

# Current Practice of Phenytoin - Revisited

*Running title: Phenytoin revisited*

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## ABSTRACT

Phenytoin is one the most widely used antiepileptic drug among other antiepileptic drugs and is one of the vital medication for basic health system. Phenytoin has been used not only for convulsive but also for nonconvulsive treatment like arrhythmia, trigeminal neuralgia, digoxin toxicity, wound healing and in other disease conditions. With the wide range of usage of phenytoin, it has a collection of adverse effects and drug-drug interactions. In order to improve the quality of life of the patients using phenytoin, a current knowledge on phenytoin prescribing is essential. Similarly, information of pharmacogenetics of phenytoin is important to identify the specific gene related particular adverse effects. Therefore, the objectives of the proposed issue are to provide an in-depth picture of the recent practice and principles of phenytoin use, identify adverse effects and possible ways to overcome them.

**Keywords:** Adverse effects, Drug-drug interaction, Genetic variations, Mode of action, Phenytoin, Pharmacokinetics

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## 1. BRIEF INTRODUCTION ON PHENYTOIN

With oral and parenteral administration, phenytoin is a hydantoin anticonvulsant which was first synthesized in 1908 [1], but it was first discovered by Merritt and Putnam in 1937 for the anticonvulsant properties. It is used in a wide variety of seizures [2, 3] and also in nonconvulsing conditions like antiarrhythmic [4], neuropathic pain [5] etc. Its mechanism of action is not clear yet. With several other therapeutic uses, it has many adverse effects and interactions with other drugs. This is the first antiepileptic drug which has no sedative action where sedation is necessary for anticonvulsant activity [6].

**Group:** (NO3) antiepileptics (NO3A BO2) Hydantoin derivatives.

**Generic name:** 5,5-Dwufenylohydantoina, 5,5-diphenylhydantoin, DPH, Dihydantoin, Diphenylan Sodium, Diphenyl hydantoin, Diphenylhydantoin, Phenytoin Sodium, Phenytoine etc.

**Trade name:** Aleviatin, Antisacer, Auranile, Causoin, Citrullamon, Comital, Convul, Danten, Dantinal, Dantoinal, Denyl, Di-Hydan, Di-Lan, Di-Phetine, Dilantin, Dilantin acid, Dilantin-125, Dintoin etc.

## 2. PHYSICAL AND CHEMICAL CHARACTERISTICS OF PHENYTOIN

### Physical characteristics

Phenytoin is white in colour, odourless and tasteless, available as solid-crystalline and solid-powder form. It is soluble in water but insoluble in chloroform, in ether and in methylene chloride. Its melting point is 295-298<sup>o</sup> C [7, 8]. On exposure to air it gradually absorbs carbon dioxide (CO<sub>2</sub>). Phenytoin may cause precipitation when mixed with other drugs. Therefore, it is not recommended to add it with infusion solution [7].

### Chemical characteristics:

Molecular formula: C<sub>15</sub> H<sub>12</sub> N<sub>2</sub> O<sub>2</sub>. Molecular weight is 252.3.

### 3. HOW PHENYTOIN ACTS: GENERAL AND MOLECULAR ASPECTS

#### General action:

In general, phenytoin acts on the neurons of the epileptic area to prevent the spread of the seizure discharge and suppressing paroxysmal electrical activity. To prevent seizure propagation, phenytoin first blocks posttetanic potentiation which is the augmentation of postsynaptic action potentials evoked by repetitive presynaptic potentiation without any significant effect on the normal metabolic and physiologic activity of the central nervous system (CNS) [7, 9].

