Unexpected outcome (positive or negative) including adverse drug reactions

Lamotrigine-induced toxic epidermal necrolysis in a young epileptic

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Summary

A 20-year-old young female presented with extensive skin rashes with bullae and extensive epidermal necrolysis about 20 days after the addition of lamotrigine (LTG) to her anticonvulsant medication. The patient was managed by stopping LTG and supportive treatment. The seizures were controlled with increase in the doses of carbamazepine. The report emphasises exercising of caution once LTG is added to a regimen containing valproic acid.

BACKGROUND

Lamotrigine (LTG) is a novel antiepileptic drug that has proven effective as an adjuvant medication in children and adults with refractory partial seizures (with or without secondary generalisation), in Lennox–Gastaut syndrome and in tonic-clonic seizures that are not satisfactorily controlled by other antiepileptic agents. The drug acts at voltage sensitive sodium channels to stabilise neuronal membranes and inhibit transmitter release, principally glutamate release.¹ The adverse events reported with the use of LTG are headache, asthenia, rash, nausea, dizziness, somnolence, aggressiveness and insomnia. Skin rashes occur in 3–10% of cases, mostly within the first 8 weeks of treatment, and are the most common reason for withdrawal of the drug. The rashes are usually erythematous or maculopapular in nature, and follow the same time course as delayed-type hypersensitivity. Severe skin reactions, such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare.^{2–8}

The risk of skin reactions is increased when the starting dose of LTG is high, when fast up-titration is applied and when the drug is added to valproic acid therapy.² The latter agent strongly inhibits hepatic metabolism of LTG, increasing its serum half-life from approximately 29 h as monotherapy to 70 h with valproic acid.⁹ We herewith present a young female who developed a life-threatening skin reaction subsequent to introduction of LTG to her antiepileptic regimen.

CASE PRESENTATION

A 20-year-old young female presented with oral ulcers and abdominal pain of 2 days duration. This was followed by a diffuse vesicular rash which involved the whole body over next 2 days including the eyelids. There was no accompanying history of fever, cough, chest pain, loose motions or insect bite. The patient was a known epileptic for past 6 years, but had been largely uncontrolled on sodium valproic acid and carbamazepine. LTG 200 mg/day had been added to her treatment regimen by a neurologist for her uncontrolled seizures 20 days earlier. Clinical examination

revealed an average built female with generalised vesicular rash with detachment of the epidermis and associated necrotic bullae, ulcerative lesions and oedema of the lips and intense congestion and chemosis of the conjunctivae (figures 1–3). Skin tenderness was elicitable and Nikolsky sign was positive. Abdominal examination revealed diffuse tenderness. Rest of the physical examination was normal. A clinical impression of LTG-induced TEN was made.

INVESTIGATIONS

The haemoglobin was 12.2 g/dl, leucocytes $11.7 \times 10^9/l$ with 75% polymorphs, and platelets $260 \times 10^9/l$. Urine dipstick was negative for proteins and glucose and microscopy was normal. Serum levels of urea, creatinine, glucose, aspartate aminotransferase, alanine aminotransferase, bilirubin, proteins, albumin and uric acid were normal. Gram staining of the blister fluid was negative for microorganisms and the cultures were sterile. Radiograph of the chest and ultrasonography of abdomen were normal. Punch biopsy of the skins was consistent with a histological diagnosis of TEN.

TREATMENT

LTG was stopped and the patient was managed with intravenous fluids, nasogastric feeding, high protein diet, saline washes and sterile aseptic dressings. Intravenous dexamethasone was administered for 3 days and prophylactic cefuroxime was administered. Financial constraints precluded the use of immunoglobulins. Conjunctival was chemosis managed with local dexamethasone and methyl cellulose.

OUTCOME AND FOLLOW-UP

The lesions started improving from fifth day and full orals could be instituted from day 15. The dose of carbamazepine was increased to 800 mg and the patient was discharged after 15 days with more than 90% of the lesions having healed (figures 4 and 5). She was controlled over a follow-up of 2 months.

Figure 1 Extensive necrolysis of the skin.

Figure 2 Denudation of large sheets of skin.

