CASE REPORT

Interaction between Methadone and Ciprofloxacin

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INTRODUCTION

The cytochrome P450 (CYP450) system comprises more than 40 individual enzymes that have been identified in humans. Six major CYP450 isoenzymes are responsible for more than 90% of oxidation of drugs in humans: 1A2, 3A4, 2C9, 2C19, 2D6, and 2E1.[1] Methadone is metabolized by several CYP450 isoenzymes (1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2D6) to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), an inactive metabolite.[2-4] CYP3A4 is considered the primary isoenzyme responsible for metabolism, followed by CYP2D6.[2]

Various drugs may inhibit the CYP450 system. Among the quinolone antibiotics, ciprofloxacin has been demonstrated in vitro to be one of the more potent of these inhibitors,[5] affecting in particular CYP1A2 and CYP3A4.[5,6] However, the clinical response is sometimes difficult to predict, and the significance of the interaction differs among patients.

This report describes a patient who was receiving a stable dose of methadone for treatment of heroin addiction and in whom severe respiratory depression developed after initiation of ciprofloxacin for aspiration pneumonia.

CASE REPORT

A man in his mid-50s* presented to hospital with fracture of the left ankle after the bicycle he was riding was struck by a car. His blood pressure was 170/90 mm Hg, heart rate 75/min, and respiratory rate 18/min. The patient had a history of hepatitis A, and both alkaline phosphatase (134 U/L; normal range 45–125 U/L) and γ-glutamyl transferase (594 U/L; normal range 10–50 U/L) were elevated. He was a smoker (3–4 packs/day) and had previously been an injection drug user (heroin and cocaine), for which methadone 50 mg PO once daily had been prescribed for at least 6 months before the current admission. He denied use of any other medication.

After undergoing open reduction and internal fixation of the left ankle on the day of admission, the patient was admitted to the orthopedic unit and continued to receive methadone 50 mg PO once daily. His other medications included dalteparin 5000 units SC daily, thiamine 100 mg PO daily, folic acid 5 mg PO daily, and methotrimeprazine 10–15 mg PO at bedtime as needed (of which 4 doses had been received before the event described below). For pain, he was receiving morphine 5–10 mg PO or SC q3h as needed (of which 9 doses PO and 2 doses SC had been received before the event), morphine 2 mg IV q1h prn (of which 4 doses had been received before the event), and acetaminophen 325 mg with codeine 30 mg 1 or 2 tablets q4h PO prn (of which 3 doses of 2 tablets each had been received before the event).

Three days after the surgery, the patient reported shortness of breath. Cefuroxime 750 mg IV q8h was started for presumed pneumonia, along with aggressive bronchodilation with nebulized salbutamol and ipratropium. The patient was transferred to the intensive care unit for close observation of hypoxic respiratory failure. At the time, oxygen saturation was 88% on 95% oxygen, and the respiratory rate was 16/min. The patient's fever spiked to 39.1°C, and he had symptoms of yellow sputum and crackles. The white blood cell count was normal, at 6.4×10^9/L (normal range 4×10^9/L to 11×10^9/L). Chest radiography showed atelectasis, consolidation in the lower left lobe, and bilateral pleural effusion. Aspiration pneumonia was diagnosed, and the patient was transferred back to the orthopedic unit later the same day.

Two days later, there was little improvement, and a consultant respirologist recommended that antibiotic coverage be broadened. Cefuroxime was discontinued, and ciprofloxacin 400 mg IV q12h and clindamycin 600 mg IV q8h were initiated. After 2 doses of each drug, the patient became extremely drowsy, pinpoint pupils were observed, and respiratory depression occurred (respiratory rate 8/min). He was given 2 IV bolus doses of naloxone 0.4 mg, with no significant improvement; the respiratory rate remained at 6–10/min.

*The patient's consent was not obtained for publication of this case report. To protect the privacy of the individual described here and his family, all unique identifying information not pertinent to the case has been omitted from this report.

Methadone, ciprofloxacin, and clindamycin were discontinued, and a 24-h naloxone infusion (0.4 mg/h) was initiated. One hour after the infusion was started, the patient's respiratory rate normalized to 18/min. Twenty-four hours later, the respiratory rate had increased to 20/min. The patient continued to receive morphine as needed for pain (with 3 doses being received during naloxone infusion), with no further adverse reaction. The antibiotic therapy was switched to ticarcillin–clavulanate 3.1 g IV q6h. Methadone was restarted 4 days later at 25 mg PO daily (half the original dose). Methotrimeprazine was withheld for 3 nights while the methadone was being held because of the patient's decreased level of consciousness, but it was resumed on the night before re-initiation of methadone and was continued nightly until discharge 5 days later. The patient was discharged on oral amoxicillin–clavulanate 500/125 mg q8h and methadone 25 mg PO daily.