#### Mechanism of action at molecular level:

- 1. Stimulation of Na<sup>+</sup>, K<sup>+</sup> pump:** It is highly believed that there are huge imbalances between Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>++</sup> and Cl<sup>-</sup> ions during seizure or paroxysmal epileptic activity. Then, phenytoin firstly stimulates Na<sup>+</sup>, K<sup>+</sup> pump which is adenosine triphosphate-dependant ionic membrane pump to balance these ions to prevent seizures. The stimulated Na<sup>+</sup>, K<sup>+</sup> membrane pump extrudes extra Na<sup>+</sup> and Ca<sup>++</sup> from intracellular compartment and moves K<sup>+</sup> back to the intracellular compartment or to the glial cells. This procedure makes the stabilization of neuronal membrane potential by ionic balance in the membrane and finally decreases the neuronal excitability [10, 11].
- 2. Blockade of ions:** Phenytoin directly block the passive Na<sup>+</sup> influx and block Ca<sup>++</sup> uptake in presynaptic terminals [10].
- 3. Enhance inhibitory environment:** Phenytoin increases the inhibitory postsynaptic potential which is chloride mediated [10, 12].
- 4. Suppress accumulation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP):** cAMP and cGMP both are biologically active compound in the central nervous system and are found in the pre and post synaptic membrane. During epileptic seizure, both of these compounds are accumulated at the seizure site. During seizure time, when neurotransmitter substance release into the synaptic cleft then adenosine triphosphate catalyzed to cAMP by enzyme adenyl cyclase in both pre and post synaptic membrane. cAMP activates protein kinase which induces phosphorylation of special proteins in the membrane structures to alter ion permeability which finally increases the excitability in the post synaptic membrane [13]. Hence, at postsynaptic level, phenytoin decreases the accumulation of cAMP and cGMP and the rest of the mechanism blocks where neuronal excitability decreases [10]. At the presynaptic membrane, phosphorylation of synaptic vesicle protein occurs which enhances neurotransmitter release. This phosphorylation is Ca<sup>++</sup> dependant. Then phenytoin blocks Ca<sup>++</sup> to decrease neurotransmitter release by means of seizure [14, 15, 16].

### 4. USE OF PHENYTOIN

Voltage gated sodium channel blocker, Phenytoin is a hydantoin-derivative anticonvulsant drug that is used not only to prevent convulsion but also for non-convulsive disorders [2, 17].

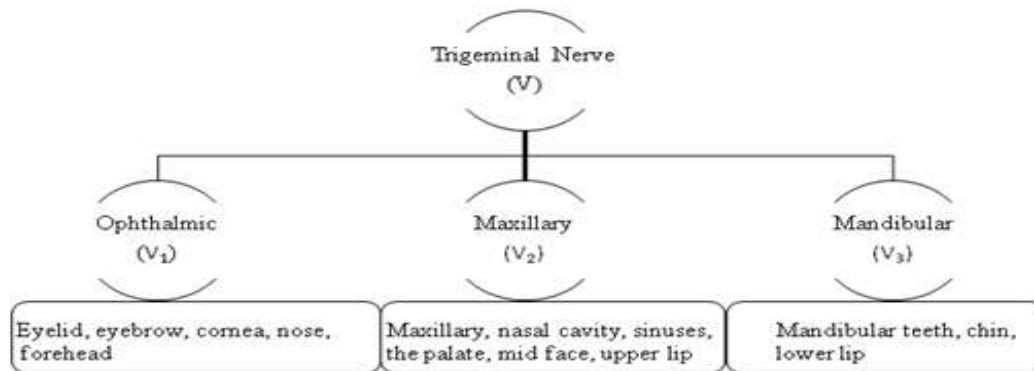
#### A. Convulsive treatment

Phenytoin is widely used individually or with other anticonvulsive drugs for the treatment of convulsion or epilepsy. It has a great role as adjunctive therapy if other drugs fail to control the seizure in case of tonic clonic, absence and myoclonic seizures [17, 18, 19, 20, 21]. Phenytoin is commonly used in status epilepticus and acute seizure with benzodiazepine [17, 22, 23, 24]. It plays a great role in preventing possible seizures after the intracranial neurosurgical procedure [25, 26, 27]. There are several evidences for usage of Phenytoin to prevent seizures in women with eclampsia but Magnesium sulfate is a better choice for preventing recurrence seizure in eclampsia [28, 29].

