Research Article

COLLECTION, DETECTION, ASSESSMENT, MONITORING AND PREVENTION OF ADVERSE DRUG REACTIONS OF ANTI-EPILEPTIC DRUGS

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ABSTRACT

An adverse drug reaction (ADR) as defined by World Health Organization (WHO) is a noxious, unintended effect of a drug, occurring at normal doses in humans for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function. ADRs rank among the top ten leading causes of mortality. The adverse effects (AEs) of antiepileptic drugs (AEDs) are highly prevalent and can be potentially life threatening. The objective of this study is to identify the ADR by chart review method, to determine the causality of the ADR by Naranjo's algorithm, to analyze the severity of the ADR by modified Hartwig method and to motivate the health care professionals to report ADRs in Neurology ward of Gauhati Medical College and Hospital (GMCH), Guwahati, Assam, India. Preventability of ADR is done by Schumock and Thorton preventability scale. A prospective observational and hospital based case control study (Jan 2011-Dec 2011) was carried out in the Neurology ward of GHMC, including both out-patient and in- patient departments. All the values are statistically determined and expressed as Mean $\pm$ SD Graph Pad prism-5 statistical software was used for the data analysis. Statistical significance was defined as $p < 0.05$. All P values were two tailed. Out of the 2880 patients treated with AEDs for various indications, 85 (2.95 %) patients were reported with an incidence of 1 or more ADRs. The most common ADR involved the CNS (44 cases). Among them ataxia was found to be the most frequently reported (15 cases), followed by nystagmus (14 cases) and somnolence (9 cases). 37 cases involved the skin and connective tissue, the most common complaint being gum hypertrophy (23 cases). GI apparatus and liver involved 41 cases, the most frequent being nausea/vomiting (21 cases) and poor appetite (12 cases). Out of the 134 ADRs recorded, most of the ADRs were of Type A ($n = 80$, 59.70 %), followed by Type C ($n = 37$, 27.61 %), Type B ($n = 16$, 11.94 %) and Type D ($n = 1$, 0.75 %). Phenytoin resulted in a total of 38 (44.7 %) ADRs when prescribed as mono therapy followed by Sodium Valproate which caused a total of 19 (22.35 %) ADRs when prescribed alone. Anti-epileptic drugs have narrow therapeutic index, physician should be encouraged to do therapeutic drug monitoring in order to ensure effective treatment and prevent adverse drug reactions.

Keywords: Neurology, ataxia, nystagmus, somnolence, phenytoin.

INTRODUCTION

An adverse drug reaction (ADR) as defined by World Health Organization (WHO) is a noxious, unintended effect of a drug, occurring at normal doses in humans for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function¹. In some countries, ADRs rank among the top ten leading causes of mortality². The adverse effects (AEs) of antiepileptic drugs (AEDs) are highly prevalent and can be potentially life threatening. Up to 61 % of patients taking conventional AEDs, such as Phenytoin, Carbamazepine, Valproate or Phenobarbital may give rise to unexpected adverse drugs events like severe cutaneous reactions, serious hematological disorders, CNS abnormalities or hepatic failure most of these disorders emerge as idiosyncratic immune-mediated disorders or related to toxic metabolic products of the AEDs which are thought to contribute to initial treatment failure in up to 40 % of patients. Each new medication provides a unique profile of pharmacokinetics, AEs and mechanisms of action, making an appreciation of how these agents are best utilized even more difficult^{3,4}. This study is aimed at reporting the various ADRs related to AED use in GMC and H and finding out the incidence of these ADRs and the offending drugs causing them. This study use different scales to analyze causality, severity, onset, preventability and predictability of ADRs.

MATERIALS AND METHODS

The study will be carried out in the Neurology ward of Gauhati medical college and hospital, including both out-patient and in- patient departments. The study will be a prospective observational, hospital based case control study. Study will be based only on those patients who experience an adverse reaction to medicine use, either during their stay in hospital or outside the hospital and visiting the outpatient and inpatient departments of Neurology. All the ADRs collected in the study were classified as either "Type A = Acute", Type B = Bizarre", "Type C = Chronic" or as "Type D = Delayed"⁵. The degree of association of an adverse effect with a drug is done (Table 1) with the help of Naranjo's algorithm where it involves a number of questionnaires, to each of which score has been provided (ranging from -1 to +2). Total score for a particular Drug-ADR combination is calculated and the association is termed as > 9 : Highly probable; 5-8: Probable; 1-4: Possible; 0: Doubtful⁶. After the causality assessment has been done, the severity of the ADR is analyzed using adapted Hart wig severity scale⁷. The scale was classified as mild: a reaction that does not required treatment or prolongation of hospital stay; moderate: a reaction that requires treatment and or prolongs hospitalization by at least one day; severe: a reaction that was potentially life threatening or contributes to the death of patient was permanently disabling requires intensive medical care or results in a congenital anomaly cancer or unintentional overdose. Preventable adverse drug reaction

was defined according to Schumock and Thornton scale⁸ as ADR which was preventable or avoidable.

