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PHENYTOIN : AN Overview

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Abstract

Phenytoin is an antiepileptic drug, in this review article we reviewed about the detail about history , chemical formula , pharmacology, pharmacokinetic , clinical trial , uses , toxicology ,adverse effect , contraindication , dosage of phenytoin. It is use as anti seizure drug having narrow therapeutic index. Their is need therapeutic drug monitoring in case of phenytoin , so study of clinical toxicology , pharmacology of phenytoin is more important. In this article we added information regarding history and clinical trial of phenytoin. Phenytoin is most effective drug in case of epilepsy so our main focus on detail study of phenytoin .

Key words:- Antiepileptic drug, Anti seizure, Pharmacokinetic, TDM, Phenytoin.

INTRODUCTION

Phenytoin is an anti-epileptic medication derived from the chemical molecule hydantoin. [1]

For about eight decades, phenytoin, an anti-seizure medication, has been undergoing clinical trials.[2]

Strong anticonvulsant phenytoin, originally known as diphenylhydantoin, is used to treat and prevent status epilepticus, complex partial seizures, and grand mal seizures.[3]

Although phenytoin intoxication seldom results in death, it can produce a variety of neurologic symptoms, such as nystagmus, ataxia, and coma. Purple Glove Syndrome seldom complicates intravenous phenytoin delivery. [4]

It is no longer regarded as useful for the management of alcohol withdrawal or toxin-induced seizures, and it is ineffective in treating absence seizures. [5]

HISTORY

Professor Heinrich Biltz (1865–1943) created phenytoin (5,5-diphenylhydantoin) as a barbiturate derivative in Germany in 1908; an American chemist working for Parke-vis Pharmaceuticals resynthesised it in Detroit in 1923. Phenytoin was screened and found to have less sedative side effects than barbiturates; as a result, Parke-Davis dismissed the medicine as being of value. [6]

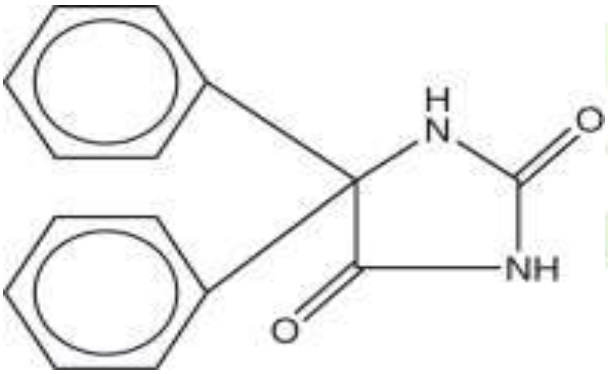
Tracy Putnam and H. Houston Merritt discovered in 1938 that phenytoin could be used to manage seizures without causing the drowsiness associated with phenobarbital, which highlighted the drug's extra utility (Merritt and Putnam, 1984). [7]

Goodman and Gilman's Pharmacological Basis of Therapeutics states that phenytoin was the result of a search among nonsedative structural relatives of phenobarbital for agents capable of suppressing electroshock convulsions in laboratory animals. This is in contrast to the earlier unintentional discovery of the antiseizure properties of bromide and phenobarbital. Although the FDA has never approved phenytoin for those uses, there are some signs that it has other effects, such as mood stabilization and anxiety reduction. [8]

CHEMICAL FORMULA:$C_{15}H_{12}N_2O_2$

Fig 1: Chemical structure of Phenytoin [9]

IUPAC NAME



The IUPAC system names this substance 5,5-diphenylhydantoin.

SYNONYMS

Diphenylhydantoin; DPH are synonyms.[10]

MECHANISM OF ACTION

Phenytoin, a hydantoin derivative, is an effective first-generation anti-convulsant drug that treats complex partial seizures, status epilepticus, and generalized tonic-clonic seizures without significantly impairing neurological function.

The blocking of voltage-dependent sodium channels in membranes that elevate action potential is the mechanism of action of phenytoin. This inhibits the spreading of the seizure focal site by obstructing the positive feedback that sustains high-frequency repetitive firing.[11]

Phenytoin, when taken as an antiarrhythmic, has many similarities to lidocaine. It lowers normal automaticity in Purkinje fibers, eliminates abnormal automaticity caused by digitalis intoxication, and has effects similar to lidocaine on re-entrant arrhythmias. It can repolarize aberrant, depolarized cells, diminish sympathetic nerve effects, and possibly alter parasympathetic nerve activity in digitalis poisoning. [12]

