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.