

Toxic epidermal necrolysis due to lamotrigine in a pediatric patient

Manish J. Barvaliya, Mahendra K. Patel, Tejas K. Patel¹, C. B. Tripathi

Department of Pharmacology, Government Medical College, Bhavnagar, ¹Department of Pharmacology, GMERS Medical College, Gotri, Vadodara, Gujarat, India

ABSTRACT

A 12-year-male child developed toxic epidermal necrolysis (TEN) probably due to lamotrigine. The patient was on antiepileptic therapy (sodium valproate and clonazepam) since 6–7 months, and lamotrigine was added in the regimen 1–2 months back. A serious cutaneous reaction is more likely to occur during the first 2 months of starting lamotrigine. The use of lamotrigine as an add-on to valproate may have precipitated the reaction. Other drugs were ruled out based on the incubation period of TEN. Drug interactions should be kept in mind with multiple antiepileptic therapies. The patient died because of the severity of reactions and delay in starting the treatment with steroids. One must be vigilant in early detection of the reaction.

Key words: Cutaneous adverse drug reaction, lamotrigine, toxic epidermal necrolysis

INTRODUCTION

Toxic epidermal necrolysis (TEN) is a rare immune-mediated life-threatening reaction for which drugs account more than 95% of cases. Incidence of TEN is 0.4–1.2 cases per million population per year.^[1] TEN is a severe form of Stevens-Johnson syndrome (SJS), in which involvement of body surface area (BSA) is more than 30%. SJS and TEN are more commonly caused by antimicrobials, antiepileptics, and NSAIDs. Among antiepileptics, phenytoin and carbamazepine are reported to cause TEN.^[2–4] Lamotrigine is also reported as a common culprit drug to cause this serious reaction in western population.^[5,6] Due to its limited utilization, it is not reported as a culprit in Indian population. Here, we report

a case of TEN developed probably due to lamotrigine in a pediatric patient.

CASE REPORT

A 12-year-old male patient was admitted in Sir Takhtsinhji General Hospital, Bhavnagar, Gujarat, India, with a history of skin lesions, redness of eye, and shortness of breath for 3 days. Based on detailed history, it was understood that the patient was having a history of intermittent fever since 4 days for which he was prescribed chloroquine, cefixime+potassium clavulanate, paracetamol, and primaquine p.o. The patient consumed only a single dose of the treatment and developed swelling over eyelids with redness of the eye within 4 h. As the time spent, the patient developed multiple blisters and vesicular lesions first over the face and followed by on chest, abdomen, back, and extremities. Initially, lesions were few and then increased in number. The patient consulted the doctor after 1 day of development of lesions. The patient did not consume the other doses of prescribed treatment for fever after the development of reaction. The patient was diagnosed as SJS and referred to our hospital. On evaluation of drug

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.103695

Address for correspondence:

C. B. Tripathi, CM 31/13, Shantinagar 2, Kaliyabid, Bhavnagar 364 001, Gujarat, India. E-mail: cbtripathi@yahoo.co.in

history, the patient was found to be a known case of epilepsy since last 6-7 months. He was on tablet sodium valproate 300 mg/day and tablet Clonazepam 0.25 mg/day. Lamotrigine 50 mg/day p.o. was added in treatment 1–2 months back. He was taking these medicines regularly and stopped them after the emergence of reaction.

At the time of admission, the patient was delirious, uncooperative, and disoriented to time, place, and person. On examination, his vitals were: temperature 101 °F, pulse rate 140/min, blood pressure 100/70 mmHg, and respiratory rate 40/min. There were multiple erythematous, flaccid, clear fluid-filled vesicles, and bullae of varying sizes along with some erosions over the face, chest, abdomen, back, and extremities. Conjunctiva and cornea were congested. Multiple erosions were noted on oral cavity and genitals. Nikolsky sign was positive. Total BSA involvement was of 66%. Diagnosis of drug-induced TEN was made clinically. No skin biopsy was performed.