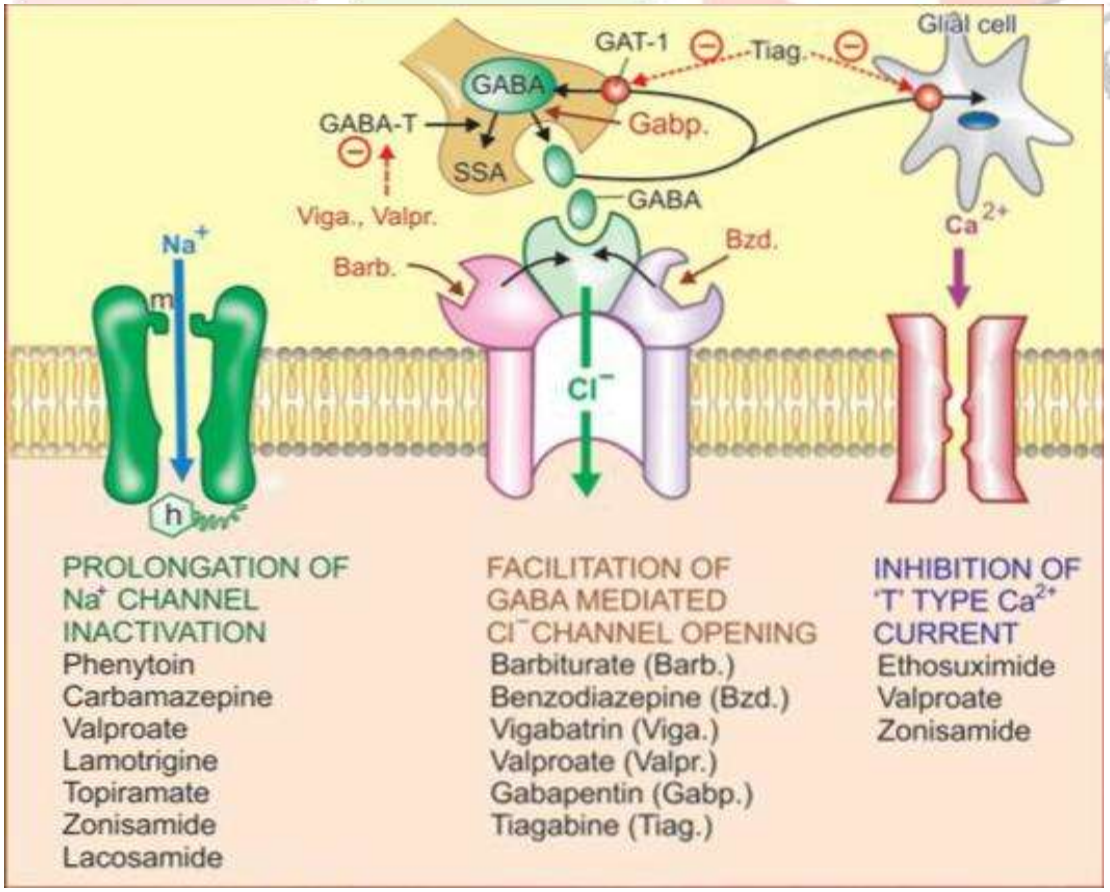
Administering phenytoin has been linked to harmful consequences. The dosage, duration, exposure, and mode of administration all affect phenytoin toxicity. The primary factor influencing toxicity is the mode of administration. It is possible to give phenytoin intravenously or orally. Furthermore, intramuscular administration of fosphenytoin, a water-soluble prodrug of phenytoin, is an option.[13]

A high dose of phenytoin suppresses the central nervous system, resulting in cerebellar dysfunction, dyskinesia, and peripheral neuropathy. Furthermore, phenytoin can cause gingival hyperplasia, generate pseudolymphomas and malignant lymphomas, and produce allergic reactions.[14]

Significant effects of phenytoin include decreased sodium and calcium ion transport in neurons, less repetitive firing, less excitement in the neural networks of the brainstem reticular formation, and a partial reduction in the effects of γ-aminobutyric acid (GABA), an inhibitory transmitter.[15]

Phenobarbital, benzodiazepines, and valproic acid altered SRF and postsynaptic GABA responses. Ethosuximide showed no effect on the SRF or GABAergic systems. Based on these findings, we hypothesize that phenytoin, carbamazepine, phenobarbital, valproic acid, and benzodiazepines work against generalized tonic-clonic seizures in humans and maximum electroshock seizures in animals by inhibiting SRF.[16]

Fig 2: Mechansim of Anticonvulsant action [17]



PHARMACOKINETICS

Phenytoin is completely absorbed at therapeutic dosages, peaking in plasma concentration between 1.5 to 3 hours. On the other hand, absorption usually lasts longer than two weeks in situations involving acute ingestions; this may be due to its effects on decreased gastrointestinal motility and poor water solubility.[18]

