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Case Report

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Hoigne Syndrome due to Clarithromycin Treatment in a Hemodialysis Patient

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Abstract

Clarithromycin is an antibiotic that is usually used to treat upper and lower respiratory tract infections. Common side effects are diarrhea, nausea, vomiting, dyspepsia and change of taste in the mouth. Other rare side effects are related to the central nervous system. The patient may experience anxiety, dizziness, insomnia, nightmares, confusion, hallucination, and psychosis. These neuropsychiatric findings are called Hoigne syndrome. Here is, the case of a 52 year old chronic hemoadialysis patient that was presented with a very rare side effect due to clarithromycin therapy prescribed for pneumonia.

Keywords: Hemodialysis, clarithromhycin, hoigne syndrome

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INTRODUCTION

Clarithromycin is a semi-synthetic macrolide antibiotic. It is generally used in the treatment of lower and upper respiratory tract infections, as well as skin and soft tissue infections. It is also effective in the eradication of Helicobacter pylori in the presence of acid suppression. It inhibits protein synthesis by binding to the 50 S ribosomal subunit of sensitive bacteria, thus, showing an antibacterial effect (1). After oral administration, clarithromycin enters enterohepatic circulation from the intestines via reabsorption. The basic elimination site is the liver; 1%-2% and 10%-12% are eliminated by the renal route when administered orally and parenterally, respectively (1, 2). Renal failure usually does not require a dose adjustment.

Common side effects of clarithromycin are diarrhea, nausea, vomiting, dyspepsia, and taste disorder in the mouth. Rarely, an increase in liver enzymes is observed (3). This hepatic dysfunction can sometimes be severe, but it is usually reversible. Allergic reactions with oral clarithromycin, ranging from urticaria and moderate skin eruption to anaphylaxis and Steven-Johnson syndrome, have been reported (4). Rare side effects affect the central nervous system. Clarithromycin may cause anxiety, dizziness, insomnia, nightmares, confusion, hallucinations, and psychosis. These neuropsychiatric findings are called Hoigne's syndrome (5). Clarithromycin-associated Hoigne's syndrome is very rare and is presented in the literature as case reports (6). Here, because of its rarity, we present Hoigne's syndrome associated with clarithromycin in a patient on hemodialysis, who was hospitalized for pneumonia.

CASE PRESENTATION

A 52-year-old male, diagnosed with chronic kidney disease due to diabetes and undergoing hemodialysis treatment for 8 months following a 3-year peritoneal dialysis, was admitted to our clinic with fever, cough,

Table 1. Naranjo's adverse drug reaction probability scale

Question	Yes	No	Do Not Know	Case Score
Are there any previous reports on the reaction?	+1	0	0	+1
Did the side effect develop after the administration of the suspected drug?	+2	−1	0	+2
Was there an improvement in side effects when the drug was discontinued or when the specific antagonist was administered?	+1	0	0	+1
Did the side effect reappear when the drug was re-administered?	+2	−1	0	+2
Are there alternative reasons (other than medication) that can cause the observed reaction?	−1	+2	0	+2
Did the reaction reappear when given a placebo?	−1	+1	0	0
Has the drug been detected in blood (or other bodily fluids) at doses known to be toxic?	+1	0	0	0
Did the observed reaction become more severe when the dose of the drug was increased and decreased when reduced?	+1	0	0	0
Did the patient develop similar reactions to the same or similar drugs in their previous exposures?	+1	0	0	0
Has the side effect been verified with objective evidence?	+1	0	0	0
aTotal score:				8

Naranjo's adverse drug reaction probability scale; total scoreis evaluated as a doubtful drug reaction when ≤0; possible drug reaction when 1-4; probable drug reaction when 5-8; and definite drug reaction when 9-13. This was taken from the 12th source.

and general condition disorder. The patient who also had diabetes, hypertension, heart failure, and suffered from depression was receiving erythropoietin, calcium acetate, acetyl salicylic acid, clopidogrel, cinacalcet, sertraline, and insulin treatment. During the examination, the fever was 38.3°C, the tonsils and pharynx were natural, and there were rales in bilateral lung basals. Laboratory tests showed the following results: White blood cell (WBC) 8970/mm^3; hemoglobin, 10.8 g/dL; platelet count, 173000/mm^3; C-reactive protein, 134 mg/l (N: 0-5); procalcitonin, 4.3 ng/mL (N: 0-0.1); Blood ureae nitrogen, 39 mg/dL; creatinine, 4.3 mg/dL; sodium, 140 mEq/L; potassium, 3.7 mEq/L.

