

REPORT

Fatal toxic epidermal necrolysis induced by sodium valproate

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Abstract: A 26 years old manual labourer from Azad Jammu Kashmir presented with four days history of an extensive exfoliation of skin involving the entire body. Histology of the lesion showed epidermal necrolysis. The patient was a recently diagnosed case of epilepsy and had been started on therapy with sodium valproate three weeks ago. Following admission in our center, intensive care and wound care were instituted according to standard protocols. Despite all therapeutic measures the patient kept on deteriorating and developed multi-organ failure with pneumonia. He died on 7th day of hospitalization.

Keywords: Toxic epidermal necrolysis. Stevens Johnson syndrome. adverse drug reactions. sodium valproate.

INTRODUCTION

The toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (i.e. Erythema Multiforme) represent a severe form of potentially life-threatening adverse drug reactions that mainly involve the skin and mucosa. There is detachment of epidermis which results in blister formation and areas of desquamated skin. The two clinical entities in fact represent severe epidermolitic drug reactions, differing by their extent of skin involvement only. (In TEN >30% of the total body surface area (TBSA) is involved while in Stevens Johnson syndrome <10% of TBSA is affected) The various drugs that may cause these conditions include anticonvulsants, sulfonamides, nonsteroidal anti-inflammatory drugs, and allopurinol etc. (Harr *et al.*, 2010; Cohen *et al.*, 2009; Stevens *et al.*, 1922).

The diagnosis is essentially clinical. Additionally skin biopsy and certain investigations which constitute prognostic criteria are carried out. The skin biopsy shows characteristic full thickness skin involvement with epidermal necrolysis owing to extensive apoptosis of keratinocyte. SCORTEN score has been devised to predict the mortality risk of TEN. It includes seven prognostic criteria. These are age over 40 years, affected body surface area of more than 10%, heart rate of over 120 beats per minute, urea of over 10 mmol/L, serum bicarbonate of less than 20 mmol/L, serum glucose of over 14 mmol/L and any underlying malignancy. Each criterion is awarded a single point, thus constituting an overall score of 7. The mortality risk is 3.2% for a score of 0-1; 12.1% for a score of 2, 35.3% for score of 3, 58.3% for a score of 4 and 90% for a score of 5 or more.

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(Harr *et al.*, 2010; Cohen *et al.*, 2009; Bastuji-Garin *et al.*, 2000).

We report our experience with a young manual labourer who presented with four days history of TEN following ingestion of sodium valproate for a recently diagnosed epilepsy. To our information no such case has been reported from Pakistan. This rarity prompts us to report our case and share our experience.

CASE HISTORY

A 26 years old manual labourer from Azad Jammu Kashmir presented with four days history of an extensive exfoliation of skin involving the entire body. The patient also had denudation of oral and lip mucosal surfaces. (figs. 1 and 2). The patient was a diagnosed case of epilepsy of recent onset and had been started on therapy with sodium valproate three weeks ago. On admission, the patient's vital signs included temperature 100 °F, pulse rate 125/min, blood pressure 110/90 mm Hg, and respiratory rate 20/min. The urine output was 1 ml/kg/hr while the central venous pressure was 10 mmHg. The entire body skin was involved (approximately 100% TBSA affected) with positive Nikolsky sign.

The laboratory investigations on admission included Hb 10.3 gm/dl, hematocrit 31.3%, leucocyte count 14,900/mm³, urea 18.9 mmol/L, creatinine 123 micromol/L, serum sodium 127 mmol/L and serum glucose of 17.3 mmol/L. The arterial blood gases showed a pH 7.24, pCO₂ 31 mm Hg, p_aO₂ 95 mm Hg, serum bicarbonate 15 mmol/L, serum potassium 3.7 mEq/L and a base excess of -16.1 mmol/L. The liver function tests, urine routine microscopic examination, blood cultures, echocardiogram and X-ray chest were also performed and did not reveal

any abnormality. Biopsy of the lesion was performed which showed features suggestive of epidermal necrolysis. The calculated SCORTEN was 5.



