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Original Research Article

Profile of cutaneous adverse drug reactions of carbamazepine

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ABSTRACT

Background: Carbamazepine, a commonly used antiepileptic drug is known to produce adverse effects including dangerous reactions like cutaneous hypersensitivity reactions such as drug induced hypersensitivity syndrome (DHS), Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The FDA released a warning that serious and potentially fatal skin reactions may occur after carbamazepine in patients positive for the HLA-B*1502 allele which occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. This study profiles the cutaneous adverse drug reactions reported in this institute over a period of 3 years.

Methods: This retrospective study was conducted at Tirunelveli Medical College Hospital by analysing patient case records based on adverse drug reactions reported between August 2014 and July 2017 in the adverse drug reaction monitoring centre. The age, gender, diagnosis, type of cutaneous ADR, duration of treatment, seriousness of reaction and outcome were recorded and analysed.

Results: Among the total 25 reactions 36% were benign and 64% were severe reactions. According to Pharmaco vigilance Program of India 80% of the reactions were serious and 20% non serious. The commonest benign skin reaction was maculopapular eruption. SJS and TEN were the two very serious reactions which affected 8 patients totally. Exfoliative dermatitis was reported in 7 patients and Drug Hypersensitivity Syndrome (DHS) in one patient.

Conclusions: Severe cutaneous reactions occur after carbamazepine and prevention of ADR requires prediction of predisposition which requires special studies of HLA or genomic assessment. These are the issues of interest for future research.

Keywords: Carbamazepine, Cutaneous adverse drug reactions, DHS, SJS, TEN

INTRODUCTION

Carbamazepine, one of the commonly prescribed antiepileptic drugs is also prescribed for other diseases like neuralgia, schizophrenia and bipolar illness and is known to produce drowsiness, vertigo, ataxia, diplopia, blurred vision, serious haematological toxicities like aplastic anaemia, agranulocytois and hypersensitivity reactions including dangerous skin reactions, eosinophilia, lymphadenopathy and splenomegaly.[1] Carbamezepine is associated with more serious, immune mediated adverse drug reactions (ADR) including cutaneous hypersensitivity reactions such as drug induced hypersensitivity syndrome (DHS), Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[2] SJS and TEN are severe cutaneous reactions with potential for elevated morbidity and mortality that require immediate intervention and timely management.[3] On 12th December 2007, the FDA released a warning to health professionals and patients that serious and potentially fatal skin reactions may occur with the administration of carbamazepine in patients positive for the *HLA-B*1502* allele This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians.[4]

This tertiary care teaching hospital in south Tamilnadu runs an adverse drug reaction monitoring centre since June 2014 under Pharmacovigilance Programme of India and from here ADRs are reported to the National Coordinating Centre. Cutaneous reactions are regularly reported by the Department of Dermatology and various other departments to the adverse drug reactions monitoring centre. Many Cutaneous reactions after Carbamazepine have been reported from the departments of Neurology, Psychiatry and Dermatology. This study has been taken up to profile the cutaneous adverse drug reactions to Carbamazepine reported in this institute over a period of 3 years.

METHODS

This study was conducted at a tertiary care teaching hospital in South Tamilnadu as a retrospective analysis of patient case records in the departments of Dermatology based on adverse drug reactions reported in adverse reactions monitoring centre between August 2014 and July 2017 (3years) in the adverse drug reaction monitoring centre. Both benign and severe cutaneous reactions reported after taking Carbamazepine were included for the study. Cutaneous reactions due to other drugs (other than carbamazepine) and other adverse drug reactions after carbamazepine (other than cutaneous reactions) were excluded. According to Pharmacovigilance Programme, a reaction is said to be serious if it results in any one of the following events like death, life threatening, hospitalization or prolongation of hospitalization, disability, congenital anomaly or required intervention to prevent permanent impairment / damage.[5]

The age, gender, diagnosis, type of cutaneous ADR, duration of treatment, seriousness of reaction and outcome were recorded in a format.

The data were analysed for quantitative and descriptive statistics.

