Research Article

A study of adverse cutaneous drug reactions (ACDR) owing to antiepileptics at a rural-based tertiary-care center, Gujarat

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Abstract

Background: Cutaneous reactions are common manifestations of adverse cutaneous drug reactions (ACDRs). It is commonly seen with antiepileptics. Antiepileptics are frequently used for neurological disorders, head injury, etc. So, it is very important to have an in-depth understanding of ACDRs owing to antiepileptics. **Aims and Objective:** To analyze the spontaneous ACDR with various clinical patterns of drug reactions owing to antiepileptics, the common ACDR owing to antiepileptics, and the most common antiepileptic drugs responsible for it. **Materials and Methods** : An observational study was carried out from April 2010 to March 2015 in the Department of Dermatology at a rural-based tertiary health-care center after ethical clearance. The study included all the patients with symptoms and signs suggestive of ACDR after intake of antiepileptic drugs. **Result:** Thirty-four cases presented with antepileptics-induced ACDR. Male and female subjects were found to be equally affected. The common age group affected was 11–20 years. Four patients showed history of ACDR, of which one patient showed history of reaction with the same drug. The commonest clinical pattern was maculopapular rash in 58.8%. Maximum number of patients had $>50\%$ body area involvement. Oral mucosa was involved in 17.64% patients. The commonest culprit was phenytoin in 74.41%, followed by carbamazepine in 20.58%. **Conclusion** : Antiepileptic drugs are very commonly prescribed drugs, and various patterns of cutaneous drug reactions are observed owing to it. The active involvement of a dermatologist for detecting the ACDRs in an initial phase and delivering the awareness regarding the need of reporting the incident could improve the scenario in under-reported hospitals.

KEY WORDS: Epilepsy; Antiepileptics; Adverse Cutaneous Drug Reactions

Introduction

Adverse cutaneous drug reactions (ACDRs) are significant and preventable sources of illness, hospitalization, heightened health expenses, and even death.[1] ACDR is very commonly reported with the incidence of about 2.2%, which is increasing as the number of new drugs are being marketed and prescribed.[2]

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ACDRs accounted for 0.7% of total admissions and 1.8% of total deaths in a South Indian hospital.[3] ACDRs may manifest from a transient rash to Stevens–Johnsons syndrome (SJS)/toxic epidermal necrolysis (TEN) or death, although milder reactions are more common. Antiepileptics are commonly prescribed drugs for various neurological disorders and for head injury by practitioners. For the first-line treatment of epilepsy, drugs such as phenytoin (PHT), carbamazepine (CBZ), valproic acid, and lamotrigine are commonly used antiepileptic drugs (AEDs) that may give rise to cutaneous reactions ranging from a skin rash to unexpected life-threatening adverse events. AEDs have been recognized as being among the most common medications associated with severe cutaneous adverse reactions, with relative risks reported to be 15%, 11%, 13%, and less than 5% for phenobarbital, CBZ, PHT, and oxcarbazepine, respectively.[4]

This study highlights various patterns of ACDRs owing to AEDs along with the commonest responsible drug with various clinical presentations. The aim of this study is to find out the prevalence and various clinical patterns of drug reactions owing to antiepileptics, the most common clinical pattern of ACDR and the commonest AEDs responsible for the ACDR.

Materials and Methods

This prospective, observational study was carried out from April 2010 to March 2015 in the Department of Dermatology, Venereology, and Leprology at a rural-based tertiary health-care center after ethical clearance was taken from the Human Resource Committee of the Institute. The study included all the patients with symptoms and signs suggestive of ACDR after intake of AED. All the data were recorded in a predesigned pro forma with the consent of patients, and analysis was done. An attention was paid to the drug history, temporal correlation with the drug, duration of the rash, appearance of signs and symptoms, morphology of the eruption, associated mucosal or systemic involvement, and improvement of lesions on withdrawal of drug. In every case, a detailed history was elicited, and a thorough clinical examination was carried out. To establish the causative agent for a particular type of reaction, a diagnosis of ACDR was reached after exclusion of other causative factors and similar disorders such as reactions owing to food, infections, and environmental factors. If more than one drug was thought to be responsible, the most likely offending agent was noted, and the impression was confirmed by subsidence of the rash on withdrawing the drug.

