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VALPROATE-QUETIAPINE INDUCED PERIPHERAL EDEMA

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INTRODUCTION

Atypical antipsychotics are widely used in the treatment of schizophrenia, bipolar disorder and other psychiatric disorders. However, antipsychotics have side effects such as myocarditis, QTc interval prolongation, neuroleptic malignant syndrome, and extrapyramidal effects. Rare side effects associated with antipsychotic drug use are increasingly reported in the literature. Pretibial edema is one of those rare drug reactions. Bilateral pretibial edema is a side effect that is rarely observed in cases where atypical antipsychotics such as olanzapine (Christensen 2003) and risperidone (Sanders & Lehrer 1998) are used. When we searched the literature on pretibial edema due to quetiapine use, we found six reported cases (O'Connor et al. 2009, Şahan & Eroğlu, 2018). To the best of our knowledge, there has been a case report of bipolar disorder where pretibial edema developed due to the combined use of quetiapine and valproate (Chen et al. 2009), which is different than the case reported herein as a sooner formation of pretibial edema due to combination therapy with quetiapine and valproate was observed in our study. Here, we present a patient receiving valproate therapy with a diagnosis of bipolar disorder who developed bilateral pretibial edema after quetiapine was added to treatment.

CASE REPORT

A 64-year-old, female married patient has been followed up with the diagnosis of bipolar disorder for 6 years. The patient's history included four episodes of mania and three episodes of depression. Paliperidone palmitate 150 mg monthly intramuscular injection and valproic acid 1000 mg treatment was underway about a year ago. She had received her last paliperidone palmitate injection two months ago and then voluntarily discontinued her treatment with this agent. About a week ago, she was admitted to our clinic with manic attack symptoms such as increased need for sleep, unusual talkativeness, racing thoughts, distractibility, increased activity. She was hospitalized with the diagnosis of manic attack based on DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-5) criteria. The patient was already receiving valproic acid 1000 mg, and quetiapine 200 mg was added to her treatment. Two days after the initiation of medications, bilateral grade 3 pretibial pitting edema was observed in the patient. Edema was not accompanied by redness, heat, or pain. Complete blood count, serum albumin, lipid profile, liver function tests, thyroid function tests, urea and electrolytes were normal in all hematological and biochemical investigations performed to rule out etiologies that may cause edema such as venous stasis, heart failure, etc. Complete urinalysis, blood pressure, and blood coagulation parameters were normal. No postural hypotension was detected, and cardiac examinations such as electrocardiogram, cardiac echocardiogram, troponins, and creatinine kinase were all normal. No bradycardia was detected, and ejection fraction (EF) was 61%. Lung examination was normal. Immunology tests performed to exclude allergic etiology, consisting of C3, C4, IgG, IgM, and IgE assays, revealed normal results. No peripheral blood eosinophilia was detected. Bilateral Doppler ultrasound of lower extremities yielded a normal result. Considering that quetiapine could be the most likely cause of edema, Naranjo Adverse Drug Reaction probability scale was calculated as 6. After discontinuation of quetiapine, the edema regressed in 2 days, and resolved completely after about five days. Additionally, at the time of the patient's admission to clinic, The Young Mania Rating Scale was scored as 38, and the score regressed to 4 at the time of the patient's discharge.

DISCUSSION

Quetiapine is metabolized mainly in the liver by the cytochrome P450 isoenzyme CYP3A4. Quetiapine is an antagonist for various neurotransmitter receptors, including serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C}, dopamine D1 and D2, histamine H1, and α1- and α2-adrenergic receptors (McIntyre et al. 2007). Several mechanisms have been proposed for quetiapine to cause edema. The first of these is that with α1 blockade, increased peripheral vessel dilation and capillary hydrostatic pressure can cause edema. Another proposed mechanism is that quetiapine inhibits the ATP-dependent K pump by blocking the M1, H1 and 5-HT2 receptors and prevents the physiological increase of IP3, reducing smooth muscle contractility, and resulting in vasodilation and edema (Ng et al. 2003). Another mechanism is that quetiapine can increase the concentration of intracellular cAMP by blocking the $5HT_2$ receptor, which relaxes vascular smooth muscles and results in edema (Karabulut et al. 2021). In addition, the hepatic activity of CYP3A4, the main metabolizing isoenzyme of quetiapine, decreases due to advanced age. Furthermore, previously reported cases have shown that bilateral pretibial edema associated with quetiapine may be a dose-dependent phenomenon, and the patient is similarly older (Rozzini et al., 2005). Although the potential mechanisms for antipsychotic-induced edema have not yet been elucidated, it has been suggested that there is a relationship between dopaminergic antagonism and idiopathic edema (Koleva et al., 2009). Thanks to various receptor subtypes, dopamine can affect natriuresis, epithelial fluid resorption, vascular smooth muscle relaxation and the renin-angiotensin system. An allergic reaction can provide an alternative explanation for drug-induced edema. However, IgE, C3, and C4 levels were all normal in our case. Again, as another reason to be considered, when quetiapine is started in patients using valproate, plasma quetiapine concentration has been shown to increase significantly (Aichhorn et al. 2006). Due to valproate, which increases quetiapine concentration, our patient may have had a high plasma quetiapine level. This may have increased the predisposition to bilateral pretibial edema despite the use of low-dose quetiapine due to the advanced age of the patient as well as the concomitant use of valproate and quetiapine. In addition, publications suggest that the decreased plasma clearance of quetiapine in elderly patients can also prolong the duration of the drug effect. Combined treatment with olanzapine and valproate has also been reported to cause bilateral pretibial edema (Yaluğ et al. 2007). In addition, long-term valproate administration may also be a predisposing factor for edema (Sanders & Lehrer 1998) and it was reported that peripheral edema may develop not only over years but also within days (Lin et all. 2009). In our case, we think that the bilateral pretibial edema developed due to quetiapine used in combination with valproate in addition to advanced age.

CONCLUSION

This case raises the question whether the frequency of drug-induced bilateral pretibial edema may increase in combined treatment with valproate and quetiapine in patients with bipolar disorder. Caution should be exercised about the dose of quetiapine planned to be initiated, especially in the elderly and in patients exposed to valproate for a long time. Further research is needed to elucidate risk factors, dose dependence and potential edema mechanisms.

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Author contributions: study design, data collection, first draft, statistical analysis, approval of the final version, U.T.; approval of the final version, H.A.C.

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