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A Case Report: Stevens-Johnson Syndrome Induced by the Combination of Lamotrigine and Valproic Acid

Haouatti F[1*,2], Toumi H[1,2], Tachema A[1,2], Boukersoul N[1,2], Mekaouche Nfz[1,2], Ould Amar N[1,2], Fetati H[1,2], Memou A[1,2], Senhaji I[1,2], Belbouche N[1,2], Boudia F[1,2], Reziga Kh[3], Fattouhi[4] and Serraj A[4]

*[*1]Pharmacovigilance service, EHU ORAN, Algeria*

[2]Pharmaceutical Research and Development Laboratory LRDP, Algeria

[3]Reanimation Service, CHU, Algeria

[4]Dermatology Service, EHU ORAN, Algeria

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ABSTRACT

Lamotrigine is pluripotent antiepileptic drug. However, it is associated with many serious adverse effects such as Stevens-Johnson syndrome, especially when co-administrated with valproic acid. We report a case of Stevens-Johnson syndrome in an adolescent in a context of polymedication of antiepileptic drugs. Lamotrigine was added to his existing treatment of valproic acid and levetiracetam. Eleven days after Stevens-Johnson syndrome was developed and a notification was sent to the pharmacovigilance service of the EHU of Oran to calculate the imputability. The patient received symptomatic treatment with methyl prednisolone and a rehydration regimen was instituted. His condition improved over the next two weeks and he finally recovered with continuous outpatient follow-up.

Keywords: Adverse effects, Stevens-Johnson, Lamotrigine, Valproic acid

INTRODUCTION

Lamotrigine (LTG) is a second-generation anti-epileptic drug, active on both focal and generalized seizures [1,2]. It is also effective in the treatment of various neuropsychiatric disorders [3]. The use of LTG is associated with the risk of serious skin adverse effects. These effects include life-threatening rashes, such as Stevens-Johnson syndrome (SJS) [4]. Children undergoing polytherapy have a higher risk of developing them [5]. As well as the combination of LTG and valproic acid (VPA) which increases the frequency and the severity of these skin reactions [6]. VPA not only decreases the clearance of LTG but also inhibits the detoxification pathways [6].

CASE REPORT

A 17-year-old adolescent with mental retardation secondary to hypoxic ischemic syndrome and generalized epilepsy, was referred to the emergency room for a febrile rash and skin detachment. Physical examination showed phlyctens, congestive facial oedema and pruritic erythematous macules affecting his face, extremities, body, and hips. The epidermal detachment interested 10% of the skin surface with a positive Nikolsky's sign. Mucosal damage (cheilitis, mouth ulcers and bilateral conjunctivitis) were associated **(Figures 1 and 2)**.

From the dermatologic point of view and considering the history and clinical presentation, the patient was diagnosed with SJS and a notification was sent to the pharmacovigilance service of Oran EHU to calculate the accountability.

The drugs investigation found a first intake of LTG (25 mg once a day) eleven days earlier and there were no other medications introduced to his treatments in the previous three months. The rest of his treatment included levetiracetam (LEV) (750 mg twice a day) and VPA (500 mg three times a day), perfectly tolerated for more than two years. Since the suspected cause was LTG, the drug was stopped immediately. The patient received symptomatic

Corresponding author: Haouatti Fairouz, Pharmacology Doctor, Pharmacovigilance Laboratory, Algerian Democratic and Popular Republic Health and Higher Education Ministry, University of Oran1, Es Senia, Algeria, Tel: 0553693495; E-mail: houattipharmaco@outlook.fr

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treatment with methyl prednisolone and a rehydration regimen was initiated. Ocular lesions were treated with rifamycin (eye drops and ointment) and oral care (mouthwash) was also indicated. His condition improved over the next two weeks and the patient eventually recovered and was discharged with continuous outpatient follow-up.

Figure 1. Skin rash over face and neck along with extensive blistering lesions with mucosal involvement.

Figure 2. Diffuse pruritic erythematous macules.

DISCUSSION

SJS is a rare but life-threatening delayed hypersensitivity reaction (type IV) [7]. Schematically, SJS is characterized by skin detachment affecting less than 10% of the body surface with erosions of the mucous membranes. In lyell syndrome, skin detachment involves more than 30% of the body surface and overlapping forms have skin detachment ranging from 10 to 30% [8]. The SJS is a mainly drug-induced phenomenon in which 85% of the cases a drug is incriminated [9].

Taking a thorough medical history is crucial to this process and can be life- saving [7].

LTG is one of the high-risk drugs known to cause SJS [10]. The risk of skin reactions rises when the primary dose of LTG is high, when doses are hastily increased and when used in co- administration with VPA [11], as VPA can reduce LTG clearance by 54% in duel therapy [12]. The inhibition of LTG by VPA is concentration-dependent [13,14], with a maximum inhibitory effect can be expected at VPA doses of approximately 500 mg per day [15]. LEV has no effect on LTG clearance in dual therapy and does not interfere with the inhibitory effect of AVP in triple therapy [12]. Our patient was on 1500 mg per day of VPA before and during the combination with LTG suggesting maximum inhibitory effect. The recommended initial dose of LTG for patients taking simultaneously VPA is 12.5 mg/day (25 mg given every other day) for the first two weeks, followed by 25 mg once a day for the next two weeks [16]. Where as in our case the initial dose was 25mg per day and it was increased to 50mg per day the following week. All of these circumstances could promote the development of this syndrome. Numerous studies have reported cases of LTG-induced SJS, particularly with the concomitant use of VPA **(Table 1)**. They have shown that there is a need to monitor the blood levels of these antiepileptic drugs.