Inclusion Criteria

All patients irrespective of age and sex suspected of showing drug reactions owing to antiepileptics seen in various outpatient departments and admitted in the wards during the period of 6 years were included in the study after taking their written informed consent.

Exclusion Criteria

There are no exclusion criteria as such.

Result

A total of 34 patients showed ACDR owing to antiepileptics. Male and female subjects accounted for 50% of the cases with the ratio of 1:1. Incidence of drug reactions owing to antiepileptics was most common in the age group of 11–20 years and seen in 20.58% patients; similar observations were found in 41–50 years, followed by 31–40 years in 17.64% patients. Time taken between taking of drug and development of lesions was 1–3 days in 20.58% of patients. About 38.7% of the patients approached within 12 h of the drug intake, which shows the symptomatic nature of drug reactions [Table 1].

Table 1: Incubation period of ACDRs

Time between taking of drug and development of lesions	Number of cases	Percentage
<1 h	0	0
1–12 h	0	0
12–24 h	4	11.76
1–3 days	7	20.58
3–7 days	5	14.7
>1 week	12	35.29
>1 month	6	17.64
Total	34	100

The most common presenting complaint in our study was redness, which accounted for 41.9% of the patients, followed by itching in 25.8% of patients. Most of the cases (64.51%) gave history of sudden appearance of skin lesions. Oral mucosa was involved in 17.64% patients. Majority of the patients (96.77%) were prescribed the drug by physicians. Maximum number of patients showed >50% body area involvement [Table 2].

Trunk was involved in 91.17% of patients, upper limbs in 82.35% patients, lower limbs in 85.29% patients, and face in 55.88% patients. About 58.8% patients presented maculopapular rash after taking antiepileptics, followed by SJS and urticaria in 11.76% and 8.82% of patients, respectively [Table 3].

Maximum drug reactions were observed with PHT in 74.41% of patients, followed by CBZ in 20.58% patients [Table 4].

None of the patients showed history of atopy or positive family history of drug reactions. Twelve (35.29%) patients showed raised levels of eosinophils. About 48.38% showed milder form of ACDR on the basis of scoring system. The World

Table 2: The body surface area involved

Body surface area (%)	Number of cases	Percentage
<25	5	14.7
25–50	6	17.64
50–75	13	38.23
>75	10	29.41
Total	34	100

Table 3: The various manifestations of drug eruptions

Pattern of drug eruption	Number of cases	Percentage
Urticarial wheals ± angioedema	3	8.82
Maculopapular rash	20	58.8
Fixed drug reaction (FDR)	1	2.94
Stevens–Johnson syndrome (SJS)	4	11.76
Toxic epidermal necrolysis (TEN)	2	5.88
DRESS	2	5.88
Vasculitis	2	5.88
Total	34	100.0

Table 4: Various patterns of drug reactions owing to various drugs

Name of drug	No. of cases	Percentage	U/A	MR	FDR	SJS	TEN	DRESS	V
Carbamazepine	7	20.58		2	1	2	1	1	
Clonazepam	1	2.94	1						
Phenobarbitone	1	2.94	1						
Phenytoin	24	74.41	2	17	1	1	1	1	1

Table 5: WHO-UMC score

Causality term	ACDR owing to antiepileptics
Certain	2
Probable/likely	18
Possible	11
Unlikely	4
Conditioned/unclassified	0
Unclassifiable	0

Table 6: Naranjo score

Definite	2
Probable	20
Possible	12
Doubtful	0

Table 7: Hartwig severity assessment scale

Level 1	1
Level 2	15
Level 3	13
Level 4	4
Level 5	2
Level 6	0
Level 7	1

Health Organization–Uppsala Monitoring Center (WHO-UMC) score showed probable risk in 18 (52.9%) patients, Naranjo scoring system also showed probable risk in 20 (58.8%) cases, and Hartwig score showed risk of level 2 in 15 (44.11%) cases [Tables 5–7, respectively]. Mortality was seen in 5.88%.

Discussion

An adverse cutaneous reaction produced by a drug is any unwanted alteration in the organization or function of the skin, its appendages, or mucous membranes, and it includes all adverse events related to drug eruption, irrespective of the causative factor.[5] The occurrence of ACDR in developed countries range from 1% to 3% among inpatients, whereas, in developing countries such as India, some studies pin it to 2%–5% of the inpatients;[6] however, there is absence of comprehensive data among outpatients.

