mhc
MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Managing ciprofloxacin-clozapine interaction with immunoassay-based monitoring: A case report

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How to cite: Waters K, Popielarz V, Lumasag J, Wiesenfeld S, Tewksbury A. Managing ciprofloxacin-clozapine interaction with immunoassay-based monitoring: A case report. Ment Health Clin [Internet]. 2025;15(3):191-6. DOI: 10.9740/mhc.2025.06.191.

Submitted for Publication: October 31, 2024; **Accepted for Publication:** March 14, 2025

Abstract

Whereas the interaction between clozapine and ciprofloxacin is well-documented, this case report emphasizes the importance of closely monitoring clozapine plasma concentrations during concurrent administration. When available, clozapine concentrations may be obtained via immunoassay to assess clozapine concentrations more quickly and subsequently adjust clozapine doses. Frequent monitoring is especially important for guiding appropriate dose adjustments in the setting of patient-specific factors that may affect clozapine concentrations, such as change in smoking status, caffeine intake, and infection status. The case report focuses on a 57-year-old female hospitalized for abdominal wall cellulitis, which necessitated antibiotic therapy. The patient's schizophrenia had been effectively managed with clozapine for several years. However, following the initiation of ciprofloxacin, she exhibited increased sedation and elevated clozapine plasma concentrations. Existing literature recognizes the interaction between ciprofloxacin and clozapine although no reports include corresponding clozapine plasma concentrations during a full course of ciprofloxacin. In this case, clozapine concentrations were drawn throughout the course of ciprofloxacin therapy using immunoassay technology, which has a quick turnaround time. This was especially helpful to guide dosing for this patient with a concurrent active infection and abrupt change in smoking status.

Keywords: clozapine, immunoassay, drug-drug interactions

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Disclosures: No conflicts of interest.

Background

Clozapine is the gold standard antipsychotic for managing treatment-resistant schizophrenia. Although highly efficacious, it is reserved for patients who have trialed at least 2 other antipsychotics because of the potential significant adverse effect profile and associated frequent laboratory monitoring.[1] Common adverse effects include sedation, weight gain, sialorrhea, orthostatic hypotension, constipation, and dizziness. Other serious adverse effects include myocarditis, seizures, metabolic abnormalities, and severe neutropenia.[2] Monitoring plasma clozapine concentrations is important to enhance treatment efficacy and minimize the risk of toxicity. A range between 250 and 550 ng/mL is generally recommended, whereas a level of >350 ng/mL is optimal for a therapeutic response. Very few patients tolerate plasma concentrations above 1000 ng/mL.[3] Increased seizure risk is a significant concentration-dependent adverse effect that may occur at concentrations as low as 500 ng/mL with a significant risk when concentrations exceed 1300 ng/ml.[4]

Many factors may impact clozapine concentrations, including genetic variations, age, sex, smoking status, and caffeine intake.[5] Clozapine undergoes hepatic metabolism via the cytochrome P450 (CYP450) enzyme system with CYP1A2 being the primary metabolizer. Most drug-drug interactions (DDIs) involving clozapine are mediated by CYP450 enzymes.[6] Because of the risks associated with high clozapine concentrations, any factor influencing its metabolism can have significant clinical consequences. For instance, tobacco smoking induces CYP1A2, resulting in lower serum concentrations of clozapine in smokers compared with nonsmokers.[7] Smokers typically exhibit 20% to 40% lower average serum concentrations of clozapine compared with nonsmokers, and discontinuation of smoking can lead to a more than a 50% increase in clozapine exposure.[8] This relationship is particularly significant considering the notably high smoking rates among individuals with schizophrenia compared with the general population.[9] Consumption of caffeine with clozapine can also result in higher than expected clozapine concentrations because of caffeine's ability to inhibit CYP1A2. It is estimated that clozapine concentrations may increase by approximately 20% in healthy young adults when consuming caffeine.[10] At least 1 case of life-threatening clozapine toxicity following significant increase in caffeine intake has been reported.[11] Other patient-specific factors, such as infection status, may also affect clozapine concentrations. It is believed that inflammatory mediators associated with infection may reduce expression of CYP1A2 by up to 90%; other metabolic pathways and drug transporters may also be affected.[12,13] In a systematic review of 40 cases of clozapine-treated patients with infections, baseline clozapine concentrations obtained via liquid chromatography-mass spectrometry (LC-MS/MS) were below 600 ng/mL. Concentrations subsequently increased to a mean concentration of 1811 ng/mL (range 744 to 4740 ng/mL) after onset of infection.[12] Of the 33 cases with a reported smoking status, 12 were current smokers.

