대한치매학회지 : 제 2 권 제 1 호 2003
Journal of the Korean Dementia Association. 2003; 2: 88-9

Reversible Angio-edema Associated with Risperidone and Valproic Acid

Yeon-Su Lee · Seol-Heui Han

Department of Neurology, Chungbuk National University Hospital, Cheongu, Korea

Address for correspondence

Seol-Heui Han, M.D.
Department of Neurology, Chungbuk National University Hospital and Chungbuk National Univerisity Medical Research Center, 62 Gaeshin-dong, Heungduk-gu, Cheongju 361-711, Korea
Tel: +82-43-269-6372
Fax: +82-42-276-8929
E-mail : shhancb@chungbuk.ac.kr

Risperidone, a benzisoxazole derivative, is a most widely used novel antipsychotic drug to treat behavioral and psychological symptoms in dementia (BPSD) because of its relatively low incidence of adverse events such as extrapyramidal symptoms. However, it is not always free from more serious side effects. We present a case of massive angioedema associated with risperidone and valproic acid.

Key Words : *Angio-edema, Risperidone, Valproic acid, Behavioral and psychological symptoms of dementia (BPSD)*

Behavioral and psychological signs and symptoms of dementia (BPSD) are not merely secondary to memory and/or cognitive impairment, but they are relatively independent of manifestation of cognitive impairment. BPSDs are often the most difficult aspect of caregiving, however, expert opinion and workgroup consensus suggest that treatment of BPSDs can delay institutionalization and thus can improve quality of life, both for patients and caregivers[1]. Risperidone (RISPERDAL) is the most widely used among the newer atypical antipsychotic drugs. Moreover it has been suggested to be relatively beneficial for the treatment of elderly patients with psychotic symptoms. Pigmentation, photosensitivity, and skin eruption are common among the side effects in the skin and appendage. Occurrence of urticaria and angioedema were reported[2]. Angioedema is well-demarcated localized edema involving the deeper layers of the skin including the subcutaneous tissue. Angioedema can be classified as IgE dependent, complement mediated, nonimmunologic, and idiopathic type on the different mechanism for eliciting clinical disease. Drug-induced angioedema is included in idiopathic type[3]. The incidence of edema associated with risperidone in premarketing clinical trial is relatively infrequent, ranging between 1/100 and 1/1,000[2]. But the occurrence of urticaria and angioedema is probably more frequent than being reported because of the self-limited nature[3].

It is well-known that anticonvulsant is efficacious when administered in combination with antipsychotics in managing severe psychotic symptoms[3]. Valproate is the latest anticonvulsant to be used to augment antipsychotic treatment in schizophrenia and related disorders. Among the adverse effects gastrointestinal symptoms such as nausea, vomiting, and diarrhea and CNS symptoms including somnolence are common. This is the first reported case of a patient who suffered massive angio-edema associated with adjuvant valproate therapy to risperidone.

CASE REPORT

Ms. P, a 76-year-old patient with moderately advanced Alzheimer disease, has been taken care of in a nursing home for 6 years. She has been receiving risperidone 3 mg daily to control her behavioral and psychotic symptoms of dementia. Her increasing BPSD has recently got worsened in such a way she has shown verbal and physical aggression. Increasing daily dosage of risperidone to 6 mg failed to mitigate her BPSD but only developed conspicuous extrapyramidal signs and agitated behavior. Sodium valproate (VPA) 300 mg/day was added

to readjusted dosage of risperidone (2 mg/day) to control the aggravated BPSD. She developed marked edema in the lower extremities and moderate edema in the upper extremities and face two weeks after taking VPA. Thorough physical examination and laboratory investigations were performed to search the cause of the edema. Biochemical and hematological screening including electrolytes, renal function, thyroid function, serum albumin and other liver profiles gave normal results. ECG, echocardiogram, chest radiographs and abdominal and pelvic ultrasosnogrphy and leg vein Doppler studies were unremarkable. VPA was discontinued and the edema resolved completely over the ensuing weeks.

COMMENTS

The atypical antipsychotic medication has become first-line therapy for the behavioral and psychotic symptoms of dementia. While the majority of patients show beneficial effects of the atypical antipsychotics, some have residual symptoms. Hence, adjunctive use of anticonvulsant is often necessary. While it is known that acute peripheral edema may occur with risperidone or valproate used separately[4, 5], it is quite unusual in that marked edema developed with the low dose of these agents. Usually patients had taken moderate-to-high doses of VPA (more than 800 mg/day) for a mean duration of 4 years before experiencing edema[4].

In our case, low dose VPA caused reversible generalized massive edema when co-administered with risperidone, thus it appears that VPA and risperidone can show synergistic effect on the development of generalized edema. The authors encourage others to be alert to this unusual untoward reaction of the combination of psychotrophic medications especially when VPA and risperidone are concerned.

REFERENCES

1. Teri L, Logsdon RG, Schindler RJ. *Treatment of behavioral and mood disturbances in dementia. Generations 1999; 23: 50-6.*
2. Baldassano CF, Ghaemi SN. *Generalized edema with risperidone: divalproex sodium treatment. J Clin Psychiatry 1996; 57: 422.*
3. Braunwald E, Fauci AS, Kapser DL, Hauser SL, Longo DL, Jameson JL. *Priciples of internal medicine. 15th ed. McGraw-Hill, 2001; 1917-8.*
4. Wassef AA, Hafiz NG, Hampton D, Molloy M. *Divalproex sodium augmentation of haloperidol in hospitalized patients with schizophrenia: clinical and economic implications. J Clin Psychopharmacol 2001; 21: 21-6.*
5. Basel-Vanagaite L, Zeharia A, Amir J, Mimouni M. *Edema associated with valproate therapy. Ann Pharmacother 1999; 33: 1370-1.*
6. Sanders RD, Lehrer DS. *Edema associated with addition of risperidone to valproate treatment. J Clin Psychiatry 1998; 59: 689-90.*