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A Case of Serotonin Syndrome with Antidepressant Treatment and Concomitant use of The Herbal Remedy (Peganum Harmala)

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ÖZET:

Antidepresan tedavi ile birlikte bitkisel tedavi (peganum harmala) kullanımı sonucu gelişen serotonin sendromu olgusu

Başka türlü sınıflandırılamayan duygudurum bozukluğu tanısı ile 22 yıldır izlenen, 6 yıldır ketiapin 1000 mg/gün ve fluoksetin 40 mg/gün kullanan 42 yaşında erkek hasta hemoroidini tedavi etmek için üzerlik otu (peganum harmala) aldıktan sonra hastanemizin acil servisine bulantı, kusma, terleme ve titreme şikayetleri ile başvurdu. İlerleyen saatlerde hastada görsel halüsünasyonların eşlik ettiği konfüzyon gelişti ve yönelim kaybı yanısıra ajitasyon gözlendi. Biokimyasal tetkikler sonucu hastada deliryumun diğer olası sebepleri ve nöroleptik malign sendrom (NMS) tanısı dışlandı. Serotonin sendromu tanısıyla hasta yoğun bakım ünitesine yatırıldı. Tüm psikiyatrik tedavisi kesildi ve siproheptadin solüsyon 32 mg/gün, klorpromazin 25 mg/gün, diazepam 30 mg/gün tedavisi başlandı. Bulantı, kusma ve ajite deliryum tablosu 48 saat içinde kayboldu. Denetime tabi olmaksızın aktarlarda satılan bitkisel ilaçlar, bir çok ilaçlarla etkileşmekte, toksik reaksiyonlara yol açmakta ya da tedavide kullanılan ilaçların etkinliğini azaltabilmektedir. SSRI sınıfı antidepresanlar ile bitkisel tedavilerin birlikte kullanımı serotonin sendromu oluşturabilir.

Anahtar sözcükler: Bitkisel tedavi, MAO-A, serotonin sendromu, nöroleptik malign sendrom, deliryum

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ABSTRACT:

A case of serotonin syndrome with antidepressant treatment and concomitant use of the herbal remedy (peganum harmala)

A forty-two-year-old male patient with a 22 year history of mood disorder, not otherwise specified using quetiapine 1000 mg/day and fluoxetine 40 mg/day for the past six years was admitted to the emergency unit with complaints of nausea, vomiting, sweating, and tremor following the ingestion of harmal (peganum harmala) to treat his hemorrhoids. In the following hours the patient developed confusion along with visual hallucinations and became agitated with a loss of orientation. Other possible causes of delirium and neuroleptic malignant syndrome (NMS) were excluded by biochemical analyses. A diagnosis of serotonin syndrome was confirmed and the patient was hospitalized in the intensive care unit. All psychiatric medications were discontinued immediately and cyproheptadine solution 32 mg/day, chlorpromazine 25 mg/day, and diazepam 30 mg/day were initiated. Nausea, vomiting, and agitated delirium were dissolved in 48 hours. Herbal supplements are sold without any control at herb sellers may interact with many medications, thus giving rise to toxic reactions or a decrease in the effectiveness of medications. An interaction between SSRIs and herbal supplements can cause serotonin syndrome.

Key words: Herbal therapy, MAO-A, serotonin syndrome, neuroleptic malignant syndrome, delirium

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INTRODUCTION

Serotonin syndrome (SS) is the result of over stimulation of 5-HT1A receptors by selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) or other serotonergic agents and herbal supplements (St John's wort, ginseng, soya extracts, or food supplements such as S-adenosyl-methionine) (1-4). SS is characterized by a triad of mental (confusion, elevated mood, coma or semicoma, agitation, nervousness, insomnia) autonomic (fever, hyperhidrosis, tachycardia, tachypnea and dyspnea, diarrhea, low and high blood pressure), and neurological (myoclonus, tremors, chills, rigidity, hyperreflexia, impaired coordination, mydriasis, and akathisia) symptoms (1-4).

Peganum harmala, also known as harmal or Syrian rue, is used as a traditional herbal remedy (5-7). The pharmacologically active compounds of P. harmala include a number of b-carboline and quinazoline alkaloids. Harmaline, harmine, harmalol, harmol, and tetrahydroharmine have been identified and quantified as the main b-carboline alkaloids in P. harmala extracts. Harmine and harmaline are competitive and reversible inhibitors of monoamine oxidase type-A (MAO-A) enzymes, whereas tetrahydroharmine is believed to inhibit serotonin uptake (8). B-Carbolines may modulate the levels of amine neurotransmitters in the CNS (9) and exhibit a wide range of psychopharmacological effects because of their binding to benzodiazepine, imidazoline, serotonin, and opiate receptors (10-11). We present here an SS case with the concomitant use of psychotropic drugs and harmal.

