RESEARCH PAPER

Antiepileptic Drugs Adverse Drug Reactions and Role of Clinical Pharmacist

Dharani Gopu, Akila Devi D*

Department of Pharmaceutics, Research scholar, School of pharmaceutical sciences, Vels Institute of science, Technology and Advanced studies, Pallavaram, Chennai, India.

Received: 10th March, 2023; Revised: 25th June, 2023; Accepted: 05th August, 2023; Available Online: 25th September, 2023

ABSTRACT

Aim: To identify the ADR of suspected adverse drugs to monitor, manage, and assess to improve patient health.

Materials and Methods: The study type is a prospective observational study done in a tertiary care hospital at Telangana. Patients prescribed with at least one antiepileptic drug and patients with chronic diseases (SLE, renal and hepatic failure, etc.) were included in the study.

Result: Sodium valproate shows relatively less adverse drug reactions (ADRs) (2.5%) when compared with other antiepileptics. Phenytoin shows the highest number of ADRs (50%), among which CNS-related ADRs, where more than 75% of were predictable clinical pharmacists can play a crucial role in the early identification and prevention of these ADRs due to Antiepileptic drugs.

Keywords: Antiepileptic Drugs, Clinical pharmacist, Adverse drug reactions, Adverse drug events, Patient Safety, Quality of life.

International Journal of Pharmaceutical Quality Assurance (2023); DOI: 10.25258/ijpqa.14.3.23

How to cite this article: Gopu D, Devi AD. Antiepileptic Drugs Adverse Drug Reactions and Role of Clinical Pharmacist. International Journal of Pharmaceutical Quality Assurance. 2023;14(3):597-600.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Antiepileptic drug (AED) therapy is the major category given to patients with epilepsy. Some of the Older AED's are- phenytoin, phenobarbital, carbamazepine, primidone, ethosuximide, valproic acid, diazepam. newer AED's- felbamate, gabapentin, lamotrigine, oxcarbazepine, topiramate, tiagabine, levetiracetam, zonisamide.

The AEDs possess various molecular targets such as phenytoin, carbamazepine oxcarbazepine rufinamide, lacosamide, eslicarbazepine acetate, blocks sodium channels, ethosuximide, pregabalin blocks calcium channels, benzodiazepines like: clonazepam, lorazepam, clorazepate dipotassium, nitrazepam, clobazam- Enhances the activity of GABA.[1] Lamotrigine and Zonisamide block both sodium and calcium channels. Primidone enhances the activity of GABA as well as blockage of calcium channels.[2] Valproic acid, the most commonly used AED enhances the activity of GABA, blockage of calcium channels blockage and sodium channels. Topiramate & felbamate enhance the activity of GABA, the blockage of calcium and sodium channels and the blockage of glutamate neurotransmitter. gabapentin, felbamate, levetiracetam has non categorized mechanism of action.[3]

Concentration-dependent acute side effects of carbamazepine are diplopia, dizziness, drowsiness, and unsteadiness. Idiosyncratic acute side effects are blood dyscrasias rash. The chronic side effects of carbamazepine is hyponatremia.[4]

Concentration-dependent acute side effects of gabapentin are dizziness, fatigue, somnolency, ataxia, pedal edema is, idiosyncratic acute side effects. The chronic side effect of gabapentin is weight gain.[5]

Concentration-dependent acute side effects of phenytoin are behavior changes, incoordination, lethargy, cognitive impairment, and nystagmus. Idiosyncratic acute side effects are immunologic reactions, rash, and blood dyscrasias.[6] Chronic side effects are skin thickening, hirsutism, cognitive impairment, metabolic bone disorder, and cerebellar syndrome.[7]

Concentration-dependent acute side effects of valproic acid are gi upset, tremors, unsteadiness, and sedation.[8] Idiosyncratic acute side effects are acute pancreatitis and alopecia; chronic side effects are menstrual cycle irregularities, weight gain, hyperammonemia, and polycystic ovary-like syndrome.[9]

MATERIAL AND METHODS

The type of study used is a prospective observational study in a tertiary care hospital in the Telangana region for a period of one year. Patients who visit the general medicine department

*Author for Correspondence: akilaajcp@gmail.com

Table 1: Antiepileptic drugs which developed 40 ADRs in 40 patients

S.No.	*Suspected drug*	*Number of patients*	*Percentage*
1	Phenytoin	20	50
2	Carbamazepine	17	42.5
3	Valproic acid	2	5
4	Sodium valproate	1	2.5

were reviewed daily and those who met my inclusion criteria: patients prescribed with at least one antiepileptic drug of both sex and a mean age of 39 ± 16.8 of age are included in the study. Mainly the patients has chronic diseases (SLE, Renal and hepatic failure, etc.) are taken as a major priority. All the necessary information from various resources like patient's case sheets, Physician's prescription (a copy of the original prescription was used for data collection), treatment charts and nurse's notes were collected and documented. The data collected include demographic details (age, gender, address, occupation), past medical history, and past medication history, laboratory reports, provisional and final diagnosis, and laboratory reports. The additional information is collected by interviewing healthcare professionals, Interviewing patients or patient caretakers and any other relevant sources. The information collected above was documented in the designed data collection form. Data collected from 752 antiepileptic drugs were prescribed in 580 patients. Among them, 40 ADRs were identified.

