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Transient Psychotic Episode Induced by *Helicobacter pylori* Triple Therapy Treatment

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Key Words

Transient psychotic episode · *Helicobacter pylori* triple therapy treatment

Abstract

The term ‘antibiomania’ refers to manic episodes that occur after a patient starts taking antibiotics. We report the case of a 49-year-old male who developed acute psychosis secondary to initiation of triple therapy for *Helicobacter pylori* eradication. Unlike with proton pump inhibitors, there have been several reported cases of central nervous system side effects and psychiatric consequences due to amoxicillin, however evidence points to clarithromycin as the likely culprit. On average onset of symptoms occurred within 1–5 days of initiating therapy. In all cases, symptoms resolved upon cessation of clarithromycin, mostly within 1–3 days. Unfortunately, the mechanism through which clarithromycin causes neurotoxicity remains unclear. Clinicians should be cognizant of psychiatric side effects secondary to clarithromycin, and discontinuation should be prompt for rapid recovery of mental status.

Introduction

Antibiomania, a term used to describe antibiotic-induced manic episodes, is a rare but genuine side effect of some antimicrobials. Clarithromycin is among those more commonly associated with psychosis, with few reported cases involving amoxicillin. Onset of these symptoms typically occurs within 7 days of medication initiation and resolution of symptoms occurs 24–48 h after medication cessation. We report the case of a 49-year-old male without any previous psychiatric history who developed acute psychosis after starting triple therapy for *Helicobacter pylori* with return of mental status to baseline after discontinuation of the regimen. The widely popular triple therapy that includes a proton pump inhibitor (PPI), amoxicillin and clarithromycin is

most commonly prescribed for patients infected with *H. pylori*. After an extensive review of the literature it was found that acute psychotic episodes in patients undergoing this treatment regimen have been reported, with clarithromycin as the probable culprit.

Case Report

A 49-year-old male with a history of gastroesophageal reflux disease and recently diagnosed *H. pylori* gastritis was brought to the emergency by his wife who had noted strange behavior in the patient 4 h prior at home. The wife initially had found the patient on the toilet non-verbal and unresponsive with a blank stare. The patient abruptly stated he felt as if he was 'leaving the planet', followed by cat-like screeching and movements. In the emergency room, the patient was noted to have bilateral upper extremity jerky movements, which resolved after 10 s without any medical intervention. No lip or tongue bites, bowel or urinary incontinence, foaming from the mouth or post-ictal confusion was witnessed. Upon further inquiry, the patient's wife of 8 years denied any psychiatric or substance abuse history. The patient did not have any history of previous seizures, stroke or transient ischemic attack. He was an emergency room attending physician maintaining his usual daily activities several hours prior to admission. There was no recent head trauma, subjective fevers, drug allergies, headaches, nausea or vomiting. Family history was negative for epilepsy or psychiatric disorders. The wife denied any recent travel. The patient's only medication was omeprazole 40 mg of 6 years duration daily for gastroesophageal reflux disease, and he had recently started on triple therapy for *H. pylori* gastritis, which included lansoprazole 30 mg twice daily, amoxicillin 1 g twice daily and clarithromycin 500 mg twice daily 5 days prior to presentation.

The patient was a well-appearing, slender, middle-aged male. He was lethargic and at times exhibiting involuntary movement of his upper extremities. Vital signs at presentation were remarkable for a pulse rate of 108 bpm. On physical examination, he was disoriented to place and time. Nuchal rigidity was absent and there was no evidence of trauma. Reflexes were normal with no focal neurologic signs. Cardiopulmonary and abdominal exams were within normal limits. Initial investigations included a finger stick glucose of 100 mg/dl along with a complete blood count, comprehensive metabolic panel, urinalysis, urine toxicology screen, and thyroid-stimulating hormone that were within normal limits. A chest X-ray and CT scan of the head were unremarkable. An electrocardiogram was significant for sinus tachycardia at 106 bpm, however acute coronary syndrome was ruled out with two consecutive negative sets of cardiac enzymes.

The patient was admitted to the medical intensive care unit for further exploration of his acute psychosis and altered mentation. All of his medications were discontinued while he was being observed. He underwent extensive testing to find an organic cause of this psychotic episode, including magnetic resonance imaging of the brain, magnetic resonance angiogram of the cranial vessels and a 24-hour electroencephalogram (EEG), which failed to show any pathologies or irregularities.

During inpatient hospitalization, symptoms began to subside within 24 h with complete resolution within 36 h. The patient became oriented and returned to his baseline mental status with no administration of antipsychotics. With no evidence of metabolic disturbances, neurologic illness, infection or organ failure, the patient's symptoms were attributed to a medication side effect. Onset of symptoms days after initiation of treatment with rapid resolution of psychosis after discontinuation of medications verified amoxicillin, clarithromycin, lansoprazole or a combination of these drugs to be the likely trigger.

