Introduction

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare, potentially life-threatening and severe epidermolytic adverse drug reactions. They are initially described as separate entities, but today considered variants of the same pathologic process and differing only for severity. Cutaneous erythema with blister formation to a various extent and hemorrhagic erosions of mucous membranes are characteristic of SJS and TEN. Frequently, fever, stinging eyes, and pain upon swallowing are the first symptoms of the disease, which may persist or even increase once the mucocutaneous lesions appear. Lamotrigine, carbamazepine and phenobarbital, antiep'i- infective sulfonamides are strongly associated with SJS/TEN in children. Valproic acid, acetaminophen, and nonsteroidal anti-inflammatory drugs as a group also increase the risk of SJS/TEN. Combined usage of antiepileptic drugs (AEDs) may cause potential pharmacokinetic or pharmacodynamic interactions which may result in more adverse effects than might occur when the AED is taken as monotherapy. Here, we report a rare case of SJS triggered by a combination of clobazam, lamotrigine and valproic acid in a 7-year-old boy. Because of inadequate seizure control, lorazepam was replaced with clobazam. Four weeks after the addition of clobazam, the patient developed SJS with a generalized rash, fever, with liver and kidney involvement, and eosinophilia one week after the initiation of treatment. All antiepileptic drugs were discontinued, and intravenous methylprednisolone, prophylactic systemic antibiotics, intravenous fluid supplement, antipyretic, special wound care, and supportive medical care for SJS were administered. He was discharged in a stable condition on the 18th day. Our case suggests that a drug-drug interaction between valproate, lamotrigine and clobazam contributed to the development of SJS. When the clobazam was added to valproic acid and lamotrigine co-medication, the lamotrigine dose should have been decreased.

Keywords: Stevens-Johnson Syndrome, toxic epidermal necrolysis, valproic acid, lamotrigine, clobazam

Case Report

A 7-year-old boy, who had been a known epileptic for
the last 6 years, was admitted with a three-day history of oral mucous ulceration, followed by a maculo-papular and bullous rash on his face, neck, trunk, and limbs, which was associated with fever. He was diagnosed with cerebral palsy at 2 and half months old. His first seizure occurred when he was 1 year old, and his anticonvulsant therapy was started with phenobarbital. When he was 2 years old, he began to receive valproic acid (350mg bd) and lamotrigine (50mg bd). The patient had been under the treatment of valproic acid (350mg bd), lamotrigine (50mg bd) and lorazepam (1mg/day) for the last 2 years. Because of inadequate seizure control, clobazam (10mg/bd) was used in place of lorazepam in his treatment regime. Four weeks after the addition of clobazam, a fever reaching 39.5°C occurred, for which he received paracetamol and ibuprofen. Two days later, an erythematous and bullous rash started on his face and neck, which rapidly spread to his trunk, arms and legs. Three days later he was admitted to our burn center.

On physical examination, he was found to have fever (38.5-39°C) and his general status was poor. Dermatologic examination revealed: oral mucosal ulcerations, hemorrhagic crust on lips and nose, bilateral hyperemic conjunctivae, erythematous papules and bullae located mainly on the face, neck, trunk, and genitalia, and sparsely on the upper and lower extremities. There were confluent bullae formation and epidermal loss located especially on his face, neck, back and genitalia that accounted for approximately 10% of the total body surface area (Fig. 1).

Laboratory examinations, including complete blood count, liver and renal function tests, electrolytes, urine analysis, and erythrocyte sedimentation rate, were all evaluated. CRP levels were measured higher (48.5mg/L) and serum albumin levels were measured lower (2.48g/dl) than normal limits. The patient had hypochromic microcytic anemia and monocytosis.

The child was diagnosed with SJS based on clinical findings and physical examinations without the need for skin biopsy. All antiepileptic drugs were discontinued, and intravenous methylprednisolone at 2mg/kg/day, prophylactic systemic antibiotics (Vancomycin 60mg/kg/day and Ceftriaxone 75mg/kg/day), and antipyretic were administered. Intravenous fluid supplement was administered to meet the daily maintenance (1500cc/m²) and loss calculated by weight. In addition, he was administered an enteral nutrition solution of 40-50 kcal/kg/day. Tetanus prophylaxis was performed. Topical rifamycine (Rifocin 250mg/3ml amp, Sanofi Aventis) and sterilized vaseline embedded gause dressing for epidermal surfaces were applied daily.

