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Net Case

Lamotrigine-induced cutaneous adverse drug reactions: A case series

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ABSTRACT

Lamotrigine is used in the management of seizures and bipolar disorder. Cutaneous adverse drug reactions (CADRs) including severe forms are not uncommon following lamotrigine. Existing data suggest that the risk for adverse events could be reduced by initiating the drug at a lower dose and going for a slow titration to therapeutic dose. Here, we report four cases of lamotrigine-induced CADR. Three of the four suffered from severe drug reactions and in none of them lamotrigine was administered according to recommended guidelines.

Keywords: Lamotrigine, Cutaneous adverse drug reactions, Slow titration

INTRODUCTION

Lamotrigine is an aromatic phenyltriazine that has found uses in the management of refractory partial and generalized seizures and also in bipolar disorders (due to its mood stabilizing effects).[1] One of the important factors limiting the use of lamotrigine is its potential to cause cutaneous adverse reactions that range from maculopapular rash to severe life-threatening forms such as Stevens–Johnson syndrome-toxic epidermal necrolysis (SJS-TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS).[1-3] As per literature high initial dose, rapid titration to therapeutic dose and coadministration of sodium valproate can increase the risk of adverse effects to lamotrigine.[1-3]

We report four cases of lamotrigine-induced CADR who were admitted in the dermatology ward of our tertiary care center.

CASE REPORTS

Case 1

A 45-year-old male patient who was suffering from bipolar disorder for previous 10 years presented with fever, diffuse erythroderma, and facial puffiness of 1 week duration. The rash was intensely pruritic. Mucosal involvement was minimal and was confined to scaling of lips. The patient was on lithium and olanzapine for 3 years and lamotrigine was added 4 weeks ago when the bipolar illness worsened. Lamotrigine was initiated at a dose of 50 mg once daily and the patient was maintained at the same dose for 1 month. Investigations revealed total leukocyte count of 11,000 cells/mm^3. Absolute eosinophil count and urine microscopy were within normal limits. Blood

and urine cultures were sterile. Liver function test showed 5 times elevation of transaminases. Renal function test was within normal limits. Peripheral smear had 16% of atypical lymphocytes. Viral markers for hepatitis and serology for human immunodeficiency virus (HIV) infection and antinuclear antibody (ANA) were negative. Detailed workup ruled out infective causes. As per the registry of severe cutaneous adverse reaction (RegiSCAR) DRESS validation scoring, the patient was diagnosed as probable DRESS. (DRESS validation score – 5, 1 point each for rash suggestive of DRESS diagnosed on the basis of facial edema and psoriasiform desquamation [Figure 1], involvement of more than 50% body surface area, presence of atypical lymphocytes in peripheral smear, elevated liver transaminases, and negative serology for HIV, ANA, and hepatitis A, B, and C viruses).[4,5] Withdrawal of lamotrigine and administration of systemic steroids that were tapered over 35 days (parenteral dexamethasone 8 mg followed by prednisolone per orally) attained resolution of symptoms. The score on Naranjo probability scale was 7 favoring a diagnosis of probable drug reaction [Table 1].[6]

Case 2

A 16-year-old female patient who was on sodium valproate for seizure disorder was prescribed lamotrigine. The drug was started at 25 mg once daily, which was increased to 50 mg after 14 days. The patient developed fever and redness of eyes 1 month after starting lamotrigine, for which she received amoxicillin clavulanic acid combination and paracetamol from a nearby doctor. The following day, the patient developed purpuric macules all over the body. She consulted the doctor again. The antibiotic, antipyretic, and eye drops were withdrawn and she was started on prednisolone 30 mg/day per orally. The lesions progressed to hemorrhagic vesicles involving more than 30% body surface area along with oral and genital erosions. She had taken the same antibiotic and antipyretic in the past without any untoward events. Her laboratory investigations were within normal limits. Suspecting TEN [Figure 2] to lamotrigine, the latter was substituted with levetiracetam and the patient was prescribed intravenous immunoglobulin G 10 g daily for 3 days, parenteral dexamethasone 8 mg, and tobramycin eye drops (as per the advice of the ophthalmologist).[7] There was a gradual, but steady improvement and the patient was diagnosed as probable TEN to lamotrigine (score 7 in Naranjo probability scale, Table 1).[6] Dexamethasone was tapered and withdrawn over 14 days.

