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Clozapine-induced myocarditis may warrant cardiac monitoring protocol

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Abstract

Background: Myocarditis, or inflammation of the heart muscle, is a black box warning associated with the use of clozapine. Although the incidence of clozapine-induced myocarditis is only 0.015% to 1.2%, recent retrospective studies have found that up to 66% of clozapine patients develop nonspecific symptoms consistent with myocarditis. Because of the difficulty in distinguishing these symptoms (including fever, tachycardia, and fatigue) from clozapine dose titration, myocarditis may be difficult to recognize. If left undetected, the condition could be fatal.

Patient Case: A 25-year-old Filipino male with a history of schizoaffective disorder, bipolar type, continued to endorse persistent and distressing command auditory and visual hallucinations despite therapy with olanzapine, 40 mg daily. Clozapine was initiated for refractory psychosis and titrated up to 125 mg over 17 days. On day 14, the patient reported "feeling sick," having chills, a nonproductive cough, and fatigue; he was febrile and tachycardic. Abnormal laboratory values included elevated troponin-1, C-reactive protein (CRP), and creatinine phosphokinase (CPK). The last dose of clozapine was administered on day 17 with resolution of the above-mentioned signs and symptoms within 3 days.

Discussion: A literature search revealed several cases demonstrating a strong association between clozapine and myocarditis. Despite suggestions from case reports for cardiac monitoring at baseline, there are no universal monitoring guidelines.

Conclusion: As a result of this patient case of clozapine-induced myocarditis, the Veterans Affairs Palo Alto Health Care System Clozapine Tracking Team developed a cardiac monitoring protocol for veterans being initiated on clozapine.

Keywords: clozapine, myocarditis, cardiac monitoring, case report, protocol

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Introduction

Cardiovascular adverse effects including postural hypotension and tachycardia are commonly associated with the use of clozapine as well as the development of metabolic syndrome, a risk factor for cardiovascular disease.[1,2] While the most widely publicized cardiac complication associated with clozapine therapy is myocarditis, cardiomyopathy and pericarditis have also been reported.[2] Myocarditis, or inflammation of the heart

muscle, is a black box warning associated with the use of clozapine.[3,4] Clozapine-induced myocarditis has a rare incidence of 0.015% to 1.2%; however, when compared with the general population, the risk of myocarditis is more than 10 000 times greater with the use of clozapine.[2,4] Furthermore, recent studies reveal the occurrence of myocarditis may have been underreported in earlier studies.[4-6]

Diagnosis of myocarditis is difficult because its symptoms are also side effects commonly associated with clozapine dose titration.[4,6,7] Studies have found that up to 66% of clozapine patients develop nonspecific symptoms consistent with myocarditis.[7] Because of the difficulty in distinguishing these symptoms (including fever, tachycardia, and fatigue) from clozapine dose titration, detection of myocarditis may be challenging. Diagnosis is further complicated because a causative mechanism by which clozapine causes cardiotoxicity remains unclear.[2,6,8] If left undetected, clozapine-induced myocarditis is fatal, with mortality rates as high as 50%.[4,7,9,10]

Monitoring of cardiac-specific laboratory tests preclozapine and postclozapine initiation is not routine at all facilities. We present a case of clozapine-induced myocarditis that led to the addition of more specific cardiac monitoring tests prior to, and following, clozapine initiation at the Veterans Affairs (VA) Palo Alto Health Care System.

Patient Case

A 24-year-old Filipino male Afghanistan war veteran with schizoaffective disorder, bipolar type, was admitted to VA Palo Alto Health Care System on a 5150 (72-hour involuntary psychiatric hold) for danger to self and grave disability secondary to medication noncompliance. He endorsed worsening command auditory hallucinations to harm himself, visual hallucinations, and delusions. His speech was disorganized, and he appeared internally preoccupied. His psychiatric history was significant for cannabis dependence and polysubstance abuse (psilocybin mushrooms, LSD, ecstasy, methamphetamine, cocaine) as well as 3 previous hospitalizations. He had no medical comorbidities or contributory family history. Previous antipsychotic trials included haloperidol up to 7 mg, which induced akathisia; risperidone up to 8 mg, with limited efficacy; and olanzapine up to 40 mg, with residual symptoms.

During his hospital course, the patient was restarted on divalproex extended release (ER) 1500 mg/d and olanzapine 40 mg/d, yet continued to endorse visual and command auditory hallucinations. The decision was made to initiate clozapine for treatment-resistant psychosis after failure and intolerance to 3 alternative antipsychotics. Clozapine was titrated up to 125 mg over 17 days, while olanzapine was reduced to 20 mg/d. Concomitant medications included olanzapine, divalproex, and clonazepam. On day 14 of clozapine treatment, the patient endorsed "feeling sick," having chills, a nonproductive cough, sore throat, headache, and fatigue with no chest pain. He was febrile (99°–100.5°F) and tachycardic (100–123 bpm).

