



Original Research Article

A Study of the Adverse Drug Effect Profile of Phenytoin in A Tertiary Hospital in North East India

Authors

Indrani Bhagawati, Bhaskarjyoti Thakuria*

Department of Pharmacology, Fakhruddin Ali Ahmed Medical College & Hospital, Barpeta, Assam, India

*Email: bhaskarthakuria4u@gmail.com

Abstract

Introduction: Epilepsy is a chronic neurological disorder characterized by recurrent seizures of cerebral origin which have been known to inflict mankind since ancient times. The seizure nearly always correlates with an abnormal EEG discharge. Epilepsy continues to be one of the commonest disorders seen in neurology clinics all over the world. Hence the antiepileptic drugs are the most abundantly prescribed drugs by the neurologist and phenytoin being the most effective, it is widely prescribed as first line drugs in spite of many newer antiepileptics. Unfortunately phenytoin has a wide spectrum of adverse effects ranging from being reversible effect to severe life threatening conditions. Objective: The objective of the current study is to analyze and evaluate the adverse effects of phenytoin in the Neurology department in a tertiary care teaching hospital in North East India.

Methodology: This study was a prospective observational study on patients in the neurology department. A random once weekly data collection was done for a period of 1 year. Patients of all ages and both sexes were included in the study. Informed consent was obtained verbally from the patient's legal guardian. Every patient was examined clinically and their side effects were detected. Patient related information and drug related information (like dose, dosage form, route of administration) was recorded on a data collection sheet. The data obtained was analysed and presented with appropriate statistical methods.

Results: Most common adverse effects of phenytoin observed in the study were gum hyperplasia (24%), dermatological changes comprising skin pigmentation, coarsening of facial features and hirsutism, CNS related ataxia, nystagmus and cerebellar involvement (20%).

Keywords: epilepsy, phenytoin, adverse drug effects, prospective study, gum hyperplasia.

INTRODUCTION & BACKGROUND

Epilepsy is defined as a chronic neurological disorder characterized by recurrent seizures of cerebral origin, presenting with episodes of sensory, motor or autonomic phenomenon with or without loss of consciousness^[1]. It demands immediate medical attention and often long term therapy. The incidence is approximately 0.3-0.5% in different

world populations with a prevalence rate of five to ten thousand people. The overall aim in treating epilepsy should be the complete control of seizures, without causing any untoward reaction due to medication. A large number of drugs are currently available for the treatment of epilepsy. Despite the tremendous advances in the management of epilepsy and even with the development of newer

antiepileptic drugs, phenytoin still remains the drug of choice. Older, conventional drugs like phenytoin, carbamazepine, valproic acid and ethosuximide are commonly used as first line drugs. They are relatively less expensive than newer drugs like gabapentin, lamotrigine, vigabatrin, etc. which have lesser adverse effects and have fewer drug interactions^{[2],[3]}. Unfortunately a first line drug like phenytoin has a number of adverse effects.

AIM

The present study was designed to investigate the association of phenytoin with its various side effects and also to correlate the side effects with the drug dosage and with the serum level of the drug.

MATERIALS AND METHODS

The present study was carried out in a tertiary care teaching hospital of north east India in a 2 year period.

A total of 200 cases who presented with epilepsy and were under the treatment of antiepileptic drugs were included in the study. Out of these 50 patients had developed side effects to the drugs and were studied. The cases were collected from the Department of Neurology in a tertiary care teaching hospital in north east India. Mentally ill patients and pregnant women were left out of the study.

A diagnosis of the side effects of the selected antiepileptic drugs was obtained after a detailed history of the present illness, the past illness and the family history of each patient. The cases were then subjected to a thorough physical examination after which laboratory investigations were carried out. Besides a routine examination of blood, other investigations were also done accordingly and where necessary, other investigations were also carried out. Patient related and drug related information like dose, dosage form, dosing pattern, duration of treatment, route of administration will be recorded on a data collection sheet.

The article was sent to the Institutional Animal Ethics committee for approval and the number is FAAMCH/128/Pt./2017/1902.

For the purpose of study the following proforma was used:

Case _____ No. _____

Hospital No. _____

Name: _____

Age: _____

Address: _____

Occupation: _____

Date of Examination: _____

History of Presentation of Primary disease:-

1. Duration of Attacks: _____

2. Frequency of Seizures _____

3. Time of Attack: _____

4. Precipitating factors _____

5. Presence or absence of – a) Premonition b) Loss of Consciousness c) Type of seizures

6. Associated features _____

7. Post-ictal phenomenon _____

8. History- past, family, personal, menstrual and obstetric 9. Diagnosis 10. Antiepileptic drugs used-

name, generic, trade, total daily dose- single/divided, route, other drugs 11. Details of ADR- symptoms,

general examination, appearance, build. Nutrition, pallor, icterus, cyanosis, clubbing, skin, gum,

tongue, JVP, lymph node, pulse, BP.

