

# PHENYTION, CARBAMAZEPINE, SODIUM VALPROATE AND LAMOTRIGINE INDUCED CUTANEOUS REACTIONS

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**Abstract-** Adverse effects of antiepileptic drugs including cutaneous reactions may not only affect the result of treatment and quality of life, but can also be fatal if severe. Skin rash is more likely to occur during the first few months of treatment. The objective of this study was description of skin rashes in users of four antiepileptic drugs. We identified skin rashes of phenytoin, carbamazepine, sodium valproate and lamotrigine in a prospective descriptive cross sectional study in 1086 cases. Patients suffering from skin diseases, systemic illness with cutaneous presentations, radiation or drug-induced rash from non antiepileptic drugs and patients unwilling to be examined monthly were excluded. All the cases were followed for 6 months. Skin rashes occurred in 2.1% (23/1086) of patients. Twelve patients were male and the remaining 11 were female. The age of patients ranged from 8 to 71 (mean 24) years. Maculopapular rash and Stevens Johnson's syndrome formed 56.5% (13/23) and 30.4% (7/23) of symptomatic cases, respectively. Toxic epidermal necrolysis, erythema multiform and psoriatic dermatitis each were detected in 4.3% (1/23) of patients. The interval between the beginning of antiepileptic as monotherapy or an add-on drug and skin rash presentation was from 3 to 45 (mean 13) days. Combination therapy was found to increase the incidence of rash, but dosage of drug did not show such effect. Special attention to skin rash in the first month of therapy and monotherapy instead of polytherapy is recommended.

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**Key words:** Antiepileptic drugs, rash, Stevens Johnson's syndrome, toxic epidermal necrolysis, hypersensitivity syndrome

## INTRODUCTION

Antiepileptic drugs (AEDs) frequently cause cutaneous eruptions, especially during initiation of new therapy. In addition to causing common and usually limited morbilliform and urticarial eruptions, which have often mild morbidity, AEDs are also incriminated to induce widespread maculopapular rash, hypersensitivity syndrome (HSS), psoriatic dermatitis and occasionally severe reactions such as Steven Johnson's syndrome (SJS), toxic epidermal

necrolysis (TEN) and erythema multiform (EM) (1,2).

Clinical and epidemiologic evidences suggest that the risk of severe reactions with AEDs is largely confined to the first few months of treatment (2). Both SJS and TEN are characterized by high fever, malaise and rapidly developing blistering exanthemas of macules and target-like lesions, accompanied by mucosal involvement. Some patients with SJS may evolve to develop TEN; in the latter disorder more than 10% of the body surface area is involved (3). SJS and TEN have an estimated annual incidence of 1-2 per million, with 16% of cases show a past history of short-term use of AEDs (4-6). Most previous reports concerning association of these reactions with AEDs are based on single cases (7) or small case series (8-12). Severe skin reactions (SJS,

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## Antiepileptics-induced cutaneous reactions

TEN and EM) may be the cutaneous manifestations of HSS, but this is not usual (13). In HSS which is defined by a triad of fever, cutaneous reaction and internal organ involvement, mucous membrane involvement is rare, but widespread exanthematous eruption that may become purpuric or transform into exfoliative dermatitis is typical. The latter syndrome is fatal in 10% of cases and is often associated with lymphadenopathy and hepatitis. Eosinophilia, atypical lymphocytosis, nephritis and carditis may also occur (13, 14).

SJS and TEN are severe albeit rare adverse reactions to AEDs such as phenytoin (PHT), carbamazepine (CBZ), phenobarbital (PHB), sodium valproate (VLP) and lamotrigine (LTG) (2, 8, 12-16). The incidence of severe reactions in first – time users of PHT and CBZ are 9/10000 and 6.2/10000, respectively (1). Children and adults receiving LTG have shown severe reactions in 0.5–1/100 and 0.3/100, respectively (13, 17-21), but rash of any type occurs in 7-12% (mean 10%) of cases (13, 17, 20, 21). We undertook this study to estimate the incidence of skin rashes including SJS and TEN in AEDs users.

## MATERIALS AND METHODS

This prospective descriptive cross-sectional study was performed in cases receiving PHT, CBZ, VLP and LTG in our center in patients 8-71 years of age. We obtained informed consent from all participants.

All patients were followed for 6 months and examined routinely every month or whenever a skin reaction occurred. Included in this study were 1086 cases enrolled by non-randomized simple sampling method.

Exclusion criteria were: 1) skin diseases with cutaneous reactions, 2) systemic diseases with skin presentations confounding the study, 3) all patients receiving radiations three months before starting AEDs and thereafter 4) use of other drugs with possible induction of rash or alleviating them and 5) unwilling patients (to be examined monthly).

Because these drugs may remain in the body for a long time after cessation, we classified a patient as exposed if he or she was using the drug or had

stopped medicine within one week of the index day. We included in the analysis only those patients who developed the skin reactions, which were validated and classified by an expert dermatologist.

All data were analyzed by SPSS and using the Fisher exact test.

## RESULTS

Age of the patients ranged from 8 to 71 (mean 24) years. The interval between initiation of the drug in monotherapy or adding a new (second) antiepileptic in polytherapy and presentation of cutaneous eruptions ranged from 3 to 45 (mean 13) days (Table 1).

Skin rashes occurred in 2.1% of cases (23/1086: symptomatic) and the remaining 1063 were asymptomatic. Male to female ratio in symptomatic cases was 12/11, fifteen of whom were under monotherapy (PHT, 9; CBZ, 5; VLP, 1) and the remaining had received two antiepileptic drugs (VLP + LTC, 3; CBZ + LTC, 1; PHT + LTG, 1; PHT + CBZ, 2; VLP + CBZ, 1) (Table 2).

