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Ciprofloxacin Strongly Inhibits Clozapine Metabolism

Two Case Reports

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Abstract

We report on two cases of drug-drug interactions between ciprofloxacin and clozapine. The first case was a 46-year-old male patient receiving a daily dose of clozapine 900 mg. He was admitted to hospital with urosepsis and was treated with a 5-day course of ciprofloxacin and amoxicillin. Two days after completion of antibacterial therapy, the patient developed symptoms of rhabdomyolysis. Clozapine therapy was discontinued and measurement of the patient's clozapine plasma concentration 1 day after cessation of clozapine therapy and 3 days after cessation of ciprofloxacin treatment showed that it was in excess of recommended therapeutic levels. The second patient was a 58-year-old male patient treated with a daily dose of clozapine 300 mg. He was admitted to hospital because of delirium and suspected urinary tract infection or pneumonia. Treatment with ciprofloxacin was initiated. Measurement of clozapine plasma concentrations prior to and 3 days after commencement of ciprofloxacin showed that clozapine concentrations doubled over that time period. We suggest that inhibition of cytochrome P450 (CYP) enzymes 1A2 and 3A4 by ciprofloxacin resulted in delayed clozapine metabolism and elevated clozapine plasma concentrations. This might cause severe adverse effects. We advise using another antibacterial agent or reducing the clozapine dose and monitoring clozapine levels when this antipsychotic agent is used in combination with ciprofloxacin.

1. Background

Clozapine is an atypical antipsychotic agent with proven effectiveness in treatment-resistant schizophrenia. It is metabolized mainly by cytochrome P450 (CYP) enzyme 1A2[1] to norclozapine,[2] the activity of which is less potent than that of clozapine. It is also metabolized to a minor extent by CYP3A4.[3] Consequently, CYP1A2 and CYP3A4 inhibitors, such as ciprofloxacin,[4,5] may delay clozapine metabolism and thereby elevate clozapine

serum concentrations. Clozapine plasma concentrations are a predictor of clinical response and the likelihood of developing adverse effects. The recommended plasma concentration of clozapine is considered to be 350–600 ng/mL.[6]

A placebo-controlled study has shown a significant effect of ciprofloxacin on clozapine serum concentrations.[3] In this study, after administration of oral ciprofloxacin 250 mg twice daily, mean clozapine concentrations increased by 29%. Furthermore, in a case report of an interaction between ciprofloxacin (500 mg twice daily) and clozapine, an even larger increase in clozapine serum concentrations was observed.[7] Thus, ciprofloxacin may increase the adverse effects of concomitantly administered clozapine, which can have serious consequences for the patient.

To further demonstrate the clinical relevance of the interaction between clozapine and ciprofloxacin, we describe two patients who received ciprofloxacin in addition to clozapine treatment with a resultant increase in clozapine plasma concentrations. Because assessment of causality in potential drug interactions requires thoughtful consideration of the properties of both patient-specific factors and the drugs involved, the Drug Interaction Probability Scale (DIPS) was used to evaluate these cases.[8] This scale evaluates the causality of a potential drug interaction using ten questions. The higher the DIPS score, the higher the probability of the interaction.

2. Case Report 1

A 46-year-old Caucasian male patient treated with a daily dose of clozapine 900 mg for paranoid schizophrenia was admitted to the Slotervaart Hospital because of urosepsis. He had been living in a psychiatric facility where he was being treated with citalopram, lorazepam and valproic acid in addition to clozapine. The patient had a smoking habit and regularly consumed coffee. In the hospital, he received immediate treatment with a 5-day course of ciprofloxacin (400 mg twice daily intravenously) combined with amoxicillin. After four days, the patient was discharged in good condition. Three days later, however, the patient was admitted to the hospital with symptoms of rhabdomyolysis.

Throughout his admission the patient had no fever, autonomic instability or rigidity, i.e. symptoms that would indicate neuroleptic malignant syndrome (NMS). The patient's creatine phosphokinase (CPK) level increased to 195 000 U/L (normal value <200 U/L). His lactic dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were, respectively, 6687 (normal 135–225) U/L, 845 (normal <45) U/L and 93 (normal <50) U/L. The urine test for myoglobin was positive.

