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The potential influence of estrogen-containing oral contraception on clozapine metabolism in a patient with known pharmacogenomic status

Alyssa K. Kuhn[1]; Meina L. Determan[2]; Jessica A. Wright, PharmD[3]; Eric Matey[4]; Jonathan G. Leung, PharmD[5]

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Abstract

Clozapine is primarily metabolized via cytochrome P450(CYP)1A2 and to a lesser extent CYP3A4, CYP2C19, and CYP2D6. Metabolic inhibitors of clozapine, such as fluvoxamine and ciprofloxacin, are important to recognize to avoid adverse drug events. Estrogen-containing oral contraceptives (eOCPs) are weaker CYP1A2 and CYP2C19 inhibitors but are associated with a 2-fold increase of clozapine concentrations. The potential for phenoconversion due to a CYP genetic polymorphism can add additional complexities when considering drug interactions. A case report is presented of a suspected interaction between newly initiated clozapine and a prescribed eOCP for which the patient's pharmacogenomic status was known. A 17-year-old, nonsmoking, White female with a history of schizophrenia was initiated on clozapine 12.5 mg at bedtime with a plan to increase by 25 mg every 4 days in the outpatient setting. The patient was a known rapid CYP1A2 metabolizer without identified sources of CYP1A2 induction and a CYP2C19 rapid metabolizer. Based on pharmacogenomic testing, there was no suspicion for significant gene-drug interactions. Yet, as the patient was prescribed an eOCP, a clozapine concentration was obtained after reaching 150 mg at bedtime. This steady-state clozapine concentration was found to be 560 ng/mL, correlating with worsening sedation and constipation. Given ongoing side effects, clozapine was lowered to 100 mg at bedtime; however, ongoing intolerance ultimately led to clozapine discontinuation. This case highlights the potential interaction between clozapine and eOCP in a CYP1A2 and CYP2C19 rapid metabolizer, leading to clozapine intolerance and discontinuation. The concomitant use of clozapine and eOCPs should be undertaken judiciously.

Keywords: clozapine, oral contraceptives, CYP1A2, pharmacogenomics, schizophrenia, estrogen, progestin

[1] Pharmacy Student, University of Wisconsin-Madison School of Pharmacy, Madison, Wisconsin, ORCID: https://orcid.org/0009-0005-3875-9199; [2] Pharmacy Student, Texas A&M University School of Pharmacy, Kingsville, Texas, ORCID: https://orcid.org/0009-0003-0479-9462; [3] Pharmacist, Mayo Clinic, Rochester, Minnesota, ORCID: https://orcid.org/0000-0001-9659-4875; [4] Pharmacist, Mayo Clinic, Rochester, Minnesota, ORCID: https://orcid.org/0000-0001-9436-8137; [5] (Corresponding author) Pharmacist, Mayo Clinic, Rochester, Minnesota, leung.jonathan@mayo.edu, ORCID: https://orcid.org/0000-0003-3836-9375

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Background

Clozapine is a second generation antipsychotic Food and Drug Administration–approved for treatment-resistant schizophrenia and reducing suicidal behavior in patients with schizophrenia and schizoaffective disorder.[1] Clozapine is also considered a treatment option for patients with bipolar disorder, tardive dyskinesia, and psychosis associated with Parkinson disease.[2] However, clozapine requires monitoring of potentially fatal adverse drug reactions (ADRs), including severe neutropenia, myocarditis, and gastrointestinal hypomotility. Other ADRs, such as fatigue, sialorrhea, and metabolic effects, may also result in clozapine discontinuation or lead to more serious ADRs without intervention.[3]

