
Letter to the Editor

PSYCHOTIC SYMPTOMS INDUCED BY CLARITHROMYCIN AND CHLORPHENIRAMINE

Dear editor,

Psychotic-like experiences and psychotic symptoms that are characteristic of psychotic disorders also emerge as a consequence of drug and substance misuse or medical illness (Binbay et al. 2012). Reporting psychotic symptoms due to drug and substance misuse is particularly important, as their mechanism of action may contribute to our understanding of the etiopathology of psychosis. Macrolide antibiotics are commonly prescribed in Turkey, ranking third among all antibiotic prescriptions (Tuna 2004). Clarithromycin—a macrolide antibiotic—is commonly used for upper and lower respiratory tract infections, as well as for *helicobacter pylori* eradication (Peter and Clissold 1992). Although the primary adverse effects of clarithromycin are related to the gastrointestinal system, several serious mental health outcomes, including mania, delirium, and psychosis, have been reported (Bandettini di Poggio et al. 2011; Abouesh et al. 2002; Sturgill and Rapp 1992). In addition, common cold medications containing chlorpheniramine that are used widely as over-the-counter preparations may have side effects, including psychotic symptoms (Hellbom 2006). This letter presents a patient that experienced psychotic symptoms after oral intake of clarithro-

mycin and chlorpheniramine, and a discussion of the possible underlying molecular mechanisms of psychotic symptoms.

A 34-year-old female presented to our outpatient clinic with her family in January 2013. Three days earlier she began to take a treatment regimen consisted of clarithromycin (500 mg per tablet), butamirate citrate (50 mg per tablet), and a combination of paracetamol, phenylephrine, and chlorpheniramine (650 mg, 10 mg, and 4 mg per tablet, respectively) b.i.d., which was prescribed for moderate symptoms of upper respiratory tract infection at the emergency department. On day 2 of the treatment she began to experience intense anxiety, disorganized speech (such as, “my mom is dead”, “my mom is vomiting”, “call an ambulance”, “I am pissing”, “give me a pamper”), inappropriate laughing, and sleeplessness.

Her psychiatric evaluation was negative for distorted and fluctuating awareness, as well as temporal, spatial, and personal orientation impairment. The patient was very anxious due to visual and auditory hallucinations. There was marked perseveration of her thought process and her thought content was dominated by perceptual disturbances. Her motor activity was increased due to psychotic symptoms and related anxiety. She had remarkable physical developmental retardation and microcephaly. She also had strabismus, hyperextensible joints, minor malformations of the hands and palms, pes cavus, and features of hypogonadism.

She had mild mental retardation, according to an earlier evaluation of her IQ performed at our hospital to determine her disability payment in 2009. Her parents reported that her phenotypical features were associated with an inherited chromosomal abnormality, but the parents had no formal

report of the chromosomal analysis which was performed in another hospital. The patient was the eldest of 3 daughters; her youngest sister also had similar phenotypical features of microcephaly, physical and mental retardation, pes cavus, and strabismus. Although the parents and other sister were physically healthy and had no phenotypical feature of chromosomal anomaly, all three had received antidepressant treatments for anxiety and depression at different times. The patients' laboratory analysis, including complete blood count, and renal, hepatic, and thyroid function tests was normal. The patient previously used risperidone, chlorpromazine, sertraline, and fluoxetine for depressive and behavioral symptoms during her adolescence. She had not been admitted for psychiatric treatment since 2003 and had no history of psychotic symptom. She was unable to attend mainstream school and has been attending a special education program since 1998.

After emergence of psychotic symptoms, the parents discontinued the infection treatment and they admitted to our outpatient clinic. Her presenting complaints dramatically subsided in one day after the oral intake of one tablet of olanzapine 5 mg and one tablet of lorazepam 1 mg. The patient returned to the level of functionality she had before using clarithromycin and chlorpheniramine.