On the fourth day following the discontinuation of the antiepileptic drugs, he had a generalized seizure lasting one minute and the seizures repeated. Valproic acid (20mg/kg/day) and phenytoin (5mg/kg/day) were started to control the seizures. He continued to have spiking fever (38.5°C). Urine, wound and blood cultures were negative, and chest radiograph showed no sign of infection. The Fluconazole (6mg/kg/day) was added to his treatment and then his fever decreased two days later.

On the seventh day of parenteral corticosteroid administration, the patient’s lesions progressively resolved and his skin showed re-epithelization (Fig. 2). The dose of parenteral corticosteroid was reduced gradually and discontinued on the 14th day. All his laboratory findings returned to normal limits. He was discharged in a stable condition on the 18th day.
Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are diseases within the spectrum of severe cutaneous adverse reactions affecting skin and mucous membranes. Both are rare, with SJS and TEN affecting approximately 1 or 2/1,000,000 annually, and are considered medical emergencies as they are potentially fatal.

Initial symptoms of both TEN and SJS can be fever, stinging eyes, and pain upon swallowing, any of which can precede cutaneous manifestations by 1 to 3 days. Skin lesions tend to first appear on the trunk, spreading to the neck, face, and proximal upper extremities. The distal portions of the arms as well as the legs are relatively spared, but the palms and soles can be an early site of involvement. Erythema and erosions of the buccal, ocular, and genital mucosa are present in more than 90% of patients. The epithelium of the respiratory tract is involved in 25% of cases of TEN, and gastrointestinal lesions can also occur. The skin lesions are usually tender, and mucosal erosions are very painful. In accordance with the literature, our case had oral mucosa ulcerations, hemorrhagic crust on lips and nose, bilateral hyperemic conjunctivas, erythematous papules and bullae located mainly on the face, neck, trunk, and genitalia, and sparsely on the upper and lower extremities. Our case was a 7-year-old boy with cerebral palsy, which might cause a delay in early diagnosis as the patient was not able to tell his initial symptoms, such as stinging eyes and pain upon swallowing.

The total body surface area (TBSA) of the detachment is the main distinguishing factor between SJS, SJS-TEN and TEN. SJS presents with epidermal detachment of less than 10% TBSA, whereas involvement of 10-30% TBSA is defined as an SJS/TEN overlap. TEN is defined as epidermal detachment of 30% TBSA or more. Epidermal loss in our case accounted for approximately 10% TBSA, so our diagnosis was SJS.

Drug exposure and non-drug risk factors are the causes of SJS/TEN. Allopurinol, anti-infective sulfonamides, carbamazepine, lamotrigine, nevirapine, oxicam-NSAIDs, phenobarbital, and phenytoin are “highly suspected drugs” for development of SJS/TEN. Aminopenicillins, tetracyclines, quinolones, cephalosporins, macrolides, diclofenac and related NSAIDs, corticosteroids, acetaminophen, pyrazolones, and acetylsalicylic acid are other “suspected” drugs. HIV and other infections, recent cancer, recent radiotherapy, and collagen vascular diseases are suspected non-drug confounding risk factors. The pathophysiology of SJS/TEN remains unknown but it is generally assumed to be an autoimmune phenomenon triggered by drug intake, viral syndrome or autoimmune disease. Moreover, SJS/TEN is associated with an impaired capacity to detoxify reactive intermediate drug metabolites.

When seizures are poorly controlled, anti-epileptic drugs (AED) are used in combination, leading to potential pharmacokinetic or pharmacodynamic interactions that cause more adverse effects than might occur when the AED is taken as monotherapy. The case presented here was under the treatment of valproic acid, lamotrigine and lorazepam for the last 2 years. There were no adverse effects and skin lesions while using these three antiepileptic drugs during this period. However, due to ongoing seizures, lorazepam was changed to clobazam, and SJS developed four weeks later. As a result, we think that the triggering factor of SJS in our case was clobazam.