Clozapine is primarily metabolized by CYP1A2 and to a lesser degree CYP2C19, CYP2D6, CYP3A4, and CYP3A5.[4,5] Medications that interact with these pathways must be carefully monitored or avoided to prevent unwanted outcomes, such as ADRs

or lack of effectiveness. CYP1A2 inducers include smoking, carbamazepine, and phenytoin.[2] CYP1A2 inhibitors include ciprofloxacin and fluvoxamine.[2] Whereas these aforementioned interactions have been well documented previously, other medications that inhibit or induce clozapine's key metabolic pathways have less data to confirm or refute their clinical significance. One such class of medication is estrogen-containing oral contraceptives (eOCPs), which have also been described as inhibitors of CYP1A2 and CYP2C19.[6] Yet, despite the lack of formal pharmacokinetic studies assessing the clinical significance of this interaction, available data from case reports and case series suggest eOCPs may decrease clozapine clearance by as much as 50%.[6–8] Within these published studies, there is no reporting of patient pharmacogenomic information, which might be important in understanding the clozapine-eOCP interaction. We describe a case in which a patient with a known pharmacogenomic profile initiated clozapine in the setting of eOCP use with poor tolerability.

Case

A 17-year-old, White, nonsmoking, female patient with a history of schizophrenia was initiated on clozapine in the outpatient setting. She had previously failed trials of risperidone, aripiprazole, lurasidone, and quetiapine. Concomitant medications prescribed when clozapine was initiated included levonorgestrel/ethinyl estradiol 0.1 mg/20 mcg daily, melatonin 3 mg at bedtime, and polyethylene glycol 17 g daily as needed for constipation. Lorazepam 0.5 to 2 mg 3 times daily as needed for anxiety or sleep was also prescribed, but none had been used in the preceding days. The patient and caregivers were educated on the additive effects of sedation and possible respiratory depression when benzodiazepines are coadministered with clozapine. Preexisting pharmacogenomic testing was available and included the following CYP phenotype (genotype) results: CYP1A2 rapid metabolizer (*1F/*1F), CYP2C19 rapid metabolizer (*1/*17), CYP2D6 normal metabolizer (*1/*1), CYP3A4 intermediate to normal metabolizer (*1/*22), and CYP3A5 poor metabolizer (*3/*3).

After starting 12.5 mg at bedtime, clozapine was increased by 25 mg approximately every 4 days. The potential interaction between levonorgestrel/ethinyl estradiol and clozapine was recognized, and the plan was to obtain a clozapine serum concentration once a dose of 150 mg at bedtime was reached. The usual practice within the clinic was to check a concentration once the patient achieves a clozapine dose of 200 to 300 mg depending on smoking status. After allowing time to reach steady state, the 12-hour postdose clozapine concentration was higher than expected at 560 ng/mL. The norclozapine concentration was 215 ng/mL. In review with the patient, there had been no major changes to diet or caffeine intake, no concern for infection, and no medications were changed. Clinically, by the time the clozapine dose reached 150 mg (ie, approximately after 4 weeks), there was the development of new fatigue with at least 15 hours per night of sleep, worsening constipation, and increased appetite associated with approximately a 5-kg weight gain. In an attempt to mitigate ADRs, the dose of clozapine was lowered to 100 mg at bedtime over weeks 4 to 8 of the clozapine trial in an attempt to improve tolerability. However, ultimately due to ongoing intolerance and limited improvement of overall psychiatric symptoms, the decision was made to taper clozapine and transition to alternative treatments.

Discussion

Clozapine initiation in a patient prescribed an eOCP was associated with poor tolerability leading to discontinuation. Based on the nomograph by Rostami-Hodjegan et al and a tool on the website smiadviser.org/clozapine-dose-planner, the patient's anticipated concentration when taking 150 mg at bedtime should have been closer to 185 ng/mL but was 3.5 times this.[9,10] The higher-than-expected clozapine concentration was suspected to be due to the interaction between clozapine and the eOCP, primarily mediated via CYP1A2. The prescribing information of clozapine defines "oral contraceptives" as moderate or weak CYP1A2 inhibitors, suggesting only monitoring with a consideration for dose adjustments versus suggesting an empiric reduction.[1] Yet clozapine may need as much as a 50% reduction due to the impact an eOCP has on CYP1A2 activity.[6,11] The eOCPs are also described as weak inhibitors of CYP3A4 and CYP2C19; however, the clinical relevance of this specifically with clozapine has not been well defined.[6,11] Yet, overall, there has not been formal pharmacokinetic studies evaluating the impact of eOCPs on clozapine metabolism, and knowledge providing insight into this interaction is derived from case reports or case series. The influence of eOCPs on CYP1A2 is evident upon review of other CYP1A2 substrates, including tizanidine and theophylline, which have clearance reduced on average by 50% and 30%, respectively, due to eOCPs.[12,13]

