Int. J. Sci. R. Tech., 2026 3(11)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

Phenytoin: A Comprehensive Review of Pharmacology, Pharmacokinetics, Therapeutic Applications, Adverse Effects, Drug Interactions and Pharmacogenomics

Aditya Nagnath Bokke, Anuradha Tukaram Biradar, Ravishankar Varma, Payal Kailash Matke

Department of Pharmaceutics, St.Wilfred's Institute, Of Pharmacy, Panvel.

ABSTRACT

Phenytoin is a well-established hydantoin derivative and an important antiseizure medication used primarily for the management of focal-onset seizures and generalized tonic-clonic seizures. It exerts its anticonvulsant activity mainly by blocking voltage-gated sodium channels and reducing repetitive neuronal firing, thereby limiting the spread of abnormal electrical activity in the brain. Phenytoin has been used clinically for several decades; however, its therapeutic application is associated with several pharmacokinetic and pharmacological challenges. The drug exhibits high plasma protein binding and nonlinear, dose-dependent pharmacokinetics because hepatic metabolism becomes saturated at therapeutic concentrations. Consequently, relatively small changes in dosage may produce significant changes in plasma drug concentrations, making therapeutic drug monitoring important in selected patients. This review provides a comprehensive overview of the chemistry, mechanism of action, pharmacological properties, pharmacokinetics, therapeutic applications, dosage forms, adverse drug reactions, drug interactions, contraindications, and therapeutic drug monitoring of phenytoin. Particular attention is given to its hepatic metabolism through cytochrome P450 enzymes, especially CYP2C9 and CYP2C19, and its ability to induce several drug-metabolizing enzymes, which can result in clinically significant drug interactions. Important adverse effects, including neurological effects, gingival hyperplasia, dermatological reactions, hepatotoxicity, and serious hypersensitivity reactions, are also discussed. The review further highlights the clinical significance of protein binding and altered albumin concentrations in interpreting phenytoin plasma levels. Recent developments in phenytoin therapy, including pharmacogenomics, individualized dosing, therapeutic drug monitoring, population pharmacokinetic approaches, and the role of HLA genetic variants in susceptibility to severe cutaneous adverse reactions, are also considered. Fosphenytoin, a water-soluble prodrug of phenytoin, is discussed with respect to its role in parenteral therapy and formulation advantages. Overall, understanding the pharmacological and pharmacokinetic characteristics of phenytoin is essential for optimizing its therapeutic efficacy while minimizing toxicity and drug-interaction risks. Advances in precision medicine and pharmacogenomic-guided therapy may contribute to safer and more individualized use of phenytoin in the future.

Keywords: Phenytoin, Antiseizure drug, Hydantoin, Epilepsy, Sodium channel blocker, Pharmacokinetics, Therapeutic drug monitoring, CYP2C9, CYP2C19, Pharmacogenomics, Fosphenytoin, Drug interactions

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures resulting from abnormal and excessive electrical activity in the brain. It affects people of different age groups and can significantly influence physical, psychological, social, and educational aspects of life. Antiseizure medications are the mainstay of pharmacological management of epilepsy and are selected according to seizure type, patient characteristics, safety profile, and potential drug interactions.

Phenytoin is one of the established antiseizure medicines and belongs to the hydantoin class of anticonvulsant drugs. It has been used clinically for many decades and continues to have an important role in the management of certain seizure disorders. Phenytoin was developed from the hydantoin class of compounds and was introduced into clinical practice in the 1930s. Unlike phenobarbital, it produces relatively little sedation at therapeutic doses, which contributed to its importance as an anticonvulsant.

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The primary pharmacological action of phenytoin is associated with the modulation of voltage-gated sodium channels in neuronal membranes. During repetitive neuronal stimulation, sodium channels undergo cycles of activation and inactivation. Phenytoin preferentially binds to and stabilizes the inactivated state of these channels, thereby reducing the ability of neurons to generate repetitive high-frequency action potentials. This mechanism decreases the propagation of abnormal electrical activity and contributes to its anticonvulsant effect.

Phenytoin is used mainly in the treatment of focal-onset seizures and generalized tonic-clonic seizures. It can also be used in selected emergency situations involving prolonged or recurrent seizures, particularly through parenteral formulations. Fosphenytoin, a water-soluble prodrug of phenytoin, was developed to overcome some formulation and administration limitations associated with intravenous phenytoin.

An important characteristic of phenytoin is its complex pharmacokinetic profile. It is highly bound to plasma proteins, particularly albumin, and undergoes extensive hepatic metabolism. Its metabolism becomes saturable within or near the therapeutic concentration range. Consequently, phenytoin can exhibit nonlinear pharmacokinetics, in which a relatively small increase in dose may produce a disproportionately large increase in plasma drug concentration. This characteristic makes dose adjustment and therapeutic drug monitoring particularly important in patients receiving phenytoin therapy.

Phenytoin also has a relatively narrow therapeutic range and is associated with numerous drug interactions. It is metabolized primarily through hepatic cytochrome P450 enzymes, particularly CYP2C9 and CYP2C19, and can induce several CYP enzymes. Therefore, phenytoin may alter the metabolism and effectiveness of other medicines administered concurrently. Conversely, other medicines can affect phenytoin concentrations, making careful evaluation of concomitant medications necessary.