RESULTS

Records analysed show 25 cutaneous adverse drug reactions due to Carbamazepine reported during the study period of 3 years.

Of these 25 patients, 12 patients were between the age of 21 and 30 years, 4 patients were above 60 years and 1 patient was below 10 years. In the study group of 25 patients, 12 were male and 13 were female (Table 1).

Of these patients 20 (80%) were prescribed carbamazepine for seizure disorders, 2 for neuralgia, 2 for bipolar illness and 1for cervical spondylotic myelopathy. Among the total 25 ADRs reported, 9 (36%) were classified as benign and 16 (64%) as severe reactions. The protocol of Pharmaco vigilance Program of India was applied to describe the seriousness of the reactions and out of 25reactions reported 80% of the reactions were classified as serious and 20% as non serious (Table 2).

Table 1: Age and gender distribution in patients reported with CADR after Carbamazepine.

	Demographic details	n (%)
1	Age range in years	
	1-10 years	1 (4%)
	11-20 years	1 (4%)
	21-30 years	12 (48%)
	31-40 years	4 (16%)
	41-50 years	1 (4%)
	51-60 years	2 (8%)
	>60 years	4 (16%)
2	Gender	
	Male	12 (48%)
	Female	13 (52%)

Table 2: The indication of Carbamazepine, type of Cutaneous reaction and seriousness of reaction.

	Indication of carbamazepine and details of reaction	n (%)
1	Indication of prescription	
	Seizure	20 (80%)
	Neuralgia	2 (8%)
	Bipolar disorder	2 (8%)
	Cervical spondylotic myelopathy	1 (4%)
2	Type of cutaneous reaction	
	Benign Reactions	9 (36%)
	Urticaria	2 (22.2%)
	Maculo papular eruption	6 (66.7%)
	Pruritus	1 (11.1%)
	Severe	16 (64%)
	Exfoliative dermatitis	7 (43.8%)
	DHS	1 (6.2%)
	TEN	7 (43.8%)
	SJS	1 (6.2%)
3	Seriousness of ADR	
	Serious	20 (80%)
	Non serious	5 (20%)

Figure 1: A patient with toxic epidermal necrolyis.

Steven Johnson syndrome and toxic epidermal necrolysis were the two very serious complications (Figure 1 and Figure 4) in the group with 8 patients affected totally. Exfoliative dermatitis was another severe reaction reported in 7 patients and Drug Hypersensitivity Syndrome (DHS/TEN) in one patient (Figure 2 and Figure 3).

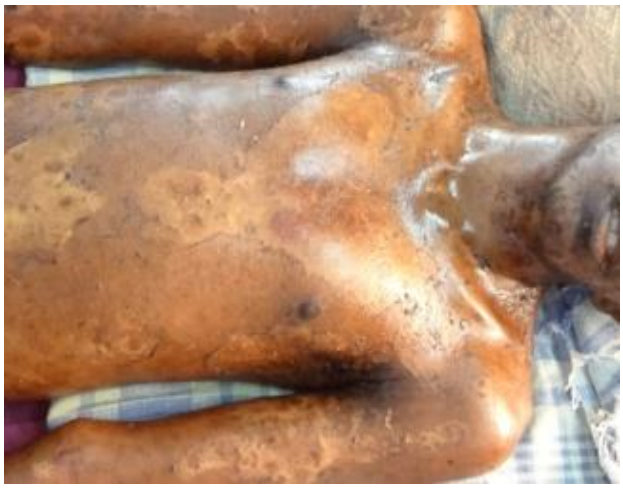

Figure 2: Patient with DHS/ toxic epidermal necrolyis.

Figure 3: Jaundice in the patient with DHS/ TEN.

