Med-Psych Drug-Drug Interactions Update

Clozapine Case Series

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Clozapine is not a drug that is ever used casually. Patients generally are afflicted with severe illnesses and have demonstrated treatment resistance and/or intolerance to other therapeutic options before clozapine is seriously considered. When the clinical stakes are this high, it is especially important that physicians gain an appreciation for the various drug–drug interactions that can significantly increase or decrease clozapine blood levels; such pharmacokinetic changes can derail clozapine treatment by producing clozapine toxicity or loss of antipsychotic efficacy, respectively. The authors present a case series of five drug–drug interactions involving clozapine, each of which illustrates different mechanisms by which the metabolism of clozapine can be altered. Exploring these cases should help clinicians anticipate and avoid these undesirable drug–drug interactions. (Psychosomatics 2007; 48:170–175)

Although clozapine does not enjoy the same widespread use as other atypical antipsychotic agents, it nonetheless occupies an important place in our armamentarium. It is generally regarded as the most effective antipsychotic available, with a very low incidence of extrapyramidal symptoms.[1] The abundance of other undesirable side effects, fairly low therapeutic index, and the need for monitoring absolute neutrophil counts have contributed to the relatively sparse use of this drug. However, it remains the last and best hope for a large number of patients who have responded to, or tolerated, little else. Since patients who find themselves taking clozapine have few other viable antipsychotic options, it is especially important to be aware of the possibility of drug–drug interactions involving clozapine. If clinicians are able to effectively anticipate and thus minimize the drug interactions that have an impact on clozapine's efficacy or tolerability, then we will be more successful in keeping patients on this important, but potentially problematic, medication.

Clozapine is principally metabolized by P450 1A2, with numerous secondary pathways, including 2C9/19, 2D6, 3A4, and UGT 1A3/4.[2–5] The UGT 1A3 and 1A4 enzymes seem to be specifically implicated in the metabolism of the active norclozapine metabolite. It appears to be an in-vitro P-glycoprotein substrate of weak affinity.[6] It is also a known mild inhibitor of 2D6.[7,8]

What follows is a series of five cases that illustrate some of the core concepts at the heart of drug–drug interactions involving clozapine. These cases will demonstrate how careful clinicians may anticipate, avoid, compensate for, and even manipulate these clozapine drug–drug interactions so as to optimize care. The first four cases involve inhibition of clozapine's metabolism, whereas the fifth deals with enzymatic induction. The discussion section of each case will refer to the above description of clozapine's metabolism, without repeating it in its entirety.

Case 1: Clozapine Plus Fluoxetine

A 36-year-old African American man with a history of schizophrenia, paranoid type, was transferred to a specialty psychotic-disorders unit for stabilization of an acute exacerbation of his generally treatment-resistant psychosis. He had been experiencing auditory hallucinations and prominent delusions of having smoked a poisonous cigarette and that his roommate was a dangerous robot. He also

endorsed severe "physical and mental pain" which were making him suicidal. Of particular concern were the violent topics of conversation when he discussed his delusional content.

On transfer, his medications consisted of clozapine (Clozaril), 200 mg bid; haloperidol (Haldol), 5 mg tid; quetiapine (Seroquel), 200 mg tid; lorazepam (Ativan), 0.5 mg tid; and diphenhydramine (Benadryl), 25 mg tid. On Hospital Day 1, his quetiapine was discontinued; his diphenhydramine was switched to benztropine; and his haloperidol was increased to 20 mg/day. A clozapine level was determined (see below), and, because he had been transferred from another inpatient unit, this laboratory value was less likely to be affected by medication non-adherence.

This patient had experienced numerous previous hospitalizations, including five in the previous 3 months. In reviewing earlier records, it was discovered that he had responded well to fluoxetine (Prozac) in the past. However, since he had not presented with a discrete major depression in the recent past, his fluoxetine had been discontinued 2 years earlier, before he had had his first trial of clozapine.

In view of his complaint of "physical and mental pain" (with no cause for pain discovered on physical examination), the treatment team decided to restart his fluoxetine at a dose of 20 mg/day. Three days after his fluoxetine was restarted, his admission clozapine level was reported as 225 ng/mL, with a norclozapine level of 144 ng/mL, on (presumably) a steady-state dose of 400 mg/day. His clozapine dose was increased to 600 mg/day. A new blood-level was obtained at steady-state on this dose. The blood-level of clozapine on 600 mg/day came back at 1,339 ng/mL (the laboratory that performed these tests defined clozapine levels greater than 700 ng/mL as "toxic"), with a norclozapine level of 488 ng/mL. Oddly, the patient did not experience any new-onset side effects, such as orthostasis, constipation, or tachycardia. His sialorrhea had also remained mild. Therefore, the lab test was repeated to verify that there was no error. The repeat levels were 1,089 ng/mL for clozapine and 406 ng/mL for norclozapine. Since he continued to tolerate this regimen without undue difficulties and he was experiencing improvement in his psychotic and mood symptoms, the treatment team opted to continue the patient on this combination despite these "toxic" clozapine/norclozapine levels.

