EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 4
Issue: 2
277-280
Year: 2017

COMPARISON OF PHENYTOIN AND VALPROATE FOR THE MANAGEMENT OF SEIZURES

Ishvar Parmar[1], Harsh Chapadia[2], Chaitanya Patel[3], Aditi Amin[4], Amr Atassi[5], Milisha Lal[6], Rono Korra[7], Bhargav Muppaneni[8], Kranthi Sunkara[9], Rumana Tokaria[10], Hitesh Talreja[11], Sapan Shah[12], Abhishek Vadher*[13]

[1]Consulting Physician, Nataraj Hospital.
[2]Physician, Chapadia Medical Center.
[3]Medical student, Jacksonpark Medical Center.
[4]Medical Graduate, Yogi Medical Care.
[5]Medical student, Chicago Lakeshore Hospital.
[6]Physician, Bharati Vidyapeeth Hospital.
[7]Observer, Griffin Memorial Hospital.
[8]Extern, Chicago Lakeshore Hospital.
[9]Observer, Promise Health Care.
[10]Clinical research associate, Tampa General Hospital.
[11]Extern, Chicago Lakeshore Hospital.
[12]Medical Graduate, Medical College, Baroda.
[13]Medical Officer, Shreeji Hospital, Baroda.

***Corresponding Author: Abhishek Vadher**
Medical Officer, Shreeji Hospital, Baroda.

Article Received on 16/12/2016 **Article Revised on 06/01/2017** **Article Accepted on 26/01/2017**

ABSTRACT
Aim: To compare the efficacy of Phenytoin and Valproate for the management of seizures. **Methods:** In this study, 50 patients were taken who were admitted to BJ medical in the department of Medicine from October 2013 to October 2015. We randomly selected 50 patients from all the patients with age >18 and admitted to BJ medical for seizures. Inclusion criteria were seizures of any kind and age >18 years. **Results:** After 1 month, out of 32 patients started on Valproate, 18 patients (56.25%) had no seizure while 11 patients (34.37%) had 1-2 seizures and 3 patient had >2 seizures. Out of 18 patients started on Phenytoin, 9 patient (50%) had no seizure while 6 patient (33.33%) patient had 1-2 seizure and 3 patient (16.66%) had >2 seizures. The p value calculated was 0.741. After 12 months, out of 24 patients on Valproate, 4 patients (16.66%) had no seizure while 12 patients (50%) had 1-2 seizures and 8 patients (33.33%) had >2 seizures. Out of 11 patients on Phenytoin, 3 patient (27.27%) had no seizure while 5 patient (45.45%) patient had 1-2 seizure and 3 patients (27.27%) had >2 seizures. The p value calculated was 0.967. **Conclusion:** There is no difference in the efficacy of Phenytoin and Valproate for the management of seizures.

KEYWORDS:

BACKGROUND
A seizure is a paroxysmal event due to abnormal excessive or synchronous neuronal activity in the brain. Important modality of seizure treatment is its prevention with medications. In this study we attempted to compare the efficacy of the two most common anti-epileptic medications, Phenytoin and Valproate. Both medications are listed on the World Health Organization Model List of Essential Medicines, which includes the most important medications needed to provide care in a basic health system. Phenytoin and Valproate are available both in oral form and in intravenous form. In this study we followed patients who are on oral formulation. Phenytoin and Valproate are less expensive medications than other anti-epileptic therapy and therefore associated with better medication compliance.

AIMS
In this study, we attempted to compare the outcomes of Phenytoin and Valproate at the end of 1 month and 12 months period of seizure treatment.

METHODS
In this study, 50 patients were taken who were admitted to BJ medical in the department of Medicine from October 2013 to October 2015. We randomly selected 50

patients from all the patients with age >18 and admitted to BJ medical for seizures. Inclusion criteria were seizures of any kind and age >18 years. Seizures were diagnosed by proper history and physical examination in conjunction with neuroimaging and EEG studies. Patients were followed up for a period of 1 year. At 1 month, the compliance was 100% and we were able to examine all of the patients. At 12 months, 8 patients from the Valproate group and 7 patients in the Phenytoin group were lost for follow up.

RESULTS

TABLE-1: NEW ONSET SEIZURE AND SEIZURE DURING THERAPY

Seizures	No. of patients	Percentage
New onset	33	66%
Seizure during therapy	17	34%
Total	50	100%

As per Table 1, among 50 patients, 66% of patients had new onset seizure and 34% of patients experienced seizure during therapy.