Statistical Analysis

Data were recorded on a pre-designed proforma and managed on an MS Office Excel spread sheet. The descriptive statistics are represented by mean $\pm$ standard deviation and percentages. The differences between the groups were determined by the parametric t-test and non-parametric fisher's exact test or chi-square tests wherever appropriate. Graph Pad prism statistical software was used for the data analysis. The Odds ratio and its 95 % confidence interval were calculated for certain risk factor of ADRs in renal failure patients. Statistical significance was defined as $p < 0.05$. All P values were two tailed.

RESULTS

The result is based on the screening of 2880 patients who were on AED therapy during the 12 months duration of the study period from Jan 2011 to Dec 2011 in the Neurology department of Gauhati Medical College and Hospital. 86 patients were reported to have AED related ADRs. 1 patient was excluded from the study as it was a known case of chronic liver disease. Thus a total of 85 patients of ADRs were included in the study. Out of the 2880 patients treated with AEDs for various indications, 85 (2.95 %) patients were reported with an incidence of 1 or more ADRs. 50 (58.8 %) patients out of the 85 were found to have 1 ADR while the rest 35 (41.2 %) patients were found to have an incidence of more than 1 ADR (Table 3). Thus a total of 134 ADRs were reported during the study period. The most common ADR involved the CNS (44 cases). Among them ataxia was found to be the most frequently reported (15 cases), followed by nystagmus (14 cases) and somnolence (9 cases). GI apparatus and liver involved 41 cases, the most frequent being nausea/vomiting (21 cases) and poor appetite (12 cases). 37 cases involved the skin and connective tissue, the most common complaint being gum hypertrophy (23 cases). Out of the 134 ADRs recorded, most of the ADRs were of Type A ($n = 80$, 59.70 %), followed by Type C ($n = 37$, 27.61 %), Type B ($n = 16$, 11.94 %) and Type D ($n = 1$, 0.75 %). In Type A, giddiness ($n = 21$, 26.25 %) was found to be the most common complaint followed by ataxia ($n = 15$, 18.75 %), nystagmus ($n = 14$, 17.5 %), poor appetite ($n = 12$, 15 %) and sedation ($n = 9$, 11.25 %). The others Type A; ADRs included drug induced tremor, constipation, blurring of vision and abdominal pain. Among Type B, Skin rashes ($n = 6$, 37.5

%) was found to be the most common ADR followed by increased liver function test (LFT) ($n = 5$, 31 %) and lymphadenopathy ($n = 3$, 18.75 %). 1 case each of anemia and neutropenia was also reported. Among Type C, gum hypertrophy ($n = 23$, 62.16 %) was found to be the most prominent ADR. The other ADRs included weight gain, oral ulcers, loss of hair, bone pain, PCOD and acute pancreatitis. Causality assessment was done using Naranjo scale revealed that out of the 134 ADRs, most ADRs (87.31 %) were found to be "probable" while the rest were classified as "possible". Severity of the patients with ADRs were analyzed that most of the ADRs were classified as "mild" (48.5 %) or "moderate" (47 %). Only 4 (4.47 %) ADRs were found to be "severe". Patients with ADRs were classified in 6 different age groups. The incidence of ADRs was found to be more prominent in the age group of 10-19 years and maximum number of ADRs was reported in patients of 18 years of age (10 out of 85). The mean age of patients with ADR was found to be 24.49 ± 1.407 , the maximum being 60 years and the minimum being 2 years. Out of the 85 patients reported with ADRs 64 were found to be males while 21 were found to be females. Most of the ADRs reported in this study were found to be in those patients who were on AED therapy for less than 6 months ($n = 40$, 47.06 %), followed by those patients who have been on AEDs for 1-3 years ($n = 26$, 30.59 %). A total of 117 AEDs were prescribed to the 85 patients with ADRs, the average being 1.3 drugs/patient. 57 (67.06 %) patients out of these 85 were receiving mono therapy with a single AED while 28 (32.94 %) of them were receiving a combination of 2 to 3 AEDs. However no definite correlation was found between the number of AEDs prescribed and the number of ADRs. 21 patients received other class of drugs along with AEDs, consisting mostly of nerve supplements, multivitamins or proton pump inhibitors. The drugs responsible for the ADRs are listed in Table 3. Phenytoin was found to be the most offending drug accounting for about 37.61 % of the total prescribed drugs which caused ADRs, followed by sodium Valproate (18.80 %), Clobazam (17.09 %) and Carbamazepine (11.11 %) being prescribed as both mono therapy and polytherapy. Phenytoin resulted in a total of 38 (44.7 %) ADRs when prescribed as mono therapy followed by Sodium Valproate which caused a total of 19 (22.35 %) ADRs when prescribed alone. In patients treated with more than one AED, the combination of phenytoin and clobazam was found to be the most offending combination accounting for 15 (17.64 %) ADRs.

