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ORPHENADRINE INDUCED PSYCHOSIS IN OLDER ADULT: A CASE REPORT

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ABSTRACT
Orphenadrine is an antihistamine agent that has a muscle relaxant, muscarinic antagonist, and an antidyskinesia properties. Hence, it is used in managing musculoskeletal pain and motor control in Parkinson's disease. Orphenadrine enhances its action through central histamine receptors. Some of the side effects of orphenadrine like restlessness, agitation, insomnia, mental confusion, headache, syncope, lightheadedness, tremor, dizziness, and drowsiness have been attributed to its central action. Despite reporting of psychotic symptoms associated with the use of other antihistamine agents like cetirizine, there is a paucity of literature on psychotic symptoms associated with the use of orphenadrine. Orphenadrine is being reported to cause paranoid delusion and auditory hallucination in an older adult.

KEYWORDS: Adult, older, induced, orphenadrine, psychosis.

INTRODUCTION

Orphenadrine is an anticholinergic medication belonging to the ethanolamine antihistamine class. It is structurally related to diphenhydramine.[1] Chemically, it is N,N-dimethyl-2-[(2-methylphenyl)-phenylmethoxy] ethanamine, an amino compound which is also called the phenyl-o-tolylmethyl ether of 2-(dimethylamino) ethanol.[2] In terms of its pharmacological profile, it acts as an N-methy-D-Aspartate receptor antagonist, a histamine 1-receptor antagonist, an antiparkinson medication, a parasympatholytic, a muscle relaxant, muscarinic antagonist, and an antidyskinesia agent.[3]

Orphenadrine is popular in the United States, where it was first authorized for use in 1957.[4] Orphenadrine comes in a number of generic formulations, including 100 mg conventional and extended-release tablets.[4] Additionally, it can be purchased under brand names like X-Otag, Norgesic, Norflex, Deenar, Banflex, and Disipal. The dose in adult is 100 mg every 12 hours and its safety has not been established in children.[3] Its onset of action is 2-4 hours and the duration of action is 4-6 hours.[3] It has 20% protein binding and largely metabolized in the liver with elimination half-life of 14-16 hours.[3]

The use of orphenadrine is associated with adverse effects like dry mouth and gastro-intestinal disturbances.[5] In the central nervous system, restlessness, agitation, insomnia, mental confusion, headache, syncope, lightheadedness, tremor, dizziness, and drowsiness have been reported.[5] In the cardiovascular system, palpitation and tachycardia have also been reported with the use of orphenadrine.[5] The adverse effects of orphenadrine also include blurry vision, mydriasis, and increased intra-ocular pressure.[5]

Orphenadrine is currently administered orally or parenterally to treat acute, painful musculoskeletal disorders.[6] The medication relaxes muscles and helps people with Parkinson's disease maintain motor control.[6] It is prescribed to relieve pain associated with acute musculoskeletal problems in addition to rest, physical therapy, and other treatments. As an anticholinergic, orphenadrine acts mostly centrally and has minimal peripheral effects. It also possesses local anesthetic and modest antihistaminic qualities.[7] Parkinson's syndrome results from an imbalance in dopamine-induced cholinergic and dopaminergic neurotransmission within the basal ganglia.[8] Orphenadrine re-establishes the physiological equilibrium, impacting to control the rigidity and tremor of Parkinson's disease and Parkinsonian syndromes.[9]

The combination of orphenadrine and haloperidol has been evaluated during the treatment of schizophrenia for the potential effects of orphenadrine on extra-pyramidal effect (EPS).[10] The study demonstrated the ameliorating effect of orphenadrine on EPS.[10] Orphenadrine has shown some measure of relief in people with depression.[11] On the other spectrum, non-sustained ventricular tachycardia has been described following the use of orphenadrine.[12] However, its effect in causing or exacerbating psychiatric symptoms has not been elaborately reported in the literature. We, therefore, present a case of acute psychosis following the use of orphenadrine in the management of musculoskeletal pain.

CASE PRESENTATION

A 70-year-old woman, has a diagnosis of chronic lumbago and a medical history of type 2 diabetes, medication induced-gastritis and hypertension. She denied any history of psychiatric illness nor prior use of psychiatric medication. The patient drinks alcohol socially and denied use of any illicit substance. The patient described a stabbing pain of severe intensity, rated 10/10, localized at the lower back, radiating to the lower extremities, transiently relieved by analgesics, and aggravated by exertion. The patient has used diclofenac tablets in the past and also used Ibuprofen tablets which gave transient relief but resulted in multiple episodes of uncomplicated gastritis. These medications belong to the class called Non-Steroidal Anti-inflammatory Drugs (NSAID) that has gastritis as its recognized side effects. The patient also reported history of chronic constipation from chronic use of opioid for the pain management. Radiological imaging studies of the lower back revealed age-related spondylitic changes. Routine blood work revealed elevated Hb A1c (8.1) Other laboratory investigations were unremarkable.

