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Rechallenge of lamotrigine after development of rash

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Abstract

Lamotrigine (LTG) is associated with the potential for a life-threatening rash (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis). The incidence has been linked to rapid titration and an interaction with valproic acid that can increase the level of LTG. Providers often have difficulty discriminating between serious versus benign rashes, and the package insert recommends discontinuing the medication at the first sign of a rash. Therefore, many patients end up being taken off LTG when it may have been effective for them. We present a case where LTG is reintroduced with a faster initial titration than what is noted in the literature after development of a rash. This case is also unique in that the patient had been on LTG for years prior to emergence of the rash and demonstrates that retrials can be successful.

Keywords: lamotrigine, rash, bipolar disorder, rechallenge

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Background

Lamotrigine (LTG) is an anticonvulsant approved by the Food and Drug Administration for Lennox-Gastaut syndrome, partial seizures, tonic-clonic seizures, and maintenance treatment in bipolar I disorder.[1] Within bipolar disorder, it has the most evidence for the treatment of depression based on several evidence-based guidelines.[2-5] One major concern with using LTG is the potential for a life-threatening rash (eg, Stevens-Johnson syndrome [SJS] or toxic epidermal necrolysis [TEN]) that may occur in up to 0.3% of adults.[1] It typically occurs between day 5 and week 8 of LTG administration because of the delay required to activate the body's immune response; however there have been case reports of SJS developing after 6 months of LTG initiation.[6-8] Patients who develop SJS or TEN may initially present as having flu-like symptoms followed by painful red or purple colored rashes characterized by widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes.[9] These classically develop in the face and upper torso and can take weeks to months of recovery time.[9] Stevens-Johnson syndrome and TEN are associated with a mortality rate of up to 10% and 45%, respectively, because of sepsis.[10] Rashes that appear earlier (eg, days 1 to 5) and do not involve a fever are more likely to be benign and are characterized as bullous-fixed drug eruptions that can be pruritic or non-pruritic in nature.[9]

The incidence of a LTG-induced rash has been linked to both a rapid titration and an interaction with valproic acid that can increase the level of LTG by up to 50%.[1] Additional risk factors for a serious rash include human immunodeficiency virus, liver disease, advanced age, and concomitant use of antivirals, hypouricemic agents, and immunosuppressive agents.[11] Since the introduction of a gradual dose titration schedule in 1994, the rate of severe rashes with LTG has declined from 1% to less than 0.1%.[8] However, the risk of benign rashes has remained consistent at 8% to 11%.[8] The package insert recommends to discontinue LTG at the first sign of a rash.[1] Therefore, many patients end up being taken off LTG and not rechallenged despite its potential effectiveness. If a patient is rechallenged with LTG, it is recommended to wait at least 4 weeks, and the recommended starting dose

TABLE 1: Recommended titration for rechallenge of lamotrigine

Days (Weeks)	Dose, mg
1 to 14 (2)	12.5 daily
15 to 28 (2)	25 daily
29 to 42 (2)	25 twice daily
43 to 56 (2)	25 every morning and 50 at bedtime
57 to 70 (2)	50 twice daily

ranges from 5 mg every 3 days to 12.5 mg daily.[9,12,13] Although most case reports involving LTG rechallenge use a slower titration,[14-17] this is not always followed in clinical practice. In addition, there is no standardized approach for how to retrial LTG because of limited data.

Case Report

A 53-year-old male was admitted to inpatient psychiatry with bipolar I disorder (current episode depressed), borderline personality disorder, posttraumatic stress disorder, alcohol use disorder, and no identifiable risk factors for rash. He was continued on the following medications from home: lurasidone 40 mg every evening for mood stabilization, propranolol 20 mg twice daily for anxiety, bupropion SR (sustained release) 100 mg every morning for depression, and trazodone 50 mg at bedtime as needed for sleep. In addition, pertinent labs (eg, liver function tests, complete blood count) and vitals were all within normal limits. He had previously been on LTG (100 mg twice daily) for 6 years, but it was stopped by his psychiatrist 6 months prior to admission due to a rash on his face and arms. Unfortunately, documentation within the electronic medical record was limited, and dermatology did not evaluate the rash as the patient was treated in the emergency department. The pruritic rash initially presented over his eyebrows and spread to his face and arms. This was suppressed using oral steroids, and LTG was not discontinued at that time. Roughly 1 month later, the rash resurfaced after finishing the course of steroids, and LTG was stopped by the provider. Interestingly, despite stopping LTG, the rash persisted for an additional 5 weeks, resulting in 2 emergency department visits, and spread to his abdomen before resolving.