Figure 1: Drugs causing ADRs

Table 1: Assessment of ADRs

Assessment	Criteria	No. of ADRs	% of ADRs
Naranjo's Score (causality)	Possible (1-4)	17	12.7
	Probable (5-8)	117	87.3
	Highly probable (>9)	0	0
Hartwig Criteria (severity)	Mild	65	48.5
	Moderate	63	47
	Severe	6	4.47

Table 2: List of ADRs reported during study period

S. No	ADR's			
	Description	Frequency (%)	System wise	Frequency (%)
1	Gum hypertrophy	23 (17.1)	Central Nervous System	44 (32.8)
2	Nausea/vomiting	21 (15.6)	Skin and Connective Tissue	37 (27.6)
3	Ataxia	15 (11.1)	GI Apparatus and Liver	41 (30.6)
4	Nystagmus	14 (10.4)	Others	12 (8.9)
5	Poor appetite	12 (8.9)		
6	Somnolence	9 (6.7)		
7	Skin rashes	6 (4.4)		
8	Increased Liver function test	5 (3.7)		
9	Weight gain	4 (2.9)		
10	Tremor	3 (2.2)		
11	Oral ulcers	3 (2.2)		
12	Loss of hair	3 (2.2)		
13	Lymphadenopathy	3 (2.2)		

Table 3: In detailed system wise classification of ADR's

Central Nervous System	Total: 44
Ataxia	15
Nystagmus	14
Somnolence	9
Tremor	3
Blurring of vision	2
Vertigo	1
Skin and Connective Tissue	Total: 37
Gum hypertrophy	23
Skin rashes	6
Loss of hair	3
Oral ulcers	3
Bone pain	2
GI Apparatus and Liver	Total: 41
Nausea/vomiting	21
Poor appetite	12
Increased Liver function test	5
Constipation	2
Abdominal pain	1
Others	Total: 12
Weight gain	4
Lymphadenopathy	3
Anaemia	1
Neutropenia	1
PCOD	1
Acute pancreatitis	1
Teratogenicity	1

DISCUSSION

Out of the 2880 patients treated with AEDs for various indications, 85 patients were found to have 134 ADRs. 50 (58.8 %) patients out of the 85 were found to have 1 ADR while the rest 35 (41.2 %) patients were found to have an incidence of more than 1 ADR (Table 3). Majority of the ADR reports received involved the CNS (44 cases) followed by GI apparatus and liver (41 cases), and skin and connective tissue (37 cases). Several studies⁹⁻¹⁴ have reported the common involvement of CNS toxicity with AEDs, as these drugs exert their actions on selected CNS receptors. Among CNS toxicities, ataxia was found to be the most frequently reported ADR (15 cases), followed by Nystagmus (14 cases) and somnolence (9 cases). Gum hypertrophy (23 cases) was

the most common complaint among skin and connective tissue while nausea/vomiting (21 cases) and poor appetite (12 cases) were the most frequent complaints involving the GI apparatus and liver. Studies done in Italy reported similar findings. Somnolence was the commonest complaint followed by gingival hyperplasia, nystagmus and ataxia in their study^{15,16}. Out of the 134 ADRs recorded, most of the ADRs were of Type A (n = 80, 59.70 %). Type A; ADRs are drug dose or concentration dependent. Most of the AEDs are having narrow therapeutic index and so therapeutic drug monitoring is required in order to avoid high plasma concentrations. Distribution of ADRs with reference to duration of drug therapy revealed that most of the ADRs reported in this study were found to be in those patients who

