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Case Report

A CASE REPORT ON LAMOTRIGINE AND SODIUM VALPROATE INDUCED STEVENS-JOHNSON SYNDROME

Shatakshi Rai [1], Rashi Bahuguna [1], Devesh Joshi [1], Saurav Bartwal [1], Nitesh [2], Yogesh Joshi [3]*

[1] Pharm D. Student, Department of Pharmacy Practice, Shri Guru Ram Rai Institute of Technology and Science, Patel Nagar, Dehradun, Uttarakhand, India

[2] Assistant Professor, Department of Pediatrics, Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun, Uttarakhand, India

[3] Assistant Professor, Department of Pharmacy Practice, School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Dehradun, Uttarakhand, India

*Corresponding Author Email: yogeshjoshi1583@rediffmail.com

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ABSTRACT

Lamotrigine and Sodium valproate are the widely used drugs worldwide for treatment of generalized as well as partial seizures. They are very efficacious drugs. There is a very severe skin reaction associated with Lamotrigine when co-administered with Sodium valproate called Stevens - Johnson syndrome (SJS). A case of 15-year-old girl was presented to the hospital with high grade fever (on and off) with rashes and blisters all over the body and extremities as she was on Lamotrigine (LTG) and Sodium valproate combination therapy for episodes of seizures. The dose of both the drugs was high due to which she developed SJS. Patient was started on alternative anti-convulsant for treatment of seizures and symptomatic skin and eye care drug therapy was given to the patient to reduce skin and eye lesions due to SJS. Patients on drug therapy of Lamotrigine and Sodium valproate should be properly monitored and therapeutic drug monitoring as well as adverse effect reporting is further necessary.

Keywords: Anti-epileptic drugs, Lamotrigine, Sodium Valproate, Stevens-Johnson syndrome, Toxic Epidermal Necrosis, Erythema Multiforme

INTRODUCTION

A new eruptive fever with stomatitis and ophthalmia was described as a severe variant of erythema multiforme and was termed by Steven and Johnson in 1922. In 1940, it was commonly called as Stevens-Johnson syndrome[1]. Stevens-Johnson syndrome is a serious dermatological condition with adverse hypersensitivity reactions that affect the skin and mucous membranes and are characterized by erythematous macules and hemorrhagic erosions of the mucous membranes and are triggered mainly by medications[2,3].

SJS is a less severe form of Toxic epidermal necrosis (TEN) and differs clinically from Erythema multiforme (EM). Erythema multiforme is characterized by mucosal erosions of raised atypical target lesions usually located on the extremities and/or the face. The characteristic findings of SJS are mucosal erosions plus widespread distribution of flat atypical targets or purpuric macules. The lesions may be present on the trunk, face and on the extremities. Compared to Erythema multiforme, SJS is more closely associated with medication use and mycoplasma pneumonia infection. It is potentially life-threatening with a mortality of up to 15%. The incidence of SJS is estimated to be between 1.1 and 7.7 cases per million, with 16% of cases showing a past history of short-term use of the anti-epileptic drug[4-5]. TEN is most severe form of drug induced skin disease and is defined as epidermal detachment of >30% of the total body surface area. SJS is characterized by epidermal detachment of <10% total body surface area, whereas 10-30% of total body surface area is covered in SJS/TEN overlap[6]. People with genes (HLA)-B12, HLA-B*5801, HLA-B*1502 are at increased risk of developing SJS/TEN[7-8].

Infectious diseases are secondary triggers of these pathologies, especially in the pediatric population, with Mycoplasma pneumoniae infection[9]. The list of responsible drugs is very broad with Lamotrigine, Sodium valproate, Carbamazepine, Phenobarbital, Phenytoin and Allopurinol being the most frequently implicated medications[10]. SJS can occur at any age and clinically they are characterized by significant involvement of skin, oral, nasal, eye, vaginal, urethral, gastro-intestinal and lower respiratory tract mucous membranes. Lesions may continue to erupt in crops for as long as 2-3 weeks. Skin rash can begin as macules that develop into papules, vesicles, bullae, urticarial plaques or confluent erythema. Bullous lesion can rupture and may lead to further fever, general symptoms and detachment of the epidermis. Mucosal involvement includes erythema, oedema, sloughing, blistering, ulceration and necrosis. Gastrointestinal and respiratory involvement may progress to necrosis. The usual management is hospitalization and depending on the degree of cutaneous involvement (skin detachment greater than 30% of the body surface area), clinical situation or associated co-morbidities, it may require entry into intensive care units[11,12].