Pneumonia was considered in the patient who presented with infiltration areas in the right lung on the chest X-ray. First, ceftriaxone at a dose of 2×1 gram was administered intravenously. At the 48th hour of the fever, the treatment was changed to 3×2.25 grams of piperacillin-tazobactam. The next day, 2×500 mg, intravenous clarithromycin was added to the treatment. Four hours after the administration of the clarithromycin dose, the patient developed a change in consciousness, audiovisual hallucinations, dizziness, and panic state. Blood pressure and blood glucose were normal. Blood electrolyte levels were also normal. The patient was consulted by the Department of Neurology because of the sudden onset of pathology, and brain tomography and diffusion magnetic resonance imaging (MRI) were requested. Brain tomography and diffusion MRI showed no acute pathology. The patient's complaints decreased after a few hours. After the administration of the clarithromycin dose the following day, the complaints began again. As the current neurological findings developed after the initiation of clarithromycin therapy, Naranjo's adverse drug side effect probability scale was used to assess the condition (Table 1). Since our patient's score was 8, it was considered as a possible drug reaction. When clarithromycin treatment was discontinued, the patient's complaints regressed dramatically. His pneumonia was improved, and he was discharged with recommendations. Informed consent was received for this study.

DISCUSSION

Clarithromycin is used in patients with renal insufficiency since it has a significant hepatic elimination. Here neuropsychiatric symptoms of patients on hemodialysis who were treated for pneumonia were associated with clarithromycin. Clarithromycin is an effective macrolide antibiotic with a broad antimicrobial spectrum. In practice, it is usually used alone or in combination in sinusitis and lower extremity infections. With oral bioavailability and high tissue penetration, there is a longer elimination half-life than the parent compound, erythromycin. Maximum serum concentrations can be obtained 2 hours after the start of treatment (1). Most of the clarithromycin is eliminated from the liver. The most common side effects include gastrointestinal disorders. This is followed by hepatic cholestasis, allergic skin rashes, tinnitus, and temporary or irreversible deafness. In intravenous use, it can cause vascularity and thrombophlebitis (1, 2).

Neuropsychiatric complaints can rarely be seen during the use of medications. There are over 200 drugs that can cause

Table 2. Summary of drug-related hoigne syndromes in the literature

Author Name and Date of Publication	Patient Group	Drug Name
Guarneri et al. (2017)	Treatment of psoriasis	Meglumine Antimoniate
Thompson et al. (2016)	Use for local anesthesia	Lidocaine
Landais et al.(2014)	Use due to infection	Ceftriaxone
Rallis et al. (2009)	Rosaceadisease	Clarithromycin
Schmied et al. (1990)	Use due to infection	Penicillin G
Dolezalová et al. (1979)	Use due to infection	Penicillin G
Dowbor et al. (1977)	Use due to infection	Penicillin G

psychiatric reactions. Interferon-alpha, antihistamines, cyclosporine, and oral contraceptives are the most commonly associated drugs (7). Although antibiotic-induced psychiatric reactions are rarely seen, in the literature, cases related to clarithromycin are presented as case reports. Hoigne's syndrome (also called antibiomania) is a rare condition that usually develops as an acute psychiatric disorder following the administration of antimicrobials (8). Hoigne's syndrome was first described in 1959 as a mania secondary to penicillin treatment (9). In this syndrome, dizziness, agitation, hallucinations, loss of consciousness and hearing problems can be observed. There are various types of hallucinations (visual, auditory, somatosensory) seen in Hoigne's syndrome (8, 9). Drug-related Hoigne's syndromes in the literature are presented in Table 2.

It should be kept in mind that Hoigne's syndrome may develop in patients receiving clarithromycin therapy. Clarithromycin causes the inhibition of hepatic cytochrome P450 (CYP) CYP3A4 isoenzyme, which may play a role in the induction of psychiatric reactions. In literature, Hoigne's syndrome, which is thought to be related to clarithromycin in patients with renal insufficiency, is limited (10).

The mechanism of Hoigne's syndrome is unclear. Although urea is not associated with visual hallucinations in patients with renal insufficiency, it is likely to strengthen the neurotoxic effects of clarithromycin. A poor kidney function modifies the structure of the blood-brain barrier and increases the central nervous system concentrations of clarithromycin (10). Side effects such as dizziness, vertigo, confusion, insomnia, and tinnitus are seen especially in the elderly with a high dose (1 g twice a day) of clarithromycin (11). Since maximum serum concentrations are reached in a short period of time during the clarithromycin treatment, neuropsychiatric findings may develop shortly after administration. In our patient, symptoms were developed within 3 to 4 hours after the application in a way similar to the cases in the literature. In our patient, the metabolic and central events that explained this table were excluded, and Naranjo's adverse drug reaction probability scale (12) score was 8. In patients with Hoigne's syndrome, the symptoms are rapidly regressing with discontinuation of the drug causing psychiatric disorder. Similarly in our patient, the clinical picture improved rapidly after discontinuation of the drug.

CONCLUSION

Hoigne's syndrome should be kept in mind if psychiatric symptoms develop in patients with renal failure who are going to be treated with clarithromycin.

Informed Consent: Informed consent was received for this study.

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