

Clozapine-induced myocarditis during co-administration of valproate: A case report

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Summary

Clozapine, atypical antipsychotic drug, is widely used in patients with schizophrenia, for whom previous therapy was inadequate or not tolerated. Clozapine-induced myocarditis (CIM) is a relatively rare but potentially life-threatening complication of clozapine therapy; however, the underlying mechanism has not been so far well elucidated. Factors predisposing to CIM include a rapid dose titration, advanced age and co-administration of sodium valproate. In this paper, we present a case of a 22-year-old male patient with refractory schizophrenia who developed CIM during low-dose clozapine treatment with co-administration of valproate and risperidone. On the basis of our case and literature review, we point out that during the first weeks of clozapine treatment patients should be actively, daily monitored for the presence of symptoms suggesting CIM. The low dose of clozapine and concurrent use of valproate are unique aspects of the report, adding new information to the discussion on safety of concomitant use of clozapine and valproate. Further investigation is required to better understand the role of co-administration of valproate and risperidone in the pathogenesis of CIM.

Key words: clozapine, myocarditis, C-reactive protein, troponin, valproate

Introduction

Clozapine, atypical antipsychotic drug, is widely used among patients diagnosed with schizophrenia, for whom previous therapy was inadequate or not tolerated. Impressive efficacy of clozapine in treatment-resistant schizophrenia has been demonstrated in clinical trials and meta-analyses [1–3]. Additionally, clozapine was shown to have anti-aggressive and anti-suicidal effects [4, 5]. However, in some patients its use may

be associated with serious side-effects. One of them is clozapine-induced myocarditis (CIM) – a relatively rare but potentially life-threatening idiosyncratic complication of clozapine therapy, with an incidence of 0.1% to 3% [6].

Here we present the case of a 22-year-old male with refractory schizophrenia who developed unremittent chest pain, increase in troponin and C-reactive protein (CRP) levels under clozapine treatment. Written informed consent to publish this case was obtained from the patient.

Case presentation

A 22 year-old Caucasian male diagnosed with paranoid schizophrenia, otherwise healthy, without history of substance abuse besides heavy smoking. For several months, despite attempted treatments (in sequence: perazine at a dose up to 300 mg/day for 3 weeks; olanzapine at a dose of 20 mg/day for 10 weeks; risperidone at a dose of 6 mg/day for 12 weeks), the patient had worsening psychotic symptoms, which completely impaired his regular day-to-day functioning. Moreover, augmentation strategies, with sertraline (at a dose of 50 mg/day for 5 weeks) and valproate (at a dose of 1,200 mg/day for 3 weeks), did not bring expected improvement.

At the time of admission to an inpatient psychiatric ward, he was suffering from impaired social functioning, delusions, auditory hallucinations, and thought disorder. On admission, his blood count level, serum chemistry profile and electrocardiogram (ECG) were within normal limits.

The treatment regimen was changed from risperidone to clozapine. Risperidone was tapered from 6 mg/day to 4 mg/day on the 15th day of therapy. Patient received valproate at a dose of 1,200 mg/day – initiated as an augmentation to risperidone. Clozapine was started at 25 mg/day and titrated up to 100 mg/day on day 15. Therapy modification brought rapid improvement of the patient's psychotic symptoms. However, on the 16th day of the therapy, the patient developed unremittent, midsternal chest pain which was aggravated by physical activity. His heart rate was 101 beats/min, his blood pressure was 125/65 mm Hg. For the following 36 hours he did not reveal any complaints to the staff on duty. On the 18th day of the therapy, an ECG showed sinus tachycardia, normal QRS complex duration and morphology, and repolarization abnormalities in the inferior leads not observed before. His lungs were clear to auscultation. Cardiac rhythm was regular with no murmurs, gallops, or rubs. His heart rate was 114 beats/min, his blood pressure was 135/80 mm Hg. Saturation of peripheral oxygen (SpO₂) was 97%. Body temperature was within normal range. There was no associated chills, cough, vomiting, diarrhea or muscle rigidity. Blood sampling demonstrated elevated levels of troponin I (38.6 ng/L and 41 ng/L after 4 h, normal value <19), CRP (26.3 mg/L, range 0–5), alanine transaminase (79.5 U/L, normal value <41), mild neutrophilia ($6.77 \times 10^9/L$, range 2.5–6.5), and monocytosis ($1.57 \times 10^9/L$, range 0.2–1). Levels of myoglobin, D-dimer, creatine kinase (including

isoenzymes CKM and CKB), and white blood cells (including eosinophils and lymphocytes) in blood sampling were within normal range. Despite the clinical picture being non-characteristic, clozapine dosage was lowered to 50 mg. Propranolol was started at the dose of 10 mg two times a day.

On the next day, in blood sampling, the level of troponin I raised to 271.1 ng/L, CRP increased to 51.4 mg/L and alanine transaminase dropped to 53.1 U/L. White blood cells count raised to $11.27 \times 10^9/L$ (range $4-10 \times 10^9/L$), neutrophilia raised to $8.44 \times 10^9/L$ and monocytosis was stable $1.41 \times 10^9/L$. The patient's heart rate was 92 beats/min and his blood pressure was 114/60 mmHg. An ECG showed the same abnormalities as the day before. Taking into account the above, clozapine was discontinued, dose of risperidone was reduced to 1 mg three times a day and a dose of valproate was maintained at 600 mg two times a day. The patient was transferred to cardiology ward.