#### B. Non-convulsive treatment

##### Trigeminal neuralgia:

Trigeminal neuralgia (TN/TGN) is a neuropathic disorder with intense pain in the face that originates from trigeminal nerve. TN is the 5<sup>th</sup> cranial nerve with three major branches; ophthalmic, maxillary and mandibular nerve [30]. During TN, one, two or all branches of the nerve may be affected, but it most commonly involves the maxillary and mandibular nerve [31]. And the pain is felt at any part of face according to the nerve affected and its distribution (Fig 1). This is described as the most painful condition [32] and the patients may even commit suicide [33] when they are unable bear this pain.



**Fig 1: Trigeminal nerve and their distribution (information taken from 34, 35)**

Therefore, it is very important to provide an effective management for TN. Once it was believed that the main cause of this pain was compression of trigeminal nerve at the opening from inside to outside of the skull, but recent research has revealed that it is the enlargement of superior cerebellar artery compressing or throbbing against the microvasculature of the trigeminal nerve near its connection with the pons that causes the damage of myelin sheath which in turn causes severe pain [36]. Compression of trigeminal nerve is one type of complication noted in varieties of diseases like multiple sclerosis [37], herpes zoster infection [38] etc. This pain is not easily controlled but can be managed with medical and surgical treatment [33].

Phenytoin is selected as a 2<sup>nd</sup> line of medical treatment of TN which blocks the voltage gated sodium channel to decrease the excitability of the nerve to reduce the nerve pain [17]. But analgesic [38] and sedatives [39] are also used with phenytoin for the better recovery. When medical treatment fails, surgical treatment is usually performed to decompress the trigeminal nerve [40].

### Wound healing:

Wound healing is a complicated procedure where the skin and/or another organ-tissue proceed to repair wound after injury [41]. Wounds may have pain, bleeding, cutting etc. depending on the types of injury. We need a proper management/treatment to accelerate the healing of a wound to prevent further complications. Till now the topical use of phenytoin is a successful use of wound healing without/minimum adverse effect.

Phenytoin significantly decreases nasal wound healing after mechanical trauma in experimental animal [42]. After use in experimental animal, phenytoin has been used in human for the treatment of wound. First clinical trial of phenytoin was carried out on periodontal patients who have surgical wounds [43]. They found out that phenytoin treatment made the wound less painful, reduced inflammation and healed quickly when compared with controls [43]. Later, some other researchers applied topical phenytoin treatment in gingival hyperplasia which was successfully managed [44, 45]. Effects of phenytoin were studied successfully in different types of wound like, leprosy [46, 47, 48, 49], burns [50, 52], venous leg ulcer [51, 53, 54], chronic wound like gluteal abscess cavities [55], other chronic wounds [56], diabetic foot wounds [57, 58, 59, 60, 61], war wounds [62, 63], excisional biopsies [64, 65], pressure/bed sores [59, 66], pyoderma gangrenosum [67], oral biopsy ulcer [68], epidermolysis bullosa [69, 70, 71], local pain and inflammation [45, 59].

Several studies believe that phenytoin stimulates fibroblast proliferation [45, 52, 66] increases formation of granulation tissue [45, 66], decreases collagenase activity [45, 52, 66] facilitates deposition of collagen/other connective tissue components [45, 52, 66], reduces bacterial contamination [45, 55, 56, 57, 62, 66, 72] and decreases wound exudates [45, 66], neovascularisation, collagenisation, reduce polymorphonuclear and eosinophil cell infiltration [55, 57, 73, increase nerve generation [63].

### Digoxin toxicity

Digoxin toxicity occurs when excessive amount of digoxin (drug) is taken within short period of time or high levels of digoxin are accumulated during chronic treatment of heart failure and/or atrial fibrillation [74]. Cardiac arrhythmia or irregular heartbeat is the common symptom of digoxin toxicity [75]. And cardiac arrhythmia causes sudden death [76, 77]. Therefore, diagnosis and proper management of digoxin toxicity is urgent to save life. Phenytoin was used successfully to prevent cardiac arrhythmia which was amiodarone induced [17, 78].

