

Pre-Tibial Edema Associated with Quetiapine: Five Case Series

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Abstract

It is known that edema is a rare side effect of quetiapine. Until now only nine cases of peripheral edema related to quetiapine have been reported in the literature. We have determined five cases of pretibial edema associated with quetiapine during two years period of time. The common feature of these cases reported here are comorbid medical disorders, such as venous insufficiency, bladder tumor, chronic obstructive pulmonary disease, diabetes mellitus with excessive elevation of blood sugar. Although treatment protocol of edema and those comorbid medical diseases have been applied separately, at the end of these treatments it is seen that PTE has not been resolved. In all cases reported here that when the dose of quetiapine is reduced, it is observed that PTE is reduced or disappeared. This result brings to mind that there could be a relation between edema and quetiapine.

Introduction

Peripheral edema could be occurred due to various reasons such as liver cirrhosis, kidney diseases, congestive heart failure, systemic diseases such as cancer, protein deficiency, prolonged immobilization, non-steroidal anti-inflammatory drugs, steroids, and the use of some antihypertensive drugs [1,2]. Moreover, edema due to antipsychotic use is a rare side effect [3-9]. Although sedation, headache, weight increase, dry mouth and dizziness are among the most common side effects of quetiapine [10], there have been only a few case reports of edema related to quetiapine [8,11-16]. The etiology of this adverse effect has not been explored yet. It is recommended that new studies and case reports would be improved for our understanding of the causes of edema related with quetiapine. In this report, it is presented that five cases of Pre-Tibial Edema (PTE) due to quetiapine usage and associated literatures.

Case 1

A 57-year-old male patient was admitted to our clinic with a diagnosis of Bipolar Disorder-1(BD) - depressive episode, with rapid cycling according to the DSM-IV-TR. He had discontinued his drug regimen 10 days ago, in admission. Valproic acid 1000 mg/day, quetiapine XR 400 mg/day and clonazepam 1 mg/day was administered. Valproic acid dose was titrated to a dose of 1750 mg/day in two weeks because of 60 µg/ml valproic acid blood level. Bilateral 3+ PTE was found on the 37th day of admission. Complete blood count, thyroid function tests, liver function tests, electrolytes, albumin, total protein, and renal function tests were within normal limits. There was no history of any physical disease. Minimal pericardial effusion and venous insufficiency (varicosis) were found as a result of medical evaluations. Oxerutin 1000 mg/day for venous insufficiency, Ibuprofen 1200 mg/day for pericardial effusion was started with the recommendation of cardiologist. Pericardial effusion did not improve following Ibuprofen; therefore Ibuprofen was discontinued during follow-up. The edema did not resolve despite treatment of venous insufficiency. By the cardiologist, edema was thought to be related with psychotropic drugs. So the quetiapine was gradually decreased and discontinued. PTE disappeared on the 21st day after quetiapine discontinuation.

Case 2

A 62-year-old male patient was admitted to our clinic with a diagnosis of BD- manic episode according to the criteria of DSM-IV-TR. The patient had no known previous manic or depressive episode. Organic etiology was investigated because of late onset of BD. Magnetic Resonance Imaging and Electroencephalography was normal. He had a history of alcohol use for 30 years and had quit alcohol 2 years ago but had started to use alcohol again in the last 2 months. The patient was admitted to the clinic for insomnia, excessive spending, making new business plans, seeing himself as the chosen one, abusive speeches, and hearing voices giving orders. B12 vitamin as cyanocobalamin

ampoule 1000 mcg/day intramuscular was administered for 3 days as the Vit. B12 level was 173 ng/ml. Quetiapine 150 mg/day, lorazepam 1 mg/day if needed was administered. Zuclopenthixol acuphase ampoule 50 mg intramuscular was administered to the patient when he became agitated. Valproic acid 250 mg/day was started on the 25th day and was titrated to a dose of 1500 mg/day on the 41st day of admission. The blood valproic acid level was 69 µg/ml. The quetiapine dose was slowly increased to a dose of 800 mg/day on the 31st day of admission. Bilateral 3+ PTE was found on the 33rd day of admission. Complete blood count, thyroid function tests, liver function tests, electrolytes, albumin, total protein, and renal function tests were within normal limits. Doppler ultrasonography was normal. The patient had symptoms of coughing and sputum production. The diagnosis was Chronic Obstructive Pulmonary Disease (COPD). Acetyl cysteine suspension 600 mg/day and ceftriaxone 2 gm/day intramuscular were recommended. A low salt diet and furosemide ampoule 20 mg/day were recommended as the PTE continued. The edema did not resolve despite furosemide and treatment of COPD. The quetiapine dose was gradually decreased and discontinued. PTE disappeared on the 12th day after quetiapine discontinuation.