CASE

A 42-year-old male patient, with a 22 year history of mood disorder, not otherwise specified (NOS) along with a family history of schizophrenia in his brother, had been using quetiapine 1000 mg/day and fluoxetine 40 mg/day for the past six years. The patient had no history of alcohol or drug abuse but he was taking thyroid replacement therapy for hypothyroidism. The patient was admitted to the emergency unit with complaints of nausea, vomiting, sweating and tremor two hours after taking one spoonful of harmal (peganum harmala) to treat his hemorrhoids. In the following hours the patient developed confusion and became agitated. Neurological examination revealed clear consciousness, limited cooperation, fluctuating orientation to time, place, and person, and bilateral mydriasis. No signs of meningeal irritation or paresis were present. Plantar reflexes were flexor bilaterally and deep tendon reflexes were hyperactive. Cranial computerized tomography (CT) imaging revealed no abnormality. Lumbar puncture was planned to exclude a central nervous system (CNS) infection but delayed in the face of the patient's agitation. Arterial blood pressure was 130/65 mmHg with a hearth rate of 99 /minute. Respiration rate and body temperature were in the normal range. A blood count showed no abnormality. Blood analysis showed some abnormalities in calcium, potassium, c-reactive protein (CRP) (8.2 mg/dl, 3.4 mmol/L, and 15.6 mg/L, respectively). Arterial blood pH was 7.47, $p0_2$ was 98 mmHg, pCO_2 was 28 mmHg, HCO was 20 mmol/L and SPO_2 was 98%. The patient developed a hyperactive delirium with loss of orientation along with visual hallucinations. The diagnosis of SS was confirmed and patient was transferred to intensive care unit (ICU). All psychiatric medications were discontinued immediately and hydration at a rate of 100 cc/hour intravenously was initiated and cyproheptadine 8 mg four times a day was started. Chlorpromazine 25 mg/day im and diazepam 30 mg/day po were added to eliminate agitation. The vomiting, nausea and agitated delirium were resolved in the following 24 hours. The patient was discharged after 48 hours.

DISCUSSION

An herb can be any form of a plant or plant product, including leaves, stems, flowers, roots, and seeds. These plants can either be sold raw or as extracts, where the plant is macerated with water, alcohol, or other solvents to extract some of the chemicals. The resulting products contain dozens of chemicals, including fatty acids, sterols, alkaloids, flavonoids, glycosides, saponins, and others (12). This broad spectrum of molecular content is associated with increased risks of drug interactions.

Fluoxetine and quetiapine were prescribed concomitantly in this case. Prolongation of QT and Torsade de Pointes have been reported in a few cases in association with the use of newer antipsychotic drugs (mainly quetiapine and amisulpride), most of the tri- and tetracyclic antidepressants, and the selective monoamine reuptake inhibitors citalopram, fluoxetine, paroxetine, and venlafaxine (13). For this reason concurrent use of fluoxetine and antipsychotics is not recommended.

In the physical examination there was no sign of spontaneous or inducible clonus/ocular clonus in this case, although tremor and hyperreflexia were present. Symptoms emerged 2 hours after the ingestion of harmal and resolved in 48 hours. As reported in literature, SS has a relatively rapid onset in a few minutes or hours when related to drug interactions. Symptoms and signs of harmal toxication have been reported to resolve in a few hours in limited case reports (14). Harmal's reversible MAO inhibition could be the leading factor in the resolution of signs in the case. Peganum harmala is an CYP2D6 inhibitor (15), and fluoxetine is a substrate and inhibitor of CYP2D6 (16). For that reason peganum harmala may elevate serum

concentrations of fluoxetine leading to SS. The principal differential diagnosis was neuroleptic malignant syndrome (NMS) (1-3). NMS may emerge at any time of antipsychotic use but typically is seen 24-72 hours after the initiation of antipsychotics or after a dose increase. There was no history of a dose increase in the case or the other signs of NMS including bradykinesia, akinesia, muscle rigidity, hyperthermia, fluctuation of consciousness, autonomic instability, leukocytosis, or an increase in serum creatine phosphokinase. There was no other cause to explain patient's clinical findings such as a metabolic abnormality or infection. The possible mechanism giving rise to SS in this vignette was the inhibition of MAO thus leading to higher doses of serotonin in the CNS in the presence of fluoxetine. The antihistamine cyproheptadine, which is also a 5-HT2A inhibitor, should be considered for treatment in moderate cases and is recommended in severe cases, despite a lack of randomized controlled trial evidence (17). Clinicians should be aware of such interactions between herbal remedies and psychotropic drugs.

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