During admission, the patient lost 7 kg of bodyweight. Despite signs of rhabdomyolysis, he did not report any pain. To prevent acute renal insufficiency, high-volume alkaline diuresis was initiated. In addition, clozapine treatment was stopped. The patient's clozapine plasma concentration, measured 3 days after the end of ciprofloxacin treatment and 1 day after cessation of clozapine therapy, was 890 ng/mL, compared with the recommended therapeutic concentration of 350–600 ng/mL. Unfortunately, no clozapine levels during ciprofloxacin treatment were available. Clozapine concentrations were undetectable within 5 days after cessation of treatment. CPK concentrations began to fall and returned to normal on day 28. LDH, AST and ALT concentrations all returned to normal on day 18. The patient's laboratory values and weight are depicted in figure 1. There were no immediate signs of worsening of psychotic symptoms after the cessation of clozapine. The patient was discharged after 2 weeks and clozapine treatment was restarted.

The DIPS score of the interaction in this patient was 5 (i.e. interaction was 'probable').

3. Case Report 2

The second patient was a 58-year-old Caucasian male patient treated with a daily dose of clozapine 300 mg. He was admitted to the Slotervaart Hospital for delirium and suspected urinary tract infection or pneumonia. He had been living in a psychiatric facility where he was treated with valproic acid, hydrochlorothiazide and clonazepam in addition to

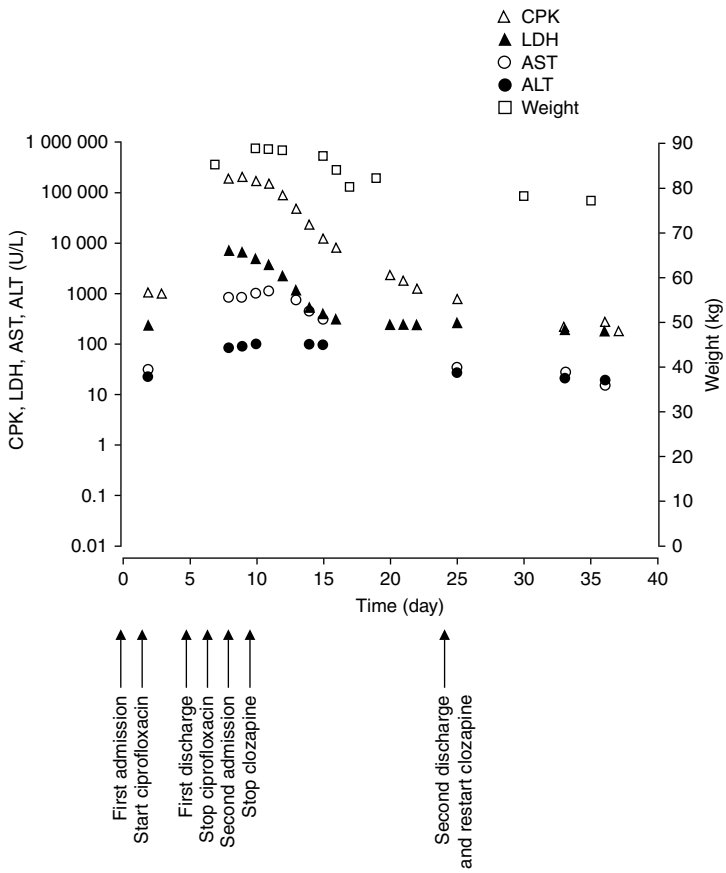

Fig. 1. Laboratory values and weight of patient in case report 1. **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **CPK** = creatine phosphokinase; **LDH** = lactate dehydrogenase.

clozapine. The patient had a smoking habit and regularly consumed coffee. In the hospital, he received immediate treatment with ciprofloxacin (200 mg twice daily intravenously). Ciprofloxacin treatment was stopped after 2 days because of the possibility of a drug-drug interaction between ciprofloxacin and clozapine. Before the addition of ciprofloxacin, AST and ALT were normal (10 and 13 U/L, respectively). After starting ciprofloxacin, these levels increased slightly to 46 and 74 U/L, respectively. The urine test for myoglobin was negative. Clozapine plasma concentrations measured prior to and 3 days after the start of ciprofloxacin were 850 and 1720 ng/mL, respectively. The patient had no clinical signs of rhabdomyolysis or other clozapine-induced adverse effects and was discharged after 5 days.

