

Early Cyclosporine Treatment of Incipient Toxic Epidermal Necrolysis Induced by Concomitant Use of Lamotrigine and Sodium Valproate

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Sir,

Adverse cutaneous reactions to drugs are among the most frequent complications of drug therapy. The most severe reaction is toxic epidermal necrolysis (TEN), a dermatological emergency with extensive epidermal necrosis resembling partial thickness burns and associated with high morbidity and mortality. Stevens-Johnson syndrome (SJS) and TEN constitute a spectrum of disease involving less than 10% and more than 30% epidermal detachment, respectively (1). Severe forms of SJS could evolve to TEN and the same drugs can induce both disorders (1). It is often impossible to distinguish between them at an early stage, since the final extent of detached epidermis is their distinguishing feature. We report here a case of incipient TEN induced by lamotrigine, where cyclosporine was used early in the course of the disease and appeared to halt its progression.

CASE REPORT

A 29-year-old woman was admitted with a 3-day history of oral mucosa ulceration, followed by a maculo-papular rash on her face, trunk and limbs, associated with fever and constitutional symptoms. Seven months previously she had been diagnosed as having epilepsy with complex partial seizures and had been on sodium valproate. As her fits were uncontrolled, lamotrigine was added to her treatment regime 3 weeks prior to this presentation. Within hours of admission she rapidly developed confluent erythema, affecting 20% of the body surface area, and painful blistering around her face and neck affecting 10% of the body surface area. Nikolsky's sign was positive in the erythematous skin adjacent to the blistering. A frozen section of a blister roof showed separation of the entire epidermis, supporting the diagnosis of SJS or TEN. Cyclosporin A was commenced intravenously at $2 \text{ mg kg}^{-1} \text{ day}^{-1}$ in 2 divided doses. Intravenous co-amoxiclav and fluid were administered as she was pyrexial and unable to swallow.

Blistering ceased in the following 24 h. Thirty-six hours later she became afebrile and her pain settled. Re-epithelialization occurred by 72 h following the introduction of cyclosporine. Cyclosporine was continued at the same dose for a further 24 h (total of 4 days) and co-amoxiclav intravenously for a further 4 days. She continued to make a full recovery.

DISCUSSION

Anti-epileptic drugs are recognized as causing SJS and TEN, often occurring within 8 weeks of therapy (2). There has been an increasing number of cases associated with lamotrigine (3, 4), a triazine anti-convulsant used in refractory epilepsy, commonly taken concurrently with sodium valproate. Sodium valproate interferes with lamotrigine metabolism, resulting in increased serum levels and prolonged half-life from 30 to 60 h (4). This increases the risk of SJS evolving to TEN, which may run a prolonged course. This was highlighted in a previous report, where blistering in TEN associated with concomitant use of lamotrigine and sodium valproate persisted for 28 days (4), in contrast to 2–15 days, which is the usual duration of blistering in TEN (4, 5).

The treatment of TEN remains controversial, while the use of cyclosporin A has been shown to be successful (3, 6–8). The pathogenesis of TEN is not fully understood, but is recognized to be a T-cell mediated immune response. This is the rationale behind the use of cyclosporine, which was first used for this condition in 1989 (6).

In this case, cyclosporine given promptly had halted further blistering within 24 h, which we believe shortened the illness and prevented the progression to TEN. Having failed to respond to 4 days initial treatment with systemic steroids, similar rapid resolution of blistering (within 24 h) was reported in lamotrigine-induced TEN when given cyclosporin A on day 7 of the illness (3). We believe that cyclosporine should be considered early in the management of lamotrigine-induced SJS/TEN to shorten what may be a progressive and prolonged course of blistering, with potentially lethal consequences.

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