Acute Manic Psychosis Induced by Triple Therapy for *H pylori*

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Commonly used medications can produce uncommon side effects. Patients with one or more chronic diseases can be taking multiple medications, increasing the risk for drug interactions. New-onset psychosis in middle-aged patients who have no history of psychiatric illness should provoke a search for reversible causes. Numerous patients are being treated with triple therapy for *Helicobacter pylori*-associated peptic ulcer disease. We describe a case of organic psychosis in a patient who recently had triple therapy for *H pylori* peptic ulcer disease added to her maintenance medications. Previous reports in the medical literature have described psychiatric complications with various components of triple therapy in patients with previously documented psychiatric disorders. When an adverse event occurs, all medications and possible drug interactions should be considered.

Case Report

A 55-year-old woman with a history of hypertension, poorly controlled diabetes, arthritis, and dyspepsia was brought to the emergency department because of strange behavior during the previous few days.

She had no previous psychiatric or substance abuse history other than chronic insomnia. She maintained her usual level of activity as a homemaker until 4 days before admission, when she began talking more and sleeping less. She declared that "God has chosen me as his prophet," and that He was speaking through her. Her husband and friends reported that the patient did not use any alcohol or other substances and did not have any history of drug allergies, fever, head trauma, headache, nausea, vomiting or change in weight. One week earlier she had received new medicines for dyspepsia from her primary care physician. Her husband indicated that she took her maintenance medications of 5 mg of glyburide, combination human insulin, and 10 mg of lisinopril, as well as 500 mg of acetaminophen intermittently. She had been on low-dose amitriptyline (25 mg) therapy, as needed, for insomnia for 5 months. Because her dyspepsia had not responded to ranitidine and omeprazole in the past, these medications were discontinued. One week before admission, she started taking twice daily 500 mg of clarithromycin, 1 g of amoxicillin, and 30 mg of lansoprazole for presumed *H pylori* peptic ulcer disease, as well as 100 mg of celecoxib.

The patient was a moderately obese, disheveled, middle-aged woman who was alert and oriented to person only, with marked hyperactivity including pacing, tapping furniture, and praying. Her speech was loud but clear, and the content was extremely religious. Her concentration was poor, and she appeared to have auditory hallucinations. Her temperature, blood pressure, heart rate, and respirations were stable. She was agitated and cooperated poorly. There was no evidence of head trauma or nuchal rigidity. When examined, she had clear lung fields on auscultation, an absence of cardiac murmurs or gallops, and no abdominal tenderness. Other than mild hypesthesia in both feet, there were no gross focal neurologic findings.

Initial finger stick blood glucose was 260 mg/dL, and she was started on a sliding scale of regular insulin. When she became more combative, the patient was given one dose of intramuscular haloperidol and lorazepam. She was observed during the next 12 hours, and while less agitated, she remained psychotic. She scored 27 out of 30 on a Mini Mental Status Examination.[1]

She was admitted to the inpatient psychiatric service. She continued her outpatient dosage regimens of glyburide, combination human insulin, celecoxib, and lisinopril, but the *H pylori* triple therapy and the amitriptyline was stopped. She received one dose of risperidone but refused sub-

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sequent doses. Results of admission laboratory analyses (including complete metabolic profile, complete blood count, thyroid function tests, and urine drug screen) were normal except for hyperglycemia and glycosuria. A chest radiograph was negative for active disease. An electrocardiogram was normal. Her agitation and psychosis cleared within 36 hours after admission. On questioning, the patient indicated that she had taken the amitriptyline as directed and did not exceed the dose. She was discharged with a diagnosis of "organic psychosis – resolved." Follow-up telephone calls to the patient and her primary care physician indicated that she did well after discharge, showing no signs of psychiatric disease after discontinuing triple therapy for *H pylori* peptic ulcer disease and amitriptyline.

Discussion

This patient developed an acute manic psychosis within a 4-day period. There was no evidence of infection, substance abuse, or hypoglycemia to account for her symptoms. The psychosis began approximately 3 days after the initiation of triple therapy with clarithromycin, amoxicillin, and lansoprazole for presumed *H pylori* peptic ulcer disease and celecoxib for arthritis pain. Serious adverse effects from insulin, glyburide, and lisinopril were believed to be unlikely.

A review of the literature failed to find psychiatric complications that were due to celecoxib and lansoprazole therapy. Paranoid ideation has been reported with amitriptyline.[2] One case of reversible psychosis[3] and one case of hallucinations[4] have been reported with amoxicillin. Clarithromycin, however, was associated with reversible psychosis in 5 patients.[5–7] One patient had been on long-term omeprazole therapy, and another was taking ranitidine without noticeable morbidity until clarithromycin was added. In both these cases,[5] there was a lag time of about 1 week between initiation of clarithromycin and the development of mental toxicity, then complete resolution of symptoms in 24 to 36 hours, such as in our patient. Two other cases were in patients with acquired immunodeficiency syndrome being treated for disseminated *Mycobacterium avium* infection.[6] The fifth case was an elderly patient with soft-tissue infection.[7] Another case of delirium has been reported with clarithromycin in a patient who had been stable on long-term fluoxetine for treatment of depression.[8]

Table 1. Medications That Inhibit the Hepatic Cytochrome P-450 Isoenzymes.

Drug	1A2	2C9	2C19	2D6	2E1	3A4
Amitriptyline	S*	S	S	S		S
Acetaminophen	S				S	
Celecoxib		S		(−)		
Lansoprazole			S(−)			S
Risperidone				S		
Insulin	(+)					
Clarithromycin	(−)					(−)

*S = substrate, (−) = inhibition, (+) = induction.

The mechanism of the psychotic effect might relate to the inhibition of hepatic cytochrome P-450 enzymes. The possibility of drug interactions increases whenever a patient receives two (or more) drugs binding to the same P-450 system. With the exception of amoxicillin, the drugs in this case affect a number of P-450 isoenzymes (Table 1). Conceivably this patient's manic psychosis could have been secondary to elevated levels of amitriptyline caused by isoenzyme inhibition by clarithromycin. The previous dose of amitriptyline had been low, however, and compliance had been questionable. The mechanism for psychosis as a result of clarithromycin alone is unclear,[5,8] particularly since diffusion of the macrolides into the central nervous system is poor.

No medication is completely benign. When patients with several chronic diseases are on several medications, the potential for drug interactions is increased, and careful attention should be paid to the indications for medication use. In such individuals, definitive testing for *H pylori* should be considered before starting triple therapy for peptic ulcer disease. This case and the others cited suggest that clarithromycin or its interaction with other agents should be considered as a possible cause of acute reversible psychosis in such patients.

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