Case 3

A 50-year-old female patient was admitted to the clinic due to BD-1, depressive episode according to the DSM-IV-TR and was using Valproic acid 1500 mg/day, Lamotrigine 100 mg/day and Quetiapine 200 mg/day. She has been using quetiapine for 3 months. She had a history of hypothyroidism, Hypertension (HT), and Diabetes Mellitus (DM) and was using Levothyroxine sodium 0.15 mg/day, calcium dobesilate 1000 mg/day, gliclazide 30 mg/day, perindopril arginine 5 mg/day and zinco 50 mg/day. Her physical examination revealed bilateral 2+ PTE. Oxerutin 1000 mg/day, 50 g diclofenac diethyl ammonium emulgel, and chondroitin polysulfate cream treatment were started by cardiovascular surgeon after venous insufficiency was revealed by venous Doppler ultrasonography. Acetylsalicylic acid 100 mg/day and furosemide 40 mg twice a week were recommended for PTE. Proteinuria and 1+ hematuria were found on urinalysis. Blood albumin levels were found to be low (total protein: 6 g/dL, albumin: 3.4 g/dL). Abdominal ultrasonography revealed a 26x17 mm bladder mass. The mass was considered to be a malignancy. The edema did not resolve despite furosemide and treatment of venous insufficiency. The quetiapine dose was reduced to a dose of 100 mg/day. The PTE decreased on the 14th day of reducing the dose of quetiapine.

Case 4

A 65-year old male was an inpatient being treated for BD-manic episode due to Cerebrovascular Event (CVE). The patient had a history of three CVE's in the last nine years with the last one about three months ago and history of an epileptic episode after CVE. Irritability, aggression, insomnia, increased speech, movement acceleration, and increased shopping and sexual desire had developed 1 to 2 days after the third CVE. At the time of admission, he was using quetiapine 125 mg/day for one month, clopidogrel hydrogen sulphate 75 mg/day, levitracetam 1000 mg/day. The levitracetam was gradually decreased and discontinued. On the 7th day of admission, Valproic acid was started because of its mood stabilizer and antiepileptic effects. The dose was gradually increased to a dose of 1250 mg/day in twenty days and the blood level was 94 µg/ml. For the presence of manic symptoms, dose of quetiapine was increased.

PTE was noticed just after increasing the dose of quetiapine to 300 mg/day, on the 6th day of admission. Complete blood count, thyroid function tests, liver function tests, electrolytes, albumin, total protein, and renal function tests were within normal limits. Chronic venous insufficiency and left carotid artery stenosis were found. Tripterten glycoside, containing horse chestnut extract, 100 mg/day and chondroitin polysulfide cream twice a day were started for chronic venous insufficiency. PTE increased from bilateral 2+ to 3+ when the quetiapine dose was increased from 300 mg/day to 400 mg/day. 3+ PTE continued, although he was treated for venous insufficiency. Considering that the PTE could be related to quetiapine, the dose of quetiapine was gradually decreased to 225 mg/day and the PTE significantly decreased on the 13th day of decreasing quetiapine. Minimal PTE continued.

Case 5

A 46-year-old female patient was admitted to the clinic due to mild mental retardation and psychotic depression. Quetiapine 300 mg/day and escitalopram 10 mg/day (increasing to 20 mg/day) were started. She had a history of Diabetes Mellitus (DM) and was treated with gliclazide 30 mg/day and metformin HCl 1700 mg/day. PTE was found on the 32nd day of the admission. The patient was found to have put on 10 kg of weight in the first month of her admission. The glucose level was 97 mg/dl at admission and 252 mg/dl at the end of the month. Metformin HCl was increased to 2550 mg/day due to the elevation in the blood sugar. Blood sugar regulation was provided. Furosemide 40 mg/day was started. Despite furosemide treatment, edema continued with the same intensity. Considering that edema could be due to quetiapine, so the quetiapine dose was decreased to 200 mg/day and a significant decrease was found in the PTE on the 7th day.

Discussion

Although in all cases defined medical cure protocol for edema is given to patients, edema has not been resolved. But after the reduction dose of quetiapine, it is observed that the edema is decreased. This result brings to mind an idea that there is a relationship between quetiapine and edema.