**Use in Cancer/tumour:**

As a  $\text{Na}^+$  ion channel blocker, phenytoin inhibits  $\text{Na}^+$  current and significantly decreases migration and invasion of breast cancer cells *in vitro* [79]. Moreover, it reduces breast tumour growth, invasion, proliferation and metastasis *in vivo* [80] and also decreases prostate growth and metastasis [81] by resisting angiogenesis [82]. Inhibition, migration and secretion in prostate cancer cells are also reported [83, 84].  $\text{Na}^+$  current facilitates the invasion by promoting cysteine cathepsin activity in caveolae via allosteric regulation of the  $\text{Na}^+/\text{H}^+$  exchanger type 1 [85] and Nav1.5 is the main regulator of a gene network which controls invasion [86]. Therefore, it was suggested that phenytoin has a great therapeutic value for blocking action of  $\text{Na}^+$  and it may have broad use in other cancers also.

**5. ADVERSE EFFECTS OF PHENYTOIN**

With many uses of phenytoin, there are lots of adverse effects also during and after using phenytoin. Here are some systematic adverse effects.

**Cardiovascular effect:**

There are no adverse effects of administration of oral phenytoin. But there are few reports of adverse effects during IV administration. Severe low blood pressure and abnormal heart rhythms were observed with rapid IV infusion [87]. During treatment of cardiac arrhythmias in elderly people, IV phenytoin causes depression of cardiac conduction, ventricular fibrillation and heart blockade [88, 89, 90]. IV phenytoin is irritant and can cause phlebitis [91].

**Neurological effects:**

There are reports about adverse effects on central nervous system during short and long term use of phenytoin even if it is dose related like therapeutic dose or toxic dose. Phenytoin can cause nystagmus on lateral gaze at therapeutic doses and vertical nystagmus, double vision, drowsy, slurred speech, cerebellar ataxia and tremor at toxic or severe doses [92]. Nystagmus is the early condition of phenytoin toxicity in plasma concentration of  $>20$  mcg/ml, but ataxia and confusion usually occur when plasma concentration is  $>30$  mcg/ml. When plasma concentration is  $\geq 50$  mcg/ml then it can cause coma and respiratory and circulatory failure occur when over 95 mcg/ml [93]. Phenytoin can cause cerebellum atrophy after being used for longer period of time as it is accumulated in cerebellum [94]. Peripheral neuropathy can arise within weeks to months but is also possible within few hours of phenytoin administration [95].

**Hepatic effects:**

Hepatitis can occur when a phenytoin hypersensitivity syndrome develops. When liver is involved in case of adverse effect of phenytoin then mortality rate is from 18% to 40% [96-101]. The hepatitis is usually anicteric [102] but when it is icterus, the prognosis is poorer [97, 98, 103]. Phenytoin induced chronic hepatitis also has been reported [104]. Hepatomegaly with or without splenomegaly may be present. Continuous rise of hepatic transaminases enzyme occurs when phenytoin is discontinued [99, 100]. Cholestasis with jaundice [105] and hepatotoxicity [106] can also occur as a side effect of phenytoin.

**Gastrointestinal (GI) tract effects:**

Nausea, vomiting, constipation and abdominal pain can occur during phenytoin therapy [107].

**Endocrine and reproductive effects:**

Phenytoin can induce hyperglycemia [108-113] and hypoglycaemia [114] also in some cases. Phenytoin therapy also has side effects on the reproductive system which is closely related with adverse effects in bony system due to deficiency of estrogen hormone. It is reported that phenytoin treatment can decrease serum estradiol (E2) [115-117]. Decreased estrogen level can cause elevated level of sex hormone binding globulin which in turn decreases the testosterone level and other adrenal endrogen which alter the sexual functioning [118, 119]. Serum estradiol can be declined due to inhibition of aromatase enzyme for the phenytoin therapy [34].

**Dermatological effects:**

Skin effect like hypertrichosis, Steven-Johnson syndrome, purple glove syndrome, rash, exfoliative dermatitis, itching, excessive hairiness, coarsening of facial feature can occur during phenytoin therapy [120- 123]. During Hypersensitivity Syndrome, skin eruption begins as a patchy macular erythema which later changes to dusky, pink-red, confluent, popular

rash and that is itchy. Sometimes erythroderma appears. Patients have periorbital and facial oedema [124]. Epidermal necrolysis is not ignorable [123,125, 126, 127].

