Cutaneous Leucocytoclastic Vasculitis Associated with Fluvoxamine

İbrahim Eren[1], İkbal Çivi[1], Mehmet Şahin[2]

ÖZET:
Fluvoksamine bağlı kütanöz lökositoklastik vaskülit

Fluvoksamin psikiyatri pratiğinde depresyon, panik bozukluğu, obsesif kompulsif bozukluk ve yeme bozukluğu tedavisinde yaygın olarak kullanılmaktadır. Lökositoklastik vaskülit postkapiller venlerde immün kompleks depolanması ile karakterize ciddi ilaç reaksiyonudur. Genellikle sistemik tutulumla birlikte ya da sistemik tutulum olmadan alt ekstremitelerde purpura şeklinde görülür. Biz obsesif kompulsif bozukluğu olan bir hastada fluvoksamine bağlı gelişen lökositoklastik vaskülit gelişimini sunmaktayız. Antidepresanlar nadiren lökositoklastik vaskülite neden olmaktadır ve bilgilerimize göre daha önce fluvoksamin ile bildirilmemiştir.

Anahtar sözcükler: Fluvoksamin, lökositoklastik vaskülit, cilt reaksiyonu, yan etkiler

Klinik Psikofarmakoloji Bülteni 2008;18:306-308

ABSTRACT:
Cutaneous leucocytoclastic vasculitis associated with fluvoxamine

Fluvoxamine is widely used in psychiatry practice in the treatment of depression, panic disorder, obsessive-compulsive disorder, and eating disorders. Leucocytoclastic vasculitis is a serious drug reaction that is characterized by immune complex deposition in the postcapillary venules. It usually presents as purpura on the lower extremities with or without systemic involvement. Here, we report fluvoxamine induced leucocytoclastic vasculitis in a patient with obsessive compulsive disorder. Antidepressants have rarely been associated with leucocytoclastic vasculitis, and to the best of our knowledge vasculitis of any type has not previously been reported in association with fluvoxamine.

Key words: Fluvoxamine, leucocytoclastic vasculitis, skin reactions, adverse events

Bulletin of Clinical Psychopharmacology 2008;18:306-308

INTRODUCTION

Fluvoxamine, a selective serotonin reuptake inhibitor, is widely used in the treatment of depression, panic disorder, obsessive-compulsive disorder, and eating disorders (1,2). It is usually well tolerated. Adverse effects of this drug have been reported in up to 5% of patients, most commonly headache, dizziness, diarhea, abdominal pain, somnolance, insomnia and fatigue (3).

Vasculitis is a rare but serious complication of psychiatric drug therapy. There have been previous reports of vasculitic reactions with fluoxetine, maprotiline, paroxetine and trazodone (4-8). Leucocytoclastic vasculitis is characterized by immune complex deposition in the postcapillary venules (7). It usually presents as a purpura on the lower extremities with or without systemic involvement (3). Here, we report fluvoxamine induced leucocytoclastic vasculitis in a patient who has been recovered without therapy.

CASE REPORT

Mrs. A, a 20-year-old woman with obsessive-compulsive disorder, had been started the treatment with fluvoxamine, 50 mg/day. She had no other past medical or psychiatric history and was receiving no other medications. The dose of fluvoxamine was increased to 100 mg/day after 4 weeks. At 6 weeks, she developed multiple purpuric eruption on the bilateral lower legs. She denied fever, any antecedent viral infection, arthritis, respiratory, gastrointestinal, urinary

[1]Associate Professor of Psychiatry, M.D., Department of Psychiatry, [2]Associate Professor of Internal Medicine, M.D, Department of Internal Medicine, Süleyman Demirel University, School of Medicine, Isparta-Turkey

Yazışma Adresi / Address reprint requests to: Doç. Dr. İbrahim Eren, Süleyman Demirel Üniversitesi, Tıp Fakültesi Psikiyatri AD, Çünür 32100, Isparta-Türkiye