Discussion

Although many of the newer selective serotonin reuptake inhibitors (SSRIs) are being used more frequently, fluoxetine remains a commonly prescribed antidepressant medication. Therefore, this is not a rare interaction. Fluoxetine, and its active norfluoxetine metabolite, together potently inhibit P450 2D6[9,10] and mildly-to-moderately inhibit 1A2, 2B6, 2C9, 2C19, and 3A4.[11–16] Fluoxetine can reasonably be considered a P450 pan-inhibitor, much like cimetidine. It is also a P-glycoprotein inhibitor.[17] Thus, the addition of fluoxetine to the regimen led to a moderate impairment in the ability of P450 1A2, 2C9/19, 2D6, and 3A4 to contribute to the metabolism of clozapine, yielding an increase in clozapine (and norclozapine) levels. Although this was likely only a minor contributor to this condition, fluoxetine's inhibition of the functioning of the extruding P-glycoprotein transporter would have somewhat increased the net absorption of clozapine, further increasing clozapine levels.

This case is unusual for both the magnitude of the blood-level increases after fluoxetine was added, as well as this patient's ability to tolerate clozapine levels that would usually produce many unpleasant side effects in most other patients. It would not be unusual for a patient with a clozapine level greater than 1,000 ng/mL to experience a troublesome array of anticholinergic symptoms: orthostasis, sedation, and perhaps even new-onset seizures. Fluoxetine has been found to increase clozapine levels by roughly 50%, on average,[18] although individual patients can certainly encounter much greater or lesser increases in clozapine levels, as this case illustrates. Because of its much more potent inhibition of P450 1A2 and 2C19, adding fluvoxamine to clozapine will typically produce three- to four-fold increases in clozapine levels.[2,19–24] One additional concern generated by this drug–drug interaction is the need to take this into account if clozapine and fluoxetine are stably coadministered, and then, at some future time, the fluoxetine is discontinued. This reversal of enzymatic inhibition would produce a decline in clozapine levels. If clozapine had been titrated to an appropriate level while it had been combined with fluoxetine, then the discontinuation of fluoxetine would necessitate a compensatory increase in the clozapine dosage to preserve a therapeutic blood level.

Case 2: Clozapine Plus Ciprofloxacin

A 64-year-old woman who carried the diagnosis of schizophrenia had been maintained on clozapine (Clozaril) 125 mg bid, which had been effective in treating her psychotic symptoms for the previous 5 years. She then developed symptoms of a mild urinary tract infection and was started

on ciprofloxacin (Cipro), 500 mg bid. Within a few days, she became dizzy and somnolent. Clozapine therapeutic drug monitoring was obtained, and clozapine/norclozapine levels were 1,043/432 ng/mL (previous clozapine/norclozapine levels had not been obtained). Her clozapine was discontinued because it was believed that her advancing age rendered her metabolically unable to tolerate this medication. The possibility of a drug–drug interaction with ciprofloxacin was not considered at the time. Ziprasidone (Geodon), 80 mg bid was then prescribed for her psychotic symptoms for a period of 2 months, but without therapeutic success. She lived in a mental-health group home and was at risk of losing her placement because of her psychotic symptoms. She was then hospitalized on a geriatric psychiatry unit. The geriatric team surmised that a drug–drug interaction might have been responsible for her previous side effects and high clozapine level. The ziprasidone was then tapered, and clozapine was slowly titrated over the next 2 weeks back to her original dosage of 125 mg bid. The patient's psychosis improved dramatically, and she was discharged back to her group home without difficulty. She did not encounter any dizziness, somnolence, or other new side effects. Her clozapine/norclozapine levels at the time of discharge from the hospital were 686/244 ng/mL. Once these results were obtained, the facility and outpatient physician following the patient were informed of the results, and recommendations were given with regard to medications to avoid in the future, so as to avoid further episodes of clozapine toxicity. A phone call 6 months postdischarge indicated that the patient was still doing well on the same dosage of clozapine.