RESULTS

A total of 580 cases with use of antiepileptic drugs are taken into study and ADR's were examined and noted. Patients which were been prescribed with anti-epileptics, 40 (13.8%)

Table 2: Types of complaints in antiepileptic drugs

Drugs	*System-related*	*No of patients*	*Percentage*	*Types of complaints*	*No of patients*	*Percentage*
Phenytoin	CNS	10	50	Giddiness	3	15
				Dizziness	2	10
				Psychosis	1	5
				Vomiting	1	5
				Dystonia	1	5
				Ataxia	1	5
	CVS	4	20	Thrombophlebitis	3	15
				Thrombocytopenia	1	5
	EYE	3	15	Nystagmus	2	10
				Diplopia	1	5
	Others	3	15	Abdominal pain	1	5
				Rashes all over the body, unable to swallow from last four days	1	5
				Difficulty in passing urine, seizures-generalized type since one day	1	5
Carbamazepine	CNS	5	29.4	Dizziness	3	17.64
				Seizures	1	5.88
				Convulsions	1	5.88
	Skin	3	17.64	lesions on the face, chest, back (upper and lower limbs) since four days, erosions in oral mucosa and genitalia since four days	3	17.64
	Gastro	3	17.64	Abdominal pain	1	5.88
				Diarrohea	1	5.88
				fever for six days, pain in the abdomen since six days and, decreased appetite, nausea for two days	1	5.88
	Liver	3	17.64	Hepatitis	2	11.76
				Jaundice	1	5.88
	Others	3	17.64	Nystagmus	2	11.76
				Hypoxia	1	5.88
Valproic acid	Liver	2	66.66	Hepatitis	2	66.66
	Others	1	33.33	Altered sensorium involuntary movements.	1	33.33

Table 3: Types of changes done in the treatment

Drug	*Drug withdrawal*	*Percentage*	*Drug altered*	*Percentage*	*No change*	*Percentage*
Phenytoin	10	25	2	5	8	20
Carbamazepine	6	15	2	5	9	22.5
Valproic acid	0	0	1	2.5	2	2.5

Table 4: Classification of ADR's based on the scales

Based on	*Naranjo's scale*	*Percentage*	*WHO scale*	*Percentage*
Probable	17	42.5	27	67.5
Possible	23	57.5	11	27.5
Conditional	0	0	02	5

Table 5: Classification of rechallenging and dechallenging based on WHO scale

	Yes	*Percentage*	*No*	*Percentage*
Rechallenging	2	5	38	95
Dechallenging	17	42.5	23	57.5

Table 6: Classification of predictable and non-predictable based on WHO scale

	Patients	*Percentage*
Predictable	30	75
Not predictable	10	25

Table 7: Classification of definitely preventable and probably preventable based on WHO scale

	No of patients	*Percentage*
Definitely preventable	3	7.5
Probably preventable	28	70

Table 8: Total number of patient's outcome

	No of patients	*Percentage*
Recovered	21	52.5
Recovering	6	15
Continuing	10	25
Unknown	3	7.5

Table 9: Classification of severity of reaction

	No. of patients	*Percentage*
1st Level	10	25
2nd Level	17	42.5
3rd Level	8	20
4th Level	5	12.5

developed ADRs. The average weight of the patients was 34.68 (mean).

Antiepileptic drugs which developed 40 ADRs in 40 patients, were distributed

Among 40 patients 20 (50%) patients developed ADRs due to phenytoin,17 (42.5%) due to carbamazepine, 2 (5%) due to valproic acid and 1 (2.5%) due to sodium valproate (Table 1).

