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CASE REPORT

Dibenzodiazepine Derivative Quetiapine- and Olanzapine-Induced Chronic Interstitial Nephritis

Liyu He[1], Youming Peng[1], Xiao Fu[1], Xiaogang Chen[2] and Hong Liu[1]

[1]*Nephrology Department, The Second Xiangya Hospital, Central South University, Key Lab of Kidney Disease and Blood Purification in Hunan, Changsha, People's Republic of China;* [2]*Institute of Mental Health, The Second Xiangya Hospital, Central South University, Changsha, People's Republic of China*

Abstract

The dibenzodiazepine derivative is a so-called "atypical" or second-generation antipsychotic that is widely regarded as one of the most effective drug treatments for schizophrenia and depression. Quetiapine and olanzapine are novel atypical antipsychotic agents that possess much improved tolerability. To the best of our knowledge, FDA has reported three cases of olanzapine-induced interstitial nephritis. Yet there have been no known clinical reports that associate quetiapine treatment with chronic interstitial nephritis (CIN). Here, we report the occurrence of CIN in the presence of edema during quetiapine and olanzapine therapy.

Keywords: edema, interstitial nephritis, olanzapine, quetiapine

INTRODUCTION

Atypical antipsychotics are antagonists for both serotonin and dopamine receptors.[1] Published evidence indicates that these agents provide antipsychotic efficacy with a lower risk of extrapyramidal symptoms than typical antipsychotics.[2] Clozapine, a dibenzodiazepine derivative, has been shown, on rare occasions, to cause acute renal failure due to interstitial nephritis.[3] Although there are many examples of two structurally related drugs that possess an identical toxicophore susceptible to bioactivation, there have been no reports about quetiapine-induced nephritis. We present the case of a patient who developed chronic interstitial nephritis (CIN) during treatment with quetiapine and olanzapine.

CASE

Mr. W, a 27-year-old previously healthy man, experienced psychotic depression symptoms in December 2004 and was transferred to a psychiatric hospital. During the following weeks of treatment with quetiapine (100 mg/day), an improvement of the psychotic and depressive symptoms was achieved. However, the emergence of dizziness and sedation precluded further increase of dose; hence after being discharged from the hospital, the patient was intermittently treated by quetiapine. In February 2008, at the mental status examination, increased insomnia, grandiosity, and infidelity were noted. The medication of quetiapine was titrated to 200 mg/day. Two weeks after the initiation of higher dose quetiapine, the patient developed bilateral leg edema. Urinary dipstick revealed 3+ protein. The patient was proposed corticosteroids 50 mg/day after one week of conservative treatment. No diuretics were prescribed nor were any other medication changes made. Three days later, his peripheral edema had completely resolved. The patient tapered the prednisone dose gradually and then discontinued over a period of 4 weeks. In the following four years, the patient was switched to olanzapine (10 mg/day) without reoccurrence of the edema. In August 2012, the patient began to display deterioration in his self-care and felt depressed to do anything; hence, he was admitted to a psychiatric hospital. The medication of olanzapine was titrated to 20 mg/day.

Address correspondence to Xiao Fu and Youming Peng, Nephrology Department, The Second Xiangya Hospital, Central South University, Key Lab of Kidney Disease and Blood Purification in Hunan, 139 Renmin Road, Changsha, Hunan 410011, People's Republic of China. Tel.: +8615802604114, +8673185292064; Fax: +8673185295843; E-mail: ympeng2011@yahoo.cn

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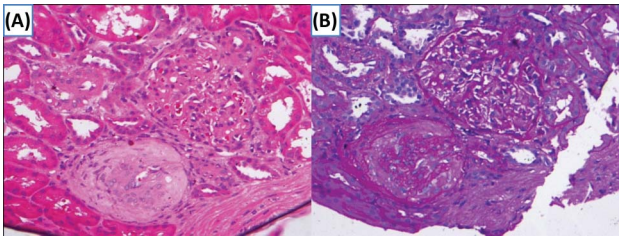

Figure 1. Renal biopsy with histological staining [(A) hematoxylin–eosin, ×200; (B) periodic acid-Schiff, ×200] showed features consistent with CIN. Glomeruli displayed focal necrosis in some areas, cells with pyknotic nuclei, and an increase in thickness of basal membrane of intraglomerular capillary. Examination of the tubulointerstitial space revealed diffuse tubular atrophy with epithelial cell desquamation and necrosis.