TABLE-2: SEIZURE DURING THERAPY

Seizures	No. of patients	Percentage
Non-compliant	10	20%
Inadequate therapeutic Response	7	14%

As per Table 2, among those 34% of patients who had seizure during therapy, 20% of the patients were non-compliant with the treatment while 14% of patients portrayed an inadequate therapeutic response.

TABLE-3: ANTI-EPILEPTIC DRUGS PRESCRIBED AMONG STUDY POPULATION

Antiepileptic therapy	No. of patient treated	Percentage
Valproate	32	64%
Phenytoin	18	36%
Total	50	100%

In our study, 32 patients (64%) were prescribed Valproate and 18 patients (36%) were prescribed Phenytoin as the treatment drug of choice.

TABLE-4: RECURRENCE RATE OF SEIZURES AT 1 MONTH PERIOD

Antiepileptic therapy	0 SEIZURES	1-2 SEIZURES	> 2 SEIZURES	P VALUE
Valproate	18/32 (56.25%)	11/32 (34.37%)	3/32 (9.37%)	0.741
Phenytoin	9/18 (50%)	6/18 (33.33%)	3/18(16.66%)	

As per Table 4, after 1 month, out of 32 patients started on Valproate, 18 patients (56.25%) did not experience any seizure during therapy while 11 patients (34.37%) had 1-2 seizures and 3 patients had >2 seizures. Of 18 patients started on Phenytoin, 9 patients (50%) did not experience any seizure while 6 patients (33.33%) had 1-2 seizures and 3 patients (16.66%) had >2 seizures. The p value calculated was 0.741. The therapeutic levels of Valproate and Phenytoin were defined as >50mcg/ml and >10mcg/ml respectively. All 32 patients on Valproate and all 18 patients on Phenytoin had their levels above the defined therapeutic index.

TABLE-5: RECURRENCE RATE OF SEIZURES AT 12 MONTHS PERIOD

Antiepileptic therapy	0 SEIZURES/ month	1-2 SEIZURES/ month	>2 SEIZURES/ month	P VALUE
Valproate	4/24(16.66%)	12/24(50%)	8/24(33.33%)	0.967
Phenytoin	3/11(27.27%)	5/11(45.45%)	3/11(27.27%)	

As per Table 5, after 12 months, out of 24 patients on Valproate, 4 patients (16.66%) had no seizure while 12 patients (50%) had 1-2 seizures and 8 patients (33.33%) had >2 seizures. Out of 11 patients on Phenytoin, 3 patient (27.27%) had no seizure while 5 patient (45.45%) patient had 1-2 seizure and 3 patients (27.27%) had >2 seizures. The p value calculated was 0.967.

DISCUSSION

Phenytoin is useful for the prevention of tonic-clonic seizures, partial seizures, but not absence seizures. The intravenous form is used for status epilepticus. Drug pharmacokinetics of Phenytoin includes oral bioavailability (70-100%), 95% protein bound, metabolism through the liver, and a biological half-life of 10-22 hours. A small increase in dose may lead to a large increase in drug concentration as elimination becomes saturated. Due to a narrow therapeutic index (10-20µg/mL) of Phenytoin, monitoring of phenytoin plasma level is necessary. Mechanism of action of Phenytoin is believed to protect against seizures as the drug causes a voltage-dependent block of voltage gated sodium channels. This resultantly blocks sustained high frequency repetitive firing of action potentials. This is accomplished by reducing the amplitude of sodium-dependent action potentials through enhancing steady state inactivation. Sodium channels exist in three main conformations: the resting state, the open state, and the inactive state. Phenytoin binds preferentially to the inactive form of the sodium channel. Because it takes time for the bound drug to dissociate from the inactive channel, there is a time dependent block of the channel. Since the fraction of inactive channels is increased by membrane depolarization as well as by repetitive firing, the binding to the inactive state by phenytoin sodium can produce voltage-dependent, use-dependent and time-dependent block of sodium-dependent action potentials.

Phenytoin is an inducer of the CYP3A4 and CYP2C19 families of the P450 enzyme responsible for the liver's degradation of various drugs.