Following oral dosing, phenytoin (diphenylhydantoin) is nearly entirely absorbed and extensively processed by the liver. Because of the dose-dependent, “saturable” pharmacokinetics of hepatic metabolism, even within the therapeutic range of plasma concentrations, slight dose increases can lead to disproportionately larger increases in plasma concentration. This results in a very varied (range 7–60 h) and dose-dependent t½,elim. Being a strong inducer of enzymes, phenytoin might increase the clearance of other medications, which can cause interactions with them.[19]

It possesses characteristics that make it more likely to be involved in pharmacokinetic interactions, several of which have been documented. These characteristics include a non-linear clearance caused by saturable oxidative biotransformation, a sluggish rate of gastrointestinal absorption and poor water solubility, a relatively high degree of plasma protein binding, and the capacity to activate hepatic microsomal enzymes.[20]

1.ABSORPTION

When phenytoin is given as a suspension through a feeding tube for continuous enteral feedings, it is absorbed very slowly. The general medical literature seems to contain very little information on this potentially dangerous issue. Serum phenytoin levels at commonly used concentrations (300–500 mg/d) may be nearly undetectable. If the medication is administered in extremely large doses, therapeutic phenytoin levels can be reached. For our patient to achieve a blood phenytoin level of 9 µg/mL, 1800 mg per day was needed in two divided doses. A continuous infusion pump was being utilized to deliver commonly used enteral feedings. One enteral feeding product did not significantly hinder phenytoin absorption, as we discovered. The process through which enteral nutrition depletes phenytoin.[21]

Phenytoin (PHT) is an antiepileptic medication that is gastrointestinally absorbed. Its combination with co-administered enteral nutrition through a nasogastric (NG) tube might cause decreased plasma PHT levels. [22]

2.DISTRIBUTION

Phenytoin is typically 90% bound to plasma proteins (mostly albumin), with only the unbound form being pharmacologically active. Protein binding fractions may be reduced in newborns, pregnant individuals, hypoalbuminemia, and uremia. It is disseminated throughout all tissues and becomes firmly tissue-bound across a vast volume of distribution.

It Is found at higher amounts in the central nervous system than in serum.[23]

The medication is widely distributed (distribution volume = 0.8 L/kg) throughout the body. Phenytoin is highly (about 90%) attached to plasma and passes the blood-brain barrier with ease.[24]

3.METABOLISM

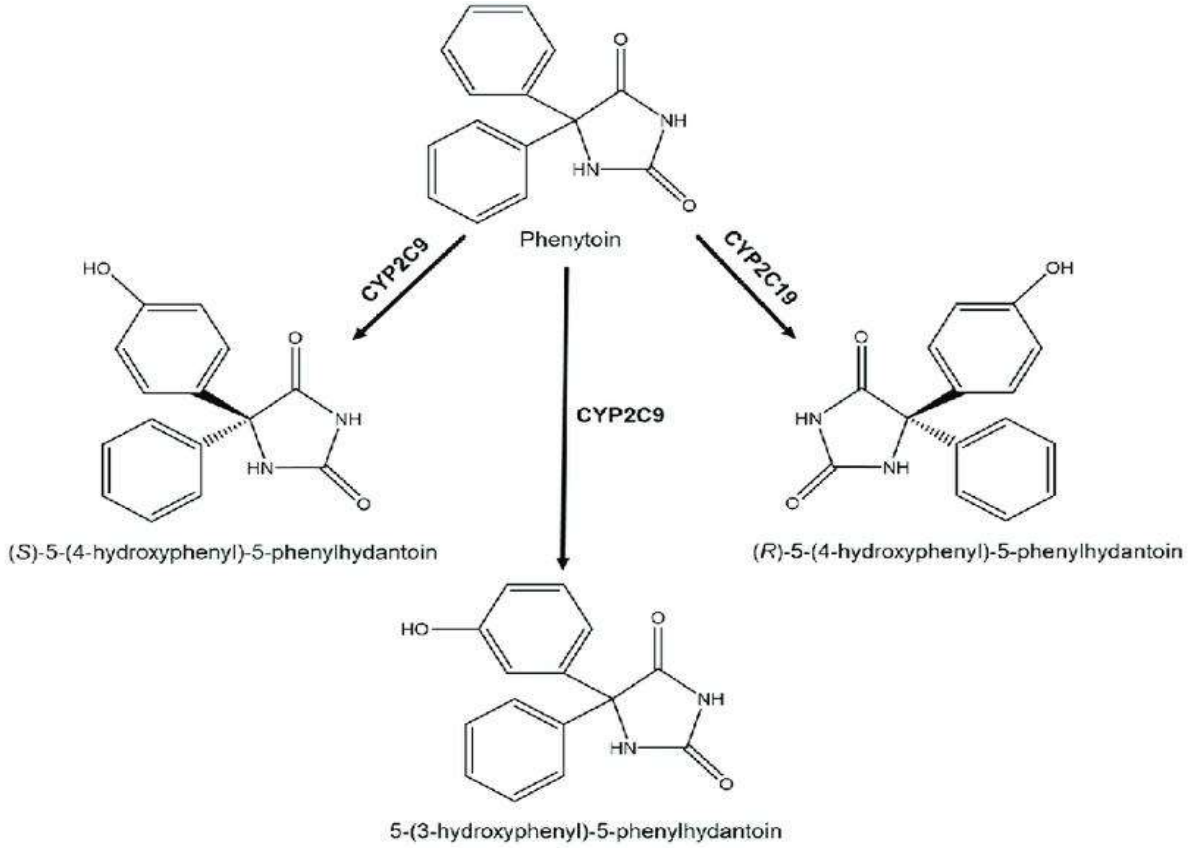
Phenytoin's primary metabolite, 5-(p-hydroxyphenyl)-5-(phenylhydantoin, is produced by a saturable metabolism, which results in a nonlinear dose-serum concentration relationship. As a result, the range of doses that individuals can take while maintaining a therapeutic serum concentration is limited, and tracking serum concentrations is especially important for dosage adjustment. Since phenytoin's binding to plasma proteins is decreased in renal failure, a smaller range of serum medication concentrations is appropriate for maintaining therapeutic management. Not only can binding be compromised in liver illness, but delayed metabolism can also happen. As pregnancy progresses, the serum levels may gradually decrease, most likely as a result of a faster metabolism. When phenytoin is introduced in pregnancy, it quickly crosses the placenta and is metabolized by the newborn.[25]

