Clozapine Toxicity From Drug-Drug Interaction When Given With Fluoxetine and Diltiazem

Omobolanle Alli-Balogun, MD, MPH[a,*]; Patrick Bidkhanian, DO[a]; Gurraj Singh, MBBS[b]; and Panagiota Korenis, MD[a]

The aim of this report is to show the risk of potentially serious adverse effects arising from drug-drug interactions involving medications routinely prescribed in psychiatric practice to patients with underlying comorbidities and to discuss preventative measures that can be put in place to reduce fatalities due to drug-drug interactions involving clozapine. There is widespread agreement on the benefits of clozapine as the gold standard established therapeutic when given for treatment-resistant schizophrenia,[1] but it can also be used for treatment-resistant bipolar disorder, mood disorders, and those with persistent suicidality.

Clozapine is an atypical second-generation antipsychotic that acts as a tricyclic dibenzodiazepine derivative,[2] as well as an antagonist acting on the dopaminergic (D_2), serotonergic (5-HT_{2A}), alpha1-adrenergic, and muscarinic cholinergic receptors.[2] The standard daily recommended dose of clozapine is between 300 and 600 mg/d and should not exceed 900 mg/d.[3] According to the World Health Organization Model List of Essential Medicines,[4] the prevalence of clozapine prescriptions among the US population has been steadily declining, with clozapine being only 3% of all antipsychotics prescribed,[5] which is lower compared to other countries (eg, 36%–38% in Australia, 26% in China, and 20%–30% in Taiwan).[6,7]

Clozapine can have a wide range of side effects when drug plasma concentration levels far exceed the recommended dose. These side effects include (1) metabolic disorders (ie, dyslipidemia, weight gain), (2) neutropenia, (3) pulmonary complications (ie, aspiration pneumonia), (4) renal failure, and (5) cardiac abnormalities.[8–11] Cardiac symptoms can range from mild tachycardia, hypotension, and hypertension,[12] which are most commonly seen, to severe cardiac effects such as arrhythmias, myocarditis, cardiomyopathy, pericarditis, pericardial effusion,[13] and cardiac failure secondary to cardiomyopathy.

Drug metabolism is a key factor contributing to the occurrence of clozapine drug toxicity. Drug metabolism occurs primarily in the liver but also involves the intestinal walls, kidneys, lungs, and plasma.[14] The liver, via enzymatic help, functions to detoxify and facilitate excretion of drug metabolites by converting them from lipid-soluble to water-soluble compounds.[14] This process is directly influenced by a family of heme proteins called cytochrome P450 (CYP450) enzymes. Clozapine is primarily metabolized by the CYP450 enzymes CYP3A4 and CYP1A2, which play a major role, and CYP2D6, which plays a minor role.[15] While CYP450 may act as the major determinant in first-pass metabolism, certain drugs have a variable degree of effect on the enzyme, influencing the rate at which CYP450 metabolizes drugs. They act on the enzyme as a substrate; as an inducer, which accelerates the rate of metabolic action; or as an inhibitor, which slows the breakdown of the administered drug. Known inhibitors include diltiazem (calcium channel blocker)[16] and fluoxetine (selective serotonin reuptake inhibitor).[17]

We present a case that attributes the side effects of clozapine in tandem to changes in blood level concentrations from drug-drug interactions with diltiazem and fluoxetine, leading to abnormal electrocardiogram (EKG) findings with evidence of QT prolongation and other cardiac abnormalities.

Case Report

A 41-year-old Black woman with a psychiatric history of schizoaffective disorder, bipolar disorder, and numerous suicide attempts presented to the inpatient psychiatric unit after contemplating another suicide. Her medical history included hypertension, diabetes mellitus, obesity, and asthma. She was started on clozapine to combat her intense and chronic impulsive suicidality. She had been on clozapine 500 mg in divided doses, 100 mg oral in the morning and 400 mg oral at bedtime; fluoxetine 20 mg/d; and diltiazem controlled delivery 180 mg twice/d for treatment of hypertension. During this admission, the patient was found to have toxic levels of clozapine despite no change in daily dose. The patient had also stopped smoking in the weeks leading up to the admission.

Her baseline EKG showed QT prolongation and premature ventricular contractions. Serum clozapine levels were as high as 1,500 µg/L (therapeutic range, 350–600 µg/L; toxicity range, >899 µg/L) at presentation, with norclozapine levels

[a]Department of Psychiatry, BronxCare Hospital System, New York, New York
[b]Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India
*Corresponding author: Omobolanle Alli-Balogun, MD, MPH, BronxCare Health System, 1276 Fulton Ave, Bronx, New York, NY 10456 (oallibal@bronxcare.org).

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of 234 µg/L. Clozapine and diltiazem were discontinued, and diltiazem was replaced with lisinopril. She started to improve after treatment commenced, with clozapine levels trending downward. Clozapine titration was restarted, and she was placed on 100 mg oral twice/d. With her EKG back to baseline, the patient was discharged to follow up at the outpatient clinic.