The interaction of clozapine with ciprofloxacin, a relatively common fluoroquinolone antibiotic, is particularly noteworthy. Ciprofloxacin inhibits CYP1A2, reducing clozapine metabolism and potentially increasing its plasma concentrations.[14] The combined use of ciprofloxacin with clozapine can result in a significant interaction with severe clinical consequences, including at least 1 reported fatality.[15] Although data exists supporting this interaction, few case reports include clozapine concentrations measured during concurrent ciprofloxacin administration.

In the case presented, clozapine concentrations were obtained frequently via immunoassay. Compared with clozapine concentrations obtained via traditional LC-MS/MS, concentrations obtained via immunoassay result much more quickly; results are available within minutes to hours compared with within several days. However, the immunoassay reports clozapine concentrations only and does not include concentrations of metabolites, such as norclozapine, its major active metabolite.[16] The antibodies used in the immunoassay may, therefore, cross-react with clozapine metabolites or other substances, leading to a falsely higher reported concentration. This difference is more prominent at higher clozapine concentrations.[17] The immunoassay may also have a narrower range of detection depending on the comparable LC-MS/MS testing method although 1 study also demonstrated that false-positive concentrations were more likely to occur via LC-MS/MS than with immunoassay.[18] However, results from clozapine assays are not significantly different than LC-MS/MS. In 1 comparison, there was an average bias between the methods tested of less than 3%.[17] For the patient discussed here, dose adjustments were made based on frequent immunoassay concentrations obtained in conjunction with clinical changes, which both reiterates the clinical relevance of the interaction between clozapine and ciprofloxacin and demonstrates the importance of timely clozapine concentration results.

Case Report

A 57-year-old female with Crohn's colitis arrived at the emergency department (ED) because of a leaking colostomy bag, redness around the abdomen, weakness, and difficulty with self-care. Her medical history included schizophrenia, type 2 diabetes mellitus, hyperlipidemia, seizure disorder, and chronic obstructive pulmonary disorder with a reported allergy to sulfa-containing drugs with a reaction of edema and swelling. The patient was a current 1-pack-per-day cigarette smoker (35-pack-year history). A full list of the patient's medications before admission can be found in Table 1. The patient had been treated for schizophrenia with clozapine for approximately 8 years and been mostly stable during that time with one known psychiatric hospitalization approximately 1 year before the case presented here. The internal medicine team diagnosed the patient with sepsis, complicated by hyponatremia, nonanion gap metabolic acidosis, and acute kidney injury.

Antibiotic selection was challenging because of several DDIs, the sulfa allergy, and impaired renal function. The patient received 1 dose each of doxycycline, vancomycin, and ceftriaxone while in the ED. Cefazolin was then initiated for the first 4 days of hospitalization. Although the cellulitis improved, erythematous and scaly plaques were noted around the colostomy site necessitating a change in antibiotic regimen. A superficial wound culture revealed the presence of *Enterobacter cloacae* complex susceptible to ciprofloxacin, gentamicin, and trimethoprim + sulfamethoxazole (TMP-SMX). TMP-SMX was not an option because of the reported sulfa allergy. The primary treatment team initiated tobramycin (patient received 1 dose) and consulted the infectious disease team. The infectious disease team first recommended to discontinue tobramycin and transition to ertapenem because of concerns about the patient's poor renal function and the extensive

TABLE 1: Medications prior to admission

Medication	Dose	Indication
Albuterol sulfate 90 HFA aerosol inhaler	2 puffs by mouth every 6 hours as needed for shortness of breath or wheezing	Chronic obstructive pulmonary disorder
Clozapine disintegrating tablet	325 mg by mouth nightly	Schizophrenia
Divalproex sodium ER	1750 mg by mouth nightly	Seizure disorder
Augmented betamethasone diproprionate 0.05% ointment	Apply topically every other day	Dermatosis
Clobetasol 0.05% ointment	Apply topically every other day as needed to peristomal wound at pouch change	Dermatosis
Latanoprost 0.005% ophthalmic solution	Place 1 drop into both eyes nightly	Glaucoma
Cholecalciferol	1000 units by mouth daily	Vitamin D deficiency
Methyl salicylate-menthol 15-10% greaseless cream	Apply twice a day to the affected areas	Topical pain relief
Tacrolimus 0.1% ointment	Apply topically daily as needed, Prn pouch change to wound base	Contact dermatitis

ER = extended release; HFA = hydrofluoroalkane; Prn = as needed.

monitoring needs associated with aminoglycosides. However, after discussion with the infectious disease pharmacist, the use of ertapenem was ruled out because of the significant DDI with carbapenem antibiotics and the patient's divalproex sodium. Concurrent use of these 2 medications could lead to a rapid decline in divalproex concentrations, increasing the risk of seizures. Ciprofloxacin was then the preferred option. However, ciprofloxacin is a strong CYP1A2 inhibitor and would likely increase the serum concentration of clozapine, a major CYP1A2 substrate. Clozapine concentrations above the therapeutic range could increase the risk of adverse effects in this patient who had been managing treatment-resistant schizophrenia with clozapine for years. Despite the DDI, the decision was made to initiate ciprofloxacin and cephalexin on day 5 of hospitalization. Both were continued for a total of 7 days. Although this patient had a history of a seizure disorder, the psychiatry consult team felt that the increased risk of seizures associated with elevated clozapine concentrations was mitigated by the therapeutic dosing of concurrent divalproex sodium.