Phenytoin is metabolized by the hepatic P450 enzyme system (mostly CYP2C9 and CYP 2C19) to inactive metabolites. It also induces CYP3A4, which explains a large number of its drug-drug interactions.

Drugs that alter the function of these enzymes by either inducing or inhibiting phenytoin would require monitoring and possible medication adjustments to phenytoin based on resulting follow-up phenytoin levels. This is because the cytochrome P450 enzyme system is primarily responsible for the metabolism of phenytoin.

- Alcohol
- barbiturates,
- carbamazepine,
- theophylline,
- rifampin, and other drugs can cause the enzyme system to reduce plasma phenytoin concentrations.[26]

Fig 3: Metabolism of Phenytoin [27]



4.EXCRETION

Only 1% to 5% of the medication is eliminated unaltered in the urine. Elimination will follow first-order kinetics for plasma concentrations less than 10 mg/L; zero-order kinetics take over once the system becomes saturated with higher drug concentrations. Consequently, a substantial overdose can cause the typical average half-life of 22 hours to become noticeably prolonged.[28]

In humans, the predominant excretion form of the anticonvulsant drug phenytoin (5,5-diphenylhydantoin) is 5-(4'-hydroxyphenyl)-5-phenylhydantoin (4'-HPPH) O-glucuronide. We have previously shown that several UDP-glucuronosyltransferases (UGTs) of UGT1A1, UGT1A4, UGT1A6, and UGT1A9 catalyze the glucuronidation of 4'-HPPH. Since peroxidase has the ability to bioactivate 4'-HPPH into a reactive metabolite, glucuronidation is regarded as a detoxification route. [29]

CLINICAL TRIALS

- Postoperative epilepsy: a double-blind trial of phenytoin after craniotomy

Epilepsy was noted in 7.9% (8/101) of patients treated with phenytoin and in 16.7% (17/102) of patients receiving a placebo in a double-blind trial of phenytoin for the prevention of postoperative epilepsy in craniotomy patients. A considerable decrease in the incidence of epilepsy was linked to therapeutic medication levels. Within a month following cranial surgery, 75% of the fits happened. Following cranial surgery, patients with meningioma, aneurysm, and head trauma with or without intracranial clots have shown high rates of epilepsy; routine prophylactic therapy with phenytoin would seem to be needed in such patients.[30]

- Study on the Efficacy of Phenytoin in the Prophylaxis of Seizures of Patients With Pneumococcal Meningitis at Least 50 Yrs Old.

Background: Despite widespread advancements in treatment, the morbidity and fatality rate for bacterial meningitis remains high.

Seizures are one kind of complication that could raise the morbi-mortality. In clinical practice, preventive phenytoin is given to high-risk patients; nevertheless, the usage of this medication varies because controlled clinical trials showing its effectiveness in conjunction with antibiotics and corticosteroids have not been conducted. Particularly in older patients, pneumococcal bouts are linked to an increased frequency of seizures and a greater death rate.