Published reports describing the interaction between clozapine and eOCPs are highlighted in the Table. In 2 cases the interaction led to side effects of nausea, vomiting, palpitations, drowsiness, weakness, and dizziness with resolution after oral contraceptive discontinuation.[14,15] Another set of cases presented with side effects of drowsiness, dizziness, anergy, constipation, and fever, which resolved upon lowering of the clozapine dose.[6,16] Last, 2 cases presented patients having psychotic relapses during the 7-day hormone-free intervals or after eOCP discontinuation.[7,8] The cases described reductions of clozapine serum concentrations between 24% and 47% upon the discontinuation of eOCPs. All prior cases represent the impact of the drug-drug interaction, but the most recent case was written in 2021, signifying the need for additional data being published to call attention to this interaction.

However, there has not yet been a report describing the clozapine-eOCP interaction when pharmacogenomic status is known. CYP1A2 rapid metabolizer is the most common phenotype among patients of European ancestry.[17,18] CYP1A2

TABLE: Prior reports of clozapine-eOCP interaction

Author, Year	Patient Details, eOCP	Total Daily Clozapine Dose	Clozapine Concentration	Adverse Events
Bookholt et al, 2014[7]	28 yo, F, SA Levonorgestrel 0.125 mg and ethinyl-estradiol 0.05 mg	650 mg	Decreased from 660 ng/mL to the lowest 220 ng/mL after DC of eOCP	Confusion, paranoia, and anxiety upon eOCP DC
Cadeddu et al, 2015[14]	29 yo, F, SA Drospirenone 3 mg and ethinyl estradiol 0.03 mg	225 mg	542 ng/mL with eOCP and recent oral fluconazole treatment	Eosinophilia, tachycardia, pericarditis without rechallenge
Gabbay et al, 2002[15]	47 yo, F, SZ Norethindrone 0.5 mg and Ethinyl-estradiol 0.035 mg	550 mg	Maximal level of 792 ng/mL with eOCP and reduction down to 378 ng/mL with eOCP DC	Drowsiness, weakness, and dizziness
Sandson et al, 2007[16]	33 yo, F, SA "OCP consisted of ethinyl estradiol"	500 mg	Increase from 448 ng/mL to 1281 ng/mL after starting eOCP	Drowsiness, anergy, and dizziness
Schoretsanitis et al, 2020[6]	33 yo, F, SZ Norethindrone 0.5 mg and ethinyl-estradiol 0.035 mg	300 mg	Concentration rose to 1416 ng/mL with eOCP; concentration of 1272 ng/mL achieved with 850 mg of clozapine per day without eOCP	Constipation and fever
Suhas et al, 2021[8]	30 yo, F, SZ Drospirenone 3 mg and ethinyl estradiol 0.03 mg	350 mg	Concentration rose to 1886 ng/mL with eOCP and decreased to 1162 ng/mL during hormone-free week	Psychotic symptoms during hormone-free week

DC = discontinuation; eOCP = estrogen-containing oral contraceptive; F = female; SA = schizoaffective disorder; SZ = schizophrenia; yo = years old.

