

Clozapine-Induced Myocarditis and Pericarditis

Zahiruddin Othman, Fazil Ahmad, Ahmad Shahril Abdul Halim,
Nurul Nadia Ismail

ABSTRACT

Objective: Clozapine is known to cause cardiac side-effects, including myocarditis, pericarditis and cardiomyopathy. A 50-year-old Malay man with schizoaffective disorder and tardive dyskinesia who developed transient tachycardia, low blood pressure and fever after 17 days of starting clozapine was studied.

Result: Elevated creatinine kinase at 532 U/l along with WBC and neutrophil count at 21.40 and 16.83 x 10⁹/l respectively indicated an acute myocarditis. Additionally, pericardium involvement was suggested by V1-V4 ST elevation and absence of T wave inversion.

Conclusion: The emergence of tachycardia, low blood pressure and fever in patient who is recently started on clozapine treatment should be investigated for cardiac complications. Old age and concomitant treatment with sodium valproate possibly increased the risk of clozapine-induced cardiac side-effects.

KEY WORDS

clozapine, myocarditis, pericarditis, tardive dyskinesia

INTRODUCTION

Cardiovascular side effects of clozapine, including tachycardia and orthostatic hypotension, are relatively common but little attention is paid to them compared to agranulocytosis. The increasing number of clozapine related cardiac complications reported in the literature^{1,2)} have given rise to concern about the risk of acute cardiac side effects, including myocarditis, pericarditis and cardiomyopathy, in patients treated with the drug. We document here case of clozapine-induced myocarditis and pericarditis with serial elevation of cardiac enzymes and ECG changes.

CASE REPORT

A 50-year-old Malay man with schizoaffective disorder and comorbid amphetamine abuse was admitted for management of acute psychosis. He was a smoker for the past 30 years. There was no history of diabetes mellitus, hypertension or other cardiovascular disease. His BMI was 19.9. Baseline ECG, renal and liver function were normal. Emerging tardive dyskinesia (TD) over a year period necessitated the use of clozapine, commenced at 25 mg daily orally and increased to 100 mg daily over 2 weeks. Other antipsychotics were stopped including olanzapine and monthly fluphenazine decanoate depot which otherwise he had received just prior to the admission. Sodium valproate 500 mg BD was continued. This treatment resulted in improvement of psychotic symptoms as well as the tardive dyskinesia.

Seventeen days later whilst on clozapine 100 mg daily, the patient developed transient tachycardia (100 bpm lasting for 12 hours), low blood pressure and fever (39°C). Nevertheless, he denied any chest pain or dyspnea. ECG showed ST elevation at V1-V4 and absence of T wave inversion indicating acute pericarditis. Blood tests now revealed ESR 36 mm/hr, CRP 106 mg/l signifying an acute inflammatory process. Raised

creatinine kinase at 532 U/l indicated presence of acute myocarditis. WBC and neutrophil count was grossly elevated at 21.40 and 16.83 x 10⁹/l respectively. Other haematological and electrolyte indices were within normal range. Clozapine was immediately stopped and intravenous hydrocortisone 100 mg was given for 3 days. His vital signs were closely monitored. Repeat CK and CKMB after 2 days were 240 and 11 U/l respectively. Repeat ECG was normalized to the baseline. Transthoracic echocardiography performed 4 days later revealed normal ventricular size and function with no pericardial effusion. The patient was discharged well 1 week later.

DISCUSSION

Hypersensitivity myocarditis is particularly difficult to recognise because the clinical features characteristic of a drug hypersensitivity reaction including non-specific skin rash, malaise, fever, and eosinophilia are absent in most cases. Drugs associated with hypersensitivity myocarditis include clozapine, sulfonamide antibiotics, methylodopa, and some anti-seizure drugs³⁾.

Our diagnosis of clozapine-induced myocarditis and pericarditis was one of exclusion, supported by its temporal relationship of onset with clozapine initiation and remission upon drug cessation. Whilst tachycardia is common side effect of clozapine²⁾, high grade fever and low blood pressure hinted more serious cardiovascular side effects. The diagnosis of myocarditis was very likely considering onset of these new symptoms were within 45 days of commencing clozapine with raised CK and CKMB above 2 upper limit of normal³⁾. Other possible causes, particularly acute myocardial infarction and neuroleptic malignant syndrome, were ruled out.

