Clarithromycin-Induced Mania after Triple Therapy to Eradicate *Helicobacter pylori*

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Antimicrobial-induced mania is a rare but important side effect of antibiotic treatment and should be regarded as a potential risk for patients, both those with and without a history of a mood disorder. Recent reports found antibiotics such as clarithromycin and ciprofloxacin to be the most frequently associated with the development of mania [1].

Onset of these symptoms typically occurs within 7 days of starting medication and resolution of symptoms occurs 24–48 hours after discontinuation of the medication [2]. We report a case of psychotic mania after a few days of treatment with triple therapy for the eradication of *Helicobacter pylori* that was added to the patient's regular chronic therapy.

PATIENT DESCRIPTION

A 66 year old woman presented to the emergency room with weakness, dizziness and melena. Her medical history included Parkinson's disease for which she was treated with carbidopa/levodopa/entacapone 1 mg three times a day and rasagiline 1 mg once a day; depression treated with citalopram 20 mg once daily; hypertension treated with enalapril 20 mg and hydrochlorothiazide 12.5 mg once a day; and osteoporosis treated with raloxifene 60 mg once a day.

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On physical examination she appeared well with no pallor and vital signs were normal. Digital rectal examination revealed obvious melena. The abdomen was soft with mild sensitivity on the left costal margin and no signs of peritoneal irritation. Complete blood count showed: hemoglobin 8.2 g/dl, hematocrit 23.3%, leukocytes 10,100, platelets 198,000, and prothrombin time (international normalized ratio) 1.12. The biochemistry panel including glucose level and liver function test was normal apart from elevated blood urea nitrogen, 43 mg/dl.

On gastroscopy, two acute ulcers were seen: one in the pre-pyloric area with bleeding stigmata which was treated successfully with argon plasma coagulation, and the second one in the duodenal bulb, a clean base ulcer with no bleeding stigmata. During hospitalization, the hemoglobin level dropped to 6.9 g/dl. The patient was treated with intravenous proton pump inhibitors continuously and transfused with four units of packed red blood cell. She was discharged with a hemoglobin level of 10.2 g/dl. Empiric triple therapy was begun for the eradication of *Helicobacter pylori:* clarythromycin 500 mg/day, amoxycillin 2 g/day and omeprazole 40 mg/day for 10 days.

After 5 days of treatment there was a sudden and dramatic change in her behavior. She was irritable, elated and insomniac, which led her family to bring her promptly to the emergency department for urgent psychiatric assessment.

The mental status examination demonstrated that she was fully oriented, partly cooperative, hostile, with pressured speech, irritable affect and elated mood. Her thought processes revealed racing thoughts, and her thought content showed delusions of grandeur: "something big is going to happen to the people of Israel and I have a very important role in it." Her impulse control was low, she lacked insight, and her judgment was poor.

A diagnosis of acute manic psychotic state was reached. Due to lack of cooperation she was admitted to a psychiatric department. During her hospitalization, the antibiotics were discontinued, olanzapine 10 mg/day was started, and she continued therapy with omeprazole 40 mg/day as the single anti-ulcer treatment. For differential diagnosis, dopaminergic anti-Parkinsonian treatment was considered a possible trigger and carbidopa/levodopa/entacapone and rasagiline were stopped.

After a few days in hospital the patient's condition improved, she was calmer and behaved appropriately. Her thoughts were more organized and there were no signs of delusions. Secondary to neurologic consultation, carbidopa/levodopa/entacapone treatment was renewed**.** In order to prevent worsening of the Parkinson symptoms, quetiapine was added and in parallel olanazpine was tapered down. Her improved behavior continued, she returned gradually to her basic premorbid behavioral state, and was discharged after 2 weeks. Follow-up gastroscopy 2 months later showed no signs of peptic ulcers or gastric inflammation. Biopsy from normal-looking antral mucosa demonstrated the presence of *Helicobacter pylori* bacteria. Since she developed serious side effects from the triple therapy, it was decided not to eradicate the bacteria and to keep her exclusively on omeprazole 40 mg/day with close clinical follow-up.

