

CASE REPORT

## Clozapine-associated cardiac dysfunction during a gastroenteritis outbreak

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We report that two young adult patients who were initiated with clozapine for severe psychosis during a hospital-wide gastroenteritis outbreak went into severe shock. Neither patient had troponin elevation. Each required left ventricular assist device support for myocarditis. Endomyocardial biopsy revealed lymphocytic myocarditis in one patient and eosinophilic myocarditis in the other. The former patient expired. Polymerase chain reaction testing was negative for Coxsackie virus. These two patients illustrate that myocarditis can occur at usual incipient doses and that there may be an epidemiologic risk associated with gastroenteritis. Although the white blood cell (WBC) count is expected to decrease with clozapine, these patients had persistently elevated WBC counts. In conclusion, physicians should exercise caution when prescribing clozapine, especially for those with diarrhea.

**Keywords:** *clozapine; eosinophilic myocarditis; cardiogenic shock; left ventricular assist; death; adverse reaction; gastroenteritis; allergy*

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Schizophrenia is a devastating psychiatric disorder; it slowly affects normal mental functions and manifests itself as paranoia, hallucinations, and delusions. While no cure exists for schizophrenia, atypical antipsychotics are commonly used to control symptoms and improve quality of life (1). Clozapine is an atypical antipsychotic agent, which has been shown to be effective in controlling debilitating symptoms, including hallucinations, delusions, apathy, and social withdrawal. Clozapine is especially effective in patients with treatment-resistant schizophrenia (2). Despite its effectiveness, clozapine has historically been under-utilized in patients due to its adverse reactions, including megacolon, agranulocytosis, and cardiotoxicity (2). Compared to typical antipsychotics, clozapine has been reported to pose similar dose-related risks of sudden cardiac death (3).

In this report, we discuss two cases of clozapine-associated cardiogenic shock concurrent with gastroenteritis, and propose that, in the context of gastrointestinal inflammation, adverse reaction rates to clozapine might be higher than that previously reported in the literature.

### Case report

Two men, aged 22 and 41 years old, presented to the same emergency department within 2 weeks of each other, with decompensating schizophrenia and bipolar disorder refractory to multiple psychopharmacologic interventions (olanzapine, aripiprazole, and fluphenazine). Symptoms included paranoia and grandiose delusions. Both patients were clozapine-naïve; neither patient had any history of structural heart defects at the time of admission to the hospital. The patients were thus started on clozapine. Dosages of 300 and 200 mg/day were administered on the 22-year-old and 41-year-old patient, respectively. Paranoia and delusions were observed to be well controlled following clozapine initiation. Both patients continued to be monitored in the psychiatry department following admission to the hospital.

Between the 9th and 13th day of clozapine treatment, both patients started developing cardiac dysfunction as infectious gastroenteritis was propagating throughout the entire hospital population. Initially, the clinical presentation of these psychiatric patients was similar to that of the

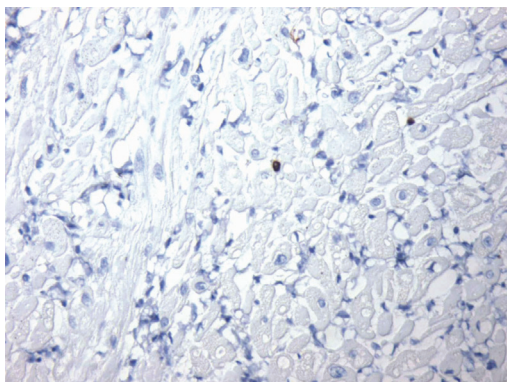
general medicine ward patients. Both had the abrupt onset of constitutional symptoms, including fever, myalgias, arthralgias, and fulminant, voluminous, explosive diarrhea.

However, these two patients rapidly worsened and were thus transferred to the medical intensive care unit. Elevated white blood cells (WBCs) levels with a left shift were observed in both patients. The 22-year-old patient acquired a respiratory tract infection while the other did not. Clozapine was stopped in both patients as cardiovascular complications occurred. Both patients showed progression to heart failure with extreme decline in ejection fraction and shock, prompting diagnoses of myocarditis requiring ventricular assist devices.