Cardiology service was consulted for further work-up; and abnormal laboratory values, which are detailed in the Table, included an elevated troponin-1 (0.19–0.75 ng/mL), creatinine phosphokinase (CPK) (104–124 U/L), and C-reactive protein (CRP) (3.72–8.32 mg/dL). His B-type natriuretic peptide (BNP) was within normal limits, with a high normal erythrocyte sedimentation rate (ESR). A soft rub was revealed on cardiac exam, and electrocardiogram (EKG) showed sinus tachycardia. Cardiology made a diagnosis of clozapine-induced myocarditis, and clozapine was discontinued on day 17. Laboratory values returned to normal limits within 3 days after clozapine discontinuation. A Naranjo scale was calculated, and the myocarditis was determined to be probably related to clozapine.[11]

After cessation of clozapine therapy and subsequent resolution of myocarditis, olanzapine was increased back to 40 mg/d, and thiothixene was initiated and slowly titrated to 20 mg/d. The patient reported a euthymic mood and denied hallucinations at his time of discharge. Per extensive discussion with cardiology service, a retrial of clozapine should not be entirely excluded in case the patient was to decompensate and demonstrate insufficient response to alternative agents. However, a retrial would require careful coordination and monitoring with cardiology service.

Discussion

Risk for myocarditis is greatest during the first 4 weeks of clozapine treatment, with 83% of clozapine-induced myocarditis cases occurring within 14 to 21 days of clozapine initiation.[6,9,12] The literature confirms that there does not appear to be a clozapine dose-dependent risk increase.[4,5,13] Symptoms that first arise are usually nonspecific, with 32% to 49% including tachycardia, fever, and chest pain.[4,12] Elevation of CRP, which is strongly associated with infection and is a nonspecific marker of inflammation, typically occurs with symptom onset.[4,12,13] Troponins have a high specificity for diagnosis and begin to rise approximately 5 days following the onset of symptoms and the increase in CRP.[4,10,13] Up to 66% of cases also report an abnormal electrocardiogram (EKG).[4] Unfortunately, commonly used tests for

TABLE: Patient laboratory parameters

Day of Therapy	Heart Rate, bpm	Temperature, °F	Troponin-1, ng/mL	CRP, mg/dL	CPK, U/L
Day 1	77	98.3	. . .	. . .	. . .
Day 14 (symptom onset)	123	99.5	. . .	. . .	. . .
Day 16	96	100.5	<0.07	3.72	104
Day 17	111	99	0.75	8.32	124
Day 1 post DC	102	100.1	0.76	11.60	145
Day 2 post DC	100	99.6	0.66	11.70	119
Day 3 post DC	90	96.2	0.18	. . .	92
Day 4 post DC	71	97.6	<0.07	. . .	78
Day 5 post DC	72	96.5	. . .	. . .	. . .
Day 6 post DC	60	96.4	<0.07	. . .	85
Day 7 post DC	68	96.7	<0.07	1.77	92

bpm = beats per minute; CPK = creatinine phosphokinase; CRP = C-reactive protein; DC = discontinuation.

diagnosing myocarditis have unpredictably low sensitivities, while sensitivities for some tests such as BNP are unknown.[9,14-17] Furthermore, myocarditis can only definitively be diagnosed by autopsy.[9]

While there are no universal cardiac monitoring guidelines, a review of the literature has identified several suggestions for improvements to current monitoring. A monitoring protocol proposed by Ronaldson et al[12] in the *Australian and New Zealand Journal of Psychiatry* recommends acquiring baseline troponin-1 or -T, CRP, and EKG. In addition, during the first month of therapy, troponin and CRP are monitored weekly and vital signs at least every other day.[12] The combination of troponin (>2 times the upper limit of normal) and CRP (>100 mg/L) is said to increase the sensitivity of these markers to 100% in symptomatic patients.[4,12] Munshi et al[4] also recommend incorporation of cardiac markers at baseline including troponin and CRP; while, Merrill et al[7] suggest ordering troponin or creatine kinase-MB (CK-MB) only if a patient develops new evidence of cardiovascular disease.[4,7]

