Severe Cutaneous Adverse Reactions Associated With High-Dose Lamotrigine for Mood Disorders: A Case Series

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Abstract

Drug-induced Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN) are rare but life-threatening immune-mediated drug reactions known as Severe Cutaneous Adverse Reactions (SCARs). These severe drug reactions have been associated with many commonly prescribed medications, including sulfonamides, allopurinol, carbamazepine, and several antiepileptic drugs including lamotrigine.[1] Although the risk of these adverse events is recognized by many medical providers, the risk may be overlooked when prescribing lamotrigine for mood disorders. Review of the literature and the experience of these cases suggest that the risk of lamotrigine-associated SCARs is increased when starting lamotrigine at high initial doses. Here we present and discuss two cases of SCARs attributed to high-dose lamotrigine prescribed for mood disorders. A third patient also presented with a SCAR related to high-dose lamotrigine prescribed for a mood disorder during this time but was lost to follow-up and was not reachable. All three patients presented to our hospital system from 2019-2020. Due to this clinical experience, we recommend that pharmacists and prescribers alike be alerted of the risk of severe cutaneous drug reactions when lamotrigine is prescribed, particularly at initial doses greater than 25 mg.

Keywords: Lamotrigine, drug reactions, DRESS, SJS, TEN, mood disorders

Introduction

Lamotrigine is an antiepileptic drug that can be used to treat partial seizures, tonic-clonic seizures, Lennox-Gastaut syndrome, and Bipolar I disorder.[1] Off-label uses of lamotrigine include unipolar depression, acute bipolar depression, fibromyalgia, panic disorder, and binge-eating disorder.[1] Though the mechanism of action of lamotrigine is not completely understood, the drug selectively binds to sodium channels and inhibits the presynaptic release of glutamate from neuronal membranes.[1] Although the dosing recommendations for lamotrigine vary based on the specific pathology being treated, the general accord is that lamotrigine should be started at a low dose, such as 25 mg, and increased in a stepwise manner over the course of several weeks.[1] Interestingly, a recent preliminary study reported no increased risk of skin rash when following a specific rapid titration protocol for lamotrigine over the course of eleven days.[2] Whether the dose is titrated over several days or several weeks, the universal agreement in recent literature is that lamotrigine should be initiated at low doses and increased gradually, rather than starting at high initial doses. This gradual increase in dosage is critical in preventing severe cutaneous adverse reactions, including DRESS, SJS, and TEN.[1-2] Because the mortality rate of these reactions range from 10-35%, avoidance is absolutely critical.[3,4] In addition to increased mortality, these reactions have the potential to cause permanent disabilities.[4] The cases described in this report underscore the importance of starting lamotrigine at a low initial dose and carefully increasing the dosage as necessary, in order to lower the risk of adverse reactions including SCARs.

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Case #1

A 35-year-old Caucasian male with a history of hypertension, tobacco use, and depression presented with a 1-day history of a painful and blistering rash covering most of his chest, face, back, and bilateral extremities **(Figure 1)**. Associated symptoms included eye irritation, oral pain and erosions, genital erosions, dysuria, fever, chills, and cough. History revealed that the patient had started 100 mg BID of lamotrigine two weeks prior for the treatment of bipolar disorder. Other medications included trazodone, propranolol, aripiprazole, sertraline, and Chantix. Examination of the skin revealed widespread, dusky necrotic patches on the face, chest, abdomen, upper extremities, back, proximal thighs, hands, and feet. There were oral and genital erosions present, as well as visible sloughing of the tongue. Sloughing of the skin with lateral traction, also known as Nikolsky's sign, was observed. Skin biopsy revealed focal epidermal and follicular epithelial necrosis consistent with the clinical impression of SJS/TEN. Since the patient had greater than 30% of body surface area involvement, a positive Nikolsky sign, mucosal involvement, and a history of starting a suspicious drug (Lamotrigine) two weeks prior, a final diagnosis of Toxic-Epidermal Necrolysis was made. Though the evidence for intervention with systemic immunosuppressants versus supportive care alone is lacking, the patient was given 50 mg of etanercept on the day of admission and 5 mg/kg/day of cyclosporine thereafter given the severity of his presentation. Aside from his extensive cutaneous involvement, the patient also had ocular, renal, pulmonary, and genitourinary complications. This required prolonged intubation with eventual tracheostomy, mechanical ventilation, septic and metabolic shock resuscitation, and long-term enteral feeding in an intensive care setting for months. Follow-up with the patient and his family 6 months later revealed that the patient remains in critical condition and is suffering from severe and permanent complications including vision loss and inability to walk.

