SAGE Open Medical Case Reports
Volume 12: 1–4

DOI: 10.1177/2050313X241283262
journals.sagepub.com/home/sco
Sage

Tug of war between clozapine and CYP450 inducers: A case report

Gaurav Taneja and Luba Leontieva

Abstract

The management of schizoaffective disorder bipolar type often involves a combination of pharmacotherapy and psychotherapy. Clozapine, an effective antipsychotic for treatment-resistant schizophrenia, and oxcarbazepine, a mood stabilizer, is a commonly prescribed medication. We present a case report of a 56-year-old male with schizoaffective disorder bipolar type who experienced subtherapeutic clozapine levels despite dose adjustments, leading to deteriorating symptoms. Oxcarbazepine, a weak CYP450 inducer, likely contributed to the subtherapeutic levels. Additionally, the pharmacogenetic analysis revealed a CYP1A2 *1F/*1F genotype, indicating normal activity with a potential for decreased serum levels and adverse events in the presence of inducers. The patient was eventually stabilized on a regimen of lithium, paliperidone, and quetiapine, avoiding oxcarbazepine. This case highlights the importance of considering individual patient factors, including pharmacogenetics when managing treatment-resistant patients. Monitoring serum clozapine levels and assessing enzyme activity before initiating therapy may help optimize treatment outcomes and minimize adverse events.

Keywords

Clozapine, inducer, oxcarbazepine, CYP450, CYP1A2, CYP3A4, psychopharmacology, psychiatry

Date received: 8 March 2024; accepted: 27 August 2024

Introduction

Schizoaffective disorder bipolar type is a complex mental health condition that requires a comprehensive treatment approach. Typically, the treatment involves a combination of pharmacotherapy and psychotherapy. Antipsychotic medication is a crucial part of most treatment plans, and specific treatment options are tailored to individual needs. In a study that examined schizoaffective treatment regimens, it was found that 93% of patients received antipsychotic medication. Furthermore, 20% of patients received mood stabilizers in addition to antipsychotics, and 19% received antidepressants along with antipsychotics.[1] With a personalized and comprehensive treatment plan, individuals with schizoaffective disorder can manage their symptoms and lead fulfilling lives.

Clozapine is considered one of the most effective antipsychotics for treating schizophrenia and is the only antipsychotic shown to be effective in treatment-resistant schizophrenia for 25%–30% of patients.[2] Additionally, its applications extend to reduce the likelihood of recurrent suicidal behavior in individuals diagnosed with schizophrenia or schizoaffective disorder and reduce aggression.[3] However, not all patients respond positively to this treatment.

Clozapine is primarily metabolized in the liver by several cytochrome P450 (CYP) enzymes, mainly CYP1A2. Other CYP enzymes involved in clozapine metabolism include CYP2D6 and CYP3A4. The metabolism of clozapine involves a complex interaction of these enzymes, and any alterations in their activity can significantly impact the drug's pharmacokinetics and therapeutic efficacy.[4,5]

Oxcarbazepine is derived from a structural modification of carbamazepine to minimize the involvement of CYP450 isoenzymes in its metabolism.[6] Oxcarbazepine, like carbamazepine, functions as a preferred antiepileptic, anti-impulsivity, and mood stabilizer with less pronounced dose-dependent effects compared to carbamazepine, which significantly induces CYP3A4. Notably, oxcarbazepine weakly induces CYP3A4 and UGT (uridine 5'-diphospho-glucuronosyltransferase) in

Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY, USA

Corresponding Author:
Gaurav Taneja, Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY, USA.
Email: gtaneja95@gmail.com

vitro,[7,8] and its effects on plasma concentrations of various drugs have been documented. Although the interaction between clozapine and oxcarbazepine has been underreported,[9,10,11] this article presents a case demonstrating an interaction between them in a patient with schizoaffective disorder, bipolar type.