On the day of admission, investigations revealed: Hb 12.0 g% (12–15 g%), total leucocyte count 5600 cells/cmm (4400–11,000 cells/cmm), serum creatinine 1.0 mg% (0.9–1.4 mg%), blood urea 25 mg% (15–40 mg%), and SGPT 30 U/L (upto 45 U/L). Peripheral smear was negative for malarial parasites. On admission, the patient was given humidified oxygen (6 l/min), Inj. dexamethasone, Inj. chlorpheniramine maleate, Inj. ciprofloxacin, Inj. vancomycin, and Inj. metronidazole along with nursing care of skin, eye, and oral cavity. The fluid and electrolyte balance was maintained through intravenous fluids. The patient was intubated due to irregularity in respiration and died within 12 h of admission due to respiratory failure.

A causality analysis was done using the Naranjo's algorithm, and ADR was found 'probable' with lamotrigine.^[7] The reaction was not preventable according to the modified Schumock and Thornton scale, and the modified Hartwig and Siegel scale showed that the reaction was severe (level 7).^[8,9] The SCORTEN score for this patient was 02 (BSA > 10%, heart rate > 120/min).^[10]

DISCUSSION

Lamotrigine is a newer antiepileptic drug used in treatment of epilepsy and bipolar disorder. TEN is a rare, but serious side effect of antiepileptic drugs, including lamotrigine. Due to its limited utilization, it is not reported as an offending agent to cause SJS and TEN in major Indian studies.^[2–4] The period of risk to cause TEN is more within initial 8 weeks.^[11] They appear to increase when it is co-administered with valproate.^[12] The patient was taking sodium valproate along with lamotrigine. Lamotrigine is metabolized by uridine glucuronyl transferase (UGT). Sodium valproate inhibits UGT,

and decreases clearance of lamotrigine. Thus, concomitant valproate therapy may lead to high plasma concentration of lamotrigine, and it also increases the risk of developing allergic reactions.^[13,14] Low initial dose, slow titration, and reduction in 50% of lamotrigine dose are required when it is added to valproate.^[15] Drug interactions should be kept in mind during prescribing multiple antiepileptic drugs.

Even though, being a common culprit, chloroquine, primaquine, cefixime, and paracetamol are not likely to be responsible for causing this reaction as the reaction started within 4 h of consuming these drugs. The presence of fever in this patient may be the prodromal feature as fever is the most common prodromal symptom experienced by the patients of SJS/TEN.^[4] TEN is caused by the cytotoxic lymphocytes mediated immune reaction and is characterized by lag period of 2–8 weeks between the exposure and disease onset. It is very rare to develop such a reaction within 4 h of consumption of drugs. In this case, TEN is more likely due to lamotrigine, as an incubation period required to develop TEN is around 2–8 weeks, and lamotrigine was added to valproate in the treatment 2 months back.^[16]

The patient did not recover on withdrawal of an offending agent and expired as the reaction was severe. This may be due to delay in starting treatment with steroids. Beneficial effects of steroids are noted if they are started with proper dose and as early as possible.^[2] A recent systemic review of treatment in drug-induced SJS and TEN in children has shown that steroids and IVIG improve the outcome of patients.^[1] As such a type of reaction is genetically determined and not preventable, one must be vigilant in early detection of the reaction, and treatment should be started with steroids or IVIG as early as possible to improve the outcome.

ACKNOWLEDGMENTS

We are sincerely thankful to Dr. Rajesh Patel and Dr. Chintu Chaudhri, resident doctors, and Dr. J. R. Gohil, Professor and Head, Department of Pediatrics, Government Medical College and Sir Takhtsinhji General Hospital, Bhavnagar, for reporting this ADR to Pharmacovigilance cell.

