Toxic epidermal necrolysis caused by lamotrigine

Mike Sladden, FRACGP, MRCP, MAE, is a clinical epidemiologist and specialist registrar, Department of Dermatology, Leicester Royal Infirmary, United Kingdom.

Neil Mortimer, MRCP, is a specialist registrar in dermatology, Department of Dermatology, Leicester Royal Infirmary, United Kingdom.

Toby Chave, MRCP, is consultant in dermatology and venereology, Truro, United Kingdom.

BACKGROUND

The use of lamotrigine is increasing. Many general practitioners prescribe it in the treatment of epilepsy and as a mood stabilising agent. It has also been suggested as the agent of choice in pregnant women with epilepsy.

OBJECTIVE

This article describes the case histories of two patients who present with oral lesions and an extensive rash after starting treatment with lamotrigine.

DISCUSSION

Toxic epidermal necrolysis (TEN) is a potentially fatal adverse mucocutaneous drug reaction. Simple maculopapular rashes occur commonly with lamotrigrine. Although rare, serious mucocutaneous reactions such as TEN can occur soon after commencement of treatment with lamotrigine, or after a dose increase in patients already established on treatment. The risk can be minimised by commencing at a low dose, avoiding rapid increases in dosage, and avoiding concomitant use of sodium valproate.

Case history 1

A 26 year old woman presented with a 3 day history of painful, swollen lips and sore eyes. She had been taking sodium valproate for epilepsy since the age of 18 years. Owing to poor epilepsy control, lamotrigine had been introduced 2 months previously. She was commenced on 25 mg alternate days, increasing to 25 mg per day 2 weeks before presentation. Examination revealed severe oral mucositis (*Figure 1*). There was a purple, papulovesicular eruption on the trunk and limbs with palmar involvement. This rash became more extensive over the next few days. Nikolsky's sign (shearing off of the epidermis with lateral pressure) was positive, and in areas large bullae developed (*Figure 2*). We diagnosed toxic epidermal necrolysis (TEN) secondary to lamotrigine, and immediately stopped the drug. She received supportive therapy and made an uneventful recovery.

Case history 2

A 60 year old woman was commenced on lamotrigine for bipolar affective disorder. The dose was titrated up rapidly to 100 mg twice per day. After 4 weeks, she developed painful mouth ulcers followed by a widespread erythematous rash. Over the next 24 hours she developed bullae and large areas of epidermal shedding (*Figure 3*). We made a diagnosis of TEN due to lamotrigine. The drug was stopped and she received intensive supportive care. The patient made a full recovery.

Discussion

Toxic epidermal necrolysis is a rare, mucocutaneous disorder with a mortality rate of 30–70%, due mainly to sepsis and haemodynamic failure. It is almost always drug related – most frequently antibiotics (particularly sulphonamides) or anticonvulsants. Toxic epidermal necrolysis starts as an acute macular exanthem, progressing to bulla formation and then full thickness epidermal loss.

Lamotrigine is used in the treatment of partial seizures and generalised tonic-clonic seizures, either as monotherapy or adjunctive treatment. It is also used as a mood stabiliser in bipolar affective disorder and to treat trigeminal neuralgia. Although simple maculopapular rashes occur commonly during treatment with lamotrigine (3–15%),[1,2] severe cutaneous reactions such as TEN are rare. Adverse reactions are more common:

- in the first 8 weeks of treatment
- with large initial doses of lamotrigine
- with rapid dose escalation,[3,4] and
- when the patient is taking concomitant sodium valproate.[3]

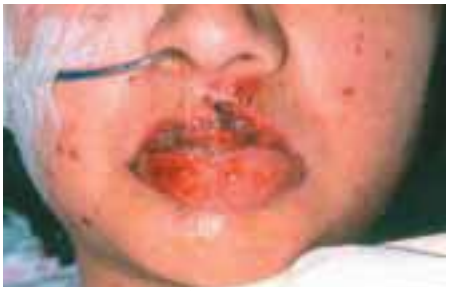

Figure 1. Severe oral mucositis in a patient with TEN

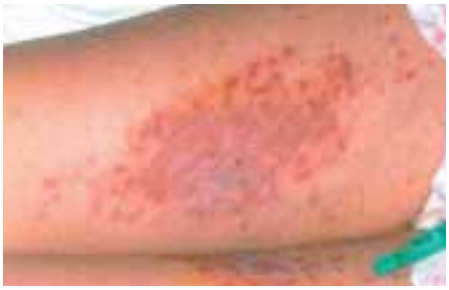

Figure 2. Large bullae in TEN demonstrating positive Nikolsky's sign

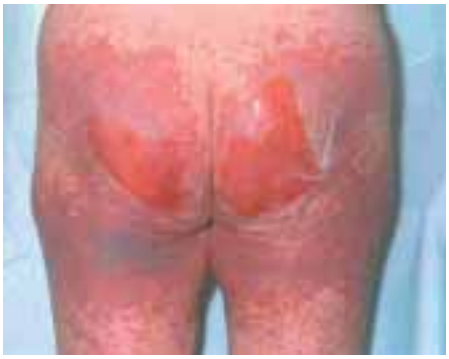

Figure 3. Confluent bullae with large areas of epidermal shedding

Management

Management of TEN should be in an experienced dermatological intensive care unit or specialised burns unit. General supportive measures are imperative, but there is little evidence to support any specific therapeutic agents in the management of TEN. Suggested treatments include intravenous immunoglobulin, cyclosporin and plasmapheresis. If patients survive TEN, skin regeneration occurs within a few weeks typically without scarring. Severe mucosal involvement however, can lead to significant complications including blindness.

There is only one previously reported case of lamotrigine induced TEN in the Australian literature,[5] however, many general practitioners provide care for patients taking lamotrigine. We present these cases to remind readers of the potential for life threatening adverse cutaneous reactions resulting from treatment with lamotrigine.

The risk of severe cutaneous side effects from lamotrigine can be minimised by commencing at a low dose, avoiding rapid increases in dosage and reducing the use of concomitant sodium valproate.

Summary of important points

- TEN is a potentially fatal adverse cutaneous drug reaction – usually developing during the first 8 weeks of treatment.
- Concomitant therapy with sodium valproate increases the risk of developing TEN.
- The risk can be minimised by starting with a low dose and slow dose titration, particularly in patients taking valproate.

Conflict of interest: none declared.

References

1. Chaffin JJ, Davis SM. Suspected lamotrigine induced toxic epidermal necrolysis. Ann Pharmacother 1997;31:720–723.
2. Yalcin B, Karaduman A. Stevens-Johnson syndrome associated with concomitant use of lamotrigine and valproic acid. J Am Acad Dermatol 2000;43:898–899.
3. Schlienger RG, Shapiro LE, Shear NH. Lamotrigine induced severe cutaneous adverse reactions. Epilepsia 1998;39(Suppl 7):S22–S26.
4. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case control study. Lancet 1999;353:2190–2194.
5. Sullivan JR, Watson A. Lamotrigine induced toxic epidermal necrolysis treated with intravenous cyclosporin: a discussion of pathogenesis and immunosuppressive management. Australas J Dermatol 1996;37:208–212.

AFP

Correspondence
Email: m.sladden@doctors.org.uk

The 5 domains of general practice

1. Communication skills and the patient-doctor relationship
2. Applied professional knowledge and skills
3. Population health and the context of general practice
4. Professional and ethical role
5. Organisational and legal dimensions