ECG abnormalities in patients treated with clozapine were common, mostly being nonspecific benign abnormality in T wave occurring up to one third of patients during the initial stage of the treatment³⁾. In this case, widespread ST elevation with non-inverted T wave was highly

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Department of Psychiatry, Universiti Sains Malaysia

16150 Kubang Kerian, Kelantan, Malaysia

Correspondence to: Zahiruddin Othman

(e-mail: zahirkb@usm.my)

indicative of acute pericarditis. There was no indication of other serous membrane inflammation, such the pleura, or effusion.

The most striking feature about myocarditis is the wide diversity of nonspecific symptoms that occur in afflicted patients and the fact that it may occur even at usual therapeutic doses. Therefore, it is important to identify those patients at risk. A recent study of 105 cases, with time to onset of 10-33 days, and 296 controls found concomitant sodium valproate more than doubled the risk (odd ratio 2.59) and each successive decade in age associated with a 31% increase in risk of myocarditis⁶.

Non-fatal outcome of this case was largely attributed to early diagnosis and treatment of the condition. Factors that had been associated with fatal clozapine-induced myocarditis include obesity (BMI > 30 kg/m²), longer duration of clozapine treatment (> 17 days) and CK > 1,000 U/l were absent in this case⁷.

Poor quality of life is independently associated with TD⁸ and depressive symptoms⁹ in schizophrenia patients. Management of TD, therefore, is an important aspect of overall patient management. The patient was not re-challenged with clozapine mainly because the indication for clozapine in this case was emerging tardive dyskinesia rather than lack of response to antipsychotics. Although, tardive dyskinesia is associated with cumulative exposure to antipsychotics, the risk can be reduced by minimizing the use of typical antipsychotics. Whether patients could be re-challenged after myocarditis remains unclear as there were only few reported cases in the literature¹⁰.

CONCLUSION

The development of tachycardia, low blood pressure and fever in patient who is recently started on clozapine treatment should be investigated for cardiac complications such as myocarditis or pericarditis. Older age and concomitant treatment with sodium valproate may increase the risk.

REFERENCES

- 1) Thanasan S, Rusdi AR. A case of suspected clozapine related myocarditis. *Malaysian Journal of Psychiatry* 2009; 18(1)
- 2) Haas SJ, Hill R, Krum H, Liew D, Tonkin A, Demos L, Stephan K, McNeil J. Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993-2003. *Drug Saf* 2007; 30(1): 47-57.
- 3) Sagar S, Liu PP, Cooper Jr LT. Myocarditis. *Lancet* 2012; 379(9817): 738-747.
- 4) Ronaldson KJ, Taylor AJ, Fitzgerald PB, Topliss DJ, Elsik M, McNeil JJ. Diagnostic characteristics of clozapine-induced myocarditis identified by an analysis of 38 cases and 47 controls. *J Clin Psychiatry* 2010; 71(8): 976-81.
- 5) Kang UG, Kwon JS, Ahn YM, Chung SJ, Ha JH, Koo YJ, Kim YS. Electrocardiographic abnormalities in patients treated with clozapine. *J Clin Psychiatry* 2000; 61(6): 441-6.
- 6) Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, Wolfe R, McNeil JJ. Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: a case-control study. *Schizophr Res* 2012; 141(2-3): 173-8.
- 7) Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, McNeil JJ. Clinical course and analysis of ten fatal cases of clozapine-induced myocarditis and comparison with 66 surviving cases. *Schizophr Res* 2011; 128(1-3): 161-5.
- 8) Othman Z, Ghazali M, Razak AA, Husain M. Severity of tardive dyskinesia and negative symptoms are associated with poor quality of life in schizophrenia patients. *International Medical Journal* 2013; 20(6): 677-80.
- 9) Razali SM, Wahid MA. Quality of life and depressive symptoms in patients with schizophrenia. *International Medical Journal* 2012; 19(2): 130-4.
- 10) Manu P, Sarpal D, Muir O, Kane JM, Correll CU. When can patients with potentially life-threatening adverse effects be re-challenged with clozapine? A systematic review of the published literature. *Schizophr Res* 2012; 134(2-3): 180-6.