Within three days, bilateral leg edema was re-observed. The patient was diagnosed with interstitial nephritis and transferred to the Department of Nephrology in our hospital.

The patient's physical examination was unremarkable, with the exception of pitting, pedal edema. His white blood cell count was at 11,200/mm^3 and eosinophil count was normal. Urinalysis revealed 3+ proteinuria (11,932 mg/24 h) but no RBCs. The patient's total serum protein was low at 44.8 g/L and serum albumin was 25.3 g/L. BUN and creatinine tests were within the normal limits. Systemic disease known to be associated with interstitial nephritis was excluded by negative serology for antineutrophil cytoplasmic, antinuclear, and antidouble-stranded DNA antibodies.

All drugs were stopped on admission and renal biopsy was done. The patient showed features consistent with CIN (Figure 1). Glomeruli displayed focal necrosis in some areas of renal cortex and medulla, cells with pyknotic nuclei, and an increase in thickness of basal membrane of intraglomerular capillary. Examination of the tubulointerstitial space revealed diffuse tubular atrophy with epithelial cell desquamation and necrosis. CIN characterized by an infiltration of lymphocytes and mononuclear cell was also seen. Immunofluorescence studies were negative.

The patient was treated by prednisone (1 mg/kg of body weight/day) for 4 weeks and progressively tapered. There was a close temporal relationship between the start of increasing dose of olanzapine treatment and relapse of interstitial nephritis. We identified olanzapine as the probable causative agent for CIN and withdrew it. Three days later after receiving prednisone, his peripheral edema had completely resolved. Subsequently, the patient was switched to sertraline 50 mg/day without reoccurrence of edema during the period of follow-up.

DISCUSSION

Quetiapine and olanzapine are atypical antipsychotics approved for the treatment of schizophrenia and bipolar disorder and have proven to be more effective than traditional antipsychotics in depressive symptoms.[4–6] Although there was no strong evidence suggesting toxicity to the kidney during quetiapine and olanzapine treatment, Mustafa Gulec et al.[7] have reported that olanzapine is dose-dependently toxic to rat kidney cells and FAD have presented three cases of tubulointerstitial nephritis thought to be related with olanzapine treatment. In terms of peripheral edema, Ng et al.[8] found the prevalence of edema to be 57%, including 10.2% to a severe degree, in outpatients actively receiving olanzapine. There are also some descriptions of quetiapine-associated edema.[9] However, the edema resolved completely after cessation of quetiapine, and urinalysis was all within the normal limits. Drug hypersensitivity reactions are the most common cause of interstitial nephritis,[10] and the clinical presentation may range from a hypersensitivity syndrome with acute renal failure to an asymptomatic increase in plasma creatinine. Our patient progressed to nephrotic-range proteinuria with normal kidney function after prescribing quetiapine and olanzapine at a higher dosage. As no evidence of hypersensitivity syndrome could be shown by clinical presentation or renal biopsy, maybe interstitial nephritis is related to drug-associated nephrotoxicity. Increasing the quetiapine and olanzapine dosage that resulted in interstitial nephritis which could reflect interstitial nephritis related to dibenzodiazepine derivatives usage might be a dose-related phenomenon.

It is not surprising that steroids had no impact on the established interstitial fibrosis and tubular atrophy.[11] Therefore, to avoid chronic damage, the most important course of intervention remains the early withdrawal of the putative causative agent. Careful monitoring of patients at risk due to prior episodes of peripheral edema and renal disease seems desirable if antipsychotic treatment with quetiapine or olanzapine is selected. Early diagnosis of interstitial nephritis by renal biopsy is essential in the treatment of interstitial nephritis to avoid irreversible renal damage.

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