

Exanthema after lamotrigine use: A clinical case

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ABSTRACT

Introduction: Lamotrigine is a phenyltriazine compound that inhibits sodium and potassium channels in presynaptic neurons. Maculopapular exanthema is a common side effect of Lamotrigine therapy, occurring most frequently during the first eight weeks of treatment in approximately 3–10% of patients.

Case Report: A 74-year-old female had started Lamotrigine 50 mg due to emotional lability and depression. About 8–9 weeks after the introduction of the drug she presented a rash with exanthema, maculopapular in appearance. The attending physician suggested discontinuation of the medication and reevaluation. Complete regression of the clinical picture occurred. No severe skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis were observed.

Conclusion: Lamotrigine is effective for a variety of types of conditions involving neuronal excitability, however, such drug exposes the individual to side reactions ranging from mild skin rashes to even those

leading to hospitalization. Measures such as adherence to the manufacturer's dosing guidelines, titration, and intrinsic characteristics of the individual can minimize this effect.

Keywords: Antiepileptic drugs, Cutaneous rash, Hypersensitivity, Lamotrigine

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INTRODUCTION

Lamotrigine is a phenyltriazine compound that inhibits sodium and potassium channels in presynaptic neurons leading to stabilization of the neuronal membrane and minimizing glutamate release [1]. It is a second-line antiepileptic drug, with mood-stabilizing action, usually applied in the treatment of several neuronal excitability abnormalities, including bipolar type I disorders characterized by the prevalence of the depressive component, epilepsy, and neuropathic pain [2].

Maculopapular exanthema is a common side effect of Lamotrigine therapy, occurring most frequently during the first eight weeks of treatment in approximately 3–10% of patients [3]. Its severity ranges from simple rash to organ involvement. Among the skin reactions considered rare and severe to Lamotrigine use are: drug-induced hypersensitivity syndrome, eosinophilia, systemic symptoms, Stevens-Johnson syndrome, and toxic epidermal necrolysis [4].

Lamotrigine-induced hypersensitivity is generally classified as a delayed type IV reaction, in which the immune system identifies the drug as a foreign antigen that binds to T-cell receptors to activate the immune system [5].

Although maculopapular exanthema does not present as a serious adverse reaction on its own, it is still a major cause of drug discontinuation. This when stopped provides regression of the rash often within a few days, however, loss of seizure control can follow, exposing the patient to considerable risk [6].

Therefore, the objective of the present study is to present a case report about rashes induced by the use of Lamotrigine, and to undertake a theoretical discussion about the presence and frequency of such effect in patients exposed to this medication.

CASE REPORT

A 74-year-old female had started Lamotrigine 50 mg due to emotional lability and depression. About 8–9 weeks after the introduction of the drug she presented a rash with exanthema, maculo-papular in appearance. Initially family members questioned for possible atopy due to exposure to dust in residence. The attending physician suggested discontinuation of the medication and reevaluation. Complete regression of the clinical picture occurred. No severe skin rashes were observed, including Stevens-Johnson syndrome and toxic epidermal necrolysis, one of the rarest rare effects most caused by such medication. Weaning from the medication did not occur due to the severity of the fleeting clinical picture. The rash was confluent, diffuse. The face, upper trunk, and extremities were also part of the spectrum of clinical presentation (Figure 1).



Figure 1: Presence of cutaneous rash on trunk and upper extremities.

DISCUSSION

Lamotrigine side effects are often mild to moderate in severity, with headache (19%), nausea (14%), infection (13%), and insomnia (10%) being most common. Diarrhea was also reported in 7% of cases and tremor in about 4%. Although the prevalence of rash in randomized studies of bipolar patients is not higher than that found with placebo, rash is considered the most common side effect of this drug. The incidence is estimated to be between 1.7% and 39%, with the vast majority being mild rashes [7]. Yet, severe skin reactions linked to Lamotrigine are also described, with cases of Steven-Johnson syndrome, toxic epidermal necrolysis, and anticonvulsant hypersensitivity syndrome (AHS) reported [8].