DISCUSSION

Many drug interactions can be traced to the CYPP450 system. However, clinically significant adverse reactions generally occur with drugs having a low therapeutic index (for which there is little difference between effective and toxic concentrations) or drugs with severe adverse effects.[7]

In the case reported here, it was suspected that the patient was experiencing methadone toxicity due to an interaction with ciprofloxacin, whereby the metabolism of methadone by the CYP3A4 and CYP1A2 isoenzymes was inhibited. This interaction resulted in a life-threatening adverse event. It is difficult to predict the potential for drug interactions with methadone because of its wide interpatient pharmacokinetic variability. The elimination half-life ranges between 15 and 60 h, depending largely upon genetically determined variability in the activity of the CYP450 isoenzymes.[2,4] As well, because of its basic and lipophilic properties, methadone is widely distributed into the tissues; its slow release from tissue-binding sites may prolong its presence in the serum, allowing cumulative effects to occur. After repeated dosing of methadone, the elimination half-life can increase to as long as 120 h.[2]

The clinical significance of a patient's response to a drug interaction with the CYP450 isoenzyme system depends on genetic variability, concomitant therapy, concurrent medical conditions, alcohol consumption, smoking, obesity, and liver function.[1] CYP3A4 is the most abundant CYP450 isoenzyme in the body, accounting for the majority of drug interactions. This isoenzyme can vary 30-fold between individuals in terms of its concentration and activity in the liver.[4] Thus, interindividual variability can be significant even in the absence of interacting substances. Furthermore, methadone's low affinity for CYP3A4 suggests that this metabolic pathway is easily inhibited. Inhibitors of this isoenzyme (e.g., ketoconazole, diazepam) can inhibit the formation of EDDP by up to 80%.[2] This patient's history of liver disease, as suggested by the history of hepatitis A and elevation of liver enzymes, may have further aggravated the toxic effects of methadone resulting from inhibition of CYP3A4 by ciprofloxacin, as other pathways for its elimination may have been diminished.

In addition, cessation of smoking during the hospital stay may have diminished the activity of CYP1A2, which would otherwise be induced by smoking.[4] As such, inhibition of CYP1A2 by ciprofloxacin might have had a greater impact in this patient than would have been the case for a nonsmoker.[8]

CYP2D6 has a secondary role in methadone metabolism and can significantly lower methadone clearance, especially in patients with poor CYP2D6 metabolism.[2] CYP2D6 can also be deficient in a small fraction of the population, which would increase sensitivity to the effects of methadone.[4] The patient described here was receiving a low dose of methotrimeprazine, a strong inhibitor of CYP2D6.[9] However, it was not until after ciprofloxacin was added to the patient's drug regimen that the respiratory depressant effects of the methadone became apparent. Although the low dose of methotrimeprazine was unlikely to have caused the severe respiratory depression, this drug in combination with ciprofloxacin may have further inhibited the metabolism of methadone. After the ciprofloxacin was discontinued and the methadone was resumed, 5 doses of methotrimeprazine were given with no untoward effects.

Other factors that may have contributed to the respiratory depression include the other opioid narcotics that the patient received postoperatively and his underlying aspiration pneumonia. Clindamycin, the antibiotic that was used in conjunction with ciprofloxacin to treat the pneumonia, may have also contributed to the respiratory depression through inhibition of neuromuscular transmission or direct inhibition of contractility.[10] Case reports have shown that clindamycin-induced neuromuscular blockade and potentiation of local anesthetic effect can ultimately lead to respiratory depression.[10,11] However, the patient's response to naloxone in the current case suggests an adverse effect of an opioid, rather than neuromuscular blockade, as the cause of respiratory depression.

Two published case reports have described an interaction between methadone and ciprofloxacin.[8,12] The first report described a patient similar to ours in whom the addition of ciprofloxacin to methadone therapy resulted in respiratory depression.[8] In that case, a 42-year-old woman who had been receiving methadone 140 mg PO daily for more than 6 years was admitted to hospital for urosepsis. Ciprofloxacin 750 mg PO twice a day was initiated. Two days later, the patient became sedated and confused. Ciprofloxacin was discontinued, co-trimoxazole was initiated, and the patient recovered 48 h later. On 3 different occasions, during 3 separate hospital admissions, the patient underwent unintentional rechallenge with ciprofloxacin for recurrent urosepsis. On all 3 occasions, the patient became sedated and recovered after discontinuation of ciprofloxacin. During the last of these episodes, the patient experienced heavy sedation and respiratory depression, both of which were reversed with naloxone 0.4 mg intramuscularly. The more severe reaction during the last episode was thought

to have been caused by an additional drug interaction. The patient had previously been taking venlafaxine, but it had been replaced with fluoxetine, a stronger CYP2D6 inhibitor that may have contributed to increased methadone toxicity.

The second, more recent case report described an interaction between methadone and ciprofloxacin resulting in torsades de pointes.[12] A 56-year-old man who was receiving maintenance therapy with methadone 120 mg PO daily experienced torsades de pointes (QTc interval 450 ms) after self-medicating with his wife's ciprofloxacin, which had been prescribed at a dosage of 400 mg PO bid for an upper respiratory tract infection. Both methadone and fluroquinolones have been associated with QT prolongation and torsades.[12] This case further suggests that ciprofloxacin should be used with extreme caution, if at all, for methadone-dependent patients.

In our case and and the similar case reported by Herrlin and others,[8] the addition of ciprofloxacin to methadone therapy led to adverse outcomes occurring within 24 to 48 h. If concomitant therapy with these 2 drugs is deemed necessary, mental status and respiratory rate should be monitored closely for several days, especially if other inhibitors of methadone metabolism are present. Patients should also be advised to report any cardiac abnormalities such as palpitations.[12]

CONCLUSIONS

We have reported a suspected drug interaction between methadone and ciprofloxacin that caused severe respiratory depression. The extent of an interaction between these drugs is unpredictable, but may be greater in patients with poor metabolism of methadone or an underlying history of liver disease, those who have stopped smoking suddenly, and those with prescriptions for other medications that inhibit the metabolic pathways of methadone. Ciprofloxacin is a commonly prescribed antibiotic, and clinicians should be vigilant for an interaction between methadone and ciprofloxacin, especially in patients who are at high risk. Alternative antibiotics should be considered.

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