Paliperidone undergoes minimal hepatic metabolism. A small fraction is metabolized in the liver, primarily through CYP2D6 and CYP3A4 enzymes, but this accounts for a minor part of its elimination. It is possible that the induction of CYP3A4 could slightly increase the metabolic rate of the small fraction that is metabolized hepatically, potentially decreasing its effectiveness.[12,13]

Case Report

We present the case of a 56-year-old Caucasian male with a psychiatric history of schizoaffective disorder bipolar type according to *DSM 5* criteria, nonsmoker, with multiple inpatient hospitalizations and medical history of hyperlipidemia, gastroesophageal reflux disease, and tongue cancer (in remission for 2 years), currently undergoing a two-month inpatient stay. His first episode of illness and first hospitalization was at the age of 26. The patient has a history of recurrent mood episodes leading to multiple psychiatric hospitalizations from 1993 as well as delusions and hallucinations that occurred during the mood episodes and in between them. He had severe manic and depressive episodes, religious delusions, a history of violence toward his father, suicidal thoughts, and attempts, and one severe self-mutilation attempt that resulted in third-degree burns due to Satanic delusions making him burn himself. He also had periods of catatonia. His recent presentation in November 2023 was prompted by active suicidal ideation (SI). Upon admission, he exhibited SI with a determined intent, coupled with delusions of guilt featuring a religious theme, as well as auditory and visual hallucinations.

The patient immigrated to the United States in his early 20s from Western Europe. He was raised in a conservative Catholic environment, is proficient in three languages, and holds two master's degrees. He has no personal history of smoking tobacco/marijuana, or any substance use disorder. His family history includes a history of depression in his mother and psychosis in his aunt. His strong religious beliefs perseverate as delusions of guilt and visual and auditory hallucinations of Satan and God during his inpatient stay.

The patient has been tried on various antipsychotic medications: haloperidol, olanzapine, aripiprazole, quetiapine, ziprasidone, risperidone, and paliperidone; mood stabilizers: valproic acid, oxcarbazepine; and benzodiazepines: lorazepam, clonazepam, zolpidem; and antidepressants: fluvoxamine, escitalopram, and trazodone. The patient had prolonged periods of stability without inpatient admissions for 5–10 years. The latest stable period was for 8 years from 2014 to 2022 when he was taking quetiapine 400 mg/day, oxcarbazepine from 1500 mg/day to 1200 mg/day, fluvoxamine 200 mg/day, and paliperidone 117 mg IM every 28 days.

Table 1. Serum clozapine levels in the patient.

Timeline	Clozapine dose (mg/day)	Serum levels (ng/mL)	Oxcarbazepine dose (mg/day)
06/01/202x	325	85	1200
11/17/202x	550	298	1200
11/26/202x	500	197	1200
12/08/202x	550	153	1200
01/02/202x	550	140	900

In 2022, paliperidone was increased to 234 mg IM every 28 days during a manic episode due to medication nonadherence, and fluvoxamine was tapered off. After a suicidal attempt in November 2022, the patient was hospitalized and prescribed venlafaxine 37.5 mg/day for 2 weeks for his depression and anxiety. In February 2023, quetiapine was increased to 650 mg/day. In March 2023, the patient burned himself due to severe delusions, which indicated nonresponse to his regimen of quetiapine and oxcarbazepine as he was in the hospital prior to the burning incident and only stayed home for 2 days.

During subsequent inpatient care, the patient was switched from quetiapine to clozapine, due to poor response to previous treatment and the severity of the burning incident. The clozapine was slowly titrated upward. On the dose of 350 mg of clozapine, his trough serum level was 85 ng/mL at steady state. He was on dissolvable clozapine to eliminate possible nonadherence.

At the time of this report writing, the patient was on clozapine at 550 mg/day oxcarbazepine at 1200 mg/day, paliperidone at 156 mg/28 days, and lorazepam at 2 mg/day. As-needed medications include hydroxyzine, senna, and magnesium hydroxide. Despite dose adjustments, the patient consistently exhibited subtherapeutic clozapine levels, measured 10–11 h after taking the highest evening dose at a steady state (see Table 1).

The patient was taking several medications to manage their condition, including clozapine, paliperidone, glycopyrrolate (3 mg/day), and benztropine (4 mg/day). Clozapine led to side effects such as drooling and sedation, managed with glycopyrrolate. It also caused constipation, which, along with constipation caused by high doses of glycopyrrolate and benztropine, was treated with docusate sodium (400 mg/day), Senna (2 tablets/day), and simethicone (240 mg/day). Paliperidone caused extrapyramidal symptoms such as pill rolling, flat affect, rigidity, and tremors, managed with benztropine. The patient did not experience weight gain or agranulocytosis.