Echocardiography revealed normal left ventricular (LV) and right ventricular (RV) size, normal systolic function (LV ejection fraction [LVEF], 0.65% in the first and 0.7% in the second measurement). There was no sign of LV or RV hypokinesis. Angiotensin-converting-enzyme inhibitor – ramipril was initiated at a dose of 1.25 mg two times a day. In the next 4 days, the chest pain resolved and troponin serum level normalized. Control echocardiography revealed LVEF at 0.7%. Given the rather mild course of the illness and normal ventricular contractility indicating low risk of edema, cardiac resonance imaging (CMR) was not performed.

During the next 2 weeks, risperidone was discontinued and treatment with zuclopenthixol was commenced with a dose of 10 mg three times a day. No chronic complications of clozapine treatment were observed. The patient was doing well, on discharge from the hospital and he returned to outpatient psychiatric care.

Discussion

Myocarditis is a potentially fatal adverse drug reaction to clozapine. CIM, a hypersensitivity reaction following initiation of clozapine, encompasses inflammation of heart muscle. Clinical symptoms of CIM usually occur after 2 to 4 weeks of treatment [6, 7]. Factors predisposing to CIM include a rapid dose titration, advanced age and co-administration of sodium valproate [7]. Our case followed the typical clinical course, with development of symptoms 16 days after initiating therapy with clozapine. Its potential risk factor for CIM was concurrent administration of valproate. According to Chopra and de Leon [8] in some cases valproate may be an inhibitor of clozapine metabolism, but the exact role of valproate in the pathogenesis of CIM remains unknown. Our patient was titrated up to 100 mg of clozapine daily on 15th day. During 19 days of treatment, he received a total of 1,175 mg of clozapine. CIM at 100 mg/day is uncommon, there are only a few case reports about low-dose CIM.

Clinical spectrum of CIM varies widely from asymptomatic to fulminant congestive heart failure. Symptoms of CIM are nonspecific, and include fever, tachycardia, eleva-

tion of CRP, eosinophil and troponin levels, respiratory, gastrointestinal or urinary tract inflammation symptoms, nausea, dizziness, chest pain, ventricular impairment [6, 9].

In the case of our patient, the first symptom was unremitting, aggravated by physical activity, chest pain. Early serological screening indicated an elevation of CRP (>5 x ULN; upper limit of normal) and troponin I (>2 x ULN). Moreover, ECG showed repolarization abnormalities in the inferior leads of ECG and tachycardia. Next day, laboratory tests showed further elevation of CRP (>10 x ULN), Troponin I (>14 x ULN). Previous observations indicate that CRP is an early marker of CIM. An increase in CRP level, usually precedes the increase in troponin (I or T) level up to 5 days, while the increase in CRP level to more than 50 mg/L foreshadows the onset of CIM [10]. Unfortunately, in our case, CRP and troponin level was not measured at the symptoms onset, therefore we were not able to conclude whether CRP elevation preceded the increase in troponin level. Previous studies and our case indicate that high increase in troponin level does not correlate with the degree of ventricular dysfunctions [6]. Fever and eosinophilia, which are presented respectively in about 75% and 62% of CIM cases [6], were not observed in our patient.

A diagnosis of myocarditis was highly suspected on the basis of the clinical symptoms and results of additional examinations. Several factors pointed toward clozapine as the cause of patient's symptoms. Firstly, involvement of other cardiac conditions was ruled out by interviews, physical examination, laboratory tests, ECG and echocardiography. Secondly, there were no potential causes of myocarditis, other than clozapine use. Thirdly, patient's symptoms were analogous to those reported in previous case reports of CIM. Fourthly, the patient was highly responsive to clozapine cessation, and fully recovered in a short period of time, which suggested drug-induced state. Fifthly, patient showed no symptoms during 4-weeks follow-up period. The application of our data to the Naranjo scale for adverse drug events yielded a score of +7. This suggests a causal role of clozapine [11].

We cannot rule out the effects of risperidone on the occurrence of myocarditis. However, animal study showed that risperidone does not induce cardiac lesion [12]. Data mining study showed no correlation between risperidone and myocarditis [13]. Additionally, in our case, myocarditis occurred after long period of risperidone treatment, during dose reduction of this drug. Furthermore, resolution of myocarditis occurred despite of the continuation of risperidone treatment.

Mortality in patients with CIM is estimated at 10% [6]. Management of CIM includes clozapine abrupt cessation, which is usually sufficient. According to monitoring protocol, established by Ronaldson et al. [10], an elevation of troponin (I or T) level >2 x ULN and/or increase in CRP level >100 mg/L should be an indication for discontinuation of clozapine. β -blocker and/or angiotensin-converting-enzyme inhibitor maybe useful in at least same cases [6]. In our case clozapine dose was halved when CIM was suspected and ceased due to further troponin elevation. Our

patient received propranolol at the dose of 10 mg and ramipril at the dose of 1.25 mg two times a day. We think that our patient benefited from prompt diagnosis and medical intervention.

On the basis of our case and literature review, we point out that during the first weeks of clozapine treatment, patients should be actively, daily monitored for the presence of symptoms suggesting CIM. The low dose of clozapine and concurrent use of valproate are unique aspects of the report, adding new information to the discussion on safety of concomitant use of clozapine and valproate. Further investigation is required to better understand the role of co-administration of valproate and risperidone in the pathogenesis of CIM.

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