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BILATERAL PEDAL EDEMA ASSOCIATED WITH OLANZAPINE TREATMENT: A CASE REPORT

OLANZAPİN TEDAVİSİ İLE ORTAYA ÇIKAN BİLATERAL AYAK BİLEĞİ ÖDEMİ: BİR OLGU SUNUMU

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Abstract

Peripheric edema could be caused by various medical conditions as well as pharmacologic agents such as antihypertensives, nonsteroidal antiinflamatory drugs, endocrine agents and immunotherapies. Olanzapine is an atypical antipsychotic that is widely prescribed for the treatment of schizophrenia and bipolar affective disorder. Most common adverse reactions of olanzapine are weight gain, postural hypotension, constipation, dizziness, akathisia, sedation. Peripheral edema was reported as an infrequent side effect, which affected 3% of the olanzapine treated patients.

In this report, we aim to draw attention of psychiatrists on this rare adverse effect by presenting a 56-year-old case, who applied to our hospital with severe depressive and obsessive-compulsive symptoms and hospitalized because of suicide risk. Before psychiatric admission, he wasn't taking any medication. He was diagnosed as major depression with psychotic features and obsessive-compulsive disorder. He was started on olanzapine 10 mg/day, quetiapine 300 mg/day and fluoxetine 40 mg/day. Two weeks after initiation of olanzapine, he was found to have bilateral pedal edema without ulceration and temperature change but minimal redness was observed. He had no history suggestive of cardiac, renal and liver dysfunction or allergic reaction against to any drug that could explain his existing edema. Possible medical conditions which may cause edema were ruled out by laboratory tests and physical examination. Olanzapine was stopped immediately and the therapy was modified to risperidone 1 mg/day. After discontinuation of olanzapine, edema was gradually resolved within two weeks.

Because olanzapine associated edema has been seen rarely, it could be overlooked by psychiatrists in comparison to its more common side effects. Although it shows self-limited and benign course, patients may feel discomfort and their compliance to treatment may decrease. Also, it may interfere with differential diagnosis of other medical conditions which may cause edema. In conclusion, we suggest that patients should be observed carefully for edema during olanzapine treatment.

Keywords: Olanzapine, Peripheric Edema, Side Effect

Özet

Periferik ödem çeşitli tıbbi hastalıkların yanı sıra antihipertansifler, nonsteroidal antiinflamatuarlar, endokrin ilaçlar ve immünoterapiler gibi farmakolojik ajanlarla ortaya çıkabilir. Olanzapin şizofreni ve bipolar mizaç bozukluğu tedavisinde sıkça reçetelenen bir atipik antipsikotiktir. En sık yan etkiler kilo alımı, postural hipotansiyon, kabızlık, başdönmesi, akatizi ve sedasyon olarak bildirilmiştir. Periferal ödem, olanzapinle tedavi edilen hastaların %3'ünü etkileyen nadir bir yan etki olarak bildirilmiştir.

Bu yazıda, şiddetli depresif ve obsesif kompulsif belirtiler ile hastanemize başvuran ve intihar riski nedeniyle yatırılan 56 yaşında bir olgu sunularak, bu nadir yan etkiye psikiyatristlerin dikkatini çekmek amaçlanmıştır. Psikiyatri başvurusu öncesinde hastanın herhangi bir ilaç kullanımı yoktur. Hastaya psikotik özellikli major depresyon ve obsesif kompulsif bozukluk tanısı konmuştur. Tedavisine olanzapin 10 mg/gün, ketiyapin 300 mg/gün ve fluoksetin 40 mg/gün ile başlandı. Olanzapin başlandıktan iki hafta sonra, ülserasyon ve ısı değişikliği olmaksızın, minimal kızarıklıkla bilateral ayak bileği ödemi geliştiği gözlendi. Hastada ödemi açıklayabilecek, kalp, böbrek ve karaciğer yetmezliğini ya da bir ilaca alerjik reaksiyonu düşündüren öykü yoktu. Ödeme neden olabilecek olası tıbbi durumlar fizik muayene ve laboratuar testleri ile dışlandı. Olanzapin hemen kesildi ve risperidon 1 mg/gün tedavisine geçildi. Olanzapinin kesilmesinden sonra ödem iki hafta içinde giderek geriledi.

Olanzapinle ilişkili ödem, nadir görülmesi nedeniyle, psikiyatristler tarafından daha sık görülen yan etkilere kıyasla ihmal edilebilir. Kendini sınırlayan ve iyi huylu bir gidişi olmasına rağmen, hastalarda rahatsızlık yaratabilir ve tedaviye uyumlarını azaltabilir. Ayrıca, ödeme neden olabilecek diğer tıbbi durumların ayırıcı tanısını zorlaştırabilir. Sonuç olarak, olanzapin tedavisi süresince hastaların ödem açısından dikkatle izlenmesi yararlı olacaktır.