With time, many newer drugs are being marketed, which can be a potential source for the occurrence of ACDRs. However, the actual incidence is difficult to determine because many milder forms of reactions are not recorded. Commonly used drugs causing ACDR are penicillins, sulfonamides, anticonvulsants, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAIDS), angiotensin converting enzyme inhibitors, fluoroquinolones, etc.[7]

A cutaneous drug reaction needs to be doubted in a patient who develops rash during a course of drug therapy. The reaction may be owing to any medicine the patient is taking, whether prescribed or self-administered, over-the-counter medicine, herbal or homoeopathic preparations, vaccines, or contrast media. Cutaneous drug reactions may be caused by various different mechanisms, but, in many cases, the exact mechanism is unknown. Several drug eruptions are the consequence of a hypersensitivity reaction with immune mechanism as the basis. Skin reactions that occur because of nonimmunological causes are more common and include cumulative toxicity, overdose, photosensitivity, drug interactions, and metabolic alterations.[8]

The frequency of ACDR in a particular population is influenced by the drug utilization habit, the reaction rates of various drugs, and pharmacogenetic traits of the population studied. Genetic variations in the metabolism of a drug, human leukocyte antigen (HLA) association to HLA-B1502, and any other underlying systemic disease play important roles.[9] In genetically susceptible patients, it is immunologically mediated. The genetically determined glutathione depleted keratinocytes will have a role in the pattern of cutaneous manifestation. Moreover, keratinocytes adducts can trigger major histocompatibility complex-dependent clonal proliferation of T cell lymphocytes.[10]

Antiepileptics are currently used by practitioners for a variety of conditions such as epilepsy, trigeminal neuralgia, and head injury. Owing to its widespread use and the serious cutaneous reactions owing to it, history of drug reaction should always be asked before prescribing antiepileptics. Large number of drugs is currently available for the treatment of epilepsy. Older/conventional drugs such as PHT, CBZ, valproic acid, and ethosuximide are commonly used as first-line drugs.

Drugs such as gabapentin, lamotrigine, vigabatrin, topiramate, tiagabine, and zonisamide are the newer ones and currently used as an add-on or alternative therapy. They have lesser adverse effects and fewer drug interactions.[11]

Cutaneous reactions are the most common variant of ADRs.[12] A wide spectrum of cutaneous reactions owing to antiepileptics range from maculopapular rash to life-threatening SJS and TEN. ACDR owing to antepileptics include pruritis,

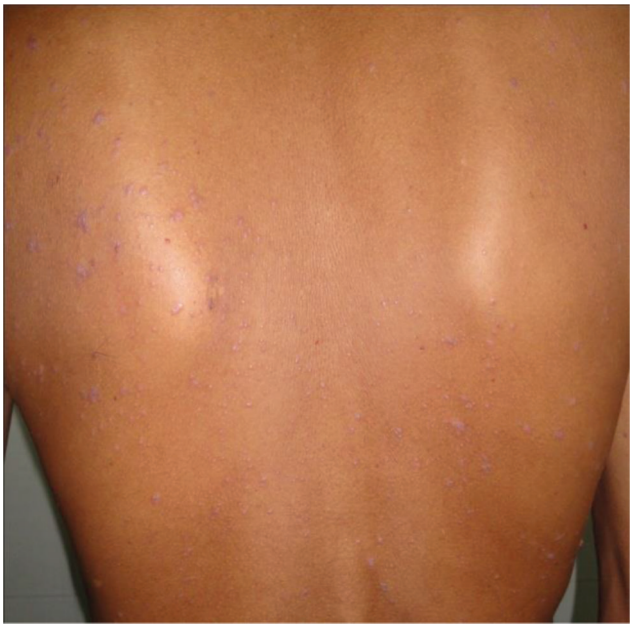

Figure 1: Phenytoin-induced maculopapular rash.