were on AED therapy for less than 3 years ($n = 14, 73.6\%$) followed by those patients who have been on AEDs for more than 3 years ($n = 5, 26.3\%$). Causality assessment using Naranjo's scale⁶ revealed that Out of the 134 ADRs, most ADRs (87.31 %) were found to be "probable" while the rest were classified as "possible". Thus most of the ADRs are having probable relationship with drug. On evaluation of the severity of ADRs by Hartwig severity scale⁷, it was evident that most of the ADRs were classified as "mild" (48.5 %) or "moderate" (47 %). Only 4 (4.47 %) ADRs were found to be "severe". Demographic details of the patients suffering from ADRs were studied and revealed that the incidence of ADR was found to be more prominent in the age group of 10-19 years and maximum number of ADRs was reported in patients of 18 years of age. (10 out of 85) Out of the 85 patients reported with ADRs 64 were found to be males while 21 were found to be females. This may be attributed to the large number of male patients visiting the ward compared to the female patients. Although mono therapy is the goal for epileptic patients^{17,18} but still treatment with AEDs is complicated due to the complex pharmacokinetics and narrow therapeutic index of the drugs¹⁹. Distribution of ADRs with reference to drug therapy 57 (67.06 %) patients out of these 85 were receiving mono therapy with a single AED while 28 (32.94 %) of them were receiving a combination of 2 to 3 AEDs. However no definite correlation was found between the number of AEDs prescribed and the number of ADRs. The therapeutic drug classes most commonly implicated in the reported ADRs were analyzed. Phenytoin was found to be the most offending drug accounting for about 37.61 % of the total prescribed drugs which caused ADRs, followed by sodium Valproate (18.80 %), Clobazam (17.09 %) and Carbamazepine (11.11 %) being prescribed as both mono therapy and poly therapy. This study finding was found similar to many other studies which have also reported Phenytoin and Carbamazepine as the most offending drugs in their respective studies^{20,21}. Gingival hyperplasia is a well known toxicity associated with long term use of Phenytoin²². Gingivitis or gum hypertrophy was found to be the most frequent complaint in this study. Phenytoin was found to be prescribed in all these patients, being present as mono therapy in 20 cases and poly therapy in 3 cases. It was found to be "probable" in all the cases, the average score being 6.04 ± 0.043 . In 16 patients out of these 23, no change of treatment was done and only oral hygiene maintenance was advised, 4 patients required a change in therapy while 3 patients were advised to take Vitamin C as additional therapy. GI symptoms like nausea and vomiting are common dose related toxicity associated with AEDs (10). 21 cases of giddiness/nausea were recorded. It was found to be "possible" in 13 cases while "probable" in 9 cases. Since AEDs act on selected CNS receptors, so adverse effects involving the CNS is not uncommon^{23,24}. Drugs like Phenytoin, Carbamazepine, Gabapentine, Lamotrigine, Topiramate and others have been found to cause CNS toxicities like somnolence, ataxia and nystagmus²⁵⁻³⁰. 15 cases of ataxia were reported. It was found to be "possible" in 8 cases and "probable" in 7 cases. Dose was reduced in 6 cases and drug stopped in 9 cases. 14 cases of Nystagmus were recorded. All were found to be "probable". Phenytoin was found to be prescribed in most of the cases (1 cases) followed by Carbamazepine (2 cases of mono therapy). Valproate related hepatotoxicity is well established in literature^{31,32}. Anorexia is the one of the first sign of abnormal liver functioning. 12 cases of poor appetite were

reported. Sodium Valproate was found to be the offending drug in all of them, being prescribed as mono therapy in 8 of them. It was found to be "possible" in 8 cases while "probable" in 4 cases. 7 patients required no change of therapy. 5 patients were additionally prescribed with a hepatoprotective while all were suggested for a LFT.

CONCLUSION

Many Adverse drug reactions are dose related (type A); therefore by monitoring the patient closely, the adverse drug reactions can often be avoidable by adjusting the doses or in some times the particular drug is withdrawn from the treatment. As the literature says that most of the anti-epileptic drugs have narrow therapeutic index, physician should be encouraged to do therapeutic drug monitoring in order to ensure effective treatment and prevent adverse drug reactions. Mono therapy should also be encouraged to prevent further complications. A regular follow up of patients on AEDs is required for the early detection and prevention of ADRs to increase patient's compliance to drug therapy and to provide a better drug therapy by prevention of related morbidity and mortality.

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