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1. Introduction

Edema is defined as a clinically apparent increase in the interstitial volume. Peripheric edema could be caused by various medical conditions, such as obstruction of venous or lymphatic drainage, congestive heart failure, nephrotic syndrome and other hypoalbuminemic states, cirrhosis and medication. Common pharmacologic agents known to cause edema are antihypertensives, nonsteroidal antiinflamatory drugs, endocrine agents and immunotherapies (Braunwald and Lascalzo, 2012). Olanzapine is a potent atypical antipsychotic that is widely prescribed for the treatment of schizophrenia and bipolar affective disorder. It does have antagonist properties at dopaminergic (D1,D2,D3), muscarinic (M1,M2), histaminergic (H1), seratonergic (5-HT2A,5-HT2C, 5-HT3,5-HT6) and adrenegic (alpha 1) receptors (Stahl, 2010). Although olanzapine is superior to typical antipsyhotics in its rare extrapramidal symptoms, it may lead to a significant weight gain and may impair glucose metabolism like other second generation antipsychotics (Al-Zoairy et al., 2013). Most common adverse reactions of olanzapine (≥5% and at least twice that for placebo) are weight gain, postural hypotension, constipation, dizziness, akathisia, sedation, headache, increased appetite, abdominal pain, extremity pain, fatigue, dry mouth, asthenia, tremor. According to premarketing trials, peripheral edema was reported as an infrequent side effect, which affected 3% of the 532 olanzapine treated patients, as compared to 1% of the 294 subjects on placebo (Lilly, 2005). There is limited information about peripheral edema associated with olanzapine in the literature. Because olanzapine associated edema shows self-limited and benign course, it could be overlooked by psychiatrists when compared to other side effects.

In this article, we report a case with bilateral pedal edema due to olanzapine treatment in order to draw attention of psychiatrists on this neglected side effect. Informed consent was obtained from the patient for this case report.

2. Case

56-year-old single, college educated male, was presented to our hospital with severe depressive symptoms for four months and obsessive-compulsive symptoms comorbid with hypochondriac concerns for two years. He was hospitalized to inpatient unit because of suicide risk on the same day. Before psychiatric admission, he wasn't taking any medication. He was diagnosed as major depression with psychotic features and obsessive-compulsive disorder with poor insight. He was evaluated also with Brief Psychiatric Rating Scale (BPRS) and total score on it was 34. He was started on olanzapine 10 mg/day, quetiapine 300 mg/day and fluoxetine 20 mg/day and titrated to 40 mg/day in a week. Two weeks after initiation of olanzapine treatment, the patient noticed bilateral swelling in his ankles which was more prominent on the left foot. Edema was barely evident on inspection and gradually worsened to grade 3 (following skin depression, indentation returns to normal 20-25 seconds) over the next 3 days at the 10 mg daily dose of olanzapine. There was no ulceration and temperature change but minimal redness was observed on the both edematous area (Figure 1). He had no history

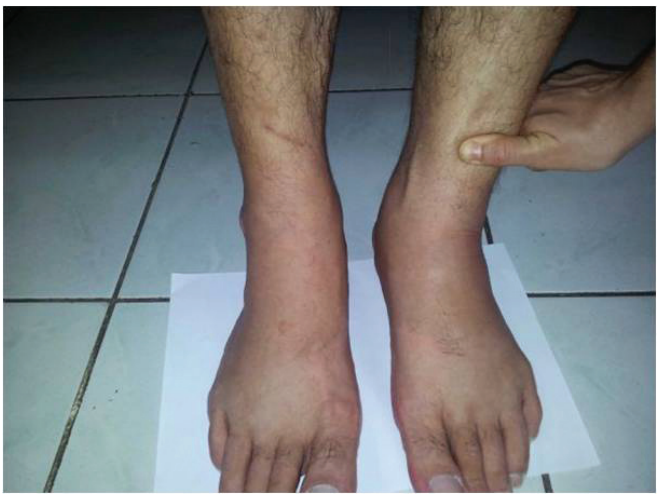

Figure 1: Minimal redness observed on the both edematous area.

suggestive of cardiac, renal and liver dysfunction or allergic reaction against to any drug that could explain his existing edema. He was evaluated by internalist to investigate the etiology of edema. Results of chest x-ray examination, echocardiography, complete blood count, electrolytes, chemistery profile and thyroid (TSH, f T3, f T4), renal (urea, creatinine), liver function (AST, ALT, GGT, alkaline phosphatase, total protein and albumin) tests were within normal limits. According to test results and consultation by internalist, all medical causes of edema were ruled out except for medication. Olanzapine was discontinued on day 15 and the therapy was modified to risperidone 1 mg/day. The edema regressed gradually within ten days without any medical intervention except for foot elevation and salt restriction in diet. At the end of hospitalization period of approximately 3 weeks, he showed substantial improvement in his depressive mood and was able to control his compulsive behaviours. The patient's obsessive thoughts was partly regressed. He had minimal edema, grade 1. He was discharged with risperidon 1 mg/day, fluoksetin 40 mg/day and seroquel 300 mg/day on day 22 and adviced to come for follow up one week after discharge. On subsequent follow up, 20 days after cessation of olanzapine, it was learn that his mood was euthymic, he has used same medication regularly and the edema did not recur. His BPRS score was 3. His laboratory tests (complete blood count, liver and renal function tests) were normal. It was seen that the edema resolved completely in physical examination.