rapid metabolizer phenotypes are a special case in which CYP1A2 is inducible in the presence of various CYP1A2 inducers (eg, smoking, cruciferous vegetables, and some medications), whereas CYP1A2 is not expected to be inducible for the CYP1A2 normal phenotype.[19] Clinically, no action is needed for gene-drug interactions involving the CYP1A2 rapid metabolizer phenotype. In this case, as the patient was not a smoker and other sources of induction were not present, the patient's CYP1A2 metabolizing activity was considered to be the same as the majority of the population. Whereas the CYP1A2 rapid metabolizer phenotype (majority phenotype as referenced earlier) alone is not likely to be clinically significant, the presence of a CYP1A2 inhibitor is expected to greatly reduce CYP1A2 metabolizing activity. Therefore, the clearance of clozapine is decreased because of this phenoconversion, leading to higher drug concentrations and an increased risk of ADRs. This patient was also a CYP2C19 rapid metabolizer, and whereas this is a minor pathway of clozapine metabolism, the influence of this phenotype on clozapine concentrations requires more research. There is currently mixed data showing both potential influence and no influence of CYP2C19 genotype-predicted activity scores on clozapine concentrations.[20–22] The patient's "poor" CYP3A5 status is also considered to represent the majority phenotype metabolism as patients with functional alleles (ie, CYP3A5*1) are less common. The patient's phenotype for CYP3A4 was also reported to be slightly reduced due to the *1/*22 genotype. A case report of a 36-year-old White man with CYP3A4 intermediate metabolizer phenotype, which is further reduced from our patient, showed an unusually high concentration of clozapine that was not attributed to any other factor.[22] Multiple studies using a combination of mRNA expression of CYP3A4 and CYP3A4 genotype demonstrated that low CYP3A4 expression is associated with higher clozapine concentrations although the CYP3A4 genotype doesn't necessarily always correlate with decreased CYP3A4 expression.[23,24] Overall, the eOCP inhibition of CYP1A2 with possible contribution from the patient's CYP3A4 phenotype (but not the other unremarkable phenotypes) could explain a clozapine concentration of 560 ng/mL when taking just 150 mg of clozapine. Whereas eOCPs may weakly inhibit CYP2C19, given that the patient had a rapid CYP2C19 phenotype, this reinforces that the eOCP-clozapine interaction is more clinically relevant to effects on CYP1A2 over CYP2C19.

One limitation of the presented case is that the development of early inflammation associated with clozapine exposure was not ruled out. Whereas baseline C-reactive protein was not abnormal, it is possible that an inflammatory process could have reduced clozapine metabolism. However, the patient did not have fever, chills, tachycardia, or chest pain and physically was doing well. Second, it was not documented if the patient was taking the hormone-free interval week at the time of the therapeutic drug monitoring. Third, the generalizability of this 1 case to (1) other patients prescribed clozapine with an eOCP, (2) patients with different biogeographical ancestry, or (3) other CYP1A2 and CYP3A4 phenotypes is unknown.[25] Fourth, other non-CYP pharmacogenomic variants may influence clozapine concentrations, including rs28379954.[26] Fifth, whereas the adherence was assessed and without reported deviations, the possibility of overadherence is possible, skewing therapeutic drug monitoring (TDM) results. Finally, hypotheses formulated from the case often relied on studies that may have only evaluated phenotypes of one CYP

pathway. Clinically, the clearance of clozapine is based on many other factors. Ongoing research exploring comprehensive models accounting for multiple CYP pathway phenotypes and other patient-specific factors is needed.[27]

Conclusion

In a young woman treated with clozapine and an eOCP, clozapine could not be tolerated and was discontinued due to ongoing side effects. Her CYP2C19 rapid and CYP1A2 "normal" metabolism phenotype did not seemingly mitigate the eOCP-clozapine interaction. More research is needed regarding the interaction of clozapine with eOCPs, but the combination is described in various case studies to affect clozapine concentrations and clozapine-related adverse effects. Clinicians should consider the potential for a clinically significant interaction between eOCPs and clozapine. Clinicians should monitor patients closely for ADRs when clozapine is concomitantly prescribed with eOCPs and utilize TDM as necessary to help more precisely manage clozapine.

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