

Stevens - Johnson Syndrome Induced by Sodium Valproate

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ABSTRACT

A case of Stevens-Johnson syndrome (SJS) following treatment with sodium valproate is presented. A 55-year-old male suffering from manic episode was treated with sodium valproate in addition to haloperidol and trihexiphenidyl. After two weeks he developed cutaneous manifestations of SJS. He was treated with systemic steroids, antihistamines and topical calamine lotion and recovered after a few weeks.

Key words: Stevens-Johnson syndrome, sodium valproate

Introduction

Sodium valproate was initially introduced as an anti epileptic agent in 1967, but over the years it has been used to treat a variety of psychiatric disorders. The milder and commonly occurring adverse effects of valproate are nausea, weight gain, hyperammonaemia, menstrual disturbances, tremor, hair loss, lethargy, sedation, behaviour changes, ataxia, dysarthria, incoordination, flushing, and reversible thrombocytopenia (Butler et al, 1999).

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rarely reported side effects valproate (Platin et al, 1995; Tsai & Chen, 1998; Poon & Ho, 2001 & Mishra et al, 2002). Rzany et al (1999), in a case-control study on the risk of SJS and TEN with various antiepileptic agents reported the univariate relative risk as 120 for carbamazepine, 91 for phenytoin, 57 for phenobarbital, 25 for lamotrigine, and 24 for valproate within the first 8 weeks of therapy. The association of SJS with valproate was confounded by concomitant short-term therapy with other causal drugs in many studies. Roujeau et al (1995) conducted a case control study to quantify the risks associated with the use of specific drugs. Drug use before the onset of disease was compared in 245 people who were hospitalized because of TEN or SJS and 1147 patients hospitalized for other reasons. The crude relative risk for SJS or TEN was as follows: carbamazepine, 90; phenytoin, 53; phenobarbital, 45 and valproic acid, 25. Poon and Ho (2001) have reported SJS in a 52-year-old man with inoperable anaplastic astrocytoma of left basal ganglion and neuropathic pain two days after the commencement of sodium valproate.

The disease may occur as a primary skin disorder or as a skin manifestation of systemic infections, malignant or chronic disease of internal organs or as a reaction to various drugs (Breathnach, 1992). The principal sign of SJS is a symmetrical distribution of grouped or isolated crops of violaceous papules, macules or nodules of size 0.5 to 1 cm with dome shaped surface. The lesions enlarge and become purplish. There may be vesicles, bullae, pustules, urticarial lesions and hemorrhagic sites. A rather characteristic lesion is erythema iris, also described as "bull's eye" or "target lesion". These are concentric erythematous rings with central clearing. The lesions may be present anywhere on the body but extensor surfaces are commonly involved. Mucous membrane ulceration is also a common finding (Breathnach, 1992). We report a case of SJS induced by sodium valproate in bipolar affective disorder because of its rarity.

Case report

Mr. R, a 55-year-old male was presented with one week history of sudden onset of mental illness, characterised by excessive talk, grandiose ideas of ability, restlessness, excessive happiness and reduced need for the sleep. After a thorough evaluation, diagnosis of manic episode was made. He had a past brief episode of mania 20 years back subsiding spontaneously. All investigations including complete haemogram and blood biochemistry were within normal limits. As an out patient, he was started on sodium valproate 600 milligram per day, haloperidol 10 milligram per day and trihexiphenidyl 4 milligram per day. Prior to our treatment he was not receiving any medications. On the 7th day after starting the therapy, he developed fever, headache and myalgia. Within 24 hours, he developed

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widespread erythematous rashes. There were multiple target lesions involving the trunk and limbs with blister formation that lacerated easily. There was mucosal involvement with hemorrhagic areas on the oral mucosa, conjunctiva, and external genitalia. Sodium valproate was discontinued on 8th day after seeing the skin reaction, however haloperidol with trihexyphenidyl was allowed to continue, as he was psychiatrically symptomatic. The skin reaction was treated with oral prednisolone (60 mg/day in tapering dosage), oral antihistamine (cetirizine 20 mg/day) and topical calamine lotion. Within a week, severe ulceration of oral mucosa was seen. Hemorrhagic crusting and grayish white membrane were visible on the lips, palms and sole. The skin lesions showed typical "target lesions" with necrotized red area and grayish red swollen margins spread all over the body. After 4 weeks, the mucosal and skin lesions started subsiding; the eyes were the first to clear and no sequelae was evident. By continuing haloperidol and trihexyphenidyl in tapering dosage he became euthymic within 4 weeks.

Discussion

SJS is a severe and extensive type of erythema multiforme characterised by a severe necrotising cutaneous reaction and involvement of several mucosal sites (oral, conjunctival, and anogenital). Late complications include pigmentation, scarring, and skin contracture. The mortality rate of SJS is 5% to 15%.

Treatment of SJS should be individually tailored according to the cause and complications of the syndrome. The most severe cases should be considered for the intensive treatment in a burns unit. Systemic corticosteroids should not be used routinely, but may be justified in the early stages of drug induced SJS. Treatment should also focus on early detection and prevention of common fatal complications such as infection. Prophylactic antibiotic therapy should be started before signs of infection manifest. Topical treatment may include hydrocolloid or gauze dressings. The clinical condition may require 3 to 6 weeks to resolve, depending upon the extent and severity of the lesions. Alternative systemic treatments are still experimental and include haemodialysis, plasmapheresis, and cyclosporin therapy (Poon & Ho, 2001).

After millions of prescriptions of sodium valproate, mostly as an anti epileptic and recently as antimanic, there are only a few reported cases of SJS due to this drug (Platin et al, 1995; Tsai & Chen, 1998; Rzany et al, 1999 & Mishra et al, 2002). In the index case, the diagnosis of SJS was

consistent with the clinical description given in standard dermatology textbooks. The algorithms for the implication of a drug in causing an adverse skin reaction is as follows- a) alternative causes, especially infections should be excluded; b) the interval between the introduction of a drug and the onset of reaction should be examined (for drug-induced SJS it is 1-3 weeks); c) any improvement after drug withdrawal should be noted; d) the physician should determine whether similar reactions have been associated with the same compound; e) any reaction with readministration of the compound should be noted (Roujeau & Stern, 1994).

In the absence of any systemic or local infection or exposure to any other drug except haloperidol and trihexyphenidyl (SJS is highly uncommon with these two drugs), the onset of SJS within the second week of starting treatment and with the fact that condition was improved with the discontinuation of sodium valproate, suggests that the condition was perhaps caused by sodium valproate. The occurrence of life threatening side effects like one described above, whatever be its frequency, is a reminder that sodium valproate treatment carries a potential risk.

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