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Adverse cutaneous drug reactions to Anticonvulsants – A study at a tertiary care center in Telangana

Dr C Sudha rani, Dr B Udayakumar, Dr A Geetakiran,
Department of DVL, Gandhi Medical College, Gandhi Hospital, Secunderabad, Telangana (State)

Abstract:
Introduction: *Adverse drug reactionspresenting with cutaneous manifestations are a common occurrence and need to be differentiated from other causes of similar manifestations. Antiepileptic drugs(AED)/Anticonvulsants are responsible for various cutaneous adverse drug reactions ranging from mild macular erythemato severe reactions like Steven Johnson syndrome and Toxic epidermal necrolysis.*
Aim: *To study the clinical profile of various anticonvulsant drug induced cutaneous reactionsand common AEDs implicated in cutaneous adverse drug reactions(CADR) in patients attending a tertiary care hospital.*
Material and Methods: *A prospective, observational study was conducted over a period of 2 years from October 2013 to September,2015. All patients with CADR to antiepilepticswere included in this study. A total of 36patients were analyzed for demographic characteristics, clinical patterns, causative drugs and co-morbidities.*
Results:*During the study period, 36 cases of CADRs were included in this study. Out of 36 patients, 22 were males and14 were females with mean age 34.84 years (range 10 years to 75 years). Most common AED implicated for cutaneous drug reactions was Phenytoin61.1% followed by Carbamazepine19.4%Maculopapular rash was the most common cutaneous manifestation observed in 52.8%.*
Conclusion: *CADRs are a common occurrence and awareness about these isimportant in the diagnosis and prevention of these reactions.Earlydiagnosis and identification of the offending drug is crucial in the management and to prevent serious outcome.*
Key Words:Drug rash, Maculopapularrash,Phenytoin, Carbamazepine

I. Introduction:

Cutaneous adverse drug reaction(CADR) an undesirable clinical manifestation resulting from administration of a particular drug either due to overdose, predictable effects or unanticipated adverse manifestations. CADRs are common comprising 10-30% of all reported ADRs [1,2] and its incidence in hospitalized patients is estimated to be 2-3 %[3]. Studies have found the incidence of CADRs in developed countries as 1–3% and indeveloping countries appear to be higher between 2 and 5% [4,5]. The incidence of developing a cutaneous reaction increases with the number of the drugs taken[6].Various endogenousand environmental factors may increase the susceptibility to develop the adverse reactions, such as genetic factors, age, gender, physiological changes, exogenous drugs and diseases. Hepatic disease, renal disease, systemic lupuerythematosus (SLE) and acute immunodeficiency syndrome (AIDS) are some of the diseasestates, associated with an increased risk of skin reactions[7].Majority ofCADRaremild,exanthematous or morbilliform rashes and self limiting. Severe reactions such as SJS/TEN and Drug rash,eosinophilia,systemic symptoms (DRESS) are associated with significant morbidity and mortality.[8]

II. Materials and Methods:

This prospective, observational study was conducted at DVL Dept,Gandhihospitalfor a period of two years.
This study comprised of all patients of cutaneous adverse reactions to anticonvulsant drugseither alone or in combination . Detailed history including history of drug intake, time of onset of reaction, past history and family history of drug reaction was taken.Detailed clinical examination was carried out in all patients with emphasis on morphology and distribution of the lesions and associated systemic involvement. The various investigations that were carried out were CUE, CBP, blood sugar,LFT,RFT ,Chest X ray, Ultrasound abdomen and Skin biopsy. Naranjo's adverse drug reaction probability scale [9] was used to select cases suspicious of drug reaction. The scale consists of 10 questions. Each question was given a score and the total score was recorded foreach patient and graded definite (>9), probable(5to 8), possible(1 to 4) or doubtful (<1) (Table 1). Only patients with definite or probable rash were taken up for study.

III. Results:

36 patients who presented with cutaneous adverse drug reactions to anticonvulsant drugs were included in the study. Of these 22 patients were males and 14 females. Age of these patients varied from 10 to 75 years with a mean of 34.84years(Table 2). Of the36patients , 22 were taking phenytoin, 7 on carbamazepine and 1patienton sodium valproate. The rest of the patients were taking different combinations of phenytoin, phenobarbitone, sodium valproate and carbamazepine.(Table 3)

The major indication for anticonvulsants use was epilepsy in 16 patients. 7 had cerebral tumors and in 6 following head injury (Table 4).The common adverse effectobserved wasmaculopapular erythema in 19 (52.8%)patients and was caused by phenytoin and carbamazepine. The next commonest adverse effect was Steven-Johnson syndrome in 5patients(13.9%),Erythroderma in 8.3%and TEN in 5.6%.Gingival hyperplasia were seen in 5.6% patients and was followed phenytoin use in both the cases(Table5)

The mean interval of maculopapular rash following phenytoin use is 5 days, carbamazepine is 33.25 days. On an average, maculopapular rash occurred after a mean interval of 12.46 days with all anticonvulsants. Mean interval in erythroderma is one month with phenytoin and 19days with carbamazepine. Stevens-Johnson syndrome followed after mean interval of 8.5 days with phenytoin and 10 days after carbamazepine. Anticonvulsant hypersensitivity syndrome to phenytoin occurred in only one instance and followed 6 weeks after phenytoin use.(Table 6)