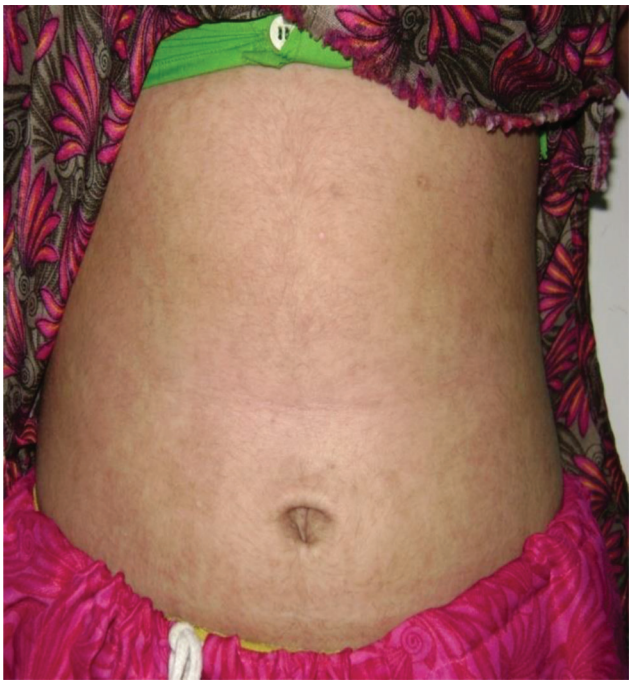

Figure 2: Carbamazapie-induced DRESS.

maculopapular and morbilliform rashes, drug rash with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis, erythema multiforme, exfoliative dermatitis, and others.[13]

PHT-induced cutaneous lesions may be restricted to maculopapular rash [Figure 1] or cutaneous nodules or consist of a generalized exfoliative dermatitis or TEN.[14] PHT may cause pseudolymphoma syndrome.[15] CBZ can cause maculopapular rashes, DRESS [Figure 2], urticaria, photosensitivity reactions, exfoliative dermatitis, erythema multiforme, SJS, and TEN [Figures 3 and 4].[16] Sodium valproate may usually substituted safely causing transient rash and stomatitis. SJS is rarely reported with it.[17] Of the newer AEDs, vigabatrin is usually well-tolerated but Lamotrigine causes rashes.[18] Lamotrigine may rarely cause TEN, but, owing to limited utilization, it is not reported as an offending agent to cause SJS and TEN in major Indian studies.[19]

It is already recognized that drug-induced skin reactions are in general more frequent in case of female subjects. However, in

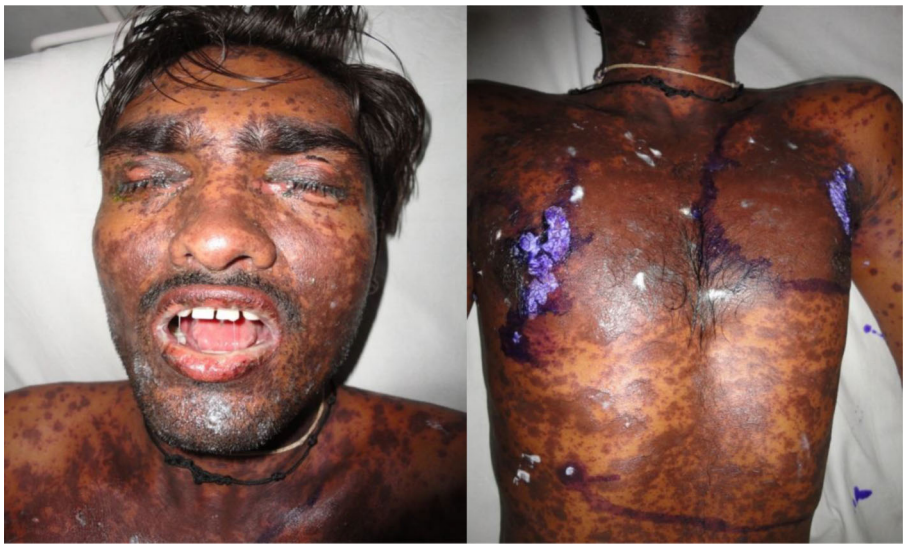

Figure 3: Carbamazepine-induced TEN.

this study, male and female subjects were equally affected with a ratio of 1:1. In general, it has been assumed that elderly patients experience skin reactions from drug therapy at higher rates,[20] a finding that may seem to correlate with falling testosterone levels in case of elderly men. In contrast to that, our study showed incidence of drug reactions to be most common in the age group 11–20 years. Błaszczyk et al.[4] found mean age group affected in male and female subjects to be 34 and 27 years, respectively. Sushma et al.[13] found that maximum number of reactions were seen in patients in the age group of 21–40 years.

