e- ISSN 0976-0342
Print ISSN 2229-7456

International Journal of Pharmacy & Therapeutics

Journal homepage: www.ijptjournal.com

Research article

A CASE STUDY ON PHENYTOIN INDUCED CEREBELLAR DEGENERATION IN EPILEPSY

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ABSTRACT

Phenytoin is an anticonvulsant which is extensively used in controlling generalized tonic-clonic seizures as well as simple and complex partial seizures. Phenytoin acts mainly by prolonging the inactivated state of sodium channel, thereby extending refractory period of neurons and also limiting the repetitive firing of action potentials. Bioavailability of phenytoin varies widely in terms of pharmacokinetic variability. Consequently, the narrow therapeutic window of phenytoin frequently causes adverse effects as well as toxicity. Phenytoin when given at higher doses is associated with various vestibular and cerebellar side effects like motor ataxia, muscle spasms, psychoses and visual disturbances. Long term use of phenytoin at therapeutic and toxic levels can lead to Epilepsy. However, phenytoin-induced cerebellar syndrome is reversible with timely withdrawal of medication. Regular monitoring of plasma concentrations, accurate dosing, and medication adherence to treatment regimens are very important. Here, we report a case of phenytoin-induced Epilepsy presenting with behavioral abnormalities, paraparesis and visual impairment. The patient's condition improved by gradually tapering the dose, followed by termination of phenytoin therapy and substitution with carbamazepine. This report emphasizes on the importance of regular monitoring of plasma drug concentration, accurate dosing of drugs having a narrow therapeutic index, and identification of noncompliance in patients treated with phenytoin.

Key Words :- Phenytoin, Cerebellar Syndrome, Epilepsy, Adverse Drug Reaction.

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Received:05.02.2021 **Revised**:12.02.2021 **Accepted**:25.02.2021

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INTRODUCTION

Phenytoin is widely used for treating generalized and partial seizures due to its stabilizing influence on neuronal membrane. Phenytoin acts mainly by prolonging the inactivated state of voltage activated sodium channels and thus governs the refractory period of neurons. Five to tenfold higher doses of phenytoin is expected to reduce the calcium influx, inhibit glutamate and facilitate γ-aminobutyric acid (GABA) responses. These effects also underlie toxicity associated with the higher serum levels of phenytoin (Shanmugarajah PD, *et al*., 2018; Hardman JG *et al*., 1996).

Three factors which govern the pharmacokinetic features of phenytoin; the extent of protein binding, non-linear elimination kinetics, its ultimate metabolism by liver. Generally up to 90% of the administered phenytoin is protein bound which exists as distinction between the total and free plasma levels of phenytoin. Even small variations in protein binding can drastically alter the amount of free drug in the serum. Phenytoin is metabolized mostly in liver by cytochrome P450 isoforms (Kuruvilla T, *et al*, 1997; McNamara JO, *et al*., 2004).

CASE REPORT

A female patient aged 21 years experiencing weakness of lower limbs since 3 months difficulty to walk. Insidious in onset gradually progressed associated with difficulty in walking. Had k/c/o epilepsy detected following on accident in 2012. Patient is on regular medication, Phenytoin -100mg. The patient's family history was insignificant with respect to her condition.

Patient Had:

History of unable to hold urine present, numbness of limbs present but no history of vomiting, headache. Patient also had history of Epilepsy since 2012 on Rx (Medications).

On examination patient had:

CNS: B/L pupils-NSRL, Finger nose tip+, Nystagamus+, Angle of deviation of mouth to Right side. B/L plantars-Extensors, Nystagamus+, Uvula deviated to Left side Past pointing+, Gum hypertrophy+, Dysdiadochokinesia, Hypertrichosis+

OTHER INVESTIGATIONS:

Computed Tomography (CT-Scan): Cerebellar Atrophy (Phenytoin Induced), Magnetic Resonance Imaging (MRI)Scan-Mild Diffuse Cerebellar Atrophy was done.