Discussion

The topic of drug interactions is becoming increasingly important in medicine. It is now known that changes in metabolic enzymes in the liver and other extrahepatic tissues explain many drug interactions. Significant pharmacokinetic

drug–drug interactions often result from the effects of previous drug administration on hepatic cytochrome P450 enzymes (P450s or CYPs). When administered simultaneously, certain drugs act as potent enzyme inducers and others as inhibitors.[14] However, cases of enzyme inhibition are more common in reports. A thorough understanding of the mechanisms of enzyme inhibition or induction is essential to implement appropriate multidrug therapy. In the future, this understanding could help identify individuals at the highest risk for drug interactions and adverse events.[15]

The patient's stable condition with his past medications for 8 years and deteriorating on clozapine raised concerns of altered drug metabolism. The patient during his inpatient stay improved regarding his active SI but continued to perseverate on topics of delusion of guilt, visual and auditory hallucinations which prompted us to correlate it clinically with clozapine levels. As shown in Table 1, serum clozapine levels were measured 10–11 h after taking the highest evening dose at a steady state.

The patient's deteriorating symptomatology on clozapine and subtherapeutic serum levels indicated a drug interaction. There are very few reported cases of the interaction between clozapine and oxcarbazepine[4,7,8,9] Oxcarbazepine is a weaker inducer than carbamazepine. The inductive effect of oxcarbazepine is dose-dependent. The larger the dose, the greater the potential for an induction. Also, the induction effect of oxcarbazepine is more effective at higher doses (900–1200 mg/day).[7,8,9] The patient is experiencing an ineffective response to treatment due to their drug levels falling below the expected therapeutic range despite dose adjustments. A possible explanation for the interaction can be due to oxcarbazepine's modest action on CYP3A4, leading to induction of clozapine and ineffectiveness of the treatment.[10,11,14]

Additionally, to better understand the patient's pharmacokinetics, a pharmacogenetics analysis was performed. The report revealed that the patient's CYP1A2 genotype is *1F/*1F and a normal CYP3A4/5 genotype is *1/*1, *3/*3. The CYP1A2 *1F/*1F genotype confers normal activity but is sensitive to induction.[5,16,17,18] In the presence of inducers, there is a risk of decreased serum levels and a risk of possible adverse events associated with active metabolites. It is highly induced by certain substances including tobacco/marijuana smoke, and inhibited by excessive coffee consumption (none of which our patient had), or other medications that can induce or inhibit drug metabolism.[19,20,21] Another plausible explanation for the nonresponsiveness to the treatment despite incremental dose adjustments can be attributed to the patient's sensitivity to CYP enzyme induction due to its genotype has compounded the issue along with oxcarbazepine's inducing effect, further reducing the drug's effectiveness.[22,23]

With respect to ineffectiveness of the treatment, the patient was put on lithium as a mood stabilizer and paliperidone with quetiapine as an antipsychotic. The patient has been stable on this regimen with no inpatient hospitalization during follow-up. Indicating that oxcarbazepine on a high dosage has a strong inducing effect on the antipsychotics with CYP450 metabolism rendering them ineffective. Future studies with larger sample sizes and long-term follow-up are warranted to validate these findings and further elucidate the optimal treatment strategies for patients with schizoaffective disorder bipolar type.

Conclusion

This case highlights the interaction among pharmacokinetics, pharmacogenetics, and treatment outcomes in patients with schizoaffective disorder bipolar type. The subtherapeutic levels of clozapine observed in our patient despite dose adjustments emphasize the importance of considering individual patient factors, such as concurrent medication use and pharmacogenetic profiles, in treatment planning.

The strong induction effect of a high dose of oxcarbazepine on CYP enzymes likely contributed to the observed subtherapeutic clozapine levels. This emphasizes the necessity of monitoring serum clozapine levels and assessing enzyme activity before initiating therapy to optimize treatment outcomes and minimize adverse events.

Furthermore, this case features the need for personalized treatment approaches in patients with treatment-resistant disorders, highlighting the critical role of individualized care in achieving effective and safe therapeutic results.

Acknowledgements

Not Applicable.

Author contributions

G.T.: conceptualization, preparation of the case, preparation of the manuscript, patient interview, table formulation, discussion, conclusions. L.L.: manuscript editing, manuscript revisions, reviewing, guidance, visualization.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article. The patient had the decisional capacity to provide the written consent. This case report conforms to the research guidelines and ethical principles of the WMA Declaration of Helsinki.

ORCID iD

Gaurav Taneja https://orcid.org/0009-0004-8237-6534

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