After oral administration, Lamotrigine is absorbed immediately and completely from the gastrointestinal tract. The fraction bound to serum proteins is 55% and the volume of drug distribution is 1.2 L/kg. It is excreted renally, especially as an inactive N2-glucuronide conjugate [9]. Its elimination half-life is about 22 h (range 13–30 h) if used in monotherapy, 14 or 70 h if used with enzyme inducers or sodium valproate, respectively. Toxicity is known to increase significantly with circulating concentrations of the drug greater than 15 mg/L [10].

It has been proposed that the rash associated with Lamotrigine is most often a delayed hypersensitivity reaction, manifesting within the first eight weeks of treatment and resolving with drug withdrawal. It is worth noting that the flu-like symptoms, lymphadenopathy, and eosinophilia support the hypothesis that there is an underlying immune mechanism [11, 12]. In patients who have had a mild skin rash, a low dose of lamotrigine can be re-introduced with a slow and gradual adjustment. But reintroduction is not recommended if the adverse reaction was severe [9].

Side effects are often mild to moderate in severity, with headache (19%), nausea (14%), infection (13%), and insomnia (10%) being the most common. Diarrhea was also reported in ref. [13].

The pathogenesis of skin reactions appears to be multifaceted. One of the most widely proposed theories of hypersensitivity reactions is based on the hypothesis of immunosensitivity and drug recognition by specific antibodies or T cells. In addition to the accidental formation hypothesis, several immune mechanisms may be involved. Drug-specific T cells have been identified for Lamotrigine [14].

The mechanisms behind skin reactions are not well understood. Many factors can affect a patient's susceptibility to this adverse side effect, and the mechanisms may differ between drugs and patients [15]. Pharmacogenetic variations in drug biotransformation seem to be crucial, but gender, age, concurrent diseases, body dimensions, drug interactions, pregnancy, and ethnicity play an important role, the latter being more frequent in women. Genes such as UGT1A4, UGT2B7, and ABCB1 variants may also influence the

pharmacokinetics of Lamotrigine and consequently explain its interindividual variability [16].

Factors that precipitate the appearance of the rash have been identified, such as: initial dose and a higher than recommended titration rate of the drug, as well as coadministration with valproate. In addition, other factors such as comorbidity with acquired immunodeficiency virus and systemic lupus erythematosus, corticotherapy at the time of drug initiation, and a family history of rash associated with Lamotrigine were reported [17].

The controversy regarding the clinical management of the cutaneous rash is noteworthy. Some authors advocate that if an isolated, benign rash appears, the dose of Lamotrigine should not be increased but reduced until it resolves. On the other hand, the same authors emphasize that if it is a severe rash, the drug should be immediately discontinued and a possible systemic involvement should be checked. Finally, some argue that Lamotrigine should be discontinued at the first sign of a rash in order to minimize the risk of a later evolution to severe [18].

The reintroduction of the drug after suspension is done when the risk-benefit analysis justifies its resumption, and provided that the patient is able to seek assistance if any sign of hypersensitivity appears. Undoubtedly, it is recommended that if the rash that motivated the discontinuation of therapy is severe, reintroduction should not be considered [18].

CONCLUSION

Given the evidence, we have identified that Lamotrigine is effective for a variety of types of conditions involving neuronal excitability, such as epilepsies, seizures, and bipolar disorders, both as an adjuvant agent and in monotherapy, and is often well tolerated. As a rule, this drug exposes the individual to side reactions ranging from mild skin rashes to those leading to hospitalization. The recommendations imposed to date aim to mitigate the likelihood of these effects and thereby improve management. Measures such as adherence to manufacturer dosing guidelines, titration, and intrinsic characteristics of the individual play an important role in this context.

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Author Contributions

Marco Orsini – Conception of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the

work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jacqueline Fernandes Nascimento – Design of the work, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Antônio Marcos da Silva Catharino – Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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