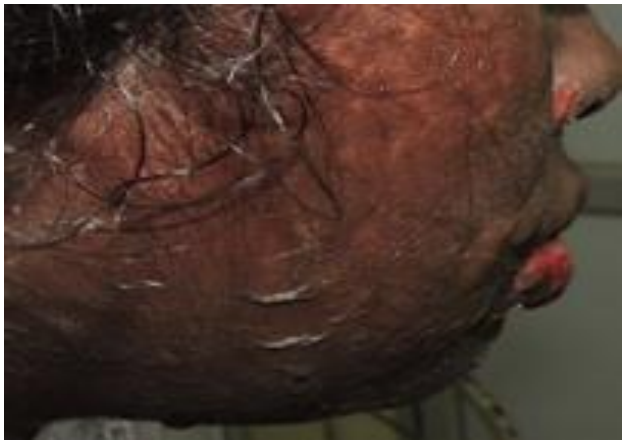

Figure 4: TEN in a patient with SLE.

DISCUSSION

Adverse drug reaction is an undesirable response evoked by a medicinal substance of which cutaneous adverse drug reaction is the most common. Most drugs produce variable types of reactions, while some have a singular pattern. Cutaneous adverse reactions to drugs occur in up to 8% of the global general population and in 2-3% of hospitalized patients. Cutaneous ADR is reported in 3% of individuals receiving anticonvulsant drugs.[6] A paradoxical fact is that many drug reactions mimic dermatoses like exanthematous reactions, urticaria, photosensitive eruptions, fixed drug eruptions, erythema multiforme etc.

Drug induced cutaneous ADRs are broadly classified as benign or severe. Reactions like exanthem, pruritus, eczema, urticaria, lichenoid drug eruptions, fixed drug eruptions, erythema nodosum and acneiform eruptions are classified as benign, while acute exanthematous pustulosis, drug reactions with eosinophilia and systemic symptoms (DRESS), drug induced exfoliative dermatitis, Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are classified as severe.[7,8]

Out of 25 cutaneous ADRs reported after taking Carbamazepine, 64% were severe reactions and 36% were benign reactions. Maculopapular or morbilliform eruptions are exanthematous eruptions that typically start on the trunk and spread peripherally in a systematic fashion. Among the benign reactions in this study, maculopapular eruptions (66.7%) were the most common followed by urticaria (22.2%) and simple pruritus. This is in consonance with Knowles SR et al, who reported that the common cutaneous adverse reactions to medications included generalized morbilliform rashes or maculopapular eruptions (50-95%) and urticaria (5-22%).[9] Out of 25 patients, 2 had urticaria and these patients required withdrawal of the drug. Pruritus presented with eruptions within 1 week of initiation of the drug and resolved within 7-14 days of the withdrawal. Studies have shown that the drug specific T cells play a major role in these cutaneous reactions.[10]

Among the 16 patients who were diagnosed with severe cutaneous reactions 43.8% of the patients had exfoliative dermatitis or toxic epidermal necrolysis each, while one of the patients had SJS and another had drug hypersensitivity syndrome (DHS). Generalized exfoliative dermatitis (GED) is a severe reaction to carbamezepine characterized by erythema and scaling affecting more than 90% of the body surface associated with increased epidermal turnover, decreased transit time and increased mitotic activity. The exact underlying mechanisms, through which these immunological pathways drive, are not clear while a complex interaction of cytokines, chemokines and adhesion molecules is hypothesized. There are no specific genetic markers for drug induced GED and withdrawal of the drug is the treatment while topical/systemic steroids may be indicated.[8] All 7 patients in this study were admitted, treated and discharged in good condition.

Drug induced hypersensitivity syndrome (DHS) is sometimes called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). This is characterized by

drug induced rash accompanied by multi organ involvement, eosinophilia (absolute Eosinophil count >500), lymphocytosis and elevated liver function tests. DHS begins 30-40 days after starting the drug. Low grade fever and pharyngitis may precede the eruptions. The eruptions are morbilliform initially and associated with oedema of face and neck. The eruptions begin on the trunk and face and spread centrifugally.[11] A 21 year old male was admitted with both skin and mucosal lesions and jaundice (Figure 2). While eliciting history it was revealed that he developed rashes 10 days after taking carbamazepine for his seizure disorder. The drug was withdrawn. His serum bilirubin, SGOT, SGPT and total WBCs were markedly raised**.** This could be a DHS/TEN overlap syndrome. The patient was referred to higher centre and the outcome is not known. The presence of the HLA-A3101 allele was associated with Carbamazepine induced hypersensitivity reactions among subjects of Northern European ancestry.[12]