Upon admission, the patient asked to restart LTG despite having room for continued titration of lurasidone, stating it was the only medication that helped in the past. After reviewing his chart, several medication trials were noted including lithium, divalproex, and several second-generation antipsychotics. The risks and benefits were weighed, and the pharmacist recommended to restart LTG at a lower dose of 12.5 mg daily and titrate up every 2 weeks as recommended in Table 1. After the patient was started on LTG 12.5 mg daily, the dose was increased to 25 mg daily after only 8 days since he was inpatient and being closely monitored. At discharge, he was on day 14 of LTG therapy; the dose was then titrated further as an outpatient at a slower rate (Table 2). The reemergence of a rash was not reported while inpatient nor in subsequent mental health visits in the following 9 months; he also did not have any subsequent admissions to inpatient psychiatry.

TABLE 2: Case patient rechallenge schedule

Days (Weeks)	Dose, mg
1 to 8 (~1)	12.5 daily
9 to 25 (~2.5)[a]	25 daily
26 to 52 (~4)	25 twice daily
53 to present	25 every morning and 50 at bedtime

[a]Discharged from hospital on day 14

Discussion

A case series published in 2010 identified 48 cases of LTG rechallenge and noted a success rate of 87 percent.[12] No patients developed SJS or TEN; the 5 unsuccessful cases were due to development of either serious rashes (2 cases), benign rashes (2 cases), or signs of inflammation without rash (1 case). The rate of rash increased when the rechallenge began within 4 weeks of the initial rash (36% vs 7%, $P = .002$) and diminished when the initial rash had no signs of potential seriousness (0% vs 23%, $P = .01$), which was defined using a rating scale developed by the research team.[12] This scale ranged from 0 to 8 with higher scores indicating more serious symptoms including the following: exfoliation or erythroderma; purpura, tenderness, or blistering; facial or mucous membrane involvement; lymphadenopathy; hematological abnormalities (eg, eosinophilia) or elevated transaminase enzymes; and constitutional symptoms (fever, malaise, arthralgia, pharyngitis, cough).[11] For patients who underwent rechallenge, the average rash-severity rating was 1.2.[12] Only 1 patient with a severity rating greater than 2 was rechallenged, and this resulted in a potentially serious rash. Comparable results were seen in another study where higher ratings lead to increased reemergence of rash upon rechallenge (scale was slightly different, ranging from 1 to 5).[13]

Most of the case reports[12-15] follow a more conservative titration schedule similar to what is recommended by the manufacturer (Table 1). Therefore, we attempted to search the literature for success rates with a more aggressive titration schedule. One case report[16] described a failed retrial of LTG with a rapid titration schedule where the patient developed a maculopapular pruritic rash and

LTG was discontinued. Another case series[17] reported that 2 out of the 8 cases used a more rapid titration schedule, and both cases were successful with retrial of LTG; 1 developed a rash but not severe enough to warrant discontinuation.

It does not appear that our case patient exhibited any of the serious symptoms described above except for some facial involvement, so he would have been likely deemed a severity of 1.[11] Another key point in our case patient was that he had 2 subsequent emergency department visits 2 weeks and 1 month after stopping LTG with an increase in rash symptoms. This is inconsistent with a LTG-induced rash, which does not typically worsen after discontinuation. When examining refill history, he had a gap of about 3 weeks where he may have run out of LTG; however, he denies missing any doses. If he was without LTG for more than 3 to 5 days, retitration should take place starting back at 25 mg daily to lower risk of the life-threatening rash.[1] This may be important as he was previously prescribed 100 mg twice daily, which is well above the initial titration dose.

Conclusion

It is important to examine the risks versus benefits before a rechallenge with LTG as the success rate (ie, absence of rash) can be quite high. Although the rash in our case patient was diffuse and had some facial involvement, he did not have any mucous membrane involvement nor blistering of the skin, and the rash worsened after discontinuing LTG. In addition, pertinent labs/vitals were normal, he denied any flu-like symptoms, and he had previously been on LTG for almost 6 years with no rash. Since it had been more than 6 months of being off LTG and he felt this medication worked best, a rechallenge seemed to be an appropriate option. Although the initial titration during his inpatient stay was more aggressive than what is recommended, he did not develop any further rash. This is another case that can be added to the literature noting a successful retrial with LTG in a patient whose rash was considered *mild* per the rating scale used by Aiken and colleagues.[12] In addition, it can also be added to the limited evidence of successful retrials with a more rapid titration schedule. It is still unknown whether it would have been safe to continue LTG despite the rash and whether retrial earlier would have led to a different outcome. Continued reports of this nature are needed to establish safe retrials in those where the benefit of LTG is deemed to outweigh the risk.

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