Anti-epileptics as a group have been reported to cause SJS with variation in its association with individual anti-epileptic medications. Although present data provides an association of SJS with combined use of all anti-epileptic drugs, the data for individual drugs are not convincing because of small numbers of exposed patients and an inability to adjust for possible variables.

Among anti-epileptic drugs, SJS has been generally reported with the use of Carbamazepine, Phenobarbital and Phenytoin especially during the early period or start of these medications (usually the first few days or few weeks). Lamotrigine and Sodium valproate are another commonly used anti-epileptic drugs and also an emerging treatment for seizures which has not been well reported to be associated with SJS in medical literature, although there have been some reports linking the use of Lamotrigine and Sodium valproate combination with this syndrome[13-14]. In this case report, the patient had developed SJS after 3-4 weeks of the use of Lamotrigine and Sodium valproate.

Case Report

A 15-year-old girl was presented to the emergency department with high grade fever (on and off), progress recorded up to 103˚F along with rashes noticed all over the face. Rashes were itchy in nature which gradually progressed to abdomen and extremities, red in color and were irregular. Blisters were also noticed that were black in color and spread all over the body. The patient had decreased urine output with red colored urine. The patient also developed high chances of bleeding from any site of the body along with abnormal behavior. The patient was a known case of acute lymphocytic leukemia (ALL) with seizure disorder and also had past surgical history of leukoencephalopathy. The patient was already on Sodium valproate syrup 5 ml (i.e. 200 mg in 5 ml twice daily) and Lamotrigine tablets 25 mg which later got increased to 50 mg, for the treatment of seizures. After the patient got admitted to the hospital various laboratory investigations were done, which showed various alterations in the Complete blood count levels (CBC), Renal Function Tests (RFT), as well as the patient's Sodium valproate blood levels were also analyzed which came out to be 8.63 µg/ml, which was in the higher range, due to which the patient developed rashes all over the body and was later diagnosed as drug induced Stevens- Johnson syndrome.

After the final diagnosis of drug induced Stevens-Johnson syndrome was reported in the patient, Sodium valproate syrup and Lamotrigine tablets were discontinued, as it was the major cause of the occurrence of SJS. After discontinuing these medications, the patient was started on Midazolam injection 4 mg and Levetiracetam injection 1 mg in 100 ml for seizures and various other medications for Stevens-Johnson syndrome like antihistamines (Pheniramine injection and Levocetirizine tablets), immunosuppressants (Cyclosporine syrup and Tacrolimus ointment), topical steroids (Dexamethasone) and antibiotics (Linezolid injection). Further, eye care management, improvement in skin lesions, and relevant routine investigation which came out to be under normal limits were followed by the improvement in the patient's condition. Sodium valproate blood levels were also found to be low; antibiotics and steroids were discontinued after 5-7 days of administration with plan of tapering of Cyclosporine syrup over four weeks. When the patient got clinically better with no episodes of seizures or appearance of new lesions evidenced during the hospital stay, the patient was discharged and was asked for the regular follow up in out-patient department.

DISCUSSION

Several anti-epileptic drugs are used in combination when seizures are poorly controlled. Lamotrigine is normally eliminated from body by enzyme UDP-glucuronosyl transferase leading to formation of two metabolites LTG-N-2 glucuronide and LTG-N-5 glucuronide. This is the major pathway by which Lamotrigine is metabolized and eliminated from the body and is called glucuronidation. The minor pathway involves enzyme cytochrome P-450 leading to formation of LTG-Arene Oxide Intermediate which is toxic in nature. As glucuronidation is the main pathway for LTG elimination, anything that inhibits UDP-glucuronosyl transferase enzymes will affect LTG levels, leading LTG metabolism to the minor elimination route in which cytochrome P450 enzymes are involved. So, in the absence of the major pathway such as N-glucuronidation, LTG can be bio activated to an LTG-Arene Oxide Intermediate (Figure 1)[15-17].