Goals: To assess phenytoin prophylaxis's effectiveness in preventing seizures in patients with pneumococcal meningitis. Hypothesis: In individuals with pneumococcal meningitis older than 50 years, preventive phenytoin administration will lower the occurrence of seizures.

Methodology: Randomized, double blind, placebo-controlled, multicenter study. Patients are going to comprised primarily of hospitals from CAIBER and REIPI, and they were randomized to either a placebo or phenytoin.

An estimated 61 patients per group make up the sample size. All centers will use the same antibiotic therapy and ICP prevention. Throughout antimicrobial therapy, phenytoin administration will continue. Overall mortality will be the secondary end-point, with the incidence of seizures during hospital stays serving as the primary end-point. Follow-up appointments will be held after one and three months.[31]

- Carbamazepine vs Phenytoin: A Controlled Clinical Trial in Focal Motor and Generalized Epilepsy

In a double-blind crossover trial, individuals with primary and secondary generalized seizures as well as partial seizures accompanied by motor signs were studied to assess the antiepileptic effects of carbamazepine and phenytoin. Ten weeks comprised each therapy session. Doses were modified based on plasma levels, and the patients were reviewed every two weeks. The goal was to maintain the levels of phenytoin and carbamazepine within the ideal plasma ranges, which are 10 to 20 and 4 to 10 mg/liter, respectively. Out of the twenty-three patients who started the trial, 19 finished it. Regarding acute side effects and seizure management, there were no statistically significant differences between phenytoin and carbamazepine.[32]

Uses

Grand mal and psychomotor epilepsy are two conditions for which phenytoin, also known as diphenyl hydantoin or dilantin, is a highly effective and frequently used anticonvulsant medication. Phenytoin has been used to treat a variety of conditions, including gastrointestinal, endocrine, neuromuscular, cardiovascular, and thinking, mood,behavior disorders.

- In epileptic Condition

There are noticeable improvements in memory, focus, and calmness, as well as changes in personality and mental state. PHT displayed improvements in temperament, irritation, overall attitude, collaboration, attentiveness, and conduct. PHT has been shown to be helpful for children with epilepsy who exhibit hypermotility, irritability, and behavioral unpredictability. PHT shown a significant decrease in psychotic symptoms.[33]

Another member of class Ib antiarrhythmics, phenytoin , is used to treat cardiac arrhythmias, especially those brought on by intoxication with digitalis. A single intravenous injection given slowly at a consistent rate of no more than 50 mg/min is the standard dose, which is 3.5–5 mg/kg bw. If necessary, this dose may be repeated. Additionally, phenytoin has been used to treat people who are intolerant of carbamazepine or trigeminal neuralgia that is refractory to it.[34]

TOXICOLOGY

Phenytoin has a limited therapeutic range, and for many people, a total serum concentration above 80 μM is associated with clinically significant damage.

Phenytoin is normally eliminated via the kidneys after being metabolized by hepatic enzymes. However, hazardous buildup of phenytoin can occur in the context of renal failure.Haemodialysis does not remove phenytoin since it is 90% albumin bound.[35]

Phenytoin toxicity can occur as a result of intentional overdose, dosage changes, medication interactions, or physiological changes. Intoxication is characterized mostly by nausea and central nervous system dysfunction (especially disorientation, nystagmus, and ataxia), with depressed conscious state, coma, and seizures occurring in more severe cases. [36]

Phenytoin's metabolic route is a major contributor to its toxicity. In the liver, parahydroxylation is the main metabolic process, which is followed by glucoronic acid conjugation. At therapeutic dosages, the hydroxylating enzyme saturates, and at low concentrations, the metabolism exhibits first order kinetics before switching to zero order kinetics .At plasma concentrations less than 10 mcg/mL, the half-life of phenytoin is 6–24 hours; however, at larger concentrations, it increases, and at concentrations of about 20 μg/mL, hazardous symptoms including nystagmus appear. Reports of fatalities have been made at 50–70 μg/mL . Our patient had a phenytoin level of 144 μg/mL, which is significantly higher above the hazardous range. The patient was taking the recommended dosage three times.[37]

CARDIAC TOXICITY

Although it is seldom ever used as an antiarrhythmic these days, phenytoin is a Vaughn Williams Class IB antiarrhythmic. Dysrhythmias and SA and AV nodal blocks can result from its actions on the heart voltage-gated sodium channels, albeit these side effects have not often been documented after oral intake. It is thought that propylene glycol, the parenteral carrier, is the primary cause of toxicity in the intravenous version. Rapid infusions of propylene glycol, a cardiac depressant, can cause asystole, hypotension, and bradycardia. It is important to use caution when administering phenytoin intravenously at a rate greater than 50 mg per minute.[38]

