Potentially serious Lamotrigine-related skin rash

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ABSTRACT

Objective: To report our experience with lamotrigine (LTG)-related skin rash in children with epilepsy.

Methods: We identified a series of consecutive children with epilepsy treated with LTG prospectively over a 5-year period ending 1st October 2005 at King Abdul-Aziz University Hospital and King Faisal Specialist Hospital and Research Center, Jeddah, Kingdom of Saudi Arabia.

Results: Of 207 children on LTG, 15 (7.2%) developed a skin rash with ages ranging between 3-12 years (mean 7.5). We used LTG as monotherapy in 3/15 and as add on in 12/15, mostly (10/15) in addition to valproic acid (VPA). The rash was mild with complete recovery in 7 children (47%). The remaining 8 (3.9% of the total) had severe rash that necessitated admission to hospital. Seven out of these 8 children were also receiving VPA. One child had superimposed secondary bacterial infection and admitted for intravenous antibiotics. Two children recovered slowly with extensive post-inflammatory hyperpigmentation. We diagnosed Stevens-Johnson syndrome in 5 children (2.4% of the total). One of these 5 children had progressive symptoms that evolved to toxic epidermal necrolysis. He required prolonged intensive care admission and developed sepsis with disseminated intravascular coagulopathy. He deteriorated despite supportive therapy, and died 5 weeks after the initiation of LTG therapy.

Conclusions: Lamotrigine is a novel antiepileptic drug with a favorable therapeutic profile and good tolerability. However, LTG-related skin rash is a potentially serious adverse event that should be carefully monitored. Although the risk is small, one should weigh this against the potential benefits, particularly in children on VPA.

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Lamotrigine (LTG) is a new antiepileptic drug (AED), which has a broad spectrum of antiepileptic properties.[1] It works on voltage gated sodium channels, thereby stabilizing the neuronal membrane and inhibiting the release of excitatory neurotransmitters such as glutamate and aspartate.[2] Multiple randomized, placebo-controlled and comparative studies demonstrated LTG efficacy in partial and generalized pediatric epilepsy.[1,2] Open label trials also documented its efficacy against infantile spasms, absence and juvenile myoclonic epilepsy.[3] Co-administration of valproic acid (VPA) and LTG has a synergistic effect with enhanced antiepileptic properties.[4] We found this combination most effective in intractable epilepsy, such as that seen in Lennox-Gastaut syndrome.[5] Children may not respond to VPA or LTG as monotherapy or with other AED combinations, however, when used together they can result in remarkable seizure control.[4,5] Lamotrigine is well tolerated and most side effects are related to the CNS including headache, somnolence, nausea, dizziness, diplopia, ataxia, and insomnia.[6] The main serious adverse event associated with LTG treatment is a hypersensitivity reaction primarily presenting as a rash, which affects 8-20% of patients.[7-10] The occurrence and severity of this idiosyncratic, immune-mediated rash are difficult to predict.[7,11] If the drug is continued or the dose escalated, the rash has a tendency to become worse.[12] Close monitoring of these patients is needed to detect features of Stevens-Johnson syndrome (SJS).[13] Skin rash is observed in higher proportions of children on VPA-LTG combination. The risk is higher if LTG was added to a patient already receiving VPA and not vice versa. Other risk factors include young age, previous history of hypersensitivity, high LTG starting dose, and rapid titration.[10] Following the increased recognition of serious skin rash, it was recommended that the starting dose should be reduced with gradual dose escalation to reduce that risk.[8,14]

In this paper, we report the experience with LTG-related skin rash in children with epilepsy in view of the updated literature. We hypothesized that based on the available pediatric literature, LTG-related skin rash is potentially serious, particularly when used in combination with VPA.