Discussion

Clozapine is an established therapy for treatment-resistant schizophrenia (TRS), showing clinically significant reduction in overall positive and negative symptoms.[18] However, clozapine remains underutilized in up to two-thirds of patients with TRS and is prescribed at a disproportionately lower rate than the estimated prevalence of TRS despite the overwhelming evidence of superior efficacy and effectiveness compared to other antipsychotics.[5,19] It can be assumed the side effects of clozapine, especially when given alongside other medications seen in drug-drug interactions, undoubtedly limit its use.

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is commonly prescribed as an antidepressant.[20] The most important difference that makes fluoxetine stand out among other SSRIs is the potential to cause drug-drug interactions through CYP450 inhibition.[20] Fluoxetine acts as a potent inhibitor on CYP1A2 and CYP2C19, with moderate action on CYP2C9, CYP2D6, and CYP3A4.[20] CYP inhibition can persist for several weeks even after medication has been stopped.[20] The continuation of fluoxetine in our patient can explain the change in clozapine blood levels despite no change in dosage. It is important for medical practitioners to take note of the drug-drug influence fluoxetine can exhibit, and appropriate dose adjustment and drug titration should be promptly initiated.

Diltiazem is a calcium channel blocker widely used for hypertension, stable angina pectoris, and supraventricular arrhythmias.[21] It acts as a CYP3A inhibitor, affecting the metabolism of many drugs[21] and increasing their bioavailability. Our patient was initially placed on diltiazem for the treatment of hypertension but was switched to lisinopril (ACE inhibitor) when toxic clozapine levels were confirmed. The combination of diltiazem and fluoxetine may have had an additive inhibitory effect on CYP, pushing clozapine plasma levels far above the safety threshold and accelerating the therapeutic benefits while magnifying the adverse effects.

Smoking habits of a patient must be considered during administration of clozapine. CYP1A2 and CYP2B6 enzymes are induced by cigarette smoking.[22] This enzyme induction results in significantly higher enzymatic activity in heavy smokers (more than 20 cigarettes/d) than in nonsmokers.[23] Within a week of smoking cessation, enzyme induction is rapidly reversed, and a new steady state of CYP1A2 is quickly reached.[24] This reduction in enzyme activity reduces drug clearance, with a mean increase in plasma clozapine concentrations of 72%,[25] which increases the risk of adverse drug reactions.[24] Patients who change their smoking frequency should be periodically assessed and considered for dose adjustment of their medication to prevent toxicity.

While clozapine toxicity can result in a multitude of consequences, greater focus and attention must be given toward cardiac complications. In a study[26] reporting 213 cases, 85% developed clozapine-induced myocarditis within the first 2 months of initiating therapy and 50 resulted in death. Our patient presented with tachycardia, with an EKG confirming the presence of QT prolongation (torsades de pointes), promoting premature ventricular contractions. The major determinant of drug-induced torsades de pointes is the duration of QT interval[27] and is a precursor for fatal arrhythmias that can eventually lead to sudden cardiac death.[28] Although patients are at greatest risk in the first month of therapy, the risk may persist as long as they are taking the drug. Fortunately, no irreversible cardiac damage was observed in this case. Despite known side effects of clozapine and risks associated with second-generation antipsychotics in general, they still occur less than with typical antipsychotics, which also possess high risk of extrapyramidal effects such as tardive dyskinesia, tremors, muscle rigidity, and parkinsonian-like symptoms.[15]

Clinicians must be vigilant and preventative measures should be taken before clozapine is administered to a patient, especially when given alongside other medications. The patient should be warned of these potentially fatal cardiovascular adverse effects. A cardiac evaluation should be considered for any personal or family history of heart disease and contraindicated in patients with known cardiac conditions. Patients should maintain a degree of caution if cardiac symptoms develop, such as chest pain, shortness of breath, or tachypnea, and should follow up with an EKG evaluation for arrhythmia, myocarditis, or cardiomyopathy, which would prompt immediate discontinuation of the drug. Along with mandated monitoring of agranulocytosis with routine white blood cell count collection, patients should also be monitored for changes in blood glucose, lipid, and troponin levels and serial creatine kinase with myocardial band fractions regularly.

An understanding of CYP metabolism is important in the recognition of drug-drug interactions. Patients with medical comorbidities that warrant drug therapies from multiple class groups should be prescribed these medications cautiously, taking into account possible drug-drug interactions that may inhibit CYP450 action, which in turn alter drug plasma concentrations and result in adverse clinical consequences.

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REFERENCES

1. Dragoi AM, Radulescu I, Năsui BA, et al. Clozapine: an updated overview of pharmacogenetic biomarkers, risks, and safety-particularities in the context of COVID-19. *Brain Sci.* 2020;10(11):840.