NEUROTOXICITY

Serum phenytoin concentrations: "ataxia at about 25–30 [mg/L], disorientation and somnolence at greater than 35 [mg/L], nystagmus appearing at approximately 20 [mg/L]." Cerebellar dysfunction is characterized by ataxia, nystagmus, and tremor. Because of its non-linear pharmacokinetics, phenytoin dosage adjustments are challenging. Phenytoin toxicity can arise from a minor dose increase that causes an unforeseen substantial rise in plasma concentration. Most of the time, when phenytoin medication is discontinued or the dosage is lowered, cerebellar symptoms go away.[39]

The following is a generalized association between adverse effects and total plasma phenytoin concentrations (the value obtained by most laboratories):

- Below 10 mg/L: Rare side effects.
- 10 to 20 mg/L: Occasional mild horizontal nystagmus with lateral gaze
- 20–30 mg/L: Symptoms of nystagmus at 30-40 mg/L include ataxia, slurred speech, tremors, nausea and vomiting.
- 40-50 mg/L: lethargy, disorientation, hyperactivity
- More over 50 mg/L: coma and convulsions.

The neurotoxic effects vary in severity depending on the concentration and can include lethargy, vomiting, ataxia, slurred speech, moderate nystagmus, coma, and death.[40]

REPRODUCTIVE TOXICITY

Children whose mothers took phenytoin during pregnancy, either with or without other antiepileptic drugs, have been reported to have severe malformations like orofacial clefts and cardiac defects, as well as minor malformations like dysmorphic facial features and nail and digit hypoplasia; growth abnormalities and mental deficiency have also been reported. A bleeding problem associated with low levels of vitamin K-dependent clotting components may put some neonates at higher risk.[41]

ADVERSE EFFECTS

Phenytoin is a recognized treatment for acute repeated seizures and status epilepticus. One of its primary advantages over benzodiazepines is a lower sedative effect. However, the danger of cardiovascular side effects from intravenous phenytoin use has caused reluctance to use it, prompting a quest for safer anticonvulsant medicines. [42]

A sustained 50 mg/kg dose of phenytoin every eight hours raises the level of serum alkaline phosphatase. The liver cell size is enhanced with histological alterations. It seems that increased glycogen storage is the cause of this.[43]

Adverse effects could include the following:

1. Rash Sedation
2. Peripheral neuropathy
3. Phenytoin encephalopathy
4. Psychosis
5. Locomotors dysfunction.
6. Hyperkinesia
7. Megaloblastic anemia.
8. Reduced bone mineral content.
9. Stevens–Johnson syndrome
10. Toxic Epidermal Necrosis
11. Immunoglobulin A deficit
12. Gingival hyperplasia
13. Dress syndrome (drug response with eosinophilia and systemic symptoms).
14. Cardiovascular collapse.
15. Hypotension and arrhythmias
16. Hydantoin syndrome in infants.
17. Purple Glove Syndrome
18. Hypertrichosis[44]

Rapid phenytoin dosing may result in hypotension, bradycardia, and arrhythmias. Administer at less than 50 mg/kg/min.[45]