SYSTEMIC EXAMINATION:

SYSTEM	Day 1-Day 10
CVS	S1S2+
R.S	B/L NVBS
P/A	Soft

GENERAL EXAMINATION:

VITALS	Day1	D2	Day3	D4	D5	D6	D7	D8	D9	D10
BP(mmHg)	110/70	110/70	110/60	100/60	110/70	110/70	110/70	110/80	110/70	110/70
PR(bpm)	94	92	96	96	94	96	92	94	96	96

LAB INVESTIGATION REPORT:

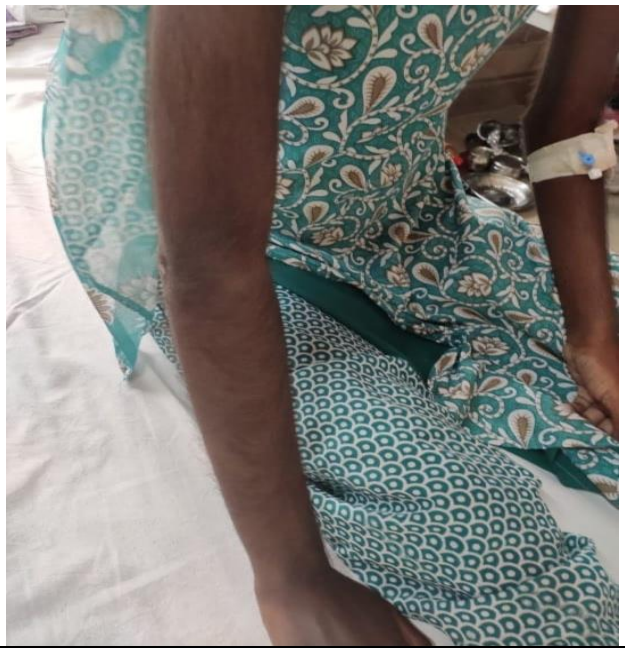
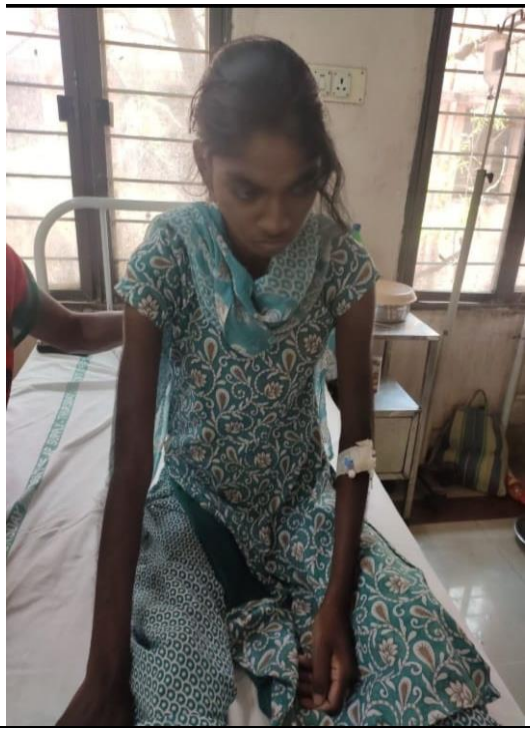
PARAMETER	LAB VALUES	REFERENCE RANGE
Hb	12g/dl	12-14g/dl
WBC	7,600cumm	4,500-11,000cumm
PLT	1.5 lakhs/cumm	1.5lakhs-4.5lakhs/cumm

DRUG CHART:

Drugs	Dose	ROA	Frequency	Duration
T.PHENYTOIN	100mg	PO	BD	(Day 1)/ D1
T.LEVITERACETAM	500mg	PO	BD	D1-D6
T.IFA	100mg	PO	OD	D1-D10
Inj.Optineuron	1 amp in 100ml NS	IV	-	D1-D10
T.Vit C	-	PO	OD	D1-D10
Inj.Ondansetron	4mg	IV	OD	D1-D10
Inj.Pantoprazole	40mg	IV	OD	D1-D10
T.SODIUM VALPROATE	50mg	PO	BD	D6-D10

FINAL DIAGNOSIS:

Epilepsy with phenytoin induced cerebellar degeneration. The patient's behavioral abnormalities started to worsen on the fifth day of admission and was diagnosed with PHENYTOIN induced hypertrichosis, gum hypertrohy and cerebellar atrophy. The MRI scan of the brain showed cerebellar atrophy, which may be due to the high doses of phenytoin. The MRI scan of the brain and the spinal cord however revealed no residual compression or edema. Patient had a complaint of constipation and vomiting after usage of Tab. IFA. So Tab. IFA was stopped on D6. The patient was also referred to a psychiatrist who suggested the possibility of phenytoin toxicity. The patient's serum phenytoin level was found to be 41.6 µg/ml, which lies outside the therapeutic range of phenytoin (10-20 µg/ml). The patient was advised to take carbamazepine following the initial tapering of doses and ultimate cessation of phenytoin therapy. A similar diagnosis was made by the ophthalmologist following the consultation for the complaints of diminished vision. Patient's phenytoin dose was tapered from and gradually stopped. Patient was simultaneously treated with Carbamazepine (200mg/day). The condition of the patient improved symptomatically and was discharged after five days. The patient was asked to consult the neurologist a week after discharge from the hospital. The patient is now stable and did not experience any episodes of seizure or abnormal gait after the discharge.

