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Original Research Article

Pattern of adverse drug reaction to antiepileptic drugs in a tertiary care hospital

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ABSTRACT

Background: Adverse drug reactions (ADRs) are a major cause of morbidity and mortality, and are the leading cause of hospital admission. The overall rate of ADRs is estimated to be 6.5% and 28% of these ADRs are preventable. Antiepileptic drugs (AEDs) are authorized for several therapeutic indications and are highly prescribed. ADRs due to AEDs range from minor maculopapular exanthem (MPE) to severe life-threatening reactions like Drug reaction eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson syndrome (SJS). Objective of the study was to evaluate the pattern of ADRs reported with AEDs in an adverse drug reaction monitoring centre (AMC) of a tertiary care hospital.

Methods: Retrospective analysis of the records was done for a period 48 months from January 2013 to December 2016. During this period, all the ADRs caused by AEDs reported to the AMC were included in the study. The study evaluated the pattern of ADRs due to AEDs. The study also assessed the gender-wise distribution, predilection for various systems, causality, severity, and preventability of ADRs. Data was analysed using descriptive statistics.

Results: A total of 319 ADRs were reported by spontaneous reporting during the entire study period. Out of the total 319 ADR reports received, antiepileptic drugs related ADRs were 35 (11%). Antiepileptic drugs which caused the ADRs included phenytoin, carbamazepine, clobazam and lorazepam. The most common system affected was dermatological (60%), followed by gastrointestinal system (17.14%), vascular system (11.42%), blood (5.8%), respiratory system (5.8%) and central nervous system (2.9%). Among the dermatological ADRs, SJS accounted for 11 cases of which 10 cases were due to phenytoin and one case was due to carbamazepine. DRESS syndrome due to phenytoin was documented in one case.

Conclusions: AEDs are the most commonly prescribed drugs for various indications. Uses of AEDs are accompanied by ADRs which vary from mild rashes and itching to SJS and DRESS/TEN. Post-marketing surveillance of the AEDs is important for compliance, therapeutic efficacy and ultimately safety of the patient.

Keywords: Antiepileptic drugs (AEDs), Carbamazepine, Drug reaction eosinophilia and systemic symptoms (DRESS), Phenytoin, Steven-Johnson syndrome

INTRODUCTION

Adverse drug reactions (ADRs) are a major cause of morbidity and mortality, and are the leading cause of hospital admission.[1] An adverse drug reaction is defined as any noxious, unintended and undesired effect of a drug which occurs at a dose used in humans for prophylaxis, diagnosis, therapy or modification of physiological functions.[2] One meta-analysis found an ADR rate of 6.7% among hospitalized patients.[3] The overall rate of ADRs is estimated to be 6.5% and 28% of these ADRs are preventable.[4] The hospital admission rate due to ADRs is over 10% in some countries, and is associated with marked socioeconomic loss.[5,6] A systemic meta-analysis using

Medline and Embase as databases for literature published between 1980 and June 2002 on the incidences of ADRs and their preventability in hospital settings showed that upto 56.6% these events were judged to be preventable.[7]

Considering the importance of monitoring ADRs to improve public health, Pharmacovigilance programme of India (PvPI) was started in 2010. As per this program, ADR monitoring centers have been started in many medical institutions all over the country to estimate the frequency of ADRs occurring with various drugs among the Indians.[8] Indian Pharmacopoeia commission (IPC) functions as National Co-ordinating Centre (NCC) at Ghaziabad for pharmacovigilance activities.

Spontaneous reporting of ADRs voluntarily by the healthcare professionals has been the core data-generating system of pharmacovigilance for years. It plays a major role in identifying and reporting of any adverse events to the pharmacovigilance coordinating centre, health/regulatory authority or to the drug manufacturer itself.[9]

Antiepileptic drugs (AEDs) are authorized for several therapeutic indications and are highly prescribed. ADRs are commonly associated with AEDs particularly the aromatic carbamazepine, phenytoin, phenobarbitone, and lamotrigine. They range from minor maculopapular exanthem (MPE) to severe life-threatening reactions like Drug reaction eosinophilia and systemic symptoms (DRESS), Stevens-Johnson Syndrome (SJS) and Toxic epidermal Necrolysis (TEN), and manifest within a few hours to weeks of the AED being initiated.[10,11] Hence this study was undertaken to evaluate the pattern of ADRs due to AEDs.