#### **Haematological effects:**

There are lots of reports about adverse effects on haematology system. And maximum reports were on chronic use of phenytoin. Leucocytosis with atypical lymphocytes, eosinophilia [123, 128], leucopenia [129], agranulocytosis [130, 131] was reported. The main toxicity occurs when used with other drugs, for example primidone. Because with combination of primidone, phenytoin can cause folate deficiency and megaloblastic anaemia. On the other side, phenytoin dependant antigranulocyte antibody may cause leucopenia due to discontinuation of phenytoin therapy. And then finally phenytoin causes a direct toxic effect with pancytopenia and agranulocytosis [132]. Reduced serum-folate concentration was found in case of chronic phenytoin administration [133- 135].

#### **Immunological effects:**

There are evidences of reduced immunological functions during phenytoin therapy [136- 140]. Drug induced lupus [141] and deficiency of IgA [122] can also occur.

#### **Lymphatic system effect:**

Lymph node reactions may occur during phenytoin therapy. For example, lymphoid hyperplasia, pseudolymphoma, lymphoma, and Hodgkins diseases. When lymphadenopathy develops, the patients should be closely monitored and if possible should use alternative anticonvulsant therapy [142].

#### **Allergic reaction:**

Phenytoin can cause allergic or hypersensitivity syndrome with fever, rash, lymphadenopathy, hepatitis, periorbital or facial oedema, haematological abnormalities, myalgia, arthralgia, pharyngitis etc. This allergic reaction may be determined genetically [124].

#### **Skeletal/bony system:**

The adverse effect of phenytoin therapy on skeletal/bony system is well established in many literatures. As a whole, metabolic bone disease and fractures are the main adverse effect for anticonvulsive therapy [143, 144]. Phenytoin therapy induces the cytochrome P450 (CYP 450) monooxygenase system which influences calcium-vitamin D axis by reducing bio-available vitamin D. This reduction causes hypocalcemia and compensatory secondary hyperparathyroidism which restores calcium from bones and induces bony loss [144, 145]. Phenytoin can induce hyperhomocysteinemia [118]. Phenytoin treatment reduces estrogen which leads to a decrease in TGF  $\beta$ 3 and due to the deficiency of TGF  $\beta$ 3, bones matrix decreases resulting into bone loss [146, 147].

#### **Psychological effects:**

The presence of suicidal tendency is still controversial among patients who receive phenytoin treatment for a long period of time. Psychiatric illness may be present in those who have family history or have past psychiatric illness [148, 149].

#### **Effects on pregnancy:**

Phenytoin is known as a teratogenic drug for pregnancy. Because phenytoin may cause craniofacial anomalies like broad and/or depressed nasal bridge, cleft lip and palate, smaller than normal head and mild mental retardation to those infants whose mother take phenytoin during pregnancy [150, 151]. This syndrome is called fetal hydantoin syndrome [150].

#### **Genitourinary effects:**

The adverse effect of phenytoin on genitourinary system is rare. But Peyronie's disease, priapism, glomerulonephritis, acute interstitial nephritis, acute renal failure, phenytoin metabolite urinary stone, nephrotic syndrome have been reported [152].

#### **Connective tissues effects on face/lips/gum:**

Chronic phenytoin treatment can cause enlargement of lips, coarsening of facial features, gingival enlargement (gums enlargement), most probably due to folate deficiency [153- 162].



## 6. PHARMACOKINETICS OF PHENYTOIN

Pharmacokinetics is the fate of drugs after using. The main principles and concepts usually come out from the studies of antiepileptic drugs. Pharmacokinetics of a drug describes drug absorption, distribution, metabolism and finally excretion from the body. These qualities can determine the clinical use of a drug including the prescription procedure and we can also know the drug efficacy. During drug combination therapy, drug interaction has a major clinical significance.

