Letters to the Editor

Fluoroquinolone Inhibition of Clozapine Metabolism

TO THE EDITOR: Pharmacotherapy in elderly patients is complicated by age-related changes in pharmacokinetics and pharmacodynamics as well as greater comorbidity of illness. Furthermore, the likelihood of polypharmacy in this population increases the risk for drug-drug interactions (1). We report a case in which clozapine cotreatment with the fluoroquinolone antibacterial ciprofloxacin led to a significant increase in clozapine plasma concentration. Prospective monitoring of clozapine plasma concentration was prompted by previous in vitro investigations that demonstrated ciprofloxacin's potent inhibition of cytochrome P450 1A2 (2), the enzyme involved in the metabolism of clozapine (3). This is the first reported case of a fluoroquinolone antibiotic interacting with any antipsychotic agent.

Mr. A, a 72-year-old man with multi-infarct dementia and behavioral disturbances, was admitted to our behavioral intensive care unit. The results of admission screening tests revealed no abnormality except for an elevated blood glucose level of 214 mg/dl. A review of his medical history revealed diabetes mellitus that was not insulin dependent, diabetic retinopathy with secondary blindness, and a diabetic ulcer of the ankle. At the time of his admission, he had been on a 3-month maintenance regimen of clozapine (6.25 mg at 3:00 p.m. and 12.5 mg at 9:00 p.m.); additional medications included glyburide, 6 mg/day; trazodone, 50 mg h.s.; and melatonin, 3 mg h.s. He was also on the last day of a 10-day course of ciprofloxacin, 500 mg b.i.d., for treatment of the ankle ulcer. Mr. A's family provided assurance of medication compliance. A clozapine plasma concentration measured at 6:00 p.m. on the day of admission was 90 ng/ml. His hospital course was uneventful. No medication changes were made except for the completion of the ciprofloxacin therapy on the second day of hospitalization. Since it was felt that ciprofloxacin may have elevated the clozapine concentration, which contributed to the agitation that had prompted admission, a second clozapine plasma concentration measure was obtained at 6:00 p.m. before discharge. Clozapine concentration was nondetectable (lower limit of assay detection=50 ng/ml). Thus, a measurable clozapine concentration was obtained only under the condition of ciprofloxacin cotreatment.

While we acknowledge the limitation of assay sensitivity, cotreatment with ciprofloxacin resulted in at least an 80% elevation of clozapine plasma concentration. The presumed basis of this interaction is the inhibition of cytochrome P450 1A2, one of the principal enzymes that mediates the clearance of clozapine (3). Other fluoroquinolones such as enoxacin are also known to potently inhibit cytochrome P450 1A2. The vulnerability of elderly patients to extrapyramidal symptoms and cardiovascular effects from traditional antipsychotics provides the basis for prescribing low-dose clozapine in this population (4). In the present case, the clozapine dose was 18.75 mg/day; young, physically healthy patients are typically treated with 300–500 mg/day. While a clozapine plasma concentration of only 90 ng/ml was seen in this patient, other patients given higher doses may potentially experience clinically significant increases in clozapine concentration from the interaction of clozapine and ciprofloxacin. However, since no clozapine concentration was available before initiation of ciprofloxacin, the interaction should be regarded as tentative. Because of the in vitro potency of ciprofloxacin to inhibit cytochrome P450 1A2 and the apparent magnitude of the change in clozapine concentration in this patient, clinicians are urged to use this drug combination cautiously.

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Neuroleptic Malignant Syndrome Following Initiation of Clozapine Therapy

TO THE EDITOR: Neuroleptic malignant syndrome, which is characterized by rigidity, fever, autonomic instability, and altered consciousness, is a potentially fatal complication of antipsychotic treatment (1). The rate of neuroleptic malignant syndrome with typical antipsychotics is 1%, but the mortality rate can reach 20%–30%. Clozapine is associated with neuroleptic malignant syndrome much less than are typical antipsychotics (1). We report a patient who developed neuroleptic malignant syndrome 16 days after the initiation of clozapine therapy and an elevated creatinine kinase level 2 days after a clozapine rechallenge.

Mr. A was a 45-year-old Caucasian man with a 20-year history of chronic paranoid schizophrenia. There was a history of head trauma. He was admitted to the hospital after his auditory hallucinations and delusions had worsened. He was taking the following medications: oral fluphenazine, 20 mg/day; intramuscular fluphenazine, 75 mg every 14 days; divalproex sodium, 2500 mg/day; and benztropine, 4 mg/day. In the past he had been treated with chlorpromazine, perphenazine, thioridazine, haloperidol, and risperidone.