A clozapine concentration drawn on day 4 of hospitalization (the day before initiation of ciprofloxacin) was 281 ng/mL. This was the first concentration obtained during this admission although it was similar to a concentration drawn during a previous admission 5 months prior (273 ng/mL) while taking the same dose of clozapine. All clozapine concentrations obtained during this admission were trough (24-hour) levels obtained via immunoassay. All clozapine concentrations and corresponding doses of clozapine can be found in Table 2. The dose of clozapine was preemptively decreased from 325 mg nightly to 200 mg nightly with plans to continue this dose throughout the 7-day course of ciprofloxacin. Clozapine package labeling recommends decreasing the clozapine dose to a third when coadministered with a strong CYP1A2 inhibitor such as ciprofloxacin.[19] In this case, the team reduced the dose by approximately 38% instead of the recommended 67%. No specific rationale was given for this dosing decision although the team did have concern that the patient would have reemergence of psychotic symptoms if the dose was reduced too significantly.

The next clozapine concentration was drawn 24 hours later following both this clozapine dose reduction and the patient receiving 1 dose of ciprofloxacin. The concentration at this time was 357 ng/mL. Despite an increase in sedation, the team was hesitant to further reduce the dose of clozapine because of concern for the reemergence of psychotic symptoms. However, on the sixth day of ciprofloxacin treatment, the patient's sedation became so pronounced that another concentration was obtained, revealing a significant increase to 692 ng/mL. The clozapine dose was reduced to 100 mg nightly. By the seventh and final day of the ciprofloxacin course, the patient's clozapine concentrations decreased to 585 ng/mL. The patient was discharged the day after the 7-day antibiotic course was completed. The patient was discharged on clozapine 100 mg nightly with the plan to gradually increase by 50 mg every 3 days until the original dose of 325 mg nightly was reached. Visiting nurse services were obtained to assist with this dose escalation. The patient had an appointment scheduled with her psychiatric nurse practitioner within a week after discharge.

Discussion

Many factors can influence clozapine concentrations, including DDIs such as that described in this case report. The CYP1A2 mediated interaction between clozapine and ciprofloxacin is clinically meaningful as demonstrated by the marked increase in clozapine concentrations throughout the course of treatment despite a preemptive clozapine dose reduction. This upward trend in plasma concentrations underscores the importance of therapeutic drug monitoring. Although valuable for guiding therapy, serum clozapine concentrations have historically been underutilized because of the delay in time between blood draw and results. Consequently, there is a

TABLE 2: Drug doses with corresponding clozapine concentrations

Day of Ciprofloxacin Regimen	Ciprofloxacin Dose (Oral)	Clozapine Dose	Clozapine Level (Trough)	Clinical Assessment
(One day) prior to ciprofloxacin initiation[a]	—	325 mg nightly	281 ng/mL	—
Day 1	500 mg BID	200 mg nightly	357 ng/mL	—
Day 2	500 mg BID	200 mg nightly	—	—
Day 3	500 mg BID	200 mg nightly	—	—
Day 4	500 mg BID	200 mg nightly	—	Increased sedation and sleeping
Day 5	500 mg BID	200 mg nightly	—	—
Day 6	500 mg BID	200 mg nightly	692 ng/mL	Worsening sedation, extremely tired despite full night of sleep
Day 7	500 mg BID	100 mg nightly	585 ng/mL	Decreasing sedation
Patient discharged on clozapine 100 mg nightly, increasing dose by 50 mg every 3 days until home dose of 325 mg at bedtime is reached.				

BID = twice daily.
[a]Day 4 of hospitalization.

gap in the current literature regarding the frequent monitoring of clozapine concentrations throughout a complete course of ciprofloxacin. Some case reports document clozapine concentrations taken prior to initiation of ciprofloxacin, followed by concentrations taken at the conclusion of the regimen.[20] No published cases provide situations in which multiple clozapine concentrations were collected during coadministration of both medications. Although our case reflects more frequent clozapine concentration monitoring than others reported in the literature, concentrations could have been obtained daily instead of before initiation of ciprofloxacin and then on days 1, 6, and 7 of the 7-day antibiotic course. Obtaining concentrations on days 2 through 5 may have led to even more rapid dose adjustment to prevent or reduce the sedation that was observed on day 4 of the regimen. Without consistent clozapine concentration monitoring, it can be difficult for health care professionals to make informed decisions around dose adjustments when relying entirely on patient observation.