Monitoring guidelines by Murch et al[6] include an EKG at baseline, followed by one at 6 months, and then, annually. However, echocardiography at 6 months is not only costly but provides no additional benefit as most cases of myocarditis occur in the first month of treatment.[6] A report by Annamraju et al[9] adopted a monitoring system of diagnostic testing and clinical criteria after a patient developed myocarditis after 12 weeks of clozapine. Monitoring includes baseline ESR, CPK, CK-MB, troponin-T, BNP, and EKG as well as an EKG again at 2, 4, and 8 weeks. Patients are given a myocarditis symptom questionnaire once weekly, and if symptoms such as fatigue, dyspnea, chest pain, fever, or edema develop, then the aforementioned diagnostic tests are repeated.[9]

Although each suggested protocol slightly differs from the other; overall, the literature supports maintaining a high level of suspicion and early recognition of symptoms. Prior to this patient case, clozapine cardiac monitoring at our facility consisted of obtaining an EKG within 1 month prior to initiating clozapine. As a result of this case, 2 changes were implemented to the clozapine-monitoring parameters at VA Palo Alto. Additional cardiac monitoring of troponin-1, CRP, and CPK within 7 days of clozapine initiation was implemented. Furthermore, troponin-1, CRP, and CPK are rechecked weekly for the first month. A clozapine daily nursing assessment note was also created, which allows for daily documentation of clozapine side effects and increased clinical surveillance as detailed in the Appendix.

Rechallenging with clozapine in patients with a history of clozapine-induced myocarditis or cardiomyopathy is generally discouraged.[3,5] However, a recent systematic review found that between 1972 and 2011, clozapine rechallenge after myocarditis was successful in 3 out of 4 cases.[18] This 75% success rate is encouraging; however, owing to the small number of cases, there are no clear recommendations for rechallenging after myocarditis.[18] Use of clozapine after previous cardiotoxicity would require a cautious weighing of risk versus benefits and should only be attempted in the setting of close monitoring and cardiology supervision.[2,3,5]

Conclusion

This case suggests that early detection of clozapine-induced myocarditis is beneficial in resolution of symptoms and prevention of further complications. Similar to previous cases, the onset of myocarditis in our patient case was within the first month of initiating clozapine and involved nonspecific flu-like symptoms including feeling ill, chills, and fatigue. As suggested by the literature, an

elevation in CRP occurred prior to troponin-1 elevation. Troponin-1, CRP, and CPK levels all increased within the first month of clozapine therapy, and a subsequent reduction in values occurred with discontinuation of clozapine. Based on the low sensitivities of these tests, clinical criteria is essential to augment diagnosis. Use of a cardiac monitoring protocol and a daily clozapine nursing assessment note are expected to help with early detection and successful resolution of clozapine-induced myocarditis.

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APPENDIX: Nursing inpatient clozapine daily assessment note

- ☐ Bowel movement
  - ☐ None
  - ☐ Patient had a BM on: _____
    - ☐ Witnessed :_____
    - ☐ Reported:_____
  - ☐ Patient received PRN bowel medication
    - ☐ Milk of Magnesia
      - Effective: o Yes o No o Results Pending
    - ☐ Sodium phosphate/Biphosphate Enema
      - Effective: o Yes o No o Results Pending
    - ☐ Magnesium Citrate
      - Effective: o Yes o No o Results Pending
    - ☐ Other:_____
      - Effective: o Yes o No o Results Pending
  - ☐ Patient has diarrhea

- ☐ Orthostatic hypotension

  BP Sitting:_____

  BP Standing:_____

  HR Sitting:_____

  HR Standing: _____
  - ☐ BP indicates orthostasis
    (change in SBP greater than 20mmHg, change in DBP greater than 10mmHg)
  - ☐ No complaints
  - ☐ Reports lightheadness
  - ☐ Reports feeling dizzy when rising from seated/lying position

- ☐ Tachycardia
  - ☐ HR: _____ o Machine OR o Manual
  - ☐ Pulse indicates tachycardia (greater than 100bpm)
  - ☐ No complaints
  - ☐ Complaints of palpitations
  - ☐ Complaints of chest pressure/pain
  - ☐ Medication for tachycardia

    o Yes o No
    - ☐ Name of medication:_____

- ☐ Flu-like symptoms
  - ☐ Temperature is within normal limits

- ☐ Temperature indicates fever (greater than 98.6˚F)
- ☐ No complaints
- ☐ Reports feeling feverish
- ☐ Reports chills
- ☐ Reports sore throat
- ☐ Reports cough
- ☐ Reports headache
- ☐ Reports neck pain/joint stiffness

☐ Hypersalivation

- ☐ No complaints
- ☐ Reports mild drooling
- ☐ Reports bothersome drooling
- ☐ Using medication for drooling

  o Yes o No

  - Name of Medication: _____
  - Effective: o Yes o No

☐ Daytime Sedation

- ☐ Slept _____ hours last night
- ☐ No complaints
- ☐ Naps throughout day
- ☐ Reports drowsiness

☐ Other:_____