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Original Research Article

Monitoring of Adverse Drug Reactions of Anti-Epileptic Agents in the Neurology Department

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ABSTRACT

Purpose: To monitor the adverse drug reaction of anti-epileptic agents. Other objectives were to study the pattern of ADRs caused by the antiepileptic drugs used in neurology department and the side effects by spontaneous reporting.
Methods: A prospective observational study was conducted in the neurology department and The patients who fulfilled the inclusion criteria were recruited in the study. The data were analyzed by SPSS Statistics ver. 20.
Results: During the study period, 54 patients developed adverse drug reaction from anti-epileptic agents in the neurology department. Most reactions occurred in the age group 31-40 years (37%) followed by 41-50 year age group (25%) developed ADRs. More common reaction or problem is skin rashes; occurred in 12 patients (20.4%). Tab Depran (clonazepam + Escitalopram) caused the highest number of adverse drug reaction in 11 patients (20.4%). All the ADRs were caused by the drug taken through the oral route. As per Naranjo probability scale, causality assessment was probable in 40 patients (74.1%).the majority of drugs were withdrawn after the occurrence of adverse drug reaction (35 patients). No serious reaction occurred at the time of the study.
Conclusion: Most of the ADRs were inevitable due to the poor predictability of the ADRs and poorly understood mechanisms to explain their causes, Pharmacovigilance program should be implemented and awareness should be created among physician about reporting any suspected adverse drug reaction so that unreported ADRs and unknown risk factor could be identified and data generated will help Indian regulatory authorities to make appropriate regulatory decision which will benefit the society & people.

Key Words: Adverse drug reaction, Neurology, Pharmacovigilance, Anti-epileptic agents

INTRODUCTION

Adverse Drug Reactions (ADRs) are recognized hazards of drug therapy. Although some ADRs are minor and resolve without sequelae, others can cause permanent disability or death. ADRs are a significant cause of morbidity and mortality and would also result in increased health care costs. According to WHO, ADR is defined as "a response to a medicine which is harmful and unintentional and takes place at strength used in human for prophylaxis, diagnostic purposes, therapeutic or alteration of physiologic function". In broad terms, an ADR is an adverse event with a causal link to the drug. Epidemiological studies have suggested that ADRs account for 5% of hospital admission. A study conducted by Lazarou found ADRs to be the 4th-6th leading cause of death in the U.S and serious ADRs accounted for 6-7% of hospital admissions. [1]

The term Pharmacovigilance first appeared in the 1960s. It is a system used to collect information, which is helpful in the surveillance of medicinal products, with particular reference to human beings and to evaluate such information scientifically. Pharmacovigilance is also known as drug safety, is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products. [2] Epilepsy is a long-lasting disorder, the trademark of which is episodic, gratuitous seizures. Several individuals with epilepsy have a combination of different types of seizure and may have other signs of neurological complications as well. [3] Occasional EEG reporting, medical history, family history, and viewpoint are alike among a group of folks with epilepsy. In these circumstances, their illness can be well-defined as a precise epilepsy syndrome. Adverse effects of anti-epileptic agents are normal, can have a significant effect on the quality of life of the patients and add-up to treatment letdown in about 40% of admitted patients. The adverse effect summaries of AEDs vary prominently and are often a decisive aspect of drug choice because of the similar efficacy proportions presented by most AEDs. The most communal adverse effects are dose-related and reversible. [4]

Along with the most common side effects of anti-epileptic drugs, like lethargicness, sleepiness, dizziness, and cognitive impairment; other side effects such as weight gaining, metabolic acidosis, nephrolithiasis, closed angle glaucoma, rashes of skin, hepatocytes malfunctioning, colitis and motor and behavioral disorder can also occur. [5] Thus, the overall aim of the study was to monitor the adverse drug reactions with the objectives to investigate the pattern of the ADRs caused by the anti-epileptic drugs used in the neurology department and the spontaneous reporting of the side effects.

MATERIAL AND METHODS

The study was conducted at the Department of Neurology in Guru Gobind Singh Medical College & Hospital, Faridkot & S.D Thapar Hospital, Moga. It was a Prospective Observational Study carried out for a period of 6 months. Total 54 subjects having ADRs due to anti-epileptic therapy were enrolled in the study and the subjects, who experienced ADRs due to the drugs other than the anti-epileptic agents, accidental and intentional poisoning, were excluded from the study. A duly signed inform consent, consisting of information about the study was taken from each subject and the study was approved by the Institutional Ethical Committee of Indo Soviet Friendship College of Pharmacy.

Data was collected from the inpatient case reports & outpatients cards in the Neurology Department. Collection of the ADRs was also done by the resident doctors, nurses, and pharmacists, by voluntary reporting through phone calls and by verbal communication. A comprehensive medical history was collected from the medication charts. The patient or the patient attendant was also quizzed and interviewed orally, to obtain the necessary information relating to the dose of cum administration of the suspected or causative drug. The study involved the use of CDSCO forms for reporting and documentation of the suspected ADRs and the ADR reporting and documentation form containing Naranjo's scale for Causality Assessment.