The patient was evaluated by the pain management team comprising the pain physicians, physiotherapist, and the nurses. It was agreed to start patient on Orphenadrine 100 mg PO bid and to apply Transcutaneous Electrical Nerve Stimulation (TENS) for 30 minutes bid to the lower back. The treatment is scheduled for 1 week while the patient is on an inpatient management care for poorly controlled diabetes.

On the first two days of treatment, the patient reported amelioration of pain with pain assessment scores of less than 4 during each assessment. On day 3 of the treatment, the patient gradually developed paranoid delusion and auditory hallucination. Within 24 hours of the new complaints, the management team reviewed the patient. On mental status examination, her thought process was disorganized with illogical speeches. She endorsed paranoid delusions of some people after her to harm her. She reported auditory hallucinations of an unidentified lady talking to her at random. Orphenadrine was discontinued. The patient was continued on TENS and topical diclofenac cream. The paranoid delusion and hallucination stopped within 36 hours after the stoppage of orphenadrine administration. The patient continued to report pain scores of less than 4 during the coming days. Blood work including electrolytes, blood sugar, urea, and creatinine were unremarkable. Cranial CT-scan was unremarkable.

The patient was followed till discharge and she did not report any incident of delusion nor hallucination.

DISCUSSION

In the index case, there was no predisposing factor for psychosis. The patient reported not abusing any substance with psychotic potential. The medication-orphenadrine was administered as an adjunct in the management of the patient's musculoskeletal pain following recorded side effects from the conventional analgesics. Orphenadrine binds to both histamine (H_1) and NMDA receptors. The mechanism by which it causes delusion is not clear. Arguably, the most pleotropic neurotransmitter in the human brain is histamine, histamine contributes to the modulation of delirium's hallmark symptoms.[13] The centrally permeable H_1 and H_2 histamine receptor antagonists have pro-delirium potentials.[13] Hallucinations, anxiety, psychosis, and catatonic stupor are among the psychological side effects of H_1 antihistamines that have been documented.[14] Cetirizine was found associated with delusion and depression in an 18-year-old woman with no prior psychiatric symptoms nor abusing substance.[15] The antihistamine effect of orphenadrine might have accounted for its hallucinating effect.

In another study, cetirizine-induced psychosis was documented in a young adult with erythema multiforme.[16] Cetirizine is a second-generation H1-antagonist that is selective for peripheral H1 receptors, mainly used to treat chronic idiopathic urticaria and allergic rhinitis.[17] Toxic psychosis was also reported in an otherwise healthy patient upon the use of diphenhydramine.[18]

The discontinuance of cetirizine in the young adult with erythema multiforme resulted in the resolution of the psychotic symptoms.[16] The same applied to the index case where the discontinuance of orphenadrine resulted in the clinical resolution of the psychotic symptoms.

In applying the Naranjo Scale,[19] a score of 5 was obtained, which translates to Orphenadrine as likely responsible for the paranoid delusion and auditory hallucination. The Naranjo Scale or Adverse Drug Reaction Probability Scale consists of 10 questions that are answered as either Yes, No, or "Do not know".[19] Different point values (-1, 0, +1 or +2) are assigned to each answer. The questions include: Are there previous conclusive reports of this reaction? Did the adverse event appear after the drug was given? Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? Did the adverse reaction reappear upon readministering the drug? Were there other possible causes for the reaction? Did the adverse reaction reappear upon administration of placebo? Was the drug detected in the blood or other fluids in toxic concentrations? Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose? Did the patient have a similar reaction to the drug or a related agent in the past? Was the adverse event confirmed by any other objective evidence? Total scores range from -4 to +13; the reaction is considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less.[19]

CONCLUSION

This case report prompts clinicians for regular evaluation of patients on an antihistamine medication, especially the older adult patient populations. While orphenadrine has been popular for its action to relax muscles and help people with parkinson's disease maintain motor control, its potential for causing psychiatric symptoms should be further assessed. Early recognition of such adverse effects provides immediate intervention to avoid unnecessary categorization of such patient.

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