Table 1: ADR probability scale devised by Naranjo et al

	Yes	No	Do not know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was administered?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
Are there alternative causes (other than the drug) that could on their have caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in blood (or other fluids) in concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0

Causality assessment; 0 - Doubtful; 1-4 - Possible ; 5-8 - Probable; >9 – Definite

Table: 2Agegroup and CADRs

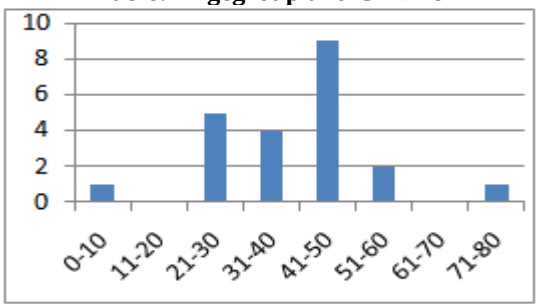


Table 3: Categorization of patients using various anticonvulsants

Drug(s)	**Number of Patients**
Phenytoin	22
Carbamazepine	7
Sodium Valproate	1
Phenytoin + Carbamazepine	2
Phenytoin + Phenobarbitone	1
Phenytoin + Sodium Valproate	2
Carbamazepine + Sodium Valproate + phenytoin	1
Total:	36

Table 4: Categorization of patients with various neurological disorders

Neurological Disorders	Number of Patients
Epilepsy	16
Tumors and space occupying lesions	7
Head injury	6
Cerebro-Vascular Accident	2
Depression	2
Numbness left half of the face and left arm	3
Total:	36

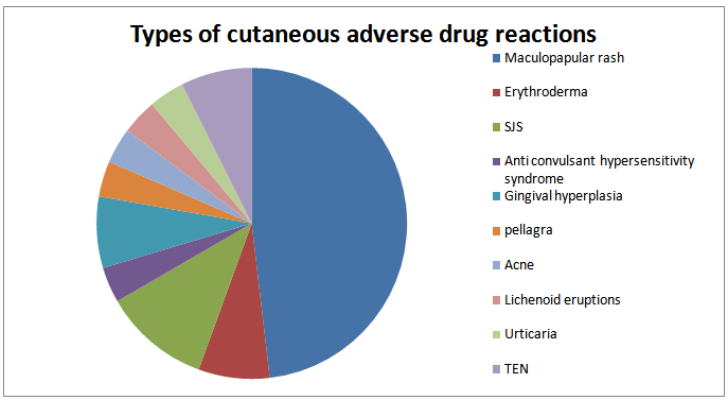
Table 5: The spectrum of adverse cutaneous effects following anticonvulsants

Type of adverse reaction	Phenytoin	Carbamazepine	Phenytoin + Phenobarbitone	Phenytoin + Carbamazepine	Phenytoin + Sodium Valproate	Sodium Valproate	Phenytoin + Carbamazepine + Sodium Valproate
Maculopapular rash	8	4	1	2	2	1	1
Erythroderma	2	1					
Steven-Johnson syndrome	4	1					
TEN	1	1					
Anticonvulsant hypersensitivity syndrome	1						
Gingival Hyperplasia	2						
Pellagra	1						
Acne	1						
Lichenoid Eruption	1						
Urticaria	1						

Table 6: Mean interval of various cutaneous adverse reactions

	Phenytoin	Carbamazepine
Maculopapular rash	5 days	53.25 days
Erythroderma	1 month	19 days
Steven-Johnson syndrome	8.5 days	10 days
Anticonvulsant hypersensitivity syndrome	6 weeks	
Gingival Hyperplasia	4 months	
Pellagra	3 months	
Acne	22days	
Lichenoid eruption	1 month	
Urticaria	2 days	

Table :7



IV. Discussion

It is well known that drugs are a common cause of skin rashes. The frequency of cutaneous reactions varies from about 2-3% of the hospitalized patients.[10] In India antiepileptic drugs account for about 4.5 to 9.25% of all drug reactions.[11,12] though western studies incriminated anticonvulsants in 20% of all drug reactions.[13] Overall prevalence of rash is about 2-3% due to antiepileptic drugs in epilepsy patients.[13] AED induced ADRS incidence reported by several studies were 16.6%and 22.2.8% respectively.[14,4]

The patients with 'definite' or 'probable' ADR according toNaranji'salgorithm[9] were included in the study. All patients in this study had 'probable' reaction with adverse drug reaction probability score ranging from 5 to7. All patients had improved following discontinuation of the suspected drug except one case of TEN.

Out of 36 patients, 22 were males (61.1%) and 14 were females (38.9%) . Age of the patients varied from 10 to 75 years with a mean of 34.84 years . This is in accordance with the study conducted by Maneeshaetal[15]. Both the studies showed male preponderance. This shows that anticonvulsant drug reactions can occur at any age, however they were more commonly observed in the 41-50 year age group in this study.