3. Discussion

The case mentioned above was evaluated as olanzapine associated pedal edema because that edema gradually dissolved when the drug was discontinued. Also the absence of any systemic disease, clinical and laboratory findings explaining edema have supported our opinion. The mechanism of peripheral edema caused by olanzapine remains uncertain. It has been thought that this adverse effect related to olanzapine was attributed to its receptor profile. There are several possible hypotheses in the literature. Firstly, olanzapine antagonizes alpha-1 (α1) adrenergic receptors, resulting in peripheral vasodilation and decreased vascular resistance, which leads to edema (Ng et al., 2003). Secondly, stimulation of muscarinic

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(M1), histaminic (H1), serotonergic (5-HT2) receptors result in activation of Inositol 1-4-5 triphosphate (IP3) and diacylglycerol (DAG) post-receptor pathway. Increased IP3 leads to rapid calcium release by binding endoplasmic reticulum (ER). Calcium released from ER causes activation of ATP-dependent calcium pump. Blockage of these receptors by olanzapine inhibits the physiological increase in IP3, that causes downregulation of ATP- dependent calcium pump, ultimately resulting in smooth muscle relaxation and then vasodilation and edema (Katzung and Trevor, 1998). Thirdly, increased intracellular cyclic adenosine monophosphate levels due to blockage of HT2 recetors by olanzapine causes smooth muscle relaxation (Ganong, 1999). This mechanism is thought to be also involved in quetiapine associated edema (McSkimming et al., 2012). Previously, correlation between high plasma concentration of cAMP and idiopathic edema has been shown (Kuchel et al., 1975). Another mechanism, peripheric dopaminergic blockage by olanzapine might change renal regulation of fluid and electrolyte balance, resulting in edema. Finally, an allergic reaction against to olanzapine has been suggested as the cause of olanzapine induced edema. Although, in that case, immunoglobulin levels have been normal, allergic mechanism between the limb edema and olanzapine have been proven with histopathological findings and moderate eosinophilia (Honma et al., 2012). Similarly, Terao et al. (1988) and Conney and Nagy (1995) have explained the risperidone associated edema by allergic pathways.

In our case, as in the others in the literature, olanzapine was stopped after the development of edema and edema did not recur with risperidone treatment. These cases suggest that underlying pathophysiological mechanisms of olanzapine and risperidone associated edema may be different from each other. In addition to this hypothesis, the literature has reported that risperidone related edema could be dose-dependent and seen mostly (6 of 9 cases), in co-medication with valproic acid, benzodiazepine and / or dopamine receptor antagonists. According to the literature, there have been 14 cases of edema associated with olanzapine. In some of these cases, olanzapine was used in combination with valproic acid, albuterol, theophylline citalopram, benzodiazepine, gabapentin, bupropion. But, the edema had been attributed to olanzapine in these combined therapies. In our case, olanzapine was combined with quetiapine and fluoxetine simultaneously. Previously, quetiapine associated edema have been reported in a few cases (Kovela et al., 2009; McSkimming et al., 2012). Among them, one case documented that recurrence of the edema with quetiapine was seen after cessation of olanzapine (Kovela et al., 2009). In our case, the combination of olanzapine with quetiapine may have contributed this patient to developing edema. If considering their similar molecular structure and affected receptor groups between quetiapine and olanzapine, increase in the risk of developing edema is expected. Although quetiapine was continued at the same dosage, regression of edema gradually after discontinuing olanzapine showed that olanzapine was strongly the offending agent. According to former cases, edema has emerged as dose-dependent and at the dosage of 2.5-20 mg/day . In our case also, olanzapine dosage was consistent with the literature. In a case report, furosemide was started to treat the edema instead of stopping olanzapine (Deshauer et al., 2006). Although furosemide is effective in the treatment of olanzapine associated edema, there is not enough data on the long-term efficacy or safety of this intervention. After considering the alternatives, we preferred stopping possible agent, adviced the patient to leg elevation and salt restriction without any diuretic usage in the management of edema.

In a study, Ng et al (2003) have found that the frequency of edema in patients treated with olanzapine was 57 % of 49 patients. Of these patients, 10.2% had severe edema (Ng et al., 2003). The results of this study has contrasts with an incidence of 3% as reported in premarketing trials (Lilly, 2005). The discrepancy between this study and documented limited case reports suggests that milder cases of pedal edema may remain unrecognized as the complication of olanzapine. Because olanzapine associated edema has benign and self-limiting course , it could be overlooked by patients and psychiatrists in comparison to its more common side effects and appears less than actual incidence. Although it seems innocuous, patients may feel discomfort and their compliance to treatment may decrease especially in severe edema. Also, it may interfere with differential diagnosis of other medical conditions which may cause edema. In conclusion, we suggest that patients should be observed carefully and edema examination should be made by psychiatrists during olanzapine treatment in order to recognize this neglected side effect.

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