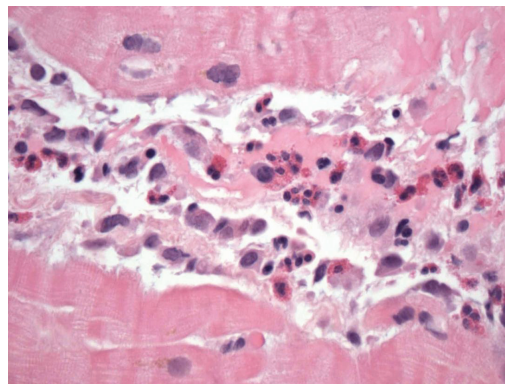
Polymerase chain reaction (PCR) tests for the presence of viral nucleic acids were negative in both patients. Cardiac biopsy in the 22-year-old patient showed lymphocyte infiltration of the myocardium (Fig. 1). Cardiac biopsy in the 41-year-old patient showed eosinophilic infiltration of the myocardium (Fig. 2). No echocardiogram was performed. The younger patient expired 2 weeks following clozapine termination, while the other stabilized and was eventually discharged.

## Discussion

National databases reporting adverse drug reactions showed the rate of clozapine-induced cardiomyopathy in the United States to be 8.9 per 100,000 person-years (2). Another study reported the incidence rate of any clozapine adverse reactions to be 0.7–1.2% among treated patients (4). The psychiatry unit of the hospital in question could accommodate up to 27 psychiatric patients at a given time. Thus, clozapine-associated myocarditis at this hospital was observed to occur at a higher rate than reported in the literature. This is consistent with an observation of a study, stating the possibly underestimated rate of clozapine-induced cardiomyopathy due to lack of reporting or failure of cardiac dysfunction symptoms recognition by mental health providers and caregivers (2).



*Fig. 1.* Cardiac muscle biopsy of a 22-year-old man with lymphocyte infiltration of the myocardium in a setting of a new-onset fever and clozapine usage.



*Fig. 2.* Cardiac muscle biopsy of a 41-year-old man with blood eosinophilia and elevation in creatine kinase in a setting of a new-onset fever and clozapine usage. Eosinophils are present in cardiac tissue.

Myocarditis may be related to clozapine dosages between 100 and 450 mg (4). The US FDA Report from the 1990s suggested that the median daily clozapine dose of 450 mg was observed in patients who survived and 400 mg of patients who died from clozapine-induced myocarditis (2). Both the patients were administered the standard dosage of clozapine ranging from 200 to 300 mg/day, ruling out the possibility of an overdose (4). Clozapine-induced cardiomyopathy mortality rate was previously estimated to be 14.8%, lower than our observation of the two patients (2).

Recent reports indicate that clozapine-related myocarditis may be more common than previously appreciated, especially in the first 2 months of treatment (3, 4). The average onset of clozapine-induced cardiomyopathy varied between 3 weeks and 4 years following clozapine initiation (2). Both patients in our report experienced adverse reactions, approximately 2 weeks into clozapine treatment, suggesting clozapine-associated cardiac dysfunction might occur sooner than reported in the context of concurrent gastroenteritis (Table 1).

Cessation of clozapine is the primary treatment of clozapine-induced cardiomyopathy (2). Standard heart failure medications and alternative anti-psychotics were earlier reported to treat cardiac and psychiatric symptoms (2). Clozapine was discontinued in the two patients as cardiac dysfunction emerged; no subsequent alternative anti-psychotic was administered. Cardiac symptoms were managed by ventricular support devices.

