



Cutaneous Adverse Drug Reactions to anti epileptics: A Three Years Retrospective Study

Authors

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Abstract

Aims: To study the clinicoepidemiological profile of drug eruptions secondary to anticonvulsants among indoor patients in a tertiary care center.

Methods: There were 31 patients with anticonvulsants induced cutaneous adverse reactions who were included from January 2015 to December 2017. Demographic characteristics of the patients, suspected drug, duration between drug intake and onset of reaction, medical history, physical examination and laboratory parameters were recorded.

Results: The mean age group of patients was 44.5 years with the male to female ratio of 2.1: 1. Interval between the drug intake and drug rash was a mean of 39.4 days. Most common presentation was maculopapular rash seen in 21 patients (67.7%) followed by Steven Johnson Syndrome/Toxic Epidermal Necrolysis. The most common offending drug was phenytoin in 23 patients followed by carbamazepine in 5. Abnormal eosinophil counts were seen in 12 patients (38.7%). Liver function abnormalities were seen in 10 patients (32.3 %).

Conclusion: Allergic drug rash to anticonvulsants is common. Phenytoin was the commonest cause. The commonest indication of using phenytoin was as a prophylactic agent in head injury.

Keywords: Adverse drug reactions, anti epileptics, maculopapular.

Introduction

An adverse cutaneous drug reaction is an undesirable clinical manifestation resulting from administration of a particular drug either due to overdose, predictable effects or unanticipated adverse manifestations. Cutaneous adverse reactions constitute 10-30% of all reported drug reactions.⁽¹⁾ In India, antiepileptics account for 4.5 to 9.25% of all drug reactions,^(2,3) whereas in the western countries antiepileptics account for up to 20% drug reactions.⁽⁴⁾ These can vary from

transient erythema to severe cutaneous drug reactions such as toxic epidermal necrolysis (TEN). As newer drugs are introduced, new patterns of drug eruptions may arise. Hence, a high degree of suspicion is required for diagnosis of drug eruptions and immediate interventions.

Aims

To study the clinicoepidemiological profile of drug eruptions secondary to anticonvulsants among indoor patients in a tertiary care centre.

Materials and Methods

A retrospective study was conducted in our department. This study included all indoor patients with the diagnosis of anticonvulsants induced drug eruptions over a period of three years from January 2015 to December 2017. Hospital records were analyzed to gather information regarding demographic characteristics including age, sex, drug suspected, duration between drug intake and onset of reaction, medical history, physical examination for pattern of drug eruption and sites of involvement. Complete blood counts, renal functions and liver functions were also recorded to analyze systemic involvements.

Results

A total of 31 patients with severe cutaneous adverse reactions secondary to aniconvulsants were included in this study, which comprised of

21 (68 %) males and 10 females (32 %). The male to female ratio was 2.1: 1.

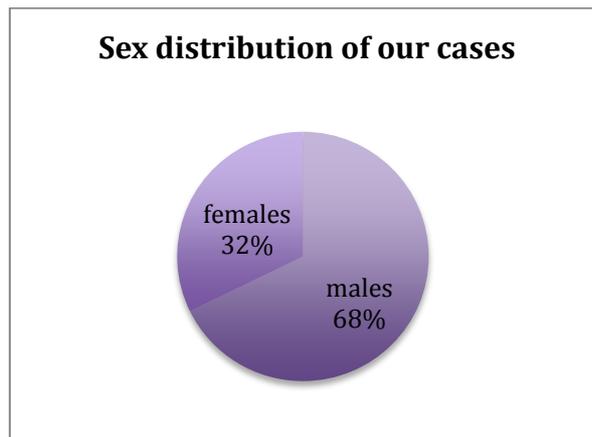


Figure 1: Sex distribution of the cases

The mean age group of patients was 44.5 years. Most patients i.e. 7 (22.5%) belonged to the age group of 41-50 years followed by 6 (19.3%) each in age groups 31-40 and 51-60 years (figure 1). Youngest subject was 11 years of age and the oldest patient was 80 years in the present study.