Side effects of Phenytoin include nausea, stomach pain, appetite loss or decrease in appetite, poor coordination, increase of hair growth, and enlargement of the gums. Potentially serious side effects include excessive sleepiness, self-harm, liver problems, bone marrow suppression, low blood pressure, and toxic epidermal necrolysis. There is evidence that use during pregnancy results in abnormalities in the baby. It appears to be safe to use when breastfeeding.

Valproate possesses a broad spectrum of anticonvulsant activity, although it is primarily used as a first-line treatment for tonic-clonic seizures, absence seizures and myoclonic seizures and as a second-line treatment for partial seizures and infantile spasms. Valproate has also been successfully given intravenously to treat status epilepticus. Drug pharmacokinetics include rapid absorption, 80-90% protein bound, hepatic metabolism through glucuronide conjugation (30-50%), mitochondrial beta-oxidation (over 40%), biological half-life 9-16 hours. Mechanism of action is induced reduction in phosphatidylinositol (3,4,5)-trisphosphate (PIP3) as a potential therapeutic mechanism. In addition, its anticonvulsant effect has been attributed to the blockade of voltage-dependent sodium channels and increased brain levels of gamma-aminobutyric acid (GABA). Valproate inhibits CYP2C9, glucuronyl transferase and epoxide hydrolase and is highly protein bound and hence may interact with drugs that are substrates for any of these enzymes or are highly protein bound themselves.

Side effects include nausea, drowsiness, dizziness, vomiting and weakness. Potential serious side effects include bleeding, low blood platelets, encephalopathy, suicidal behavior and thoughts, low body temperature, hepatotoxicity, pancreatitis and fetal abnormalities.

Our study shows comparison of Phenytoin and Valproate for the management of seizures in a total of 50 patients. All of the patients were > 18 years of age. Out of these 50 patients, 33 patients (66%) had new onset of seizure and 17 patients (34%) had seizure during ongoing therapy. Of the 17 patients who had seizure during treatment, 10 patients (20%) were non-compliant with the medication of choice and 7 patients (14%) revealed inadequate therapeutic response. Valproate was started among 32 patients (64%) and 18 (36%) patients were started on Phenytoin. At the end of a period of one month of treatment, of 32 patients started on Valproate, 18 patients (56.25%) experienced no seizure while 11 patients (34.37%) had 1-2 seizures and 3 patients had >2 seizures. Out of 18 patients started on Phenytoin, 9 patients (50%) were seizure-free while 6 patients (33.33%) had 1-2 seizures and 3 patients (16.66%) had >2 seizures. (p value = 0.741). At 12 months follow up, 8 patients from the Valproate group and 7 patients in the Phenytoin group were lost for follow up. Out of 24 patients on Valproate, 4 patients (16.66%) had no seizure while 12 patients (50%) experienced 1-2 seizures and 8 patients (33.33%) had >2 seizures. Of 11 patients on Phenytoin, 3 patients (27.27%) had no seizure while 5 patients (45.45%) had 1-2 seizures and 3 patients (27.27%) had >2 seizures. (p value = 0.967). This data shows that there is no statistical difference between the two drugs, Phenytoin and Valproate, for the management of seizures at the end of 1 month and 12 months of a treatment period.

CONCLUSION

There is no difference in the efficacy of Phenytoin and Valproate for the management of seizures.

LIMITATIONS OF STUDY

This study only had 50 patients. In order to be more conclusive, one needs more patients in the study.

REFERENCES

1. "Phenytoin". The American Society of Health-System Pharmacists. Retrieved Aug 22, 2015.
2. Lippincott's Modern Pharmacology with Clinical Applications pg no: 377 5th Edition.
3. Dilantin. (2015). In MIMS. Retrieved from https://www.mims.com/Hongkong/drug/info/Dilantin/?type=full#Actions.

4. Rossi, S, ed. (2013). Australian Medicines Handbook (2013 ed.). Adelaide: The Australian Medicines Handbook Unit Trust.
5. Olsen KB, Taubøll E, Gjerstad L (2007). "Valproate is an effective, well-tolerated drug for treatment of status epilepticus/serial attacks in adults".
6. Kwan SY (2010). "The role of intravenous valproate in convulsive status epilepticus in the future".
7. Chang P, Walker MC, Williams RS (2014). "Seizure-induced reduction in PIP3 levels contributes to seizure-activity and is rescued by valproic acid";.