Systemic examination:

CNS: Higher examination _____ Cranial nerves

Motor _____ Sensory

Reflexes _____ Gait

Examination of cranium and spine

Sign of raised ICT

CVS: _____

RESP: _____

GIT: _____

Investigation:

1. BLOOD: TC _____ DLC _____ ESR _____ HB _____

_____ Sugar _____ Urea _____

Creatinine _____

2. X-ray: PA view Chest, AP & Lat. Skull, CT Scan, Angiogram

3. Other investigations (where indicated)

CSF _____ LFT _____ RFT _____

CT _____ BT _____

4. EEG

5. DRUG LEVELS

After onset of ADR

DISCUSSION

A seizure is a paroxysmal event due to abnormal, excessive, hypersynchronous discharges from an aggregate of CNS neurons. Epilepsy describes a condition in which a person has recurrent seizures due to a chronic, underlying process. Antiepileptic drug therapy is the mainstay of treatment for most patients with epilepsy. The overall goal is to completely prevent seizures without causing any untoward side effects, preferably with a single medication and a dosing schedule that is easy for the patient to follow. Unfortunately no anti-epileptic drug is completely safe and a wide spectrum of adverse effect is seen with these drugs. The severity of these adverse effects ranges from minimal impairment of the CNS to death from aplastic anemia.

In this study adverse effects of phenytoin were observed and then correlated with its serum level. A total of 50 cases who had presented in the neurology department in tertiary care hospital of north east India and had developed adverse reactions to it were studied.

Distribution of cases: Out of the 50 cases, 30 were males and 20 were females. This reflects a male: female ratio of 3:2.

Most of the patients who had presented with ADR were suffering from primary epilepsy (30%), other significant diseases included neurocysticercosis (20%), tuberculoma (8%), & intracerebral tumours or secondaries (6%). There were 2 cases each of trigeminal neuralgia & post traumatic epilepsy and 1 case each of post encephalitic seizure and AV malformation. 22% of the cases were comprised of cerebrovascular accident patients and in some of these antiepileptic drugs were given prophylactically.

Adverse Drug Reactions

The most common long term side effects of Phenytoin observed in this study were Gum Hyperplasia (24%) and dermatological changes

comprising skin pigmentation, coarsening of the facial features and hirsutism (24%) and Central Nervous System related effects comprising Ataxia, Nystagmus and Cerebellar involvement (22%). The mean time of detection of Gum Hyperplasia was 2 years after starting the drug which occurred at a dose of 300 mg/day in 3 patients and 200 mg/day in 3 patients. Bilateral cerebellar signs were observed after a mean time of 2 ½ years. The dermatological changes also occurred after a mean period of drug ingestion of 2 and ¼ years. Thus the side effects are probably due to the cumulative effect of the drug. One patient developed nystagmus with the dose of 200 mg/day after 6 months of therapy. Other long term side effects include megaloblastic anaemia in 3 patients after a mean time of 2 years of therapy, lymphadenopathy in 3 cases after 1½ years of therapy. There was one interesting case of peripheral sensory motor neuropathy in a patient who had been taking Phenytoin 200 mg/day for 3 years. Two short term side effects were observed for phenytoin. A morbilliform rash with itching was observed in 5 patients after an average of 16 days of therapy. Five patient developed hypersensitivity syndrome with fever, rash and lymphadenopathy after 4 weeks of therapy which reverted after stopping the drug.

Table I showing the ADRs related to phenytoin

	PHENYTOIN ADR	Number of cases	Mean time of detection after starting drug	Dose	
				300	200
A	Gum hyperplasia	12	2 years	7	5
B	Nystagmus without other cerebellar s/s	4	6 months	3	1
C	Cerebellar symptoms and signs (bilateral)	7	2 ½ years	3	4
D	Anaemia (megaloblastic)	3	2 ½ years	2	1
E	Steven Johnson syndrome	2	3 ½ weeks	1	1
F1	Maculopapular rash	5	16 days	3	2
F2	Pigmentation, hirsutism	7	2 ¼ years	2	5
G	Neuropathy	2	3 years	1	1
H	Lymphadenopathy	3	1 ½ years	1	2
I	Hypersensitivity syndrome	5	4 weeks	1	4

Table II showing the various side effect of Phenytoin and the corresponding drug levels

	Side effect	Number of cases	Mean drug level (µg/ml)
A	Gum hyperplasia	12	16
B	Nystagmus	4	24
C	Cerebellar s/s	7	20
D	Megaloblastic anemia	3	18
E	Steven Johnson syndrome	2	10
F1	Maculopapular rash	5	11
F2	Pigmentation	7	14
G	Neuropathy	2	20
H	Lymphadenopathy	3	14
I	Hypersensitivity syndrome	5	12

Schlienger (1998) reported that the hypersensitivity syndrome occurs approximately in 1 in 3000 exposures usually within first 2-8 weeks after initiation of therapy [4]. Hamer & Morris (1999) have described the hypersensitivity syndrome in patients on conventional anticonvulsants, but not after new anticonvulsant drugs like Gabapentin or Topiramate [5]. Two cases of Stevens–Johnson syndrome was observed after 3 & ½ weeks of therapy, one of which proved fatal.