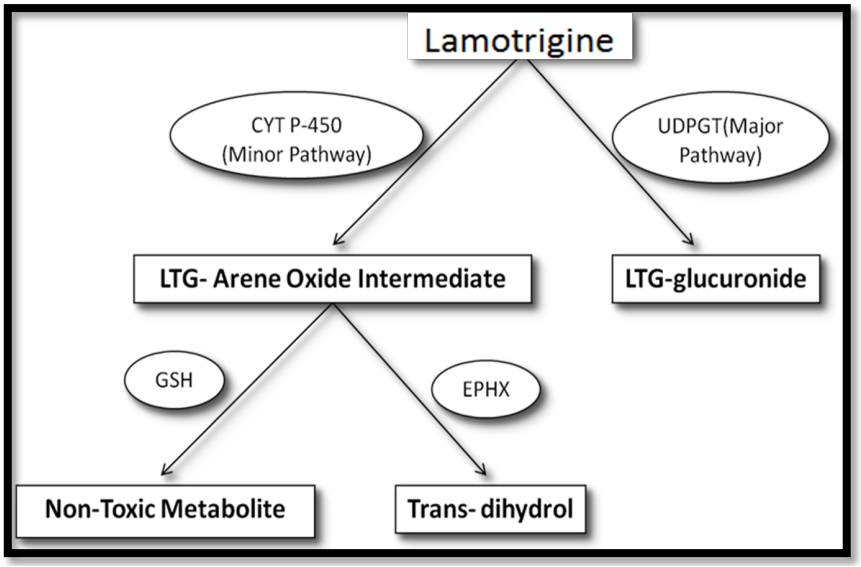

Figure 1: Metabolism pathways of Lamotrigine

*UDPGT = uridine diphosphate glucuronosyltransferase; EPHX = epoxide hydrolase; GSH = glutathione

Arene oxides are toxic intermediates and are chemically reactive. Arene oxides can be mainly detoxified by rearrangement to arenols, but enzymatic hydration by EPHX to trans-dihydrols and enzymatic conjugations with GSH forming non-toxic metabolites also play very important roles. If arene oxide is not effectively detoxified by these pathways, an increase in arene oxide levels

will take place, and this reactive metabolite will bind covalently with nucleophilic groups of proteins, DNA and RNA, leading to cellular damage[18-19].

Sodium valproate is mainly metabolized by the liver, and it is a known inhibitor of UDP-glucuronosyl transferase. According to some investigations, there was a significant increase in Lamotrigine serum concentrations by concomitant administration of Sodium valproate, indicating a decrease in Lamotrigine clearance when Sodium valproate was added to the therapy. As Sodium valproate is the inhibitor of GSH-s-transferase and epoxide hydrolases (EPHX), arene oxide is not converted to non-toxic metabolites and trans-dihydrols respectively. Therefore, the level of arene oxides gets increased in body leading to adverse effects, mainly rash and other cutaneous reactions[20-24].

Sodium valproate is metabolized by three main routes: glucuronidation (50%), β-oxidation in mitochondria using L-carnitine (40%) and ω-oxidation leads to formation of a toxic metabolite, 4-en-valproic acid (10%). Sodium valproate chronic therapy or Sodium valproate overdose produces L-carnitine (LCAR) depletion and this could impair β-oxidation leading to increase in ω-oxidation pathway and further the formation of toxic metabolites leads to mucocutaneous reaction. Moreover, impairment of β-oxidation leads to hyper ammonemia which is the major cause of seizures; so, combination therapy with L-carnitine is recommended[25-27].

CONCLUSION

The present case report provides the clinical evidence that the combination of Lamotrigine and Sodium valproate increase the chance of various skin reactions leading to Stevens-Johnson syndrome. Hence, when the patient is prescribed with Lamotrigine and Sodium valproate in drug therapy, therapeutic drug monitoring should be done so as to avoid any drug interaction between them and to provide greater efficacy during the course of treatment. Physician has made the patient/guardian aware regarding various adverse effects which may occur during the therapy. The patient undergoing Sodium valproate and Lamotrigine therapy should also be prescribed L-carnitine as a supplement to avoid ω-oxidation of Sodium valproate which forms toxic metabolites.

Ethical statement

Consent was taken from the patient's guardian before starting case study and it was stated that the study was carried out as per Declaration of Helsinki 2004[28].

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