Telefon / Phone: +90-246-211-2403

Faks / Fax: +90-246-237-1762

Elektronik posta adresi / E-mail address: e-mail:drieren@yahoo.com

Kabul tarihi / Date of acceptance: 28 Mayıs 2008 / May 28, 2008

symptoms, and allergic diseases. Physical examination revealed a normal body temperature and a regular heart rate with 82 beats/min and arterial blood pressure of 110/60 mmHg. Heart and lung examination was normal, and no lymphadenopathy, hepatosplenomegaly or abdominal tenderness were present. Skin examination revealed a purpuric rash, about 1-6 mm in diameter on lower legs. The buttocks were spared. Neurologic and other physical examination findings were unremarkable. Laboratory tests revealed the following results: the hemoglobin concentration was 130 g/l, leucocyte count 10300 with normal differential count, and platelet and eosinophil count, prothrombin time, and partial thromboplastin time were within normal range. Routine biochemical blood tests were also normal. Serological tests for infection with hepatitis B and C viruses, epstein-Barr virus, cytomegalovirus, brucella, mycoplasma, and toxoplasma were negative. Anti-HbsAg also was negative. Antinuclear antibody, antineutrophlic cytoplasmic antibody, rheumatoid factor, and cryoglobulins were also negative. C3, C4, and immunoglobulin levels were normal. Urinalysis was negative for haematuria, proteinuria, and granular casts. The fecal occult blood test was negative. The chest radiograph was normal. A skin biopsy was performed and histopathological examination demonstrated small vessel vasculitis characterized by neutrophilic infiltration, nuclear dust, and focal fibrinoid deposits within the vessels walls, complete fibrinoid necrosis of the blood vessel, and erythrocyte extravasation in the adjacent dermis. Allergic reaction and vasculitis history of patient were not reported. There were not any psychiatric disorders and vasculit history in patient's family.

Treatment with fluvoxamine was discontinued. Subsequently, the skin lesions completely resolved within a few days without specific treatment. The patient had no further episodes of skin rash during a follow up period of four months.

DISCUSSION

We present a patient who developed biopsy-proven leucocytoclastic vasculitis six weeks after the onset of fluvoxamine treatment. Adverse effects of the skin attributed to fluvoxamine include rashes, allergic reactions (9). Leucocytoclastic vasculitis is a serious drug reaction. Antidepressants have rarely been associated with leucocytoclastic vasculitis, and to the best of our knowledge vasculitis of any type has not previously been reported in association with fluvoxamine (4,6,7). Moreover, to our knowledge, this is the first report of cutaneous vasculitis induced by fluvoxamine.

Numerous causative factors or associated disorders accused in the pathogenesis of cutaneous vasculitis are: infections, medications, chemicals, bacteria, viruses, malignancies, collagen skin, vascular diseases, and chronic active hepatitis (10). Nonsteroidal anti-inflammatory drugs, anticonvulsants, propylthiouracil, iodides, levamisole, phenothiazines, sulfonamides, iodides, penicillins, tetracycline, retinoids, and quinolones are the most common drugs associated with leucocytoclastic vasculitis (11). A causal relationship with fluvoxamine seemed obvious in our case. The patient did not have a positive medical and family history of rheumatic diseases and screening tests in blood and urine showed no signs of infection. In the absence of any other known cause, development of the skin reaction six weeks after initiation with fluvoxamine treatment, and rapid reversal of it after withdrawal of the drug, the patient's leucocytoclastic vasculitis was attributed to fluvoxamine use.

The exact mechanism by which drugs cause vasculitis is unknown. Pathogenesisof leucocytoclastic vasculitis is complex and often multifactorial. Medications cause approximately 10% of leucocytoclastic vasculitic skin lesions. Drug-induced vasculitis may be caused by antibodies directed against heterologous protein drug-related haptens, by direct drug toxicity on vessel walls, by autoantibodies reacting with endothelial cells, or by a cytokine-mediated reaction to the vascular endothelium associated with interferon-gamma and interleukin-6 (11).