Pharmacokinetic and pharmacodynamic are two basic types of drug interactions. Pharmacokinetics is related with drug dispositions that can be measured by changes of drug concentration in plasma. These interactions involve absorption, distribution or excretion of affected drug and these are the most well-known interactions [163]. Pharmacodynamic interactions are involved between two or more drugs which have similar or opposing pharmacological mechanisms of action. These interactions can take place in the cellular level that can lead to additive, supra-additive or infra-additive effects of therapeutic response or drug toxicity.

**Absorption:** Absorption is the entry of drug molecules into the systematic circulation through

- a. mucus membrane of the gut
- b. mucus membrane of the lungs
- c. the skin or
- d. from the site of an injections.

Phenytoin can be administered as oral suspension [164], oral (tablet and capsule) and intravenous (IV) route [165] depending on the condition of the patients. Oral capsule has phenytoin sodium salt which is a crystalline extended-release form [166, 167, 168] and slowly absorbs in the gastrointestinal tract. Capsule is usually prescribed to elderly patients and adolescents. On the other hand phenytoin acid is available in chewable tablets and suspensions which is rapidly absorbable. Intravenous (IV) Phenytoin is necessary for the patients who cannot receive the drug orally or who need a rapid onset of the drug effect during emergency. Phenytoin also can be used as parenterally [169].

Absorption of Phenytoin depends on the interaction of drugs and some other factors like the route of administration, format of Phenytoin (tablet, capsule, IV) etc. Phenytoin is poorly absorbed from the stomach since the acidic gastric juice makes it almost totally insoluble. Usually phenytoin is slowly absorbed in small intestine due to its large surface area and low acidity ( $P^H$ : 7-7.5). Upper small intestine is the best site for the absorption in the presence of bile salt. After then jejunum and ileum show more significant absorption compared to duodenum. Phenytoin absorption gradually decreases in large intestine and is almost absent in the rectum [170]. Large doses are more slowly absorbed. In case of severe oral poisoning, this absorption may continue for up to 60 hours [171].

By the discussion of the route of administration, intravenous (IV) route of phenytoin is the most preferable administration for the acute and emergency condition comparing intramuscular (IM) and oral routes because of rapid absorption and rapid therapeutic serum level. On the other hand, phenytoin is more absorbed by oral route than IM route. Localized tissue injury, necrosis and abscess may occur at IM site as a result of complication. In spite of some complications of IM route, IM administration is still preferable in those cases where IV and oral administrations are not applicable, but profound delay of absorption occurs. Dosage adjustment is necessary in IM and oral routes to maintain therapeutic levels [172].

Food has an important role in the absorption of phenytoin. Phenytoin absorption dramatically declines when taken with high fat food which has side effects or loss of seizure control [173]. Nasogastric feeding is also another factor which can decrease the absorption of phenytoin. Phenytoin can be bind with the constituents of nasogastric formula which can form insoluble complexes that are not absorbable [174- 176]. Panomvana [177] also searched the effect of nasogastric feeding on absorption of phenytoin. This study found out that extended release (capsule) phenytoin can lower the absorption comparing immediate release (tablet) phenytoin. In general, the possible mechanism is that either interaction of phenytoin with protein hydrolysate in nasogastric food can decline bioavailability [178- 180] or phenytoin bind with nasogastric tube lumen [181] or this interaction is related with PH [180, 182, 183]. However, the exact mechanism is still unknown. Antacids which decrease the acid in the stomach can interrupt the absorption of phenytoin as we need that acid for the absorption of phenytoin mainly when large doses of antacids were taken [163, 184]. Activated charcoal delays and declines absorption of phenytoin [185].