The fluphenazine and benztropine treatments were withdrawn, and a regimen of clozapine, 25 mg/day, was initiated on the third day of hospitalization. At first, the clozapine dose was decreased to 12.5 mg/day because of sedation but was then titrated to 50 mg/day. The tapering of the divalproex sodium therapy concluded on day 17; sedation subsequently resolved. After the clozapine dose was increased to 100 mg/day, Mr. A complained of neck pain and developed neck rigidity. Clozapine treatment was discontinued immediately on day 19. Between days 19 and 22, Mr. A was sedated and confused and experienced fever (101.2°F–103.0°F), tachycardia (120–144 bpm), low blood pressure (90/65 mm Hg), and tachypnea (25–30 breaths/min). His creatinine kinase level increased from 92 to 717 IU/liter. His WBC count increased from 8700 mm^3 to 10,600 mm^3.

There was no infectious etiology that could acount for the fever. Results of a chest radiograph, lumbar puncture, blood tests, and examination of blood, CSF, and urine cultures revealed no abnormality. A computerized tomography scan of the head revealed severe cerebral atrophy. Malignant hyperthermia, lethal catatonia, heat stroke, and other medical conditions were ruled out.

On day 21, Mr. A's vital signs, mental status examination results, and laboratory values started to improve and returned to normal by day 24. After 8 days, a rechallenge with clozapine, 12.5 mg/day, was initiated. Mr. A's creatinine kinase level increased to 2722 IU/liter on the second day. Clozapine treatment was stopped, and the creatinine kinase level dropped to 1093 and 620 IU/liter on day 30 and day 31, respectively. Treatment with fluphenazine and divalproex sodium was reinstituted, and Mr. A was discharged.

Clozapine seems to be a good alternative for patients with a history of neuroleptic malignant syndrome, even for those who develop neuroleptic malignant syndrome during clozapine treatment (1, 2). There are no available data yet about neuroleptic malignant syndrome liability or potential utility of other atypical antipsychotics. Olanzapine, which has a chemical and pharmacological profile similar to that of clozapine, may be another alternative for treatment of psychosis in patients with a history of neuroleptic malignant syndrome. Clinicians should maintain vigilance regarding recurrence of neuroleptic malignant syndrome during rechallenge with clozapine.

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Diazepam-Responsive Neuroleptic Malignant Syndrome: A Diagnostic Subtype?

TO THE EDITOR: The efficacy of diazepam in the treatment of neuroleptic malignant syndrome has been disputed. In this report we describe the case of a patient with neuroleptic malignant syndrome who recovered upon continuous administration of intravenous diazepam.

Ms. A, a 55-year-old woman who had been taking neuroleptic drugs for treatment of schizophrenia, was admitted to the hospital because she had been almost continuously mute and had exhibited no voluntary movement for 2 days. On admission, she had a fever (38°C), tachycardia (104 bpm), and hypertension (190/130 mm Hg), with moderate muscular rigidity, tremor, and diaphoresis. Serum creatinine kinase and myoglobin levels were 506 IU/liter (normal range=20–120) and 262.7 ng/ml (normal range=18.8–58.0), respectively. Treatment with bromocriptine mesylate (5–10 mg/day), given from the second day, was stopped on the 12th day because of hematemesis. Dantrolene therapy (50–100 mg/day) was administered from the 13th day but had no effect.

On the 18th day, Ms. A's condition deteriorated. She was unresponsive, and the rigidity and tremor became more marked. Upon intravenous administration of diazepam, 10 mg, she suddenly became verbal, and the tremor and rigidity improved. However, since her condition worsened again about 3 hours after the injection, continuous intravenous administration of diazepam (15–20 mg/day) was added to the dantrolene therapy. After the start of this continuous administration, mental, extrapyramidal, and autonomic dysfunction symptoms rapidly improved. By the 24th day, all of the symptoms of neuroleptic malignant syndrome had disappeared.

Three similar cases have been described previously (1, 2). The clinical features common to these cases and ours are as follows: 1) the patients were mute (similar to catatonic syndrome [3]) before intravenous diazepam administration, 2) intravenous diazepam administration induced a sudden transient communicative state and resulted in improvement of extrapyramidal symptoms, and 3) subsequent continuous diazepam administration resulted in improvement of the general clinical condition. These cases suggest the possibility that diazepam-responsive neuroleptic malignant syndrome is a subtype of neuroleptic malignant syndrome. This subtype might be called catatonic-syndrome type neuroleptic malignant syndrome, since benzodiazepines have been reported to be effective in the treatment of catatonic syndrome regardless of its etiology (3). A review by Addonizio et al. (4) mentions that benzodiazepine therapy was effective in three (14%) of 21 patients with neuroleptic malignant syndrome. A trial administration of intravenous diazepam for neuroleptic malignant syndrome patients with catatonic syndrome, followed by continuous diazepam therapy if the trial administration is effective, is recommended.

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