Discussion

The term 'antibiomania' refers to manic episodes that occur after a patient starts taking antibiotics. According to the World Health Organization, the Food and Drug Administration and the published literature, it was found that clarithromycin and ciprofloxacin are those most commonly linked to antibiomania [1]. Our report

describes a patient who was being treated for *H. pylori* with triple therapy, which included the antimicrobials amoxicillin and clarithromycin, in addition to a PPI (lansoprazole). *H. pylori* is a Gram-negative bacterium that is found in the stomach of humans and which may lead to complications such as chronic gastritis, peptic ulcer disease and, more severely, gastric carcinoma. Identification of the organism warrants treatment, initially with triple therapy. Treatment duration lasts between 7 and 14 days with re-testing for *H. pylori* to verify eradication. Although the incidence of antibiomania as a side effect of antimicrobials is low, it should still be recognized as a risk for patients undergoing treatment.

The side effect profile of triple therapy is extensive with more common reactions relating to the gastrointestinal tract. Commonly reported adverse reactions to PPIs include nausea, vomiting, diarrhea, abdominal pain, dizziness and fatigue [2]. Adverse effects of penicillins, specifically amoxicillin, are typically related to allergic reactions as well as gastrointestinal symptoms including severe colitis. Clarithromycin may also cause similar gastrointestinal symptoms as amoxicillin including headache and irritability. Unlike with PPIs, there have been several reported cases of central nervous system (CNS) side effects and psychiatric consequences due to amoxicillin and clarithromycin.

Based on our review of the literature, acute psychosis from acid suppression therapy has not been well documented. A case of acute mania in a 60-year-old woman has been described secondary to use of ranitidine (a histamine H₂-receptor antagonist) with resolution of symptoms after discontinuation of the offending medication [3]. Despite this report, our research lacked support of acute psychotic episodes secondary to acid suppression therapy via proton pump inhibition. In our patient, a history of long-term PPI use disqualified this element of triple therapy from being the likely trigger of acute psychosis.

A review of the literature linking acute psychosis to amoxicillin yielded a few reported cases. Beal et al. [4] reported a patient with mania and psychosis 10 days after initiation of amoxicillin for a urinary tract infection with complete resolution of these symptoms 12 days after discontinuation of the antibiotic. Similarly, a patient prescribed amoxicillin-clavulanate for suspected pneumonia developed agitation and bizarre behavior with visual hallucinations and delusions within 2 h of administering antibiotics [5]. Another two reports described visual and auditory hallucinations within 1–2 days of starting amoxicillin in patients with no underlying psychiatric disorders [6, 7]. All of these cases showed complete resolution of acute psychiatric symptoms upon cessation of amoxicillin.

Clarithromycin is classified as a macrolide antibiotic derived from its parent compound, erythromycin [8]. Uses of this antibiotic include treatment of respiratory tract infections, infections due to *Mycobacterium avium* complex (*M. avium* or *M. intracellulare*) and *H. pylori*. In addition to gastrointestinal complaints, clarithromycin may also produce symptoms of confusion, insomnia, dizziness, and lightheadedness. CNS side effects including psychosis and depersonalization have also been reported, more so than with amoxicillin.

A number of these cases presume drug interactions as the trigger for psychosis when a patient is receiving two or more medications. Clarithromycin is metabolized via the

CYP3A pathway, specifically via cytochrome P450 isoenzyme by oxidation and demethylation [9, 10]. Many occurrences of clarithromycin-induced psychosis can be explained in patients receiving other drugs also metabolized through this same mechanism. Clarithromycin occupies and inhibits the P450 enzyme during metabolism, resulting in accumulation of the co-administered drug(s), leading to toxic levels. Pollak et al. [11] reported fluoxetine toxicity in a patient who had been on fluoxetine for 16 months and experienced psychosis within 1 day of starting clarithromycin. There are also reports of patients with HIV on highly active antiretroviral therapy in whom neuropsychiatric reactions are described upon initiation of clarithromycin [12]. Corticosteroids are a known trigger for psychotic episodes, and there have been studies revealing a correlation between dose of the steroid and prevalence of psychosis [13, 14]. Finkenbine and Frye [15] report psychosis in a patient on prednisone and clarithromycin, likely due to decreased clearance of prednisolone. Transient carbamazepine overdose as a result of delayed metabolism [16, 17] and serotonin syndrome with psychosis caused by intake of both clarithromycin and paroxetine have also been described [18]. In the aforementioned cases, onset of symptoms on average occurred within 1–5 days of initiating therapy. In all cases, symptoms resolved upon cessation of clarithromycin, mostly within 1–3 days.