Discussion

As with fluoxetine, the popularity of newer fluoroquinolones has not fully displaced the use of ciprofloxacin. It remains a common antibiotic choice. Ciprofloxacin is a potent inhibitor of P450 1A2 and 3A4.[25–27] Thus, the addition of ciprofloxacin to her clozapine strongly impaired the ability of 1A2 and 3A4 to contribute to the metabolism of clozapine, yielding an increase in clozapine (and norclozapine) levels and her side effects of dizziness and somnolence. One study found that clozapine levels increased by roughly 30% with this combination.[28] In this case, the increase was slightly greater than 50%, perhaps due to a higher dosage of ciprofloxacin than in that study. This case is also important because it illustrates the crucial principle that if one does not keep drug–drug interactions in mind as a possible explanation for an adverse clinical event, then many such interactions will be missed. In this case, that is exactly what led to the temporary derailment of this patient's treatment. Fortunately for her, this drug–drug interaction was retrospectively recognized, which enabled her treatment team to reconsider and successfully restart clozapine.

Case 3: Clozapine Plus Ethinylestradiol

A 33-year-old woman diagnosed with schizoaffective disorder had previously failed trials of risperidone (Risperdal), olanzapine (Zyprexa), and haloperidol (Haldol). Her psychiatrist decided to initiate a trial of clozapine (Clozaril), eventually titrating to a dose of 500 mg/day (blood level: 448 ng/mL). Several months later, she wanted to begin taking birth control pills, so her internist prescribed an oral contraceptive containing ethinylestradiol. Within 1 week of beginning the contraceptive, the patient experienced marked drowsiness, anergy, and dizziness. She reported this sequence of events to her psychiatrist, who was able to see her immediately. The psychiatrist determined that she was orthostatic and arranged for her to be evaluated in the emergency room. She was stabilized in the ER, and blood was drawn to determine the cause of her new symptoms. Her oral contraceptive was also discontinued. Three days later, she was feeling much better; the lab reported that her initial clozapine level had increased to 1,281 ng/mL. Her clozapine blood level had since returned to a value of 577 ng/mL. After several weeks and some research into this drug–drug interaction, the patient and her psychiatrist opted to restart the oral contraceptive, but they also decreased the dosage of clozapine. After some titration and further testing of clozapine levels, the patient found that a clozapine dosage of 200 mg/day, combined with the oral contraceptive, produced a clozapine blood level of 531 ng/mL and no new side effects.

Discussion

As many as one-fourth of all women take ethinylestradiol, so this is a greatly underrecognized drug–drug interaction. Ethinylestradiol is an inhibitor of both 1A2 and 2C19.[29,30] Thus, the addition of the ethinylestradiol impaired the ability of 1A2 and 2C19 to contribute significantly to the metabolism of clozapine. This decrease in the metabolism of clozapine led to a significant rise (almost triple) in the clozapine blood level, even though the clozapine dosage had not been changed. This metabolic decrease resulted in the patient's sedation, orthostasis, and anergy, which the psy-

chiatrist eventually corrected and compensated for by significantly decreasing the clozapine dosage while co-administering the oral contraceptive. After P450 1A2, 2C19 is probably the enzyme most critical to the metabolism of clozapine,[4] which possibly explains why this interaction seems to produce greater increases in clozapine levels than the ciprofloxacin/clozapine drug–drug interaction. Also, as with the clozapine/fluoxetine case, one must be aware of the effects of discontinuing ethinylestradiol, because this would lead to a decrease in the clozapine blood level and necessitate a compensatory increase in the clozapine dose to maintain a therapeutic blood level.

Case 4: Clozapine Plus Cimetidine

A 47-year-old male patient diagnosed with chronic undifferentiated schizophrenia had experienced only partial responses with typical antipsychotics, risperidone, and quetiapine. His psychiatrist decided to initiate a trial of clozapine (Clozaril). The patient was titrated to an initial target dosage of 400 mg/day, which produced blood levels of clozapine at 120 ng/mL and norclozapine at 38 ng/mL. For idiosyncratic reasons, the patient refused to take more than 400 mg/day of clozapine, although he was amenable to any maneuvers that would increase his clozapine levels. Since he was also afflicted with gastroesophageal reflux, his psychiatrist decided to add cimetidine (Tagamet), 300 mg bid, to both address this somatic concern as well as to deliberately increase the patient's clozapine and norclozapine levels without increasing his clozapine dosage. After 1 month on this combination, his repeat blood levels showed clozapine at 278 ng/mL and norclozapine at 122 ng/mL. In concert with these blood-level changes, his paranoid delusions toward his parents were gradually improving. He also experienced increased sialorrhea, although he was not especially concerned by this side effect. His clozapine was maintained at 400 mg/day, and his cimetidine was further increased to 600 mg qAM and 900 mg qHS, leading his levels to further increase to clozapine at 502 ng/mL and norclozapine at 176 ng/mL. Over the next few months, his delusions and somatic preoccupations became even less prominent, although they never completely remitted, and his side effects remained quite tolerable.

