thrombocytopenia induced by quetiapine monotherapy in a patient with a diagnosis of BD-I manic episode. Hematological abnormalities were resolved after discontinuation of quetiapine therapy. To the best of our knowledge, this is the first report of neutropenia and thrombocytopenia induced by quetiapine monotherapy from Turkey and the second such report in the literature.

The review of the literature revealed three cases

Table 1. Review of case reports of leukopenia, neutropenia and thrombocytopenia with quetiapine (total 21 reports)

First Author	Age (Years), Sex	Indication	ANC	Platelet	Mono/combination therapy	Management/Outcome
Fan[6] (2015)	23, M	BD-mania	1,719x10^9/ L	136x10^9/ L	Quetiapine 400mg + VPA 1000mg	VPA continued;changed to olanzapine Improved 4 days after drug changed
Crépeau-Gendron[14] (2015)	19, F	Schizophrenia	0.8x10^9/L	NR	Quetiapine XR 1200mg	Changed to lithium and aripiprazole Improved after drug changed
Shewmaker[13] (2013)	31, F	Delirium	0.89x10^9/L	NR	Quetiapine 100mg + vancomycin	Changed to olanzapine; Improved 3 days after drug changed
Estabrook[20] (2012)	26, M	Psychosis	0.75x10^9/L	NR	QuetiapineXR 600mg + Divalproex ER 1500 Mirtazapine 30mg +Clonazepam 1 mg	Other drugs were continued; changed to ziprasidone; Improved 11 weeks after drug discontinuation
Chang[10] (2012)	56, F	BD	1.16x10^9 /L	55x10^9 /L	Quetiapine 400 mg + VPA 500 mg+ estazolam 2 mg	Firstly VPA discontinued; neutropenia continued and quetiapine discontinued
Hung[8] (2012)	85, M	Dementia	1.748x10^9/L	NR	Quetiapine 100mg + VPA 200mg	Quetiapine and VPA discontinued;changed to olanzapine
	60, F	BD-mania	1.91x10^9 /L	NR	Quetiapine 400mg + VPA 500mg	VPA continued;Improved one week after drug discontinuation
Lander[2] (2011)	53, F	Schizophrenia	1.1x10^9 /L	NR	Quetiapine 800mg	Changed to aripiprazole; resulted in neutropenia
Wang[15] (2011)	34, F	Schizophrenia	NR	NR	Quetiapine 400mg	Changed to ziprasidone 120 mg/day
Handoo[12] (2010)	16, F	BD-mania	NR	118x10^9/L	Quetiapine 400 mg + VPA 1000mg	Firstly VPA discontinued; thrombocytopenia continued and quetiapine discontinued; changed to lithium 600mg/gün Improved after drug discontinuation
Alexander[1] (2010)	38, M	Schizophrenia	0.89x10^9/L	NR	Quetiapine 400mg	NR
Shankar[9] (2007)	45, M	BD-mania	1.1x10^9/L	146x10^9/L	Quetiapine 600mg + VPA 1500mg zuclopenthixol depot 150 mg/2 weeks	VPA + Zuclopenthixol depot continued; Changed to risperidone Improved after drug discontinuation
Cowan[4] (2007)	36, F	Schizophrenia	1.0x10^9 /L	NR	Quetiapine 600mg + divalproex 1250	Quetiapine and VPA discontinued; changed to zuclopenthixol depot; Improved 3 days after drug discontinuation
Nair[21] (2005)	33, F	Schizophrenia	1.1x10^9 /L	NR	Quetiapine 800mg + VPA 500mg	Quetiapine + VPA were discontinued; changed to aripiprazole;
Iraqi[11] (2003)	71, M	Parkinson disease	NR	120x10^9/L	Quetiapine 50mg + Carbidopa/ levodopa Sertraline + hydrochlorothiazide	Quetiapine was stopped. Other drugs continued; Improved 7 days after drug discontinuation
Oluboka[18] (2003)	41, F	Schizophrenia	0.2x10^9/L	NR	Quetiapine 600 mg	Changed to chlorpromazine
Croarkin[5] (2001)	24, M	Schizophrenia	0.504x10^9/L	NR	Quetiapine 50mg	Changed to olanzapine; Improved 7 days after drug discontinuation
Clark[22] (2001)	23, F	Schizophrenia	0.9x10^9 /L	NR	Quetiapine 600mg + VPA 500mg	Quetiapine was discontinued; changed to olanzapine VPA continued; Improved 3 months after drug discontinuation
Ruhe[7] 2001	48, M	Schizophrenia	NR	NR	Quetiapine 600mg + olanzapine 20mg + lithium carbonate 800mg	All of drugs were discontinued; changed to zuclopenthixol depot
	22, M	Schizophrenia	NR	NR	Quetiapine 750mg	Quetiapine was discontinued; changed to clozapine
	23, M	Schizophrenia	NR	NR	Quetiapine 600mg + flupenthixol depot	Improved after quetiapine discontinuation
Tang et al.[23] 2014	62, F	BD	770/uL	NR	Quetiapine 150 mg	Quetiapine was discontinued; changed to lithium and haloperidol; neutropenia improved
Huynh et al,[24] 2005	25, M	BD	NR	14×10^3/mm ^{3}	Quetiapine 100 mg	Quetiapine was discontinued; plasmapheresis was instituted; patient improved
Diaz et al.[25] 2001	53, F	Schizophrenia	1,400/mm^3	NR	Quetiapine 400 mg	Improved 3 days after discontinuation

