

Rapid Rechallenge with Clozapine Following Pronounced Myocarditis in a Treatment-Resistant Schizophrenia Patient

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Abstract

Clozapine is an atypical antipsychotic which is often effective in patients who fail to respond to other antipsychotics, but its use carries substantial risk. Myocarditis is one of the life-threatening adverse effects, which occurs in about 1% of exposed patients. Rechallenge with clozapine is controversial, particularly shortly after the occurrence of the myocarditis, and when there is clear and convincing evidence of cardiac damage. Aggressive use of clozapine, however, may be critical for the recovery of patients early in the course of their illness. Here we report a successful case of clozapine rechallenge following an initial aggressive dosage titration in an inpatient setting.

Key Words: Clozapine, Adverse Effects, Schizophrenia, Myocarditis

Introduction

Clozapine is the most effective medication for treatment-resistant schizophrenia but is associated with fatal adverse reactions including myocarditis (1). Typically, patients are not rechallenged following a life-threatening adverse event with clozapine, although recently this has become more common practice for severe neutropenia (2) (the most recognized of the diverse potential fatal reactions). Myocarditis typically resolves rapidly with drug

discontinuation (1), but of the thirteen previous cases of rechallenge (3-8), rechallenge in nine occurred six months to two years later, despite rapid deterioration in mental status. Six of the nine were reported as successful (3, 5-8). Of the four cases in which rechallenge occurred earlier (9-14 days), two failed (4, 7) and two involved questionable evidence of myocarditis (i.e., minimal to no troponin elevation, minimal to no inflammatory response, normal hemodynamics) (6, 8). This has led to recommendations that continuation of clozapine or rapid rechallenge be limited to cases with minimal evidence of cardiac involvement (6). Such delays can be deleterious, however, particularly in younger patients where prolonged psychosis is associated with poor prognosis.

Case

Mr. D was a 20-year-old male who began to withdraw and develop intense command hallucinations and paranoia during his first year of college in the fall of 2010. Prior to that he had been an excellent student, good athlete and had many friends. He was seen in our outpatient clinic one year later after failing an effort to return to school in the fall of 2011.

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He was noted to have worsening auditory hallucinations after adequate trials of risperidone 3 mg/day, ziprasidone 80 mg/day and perphenazine 24 mg/day. He was started on lurasidone 80 mg/day, but was hospitalized on an inpatient psychiatric unit one week later after threatening his mother in response to command hallucinations. Lurasidone was titrated up to 240 mg/day, but his symptoms did not improve and after three weeks on the inpatient unit he was transitioned to olanzapine 40 mg/day. The patient continued to complain of extreme paranoia and marked auditory hallucinations, so one week later he was started on clozapine. Clozapine was rapidly titrated upward to a dose of 450 mg over an eleven-day period (1,500 mg total over first nine days) in an effort to produce a rapid therapeutic response. At the time he was only taking olanzapine, had a BMI of 25 and was noted to be physically active on the unit. Starting day nine he reported a reduction in auditory hallucinations and paranoid ideation.

This case illustrates that clozapine can be successfully reintroduced shortly after the occurrence of myocarditis, even when accompanied by significant elevations in troponin levels and inflammatory markers, as well as reduced cardiac function.

On the eleventh day, Mr. D developed pleuritic chest pain, headache, nasal congestion, and sore throat and his clozapine was discontinued. EKG showed non-specific T-wave changes, and he was transferred to the coronary care unit where an echocardiogram and cardiac MRI showed mild global hypokinesia and reduced ejection fraction. On days 12–15 he exhibited fever, tachycardia, leukocytosis, and elevated troponin I and C-reactive protein levels (high sensitivity: 124 mg/dl, ULN <10 mg/dl) (see Figure 1). He was placed on an ACE inhibitor and beta blocker and restarted on olanzapine. His vital signs and troponin levels rapidly normalized, though he exhibited a second peak of leukocytosis (days 18–23), this time accompanied by an elevated eosinophil count. Viral titers and infectious work-up were entirely negative. Over the next week his chest pain resolved, while his laboratory values and echocardiogram were normalized. His mental status, however, rapidly deteriorated, and on day 18, six days after clozapine was discontinued and after discussion with the patient, family and cardiologist, he was restarted on clozapine 25 mg. Clozapine was then increased in 25 mg intervals to 100 mg/day while the patient

was still on the coronary care unit. Ten days after transfer to the CCU, the patient was returned to the psychiatric unit under the care of one of the authors (MBG).