Case 3

A 36-year-old female patient who was prescribed lamotrigine (for mood disturbances) at a dose of 25 mg twice daily which was increased to 50 mg twice daily after 2 weeks presented with pruritic maculopapular rash 3 weeks after starting the drug. The patient had no other constitutional symptoms and the laboratory parameters were within normal limits. The patient responded to withdrawal of the drug and the administration of antihistamine (pheniramine maleate 25 mg twice a day) and emollient. Diagnosis of probable maculopapular drug rash to lamotrigine was made (Naranjo probability score – 7, Table 1).[6]

Case 4

A 24-year-old female patient who was receiving sodium valproate since the age of 16 stopped the drug on her own 2 years ago. She was prescribed lamotrigine as monotherapy when she developed seizure recurrence. Drug was initiated at 25 mg during the 1st week and increased by 25 mg/week till 100 mg. One week after taking 100 mg of lamotrigine, the patient presented with features suggestive of DRESS (fever,

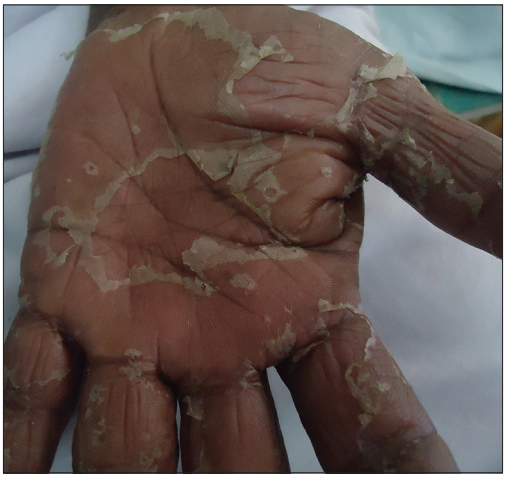

Figure 1: Psoriasiform desquamation of palms in lamotrigine-induced drug reaction with eosinophilia and systemic symptoms.

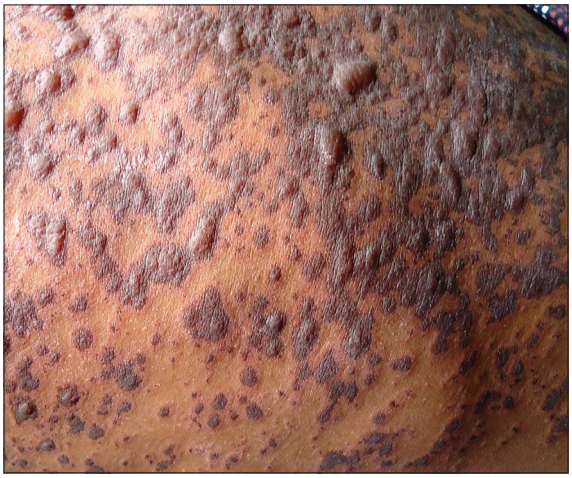

Figure 2: Epidermal necrosis and hemorrhagic vesicles in lamotrigine-induced toxic epidermal necrolysis.

Table 1: Naranjo probability scale in suspected lamotrigine-induced adverse drug reaction.

Naranjo adverse drug reaction probability scale																
Question	**Case 1**				**Case 2**				**Case 3**				**Case 4**			
	Yes	**No**	**Do not know**	**Score of the patient**	**Yes**	**No**	**Do not know**	**Score of the patient**	**Yes**	**No**	**Do not know**	**Score of the patient**	**Yes**	**No**	**Do not know**	**Score of the patient**
Are there previous conclusive reports on this reaction	+1	0	0	+1	+1	0	0	+1	+1	0	0	+1	+1	0	0	+1
Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2	+2	−1	0	+2	+2	−1	0	+2	+2	−1	0	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1	+1	0	0	+1	+1	0	0	+1	+1	0	0	+1
Did the adverse event reappear when the drug was readministered?	+2	−1	0	0	+2	−1	0	0	+2	−1	0	0	+2	−1	0	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	+2	−1	+2	0	+2	−1	+2	0	+2	−1	+2	0	+2
Did the reaction reappear when a placebo was given?	−1	+1	0	0	−1	+1	0	0	−1	+1	0	0	−1	+1	0	0
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0	+1	0	0	0	+1	0	0	0	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0	+1	0	0	0	+1	0	0	0	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0	+1	0	0	0	+1	0	0	0	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	+1	+1	0	0	+1	+1	0	0	+1	+1	0	0	+1
Total score				7				7				7				7

Table 2: The dose of lamotrigine received by our patients and the recommended initial dose and titration of lamotrigine.