Methods. We identified a series of consecutive children with epilepsy treated with LTG prospectively over a 5-year period ending the 1st of October, 2005. Patients were identified through referrals to the pediatric neurology services at King Abdul-Aziz University Hospital (KAUH) and King Faisal Specialist Hospital and Research center (KFSH&RC), Jeddah, Saudi Arabia. Both are multispecialty adult and pediatric hospitals providing tertiary medical care for most of the regional population of western Saudi Arabia. Patients received LTG as monotherapy or add on for treating children with epilepsy. The LTG initial dose was not to exceed 25 mg/day or 1.5 mg/kg/day. The dose was doubled every 2 weeks until the minimum effective dose was reached (achieving a seizure free outcome) or up to a maximum dose of 10 mg/kg/day (as monotherapy), 5 mg/kg/day (with VPA), or 15 mg/kg/day (with enzyme inducers).[15] The risk of drug induced rash was explained to all parents, who were instructed to stop and seek medical advice at the first sign of such eruptions. They were warned that the rash could become more severe if they do not stop the drug immediately. Follow up by one pediatric neurologist was performed to document the occurrence of skin rash. The period of follow-up visits were standardized at 2, 4, and 6 weeks after LTG introduction. To be included, diffuse erythematous rash should have been recognized 1-4 weeks following LTG therapy and documented by the treating physician. Patient and disease related data were collected at the time of initial presentation with skin rash. Clinical course and outcome data were also collected on follow-up visit or hospitalization records if required.

Results. During the study period, we gave 207 children LTG for epilepsy. Most children had tried other AEDs with no response. A total of 15 (7.2%) children developed a skin rash (**Table 1**). There were 7 males and 8 females with ages ranging between 3-12 years (mean 7.5). Four of these children had a previous history of hypersensitivity to other AEDs. We used LTG as monotherapy in 3/15 and as add on in 12/15, mostly (10/15) in addition to VPA therapy. The initial LTG dose ranged between 5-25 mg/day (mean 9.5). The rash developed in the 2nd-4th weak (mean 2.8) after the initiation of LTG. Systemic symptoms were evident in 11 (73%) children in the form of malaise, anorexia, fever, and irritability. The rash was mild with complete recovery after LTG discontinuation in 7 children (47%). Two of the 4 children with a previous history of hypersensitivity to other AEDs recovered completely.

Also, 4 out of the 5 children not on concomitant VPA therapy recovered well when compared to only 3 of the 10 patients on VPA (**Table 1**). We continued LTG in one case (patient 10) as the rash disappeared spontaneously after dose reduction. The remaining 8 (3.9% of the total) had severe rash that necessitated admission to hospital for symptomatic therapy. Seven out of these 8 children were also receiving VPA. These children had targetoid lesions with diffuse erythematous maculopapular eruptions. One child (patient 14) had superimposed secondary bacterial infection and we admitted him for intravenous antibiotic therapy. Two other admitted children recovered slowly with extensive post-inflammatory cutaneous pigmentary change on follow-up. This slowly recovered over a period of few

Table 1 - Clinical details of 15 children with Lamotrigine-related skin rash.

No.	Age (years)	Gender	Onset (weeks)	Systemic symptoms	Other AED	Duration of symptoms	Outcome
1.	3	M	3	+	PHB	1 weeks	Rapid recovery
2.	4	F	2	+	VPA	3 weeks	Hospitalized (SJS)
3.	5	F	3	-	-	1 weeks	Rapid recovery
4.	6.5	M	2	+	VPA	Progressive	Death (TEN)
5.	7	F	2	-	VPA, TPM	3 weeks	Hospitalized (SJS)
6.	7	M	4	+	VPA, CBZ	1 weeks	Rapid recovery
7.	7	F	3	+	VPA	2 weeks	Post-inflammatory hyperpigmentation
8.	7.5	F	4	-	TPM, CBZ	1 week	Rapid recovery
9.	8	M	2	+	-	3 weeks	Hospitalized (SJS)
10.	8	F	3	+	VPA	1 weeks	Rapid recovery
11.	8.5	F	3	+	-	1 week	Rapid recovery
12.	9	M	2	+	VPA	3 weeks	Post-inflammatory hyperpigmentation
13.	9	M	3	-	VPA	2 weeks	Hospitalized (SJS)
14.	11	F	2	+	VPA, TPM	3 weeks	Sepsis
15.	12	M	4	+	VPA	1 week	Rapid recovery

PHB - Phenobarbitone, VPA - Valproic Acid, TPM - Topiramate, CBZ - Carbamazepine, SJS - Stevens-Johnson syndrome, TENS - toxic epidermal necrolysis

months. We diagnosed SJS in 5 (2.4% of the total) children with additional erosions of the conjunctiva, oral, and genital mucosa. One of these 5 children (patient 4) had progressive symptoms that evolved to toxic epidermal necrolysis (TEN), confirmed by skin biopsy. He required prolonged ICU admission and developed sepsis with disseminated intravascular coagulopathy. He deteriorated despite supportive therapy and died 5 weeks after the initiation of LTG therapy.