Pattern of experiencing ADR

Among 40 patients, 20 (100%) patients developed ADR's due to phenytoin where 10 (50%) developed symptoms related to CNS system , 4 (20%) related to CVS, 3 (15%) related to eye, 3 (15%) related to other systems, 17 (100%) patients due to carbamazepine where 5 (29.4%) developed symptoms related to CNS system , 3(17.64%) related to skin, 3 (17.64%) related to gastro, 3 (17.64%) related to liver, 3 (17.64%) related to other systems, 3 (17.64%) patients due to valproic acid where 2 (66.66%) are related to liver, 1 (33.33%) patient developed due to other system. In 20 (50%) patients developed ADR's due to phenytoin where 3 (15%) developed symptoms of giddiness, 2 (10%) developed dizziness, 1 (5%) developed psychosis, 1(5%) developed vomiting, 1(5%) developed dystonia, 1 (5%) developed ataxia, 3 (15%) developed thrombophlebitis, 1(5%) developed thrombocytopenia, 2 (10%) developed nystagmus, 1(5%) developed abdominal pain, 1(5%) developed rashes all over the body, 1 (5%) developed difficulty in urine. For 17 (100%) patients developed ADRs due to carbamazepine where 3(17.64%) developed dizziness, 1(5.88%) developed seizures, 1 (5.88%) suffered with convulsions, 3 (17.64%) suffered from lesions all over the face and chest, 1 (5.88%) suffered with abdominal pain, 1 (5.88%) developed diarrhea, 1 (5.88%) developed fever, decreased appetite, 2 (11.76%) developed hepatitis, 1 (5.88%) developed jaundice, 2 (11.76%) developed nystagmus, 1 (5.88%) developed hypoxia, 3 (17.64%) patients developed ADR's due to valproic acid where 2 (66.66%) developed hepatitis, 1 (33.33%) developed altered sensorium (Table 2).

Management of ADRs

Among 40 patients (100%), 10 patients (25%) have withdrawn the drug phenytoin, two patients (5%) have altered drug phenytoin, eight patients (20%) did not change the drug. In six patients (15%) have withdrawn the drug carbamazepine, two patients (5%) have altered the drug, 9 patients (22.5%) did not change the drug. 1pt (2.5%) have altered the drug valproic acid, two patients (5%) did not change the drug (Table 3).

Assessment of ADR

Among 40 patients (100%), 17 patients (42.5%) fall under the category probable, 23 patients (57.5%) fall under the category possible. Based on WHO scale 27 patients (67.5%) fall under the category probable, 11 patients (27.5%) fall under possible, 2 patients (5%) fall under conditional (Table 4).

Among 40 patients, 2 patients (5%) have rechallenged the drugs, 38 patients (95%) have not rechallenged, for 17 patients (42.5%) have dechallenged the drugs, 23 patients (57.5%) have not dechallenged (Table 5).

Predictable ADR

Among 40 patients, 30 patients (75%) ADRs are predictable, 10 patients (25%) are not predictable (Table 6).

Table 10: Treatment for ADR reaction

Drug	*Symptomatic*	*Percentage*	*Specific*	*Percentage*	*Nil*	*Percentage*
Phenytoin	11	27.5	1	2.5	8	20
Carbamazepine	4	10	6	15	7	17.5
Valproic acid	1	2.5	0	0	2	5

Preventable ADR

Among 40 patients, 3 patients (7.5%) ADRs are definitely preventable, 28 patients (70%) are probably preventable (Table 7).

Outcome

Among 40 patients, 21 patients (52.5%) have recovered, 6 patients (15%) are recovering, 10 patients (25%) are continuing, 3 patients (7.5%) are unknown about income (Table 8).

Severity

Among 40 patients, 10 patients (25%) are in level 1 severity, 17 patients (42.5%) are in level 2, 8 patients (20%) are in level 3, 5 patients (12.5%) are in level 4 (Table 9).

Treatment

Among 40 patients, 11 patients (27.5%) are given symptomatic treatment for phenytoin-induced ADR, 1 pt (2.5%) are given specific treatment, 8 patients (20%) did not receive any treatment. four patients (10%) received symptomatic treatment for carbamazepine-induced ADR, 6 patients (15%) are given specific treatment, 7 patients (17.5%) did not receive any treatment. 1 pt (2.5%) was given symptomatic treatment for valproic acid, and 2 patients (5%) were not treated (Table 10).

DISCUSSION

Phenytoin has been associated with skin eruptions in 5 to 10% of patients. Considered to arise from a cell-mediated hypersensitivity-type reaction, which is variable in severity and resolves upon discontinuation of the drug.[10] Nystagmus: Phenytoin has caused dose-related nystagmus where eye movement changes when a head position changes. It is generally a gaze-evoked nystagmus, causing a horizontal jerky nystagmus on lateral gaze, but it can have a vertical direction.[11] Seizures are characteristic of an unusual type of phenytoin toxicity referred to as phenytoin encephalopathy, characterized by increasing seizures, electroencephalogram (EEG) changes, alteration in mental function, and certain motor and sensory disturbances.[12] It is usually associated with toxic doses (but may appear in patients on usual doses) and is generally reversible upon discontinuation of phenytoin.[13] Carmazepime: Dizziness: One of the most commonly reported adverse reactions.

CONCLUSION

Sodium valproate shows relatively less ADRs (2.5%) when compared with other antiepileptics. Phenytoin shows the highest number of ADRs (50%), among which CNS-related ADRs were more as 75% of those ADRs were predictable clinical pharmacist can play crucial role in early identification and prevention of these ADRs due to antiepileptic drugs.

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