Accountability makes it possible to formalize and clarify the assessment of the causal link between the taking of a drug and the occurrence of an adverse effect and, as such, is an aid in clinical practice for the diagnosis and management of an adverse effect in a given patient [27]. This operation implicates the entire pharmacovigilance system, since without reporting, there is no accountability or monitoring of drugs in the general population [28].

SJS occurs between the 5th day and the 8th week due to the delay required to activate the body's immune response [29]. The imputability of LTG has been retained in a suggestive timeline. Using the updated French imputability method, which is an algorithmic method based on the evaluation of eight criteria divided into intrinsic (chronological and semiological) **(Figure 3)** and extrinsic (literature data) factors.

Table 1. Clinical data and drug history of SJS in patients taking LTG with VPA.

Study	Year	Number of cases	Sex	Age (years)	VPA	LTG	Time*	Prognostic**
Vazquez et al. [6]	2018	01	M	08	375mg 3/day	25 mg/day (2weeks) 50 mg/day (2weeks)	04	12
Maduemem et al. [17]	2017	01	M	09	400 mg 2/day	12.5 mg/day (0.4 mg/kg/day)	06	12
Kavitha et al. [11]	2015	01	F	35	600 mg/ day	25 mg/day	01	12
Kaur et al. [18]	2013	02	F	46	300 mg/Day	50 mg 2/day	02	45
			F	26	750 mg/ Day	25 mg/day	04	/
d'Oflaz et al. [19]	2011	01	F	24	1000 mg/Day	25 mg/day	02	30
Sahin et al. [20]	2008	01	M	23		25 mg and increased 50 mg/day	02	12
Kocak et al. [21]	2007	01	F	23	500 mg 2/day	50 mg 2/ day	03	18
Chang et al. [22]	2006	01	F	32	1000 mg/Day	12.5 mg/day and increased 25 mg/day	02	14
Famularo et al. [23]	2005	01	M	24	600 mg/ Day	12.5 mg/day and increased 25 mg/day	04	30
Hashim et al. [24]	2003	01	F	29	/	/	03	08
Yalcin et al. [25]	2000	01	F	33	/	25 mg/day increased to 150 mg/day	04	10
Bhushan et al. [26]	2000	01	M	30	500 mg 4/day	25 mg/j	01	30

**Time before the start of SJS in weeks after introduction of LTG*
***Favourable prognosis and hospital discharge in days*

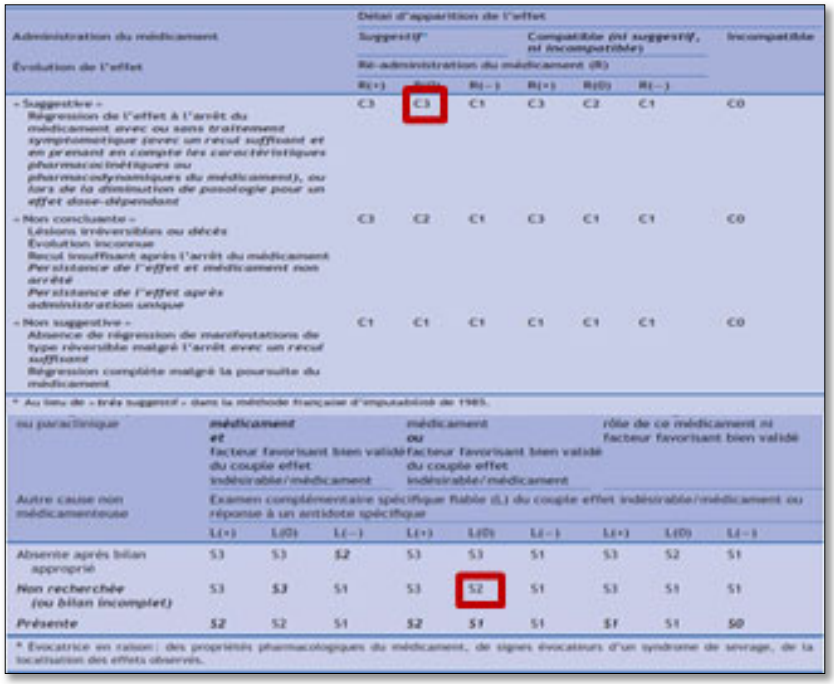

Figure 3. Decision tables of the Score of the French imputability method updated in 2011 [27].

The intrinsic imputability score for LTG was I5 (Chronological criterion: C3 Semiological criterion: S2) **(Figure 4)** while the extrinsic imputability was B4 whereas VPA and LEV was I1 B2 and I1 B4 respectively.

Combinaison des scores chronologiques (C) et sémiologiques (S)	Score d'imputabilité intrinsèque (I)
C0 ou S0	I0
C1S1	I1
C1S2 C2S1	I2
C2S2	I3
C1S3 C3S1	I4
C2S3 C3S2	I5
C3S3	I6

Figure 4. Intrinsic imputability score (I) of the French imputability method updated in 2011 from the combination of chronological (C) and semiological (S) scores [27].

CONCLUSION

This clinical case reminds us that only a rational prescription of anti-epileptic drugs can reduce the risk of dermatological accidents. The concomitant use of VPA and LTG can double the concentration of the latter, so a 50% reduction of LTG is recommended. Our pharmacovigilance survey encourages monitoring the blood concentration of antiepileptic drugs at the beginning of a new treatment with LTG. The calculation of imputability is not always easy, so a declaration of adverse effects must be actively carried out through the patient's electronic file in the pharmacovigilance service.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest in connection with this article.

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