The patient's general clinical picture, including abrupt onset of delusions, hallucinations, and disorganized speech, was in accordance with a diagnosis of substance-induced psychotic disorder. The patient had severe anxiety due to ego-dystonic experiences. The presenting symptoms were most likely related to clarithromycin, chlorpheniramine, and phenylephrine. The literature includes a substantial number of case reports of psychosis, psychotic symptoms, mania, and delirium related to clarithromycin (Shah et al. 2012; Erkek et al. 2009; Kouvelou et al. 2008; Ozsoylar et al. 2007; Abouesh et al. 2002). There are also few reported cases of psychosis induced by over-the-counter cold medications, including chlorpheniramine (Sharma et al. 2005; Brown et al. 1990). Phenylephrine was also reported to impair prefrontal cognitive functions due to its α_1 adrenergic agonistic effect (Arnsten et al. 1999).

Among case reports, the most commonly reported impairments related to clarithromycin were cognitive dysfunction, disorganized thinking, and disorganized speech (Bandettini di Poggio et al. 2011). Clarithromycin probably disrupts inhibitory processes associated with cortical regulatory functions, leading to clinical manifestation of disinhibition (Brooks and Hoblyn 2005). Hence, subtle thoughts progress to auditory or visual hallucinations, and then to paranoid ideation or delusions, followed by anxiety accompanying the abrupt shift in the intensity of ordinary thoughts. The final clinical presentation can be mania, psychosis, or delirium, depending on patient age, predisposition, and underlying co-morbidities.

Some have proposed theories to explain the underlying mechanism of the disinhibitory effect of clarithromycin. One such

hypothesis implicates γ -amino butyric acid (GABA) antagonism (Brooks and Hoblyn 2005). Inhibition of GABA probably leads to infiltration of overloaded stimuli from subcortical centers, such as the thalamus, to the cortex, finally exhibiting a syndromal combination of hallucination, delusion, affective dysregulation, or cognitive impairment (Barch and Ceaser 2012). Another hypothesized mechanism is inhibition of the cytochrome P450 enzyme system in response to clarithromycin (Shah et al. 2012). Co-administration of molecules that are metabolized in the same enzyme system as clarithromycin is may lead to toxic plasma concentrations, which in turn might cause the emergence of psychiatric symptoms. Thus, in most cases of clarithromycin-induced psychosis co-administered drugs metabolized by the same microsomal enzyme system were also ingested (Bandettini di Poggio et al. 2011).

In the presented case enzyme inhibition due to clarithromycin might have caused an increase in the plasma concentration of chlorpheniramine and phenylephrine. Chlorpheniramine is an antihistaminergic molecule that is also known for serotonin and noradrenalin re-uptake inhibition (Carlsson and Lindqvist 1969). Enzymatic interaction between clarithromycin and chlorpheniramine might result in impaired monoaminergic transmission and the emergence of psychotic symptoms. A serious adverse effect of co-administration of clarithromycin and chlorpheniramine with selective serotonin re-uptake inhibitors is serotonin syndrome (Ayoğlu et al. 2009; Jaber et al. 2006; Pollak et al. 1995). Such cases are probably associated with drug-drug interaction; however, both molecules may have direct serotonergic effects in the brain (Miyata et al. 2011). Furthermore, 14-OH-clarithromycin, a lipid-soluble active metabolite of clarithromycin, might also have some effects on brain functions (Ozsoylar et al. 2007). Nonetheless, not all patients taking clarithromycin or chlorpheniramine experience psychotic symptoms; there must be a particular underlying vulnerability. In the presented case such vulnerability might have been a consequence of chromosomal abnormality. Schizophrenia—the prototype of psychotic disorders—is associated, in part, with some structural chromosomal abnormalities (copy number variation) (Bassett et al. 2010). Although there was no clearly identified chromosomal anomaly in the presented patient, her clinical picture as reported herein might have been associated with subtle cortical and subcortical impairment, which in turn resulted in clinically relevant symptoms following use of clarithromycin and chlorpheniramine.