Data analyses

The data collected was analyzed via IBM SPSS Statistics version 20. Descriptive statistics were used to find out the frequencies and the descriptives of the parameters taken in the study and the Naranjo's scale was used for Causality Assessment of the ADRs.

RESULTS

Out of 54 patients who reported ADR, the majority of them fall under the age group of 31- 40 years that is 20 (37%) patients. The mean age of all the subjects

participated in the study was found to be 32.46±5.42. 35 (64.8%) were male patient and 19 (35.2%) were female patients.

Total 12 drugs were reported for causing adverse drug reactions during the study period. The majority of reactions and the problems were caused by the drug Tab. Depran (Clonazepam+ Escitalopram). Tab Depran caused an adverse drug reaction in 11(20.4%) patients. Tab. Eptoin (phenytoin) caused a second highest number of adverse drug reactions after Tab. Depran than any other drug that is in 8 (14.8%) patients. The descriptive analysis of drugs are shown in Table-1

Table 1: Drugs wise distribution of ADRs in patients

Brand and generic name of the medication	No of patients (n=54)	Percent
Tab. Tagretol (Carbamazepine)	4	7.4
Tab. Levera (Levetiracetam)	4	7.4
Tab. Depran (Clonazepam + Escitalopra)	11	20.4
Cap. Diamox (Acetazolamide)	2	3.7
Cap. Pregabid Me (Methylcobalamin + Pregabalin)	5	9.3
Tab. Kronostar (Sodium Valproate)	5	9.3
Tab. Eptoin ER (phenytoin)	3	5.6
Tab. Eptoin (phenytoin)	8	14.8
Tab. Lobazam (Clobazam)	7	13.0
Tab. Gardenal (Phenobarbital)	5	3.6
Tab. Articalm (Escitalopram)	1	1.9
Tab. Petril MD (Clonazepam)	1	1.9
Total	**54**	**100**

The highest number of ADRs were reported with the dose of 10/0.5 mg. Dose 10/0.5 mg was used in 11(20.4%) patients. Dose 10/0.5 mg was mainly used for Tab. Depran (Clonazepam+ Escitalopram). In this combination, clonazepam was 0.5 mg and escitalopram was 10 mg. On the evaluation of route of administration of the drug, all the 54 patients having adverse drug reactions, took the drug by per oral route and the majority of the patients that are 31 (57.4%) took the medication with BD (twice a day) frequency. BD frequency was considered to be highly probable to cause the adverse drug reactions.

The majority of the reactions and problems caused by drug were skin rashes. Skin rashes were reported in 11(20.4%) patients. The second most common reaction or problem was sedation. Sedation was reported in 8(14.8%) patients as represented in Table 2.

Table 2: Reaction or problem wise distribution of ADRs in patients

Reaction or problem	No. of the patients (n=54)	Percent
Vertigo	4	7.4
Sedation	8	14.8
Loss of Appetite	2	3.7
Constipation	1	1.9
Skin rashes+Dry mouth	1	1.9
Increased Sweating	1	1.9
Weight Gain	1	1.9
High Sedation	4	7.4
Constipation	1	1.9
Skin rashes	11	20.4
Sedation + Aggression	1	1.9
Drowsiness + Lethargy	4	7.4
Drowsiness + Dizziness	2	3.7
Weight gain + Erectile dysfunction	1	1.9
Stomach Upset + Increased Appetite	1	1.9
Drowsiness + Aggression	2	3.7
Stomach Upset + Weight gain	1	1.9
Dry mouth + Constipation	1	1.9
Diarrhea	1	1.9
Skin rashes + Sedation	1	1.9
Skin rashes + Gastritis	1	1.9
Tremor	1	1.9
Behavioral Changes	1	1.9
Gum Hypertrophy	2	3.7
Total	**54**	**100**

The indication of therapy in 39(72.2%) patients was the treatment of epilepsy. Whereas, 9(16.7%) patients received the therapy for the treatment of anxiety and 6(11.1%) patients for depression.

On the evaluation of causality assessment as per the Naranjo's probability scale, the causality was assessed. Out of 54 patients, causality assessed was "probable" in the majority of the patients that is in 40 (74.1%) patients as shown in Figure 1.

On the evaluation of actions taken by the physician after ADR occurrence, the majority of actions performed were the "withdrawal" of the drug. The drug was withdrawn in 35 (64.8%) patients as depicted in Figure 2.

After evaluating the outcomes of the treatment given by the physician it was noticed that the ratio of the patients recovering and recovered from the adverse

drug reactions was 1:1. 27(50%) patients were recovered from the adverse drug reactions while the remaining 27(50%) patients were still recovering during the course of the study.

