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Phenytoin Induced Irritable & Hyperactive Behaviour

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Abstract: Phenytoin is an Anticonvulsant mainly acts by promoting Na+ efflux or decreases Na+ influx from membranes in motor cortex neurons; stabilizes the neuronal membrane. Slows conduction velocity.Indicated in Seizures. A child of 12 years old of female patient came to pediatrics department with chief complaints of seizures not associated with fever. Generalised tonic clonic activity with loss of consciousness for 10 min and admitted in pediatrics department-II and his treatment chart was phenytoin 100mg PO OD and valproic acid 200mg – 200 mg – 200 mg Po 2tablets TID. During his second day of treatment child developed fever of 1020F and cough and to reduce the condition physician prescribed paracetamol 500mg Po BD and syrup chlorpheneramine maleate 5ml Po BD and increased the phenytoin dose 100 mg 2 tablets OD. On the 12th day of treatment child was irritable with hyperactive behaviour. Better vigilance is necessary for implementation of safe and effective treatment for each individual patient.in order to prevent serious adverse drug reactions of this drug, close monitoring drug treatment course, creating awareness, recognition of the problem and careful management of all the patients who receive medication are essential, because use of phenytoin causes Drowsiness, Fatigue, Ataxia, Irritability, Headache, Restlessness, Slurred speech, Nervousness, Nystagmus, Dizziness, Vertigo, Dysarthria, Paresthesia, Rash, Pruritus, Gingival hyperplasia (pediatric patients), Ataxia, Paradoxical seizure, Drug withdrawal seizure, Diplopia, Psychosis (high dose), Toxic amblyopia, Encephalopathy, AV conduction disorder, Ventricular fibrillation, Nausea, Vomiting, Constipation, Diarrhea, Megaloblastic (folate-deficiency) anemia, Hypocalcemia, Hepatotoxicity, Hypertrichosis, Lymphadenopathy, Purple glove syndrome, Rash, Allergic reactions in the form of rash or, rarely, more serious forms (drug reaction with eosinophilia and systemic symptoms, or DRESS) or anaphylaxis, Purpuric rash, Toxic epidermal necrolysis, Bullous dermatosis, Coarsening of facial features,Periarteritis nodosa,Immunoglobulin abnormalities, Altered taste sensation, including metallic taste, Peyronie disease

Keywords: Volume of distribution, blood pressure, pulse rate, respiratory rate.

INTRODUCTION

Phenytoin sodium is an anticonvulsant that is used to treat a wide variety of seizures. It is also an anti-arrhythmic and a muscle relaxant. The mechanism of therapeutic action is not clear, although several cellular actions have been described, including effects on ion channels, active transport, and general membrane stabilization. The mechanism of its muscle relaxant effect appears to involve a reduction in the sensitivity of muscle spindles to stretch. Phenytoin has been proposed for several other therapeutic uses, but its use has been limited by its many adverse effects and interactions with other drugs.

Phenytoin Sodium is the sodium salt form of phenytoin, a hydantoin derivate and non-sedative antiepileptic agent with anticonvulsant activity. Phenytoin sodium promotes sodium efflux from neurons located in the motor cortex, thereby stabilizing the neuron and inhibiting synaptic transmission. This leads to a reduction in posttetanic potentiation at synapses, an inhibition of repetitive firing of action potentials and ultimately inhibits the spread of seizure activity.

Absorption & Bioavailability: May vary between different manufacturers; dependent on formulation. Onset: 1 week (PO); 2-24 hr (PO with loading dose); 0.5-1 hr (IV) Peak plasma time: 1.5-3 hr

(immediate-release); 4-12 hr (extended-release) Distribution via Protein bound: 95% (adults); 85% (infants); 80% (neonates) Vd: 0.6-0.7 L/kg (adults); 0.7 L/kg (children); 0.7-0.8 L/kg (infants); 0.8-0.9 L/kg (full-term neonate); 1-1.2 L/kg (premature neonate). Metabolized by hepatic P450 enzyme CYP2C9 Metabolites: Inactive, Enzymes induced: CYP3A4. Elimination Half-life: 22 hr (PO); 10-15 hr (IV). Excretion: Urine Pharmacogenomics HLA variants

- Patients with HLA-B*1502 with are more likely to have a severe dermatologic reaction (eg, toxic epidermal necrolysis, Stevens-Johnson syndrome) when taking phenytoin
- This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including Han Chinese, Filipinos, Malaysians, South Asian Indians, and Thais [1].