2. Stahl S. *Prescriber's Guide: Stahl's Essential Psychopharmacology*. 7th ed. Cambridge: Cambridge University Press; 2020:191.
3. Subramanian S, Völlm BA, Huband N. Clozapine dose for schizophrenia. *Cochrane Database Syst Rev*. 2017;6(6):CD009555.
4. WHO model list of essential medicines - 21st list, 2019. Accessed February 3, 2022. https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06
5. Kelly DL, Wehring HJ, Vyas G. Current status of clozapine in the United States. *Shanghai Jingshen Yixue*. 2012;24(2):110–113.
6. Conley RR, Kelly DL, Lambert TJ, et al. Comparison of clozapine use in Maryland and in Victoria, Australia. *Psychiatr Serv*. 2005;56(3):320–323.
7. Xiang YT, Wang CY, Si TM, et al. Clozapine use in schizophrenia: findings of the Research on Asia Psychotropic Prescription (REAP) studies from 2001 to 2009. *Aust N Z J Psychiatry*. 2011;45(11):968–975.
8. Wenthur CJ, Lindsley CW. Classics in chemical neuroscience: clozapine. *ACS Chem Neurosci*. 2013;4(7):1018–1025.
9. Broich K, Heinrich S, Marneros A. Acute clozapine overdose: plasma concentration and outcome. *Pharmacopsychiatry*. 1998;31(4):149–151.
10. Sparve E, Nordberg P, Forsberg S, et al. Acute clozapine intoxication. *J Clin Psychopharmacol*. 2009;29(3):302–304.
11. Sartorius A, Hewer W, Zink M, et al. High-dose clozapine intoxication. *J Clin Psychopharmacol*. 2002;22(1):91–92.
12. Stuart JE, Jonathan EL. Psychiatric disorders. In: Tierney LM Jr, Mcphee SJ, Papadakis MA, eds. *Current Medical Diagnosis and Treatment*. Lange Medical Books/McGraw Hill; 2004:1001–1061.
13. Semple D, Smyth R, Burns J, et al, eds. *Oxford Handbook of Psychiatry*. Oxford: Oxford University Press; 2005:218–222.
14. McDonnell AM, Dang CH. Basic review of the cytochrome P450 system. *J Adv Pract Oncol*. 2013;4(4):263–268.
15. Dean L, Kane M. Clozapine Therapy and CYP Genotype. In: Pratt VM, Scott SA, Pirmohamed M, et al, eds. *Medical Genetics Summaries*. Bethesda, MD: National Center for Biotechnology Information; 2012.
16. Sutton D, Butler AM, Nadin L, et al. Role of CYP3A4 in human hepatic diltiazem N-demethylation: inhibition of CYP3A4 activity by oxidized diltiazem metabolites. *J Pharmacol Exp Ther*. 1997;282(1):294–300.
17. Isoherranen N. The effects of multiple dose fluoxetine and metabolites on CYP1A2, CYP2C19, CYP2D6 and CYP3A4 activity. Accessed February 3, 2022. https://clinicaltrials.gov/ct2/show/study/NCT01361217
18. Lewis SW, Davies L, Jones PB, et al. Randomized controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment. *Health Technol Assess*. 2006;10(17):iii–iv, ix–xi, 1–165.
19. Forrester T, Siskind D, Winckel K, et al. Increasing clozapine dispensing trends in Queensland, Australia 2004–2013. *Pharmacopsychiatry*. 2015;48(4-5):164–169.
20. Hemeryck A, Belpaire FM. Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab*. 2002;3(1):13–37.
21. Pinto AG, Horlander J, Chalasani N, et al. Diltiazem inhibits human intestinal cytochrome P450 3A (CYP3A) activity in vivo without altering the expression of intestinal mRNA or protein. *Br J Clin Pharmacol*. 2005;59(4):440–446.
22. Lucas C, Martin J. Smoking and drug interactions. *Aust Prescr*. 2013;36(3):102–104.
23. Tantcheva-Poór I, Zaigler M, Rietbrock S, et al. Estimation of cytochrome P-450 CYP1A2 activity in 863 healthy Caucasians using a saliva-based caffeine test. *Pharmacogenetics*. 1999;9(2):131–144.
24. Faber MS, Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. *Clin Pharmacol Ther*. 2004;76(2):178–184.
25. Meyer JM. Individual changes in clozapine levels after smoking cessation: results and a predictive model. *J Clin Psychopharmacol*. 2001;21(6):569–574.
26. Wooltorton E. Antipsychotic clozapine (Clozaril): myocarditis and cardiovascular toxicity. *CMAJ*. 2002;166(9):1185–1186.
27. Cubeddu LX. QT prolongation and fatal arrhythmias: a review of clinical implications and effects of drugs. *Am J Ther*. 2003;10(6):452–457.
28. Shah SK. QT interval prolongation: life-threatening consequences of life saving drugs. *Pharmacol Drug Dev Ther*. 2018;3(1).