GUM HYPERTROPHY	HYPERTRICHOSIS
	
	

DISCUSSION

Phenytoin, being a popular anticonvulsant widely used for both generalized and partial seizures, is generally considered safe. The pharmacokinetics of phenytoin follow a non-linear path i.e. the rate of elimination varies as a function of concentration. At very low plasma levels, the elimination follows first order kinetics (Chadwick D, *et al*., 1976). However, in the therapeutic range, only a small proportion of the drug is metabolized because of saturation of enzymatic pathways. Above the therapeutic range, even a small increase in the dose can markedly elevate the plasma concentration as well as the half-life of phenytoin. This shift from first order to zero order kinetics occurs

unpredictably (Brostoff JM, *et al*., 2008). At plasma concentrations of 10µg/ml, the plasma half-life of phenytoin ranges between 6 to 24 h, which however may vary with higher concentrations. Normally, approximately 90% of the circulating phenytoin is bound to albumin, whereas the therapeutic free phenytoin levels are 1-2µg/ml. The inappropriate absorption of phenytoin into cells which leads to undesirable side effects, is largely from the free plasma pool. Individuals with decreased protein binding may show clinical toxicity even at normal level total phenytoin in blood plasma. However, such individuals have an elevated free phenytoin level. Thus, the measurement of free drug concentration in the serum can be a useful aid in the assessment of phenytoin toxicity (McLain LW, *et al*, 1980).

Phenytoin has a potential to cause various adverse effects, at both therapeutic and toxic doses. Many dose-based adverse drug reactions have been reported for phenytoin, among which sedation, gum hypertrophy and hirsutism are the most common ADRs at therapeutic doses. Cerebellar and vestibular toxicity, which manifest as dizziness, ataxia and nystagmus, have been reported at therapeutic doses as well as when the serum drug levels are above the therapeutic range. (Lüders H, *et al*, 1998).
The plasma drug concentration rises disproportionately, when the dose of phenytoin is increased. Thus, the plasma concentration of phenytoin can rise from sub therapeutic level to toxic levels even with small increase dose. Therefore, accurate dosing and maintenance of correct levels of phenytoin in serum are of prime importance to prevent toxicity (William McLain Jr, L., J., 1980).

In the present case study, the patient showed symptoms of PHENYTOIN induced hypertrichosis, gum hypertrohy and cerebellar atrophy. The serum phenytoin concentration of the patient was 41.6 µg/ml. These transient neurotoxic and ophthalmic side effects have been reported to occur during first few hour of drug intake. However there is no definite correlation of serum levels of phenytoin with neurological features of toxicity. Toxic adverse effects of phenytoin may also develop at various therapeutic doses. The correlation between serum level of anti-epileptic drugs, and their side effects has always been unpredictable.The casualty assessment of the adverse event of the patient in the present study scored 8 on the Naranjo scale, which definitely indicates a probable adverse drug reaction (Ghatak NR, *et al*, 1976; Luef G, *et al*, 1994).

CONCLUSION

Phenytoin is generally considered safe for use to control seizures and is extensively used in the treatment of all types of partial and Grand mal seizures. However, the patient in this case study started recovering steadily after the drug was withdrawn. Hence, regular monitoring of adverse drug reaction should be considered in patients undergoing phenytoin therapy on long term basis. These adverse effects are acute or chronic in nature. As most of these effects are reversible on cessation of therapy, early identification and appropriate management of adverse drug reactions are of prime importance. The present study also emphasizes on the importance of regular monitoring of plasma drug concentration, accurate dosing of drugs having a narrow therapeutic index, and identification of noncompliance in patients treated with phenytoin.

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Cite this article:
A Case Study On Phenytoin Induced Cerebellar Degeneration In Epilepsy. *International Journal of Pharmacy & Therapeutics*, 12(1), 2021,7-11.