Discussion

This case represents the unusual, but far from unique, circumstance in which the clinician deliberately attempts to make beneficial use out of an anticipated drug–drug interaction. Cimetidine is a moderate-to-potent inhibitor of virtually the entire range of P450 enzymes, and is thus considered a "pan-inhibitor."[31,32] Thus, the addition of cimetidine to this patient's clozapine impaired the ability of P450 1A2, 2C9/19, 2D6, and 3A4 to metabolize the clozapine. This decrease in metabolism yielded a significant increase in clozapine + norclozapine levels even though the clozapine dosage remained constant.[33] Although the maneuver worked well for this patient, the contrived use of drug–drug interactions entails some risk, as it introduces greater metabolic complexity and therefore a more inconsistent relationship between clozapine dosages and blood levels. Also, as with the clozapine/fluoxetine and clozapine/ethinylestradiol cases, one must be aware of the effects of discontinuing cimetidine, as this would lead to a decrease in the clozapine blood level and necessitate a compensatory increase in the clozapine dosage to maintain a therapeutic blood level.

Case 5: Clozapine Plus Smoking

A 27-year-old man diagnosed with schizophrenia was admitted to a psychiatric hospital because of his persistent paranoid delusions and command auditory hallucinations telling him to kill himself. He had failed trials of haloperidol (Haldol), thiothixene (Navane), olanzapine (Zyprexa), aripiprazole (Abilify), and quetiapine (Seroquel), and so a clozapine (Clozaril) trial was therefore proposed. The patient was started on clozapine, and his dosage was titrated to 500 mg/day, yielding a clozapine blood level of 417 ng/mL. Over the ensuing several weeks, he experienced a significant remission of his psychotic symptoms. After 2 months in the hospital, he was transitioned to a "quarter-way" house on the grounds of the hospital, and he began attending the Day Hospital. The inpatient unit was "smoke-free," and he had been using Nicotrol inhalers as a substitute. However, immediately after discharge, he resumed his two-pack/day smoking habit. Three weeks after discharge, he required rehospitalization because of a significant return of his paranoia and hallucinations. A clozapine level obtained upon readmission was only 192 ng/mL, even though he was consistently compliant with his medications.

A consultation with the hospital's psychopharmacology service ensued, where it was suggested that smoking had decreased his clozapine levels. Since the patient was determined to continue smoking as an outpatient, a plan was crafted to rapidly titrate his clozapine dosage to 900 mg/day in the week after discharge from the hospital.

When he had again restabilized, this plan was enacted. Although the patient did experience some increase in sedation and constipation at first, he did eventually tolerate the higher dosage of clozapine without difficulty, and he maintained his response to clozapine even after resuming smoking. His outpatient clozapine level was 392 ng/mL.

Discussion

This is an especially important case, given the ubiquity of smoking. Smoking tobacco products mobilizes polycyclic aromatic hydrocarbons, which act as potent inducers of P450 1A2.[34,35] It is worth noting that nicotine patches and inhalers do not produce this effect, and neither does chewing-tobacco. In this case, the increased production of P450 1A2 was induced by this patient's resumption of smoking after discharge from the inpatient setting. The greater availability of this main enzyme involved in the metabolism of clozapine led to an increased rate of metabolism and a corresponding decrease in the clozapine level. This resulted in a partial loss of antipsychotic efficacy. A 50% decrease in clozapine levels would be typical for this interaction.[36,37] As with several of the case examples above that involved enzymatic inhibition, one must be mindful of reversals of induction, as well. For example, there are patients who have been compliant with their clozapine regimens while smoking as outpatients, and their clozapine dosages have taken their smoking and corresponding 1A2 induction into account; then, for some reason, these patients require admission into non-smoking settings. Within several days, the discontinuation of smoking leads to a return of 1A2 availability back to lower, baseline levels. This results in increases in clozapine levels. A 100% increase in clozapine levels would be typical. There are many reports of significant morbidity, including seizures and aspiration pneumonia, resulting from this scenario.[38,39] With some foresight, these situations can be predicted and avoided, or, at least, their impact can be minimized.

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