The DIPS score of the interaction in this patient was 6 (i.e. interaction was 'probable').

4. Discussion

The two cases described here suggest that there might be a pharmacokinetic interaction between ciprofloxacin and clozapine. Inhibition of CYP1A2 and CYP3A4 by ciprofloxacin could reduce clozapine metabolism, which might lead to toxic clozapine levels with serious consequences. In the first patient, the clozapine plasma concentration 3 days after cessation of ciprofloxacin therapy and 1 day after cessation of clozapine treatment (890 ng/mL)

was still higher than the recommended target concentration (350–600 ng/mL). In this patient, unfortunately, no clozapine concentrations measured just before commencement of or during ciprofloxacin therapy were available. Conversely, these values were available in the second patient, and showed that clozapine plasma concentrations doubled after the addition of ciprofloxacin. Ciprofloxacin treatment in this patient was stopped 2 days after initiation and the patient did not experience clozapine-induced adverse effects.

The first patient received 5 days of ciprofloxacin therapy. This patient's laboratory values suggested leakage of intracellular muscle constituents into the circulation, as reflected in raised CPK, LDH, AST and ALT values. In addition, this patient lost 7 kg of weight during the admission. These symptoms indicate the presence of severe rhabdomyolysis. That the patient did not experience pain is remarkable, but may be explained by the altered pain perception in schizophrenic patients.[9,10] Clozapine treatment has previously been associated with rhabdomyolysis.[11-13] Furthermore, while rhabdomyolysis caused by antipsychotic drugs is generally considered to be part of NMS, antipsychotic drugs may also cause rhabdomyolysis without other signs of NMS.[14,15] This also appeared to be the case with the first of our patients.

It may be argued that our findings could be explained by other factors. Firstly, both patients smoked cigarettes and regularly drank coffee. CYP1A2 is induced by tobacco and inhibited by caffeine. Schizophrenic patients have the tendency to change their smoking habits and caffeine intake during some periods such as during a hospital admission. This might have affected clozapine concentrations in our patients and thereby could have influenced both the efficacy and adverse effects of the drug. Infections can also interfere with clozapine metabolism because cytokines that are released might affect the activity of CYP1A2.[16] In the current cases, however, the elevations in clozapine concentrations and, in the first patient, occurrence of rhabdomyolysis were most likely caused by ciprofloxacin treatment because addition of ciprofloxacin directly resulted in elevations in clozapine concentrations. The DIPS scores of the interactions (5 and 6) also indicated that the elevated clozapine concentrations and occurrence of rhabdomyolysis were probably caused by addition of ciprofloxacin. Raised clozapine concentrations after addition of ciprofloxacin have been described previously.[3,7,17]

It is important to note that the first patient developed severe rhabdomyolysis when the clozapine plasma concentration exceeded the recommended concentration following addition of ciprofloxacin, whereas doubling of the clozapine plasma concentration after ciprofloxacin therapy in the second patient did not result in clozapine-induced adverse effects. These cases illustrate that the consequences of the interaction of clozapine and ciprofloxacin may be diverse. This in turn emphasizes the importance of monitoring clozapine plasma concentrations and of paying attention to clozapine-induced adverse effects during treatment with fluoroquinolone antibacterial agents.

5. Conclusion

Ciprofloxacin may inhibit clozapine metabolism, leading to elevated clozapine plasma concentrations. This can result in severe adverse effects such as rhabdomyolysis. If use of ciprofloxacin is indicated in a patient taking clozapine, we advise reducing the clozapine dose and monitoring for clinical signs and clozapine plasma concentrations before and during therapy. In addition, smoking habits and coffee consumption should be closely monitored and their effect on clozapine plasma concentrations should be considered.

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