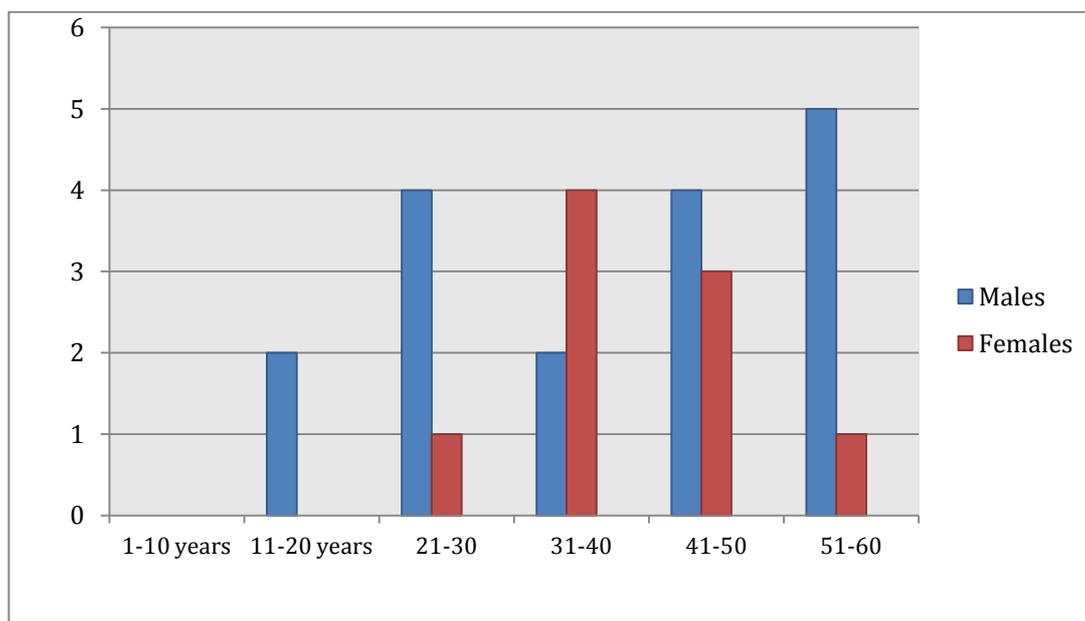


Figure 1: Age and sex distribution of the cases

The interval between the drug intake and onset of cutaneous eruptions had a mean of 39.4 days. This period in different patients varied from 2 days to 98 days. Most of the patients developed rash while they were taking the incriminated drug.

Various patterns of drug eruptions observed were maculopapular rash, drug rash with eosinophilia

and systemic systems (DRESS), exfoliative dermatitis, Steven Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) (Figure 2). The most common presentation was maculopapular seen in 18 patients (58%).

