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Case reports

Suspected lamotrigine-induced toxic epidermal necrolysis

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Abstract

Toxic epidermal necrolysis and Stevens-Johnson syndrome are rare, life treatening cutaneous reactions. Most cases of toxic epidermal necrolysis are drug induced. The drugs with the highest estimated incidence include co-trimoxazloe (trimethoprim-sulfamethoxazole), sulfadoxine-pyrethamine, and carbamazepine.

Among other drugs, the reported reaction rates are relatively low for lamotrigine and sulbactam-ampicillin. We describe a patient who developed toxic epidermal necrolysis after either administration of lamotrigine or of ampicillin.

Key words : toxic epidermal necrolysis ; Lyell's syndrome ; lamotrigine ; ampicillin.

Introduction

Lamotrigine (LTG) is a novel anti-epileptic drug that has proven effective as an adjuvant medication in children and adults with refractory partial seizures (with or without secondary generalization), in Lennox-Gastaut syndrome and in tonic-clonic seizures that are not satisfactorily controlled by other anti-epileptic agents. The drug acts at voltage-sensitive sodium channels to stabilize neuronal membranes and inhibit transmitter release, principally glutamate release (Leach *et al.*, 1986).

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 (Sachs *et al.*, 1997, Bouqet H. *et al.*, 1999, Sadler M., 1999, Rzany B. *et al.*, 1999, Fernandez-Calvo C *et al.*, 2000, Yalçın B. *et al.*, 2000, Calabrese J. R. *et al.*, 2002). 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 (VPA) therapy (Sachs *et al.*, 1997). The latter agent strongly inhibits hepatic metabolism of LTG, increasing its serum half-life from approximately 29 hours as monotherapy to 70 hours with VPA (Faught *et al.*, 1990).

Ampicillin is another drug reported to induce toxic epidermal necrolysis (Pevny and Rockl, 1975, Tagami *et al.*, 1983, Kaupinen and Stubbb, 1984, Robbens *et al.*, 1985, Chan *et al.*, 1990, Scully and Frieden, 1992, Romano *et al.*, 1993, Surbled *et al.*, 1996). Delayed type hypersensitivity to semisenthetic penicillins is thought to be the reason for development of TEN after administration of this drug (Romano *et al.*, 1993).

Case study

A 23-year-old female with juvenile myoclonic epilepsy had been treated with VPA 750 mg/day for 6 years, but was still experiencing seizures 3-5 times per month. Her dose of VPA was increased to 1000 mg/day and a good therapeutic level of the drug was achieved (90 mg/mL) however, the seizures continued. Due to inadequate seizure control, the patient's VPA regimen was supplemented with LTG 25 mg every other day. Eleven days after starting this protocol, the woman was admitted to hospital with fatigue, fever, nausea, vomiting, and a diffuse maculopapular rash.

Routine laboratory assessments of leukocyte count, C-reactive protein level, erythrocyte sedimentation rate, hepatic enzyme levels, renal function, and serum electrolyte levels were all within normal limits. Urine, blood, and throat cultures were negative. The patient was diagnosed with drug-induced erythema multiforme minor, and LTG was discontinued immediately. She was started on cetirizine 10 mg/day per os (PO), methylprednisolone 40 mg/day PO, and sulbactam-ampicillin 2 g/day PO as she also had tonsiller hyperemia. The rash began to resolve after 5 days.

On the 8th day after the LTG treatment was stopped, the patient developed a sore throat and ear pain. Her postnasal secretions were highly purulent. The rash disseminated again, this time very

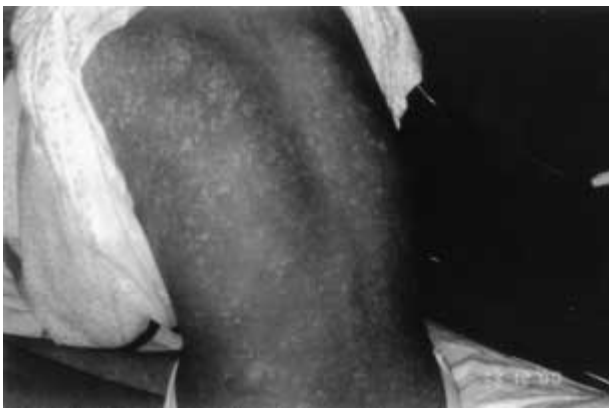

FIG. 1. — Widespread bullous and necrotic eruptions on the patient's abdomen and back.

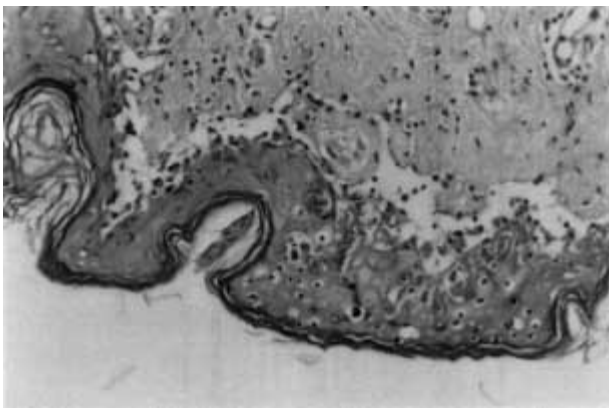

FIG. 2. — Detachment of the epithelium from the subepidermal layer in a punch biopsy of lesional skin from the abdomen (Hematoxylin-Eosin × 200).