Yours sincerely

REFERENCES

- Abouesh A, Stone C, Hobbs WR (2002) Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. *J Clin Psychopharmacol* 22: 71–81.
- Arnsten AF, Mathew R, Ubriani R (1999) Alpha-1 noradrenergic receptor

- stimulation impairs prefrontal cortical cognitive function. *Biol Psychiatry* 45: 26-31.
- Ayoğlu H, Atasoy N, Özer Y (2009) Serious serotonin syndrome associated with paroxetine and clorpheniramine use: A case report. *Anatol J Clin Investig* 3: 192-195.
- Bandettini di Poggio M, Anfosso S, Audenino D et al (2011) Clarithromycin-induced neurotoxicity in adults. *J Clin Neurosci* 18: 313-8.
- Barch DM, Ceaser A (2012) Cognition in schizophrenia: core psychological and neural mechanisms. *Trends Cogn Sci* 16: 27-34.
- Bassett AS, Scherer SW, Brzustowicz LM (2010) Copy number variations in schizophrenia: critical review and new perspectives on concepts of genetics and disease. *Am J Psychiatry* 167: 899-914.
- Binbay T, Drukker M, Elbi Het al (2012) Testing the psychosis continuum: Differential impact of genetic and nongenetic risk factors and comorbid psychopathology across the entire spectrum of psychosis. *Schizophr Bull* 38: 992-1002.
- Brooks JO III, Hoblyn JC (2005) Secondary mania in older adults. *Am J Psychiatry* 162: 2033-8.
- Brown TM, Golden RN, Evans DL (1990) Organic affective psychosis associated with the routine use of non-prescription cold preparations. *Br J Psychiatry* 156: 572-5.
- Carlsson A, Lindqvist M (1969) Central and peripheral monoaminergic membrane-pump blockade by some addictive analgesics and antihistamines. *J Pharm Pharmacol* 21: 460-4.
- Erkek N, Senel S, Karacan C (2009) Visual hallucinations possibly associated with clarithromycin administration at therapeutic dosage in two children. *Med Princ Pract* 18: 332-4.
- Hellbom E (2006) Chlorpheniramine, selective serotonin-reuptake inhibitors (SSRIs) and over-the-counter (OTC) treatment. *Med Hypotheses* 66: 689-90.
- Jaber BL, Lobon LF, Madias NE (2006) The serotonin syndrome complicating co-prescription of paroxetine and clarithromycin. *Am J Med* 119: e3.
- Kouvelou E, Pourzitaki C, Aroni F et al (2008) Acute psychosis induced by clarithromycin in a healthy adult? *J Clin Psychopharmacol* 28: 579-80.
- Miyata S, Hirano S, Ohsawa M et al (2011) Chlorpheniramine exerts anxiolytic-like effects and activates prefrontal 5-HT systems in mice. *Psychopharmacology (Berl)* 213: 441-52.
- Ozsoylar G, Sayin A, Bolay H (2007) Clarithromycin monotherapy-induced delirium. *J Antimicrob Chemother* 59: 331.
- Peter DH, Clissold SP (1992) Clarithromycin. A review of its antimicrobial activity, pharmacokinetic properties and therapeutic potential. *Drugs* 44: 117-64.
- Pollak PT, Sketris IS, MacKenzie SL et al (1995) Delirium probably induced by clarithromycin in a patient receiving fluoxetine. *Ann Pharmacother* 29: 486-8.
- Shah M, Subhani M, Rizvon K et al (2012) Transient Psychotic Episode Induced by Helicobacter pylori Triple Therapy Treatment. *Case Rep Gastroenterol* 6: 381-6.
- Sharma A, Dewan V, Petty F (2005) Acute psychosis with Coricidin cold medicine. *Ann Pharmacother* 39: 1577-8.
- Sturgill MG, Rapp RP (1992) Clarithromycin: review of a new macrolide antibiotic with improved microbiological spectrum and favorable pharmacokinetic and adverse effect profiles. *Ann Pharmacother* 26: 1099-108.
- Tuna S (2004) Türkiye'de antibiyotik kullanım verileri. *İyi Klinik Uygulamalar Dergisi* 8: 35-42.

Tolga Binbay, MD,

Atatürk Public Hospital, Psychiatry Unit, Sinop, 57000.

e-mail: tolgabinbay@yahoo.com