METHODS

This retrospective observational study analysed the ADRs due to antiepileptic drugs that were reported by spontaneous reporting to ADR monitoring centre (AMC), functioning from Department of Pharmacology, ESIC-MC and PGIMSR. The total study period was for 48 months from January 2013 to December 2016. During this period, all the ADRs caused by antiepileptic drugs reported to the AMC were included in the study.

The ADRs reported to AMC were analysed by pharmacovigilance team comprising of Pharmacologists, pharmacovigilance associate, pharmacist and clinicians. ADRs due to various AEDs were analysed for gender and system predilection. Causality of ADRs analysed by Naranjo's scale was graded as definite, probable, possible and doubtful.[12] The severity of ADRs was analysed using modified Hartwig Siegel's severity assessment scale as mild, moderate and severe.[13] Preventability of the ADRs was assessed using modified Schumock and Thornton scale.[14] Data was analysed using descriptive statistics.

RESULTS

A total of 319 ADRs were reported by spontaneous reporting during the entire study period and among the 319 ADRs reported, 176 patients were males and 143 patients were females as shown in Figure 1.

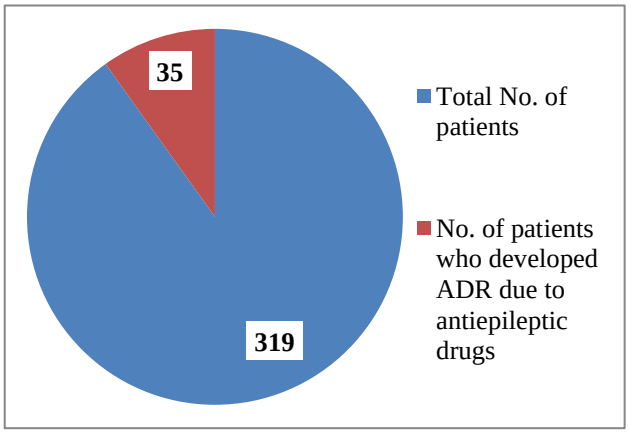

Figure 1: Number of patients developing ADRs due to antiepileptic drugs.

Out of the total 319 ADR reports received, AEDs related ADRs were 35 (11%). Out of 35 patients who had ADR due to AEDs, there were 10 females and 15 males (Figure 2). The age of the patients ranged from 18 to 65 years.

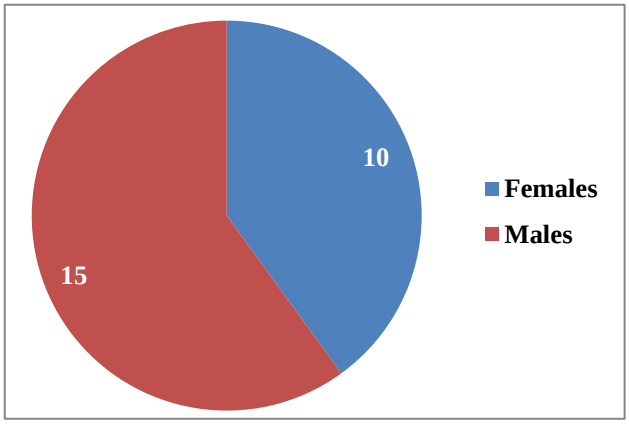

Figure 2: Incidence of ADRs among males and females.

Antiepileptic drugs which caused the ADRs were phenytoin, carbamazepine, clobazam and lorazepam (Figure 3).

The most common system affected was dermatological (60%), followed by gastrointestinal system (17.14%), blood (5.8%) and vascular system (11.42%), central nervous system (2.9%) and respiratory system (5.8%) (Figure 4). Dermatological ADRs included from rashes and itching to SJS and DRESS. Gastrointestinal ADRs included hepatitis, nausea and vomiting. Hematological ADRs included eosinophilia. Breathlessness was seen

among respiratory ADRs and cardiovascular ADRs included low blood pressure. Among the dermatological ADRs, SJS accounted for 11 cases of which 10 cases were due to phenytoin and one case was due to carbamazepine. DRESS syndrome due to phenytoin was documented in one case.