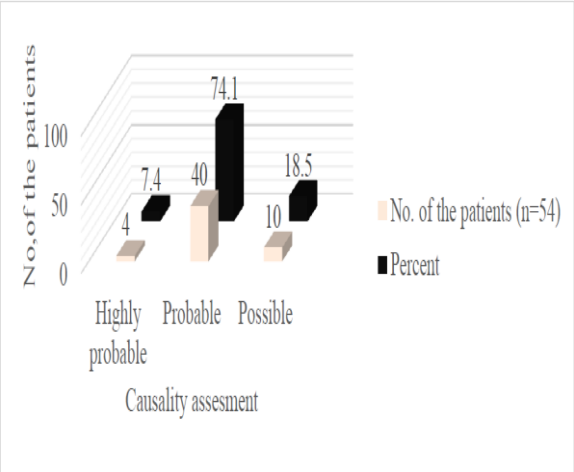

Figure 1: Causality assessment as per Naranjo's scale

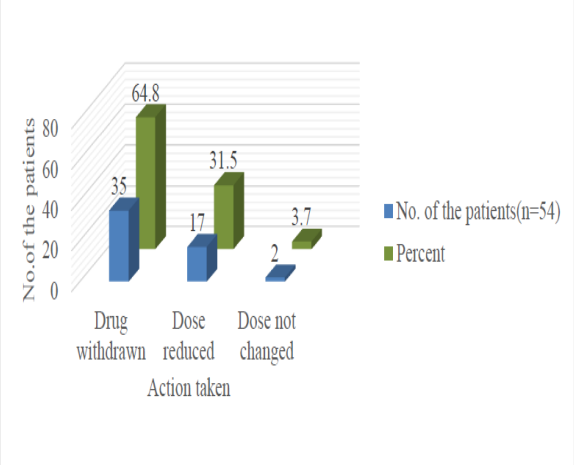

Figure 2: Action taken by the physician

DISCUSSION

The results of our study represent a successful prospective observational study of ADR monitoring of anti-epileptic drugs in the neurology department. ADRs were found to be most prevalent (37%) in the age group of 31 - 40 years. It is likely that this population is attending the hospital more frequently and is a major population receiving drug therapy. A number of factors determining the incidences of ADRs have been identified, including age, female gender and number of drugs administered. A study reported a pronounced increase in the incidence of ADRs above the age of 60 years. [5] Similarly, another study evident that a high incidence of ADRs in older patients receiving a higher number of drugs. [6] In our study, the ADRs were detected by means of intensified surveillance and found that the majority of the patients (37(64.8%)) were of the male gender. The highest number of ADRs was the skin rashes occurred in 11(20.4%) patients and sedation was the second most common reaction reported in 8 (14.8%) patients. The majority of reactions and the problems were caused by the drug Tab. Depran (Clonazepam+ Escitalopram), reported in 11(20.4%) patients. We found that the leading drugs causing an ADR in the neurological wards were the anti-epileptics and anti-anxiety, followed by the antidepressants. A study was conducted in the year 2002 that reported the same. [7] As per Naranjo's probability scale, causality assessment was "probable" in 40 patients (74.1%) that are in the majority of the patients. In contrast, a clinical study reported that most of the ADRs (93.7%) were classified as "possible" and only 10 ADR reports were "probable". [8] The majority of drugs were withdrawn after the occurrence of adverse drug reactions in 35 patients (64.8%). A study was conducted in the same manner where 231 suspected offending drugs were reported to induce various ADRs. Of which, the majority (92.6%) of the drugs were withdrawn for the management of ADRs. [9] On the evaluation of the outcomes, 27(50%) patients were recovered from the adverse drug reactions after the suitable actions taken by the physician and the remaining 27(50%) patients were still recovering.

The incidence of adverse drug reactions is not directly proportional to the number of drugs being taken but increases remarkably as the number of drugs rises. Polypharmacy needs to be discouraged to reduce the chances of ADRs resulting from drug-drug interactions. The Boston Collaborative group (1972) reported 36 % ADRs, 6.9 % of which were attributed to drug-drug interactions in a cohort of 10,000 patients. [10] Pharmacovigilance program

setup is beneficial in the reduction of such drug reactions and will for sure improve the quality of life of the patients.

CONCLUSION

Our study helped us to access the incidence and the pattern of the ADR's. As well as the study also helped us to describe the patterns of the ADR's in the Neurology Department. More studies are needed to establish the criteria of substitute and switch therapy, evaluate the the best combination for second-line therapy and direct treatment guidelines for recourses constrained strength. Since ADRs accounts for the 4th-6th leading cause of death and 6-7% of hospital admissions, there is a need for attentive ADR monitoring to decrease morbidity and mortality due to ADRs which requires further studies on large populations.

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