Monitoring serum concentrations of antiepileptic drugs has become a routine practice especially in patients on phenytoin therapy because of dose related toxicity and poor seizure control in mentally retarded patients in whom assessment of toxicity may be difficult, and pregnant patients [6]. Phenytoin has a non-linear relationship between the dose and the serum concentration [7] and a dose related neurotoxicity. This results in a narrow therapeutic window and monitoring is necessary to avoid neurotoxicity. This results in a narrow therapeutic window and monitoring is necessary to avoid neurotoxicity in patients who continue to have seizures. In this study, the serum levels of the offending drug was measured in all cases who presented with adverse drug reactions and an attempt was made to correlate the serum levels of the drug with the side effect seen.

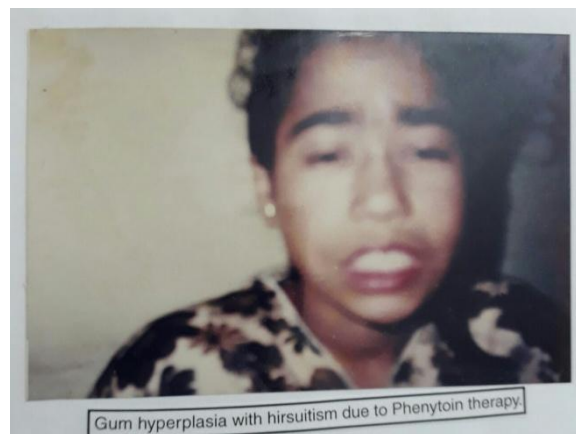


Figure I showing gum hyperplasia and hirsutism due to phenytoin therapy



Figure II showing Steven Johnson syndrome due to Phenytoin

The dose related side effects of phenytoin are reported to be drowsiness, unsteadiness, slurred speech, abnormal movement disorders and impaired cognitive functions while gum hyperplasia, pigmentation, hirsutism and coarsening to be due to chronic toxicity of the drug.

In this study bilateral cerebellar symptoms and signs as well as isolated nystagmus was seen at drug levels of 20 µg/ml 24 µg/ml. Since the therapeutic serum levels of phenytoin is 10-20 µg/ml, these values emphasize the importance of serum level monitoring in patients on phenytoin therapy. The risk of nystagmus has been reported to be increased beyond levels of 20 µg/ml and that of ataxia and other cerebellar manifestation beyond serum levels of 30 µg/ml. Significantly diminished mental capacity is seen at levels beyond 40 µg/ml. Thus phenytoin is especially likely to result in a dose related toxicity.

The chronic toxic effects of phenytoin observed in this study were gum hyperplasia, pigmentation of skin, coarsening of facial features, hirsutism and folate deficiency anemia. These effects are seen even with normal therapeutic levels of the drug in serum and this was observed in the present study. The mean serum levels of phenytoin in patients with chronic dermatological features, gum hyperplasia, megaloblastic anemia and neuropathy were 14µg/ml, 16µg/ml, 18µg/ml and 20µg/ml respectively. The allergic manifestations of phenytoin were also observed at normal serum therapeutic ranges of the drugs. For example, the maculopapular rashes were seen at levels of 11µg/ml, hypersensitivity syndrome at 10 µg/ml. These reactions are probably due to an autoimmune reaction and are not related to the concentration of drug in the serum.

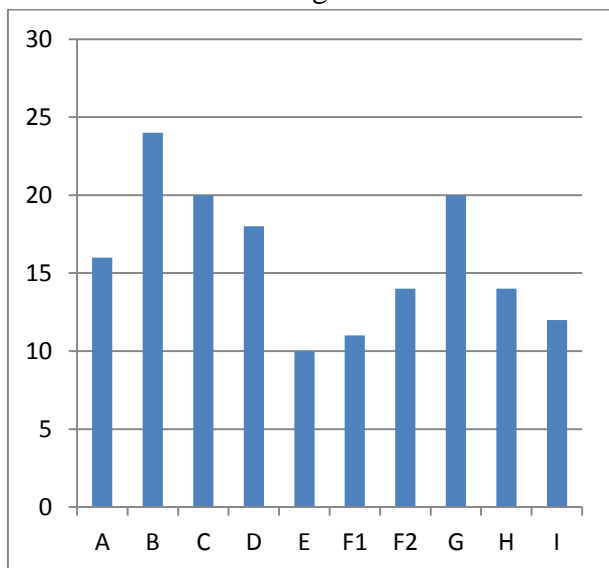


Figure III shows the adverse drug effects related to Phenytoin correlated with the drug level