### **Distribution of phenytoin:**

After taking phenytoin orally or intravenously, phenytoin is broadly distributed throughout the body and it has a little concentration in selective areas. After distribution in the body, 70-95% of phenytoin binds with plasma protein with

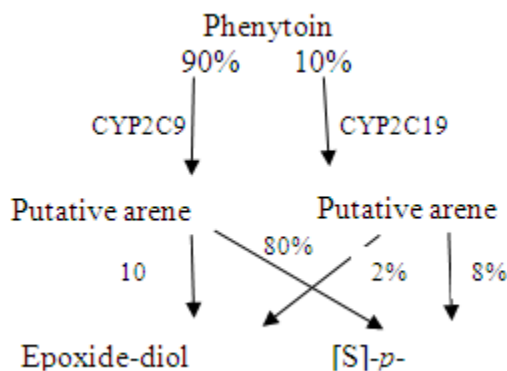
maximum plasma solubility approximately 75 g/mL at 37<sup>0</sup> C temperatures. The concentration of free phenytoin is higher in neonates compared to adult, elderly and in later pregnancy. This free phenytoin can cause malnutrition, liver diseases, AIDS, nephrotic and uraemic states in the presence of hypoalbuminaemia and diabetes in presence of high level of glycated albumin. Phenytoin concentration is higher in brain comparing plasma and higher in white matter than grey matter. It is equally distributed in cerebrospinal fluid (CSF), tear and saliva as in free plasma fraction. Bioavailability has not changed much during pregnancy. Phenytoin can be distributed in breast milk also [186].

**Biological half-life of phenytoin:** Phenytoin has a variable, dose dependant half-life after therapeutic oral doses. Average half-life of phenytoin is 20-30 hours for the normal therapeutic dose [187, 188]. But in overdose in adult, the range is from 24-230 hours [189- 191].

**Metabolism of phenytoin:**

Phenytoin is mainly metabolized by the hepatic P450 mixed oxidase system. At normal doses 90% phenytoin is metabolized by isoform CYP2C9 activity and rest 10% phenytoin by isoform CYP2C19 activity. Both activities produce short lived Putative arene oxide which later converts to the major metabolites [S]-p-hydroxyphenytoin (HPPH). And minimum arene oxide goes to the Epoxide-diol pathway. 60-80% of phenytoin converts to HPPH which is excreted via the kidney. CYP2C9 gene mutation is responsible for slow metabolism [186, 192, 193]. The complete metabolic system of phenytoin was shown in Fig 2 as a schema. Phenytoin is more rapidly metabolized in children than adults [194].

The first step in the enzymic degradation of phenytoin is rate limited. Therefore, the dose to serum level ratio is not linear. When dose is increased the plasma level increases linearly at the beginning till the point of enzymic saturation is reached in a much steeper fashion. For that reason the clearance and half-life of phenytoin depends on the plasma level of phenytoin. If plasma concentrations are higher, the half-life is longer and clearance is less, because of the saturation of the enzyme system [7, 186].



**Excretion of phenytoin:**

The total clearance of phenytoin from plasma is 5.9 ml/min/kg [195]. 23-70% hydroxylated metabolites of phenytoin is excreted in the urine. With this percentage, 4% is unchanged and 5% is either free or in conjugated form. 5% is excreted through faeces [196]. Small amount is excreted in the milk.

**7. DRUG-DRUG INTERACTION OF PHENYTOIN**

Drug-drug interaction of phenytoin with other drugs including other antiepileptic drugs was shown in a tabulated form. Few drug interactions of phenytoin were shown here in Table 1.

**Table 1: Drug interactions of Phenytoin:**

Phenytoin+other drugs	Possible mechanism	Results after interaction	References
Capecitabine (anticancer drug)	inhibition of CYP2C9 isozyme	Intoxication	[197- 199]
Valproic acid	Inhibit phenytoin metabolism	Intoxication/increase concentration	PHT [200]
Tolbutamide	Inhibit phenytoin metabolism	Intoxication/increase concentration	PHT [201]

