Lamotrigine-induced Rash: Can We Stop Worrying?

Lamotrigine-induced Rash: Worth a Rechallenge

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PURPOSE: The only serious adverse event associated with lamotrigine (LTG) treatment is a hypersensitivity reaction primarily occurring as a rash. Despite this concern, LTG is an antiepileptic drug (AED) with one of the most favorable efficacy/tolerability ratios compared with the new as well as the old AEDs. Thus, this study aimed to evaluate the results of rechallenge with LTG after the initial rash.

METHODS: In total, 688 patients (350 as monotherapy, and 338 as add-on therapy) with either idiopathic generalized epilepsy or focal epilepsy were treated with LTG. The patients with LTG-induced rash were rechallenged with LTG. The dosage schedule was 5 mg every day or every second day for 14 days, increased by 5 mg every 14th day to 25 mg/day. After achieving the daily dosage of 25 mg/day, the uptitration was completed by following the current guidelines.

RESULTS: In 52 patients, a rash developed. The LTG-induced rash occurred in 6%, whereas 12 (1.8%) developed a rash shown to be coincidentally associated with the initiation of LTG therapy. In their cases, LTG was continued with success without intermission. Nineteen (38%) of the initial cohort were rechallenged with LTG, with a success rate of 84%.

CONCLUSIONS: This study is the first to provide a successful recipe verified in time for the rechallenge with LTG after the initial drug-induced rash. The concurrent use of valproate was not found in this study to represent an additional risk factor for the occurrence of the rash during rechallenge with LTG. Our results agree with previous findings that women are more likely to develop the rash ($P < 0.009$).

COMMENTARY

Of all the adverse events associated with lamotrigine (LTG), without a doubt, rash has been *the* one to cause the greatest concern. Indeed, before its release in the United States in 1994, LTG trials were complicated with severe rashes, presenting as Stevens–Johnson syndrome, toxic epidermal necrolysis, or severe hypersensitivity syndrome involving multiorgan dysfunction. The serious rashes led to the inclusion of a black-box warning in the prescribing information. The incidence of rashes associated with LTG was initially estimated at approximately 0.8% in pediatric patients (aged 16 years or younger) and 0.3% in adults, when used as adjunctive therapy for patients with epilepsy. The relatively high incidence of serious rash was attributed to a high initial dose and rapid titration, which prompted the manufacturer, in 1993, to recommend a lower initial dose and slower titration schedules. Thus, the starting dose of LTG was cut from 50 mg/day to 12.5 mg/day, when used as adjunct therapy with valproic acid, and from 100 mg/day to 50 mg/day, when added to a regimen of enzyme-inducing antiepileptic drugs (AEDs) (1).

The administration of LTG as an adjunct therapy to valproic acid has been identified as one of the risk factors for the rash (1). It is not the result of a pharmacodynamic interaction, but rather from a pharmacokinetic interaction between the two AEDs. Valproic acid (VPA) inhibits the clearance of LTG and, hence, coadministration results in higher LTG serum concentrations (2). Failure to adjust the dose of LTG to the decreased metabolic rate, which is about 50% lower (2), increases the risk of rash. This finding is further supported by a study demonstrating that the addition of VPA to an established LTG regimen does not yield a higher risk of rash (3).

A decrease in the incidence of LTG-related severe rashes since the implementation of the new dosing paradigms in 1993 confirmed the pathogenic role of high initial LTG doses and rapid titration schedules in their occurrence. For example, a review of yearly data collected in a population-based German registry of severe cutaneous disorders before and after the implementation of dosing regimens revealed 5 cases of LTG-related Stevens–Johnson syndrome from 4,450 exposures in 1993, whereas in 1994, this number decreased to 2 of 7,610 exposures, and by 1999, to 3 of 17,648 exposures (1,4). Furthermore, in clinical trials of bipolar and other mood disorders that followed

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the new dosing regimens, the rate of serious rash was 0.08% in adults treated with LTG monotherapy and 0.13% when used as adjunctive therapy—well below previous rates.

Data from the same German registry, collected between 1998 and 2001, have shown that when the new LTG dosing regimen is used, the risk of serious rash becomes comparable to that of other AEDs. Similarly, in a study published in April 2005, Mockenhaupt et al. (4) compared the risk of Stevens–Johnson syndrome and toxic epidermal necrolysis among five newly prescribed AEDs: carbamazepine, phenytoin, phenobarbital, VPA, and LTG. The investigators found that the risk of hospitalization related to these severe rashes was comparable among carbamazepine, phenytoin, phenobarbital, and LTG but lower for VPA.

Around the same time as the publication of the Mockenhaupt et al. study, a group of investigators in Denmark reported the results of a retrospective study, reviewed here, in which 16 (84%) of 19 patients were successfully "rechallenged" with LTG, after having experienced an LTG-related rash. Unfortunately, the Danish study failed to tell the entire story! First, the authors neglected to provide any data on the severity of the rash of patients who were and were not rechallenged or to offer any explanations for the criteria used by clinicians to rechallenge patients. Only 19 of 40 patients with a rash that was clearly associated with LTG administration were rechallenged. This study would have yielded more clinically meaningful information had the authors indicated differences with respect to the severity of the rash among the 19 patients who were rechallenged and the 21 patients who were not. Such detail, in turn, would have allowed criteria and firm strategies to be established for rechallenging with LTG after a rash.

This study was, by no means, the first to report successful rechallenge with LTG, as several individual case reports and small case series previously had been published, most of which included patients with nonserious rash. To date, no reliable data suggest that it is safe to rechallenge patients with LTG who have experienced serious rashes, and given the obvious ethical concerns, it is unlikely that such data would ever be forthcoming. Thus, rechallenge with LTG (or other AEDs, for that matter) should be restricted to patients with nonserious rashes.

Will these data change the concerns clinicians have had about LTG-related rash for all these years? The information may reassure some of the clinicians who were reluctant to prescribe this AED under any circumstance. More important, however, is the fact that the data do place the risk of LTG-related rash in a more realistic perspective: if the new dosing paradigm is followed, LTG has a risk comparable to that of other frequently prescribed AEDs that are known to cause a serious rash and for which clinicians must continue to observe standard practice precautions. In the case of nonserious rash, a rechallenge with LTG can potentially be considered.

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