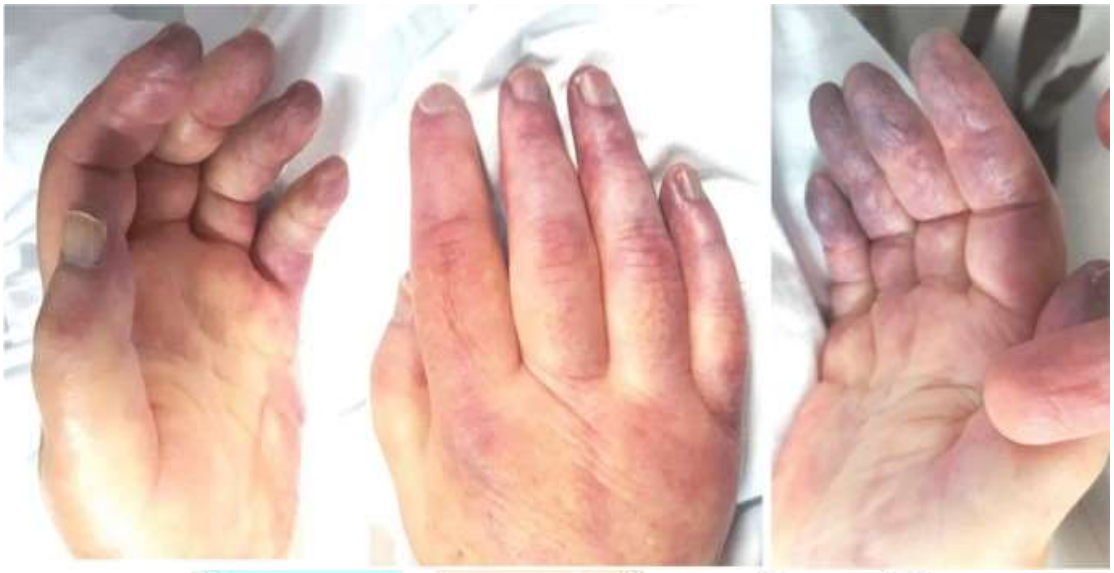
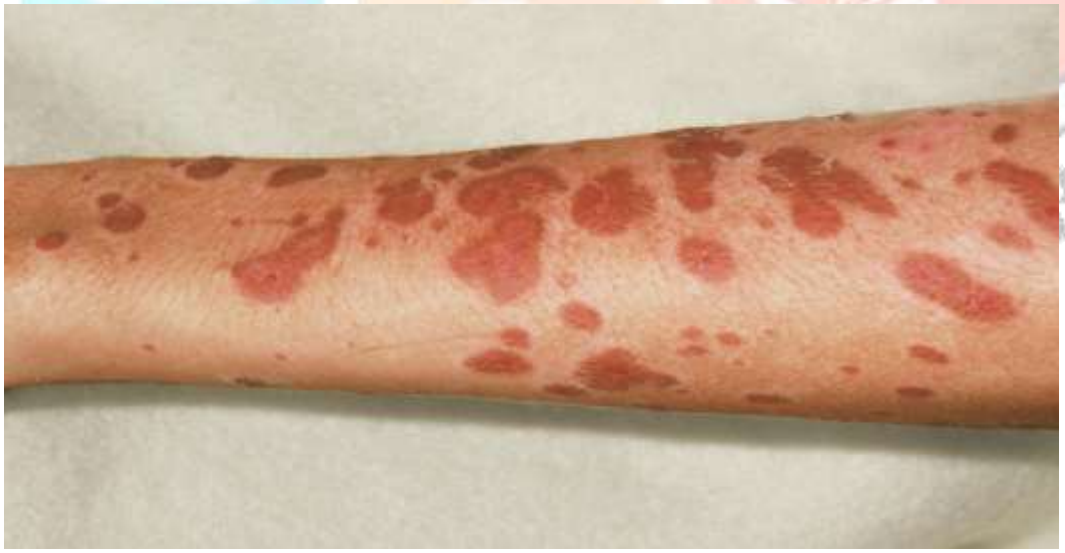


Fig 4 : Purple Glove Syndrome [46]

Fig 5: Stevens–Johnson syndrome [47]



CONTRAINDICATIONS

Individuals who are hypersensitive to hydantoins or phenytoin should not take phenytoin, and individuals who are hypersensitive to levetiracetam or any of its inactive constituents should not take levetiracetam.[48]

- During pregnancy, phenytoin crosses the placenta and causes congenital anomalies known as “fetal hydantoin syndrome,” which include deformed fingers, a large jaw, and wide-set eyes.
- Goes into lactation and produces breast milk
- There have been isolated reports of malignancies, including neuroblastomas.[49]

According to Hanson et al., 11% of pregnant women receiving phenytoin treatment for epilepsy also had fetal hydantoin syndrome (FHS). Moreover, 30% of children born during pregnancy displayed some of the symptoms of the syndrome, including epicanthic folds, hypertelorism, broad flat nasal bridges, an upturned nasal tip, wide prominent lips, distal digital hypoplasia, intrauterine growth retardation, and diminished mental capacity.[50]

AVAILABLE DIFFERENT FORMULATION

Minor formulation adjustments to the Dilantin capsules were announced by the manufacturer. Pre-mixed sucrose and maize starch were utilized in place of separate excipients in the 30 mg and 100 mg capsules due to the addition of lactose. Bioequivalence between the new and old formulations was demonstrated. During the transition, the manufacturer advised patients to be closely monitored. To attain the clinically effective serum total concentration of phenytoin of 10 to 20 mcg/mL, this involved monitoring phenytoin levels 7 to 10 days after beginning the new formulation and, if necessary, modifying the dose.