Phenylbutazone	Inhibit phenytoin metabolism	Intoxication/increase concentration	PHT	[201]
Carbamazepine	inhibition of CYP2C9 isozyme	Increase/decrease concentration	phenytoin	[202]
Felbamate	inhibition of CYP2C9 isozyme	Intoxication/increase concentration	PHT	[203]
Oxcarbazepine (OXC)	inhibition of CYP2C9 isozyme	Intoxication/increase concentration	PHT	[204]
Phenobarbital (PB)	inhibition of CYP2C9 isozyme	Increase/decrease concentration	phenytoin	[202]
Primidone (PRM)	inhibition of CYP2C9 isozyme	Increase/decrease concentration	phenytoin	[202]
Tiagabine (TGB)		No effect on phenytoin		
Ethosuximide (ESM)		No effect on phenytoin		
Lamotrigine (LTG)		No effect on phenytoin		
Topiramate (TPM)		No effect on phenytoin		
Zonisamide (ZNS)		No effect on phenytoin		
Vigabatrin (VGB)	Unknown	decrease phenytoin concentration		
Entacids	Decrease absorption and protein binding	Intoxication/increase concentration	PHT	186
Large doses of Salicylates	Decrease absorption and protein binding	Intoxication/increase concentration	PHT	186
Tobutamide	Decrease absorption and protein binding	Intoxication/increase concentration	PHT	186
Phenylbutazone	Decrease absorption and protein binding	Intoxication/increase concentration	PHT	186

## 8. IMPORTANCE OF THERAPEUTIC DRUG MONITORING OF PHENYTOIN

There are several factors are monitored during phenytoin therapy.

### 1. Narrow therapeutic index (NTI):

NTI is one of the most important issues that need to be monitored during drug therapy. To prevent high morbidity, mortality and health costs [205- 207], therapeutic drug monitoring is necessary. NTI –drugs have small differences between their therapeutic and toxic doses and small changes of dosage or interactions with other drugs can cause adverse effects [208]. We need close monitoring of phenytoin therapy as phenytoin has NTI or narrow therapeutic window. Hence, a fine balance should be determined between efficacy and dose related side effects [209].

### 2. Free or unbounded phenytoin level:

Phenytoin is highly protein bounded and free or unbound phenytoin can make the pharmacological effect. Any factor like drug-drug interaction or with other diseases like renal impairment, uraemia etc. can increase the changes of phenytoin pharmacokinetics and /or efficacy and toxicity due to increase in the free phenytoin level [210].

### 3. Enzymetic system:

Phenytoin shows non-linear pharmacokinetics. It means the enzyme system related with phenytoin metabolism gradually becomes saturated which causes the decrease in the rate of elimination of phenytoin even when the dose is increased [210]. For these above reasons, monitoring of phenytoin level is clinically important to ensure therapeutic efficacy in individual patients.

## 9. PHARMACOGENETICS OF PHENYTOIN

Phenytoin has a number of adversarial effects which may be a hurdle in the successful treatment of the patients. The chief aim of pharmacogenetics of phenytoin is to identify the gene in order to reduce adverse effects and dose adjustment which may improve the quality of life of epilepsy patients. Therefore, to recognize phenytoin related gene and alleles in phenytoin



usage and dosing is important and well described in the guideline [211]. Like other drugs, the cytochrome P450 (CYP) enzymes are responsible for phenytoin metabolism in the liver. Genetic variations of this enzyme-producing gene cause decreased metabolism and increased plasma concentration several times higher than normal, which in turn increase phenytoin toxicity and adverse drug reactions. *CYP2C9\*3* is the most common mutant allele among idiopathic epilepsy patients. *CYP2C9* genotype based phenytoin therapy is important due to the genetic variations associated with therapeutic and adverse responses to phenytoin [212]. *CYP2C9\*2* and *CYP2C9\*3* alleles are the code for enzymes with reduced activity most commonly observed in Europeans, linked with phenytoin induced neurotoxicity [213]. In a study of Mexican Mestizo (MM) patients with epilepsy, *CYP2C9* IVS8-109 T allele was recently found to reduce *CYP2C9* enzymatic activity on phenytoin [214]. The hydroxylation capacity of phenytoin decline with the mutations of *CYP2C9/19* and *CYP2C9* impairment is greater compared to *CYP2C19*.

For that reason, patient with the Leu359 allele in *CYP2C9* has higher serum concentration of phenytoin with low doses. On those cases the patients with *CYP2C19* mutations should be given higher daily doses [215]. Phenytoin-induced cutaneous adverse reactions of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are associated with *HLA-B\*15:02* allele [216, 217] and most prevalent in Asian and Oceanian populations.

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## BIOGRAPHY OF TAHAMINA BEGUM

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