Discussion. The patients described herein confirm that LTG-related skin rash is potentially serious, as approximately 4% of the children required hospitalization, 2.4% had SJS, and one child died with TEN. In general, children are at increased risk for developing LTG-related skin rash when compared to adults.[10] Increased liver cytochrome P450 catalyzed metabolism could result in increased formation of the reactive metabolite and a higher incident of rash.[10] In addition, children frequently receive higher mg/kg doses resulting in increased LTG reactive metabolites. We had a lower overall incidence of skin rash (7.2%) as compared to the rate in other studies (8-20%), most likely because of our dosing and slow increment. Other authors used an even lower initial dose (5 mg/day) and much slower titration by 5 mg every 2 weeks.[7,9] The incidence of LTG-related skin rash in these studies was 5-6%. Most of our children with severe rash (8/15) were also receiving VPA (7/8), which is similar to other literature reports.[16] Valproic acid interferes with the metabolism of LTG by inhibiting hepatic glucuronides, leading to increased LTG blood levels.[12,16] Therefore, LTG dose should not exceed 5 mg/kg/day when used with VPA.

Steven and Johnson described SJS in 1922. The syndrome includes systemic symptoms (fever) and a variety of skin and mucous membrane lesions including erythematous papules, targetoid lesions, bullae, and erosions.[17] It is a hypersensitivity reaction to infections or drugs, such as phenytoin, carbamazepine, and LTG. Most reported cases of severe skin rash and SJS included patients treated with both VPA and LTG.[16] However, serious SJS and TEN from LTG are infrequent.[18] Chaffin and Davis reported a suspected case of LTG-induced TEN in an adult patient.[16] His symptoms started 14 days after LTG therapy with a rapidly progressive rash. They discontinued the LTG and he recovered after 26 days of hospitalization.[16] Our patient with TEN had progressive symptoms and a complicated course that resulted in fatal outcome. A low starting dose, slow titration, and by excluding children with a previous history of hypersensitivity, may lessen these risks.[4,7,9] Only 4 of our children had a previous history of hypersensitivity to other AEDs and 2 of them had complete recovery. Ketter et al[9] suggested a "limited antigen exposure" regimen, immediately before and during LTG therapy. They did not start LTG within 2 weeks of a rash, viral illness, or vaccination. They also asked their patients to avoid new medications, new foods, detergents, and fabric softeners in the first 3 months of treatment. Following these recommendations, skin rash occurred in 5% of their patients.[9] Milder maculopapular skin rash beginning within 2 weeks of therapy may disappear spontaneously in some patients, despite the continuation of therapy.[13] This is similar to one of our patients where the rash disappeared spontaneously after dose reduction. The rash was mild with complete recovery after LTG discontinuation in 7 of our 15 children. Recently, some authors reported successful rechallenge with LTG after the initial drug-induced rash.[7] It is possible that the rash in some of these children was not related to LTG, which explains the successful rechallenge. Reintroducing LTG in children with history of rash that developed within the first 4 weeks of therapy should be taken with extreme caution. Such a child may be sensitized to LTG, which results in a stronger and severer reaction if LTG is reintroduced. Of possible relevance is a rare LTG-related lupus case diagnosed in an adult female patient.[19] Her symptoms and lupus serology gradually normalized after drug withdrawal.[19]

To conclude, LTG is a novel antiepileptic drug with a favorable therapeutic profile. The drug has good tolerability; however, skin rash is a potentially serious adverse event that the parents should carefully monitor and promptly report to the treating physician. Although the risk is small, we should weigh this against the potential benefits, particularly in children on VPA.

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