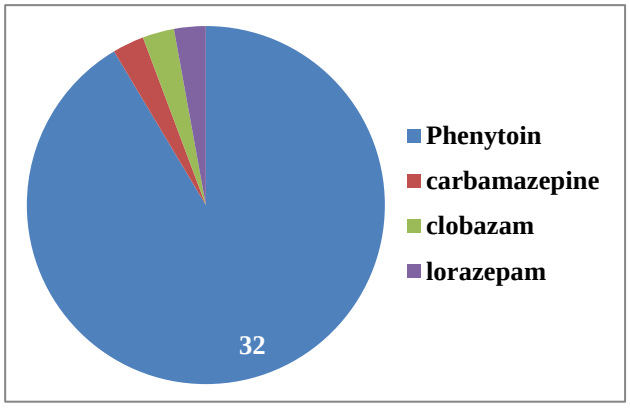

Figure 3: ADRs due to antiepileptic drugs.

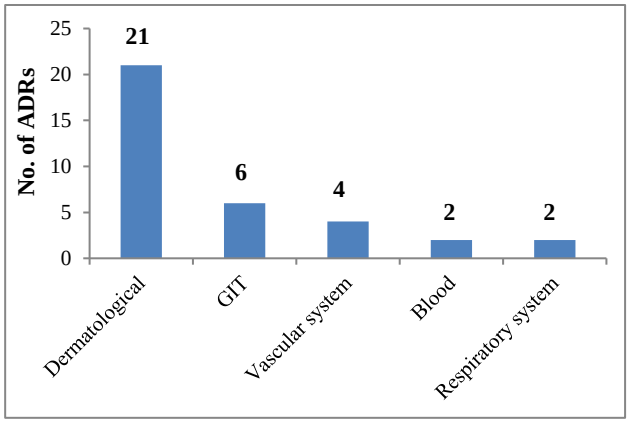

Figure 4: System-wise ADRs due to AEDs.

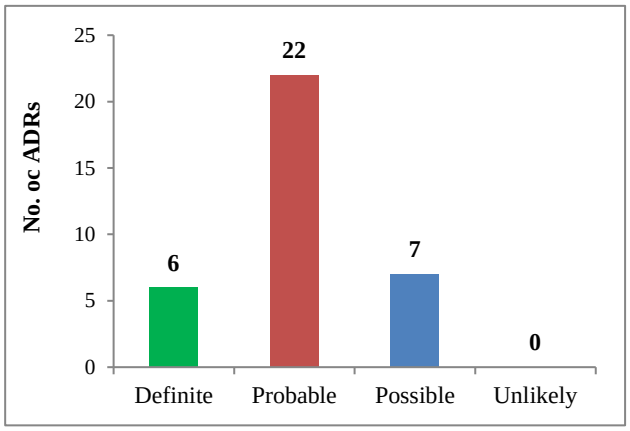

Figure 5: Causality assessment using naranjo algorithm.

Causality was assessed using Naranjo algorithm score and it was found that 6 (17%) of the ADRs were definite, 22 (63%) were probable and 7 (20%) were possible (Figure 5).

Severity was assessed using modified Hartwig Siegel's severity assessment scale and it was found that most of the ADRs were mild 19 (54%), moderate 16 (46%) and none of the reactions were severe (Figure 6).

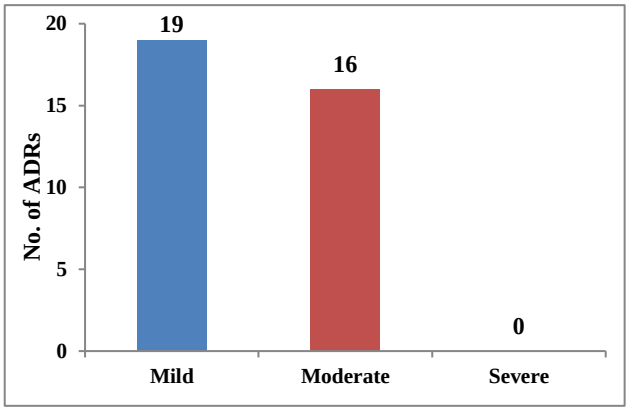

Figure 6: Grading of severity using Hartwig's severity assessment scale.

Preventability of the ADRs was assessed using modified Schumock and Thornton scale. None of the reactions were definitely preventable and 14 (40%) of the ADRs were probably preventable and 21 (60%) of the reactions were not preventable (Figure 7).