In addition to the DDI, other factors may have affected clozapine concentrations for the patient described here. The patient was an everyday smoker prior to admission. Because a baseline clozapine concentration was not drawn until day 4 of hospitalization, it is not possible to determine if this first concentration was reflective of the patient's concentration prior to admission. Caffeine consumption can also result in a lower-than-expected clozapine concentration as described previously. Unfortunately, it is not known whether this patient was consuming caffeine prior to or during hospitalization. This patient was also actively being treated for an infectious process that has been demonstrated to increase clozapine concentrations. However, in the systematic review discussed previously, clozapine concentrations increased to a much higher degree than what was observed in the patient presented here. Therefore, although the infection may have contributed to elevations in clozapine concentrations, it was likely not the only causative factor.

Our case report showcases the use of immunoassay technology for monitoring clozapine concentrations, allowing for more consistent tracking of plasma concentrations throughout the 7-day course of ciprofloxacin therapy. The immunoassay-based clozapine concentration test offers results significantly faster than traditional laboratory methods with an expected turnaround time of less than 30 minutes.[18] The standard method for measuring serum clozapine concentrations via LC-MS/MS may have a 3- to 7-day turnaround time as it often requires off-site processing.[18] Having clozapine concentrations available more quickly alleviates logistical challenges with external labs and expedites the process. This gives providers the advantage of closely monitoring adverse effects alongside pharmacokinetic-related changes in patients. Whereas immunoassay technology is promising, there is the potential of cross-reactivity with clozapine metabolites leading to elevated reported concentrations although this is more common at higher clozapine concentrations.[17,21] The immunoassay does not measure the concentration of clozapine metabolites such as norclozapine; historically, the ratio of clozapine to norclozapine has been a component of clozapine therapeutic drug monitoring although it is likely not related to clinical response.[22] This metabolic ratio primarily indicates CYP1A2 activity; CYP1A2 inhibition can result in metabolic ratios between 1.8 and 2.6, whereas during a severe infection, the metabolic ratio is expected to average around 3. Although this information may provide further clarity on potential causes of the clozapine concentration elevation, it is unclear how this information would have changed this patient's treatment plan.[23] Further studies are required to assess the limitations of the immunoassay method and define its role in clozapine drug monitoring. Cost is another important consideration when making a determination about frequency and type of clozapine concentrations. Although cost may vary significantly across practice sites, at our institution, the immunoassay carries a significantly lower cost to the patient of approximately $190 compared with approximately $690 for the send-out LC-MS/MS lab.

Whereas our patient case and existing literature clearly document the rise in serum clozapine concentrations because of

ciprofloxacin coadministration, it can be difficult to predict the extent to which the interaction will clinically affect a patient. Outcomes can vary significantly based on patient-specific factors, including genetics, infection status, smoking status, caffeine intake, and other DDIs, making it difficult to standardize dosing regimens for their combined use. For instance, a case report details the initiation of ciprofloxacin in a patient receiving clozapine (with both medications dosed similarly to those in our case), resulting in the sudden death of the patient.[8] The past medical history and patient profile of both this case and our case contain many similarities despite drastically different patient outcomes. The baseline clozapine concentration was not reported in this case, but the femoral concentration obtained postmortem was 2900 ng/mL. Other published cases report 2- to 5-fold increases in clozapine concentrations after initiating ciprofloxacin.[8,20,21,24] Conversely, other reports document no significant adverse effects in patients on similar regimens of clozapine and ciprofloxacin with 1 instance involving the administration of both medications at higher total daily doses.[20,21]

Given clozapine's narrow safety margin, the patient's health care team should thoroughly discuss the implications of coprescribing clozapine and ciprofloxacin before administration. When possible, concurrent use of these medications should be avoided to minimize the risk of adverse effects. If their combined use is necessary, regular monitoring of clozapine concentrations can be extremely beneficial for guiding prescribing practices and enhancing patient safety. If available, testing via immunoassay may allow for more consistent monitoring of concentrations with timely results.

Conclusion

Many factors may have affected changes in clozapine concentrations in this case, including the established DDI between clozapine and ciprofloxacin, an active infection, and abrupt smoking cessation. It is difficult to predict the extent that patient-specific factors will influence clozapine concentrations. Our case demonstrates that use of the clozapine immunoassay with a significantly shorter turnaround time in conjunction with observed changes in clinical status allowed for rapid adjustments to clozapine dosing. If available, immunoassay testing should be considered for patients managed with clozapine in order to guide dose adjustments, especially in the setting of one or more factors that are known to influence clozapine concentrations.

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