Cases	Weeks 1–2		Weeks 3–4		Week 5 onward till maintenance dose is reached	
	Received by patient	Recommended	Received by patient	Recommended	Received by patient	Recommended
Case 1	50 mg once daily	25 mg once daily	50 mg once daily	25 mg twice daily	-	Increase by 50 mg/day every 1–2 weeks
Case 2 (coadministered with sodium valproate)	25 mg once daily	25 mg alternate days	50 mg once daily	25 mg once daily	-	Increase by 25–50 mg/day every 1–2 weeks
Case 3	25 mg twice daily	25 mg once daily	50 mg twice daily	25 mg twice daily	-	Increase by 50 mg/day every 1–2 weeks
Case 4	25 mg once daily during the 1st week and 50 mg once daily during the 2nd week	25 mg once daily	75 mg once daily during the 3rd week and 100 mg once daily during the 4th week	25 mg twice daily	-	Increase by 50 mg/day every 1–2 weeks

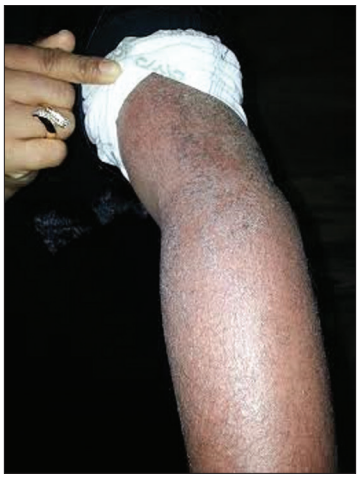

Figure 3: Psoriasiform desquamation of upper arm in lamotrigine-induced drug reaction with eosinophilia and systemic symptoms.

generalized psoriasiform desquamation [Figure 3], facial edema, elevated liver transaminases, multiple lymphadenopathy, elevated absolute eosinophil count (960 cells/mm^3), atypical lymphocytes in peripheral smear and negative serology for HIV, ANA, and hepatitis A, B, and C viruses, RegiSCAR DRESS validation score – 7).[4,5] Substitution of lamotrigine with levetiracetam and administration of systemic corticosteroids (Initial dose was parenteral dexamethasone 6 mg once a day. After 5 days, this was substituted with 30 mg prednisolone/day per orally. Prednisolone was tapered over 30 days and stopped) attained resolution of symptoms (Naranjo probability score – 7, Table 1).[6]

DISCUSSION

Lamotrigine is approved by the United States Food and Drug Administration, as an add-on or monotherapy for partial and generalized seizures in adults for bipolar disorder and for seizures associated with Lennox-Gastaut syndrome.[8,9] About 10% of those who are prescribed lamotrigine are reported to develop adverse drug reactions which could be severe forms like DRESS/SJS-TEN.[9] The skin rash of lamotrigine is dependent on the initial dose and the rate of titration to therapeutic dose.[1-3]

The drug is metabolized mainly by glucuronidation and minor amounts are converted to arene oxide intermediates. Drugs like sodium valproate that inhibit glucuronidation and prolong elimination half-life of lamotrigine increase the risk of adverse reactions to the latter.[1,3]

A lower initial dose and slower upward titration are recommended when lamotrigine is coadministered with sodium valproate [Table 2].[1-3]

In our series, all the four patients who manifested cutaneous adverse reactions were prescribed lamotrigine at higher than the recommended initial dose; the subsequent titration was also faster than the recommended schedule [Table 2].[1-3] Three of the four patients (DRESS-2, TEN-1) developed severe cutaneous adverse reactions.

Our cases highlight the importance of adhering to standard guidelines in initiating and titrating lamotrigine.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

Dr Sarita Sasidharanpillai is on the editorial board of the Journal.

REFERENCES

1. Bourgeois BF: Antiepileptic drugs (AEDs). In: Wallace SJ, Farrell K, editors. Epilepsy in Children. 2nd ed. England: Edward Arnold Publishers Limited; 2004. p. 387-404.
2. Sasidharanpillai S, Sabitha S, Riyaz N, Binitha MP, Muhammed K, Riyaz A, *et al*. Drug reaction with eosinophilia and systemic symptoms in children: A prospective study. Pediatr Dermatol 2016;33:e162-5.
3. Zaccara G, Franciotta D, Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. Epilepsia 2007;48:1223-44.
4. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, *et al*. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: Does a DRESS syndrome really exist? Br J Dermatol 2007;56:609-11.
5. Chen YC, Chang CY, Cho YT, Chiu HC, Chu CY. Reply to: "Using a diagnostic score when reporting the long-term sequelae of the drug reaction with eosinophilia and systemic symptoms". J Am Acad Dermatol 2013;69:1060-2.
6. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
7. Jagadeesan S, Sobhanakumari K, Sadanandan SM, Ravindran S, Divakaran MV, Skaria L, *et al*. Low dose intravenous immunoglobulins and steroids in toxic epidermal necrolysis: A prospective comparative open-labelled study of 36 cases. Indian J Dermatol Venereol Leprol 2013;79:506-11.
8. Schiller Y, Krivoy N. Safety and efficacy of lamotrigine in older adults with epilepsy and co-morbid depressive symptoms. Clin Med Insights 2009;1:825-33.
9. Al-Quliti KW, Al-Amri MS. Lamotrigine-related severe cutaneous adverse reaction in patient with epilepsy. J Neurol Disord 2015;S1:005.

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