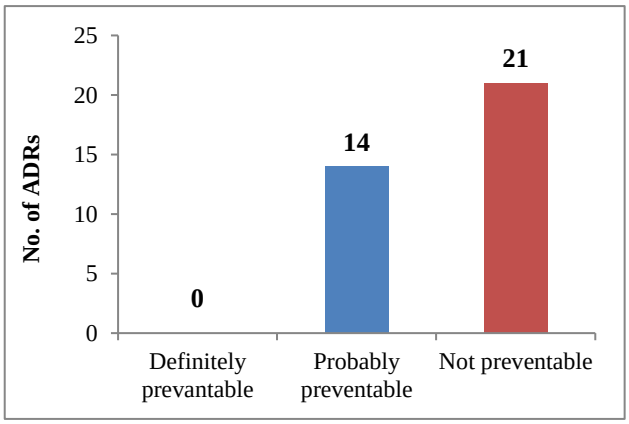

Figure 7: Preventability of the ADRs assessed by Schumock and Thornton scale.

DISCUSSION

This retrospective study evaluated the pattern of ADRs among the patients who received AEDs for medical and surgical indications. The study also assessed the gender-wise distribution, predilection for various systems, causality, severity, and preventability of ADRs. In our study, the number of ADRs among males was more compared to females. ADRs reported included rash, itching, maculopapular rash, nausea, vomiting, SJS, DRESS and hepatitis. The most frequently reported ADRs

of moderate severity were SJS, DRESS and hepatitis. Drugs implicated in causing these ADRs were due to phenytoin, followed by carbamazepine, clobazam and lorazepam.

SJS is uncommon, acute and potentially life-threatening adverse cutaneous drug reactions, often related to drug use. They are the result of extensive death of keratinocytes, which leads to the separation of areas of skin in the dermal-epidermal junction, producing the appearance of scalded skin. The disease runs an unpredictable course, an initially benign-appearing dermatosis can progress rapidly.[10,11]

The present study found that dermatological system was most commonly affected followed by gastrointestinal (GI) and vascular system. More than 90% of SJS occurs within the first 2 months of AED use. Commonly, some of the drugs such as phenytoin and carbamazepine have a high incidence to cause SJS, and also, these kinds of reactions are independent of dose or the drug and are idiosyncratic.[15]

In a case series reported by Bhavi ST, et al, one patient died due to SJS.[16] In our study none of the reactions were severe or lethal. Most of the reactions were moderate and required medical treatment with steroids, antihistamines, proton pump inhibitors (PPI) and clotrimazole mouth paint.[17] Recent studies have suggested a strong association between HLA-B∗1502 and AED-induced SJS in patients of Chinese/Asian ethnicity.[18]

DRESS is a rare but serious ADR presenting with variable signs of both cutaneous and internal organ involvement. Generally, symptoms develop 2 to 8 weeks after initiation of the causative medication.[19,20] Drugs most commonly implicated include AEDs, allopurinol, sulphonamides, minocycline, and nonsteroidal anti-inflammatory drugs (NSAIDs). In our study, DRESS syndrome due to phenytoin was reported in one case. This patient presented with maculopapular rash, eosinophilia and lymphadenopathy. Withdrawal of suspected agent is the most important step in management of DRESS. Phenytoin was withdrawn in this patient within the first day of hospitalization. Medical treatment with corticosteroids and antihistamines improved the patient's condition. In a descriptive retrospective study of hospitalized patients at the King Chulalongkorn Memorial Hospital between January 2004 and December 2014, a total of fifty two patients due to DRESS were included in the study. Out of 52 patients, 23.1% of patients had DRESS due to phenytoin and it was the most common drug to cause DRESS followed by other drugs.[21]

CONCLUSION

AEDs are the most commonly prescribed drugs for various indications. The present study found that dermatological system was the predominant organ system affected by AEDs. ADRs due to AEDs ranged from rashes and itching to SJS and DRESS with systemic involvement. ADR reporting and monitoring program targets to identify and quantify the risks associated with the drug use and thus promoting rational use of drugs. Hence awareness is required among all the health care fraternity and consumers to practically involve in ADR reporting. Careful drug selection for epileptic patients must be highlighted in order to improve outcome, reduce ADRs and improve patient compliance.

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