Skin lesions comprised of SJS (Fig.1) in 30.4% (7/23 or 0.64% of total patients), psoriatic dermatitis, erythema multiform and toxic epidermal necrolysis (Fig 2) each in 4.3% (1/23 or 0.09% of total) and maculopapular rash (Fig.3) in 56.5% (13/23 or 1.2% of total cases) of symptomatic cases (Table 3).

None of the symptomatic cases had received more than the advisable dose (though rapid increment of LTG was detected in two cases), but 35 cases (3.3%) in the asymptomatic group had used excessive treatment with a *P* value of 0.99 which was statistically meaningless.

**Table 1.** Interval between presentation of rashes and starting of AEDs

Drug	Range (day)	Mean (day)
Phenytoin	3-28	10
Carbamazepine	3-20	15
Sodium Valproate *	45	45
Lamotrigine	5-28	12

Abbreviation: AEDs, antiepileptic drugs.

\*Only one case.

**Table 2.** Cutaneous reactions and their percentage in relation with drugs\*

	Maculopapular rash	Erythema multiform	SJS	TEN	Psoriatic dermatitis	Total
<b>Monotherapy</b>						
Phenytoin	8 (88.9)	--	1 (11.1)	-	--	9(100)
Carbamazepine	4 (80)	--	1 (20)	-	--	5(100)
Sodium Valproate	-	--	--	-	1(100)	1(100)
<b>Polytherapy</b>						
Sodium Valproate + Lamotrigine	1(33.3)	--	2(66.7)	-	--	3(100)
Carbamazepine + Lamotrigine	-	--	--	1(100)	--	1(100)
Phenytoin + Lamotrigine	-	--	1(100)	-	--	1(100)
Phenytoin + Carbamazepine	-	--	2(100)	-	--	2(100)
Carbamazepine + Sodium valproate	-	1 (100)	--	-	-	1(100)

Abbreviations: SJS, Steven Johnson's syndrome; TEN, toxic epidermal necrolysis.

\*Data are given as number (percent).

With regard to polytherapy, we detected that three cases in the symptomatic group (13%: 3/23) and 31 patients in the asymptomatic group (2.9%: 31/1063) had been treated with a combination of VLP and LTG, which was statistically significant ( $P=0.04$ ).

On the other hand 5 cases with SJS and unique cases of TEN had received LTG in combination with other AEDs, thus co-administration of AEDs significantly increased the incidence of rashes, but no correlation was detected between drug dosage and the incidence of the cutaneous eruptions.



**Fig.1.** Steven Johnson's syndrome in a young patient receiving antiepileptic drugs.



**Fig.2.** Toxic epidermal necrolysis in a patient receiving carbamazepine plus lamotrigine.



**Fig.3.** Maculopapular rash in a patient receiving antiepileptic drugs.

## DISCUSSION

Patients included in our study had a mean age of 24 years, with a male to female ratio of 12/11; that is similar to Schlienger’s research in evaluating LTG – induced severe reactions (23) and Leong’s study about allergic reactions due to PHT (19).

In this study rashes had an overall occurrence of 2.1% (23/1086, severe and mild types being 0.82% and 1.3%, respectively) which was lower than figures (7-12%) reported previously by Dooley and Thome-Souza (16, 17). This difference may be related to the location of study, genetic or ethnic factors and possibly referring of some patients with rash to other centers, but in view of the premise of our research this result can be justified and acceptable.

Clinical trials by Tennis and Stern (1) and Rogvi-Hansen (22) indicated that the incidence of rash in LTG users has no significant difference with those for PHT and carbamazepine (12% vs 14 and 9% respectively), whereas most of our cases with maculopapular rash and more than half of patients complicated with SJS had received PHT per se and PHT plus CBZ or LTG respectively, suggesting that cutaneous reactions are more common in patients using PHT.

With regard to pathology, more than 60% of skin rashes were mild (maculopapular: 56.5%, psoriatic dermatitis: 4.3%) which was compatible with earlier studies; in contrast, severe types including SJS and TEN had higher (probably due to genetic effects) prevalence.

**Table 3.** Percentage of cutaneous reactions in symptomatic cases

Skin lesion	Number	Percent*	Percent †
Maculopapular rash	13	56.5	12
Erythema multiform	1	4.3	0.09
Psoriatic dermatitis	1	4.3	0.09
SJS	7	30.4	0.64
TEN	1	4.3	0.09

Abbreviations: SJS, Steven Johnson’s syndrome; TEN, toxic epidermal necrolysis.

\* in symptomatic cases.

† in all cases.

It is also noticeable that none of the patients receiving lamotrigine as monotherapy showed skin rash, but five patients under combination therapy with LTG and one of the other AED had been complicated with rashes (SJS, 3; TEN, 1 and maculopapular rash, 1), indicating that LTG-induced rash is more likely to occur with polytherapy. The reason of the latter finding, though correlates with Rzany’s report (4) has not been known till to date. In addition several researches pointed out that higher starting dose and rapid increment of dose are risk factors for LTG-induced rash (18, 20, 24), the latter risk factor was true in two of our patients.

Askmark *et al.* (25) and Mochenhaupt *et al.* (26) reported that skin reactions were more likely to occur in the first 2 months with CBZ and after two weeks in LTG users, which was nearly the same as our study.

According to the aforementioned data, we recommend: 1) to inform all patients about skin complications that are not uncommon, specially in the first 2 months, 2) to avoid polytherapy as far as possible, 3) and conducting an another study depicting genetic-related responses of AEDS in particular .

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