Comorbid factors leading to clozapine-induced myocarditis have been reported (2) to be due to prior exposure to illicit drugs and alcohol; yet, the two patients in our report had no history of drug abuse (2). Gastrointestinal infection has not been previously reported in cases of clozapine-induced myocarditis (2). Explosive diarrhea concurrent with clozapine use has been reported, but not in the context of cardiac disease (5). These cases raise the possibility that clozapine, in drug-naïve patients, with

Table 1. Two cases with adverse reactions to clozapine during a gastroenteritis outbreak

Pt #	Sex	Age	Admission date	Clozapine dosage	Psychiatric evaluation	Diarrhea/fever	1. Eosinophil 2. WBC 3. Absolute eosinophil	Pneumonia	Cardiac status
1	M	22 (deceased)	3/17/2010	300 mg/day	Schizophrenia (paranoia)	<ul style="list-style-type: none"> <li>• Diarrhea 2 weeks after clozapine</li> <li>• Fever 103°F</li> </ul>	1. 3.0% 2. 11,400 3. 342	Yes; respiratory tract infection	<ul style="list-style-type: none"> <li>• Cardiogenic shock</li> <li>• Biventricular assist device</li> <li>• Cardiac biopsy with lymphocyte infiltration of heart muscle</li> </ul>
2	M	41	3/26/2010	200 mg/day (100 mg twice a day)	Bipolar disorder	<ul style="list-style-type: none"> <li>• Diarrhea concurrent with clozapine</li> <li>• Fever 104.2°F</li> </ul>	1. 3.0% 2. 11,600 3. 348	No	<ul style="list-style-type: none"> <li>• Cardiogenic shock</li> <li>• Ventricular support</li> <li>• Cardiac biopsy with eosinophils</li> </ul>

co-morbid gastroenteritis, may potentiate the development of cardiac disease.

Clozapine has protean biological effects. These include immunomodulatory and epigenetic effects (6). Viral gastroenteritis due to Coxsackie virus can cause myocarditis. Viral infection can also exert immunological effects (7). However, these patients did not have Coxsackie virus because the PCR was negative. Clozapine is expected to induce gastroparesis, but both patients presented with diarrhea (hypermotility) (8). In addition, clozapine is anticipated to induce agranulocytosis; yet, elevated WBCs were observed in both patients (9).

Increasing numbers of cases of clozapine-related cardiac dysfunction may occur as patients on clozapine age and clozapine use increases (2). Despite its effectiveness in controlling psychotic symptoms, clozapine should be cautiously administered in cases with a comorbid inflammatory milieu. We urge physicians to be aware of the potential interaction of clozapine with gastroenteritis, leading to heart failure.

### Conflict of interest and funding

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### References

- American Psychiatric Association (2013). DSM 5. Arlington, VA: American Psychiatric Association.
- Alawami M, Wasywich C, Cicovic A, Kenedi C. A systematic review of clozapine induced cardiomyopathy. *Int J Cardiol* 2014; 176(2): 315–20.
- La Grenade L, Graham D, Trontell A. Myocarditis and cardiomyopathy associated with clozapine use in the United States. *N Engl J Med* 2001; 345: 224–5.
- Hass SJ, Hill R, Krum H, Liew D, Tonkin A, Demos L, et al. 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.
- Karmacharya R, Mino M, Pirl WF. Clozapine-induced eosinophilic colitis. *Am J Psychiatr* 2005; 162: 1386–7.
- Hinze-Selch D, Becker EW, Stein GM, Berg PA, Mullington J, Holsboer F, et al. Effects of clozapine on in vitro immune parameters: A longitudinal study in clozapine-treated schizophrenic patients. *Neuropsychopharmacol* 1998; 19(2): 114–22.
- Onyimba JA, Coronado MJ, Garton AE, Kim JB, Bucek A, Bedja D, et al. The innate immune response to coxsackievirus B3 predicts progression to cardiovascular disease and heart failure in male mice. *Biol Sex Differ* 2011; 2: 2.
- Every-Palmer S, Nowitz M, Stanley J, Grant E, Huthwaite M, Dunn H, et al. Clozapine-treated patients have marked gastrointestinal hypomotility, the probable basis of life-threatening gastrointestinal complications: A cross sectional study. *EBioMedicine* 2016; 5: 125–34.
- Cohen D, Bogers JP, van Dijk D, Bakker B, Schulte PF. Beyond white blood cell monitoring: Screening in the initial phase of clozapine therapy. *J Clin Psychiatr* 2012; 73(10): 1307–12.