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## Psychiatric adverse reaction induced by Clarithromycin

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### KEY WORDS

*Clarithromycin; drug allergy; mania; macrolides; neurotoxicity*

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Clarithromycin is an antibiotic of the macrolide family, widely used in respiratory and ENT infections. Immediate hypersensitivity reactions are uncommon. The most frequent side effects are gastrointestinal disturbances, hepatotoxicity and ototoxicity. There are few reports on allergic reactions to macrolides (1-4). We present a case of a 28 years old non-atopic man with a history of irritable bowel syndrome and sulfamide allergy, who was referred to our Allergy Department for an adverse reaction to clarithromycin. He referred the appearance of facial and palmar erythema without pruritus or respiratory symptoms after the first tablet of clarithromycin 500 mg prescribed for pharyngitis. Three hours later, he started with dizziness, anxiety and emotional lability. Symptoms resolved spontaneously over four hours. He had previously taken clarithromycin with good tolerance.

Skin prick test with macrolides (clarithromycin, midecamycin, roxithromycin, azithromycin, erythromycin) were all negative.

Single blind placebo-controlled oral challenges with progressively increasing doses of erythromycin and clarithromycin on separate days were conducted under close medical supervision in our Allergy Department. The patient tolerated up to 500 mg of erythromycin, but 40 minutes after the intake of a cumulative dose of 500 mg of clarithromycin, he experienced dizziness and derealization, perceiving ideas and concepts as running very fast but no perception of rotation. This experience was associated with panic-anxiety and emotional lability, abruptly shifting from elation to unmotivated crying. The episode resolved spontaneously within two hours, and he did not present any type of skin reaction.

Given the psychiatric adverse reaction observed during the drug challenge, further studies were carried out including electroencephalogram (EEG), brain computed tomography (CT), blood cell count, blood biochemistry and immunoglobulins (IgE, IgA, IgM and IgA). All these tests were unaltered. A psy-

chiatric evaluation including clinical interviews by senior psychiatrist and psychological examinations of personality came to the conclusion that the patient suffered from a depersonalization-anxiety syndrome secondary to clarithromycin with no primary underlying psychiatric disorder.

The patient was finally diagnosed of adverse reaction to clarithromycin secondary to neurotoxicity, and he was recommended to avoid it. The psychiatric manifestations induced by clarithromycin seem to be selective in our patient since he tolerated erythromycin, a drug that was allowed as an alternative macrolide.

Psychiatric manifestations induced by clarithromycin have already been reported in adult and pediatric patients, and they include emptiness, depersonalization, paranoid ideation, aggressive behavior, anxiety, confusion, hallucinations, emotional lability, agitation, delusions of grandeur, nervousness and sleep disorders (5,6). The symptoms resolve after drug withdrawal, normally within few days, spontaneously or with antipsychotic drugs (7,8,9). However, in some cases the duration of psychiatric symptoms can last months after withdrawal of clarithromycin (5,6).

The mechanisms involved in macrolide induced psychiatric reactions are not well established. Several theories have been proposed: 1) drug interactions due to the inhibition of cytochrome P450 by clarithromycin; 2) accumulation of the active metabolite 14-OH of clarithromycin in the central nervous system; 3) increased levels of blood cortisol and prostaglandins, hormones that are associated with mania (6,10,11).

In our case, the patient reported in the first reaction mild and transient skin symptoms, suggesting a possible hypersensitivity to the antibiotic, and hours later psychiatric symptoms appeared. The latter were not sufficiently emphasized by the patient at the first visit and therefore overlooked by the allergist who collected the medical history. However, during the drug challenge in our Allergy Department, psychiatric symptoms appeared earlier than in the reported reaction and were of a higher intensity, while signs and symptoms of skin involvement were absent. Fortunately, the reaction was self-limited and resolved spontaneously within hours without anti-psychotic drugs. The patient did not present any residual symptoms at follow up (up to one year) and the EEG performed one week after oral intake was normal.

We present this case to draw attention of allergists to psychiatric manifestations associated with clarithromycin, a type of adverse reaction uncommonly seen in Allergy clinics. Although these reactions usually resolve within hours or a few days, sometimes without the use of psychiatric medications, there are also cases of severe symptoms that persist for months. It is therefore essential that allergists are aware of this type of psychiatric adverse effects when taking the medical history, and avoid diagnostic challenge procedures.

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