COMMENT

The term 'antibiomania' refers to manic episodes that occur after a patient starts taking antibiotics [2]. The mechanism by which antimicrobials induce mania is still unknown and it is considered idiosyncratic in nature [1]. Clarithromycin and ciprofloxacin are thought to be the two antibiotics that are most frequently associated with the development of mania [3].

The first description of clarithromycin-induced mania in the published literature was in 1995: two patients were receiving treatment for *Mycobacterium avium* infection. In 2002, Neff et al. [4] reported a case of clarithromycin-induced mania after triple therapy for *Helicobacter pylori* in a patient with dyspepsia who did not respond to H2 blocker or to proton pump inhibitors.

We have described a female patient with Parkinson's disease and depression who developed bleeding peptic ulcer. Five days after initiating triple therapy with amoxicillin, clarithromycin and omeprazole, she developed acute manic psychosis. There was no evidence of infection, hypoglycemia or neurologic signs of cerebrovascular accident. The patient stopped the antibiotics and received prompt therapy with antipsychotic medication, which led to improvement in her mental status. She continued with omeprazole for anti-ulcer therapy with no recurrent episode of bleeding. Since there are only isolated reports in the literature linking acute psychosis to amoxicillin, we thought clarithromycin to be the most likely drug culprit. Clarithromycin is a semisynthetic macrolide antibiotic derived from its parent compound erythromycin. In addition to gastrointestinal complaints, clarithromycin may also produce symptoms related to the central nervous system (CNS), such as confusion, insomnia, dizziness and lightheadedness [1]. Several theories have been proposed for the mechanism of acute manic psychosis from clarithromycin:

Accumulation of the active metabolite 14-OH of clarithromycin in the CNS; clarithromycin and its metabolites may be directly toxic to the CNS via its lipid-soluble active metabolite 14-hydroxyclarithromycin.

Increased levels of blood cortisol and prostaglandins, hormones that are associated with mania by interaction with glutaminergic and γ-aminobutyric acid pathways.

Drug interactions due to the inhibition of cytochrome P450 by clarithromycin with a resultant accumulation of clarithromycin is the most commonly accepted theory [2]. Clarithromycin is metabolized via the CYP3A and CYP2C19 pathways, specifically via the cytochrome P-450 system by oxidation and demethylation.

An example of this theory in the literature is the report by Neff and Kuo [4] of a patient with no known psychiatric disorders on low dose amitriptyline for insomnia, who developed manic psychosis 1 week after starting clarithromycin for the eradication of presumed *Helicobacter pylori* peptic ulcer disease. Similarly, Pollak et al. [5] reported on fluoxetine toxicity in a patient who had been on fluoxetine for 16 months and experienced psychosis within 1 day of starting clarithromycin. Treatment of antibiotic-induced mania generally involves discontinuing the offending agent. However, if symptoms do not resolve quickly or the patient's level of functioning is impaired, it may be necessary to add a psychotropic medication, such as an antipsychotic with or without benzodiazepine [3].

CONCLUSIONS

Acute drug psychosis is a rare condition but should always be considered when other causes such as infection, toxic or metabolic causes are absent. Patients taking several medications secondary to chronic disorders, as in our case, are particularly prone to drug interaction. Testing for *Helicobacter pylori* should show a definitive result before starting triple therapy for peptic ulcer disease, and clinicians should be familiar with the potential psychiatric side effects.

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References

1. Ortiz-Dominguez A, Berlanga C, Gutierrez-Mora D. A case of clarithromycin-induced manic episode (antibiomania) [Letter]. *Int J Neuropsychopharmacol* 2004; 7: 99-100.
2. Shah M, Subhania M, Rizvon K, Mustacchia P. Transient psychotic episode induced by Helicobacter pylori triple therapy treatment. *Case Rep Gastroenterol* 2012; 6: 381-6.
3. Lally L, Mannion L. The potential for antimicrobials to adversely affect mental state. *BMJ Case Rep* 2013; 2013: 1-3.
4. Neff NE, Kuo G. Acute manic psychosis induced by triple therapy for H pylori. *J Am Board Fam Pract* 2002; 15 (1): 66-8.
5. Pollak PT, Sketris IS, MacKenzie SL, Hewlett TJ. Delirium probably induced by clarithromycin in a patient receiving fluoxetine. *Ann Pharmacother* 1995; 29: 486-8.