rapidly, with bullous and necrotic lesions erupting on all regions of the body in just a few hours (Fig. 1). There were aphthous lesions in the oral mucosa, the patient's conjunctiva were hyperemic, and her ocular secretions were purulent. Ophthalmologic examination revealed bilateral conjunctivitis with no corneal involvement, and epithelial detachment in the conjunctiva. The patient's liver enzymes had risen to 1.5-2 times normal. At this stage, she was transferred to the burn unit for special care of her skin lesions. The prednisolone dose was increased to 80 mg/day PO, sulbactam-ampicillin was stopped and new treatment was initiated with cefuroxime sodium 3 × 750 mg/day IV, clindamycin 2 × 600 mg/day IV, and fluconazole 150 mg/day PO. A punch biopsy was taken from lesional skin on the abdomen. This showed edema and mononuclear inflammatory cell infiltration in the perivascular region, and focal areas of epithelial detachment from the subepidermal layer. The bullous lesions featured necrotic cells in the basal lamina of the epithelium. These findings were compatible with TEN (Fig. 2).

The patient recovered with fluid replacement, nutritional support, and anti-bacterial treatment. She was discharged from hospital after 30 days, but had blurred vision in both eyes due to permanent defects in the conjunctival epithelium.

Discussion

TEN and SJS are related mucocutaneous disorders with an estimated incidence of 0.4-1.2 patients per year (Roujeau *et al.*, 1995, Chaffin *et al.*, 1997). Both diseases 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% (Chaffin *et al.*, 1997, Rzany B. *et al.* 1999, Forman R. *et al.*, 2002, Sane S. P. *et al.*, 2000, Garcia-Doval I. *et al.*, 2000). Although precise diagnostic boundaries between the two disorders have not been established, cases with limited areas of epidermal detachment (less than 10%) are usually considered as SJS, and those with extensive detachment (more than 30% of all epidermis) are diagnosed as TEN (Chaffin *et al.*, 1997). TEN is often characterized by sheet-like loss of epidermis and raised flaccid blisters that spread under pressure and with erythematous areas showing a positive Nikolsky's sign (dislodgment of epidermis by lateral pressure). In TEN, maximal rash involvement is reached within 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 sequel (Chaffin *et al.*, 1997).

More than eighty percent of all TEN cases are caused by drugs (Chaffin *et al.*, 1997). The agents mainly associated with this condition are certain antibiotics (sulfonamides, aminopenicillins, cephalosporins, quinolones, vancomycin, rifampicin, trimethoprim-sulfamethoxazole, tetracyclines, ethambutal), anti-epileptics (phenytoin, carbamazepine, phenobarbital, LTG), allopurinol, imidazole, and, rarely, non-steroidal anti-inflammatory drugs and analgesics. Other reported causes include chemicals, bacterial and viral infections, immunizations, malignancies, and radiotherapy (Roujeau *et al.*, 1995, Chaffin *et al.*, 1997).

The pathogenesis of TEN remains unclear ; however, immunological mechanisms, particularly T-cell-dependent reactions such as cell-mediated cytotoxicity, have been proposed (Sachs *et al.*, 1996). Another possible mechanism is altered drug metabolism resulting in reactions mediated by toxic intermediate metabolites (Wadelius *et al.*, 1996). LTG is mostly metabolized through glucuronidation by the liver. VPA 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. reported three cases of TEN due to LTG. All three of these individuals reacted within 14 days after LTG was added to VPA, and the skin reactions progressed even after the drugs were discontinued. The patients recovered in 3-4 weeks. Chaffin and colleagues (1997) 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 generalized, 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 (Chaffin *et al.*, 1997). Vukelic and coworkers (1997) reported a 22-month-old patient with refractory myoclonic epilepsy who developed TEN 14 days after LTG was added to VPA. 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 (1999) also reported SJS and TEN that occurred in two children, aged 9 and 13 years, 3 and 28 days respectively after addition of LTG to their usual anticonvulsant therapy (valproate, clonazepam and hydrocortisone in the first, sodium valproate in the second case). In these patients as sore throat and fever of 38.5°C had developed similar to our patient (in the first case 3, and in the second 10 days after beginning of LTG), sulfamethoxazole-trimethoprime and amoxicillin had to be given respectively. The authors stated that in the first case imputability of sulfamethoxazole-trimethoprime appeared to be excluded as it was begun after onset of cutaneous reactions ; in the second the imputability of LTG was greater than that of amoxicillin as the child had frequently taken amoxicillin without previous untoward effects. The outcome was favorable in both cases.

Our patient developed fever and erythema multiforme minor 11 days after LTG was added to her VPA treatment. The fact that no other drugs were administered during this time led us to suspect an adverse effect of LTG. The patient had been taking VPA for many years, so it was unlikely that this agent had caused the reaction. However, the VPA therapy may have increased her risk for developing problems with LTG. In our case, the lesions continued to progress for the first 3-4 days after LTG was stopped. Subsequently, the rash diminished. We suspect that the serious deterioration that occurred on day 19 was due to aggravation of the symptoms by a superimposed sinus infection ; to the addition of sulbactam-ampicillin on 11th day to the treatment regime ; or most probably to a combination of both of these factors. As we could not perform any allergological testing or patch testing with lamotrigine or ampicillin it is not certain which drug was the definite culprit.

When a rash develops during LTG treatment, the drug should be stopped immediately and the patient should be examined within 24 hours. Unless the rash can be clearly attributed to another cause, LTG should be permanently withdrawn from the regimen. Also any other drug that would cause skin reactions like ampicillin should be avoided. If the patient has a fever or shows severe oral ulceration, lymphadenopathy, skin desquamation or blistering, or other systemic signs and symptoms, they should be hospitalized. Outpatient treatment with antihistamines or corticosteroids is not reliable.

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