Toxic epidermal necrolysis and Stevens Johnson syndrome are acute life threatening mucocutaneous reactions characterized by extensive necrosis and detachment of the epidermis.[13] These reactions are reported to be associated with keratinocyte apoptosis at the level of the FAS receptor and its ligand. It is also hypothesized SJS/TEN are related to perforin released from lymphocytes, in low concentration that activates apoptosis and causes skin epidermis necrosis.[14] In SJS/TEN influenza like symptoms often precede the eruptions by a few days. Initially the skin lesions are usually macular and appear on the face spreading rapidly usually within 4 days. This is followed by desquamation or may form atypical targets with the purpuric centres that coalesce to form bullae and then slough. The skin lesions are inflammatory. In SJS always 2 or more mucosal surfaces are eroded and the oral mucosa and the conjunctiva are the most commonly affected. The patient may have photophobia, difficulty in swallowing, rectal erosions, painful urination and cough due to the mucosal involvement of the respective system. If it involves more than 10% of the skin surface it is SJS/TEN overlap and if more than 30% of the skin surface is involved it is TEN.[13] These two terms describe phenotypes within a severity spectrum and both the names are used to describe the syndrome like SJS/TEN.[8] Incidence of TEN is 0.4-1.2 per million person years and 1.2 to 6 per million person years for SJS. More than 100 medications are known to cause SJS/TEN. The incidence of SJS/TEN in patients taking Carbamazepine is 14 per 1, 00,000.[15] Latent period between the drug initiation and onset of SJS/TEN is about 7-10 days but it may range from 5 to 28 days.[8] In this study the latent period varied from 2 weeks to 9 weeks**.** According to a study conducted in Germany more than 90% of SJS and TEN cases occurred in the first 63 days of AED use.[16] Out of 25 total reported ADRs approximately one third of the reactions were SJS/TEN (Figure 1). All those patients required hospitalisation for 2 to 6 weeks and they were treated with systemic steroids and antibiotics. There was no mortality. Among the 8 patients with SJS or TEN only one patient developed symblepharon and was surgically managed by the ophtholmologist. One patient diagnosed with TEN had increased total count, elevated liver enzymes and histopathological examination confirmed TEN. That patient (Figure 3) was a known case of Systemic Lupus Erythematosus (SLE) with neuropsychiatric symptoms and seizure for which carbamazepine had been prescribed. She developed TEN 2 weeks after commencing the drug and she had elevated liver enzymes which might be due to the disease or drug. Chung et al, proved that there is a strong association in Han Chinese between a genetic marker, the human leukocyte antigen HLA-B*1502, and Stevens-Johnson syndrome induced by carbamazepine.[17] The relatively high incidence of *HLA-B*1502* in many Asian populations has resulted in the FDA's decision to recommend testing for all Asians. Several reports have implicated carbamazepine as among the most common causes for SJS/TEN in Indians too.[18,19]

According to the Pharmaco vigilance programme an ADR is said to be serious if it resulted in death, life threatening events, hospitalization or prolongation of hospitalization, disability, congenital-anomaly or required intervention to prevent permanent impairment / damage. Among the 25 CADRs reported after CBZ, 80% were labelled serious and life threatening and required hospitalization and acute intervention.

This study could not reveal the incidence as the exact number of patients who were prescribed carbamazepine during the study period is not known.

CONCLUSION

Carbamazepine is a common drug used for certain types of epilepsy like the Complex Partial Seizures. It is found to be effective for specific types of epilepsy and hence finding alternate drugs is difficult, even with the advent of newer AED's. Carbamazepine is also used for other indications like neuralgia, bipolar disorders etc. Adverse drug reactions to carbamazepine are common and are usually benign in character, but severe reaction like SJS/TEN are reported. These reactions could lead to high morbidity and mortality. Hence early identification of the ADR is essential to save life. Prevention of ADR due to Carbamazepine requires prediction of predisposition which requires special studies of HLA or genomic assessment. These are the issues of interest for future research.

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