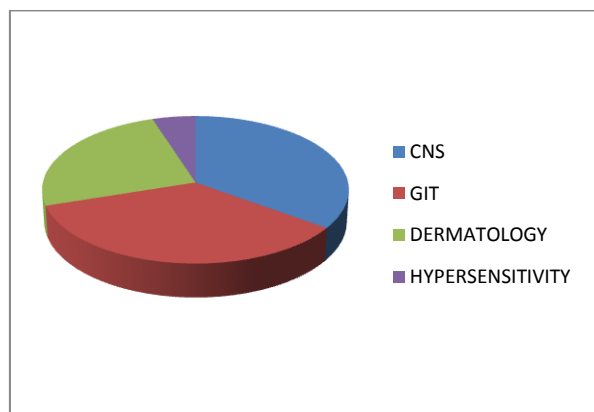


Figure IV shows the distribution of adverse drug effects related to phenytoin

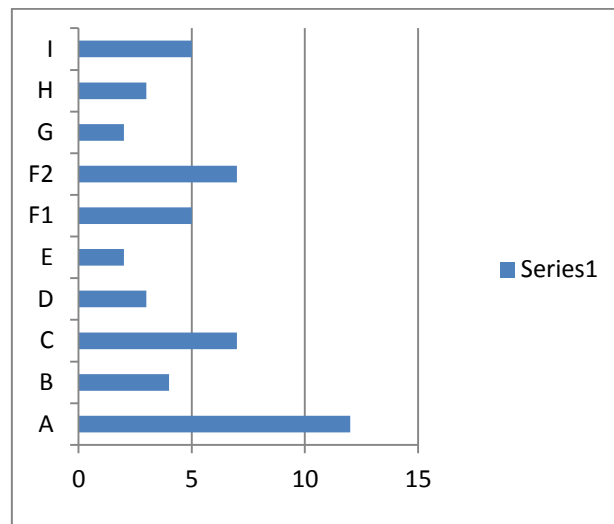


Figure V shows the distribution of adverse drug effects of Phenytoin correlated with the number of cases

SUMMARY

This study described cases of adverse drug reactions due to phenytoin. After eliciting detailed history and clinical examination the cases were subjected to laboratory investigations like routine blood, EEG, CT scans and the serum levels of the offending drug. The male: female ratio of the cases was 3:2.

The most common long term side effects observed were gum hyperplasia (38%) and dermatological features like hirsutism, coarsening of facial features and pigmentation (24%). Two cases of folate deficiency megaloblastic anemia and one case of peripheral neuropathy were seen. These patients were receiving doses of 200-300 mg/ day for a mean time of 2-3 years. The dose related side effects of phenytoin seen in the study were ataxia with other bilateral cerebellar signs (20%) and one case of isolated nystagmus. Acute allergic reactions to phenytoin such as maculopapular rash (20%), hypersensitivity syndrome (1 case), Stevens-Johnson syndrome (2 cases) and lymphadenopathy (3 cases) were observed in the study. These patients were also receiving conventional doses of 200-300 mg/day.

The serum levels of phenytoin was estimated and it was found that toxic CNS manifestations like nystagmus and cerebellar signs were observed at serum levels of 20-24 µg/ml. However, the chronic toxic effects of phenytoin like gum hyperplasia,

pigmentation, hirsutism, etc. were seen at levels of 14-16 µg/ml which falls in the normal therapeutic range. Allergic manifestations like Stevens-Johnson & maculopapular rash were seen at levels of 10-11 µg/ml.

CONCLUSION

Though this was a limited study of the adverse drug reactions of phenytoin, an antiepileptic drug, a wide range of possible side effects of these drugs were highlighted. This study revealed the common patterns of adverse drug reactions seen on short and long term therapy with phenytoin.

The side effects observed in the study were similar to those described in other studies. Moreover this study showed the importance of monitoring the serum levels of the drug in patients on chronic antiepileptic drug therapy.

The major limitation of the study was the lack of sophisticated laboratory facilities for more frequent drug level monitoring. Ideally drug levels after manifestation of toxic effects should have been compared with the serum levels of the drug before appearance of these toxic manifestations.

Further study involving a larger number of cases of adverse drug reactions to the above mentioned antiepileptic drugs is necessary for a more meaningful and statistically relevant interpretation of this common problem facing epileptic patients who require long term drug therapy.

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