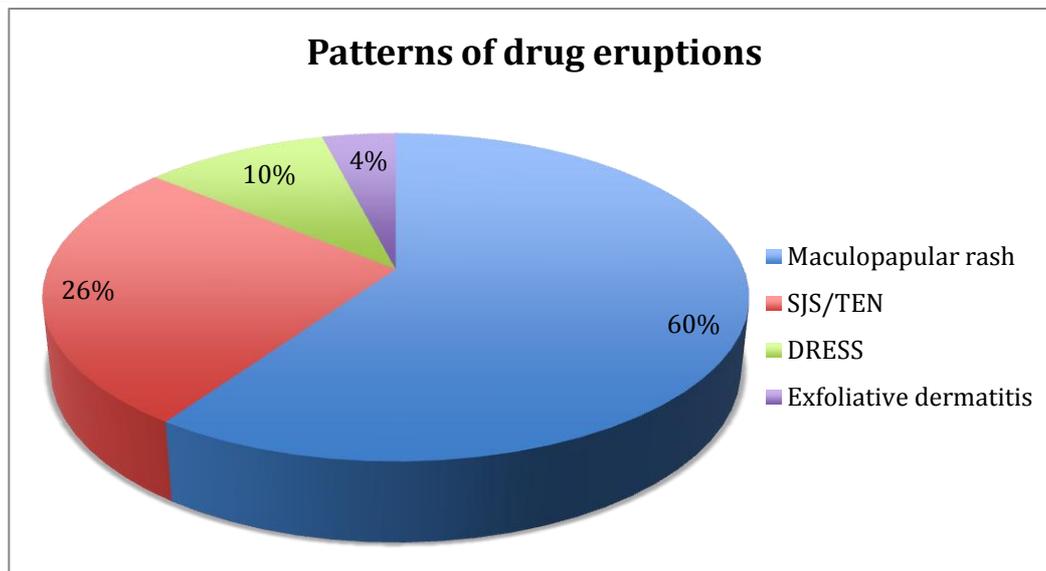


Figure 2: Types of adverse cutaneous reactions

On physical examination, generalized body involvement was more commonly seen as compared to localized involvement. Generalized involvement was seen in 25 patients (80%). Mucosal involvement was observed in 12 patients (38.7%). The site of onset was acral (hands, feet, palms) in 16 patients (51.6%). The laboratory parameters revealed elevated eosinophil counts (>500/mm³) in 12 patients (38.7%). Liver function abnormalities in the form

of more than two fold rise in the level of aminotransferases were seen in 10 patients (32.2%). Renal functions were abnormal in 2 patients (6.4%). Overall, the most common offending drug was phenytoin in 23 patients (67.7%) followed by carbamazepine in 5 (16%), oxcarbamazepine in 2 (6.4%) and lamotrigine in 1 patient (3.2%). (Figure 3)

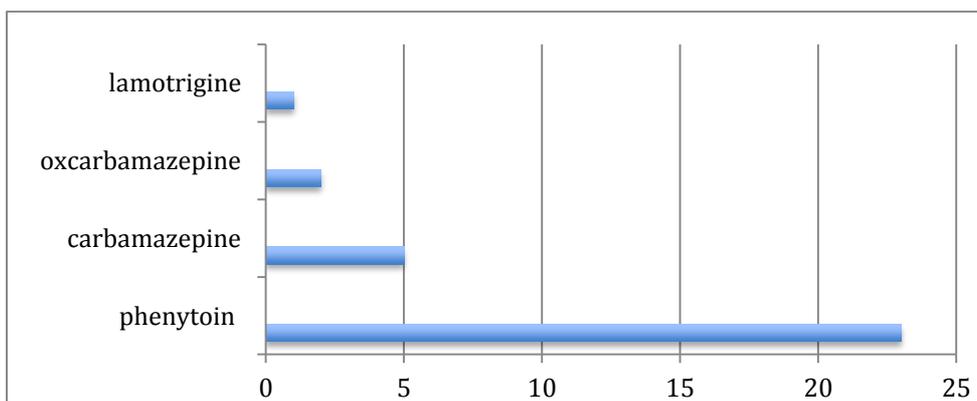


Figure 3: Drugs implicated for causing rash in our study

Phenytoin was implicated in causing all types of rash observed (Table 1).

Table 1: Correlation of pattern of rash and implicating drug

	Maculopapular Rash	DRESS	SJS/TEN	Exfoliative Dermatitis
Phenytoin	15	3	4	1
Carbamazepine	3	0	2	0
Lamotrigine	0	0	1	0
Oxcarbamazepine	0	0	1	1

Withdrawal of offending drug and institution of oral corticosteroids produced relief in all except 2 patients, who succumbed to complications and associated comorbidities. Both of them were patients of TEN secondary to Phenytoin.

Discussion

Antiepileptic drugs constitute a widely prescribed group of drugs commonly used for the control of seizures. They are also increasingly used for several non-epileptic neurological conditions, such as trigeminal neuralgia, neuropathic pain syndromes, migraine, psychiatric disorders and as a prophylactic drug in head injury. Antiepileptic drugs are a common cause for cutaneous adverse reactions having a prevalence of 2-3% overall among epilepsy patients. (1-13).