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Case #2

A 46-year-old Caucasian female presented with an erythematous, papulosquamous skin rash covering most of her body with sparing of the palms, soles, conjunctivae, mouth, and vagina with an associated itching and burning sensation **(Figure 2)**. History revealed that the patient began taking lamotrigine 100 mg BID for an unspecified mood disorder approximately 3.5 weeks prior. She tested negative for infectious etiologies including COVID-19, influenza, mononucleosis, and streptococcus. The rash began on her arms and generalized across her entire body over the subsequent two days. Additional signs and symptoms included subjective fever, edema of her hands, lips, and face, as well as tender cervical, supraclavicular, and axillary lymphadenopathy. Pertinent labs included negative anti-nuclear antibody testing, normal complement levels, a normal complete blood count with mild peripheral eosinophilia, elevated C-reactive protein, and negative rapid plasma reagin. Skin biopsy was non-specific but showed a superficial perivascular infiltrate with edema. Given the clinical constellation of diffuse rash, facial edema, fever, and tender lymphadenopathy within weeks of starting lamotrigine, the RegiSCAR score was calculated as 4, indicating probable DRESS. The patient discontinued lamotrigine and was treated with IV methylprednisone and topical triamcinolone ointment with gradual improvement. Follow-up with the patient eleven months later revealed that she remains uncomfortable in her skin, experiences intermittent rashes accompanied by a feeling of warmth, and can no longer wear tight-fitting clothing.

Discussion

Lamotrigine is an antiepileptic medication used at times for the treatment of mood disorders but can be associated with SCARs especially when given without appropriate low starting dose and gradual increase in dosage. A boxed warning on the drug indicates the incidence of SJS as "0.3% to 0.8% in pediatric populations and 0.03% to 0.08% in adult populations."[1] In this report, we discuss our experience with severe cutaneous adverse reactions, including DRESS and TEN, due to lamotrigine in patients who presented to our hospital system from 2019-2020.

DRESS is a drug-induced hypersensitivity syndrome that may be difficult to diagnose. DRESS can often mimic the symptoms of other cutaneous and systemic infectious pathologies and classically appears 2-6 weeks after exposure to the offending medication but can appear up to 3 months after drug exposure. The clinical presentation of DRESS includes the development of a rash after exposure to a new medication and may also be associated facial edema, lymphadenopathy, fever, peripheral eosinophilia, re-activation of HHV-6 or HHV-7, atypical lymphocytes on peripheral smear, and involvement of internal organs such as the liver, heart, and thyroid gland.[5] The likelihood of a diagnosis of DRESS may be estimated using a RegiSCAR score[5], a systematic calculation that factors in clinical and laboratory findings associated with DRESS. While fulminant liver failure is the most feared complication of DRESS, most patients with DRESS have a full recovery.[5]

SJS and TEN typically occur 7-14 days after medication exposure and are characterized by early dusky and tender erythema of the skin followed by detachment and sloughing of the epidermis, bullae, and shedding of the mucosa. The distinction between SJS and TEN is the percentage of total body surface area (BSA) involvement, with SJS involving up to 10% BSA, SJS-TEN overlap involving between 10-30% BSA, and TEN involving more than 30% BSA. Not surprisingly, TEN has a significantly higher mortality rate (30-35%), than SJS (5-15%).[3] Due to the immunologically mediated pathophysiology of these reactions, it is important to note that women are nearly twice as likely to experience these reactions as men.[4]

The cases presented in this report underscore the importance of educating pharmacists and other medical providers on the risk of SCARs when prescribing lamotrigine, especially at higher initial doses. As depicted above, reactions to lamotrigine can cause life-altering and life-threatening effects, including long-term disability and increased mortality. To prevent these events from occurring, we recommend that pharmacists and prescribers alike be alerted of this risk when an order for lamotrigine is placed, specifically at initial doses greater than 25 mg.

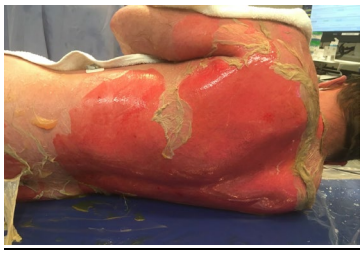

Figure 1. Toxic Epidermal Necrolysis. Desquamating rash covering the entire back of a patient with > 30% total body surface area involvement.

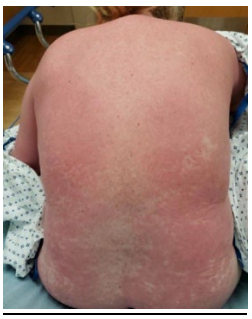

Figure 2. Erythematous and papulosquamous rash associated with Drug-Induced Eosinophilia and Systemic Symptoms (DRESS).

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