The most common presenting complaint in our study was redness, which accounted for 41.9% of the patients, followed by itching in 25.8% of patients. About 38.7% of the patients presented within 12 h of the drug eruption in most of the cases. Most common cause for which the patients had taken the antiepileptic drug was head injury in 83.87% of patients. Time taken between taking of drug and development of lesions was 1–3 days in 20.58% of patients. Karimzadeh and Bakrani[21] found that majority of the patients developed lesions within 1–7 days of intake of the offending drug.

Four patients showed history of drug reaction, of which one patient showed history of reaction to the same drug. Karimzadeh and Bakrani,[21] in their study, observed that no patient showed history of treatment with AEDs.

None of the patient showed history of atopy or positive family history of drug reactions. Karimzadeh and Bakrani[21] found that patient and family history of atopy has no significant correlation with AEDs-related cutaneous reactions.

Maximum number of patients showed >50% body area involvement. Trunk was involved in 91.17% of patients, upper limbs in 82.35% patients, lower limbs in 85.29% patients, and face in 55.88% patients. Oral mucosa was the commonest mucosa involved in 17.64% patients.

In our study, 58.8% patients showed maculopapular rash, 5.88% DRESS, and 11.76% SJS, while in the study done by Karimzadeh and Bakrani, it was found that 100% of the patients showed maculopapular rash initially, and DRESS and SJS in 5.7% and 2.8% patients, respectively.[4] Sushma et al found equal incidence of maculopapular rash and SJS which was 35%.[13]

Maximum drug reactions were observed with PHT in 74.41% of patients, followed by CBZ in 20.58% patients. Malekafzali and Najibi[22] reported that PHT is the most prevalent cause in 32% patients.

The mean absolute eosinophil count was abnormal in many eruptions, with values more than 500 cells/mm^3 in 12 patients, and counts above 1,000 were seen in three patients. Higher mean eosinophil counts were seen in the severe types of drug eruptions. According to Romagosa et al.,[23] a peripheral eosinophil count carries little diagnostic value in the setting of adverse cutaneous drug eruptions. Guidelines of the American Academy of Dermatology state that eosinophil counts more than 1,000 cells/mm^3 indicate a serious drug-induced cutaneous eruption.[9]

The causality assessment system proposed by the WHO Collaborating Center for International Drug Monitoring, WHO–UMC, and the Naranjo Probability Scale are the generally accepted and the most widely used methods for causality assessment in clinical practice as they offer a simple methodology.[24] In the causality assessment using the WHO guidelines, there were two certain, 18 probable, and 11 possible cases. Naranjo score showed 20 probable and 12 possible cases. Hartwig et al.[25] categorized ADRs into seven levels as per their severity. Levels one and two fall under mild category, whereas levels three and four under moderate, and levels five, six, and seven fall under severe category.[25] Levels five and six include all potentially life-threatening reactions that cause permanent damage and require intensive medical care. Level seven includes lethal reactions, which directly or indirectly contribute to death of the patient. In our study, Hartwig score showed level two in 15 cases and level three in 13 cases.

To conclude, the pattern of ACDRs and the drugs causing them are remarkably different in our population. A sound knowledge of these drug eruptions may help the clinician to better manage their cases. The strength of our study was that we analyzed various types of ACDRs owing to antiepileptics at tertiary-care center.

Limitation

We have not enrolled all the patients who were on antiepileptics, but we enrolled the patients who developed ACDR owing to antiepileptics. Not all cases were enrolled from all the departments.

Strength

The study was carried out for a long duration of 6 years.

Conclusion

Antiepileptics are frequently used by neurologists, physicians, and surgeons for epilepsy and head injury. ACDRs owing to antepileptics are serious and avoidable causes of morbidity and mortality, which increase the burden of work. Anticipating, recognizing, and managing ADRs is of prime concern so as to minimize the incidence of ADRs.

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