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CASE REPORT

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Lamotrigine Induced Hypersensitivity in Aged: A Case Report

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ABSTRACT

Lamotrigine is an antiepileptic drug widely used to control seizures. It has many adverse events but in rare instances, it can cause drug hypersensitivity syndrome (DHS). We describe a case of lamotrigine induced drug hypersensitivity characterized by febrile erythema and eosinophilia. The suspect drug was replaced by valproate leading to marked improvement.

KEYWORDS: Lamotrigine, Hypersensitivity, Drug Reaction

INTRODUCTION

Lamotrigine is an antiepileptic medication which controls seizures or fits by decreasing the abnormal and excessive activity of the nerve cells in the brain. Common side effects of lamotrigine include headache, dryness in mouth, sleepiness, dizziness, joint pain, agitation, tremors, tiredness, irritability, and gastrointestinal disturbance. Lamotrigine is a recent anticonvulsant indicated in all forms of epilepsy. It is made up of a triazinic compound that causes stabilization of neuronal membranes by acting on voltage-gated sodium channels and inhibits the action of excitatory neurotransmitters, particularly glutamate. Lamotrigine is primarily metabolized in the liver by glucuronide conjugation and does not seem to interfere with cytochromes P450, unlike aromatic antiepileptics (phenobarbital, phenytoin, carbamazepine, etc.[1,2] It can induce hypersensitivity syndrome clinically and biologically similar to that observed with standard antiepileptic drugs.

CASE REPORT

A 79-year-old man was admitted at our clinic for a febrile rash. His history was marked by pulmonary embolism, vascular dementia treated with donepezil and secondary epilepsy treated with lamotrigine 50 mg/day for 4 weeks. Other medications were lysine acetylsalicylate 75 mg/day and mirtazapine 15 mg/day. Four days prior to hospitalization, the patient suddenly had a febrile maculopapular rash of all four limbs, gradually spreading to the trunk. Immediately suspecting an adverse effect of lamotrigine, this treatment was immediately discontinued and replaced with 200 mg/day of valproate. On admission, physical examination found fever of 38°C and morbilliform pruritic skin erythema affecting the face, trunk, and limbs. There was no mucosal involvement. Neurological examination found no meningeal syndrome or focal signs. The cardiopulmonary and digestive examinations were normal. No lymphadenopathy or organomegaly was detected. As of admission, donepezil and valproate treatments were discontinued and anticonvulsant treatment with clonazepam was initiated. From a laboratory perspective, there was an inflammatory syndrome with C-reactive protein (CRP) of 72 mg/L, hypereosinophilia of 2,200 then 6,000 elements/mm3, as well as increased muscle enzymes. Liver parameters were normal. The viral and bacterial serologies were negative. A skin biopsy found activated perivascular lymphocytic infiltrate with the presence of polymorphonuclear eosinophils consistent with drug-induced toxidermia. An electroencephalogram was unremarkable. Erythema of the skin began to regress spontaneously three days after valproate discontinuation and then disappeared permanently within one week. The CRP and polymorphonuclear eosinophil count normalized in two weeks.

DISCUSSION

The diagnosis of drug hypersensitivity syndrome to lamotrigine was retained in reported case. The time to onset of rash was less than eight weeks, the association with hypereosinophilia and biological inflammatory syndrome, the absence of any infectious cause, the histological appearance, and the favorable course after discontinuation of the implicated drug led to this

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diagnosis. If a skin reaction to lamotrigine was rightly suspected initially, the immediate introduction of valproate as a switch to lamotrigine helped to decrease lamotrigine elimination and promote the persistence of clinical and biological symptoms of drug hypersensitivity syndrome. It should be emphasized that although the patient is on donepezil, the notable increase in muscle enzymes could be connected with cases of rhabdomyolysis due to lamotrigine already described in the literature.[3] DHSs secondary to the intake of aromatic anticonvulsants are metabolically different from those induced by lamotrigine, even if all result from a T-cell oligoclonal response.[2,4] There is no evidence of cross-allergy between these anticonvulsants.[2,5] However, the combination of lamotrigine with aromatic antiepileptic drugs or sodium valproate increases the risk of skin reaction[6,7], whether or not these drugs are prescribed simultaneously or even consecutively as shown in our case. Thus, in a published series, the 26 cases of lamotrigine-induced DHS all occurred after treatment combining this drug with either valproate in 60% of cases or with conventional anticonvulsants in 40% of cases.[6] As a rule this risk when taking lamotrigine occurs within eight weeks of treatment initiation and skin reactions have no specificity in relation to those observed with other anticonvulsants. These allergic skin reactions are promoted by an overly high initial dosage and/or a combination with valproate known to double the half-life of lamotrigine by inhibiting its catabolism.[2,6] This combination increases the incidence of rash by 21% in adults and by 34% in children.[7] Aromatic or nonaromatic anticonvulsant drugs are the drugs most commonly involved in the unpredictable onset of DHS. Its clinical presentation is extremely variable, ranging from simple fever to multisystemic involvement with or without hypereosinophilia.[2,8] The clinical study of the 26 observations did not reveal any notable difference between the DHS cases and those observed with the other anticonvulsants, although these authors found less frequency of hypereosinophilia and lymphadenopathy and constant presence of fever.[6] Recovery is the rule after discontinuing the implicated drug within three to eight weeks.[2] The majority of skin manifestations are benign and regress upon treatment discontinuation, however, severe reactions occur in one in every 1,000 cases similar to Stevens-Johnson syndrome or Lyell's syndrome.[7,9] These clinical and laboratory features of DHS have no specificity in the elderly subject. Similarly, current literature data do not indicate that the frequency of DHS is higher in this population. In any case, the occurrence of such a syndrome in a readily multi-pathological population can be an important factor in morbidity and mortality rates.

CONCLUSION

In conclusion, although rare, this type of DHS must not be ignored in the geriatric setting where lamotrigine is readily prescribed.

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