It is known that clearances of most conventional antiepileptics are not affected by co-therapy with clobazam. However, clearances of valproic acid and primidone are significantly reduced by clobazam. When clobazam is
added to a therapy regimen that includes valproic acid, the patient should be closely monitored for possible adverse drug reactions caused by elevated valproic acid serum concentrations, and monitoring of valproate serum levels should be considered.\(^{10}\)

Furthermore, co-administration with valproic acid has been shown to significantly increase the plasma concentrations of lamotrigine and the risk of a potentially serious and life-threatening rash induced by lamotrigine, including SJS/TEN.\(^{11,12}\) The clobazam has no significant pharmacokinetic interaction with lamotrigine.\(^{13}\) In a major retrospective study of 1,890 outpatients with epilepsy, researchers assessed the rates of rash associated with 15 AEDs. The highest rash rates occurred with phenytoin (5.9%), lamotrigine (4.8%) and carbamazepine (3.7%). The lowest rash rates occurred with felbamate, primidone, topiramate (all <1%), levetiracetam (0.6%), gabapentin (0.3%), and valproate (0.7%).\(^{14}\)

It has been suggested in the literature that rapid elevation of lamotrigine levels may increase the occurrence of lamotrigine-related skin lesions and rash.\(^{15}\) As valproic acid decreases lamotrigine clearance by 60%, the combined usage of these drugs may easily result in increased lamotrigine levels.\(^{15}\) Based on this information, we think that the clobazam elevated valproic acid serum concentration. These elevated valproic acid levels led to an increase in the plasma concentration of lamotrigine. So, in our case, the reason for SJS development was thought to be related to a secondary increase of plasma levels of lamotrigine. However, we were not able to confirm this by plasma lamotrigine measurement.

SJS/TEN usually occurs within the first 2 months of treatment, with a sharp decrease of incidence thereafter.\(^{16}\) In various studies, this period was reported to be between 1 and 8 weeks.\(^{17,18}\) In our case, the skin rash was seen 4 weeks after the addition of clobazam to the treatment. However, clobazam is a relatively safe AED in terms of anti-convulsant hypersensitivity syndrome. SJS/TEN due to clobazam usage is infrequent. We identified one published report of a case in which TEN was caused by clobazam.\(^{19}\)

In this case, TEN was reported to occur at photo-exposed areas in a patient who was receiving clobazam, which was different from our case. Thus, we think that clobazam may not be the primary reason albeit the triggering factor of the SJS.

Another case of SJS triggered by the combination of clobazam, lamotrigine and valproic acid treatment has been reported in the literature.\(^{16}\) In this case, lamotrigine therapy had been withdrawn, and treatment with valproic acid and clobazam had been continued. The skin lesions of the patient subsided after discontinuation of lamotrigine, which shows that the reason for SJS was lamotrigine. In our cases, lamotrigine, valproic acid and clobazam were all withdrawn. Valproic acid and fenitoin were started two days later due to recurrence of seizures. Re-epithelialization was nearly completed 8 days after usage of parenteral corticosteroids.

The treatment of SJS/TEN is similar to the treatment of major burns and it is reported that early transfer to a burn center is important for the outcome. In addition to supportive treatment and wound care, treatment with immunosuppressive drugs was expected to be useful in SJS/TEN because of the immunologic background of the disease. Corticosteroids inhibit inflammatory and immune response and have been the first-line drug for the treatment of SJS/TEN for 30 years.\(^{1}\) In our case, parenteral corticosteroid was administered and the skin lesions subsided. Although intravenous immunoglobulin (IVIG) is also used for treatment of SJS/TEN, the largest trial including 281 patients showed no benefit from using IVIG, so we did not use this during the treatment of our patient.\(^{18}\)

**Conclusion**

In conclusion, we reported a case in which a drug-drug interaction between valproate, lamotrigine and clobazam contributed to the development of SJS. It should be kept in mind that when clobazam is added to valproic acid and lamotrigine co-medication, the serum level of lamotrigine can be increased. Plasma lamotrigine levels should be followed up; in case of an elevation, the dosage of lamotrigine may be titrated. Physicians should be alert and inform the patient and his/her family of the possible development of SJS/TEN when clobazam treatment is combined with valproic acid and lamotrigine.
BIBLIOGRAPHY


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