In this study, 61.% of the patients demonstrated ADR's to phenytoin, 19.4% to carbamazepine and the rest to various combinations of anti convulsants. In the study by Maneesha et al[15], carbamazepine was the commonest drug followed by phenytoin(20%) and phenobarbitone(10%). In thestudy by Rita Voraet al[16]maximum reactions 74.41% observed with PHT followed by CBZ in 20.58%.Malekafzali and Najibi[17] reported that PHT is the commonest cause in 32% patients.Carbamazepin and phenytoin were the causative AEDs for SJS/TEN (67.8%) and DRESS (43.6%), respectively in the study byYangCYet al.[18]

In this study, 16 patients (44.4%) on anticonvulsants were epileptics, Six(24%) had tumors and other space occupying lesions and four were suffering from neurotrauma.(Table:4).Various cutaneous ADR's induced by different anticonvulsant drugs aremaculopapular eruptions, SJS, TEN,AHS,urticaria, Lichenoid eruption, erythroderma, gingival hyperplasia, acne and pellagra.(Table: 7)

In the study by Rita Vora et al.[16] 58.8% patients showed maculopapular rash, 11.76% SJS, 8.82% urticaria, 5.88% DRESS while in the study done byKarimzadeh and Bakrani, it was found that 100% of the patientsshowed macula papular rash initially, and DRESS and SJS in 5.7%and 2.8% patients, respectively.[19] Sushma et al found equalincidence of macula papular rash and SJS which was 35%.[20]

Inour study macula papular rash was the commonest observed in 19/ 36 patients (52.8%), Severe cutaneous ADR'S occurred in 11/36 (30.6%) patients shown in fig.{images1,2,3} . In the study by Maneeshaetal[15],maculopapular rash accounted for 65% of cases. In a study by Balachandranetal[21], 16/ 21 patients had maculopapular rash (76.19%).

Severe CADRS were seen in 7/ 20 patients(35%) and 5/ 21 patients(23.8%) in the studies conducted bymaneesha et al andbalachandran et al respectively. Similar results were observed in our study.

One case of phenytoin inducedAHS was noted 6 weeks after initiating treatment. According to Puneetbhargawa[22], in a study of 60 cases of AHS,phenytoin was the most common offending drug followed by carbamazepine.

5 cases of SJS and 2 cases of TEN were observed. Phenytoin was implicated in 5 cases and carbamazepine in two. Anticonvulsant drugs such as phenytoin, carbamazepine, phenobarbitoneseem to carry equally high risk for the occurrence of SJS; their relative risks reported to be 15%, 11%, 13%, and lessthan 5% for phenobarbital, CBZ, PHT, and oxcarbazepinerespectively.[19]

Carbamazepine was found to elicit the highest incidence of SJS-TEN per user. Valproic acid often used as an alternative to phenytoin was found to have an equally high risk[23]. The mean incubation period of 12±9 days was observed with phenytoin and 11±3 days with carbamazepine. The causal association of valproic acid seems to be complicated by concomitant short term therapy with other anticonvulsant drugs[24].Lamotrigine also has the potential for severe skin reactions. In a study by Rzany B et al[24], 73 of the 352 SJS/TEN cases were on antiepileptic drugs. Among them 36 reported intake of phenobarbital, 14 of phenytoin, 21 of carbamazepine, 13 of valproic acid and 3 of lamotrigine.

3 cases of erythroderma, 2 caused by phenytoin and the other by carbamazepine were observed in the study. In a previous study of 50 cases of erythroderma conducted at the Department of Dermatology[25]9/50 were induced by anticonvulsants of which 7 due to phenytoin and 2 due to carbamazepine. In this study, patients developed erythroderma after 19 days with carbamazepine and 4 weeks with phenytoin with an average of 24.5 days.

Urticaria is a common drug reaction and can occur with any medication. Phenytoin has been reported to cause urticarial eruption. In this study, urticarial accounted for one case.

Two cases of gingival hyperplasia were observed {image 4}. Both were taking phenytoin for 2 and 6 months. Incidence of phenytoin induced hyperplasia is variable and considered to be independent of dosage and duration of treatment. There was moderate improvement in both cases after stopping the treatment.

One case of acne was observed in the study following anticonvulsant use. Phenytoin was believed to aggravate or cause acne. But in a study by Greenwood et al[26] the severity and rate of excretion of sebum were

assessed in epilepsy patients on various anticonvulsants. The apparent increase in acne may be due to abnormalities in keratinization induced by phenytoin rather than hormonal factors alone.[27]

In this study one patient developed pellagra 3 months after starting phenytoin . Improvement of skin lesions after withdrawal of the drug indicated its probable causal relationship . Alteration of the absorption of either niacin or other related essential vitamins has been proposed.

Lichenoideruption is a rare association, one patient developed one month after starting phenytoin. Histopathology revealed lichenoid eruption.

V. Conclusions

In our study phenytoin and carbamazepine accounted for most of the drug reactions.All patients recovered from the illness after withdraw of the drug and appropriate treatment.One case of TEN succumbed to complications.More broad based prospective studies will suggest the precise potential of different anticonvulsant drugs including the newer ones in the occurrence of adverse drug reactions.

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