ANC: absolute neutrophil count; NR:not reported; BD: Bipolar disorder; VPA:valproic acid

of quetiapine-related neutropenia and thrombocytopenia[1,9,10]. Quetiapine was used in combination with valproate in two cases while in the other[9,10], similar to our case, hematological side-effects developed with quetiapine monotherapy1. Hematological side-effects resolved in all cases when quetiapine was discontinued. In the reported cases, neutropenia and thrombocytopenia occurred in the 2nd week, 5th week and 4th year of treatment at a daily quetiapine dose range of 400-600 mg. In our case, adverse effects developed in the 3rd week of treatment with 600 mg of quetiapine. There has been only one case report describing quetiapine-associated pancytopenia[11]. Additionally, thrombocytopenia alone was reported in a case receiving a quetiapine and valproic acid combination[12].

The cause of quetiapine-induced neutropenia and thrombocytopenia is unclear. Studies investigating antipsychotic-related leukopenia have been performed with clozapine. Since the pharmacological profile and chemical structure of quetiapine are similar to those of clozapine, it has been suggested that quetiapine may lead to neutropenia and thrombocytopenia through direct toxicity or immune-mediated destruction[6,12-15]. The electrophilic nitrenium ion generated by the oxidation of clozapine is thought to bind to neutrophils[12]. It has been suggested that the bound nitrenium ions either lead to direct cell death or cause neutrophil apoptosis due to oxidative stress[16,17]. According to another theory, however, the formation of neutrophil antibodies with the binding of nitrenium ions to neutrophil proteins leads to neutrophil destruction through immune-mediated toxicity. The above mentioned theories for neutropenia are also proposed to apply for thrombocytopenia. However, it is unclear whether these mechanisms hypothesized for clozapine-related neutropenia would also apply to quetiapine.

Dose dependence has also been proposed in quetiapine-related neutropenia[18]. Advanced age and low body weight are factors that lead to higher plasma quetiapine concentrations. Valproate has been observed to increase plasma quetiapine levels by 77% due to its inhibitory effect on cytochrome p450[19]. This observation explains why neutropenia is more common in elderly patients receiving a combination of quetiapine and valproate. The majority of cases reported in the literature were using quetiapine and valproate combination therapy[4,5,9,10,20-22]. Our case is distinct in that neutropenia, leukopenia, and thrombocytopenia were induced by quetiapine monotherapy at a standard therapeutic dose of 600 mg. The patient had normal weight, however, his advanced age may also be a factor contributing to a higher plasma quetiapine concentration due to fact that reduced renal clearance with aging.

Monitoring blood counts is recommended during clozapine therapy since the occurrence of adverse effects of neutropenia associated with clozapine is well-known. Our report underlines the importance of checking blood counts during administration of quetiapine, although there are no guidelines on this issue. We think that clinicians should be aware of this rare but hazardous side-effect.

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