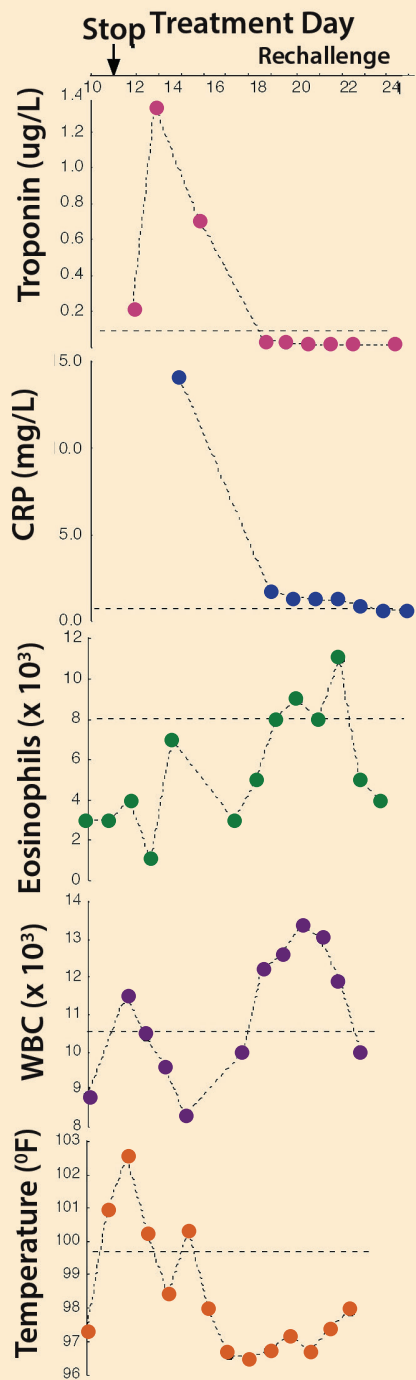
Clozapine dosage was maintained at 100 mg/day due to a concern that previous rapid dose escalation may have contributed to the myocarditis. He was discharged on day 30 with episodic non-command hallucinations on clozapine 125 mg/day (blood level 114 ng/ml) with instructions to titrate up to 200 mg/day over the next 10 days. Over the next six weeks clozapine was titrated up to 750 mg (blood level 695 ng/ml) and his auditory hallucinations and paranoia resolved, while inflammatory markers and troponin levels were unchanged. Six months after the initial discharge his echocardiogram was normal, and one year post-discharge he continued to tolerate clozapine without further sequelae.

Discussion

This case illustrates that clozapine can be successfully reintroduced shortly after the occurrence of myocarditis, even when accompanied by significant elevations in troponin levels and inflammatory markers, as well as reduced cardiac function. The risks appeared to be justified given the patient's young age, good premorbid function, rapid and sustained deterioration following the initial onset of schizophrenia, and good initial response to clozapine in contrast to his minimal response to a broad range of other antipsychotics. Furthermore, previous reports had shown that rechallenge could be successful, albeit not in as severe a case or with such a brief delay as reported here.

The mechanism of clozapine-induced myocarditis remains unclear but is thought to include an IgE-mediated hypersensitivity reaction or a direct toxic effect on the cardiac muscle followed by inflammatory infiltrates (10). It is unclear whether the temporal delay in the elevation of the eosinophil count (see Figure 1) argues more for one or the other of these possibilities, but in any event it resolved while clozapine was being reintroduced. This case of myocarditis appears quite typical, as most occur within three weeks of starting medication (9) and rapidly resolve with drug discontinuation. The current literature supports the view that the rapid initial titration of clozapine may have contributed to the onset of myocarditis, while other putative risk factors (i.e., concurrent depakote treatment, advanced age, increased BMI) were not present (11). The literature suggests that the risk of myocarditis with a cumulative dose of 1,500 mg clozapine over the first nine days would be at least 4 times higher than for patients with cumulative doses below 500 mg. Hence, the successful rechallenge may be attributable to the slower titration schedule, and clinicians should be advised to avoid such rapid titration schedules. With the above caveats in mind, this case report provides

Figure 1 Clinical Course Following Discontinuation and Rechallenge with Clozapine



20-year-old male inpatient with schizophrenia developed chest pain and a viral syndrome on day 11 after starting clozapine. Clozapine was stopped (arrow) and he was transferred to the coronary care unit due to evidence of acute cardiac dysfunction. His mental status rapidly deteriorated despite starting olanzapine 10 mg. A decision was made to rechallenge with clozapine on day 18 and titrate in 25 mg/day intervals to 100 mg/day. Note the delayed occurrence of asymptomatic eosinophilia around the time of the rechallenge.

evidence that rapid reintroduction of clozapine may be successful following clinically significant myocarditis.

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