DISCUSSION

TEN and SJS are related mucocutaneous disorders with an estimated incidence of 0.4–1.2 patients per year, women being more affected than men^{10 11} and are associated with high rates of morbidity and mortality. Overall mortality for SJS ranges from 5% to 25%, and that for TEN ranges from 15% to 40%.^{5 11–14} SJS and TEN are considered as a continuum of disease with limited areas (less than 10% of body surface area) of epidermal detachment usually considered as SJS and more extensive (30% body surface area) termed as TEN.¹¹ TEN is often characterised by sheet-like loss of epidermis as was observed in our patient (figures 1 and 2). Associated with the epidermal loss are bullous lesions that spread under pressure and erythematous areas showing a positive Nikolsky's sign (dislodgment of epidermis by lateral pressure). In TEN, the maximal rash involvement is reached in about 4 days and sometimes within hours, whereas the corresponding time for SJS is 1–14 days. About 90% of patients with TEN develop painful erosions in their mucosal membranes, approximately 85% have conjunctival lesions, and about 35% of those who survive experience ocular sequelae.¹¹ Although our patient did have mucosal and conjunctival lesions, she was not left with any ocular sequel.

More than 80% of all TEN cases are caused by drugs.¹¹ The agents mainly associated with this condition are antibiotics, antiepileptics, allopurinol, imidazoles and rarely, non-steroidal anti-inflammatory drugs and analgesics. Other reported causes include chemicals, bacterial and viral infections, immunisations, malignancies and radiotherapy.^{10 11}

Immunological mechanisms, particularly T cell dependent cytotoxicity have been proposed in the pathogenesis of TEN.¹⁵ Another possible mechanism is altered drug metabolism resulting in reactions mediated by toxic intermediate metabolites.¹⁶ LTG is mostly metabolised through glucuronidation by the liver. Valproic acid increases the half-life of this drug by decreasing its glucuronidation through competition. Most reported cases of SJS or TEN due to LTG have occurred in patients who were co-medicated with these two drugs. Wadelius *et al*,¹⁶ reported three cases of TEN due to LTG. All three of these individuals reacted within 14 days after LTG was added to valproate, and the skin reactions progressed even after the drugs were discontinued. The patients recovered in 3–4 weeks. Chaffin and colleagues¹¹ reported a 74-year-old man with partial seizures who developed TEN 14 days after LTG was added to carbamazepine therapy. This patient developed a non-pruritic rash that became generalised, covering his whole body within 2 days. There was extensive oral/mucosal involvement, and a positive Nikolsky's sign on biopsy confirmed the diagnosis. The lesions resolved in 1.5 months.¹¹ Vuckelic and colleagues¹⁷ reported a 22-month-old patient with refractory myoclonic epilepsy who developed TEN 14 days after LTG was added to valproic acid. The child presented with high fever and a sunburn-like rash that covered two-thirds of the skin surface. LTG was discontinued but the eruption worsened, eventually involving the conjunctivae, the oral cavity and the trachea. A skin biopsy confirmed the diagnosis of TEN. After 4 weeks in the intensive care unit, the patient made a full recovery. Bocquet and colleagues also reported SJS and TEN that occurred in two children, aged 9 and 13 years, 3 and 28

Figure 3 Exudation, ulceration and chemosis of the face.

Figure 4 Recovered and healed skin.

days respectively after addition of LTG to their usual anti-convulsant therapy. Our patient developed fever and skin rashes 20 days after addition of LTG to her anticonvulsant regimen. In our patient no other drug was administered after starting LTG, she had been taking other drugs for a long time and there was a regression of all the symptoms after withdrawal of LTG. This clarifies the aetiological association of TEN with the LTG. However valproic acid could have increased her risk for development of TEN.

The cornerstone of treatment for TEN is fluid replacement, nutritional support, surveillance and aggressive treatment for infection.¹⁸ It is managed as an acute emergency. The administration of corticosteroids in treatment

Figure 5 Healed facial lesions.

of TEN is still controversial;^{19 20} however, may be helpful in short courses if given early. Antibiotics are given only if there is evidence of infection. The role of cyclosporine, plasmapheresis, intravenous immunoglobulins (IVIG) and cyclophosphamide has also been studied for treatment. Treatment with IVIG has shown promising outcome in recent trials.^{21–24} A recent study on the pathogenesis and therapeutic options for TEN showed that the hallmark of SJS/TEN was epidermal cell apoptosis, which may be mediated through keratinocyte Fas-FasL interaction or through cytotoxic T cell release of perforin and granzyme B. IVIG contains anti-Fas antibodies which can inhibit apoptosis,²¹ hence the reason for its usage. Bad prognostic factors for TEN include age >40, underlying malignancy, detachment involving >10% of body surface area, blood glucose >250 mg/dl, HCO_3^- <20 and BUN >10 mmol/l. The mortality ranges from 30% to 50%.

Our case emphasises that whenever LTG is added to a regimen containing valproic acid, the patient must be closely monitored for any skin rash which can necessitate immediate withdrawal of the offending drug so that potentially fatal consequences are prevented.