Medical disorders are found in our cases after PTE, such as venous insufficiency in cases 1,3,4, bladder tumor in case 3, chronic obstructive pulmonary disease in case 2, excessive elevation of blood sugar of the patient with DM in case 5. Despite furosemid and the treatment of these medical conditions, there are any changes in edema. There upon it is thought that edema could be related with drugs. After discontinuation of quetiapine, PTE is disappeared within 21 days in case 1 and 12 days in case 2. It is preferred to decrease the dose of quetiapine in cases 3,4 and 5, because of beneficial effects for psychiatric status. The PTE is reduced within 7-14 days in all these three cases. The reduction of the edema by decreasing the dose of quetiapine made us think about the relationship between quetiapine and edema. In case 3, bladder tumor and venous insufficiency are detected. Edema associated with malignancy and venous insufficiency cannot be ruled out. However, there were any changes with the additional treatments for PTE. Decreasing the dose of quetiapine from 200 mg/day to 100 mg/day resulted with the reduction of the edema from 2+ to trace within 2 weeks, in case 3. No precise mechanism has been identified for atypical antipsychotic associated edema; however, several possibilities have been suggested. They may

produce edema by increasing vascular permeability, which is similar to the pathophysiology involved in edema due to inflammation and cell injury [17]. In the presence of an underlying medical condition which leads to an inflammatory process in the veins, such as DM [18], CVE [19], COPD [20] and bladder tumor [21], quetiapine may have facilitated the emergence of edema. In our all cases, edema did not resolve with the treatment of medical disorders. The PTE reduced or disappeared only the reduction of the dose or discontinuation of quetiapine, in all cases reported above. In the literature, it is suggested that pedal edema associated with atypical antipsychotic medications does not require any additional treatment; either reduction of the dosage or switching to a different medication is usually sufficient. In our all cases, there is a similar condition [8].

Most of our cases had combined drug use for a medical condition and the psychiatric disorder. Each case was using a different combination of drugs for his/her medical conditions, making it impossible to discuss these drugs in relation to the edema. The disappearance of the edema after the quetiapine was decreased or discontinued indicates that the edema could be related to quetiapine. Most of the cases about this relation reported in the literature those were being treated with combined drugs due to medical conditions or psychiatric disorders [13,15]. McSkimming et. al. reported that the combination of valproate and quetiapine may lead to susceptibility to edema development in their case report [13]. It is reported that the effect and side effects of quetiapine are more dependent on the real plasma concentration of the active drug rather than the recommended dose and that the plasma concentration of quetiapine increases 77% when used together with valproate, thus, increasing the risk of side effects [22]. We could not evaluate the plasma level of the active drug of quetiapine, in all cases.

The age range of our cases were 46 to 65 years. Most of the cases reported in the literature were similarly in over 40 years of age group [11-14]. Advanced age is suggested as an important factor in decreasing the hepatic activity of CYP3A4, an enzyme metabolizing quetiapine, and leading to a higher plasma quetiapine concentration in the literature [22]. Advanced age in our patients may have contributed to the edema.

Many mechanisms could play a role in the development of edema due to quetiapine. Quetiapine antagonizes alpha-1 adrenergic receptors, causes peripheral vasodilation and increased capillary hydrostatic pressure, and eventually causes fluid to pass into the interstitial area. It also blocks 5-HT₂ receptors, increases intracellular cyclic adenosine monophosphate levels and causes relaxation of smooth muscles [23]. It inhibits muscarinic-1, histaminergic-1 and 5-HT₂ receptors and inhibits the increase of inositol triphosphate, which plays a role in the mobilization of intracellular calcium stores necessary for smooth muscle contraction. It is thought to be able to cause smooth muscle relaxation, vasodilatation and edema in this way [15]. Another alternative explanation for drug-related edema is an allergic reaction. Edema related to the elevation of Ig E, C3, C4 has been suggested as the most probably explanation in a case where ziprasidone-related edema was reported [24]. The sudden start of edema in cases developing edema due to quetiapine in the case series reported by Koleva et al. was thought to indicate a possible allergic mechanism [14]. It was suggested that an Immunoglobulin E (IgE)-mediated allergic reaction can cause relaxation in smooth muscles and lead to quetiapine-related edema [14,16]. Ig E levels were

unfortunately not evaluated in our cases.

It is suggested that clinicians should be aware of the relation between edema and quetiapine. Cases reported here have advanced age and comorbid medical conditions. Despite the treatment of comorbid medical conditions in the reported cases above, edema didn't resolve and it resolved with the reduction of the dose or cessation of the quetiapine. Performing a detailed physical examination, taking drug interactions into account and investigating whether another medical disease has been added to the background are recommended in cases using quetiapine that develop PTE. In addition, although comorbid medical conditions, the edema that may be associated quetiapine should be kept in mind. On the contrary to the above written explanations, it could be thought that the addition of any new unexplored medical conditions might have been facilitated the emergence of edema. In future studies, these possibilities should be taken in to consideration. We hope this article will help physicians to be aware of this potential vascular complication earlier.

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