CASE REPORT

A child of 12 years old of female patient came to pediatrics department with chief complaints of seizures not associated with fever. Generalised tonic clonic activity with loss of consciousness for 10 min and admitted in pediatrics department-II and his treatment chart was phenytoin 100mg Po OD and valproic acid 200mg – 200 mg – 200 mg Po 2tablets TID. During his second day of treatment child developed fever of 102^0F, cough, fresh 2 episodes of seizures and to reduce the condition physician prescribed paracetamol 500mg Po BD and syrup chlorpheneramine maleate 5ml Po BD and increased the phenytoin dose 100 mg 2 tablets OD. On the 12^{th} day of treatment child was irritable with hyperactive behaviour. On general examination, patient was drowsy and coherent. On physical examination PR-84/min, RR:20/min, spo_2: 97% with RA, Resp: BAE+, CVS: $S_1 S_2$ +. On laboratory examination shows Hb: 8.5gm, total count:5, 6000, differential count:$P_{61}L_{51}E_3$, ESR:30, Platelets:30,000, sodium:138meq/lit, chlorides: 99meq/ lit, Potassium: 4.7 eq/lit, serum creatinine: 0.4mg/dl, widal test: < 1:20 dilutions, smear for MP : Negative, CT Scan: small hyper dense speck noted in the left basal ganglia (HV – 60) and treatment was phenytoin 100mg PO OD and valproic acid 200mg – 200 mg – 200 mg Po 2tablets TID. During his second day of treatment child developed fever of 102^0F and cough and to reduce the condition physician prescribed paracetamol 500mg Po BD and syrup chlorpheneramine maleate 5ml Po BD and increased the phenytoin dose 100 mg 2 tablets OD. On the 12^{th} day of treatment child was irritable with hyperactive behaviour. Patient was referred to physician of head of the department to confirm the ADR was due to phenytoin high dose. On analysis compared to all other drugs prescribed, phenytoin pharmacology and literature support the occurrence of irritability. In order to confirm the relationship between the effect and drug we have also done dechallenge test i.e. drug was withdrawn from treatment regimen, and reduced the dose of phenytoin 100 mg OD.

DISCUSSION

The symptoms experienced by the patient in question are understandable in terms of the complex pharmacokinetics, narrow therapeutic index and individual variability in the metabolism and elimination of phenytoin. The patient developed exaggerated side effects gradually over a period of 6 weeks after the dosage increase, which can be explained by the gradual build up of the drug over the time as the pharmacokinetics of phenytoin follows a nonlinear path changing from first order kinetics to zero order; hence, even minor dosage changes can result in variable concentrations as the elimination is saturated [2]. Furthermore the patient experienced episodic toxic effects about 2 to 2.5 hours after drug intake; peak plasma concentration is reached in 2.5 to 12 hours after the oral intake of phenytoin and even earlier peaks have been reported [3]. Previous research has reported these types of transient neurotoxic side effects as occurred in this case during the first few hours of drug ingestion due to excessive fluctuation in plasma concentration of phenytoin between intake and time to peak plasma concentration.

Table 1: causality assessment of suspected ADR

ADR scale	WHO – UMC	Naranjo's
Assessment	Probable	Probable

Table-2: Analysis of observed ADR

Severity assessment	Moderate level – 4(a)
Preventability	Probably preventable
Predictability	Type - A

During treatment course as a clinical pharmacist we have identified adverse drug reactions as follows, the patient was under the medication with Tab. phenytoin based upon the literature reviews and based on examination and other investigations we have concluded that this condition is due to the drug phenytoin and performed casuality assessment, severity, preventability, predicatability. After the identification we have immediately withdrawn the drug cefotaxime and provided appropriate treatment.

CONCLUSION

Better vigilance is necessary for implementation of safe and effective treatment for each

individual patient.in order to prevent serious adverse drug reactions of this drug, close monitoring drug treatment course, creating awareness, recognition of the problem and careful management of all the patients who receive medication are essential, because by use of phenytoin causes Fatigue, Ataxia, Irritability, Headache, Restlessness, Slurred speech, Nervousness, Nystagmus, Dizziness, Vertigo, Dysarthria, Paresthesia, Rash, Pruritus, Gingival hyperplasia (pediatric patients), Ataxia, Paradoxical seizure, Drug withdrawal seizure, Diplopia, Psychosis (high dose), Toxic amblyopia, Encephalopathy, AV conduction disorder, Ventricular fibrillation, Nausea.

Vomiting, Constipation, Diarrhea, Megaloblastic (folate-deficiency) anemia, Hypocalcemia, Hepatotoxicity, Hypertrichosis, Lymphadenopathy, Purple glove syndrome, Rash, Allergic reactions in the form of rash or, rarely, more serious forms (drug reaction with eosinophilia and systemic symptoms, or DRESS) or anaphylaxis, Purpuric rash, Toxic epidermal necrolysis, Bullous dermatosis, Coarsening of facial features, Periarteritis nodosa, Immunoglobulin abnormalities, Altered taste sensation, including metallic taste, Peyronie disease

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