REFERENCES

1. Del Pozzo-Magana BR, Lazo-Langner A, Carleton B, Castro-Pastrana LJ, Rieder MJ. A systematic review of treatment of drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *J Popul Ther Clin Pharmacol* 2011;18:121–33.
2. Barvaliya M, Sanmukhani J, Patel T, Paliwal N, Shah H, Tripathi C. Drug-induced Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS-TEN overlap: A multicentric retrospective study. *J Postgrad Med* 2011;57:115–9.
3. Sharma VK, Sethuraman G, Minz A. Stevens Johnson syndrome, toxic epidermal necrolysis and SJS-TEN overlap: A retrospective study of causative drugs and clinical outcome. *Indian J Dermatol Venereol Leprol*

Barvaliya, *et al.*: Lamotrigine induced toxic epidermal necrolysis

- 2008;74:238-40.
4. Sanmarkan AD, Sori T, Thappa DM, Jaisankar TJ. Retrospective analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis over a period of 10 years. *Indian J Dermatol* 2011;56:25-9.
 5. Varghese SP, Haith LR, Patton ML, Guilday RE, Ackerman BH. Lamotrigine-induced toxic epidermal necrolysis in three patients treated for bipolar disorder. *Pharmacotherapy* 2006;26:699-704.
 6. Ferrándiz-Pulido C, García-Fernández D, Domínguez-Sampedro P, García-Patos V. Stevens-Johnson syndrome and toxic epidermal necrolysis in children: A review of the experience with paediatric patients in a University Hospital. *J Eur Acad Dermatol Venereol* 2011;25:1153-9.
 7. Naranjo CA, Busto U, Seller EM, Sandor P, Ruiz I, Roberts EA, *et al.* A method for estimating the probability of adverse drug reaction. *Clin Pharmacol Ther* 1981;30:239-55.
 8. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hosp Pharm* 1992;27:538.
 9. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm* 1992;49:2229-32.
 10. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: A severity-of-illness score of Toxic Epidermal Necrolysis. *J Invest Dermatol* 2000;112:149-53.
 11. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: A case-control study. Study group of the International case control study on severe cutaneous adverse reactions. *Lancet* 1999;353:2190-4.
 12. Feliciani C, Verrotti A, Coscione G, Toto P, Morelli F, Di Benedetto A, *et al.* Skin reactions due to anti-epileptic drugs: Several case-reports with long-term follow-up. *Int J Immunopathol Pharmacol* 2003;16:89-93.
 13. Anderson GD, Yau MK, Gidal BE, Harris SJ, Levy RH, Lai AA, *et al.* Bidirectional interaction of valproate and lamotrigine in healthy subjects. *Clin Pharmacol Ther* 1996;60:145-56.
 14. Kocak S, Girgin SA, Gul M, Cander B, Kaya H, Kaya E. Stevens-Johnson syndrome due to concomitant use of lamotrigine and valproic acid. *Am J Clin Dermatol* 2007;8:107-11.
 15. Johannessen SI, Landmark CJ. Antiepileptic drug interactions - principles and clinical implications. *Curr Neuropharmacol* 2010;8:254-67.
 16. Levi N, Bastuji-Garin S, Mockenhaupt M, Roujeau JC, Flahault A, Kelly JP, *et al.* Medications as risk factors of Stevens-Johnson syndrome and toxic epidermal necrolysis in children: A pooled analysis. *Pediatrics* 2009;123:297-304.

How to cite this article: Barvaliya MJ, Patel MK, Patel TK, Tripathi CB. Toxic epidermal necrolysis due to lamotrigine in a pediatric patient. *J Pharmacol Pharmacother* 2012;3:336-8.

Source of Support: Nil, **Conflict of Interest:** None declared.

Staying in touch with the journal

1) Table of Contents (TOC) email alert

Receive an email alert containing the TOC when a new complete issue of the journal is made available online. To register for TOC alerts go to www.jpharmacol.com/signup.asp.

2) RSS feeds

Really Simple Syndication (RSS) helps you to get alerts on new publication right on your desktop without going to the journal's website. You need a software (e.g. RSSReader, Feed Demon, FeedReader, My Yahoo!, NewsGator and NewzCrawler) to get advantage of this tool. RSS feeds can also be read through FireFox or Microsoft Outlook 2007. Once any of these small (and mostly free) software is installed, add www.jpharmacol.com/rssfeed.asp as one of the feeds.