Exact pathogenesis of cutaneous drug rash due to AED is not known. The e haptens/prohaptens theory and the hypothesis of pharmacological interactions between drugs and immune receptors (p-i) are thought to be two different mechanisms. The rate of adverse drug reaction depends upon how commonly the drug is used. Certain HLA alleles have a predilection for cutaneous adverse reaction to specific anti convulsants.⁽⁵⁾

The present study observed a male preponderance, with male to female ratio being 2.1:1. Male preponderance is in concordance with previous studies.^(6,7,8,9,10) However, female preponderance has been seen in one study.⁽¹¹⁾ The mean age of our patients was 44.5 years. Most patients i.e. 7 (22.5%) belonged to the age group of 41-50 years as has been seen in previous studies also.⁽¹⁰⁾

The most commonly observed eruption in the present study was maculopapular rash in 60% followed by SJS/TEN. Few authors have reported similar results in that maculopapular rash were the commonest in percentages varying from 52.9% to 76.19%.^(9,10,12,13,14) DRESS and exfoliative dermatitis were the only other eruptions observed in the present study. Adverse drug reaction to antiepileptics also presented as pruritus, acne, pellagra, urticarial, lichenoid, scarlatiniform and

morbilloform rashes in other studies.^(10,15) These authors included all patients consuming the drug among both outdoor and indoor patients. Whereas, in this study, only indoor patients with severe cutaneous drug reactions were included explaining the limited cutaneous manifestations.

The interval between drug exposure and onset of rash had a mean of 39.4 days with earliest being 2 days. Phenytoin was the most common drug implicated in the present study as reported previously^(10,16,17) followed by carbamazepine. In contrast, Wang et al observed lamotrigine to be the commonest drug among Chinese population.⁽¹¹⁾ Also, Maneesha et al and Karimzadeh et al reported carbamazepine and phenobarbitone as the commonest causes of ADR respectively.^(9,14)

The laboratory parameters revealed elevated eosinophil counts ($>500/\text{mm}^3$) in 12 patients (38.7%) which is more as compared to previous.^(6,18) Systemic involvement was seen in this study but the prevalence was low as compared to previous study. Liver and renal function abnormalities were seen in 32.2% and 6.4% cases as compared to 47.34% and 21.04% respectively. This study was conducted over a longer duration including larger number of patients.⁽¹⁹⁾

Cutaneous eruptions tend to involve more than 50% of body surface area as reported by Vora et al in majority of their patients.⁽¹⁶⁾ Similarly, this study observed generalized body involvement in 25 patients (80%). Mucosal involvement was observed in 12 patients (38.7%) whereas others have reported in 17.64%.⁽¹⁶⁾

The overall mortality was observed in 6.4% patients with TEN being the primary diagnosis in these cases. The mortality in SJS/TEN is reported to be 16.39%⁽²⁰⁾. Also, these patients had associated comorbidities such as old age, immunosuppression due to carcinoma with cranial metastasis and the other had seizure disorder.

The indications for using antiepileptics were seizure disorder, tubercular meningitis, congenital malformations with mental retardation, neurocysticercosis, brain metastasis and head injury. Among the 23 patients on phenytoin, 13

(56.5%) were prescribed phenytoin prophylactically in cases of head injury. Prophylactic use of phenytoin leading to cutaneous adverse reaction in case of head injury has been mentioned in 6 out of 36 patients in a study by Sudha Rani et al.⁽¹⁰⁾ Phenytoin is indicated in subcortical parenchymal injury or the presence of septic foci in brain in case of head injury. Also, antiepileptics are required in first 7 days of head injury⁽²¹⁾, after which the risk of administering phenytoin should be weighed against the risk of severe cutaneous reactions. Even alternative antiepileptics may be prescribed instead of phenytoin, carbamazepine, lamotrigine and related drugs, which may decrease the burden of severe adverse cutaneous reactions in such patients. Severe cutaneous drug reactions decrease adherence and are barriers in treatment of such cases.

Conclusion

Allergic drug rash to anticonvulsants is common. Maculopapular rash was the commonest presentation. Phenytoin was the commonest implicated drug. The indication for use of phenytoin was for prophylaxis in head injury cases. Prophylactic use of anticonvulsants in head injury should be limited to first 7 days of trauma.

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