It seems that it's an immune-mediated reaction to a precipitating antigen (3). Leucocytoclastic or hypersensitivity vasculitis is characterized by a vasculitis of the small vessels following exposure to various antigens, for example a drug. Immun complex

formation stimulates the classic complement cascade that attracts neutrophils and basophils. Stimulated polymorphonuclear leucocytes release lysosomal enzymes that destroy the functional integrity of the vessel wall. This results in diapedesis of erythrocytes, edema and heavy leucocytic infiltrate, thus creating the palpable purpura. Venules are more susceptible to injury because of lower oxygen content, stasis, and slower flow (3).

Vasculitis is a clinicopathological process characterized by inflammation and necrosis of blood vessels. Since inflammation of the blood vessels can potentially involve any vessel in the body, dysfunction of any organ system may be part of a vasculitis process. It usually begins on the lower legs in ambulatory patients because of hydrostatic forces and turbulence of flow at vessel bifurcations (12). The acute eruption may be accompanied by systemic symptoms, such as malaise, myalgia, arthralgias, arthritis, abdominal pain, and moderate fever. The skin is the most common organ involved but any other organ can be affected and can cause specific symptoms. Because of necrosis of large areas of the overlying skin, ulceration and eventual scarring may result (10).

Taking the invalidating character of this disorder, discontinuation of the drug is recommended. Drug induced vasculitis usually subsides after discontinuation of the offending medication (10). The course of leucocytoclastic vasculitis is variable. The prognosis depends on the severity of internal organ involvement. Patients with the mildest forms of disease may require no specific treatment. Many modalities including antihistamines, nonsteroidal anti-inflammatory drugs, antiserotonins, corticosteroids, and cytotoxics have been employed for mild to moderate cases with varying degrees of success (13).

Fortunately in the presented case, prognosis was fairly well. Systemic involvement was absent. The patient's condition was remitted after cessation of drug and did not require any other therapies. Physicians should be alert to this potential serious complication with fluvoxamine use.

References:

1. Benfield P, Ward A. Fluvoxamine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness Drugs 1986; 32: 313-334
2. De Wilde JEM, Doogan DP. Fluvoxamine and chlorimipramine in endogenous depression. J Affect Dis 1982; 4: 249-259
3. Buchberger R, Wagner W. Fluvoxamine: safety profile in extensive post-marketing surveillance Pharmacopsychiatry 2002; 35:101-108
4. Mann SC, Walker MM, Messenger GG, Greenstein RA. Leukocytoclastic vasculitis secondary to trazodone treatment (letter). J Am Acad Dermatol 1984; 10:669-670
5. Margolese HC, Chouinard G, Beauclair L, Rubino M. Cutaneous vasculitis induced by paroxetine Am J Psychiatry, 2001; 158: 497
6. Oakley AM, Hodge L. Cutaneous vasculitis from maprotiline (letter). Aust NZ J Med 1985; 15:256-257
7. Ratnam KV, Boon YH, Pang BK. Idiopathic hypersensitivity vasculitis: clinicopathologic correlation of 61 cases. Int J Dermatol 1995; 34: 786-789
8. Roger D, Rolle F, Mausset J, Lavignac C, Bonnetblanc JM. Urticarial vasculitis induced by fluoxetine (letter). Dermatology 1995; 191:164
9. Beauquier B, Fahs H Secondary dermatologic effects of serotonin reuptake inhibitor antidepressants: hypothesis of cross-reacting allergy. Apropos of 2 cases L'Encephale 1998; 24: 62-64
10. Claudy A. Pathogenesis of leucocytoclastic vasculitis. Eur J Dermatol 1998;8:75-79
11. Jain KK. Drug-induced cutaneous vasculitis. Adverse Drug React Toxicol Rev 1993; 12:263-276.
12. Arvan ME, Brodell RT. A palpable clue to vasculitis. Postgrad Med 1999; 105: 29-232
13. Fan PT, Davis JA, Somer T, Kaplan L, Bluestone R. A clinical approach to systemic vasculitis. Semin Arthritis Rheum,1980; 9: 248-304