Fig. 1: Characteristic exfoliative skin loss, frontal view of the patient.



Fig. 2: Characteristic exfoliative skin loss, posterior view of the patient.

The patient was admitted in Intensive Care Unit. Following admission, supportive therapeutic measures were instituted with fluid/electrolytic maintenance, nutritional support, analgesia, and antibiotic cover. The wound care measures included initial debridement and desloughing followed by daily paraffin soaked gauze

dressings according to standard protocols. Despite all these therapeutic measures the patient kept on deteriorating and developed multi-organ failure with pneumonia. He died on 7th day of hospitalization.

DISCUSSION

Toxic epidermal necrolysis is a very rare disease. On average, the reported annual incidence is 0.5-1.4 cases per million population. The reported mortality rate is 10-70%. The mortality depends on the SCORTEN score and the quality of intensive care instituted. The TEN typically heals slowly, taking 3-6 weeks. The recovery depends on the body surface area affected, depth of skin involvement and any associated complications that may occur during the course of illness (Cohen *et al.*, 2009; Abood *et al.*, 2008; Bastuji-Garin *et al.*, 2000).

In our case the offending drug was sodium valproate. The other drugs implicated in the published literature include phenytoin, carbamazepine, sulfonamides, amoxicillin, ibuprofen, ciprofloxacin etc. Viral infection has also been reported as a cause of the condition (Cohen *et al.*, 2009; Frangogiannis *et al.*, 1996; Stevens *et al.*, 1922). There is an estimated risk of 1-10 cases of TEN per 10,000 new users of antiepileptic agents during the first two months of their initiation of antiepileptic treatment (Mockenhaupt *et al.*, 2005).

We managed our patient with supportive therapies. At present there exist no standard guidelines for managing TEN. Many pharmacological therapies are mentioned in the literature, however a general consensus and evidence base is lacking (Lindford *et al.*, 2011). TEN and other burn-like syndromes are similar in many aspects to second-degree burns and the wound management is likewise similar to that of partial thickness burns (Atiyeh, 2003; Abood, 2008). The first line measures for TEN essentially include prompt identification and withdrawal of the offending drug(s), supportive therapy in an ICU setting, fluid/electrolytic and nutritional support, wound care as burns, prevention and treatment of infection. The second line measures include a number of pharmacological therapies such as high-dose intravenous immunoglobulin (IVIG) therapy, intravenous steroids, immunomodulating agents such as cyclophosphamide, ciclosporin, and plasmapheresis. However with none of these therapies there has been a consistent or conclusive evidence of benefit towards the patients' survival (Hashim *et al.*, 2004; Brown *et al.*, 2004; Shortt *et al.*, 2004; Frangogiannis *et al.*, 1996). As third line measures, several wound care measures such as the use of moist expose burn ointment, use of suprathel dressings and skin allografts are now being tested, and the long term results of their efficacy are yet awaited (Atiyeh, 2003; Lindford *et al.*, 2011).

In our case the patient presented after four days of skin exfoliation and had involvement of the entire body skin with a SCORTEN score of 5. Noordally *et al* (2012) have reported a naproxen induced fatal case of TEN where the patient had associated severe rhabdomyolysis. Lindford *et al.* (2011) have reported a 17 years girl who survived a lamotrigine induced TEN affecting 80% TBSA with a SCORTEN score of 2. The patient was managed with Suprathel and skin allograft in addition to IVIG and steroids. Atiyeh (2003) have reported a sulfonamide induced TEN of 90% TBSA who was successfully managed with moist exposed burn ointment.

In conclusion, we report the first fatal case of TEN induced by sodium valproate in our population. There was involvement of the entire body skin and denudation of oral mucosa. The high SCORTEN score in our patient, and his delayed presentation for treatment contributed to the multi-organ failure and mortality. The doctors advising antiepileptic agents to new users should be mindful of this potentially life threatening untoward effect.

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