The mechanism by which clarithromycin produces psychosis alone remains unclear. Gomez-Gil et al. [19] described two middle-aged females without any past psychiatric history who presented with bizarre behavior and an inability to comprehend after initiation of clarithromycin therapy for *H. pylori* infection. The onset of symptoms occurred within 7 days in each patient, similar to our patient; however amoxicillin was not included in their regimen. Symptoms subsided within 24 h after discontinuation of clarithromycin. Similarly, a 65-year-old female undergoing treatment with clarithromycin and omeprazole developed a manic episode 3 days after initiation of this antimicrobial with resolution of symptoms occurring 2 days after medication was stopped [20]. Clarithromycin has been known to cause acute psychiatric episodes in the treatment for various infections in addition to *H. pylori*. Vicente de Vera et al. [21] described a patient with no previous psychiatric history who developed agitation and delirium 3 days after starting clarithromycin treatment for a community-acquired pneumonia with complete resolution of symptoms after removing treatment. Clarithromycin used for treatment of *M. avium* complex triggered reversible mania in two patients with AIDS not on highly active antiretroviral therapy. Acute psychotic symptoms resolved after clarithromycin was discontinued and recurred when it was resumed. A trial of azithromycin, another macrolide antibiotic, did not induce psychotic episodes in these patients [22]. A group of elderly patients (n = 13, mean age 70 years) with chronic mycobacterial lung disease without HIV were monitored after receiving clarithromycin monotherapy. Common side effects included bitter taste and nausea, with 7 of the 13 patients experiencing confusion and insomnia. Symptoms resolved following discontinuation of treatment [23]. A 52-year-old female being treated for acute bronchitis with clarithromycin twice daily developed acute psychosis with symptoms of disorganized behavior, paranoid ideation, anxiety, confusion and depersonalization 24 h after initiation of therapy. She returned to baseline 3 days after terminating treatment [24]. There are several other reports in the literature describing mania after starting clarithromycin monotherapy with extinction of symptoms within several days (average 3–5 days) of discontinuing this drug [25–29].

Neurotoxicity of clarithromycin leading to non-convulsive status epilepticus (NCSE) has also been associated with this antibiotic. NCSE can manifest as changes in consciousness without evidence of clinical seizures. The diagnosis is made by ‘continuous epileptiform activity’ on EEG. Bandettini di Poggio et al. [8] reported the first case of clarithromycin-induced delirium due to NCSE in a 74-year-old woman being treated for bronchitis with clarithromycin. Among previously reported cases of clarithromycin-induced neurotoxicity, only 6 patients were evaluated with an EEG, with 5 showing no evidence of epileptic activity. An EEG was performed in our patient excluding the possibility of epileptiform activity induced by clarithromycin. EEG is an important tool in working up a patient presenting with acute psychosis suspected to be secondary to an antimicrobial because with NCSE there is response to treatment with benzodiazepines in addition to drug cessation.

The cause of CNS toxicity as a result of clarithromycin use remains uncertain. A commonly accepted theory with polypharmacy includes the suppression of cytochrome p450 by clarithromycin with a resultant accumulation of clarithromycin and/or the associated drug(s). Clarithromycin alone may be directly toxic to the CNS via its lipid-soluble active metabolite 14-hydroxyclearithromycin [25]. Clarithromycin and its metabolite have also been known to alter cortisol and prostaglandin metabolism, and interact with glutaminergic and γ -aminobutyric acid pathways possibly leading to CNS side effects [1, 12]. Though these are all plausible explanations, how clarithromycin causes neurotoxicity remains a matter of debate requiring further research.

Conclusion

Acute psychosis in patients without previous psychiatric illness entails a wide differential requiring extensive investigation. Initial workup should focus on causes secondary to infectious processes, along with both toxic and metabolic etiologies, however medications must be thoroughly reviewed. Antibiotomania is an infrequent but valid consequence of antimicrobials and must be included in the differential as a trigger for acute psychosis. In our patient, amoxicillin and clarithromycin had been started several days prior to the onset of psychosis for eradication of *H. pylori*. After ruling out other possible causes of psychosis, it was concluded that either amoxicillin or clarithromycin were the likely triggers. Based off an extensive literature review, clarithromycin was the likely agent responsible for symptoms. Unfortunately, the mechanism through which clarithromycin causes neurotoxicity remains unclear. Clinicians should be cognizant of the psychiatric side effects secondary to clarithromycin and discontinuation should be prompt for rapid recovery of mental status.

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