Learning points

- ▶ Skin rashes occur in 3–10% of patients receiving LTG.
- ▶ Risk of skin reactions is higher with a higher starting dose of LTG, fast up-titration and when the drug is added to valproate therapy.
- ▶ Patients started on LTG need to be closely monitored for skin reactions especially if the drug is added to a regimen containing valproate.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Leach MJ**, Marden CM, Miller AA. Pharmacological studies on lamotrigine, a novel potential antiepileptic drug: II. Neurochemical studies on the mechanism of action. *Epilepsia* 1986;**27**:490–7.
2. **Bocquet H**, Farmer M, Bressieux JM, *et al*. Toxic epidermal necrolysis and Steven-Johnson syndrome with lamotrigine. *Ann Dermatol Venerol* 1999;**126**:46–8.
3. **Sachs B**, Rönna AC, von Schmiedeberg S, *et al*. Lamotrigine-induced Stevens-Johnson syndrome: demonstration of specific lymphocyte reactivity in vitro. *Dermatology (Basel)* 1997;**195**:60–4.
4. **Sadler M**. Lamotrigine associated with insomnia. *Epilepsia* 1999;**40**:322–5.
5. **Rzany B**, Correia O, Kelly JP, *et al*. 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.
6. **Fernández-Calvo C**, Olascoaga J, Resano A, *et al*. [Lyell syndrome associated with lamotrigine]. *Rev Neurol* 2000;**31**:1162–4.
7. **Yalçin B**, Karaduman A. Stevens-Johnson syndrome associated with concomitant use of lamotrigine and valproic acid. *J Am Acad Dermatol* 2000;**43**(5 Pt 2):898–9.
8. **Calabrese JR**, Sullivan JR, Bowden CL, *et al*. Rash in multicenter trials of lamotrigine in mood disorders: clinical relevance and management. *J Clin Psychiatry* 2002;**63**:1012–19.
9. **Faught E**, Morris G, Jacobson M, *et al*. Adding lamotrigine to valproate: incidence of rash and other adverse effects. Postmarketing Antiepileptic Drug Survey (PADS) Group. *Epilepsia* 1999;**40**:1135–40.
10. **Roujeau JC**, Kelly JP, Naldi L, *et al*. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995;**333**:1600–7.
11. **Chaffin JJ**, Davis SM. Suspected lamotrigine-induced toxic epidermal necrolysis. *Ann Pharmacother* 1997;**31**:720–3.
12. **Forman R**, Koren G, Shear NH. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of 10 years' experience. *Drug Saf* 2002;**25**:965–72.
13. **Sane SP**, Bhatt AD. Stevens-Johnson syndrome and toxic epidermal necrolysis-challenges of recognition and management. *J Assoc Physicians India* 2000;**48**:999–1003.
14. **Garcia-Doval I**, LeCleach L, Bocquet H, *et al*. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol* 2000;**136**:323–7.
15. **Sachs B**, Rönna AC, Ruzicka T, *et al*. Lamotrigine and toxic epidermal necrolysis. *Lancet* 1996;**348**:1597.
16. **Wadelius M**, Karlsson T, Wadelius C, *et al*. Lamotrigine and toxic epidermal necrolysis. *Lancet* 1996;**348**:1041.
17. **Vuckelic D**, Bozinov D, Tesovic I, *et al*. Lamotrigine and toxic epidermal necrolysis. *Dermatology* 1997;**195**:307.
18. **Stern RS**. Improving the outcome of patients with toxic epidermal necrolysis and Stevens-Johnson syndrome. *Arch Dermatol* 2000;**136**:410–11.
19. **Wong KC**, Kennedy PJ, Lee S. Clinical manifestations and outcomes in 17 cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Australas J Dermatol* 1999;**40**:131–4.
20. **Pasricha JS**, Khaitan BK, Shantharaman R, *et al*. Toxic epidermal necrolysis. *Int J Dermatol* 1996;**35**:523–7.
21. **Khalili B**, Bahna SL. Pathogenesis and recent therapeutic trends in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Ann Allergy Asthma Immunol* 2006;**97**:272–80.
22. **Tan AW**, Thong BY, Yip LW, *et al*. High-dose intravenous immunoglobulins in the treatment of toxic epidermal necrolysis: an Asian series. *J Dermatol* 2005;**32**:1–6.
23. **Metry DW**, Jung P, Levy ML. Use of intravenous immunoglobulin in children with stevens-johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature. *Pediatrics* 2003;**112**(6 Pt 1):1430–6.
24. **Mangla K**, Rastogi S, Goyal P, *et al*. Efficacy of low dose intravenous immunoglobulins in children with toxic epidermal necrolysis: an open uncontrolled study. *Indian J Dermatol Venereol Leprol* 2005;**71**:398–400.

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