In 2018: 30 mg capsules of phenytoin were being taken by 1,096 people. A total of 3,855 individuals were using 100 mg capsules of phenytoin.[51]

BRAND	FORM.	PILL IMAGE
Dilantin Infatabs oral -	50 mg chewable tablet	
phenytoin oral -	100 mg/4 mL suspension	
phenytoin oral -	100 mg/4 mL suspension	
phenytoin oral -	125 mg/5 mL suspension	
phenytoin oral -	125 mg/5 mL suspension	
phenytoin oral -	50 mg chewable tablet	
phenytoin oral -	50 mg chewable tablet	
phenytoin oral -	50 mg chewable tablet	

Fig 6: Different formulation available in market [52]

ADULT DOSAGE

Capsule- immediate release

- 30mg
- 100mg

Capsule- extended release

- 100mg
- 200mg
- 300mg

Tablet – Chewable

- 50mg

Oral Suspension

- 125mg/5mL

Injectable solution

- 50mg/ml

Seizures

- Status epilepticus

Load 10-15 mg/kg or 15-20 mg/kg at 25-50 mg/min,

Maintenance: 100 mg IV/PO q6-8hr PRN

Administer IV slowly; not to exceed 50 mg/min

Anticonvulsant

- Tablet

100 mg PO TID

Maintenance: 300-400 mg/day; increase to 600 mg/day if necessary

May adjust dose no sooner than 7-10 day intervals when indicated

- Suspension

125 mg PO TID, initially

Increase to 625 mg/day if necessary

May adjust dose no sooner than 7-10 day intervals when indicated.

Extended release

Loading dose: 1 g divided into 3 doses (400, 300, 300 mg) administered at 2 hr intervals; initiate dosage 24 hr after loading dose.

Loading dose not for administration to patients with a history of renal or hepatic disease; reserve for patients who require rapid steady serum levels, when IV administration not desirable, and for patients in a clinic or hospital setting where phenytoin levels can be closely monitored.

Treatment (naïve): 100 mg PO TID initially.

May adjust dose no sooner than 7-10 day intervals.

Therapeutic range: 10-20 mcg/mL (total) or 1-2 mcg/mL free drug

Phenytoin.[53]

PEDIATRIC DOSAGE

Capsule, immediate- release

- 30mg
- 100mg

Capsule- extended release

- 100mg
- 200mg
- 300mg

Tablet

- 50mg

Oral suspension

- 125mg/5mL

Injectable solution

50mg/mL

Status epilepticus

15-20 mg/kg IV in single or divided dose; if necessary may administer additional dose of 5-10 mg/kg 10 min after loading dose.

Maintenance: 4-8 mg/kg/day IV divided twice daily.

Control of Tonic-Clonic and Complex Partial Seizures

- INITIAL DOSAGE

Neonates: 5 mg/kg/day in 2 divided doses.

6 months to 16 years: 5 mg/kg/day in 2-3 divided doses.

- NEONATES (<28 DAYS)

Initial: 5-8 mg/kg/day IV/PO divided q8-12hr

- AGE-BASED MAINTENANCE DOSE

6 months-4 years: Usual range, 8-10 mg/kg/day IV/PO divided two to three times daily.

4-7 years: Usual range, 7.5-9 mg/kg/day IV/PO divided two to three times daily.

7-10 years: Usual range, 7-8 mg/kg/day IV/PO divided two to three times daily.

10-16 years: Usual range, 6-7 mg/kg/day IV/PO divided two to three times daily.

Anticonvulsant (Nonemergent)

Children and adolescents

- IMMEDIATE RELEASE

Tablet and suspension

5 mg/kg/day PO in 2-3 divided doses, initially; may make dose adjustments no sooner than 7-10 day intervals.

Maintenance: 4-8 mg/kg/day PO; not to exceed 300 mg/day; higher doses may be considered in infant and young children (range: 8-10 mg/kg/day in divided doses).

- EXTENDED RELEASE

5 mg/kg/day PO, initially in 2-3 equally divided doses; may adjust dose no sooner than 7-10-day intervals.

Maintenance: 4-8 mg/kg/day PO not to exceed 300 mg/day.

Dosing Considerations

<6 years: Potential toxic dose, 20 mg/kg

Therapeutic range: 10-20 mcg/mL (total) or 1-2 mcg/mL free drug.

ALWAYS administer IV slowly; not to exceed 1-3 mg/kg/min

Phenytoin.[54]

CONCLUSION

The effects of genetic variation on plasma drug levels and metabolism have been investigated in both healthy populations and epileptic patients. The pharmacokinetics of phenytoin have also been comparatively well-studied. Less research has been done, nevertheless, to determine how these changes in metabolism impact ADRs, medication response, and resistance. Studies examining various variations and haplotypes and their consequences in well-defined populations are required, ideally focusing solely on phenytoin.[55]

Phenytoin is an anti-epileptic medication derived from the chemical molecule hydantoin. Phenytoin is an antiepileptic medication used to treat seizures in patients with epilepsy. Phenytoin acts by targeting and inhibiting voltage-gated sodium channels in the nervous system, reducing the aberrant electrical activity in the brain that leads to seizures.[56]

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