Although phenytoin has established therapeutic benefits, its use can be associated with several adverse effects. Common concentration-related effects include nystagmus, ataxia, diplopia, dizziness, and other neurological symptoms. Long-term therapy may be associated with effects such as gingival hyperplasia, hirsutism, peripheral neuropathy, and disturbances in bone health. Rare but potentially serious adverse reactions include severe cutaneous reactions, including Stevens–Johnson syndrome/toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS).

Pharmacogenomics has become an important area in the understanding of phenytoin-associated adverse reactions. Genetic variants, particularly HLA-B*15:02, have been associated with an increased risk of severe cutaneous adverse reactions in susceptible populations. Other genetic markers, such as HLA-A*31:01, have also been investigated in relation to phenytoin hypersensitivity. These findings demonstrate the potential importance of genetic information in individualized antiseizure drug therapy.

Therapeutic drug monitoring is another important aspect of phenytoin therapy. Measurement of plasma phenytoin concentrations can assist in optimizing treatment, particularly when there are concerns about toxicity, lack of seizure control, drug interactions, altered protein binding, or changes in organ function. Because phenytoin is highly protein-bound, measurement or estimation of the free (unbound) concentration may be particularly useful in patients with altered albumin concentrations or other conditions affecting protein binding.

Despite the availability of newer antiseizure medications, phenytoin remains an important drug in clinical pharmacology because of its established efficacy, extensive clinical experience, and distinctive pharmacokinetic and pharmacogenomic characteristics. However, its narrow therapeutic range, nonlinear pharmacokinetics, drug interactions, and potential for serious adverse reactions present important challenges in clinical use.

Therefore, a comprehensive review of phenytoin is relevant for understanding its chemical and pharmacological properties, mechanism of action, pharmacokinetics, therapeutic applications, adverse drug reactions, drug interactions, therapeutic drug monitoring, pharmacogenomics, formulation approaches, and future perspectives. A better understanding of these aspects may contribute to safer and more individualized use of phenytoin in the management of seizure disorders.

Chemical Structure and Chemistry of Phenytoin

1. Chemical structure

- Phenytoin is a hydantoin derivative and chemically belongs to the 5,5-disubstituted hydantoin class.
- Chemical name: 5,5-diphenylimidazolidine-2,4-dione
- Molecular formula: $C_{15}H_{12}N_2O_2$
- Molecular weight: 252.27 g/mol
- Drug class: Hydantoin anticonvulsant
- IUPAC name: 5,5-diphenylimidazolidine-2,4-dione

2. Structural features

The molecule contains:

A. Hydantoin ring

Phenytoin contains a five-membered imidazolidine-2,4-dione ring.

The ring contains two nitrogen atoms and two carbonyl (C=O) groups.

This ring is responsible for the basic hydantoin chemical framework.

B. Two phenyl groups

Two phenyl (C_6H_5) groups are attached to the same carbon at position 5 of the hydantoin ring.

Therefore, phenytoin is also called 5,5-diphenylhydantoin.

Mechanism of Action

Phenytoin is an antiepileptic (antiseizure) drug that mainly controls seizures by blocking voltage-gated sodium (Na^+) channels in neurons.

1. Normal neuronal action

Normally, when a neuron is stimulated:

Stimulus → Na^+ channels open → Na^+ enters neuron → depolarization → action potential

After the action potential, sodium channels become inactivated temporarily and then return to their resting state.

In epilepsy, neurons can undergo rapid and repetitive firing, producing excessive electrical activity that can spread to other areas of the brain.

2. **Phenytoin blocks voltage-gated Na^+ channels**

Phenytoin binds preferentially to the inactivated state of voltage-gated sodium channels.

It does not simply prevent every action potential. Instead, it makes sodium channels less available for rapid repeated activation.

Phenytoin → binds to inactivated Na^+ channels → delays their recovery → decreases channel availability

3. **Use-dependent / frequency-dependent blockade**

This is a key feature of phenytoin.

When neurons fire rapidly, sodium channels repeatedly enter their inactivated state. Phenytoin has greater effects under these conditions.

Therefore:

Normal neuronal firing → relatively less affected

Rapid repetitive firing → greater Na^+ channel blockade

This allows phenytoin to preferentially suppress the abnormal high-frequency firing associated with seizures.

4. **Reduction in repetitive neuronal firing**

Because fewer sodium channels are available for activation:

↓ Na^+ channel availability

↓ Na^+ influx during repeated firing

↓ ability of neuron to generate rapid action potentials

↓ repetitive neuronal discharge

Thus, phenytoin suppresses the sustained high-frequency firing of neurons.

5. Prevention of seizure propagation

A seizure can spread from an initially abnormal group of neurons to surrounding neuronal networks.

By reducing repetitive neuronal firing and propagation:

Abnormal electrical discharge → Na^+ channel blockade → ↓ repetitive firing → ↓ spread of seizure activity → anticonvulsant effect

Therefore, phenytoin primarily prevents the propagation of seizure activity rather than producing generalized suppression of normal neuronal function.

6. Effect on neurotransmitter release

Reduced repetitive action-potential firing also decreases excessive neuronal activity and can reduce the downstream release of excitatory neurotransmitters.

This contributes to limiting the spread of abnormal electrical activity, although voltage-gated Na^+ channel inhibition is the principal mechanism.

7. Effect on cardiac sodium channels

Phenytoin also affects voltage-gated sodium channels in cardiac tissue. At therapeutic concentrations its primary clinical role is antiseizure therapy, but excessive concentrations or rapid IV administration can affect cardiac conduction and cause hypotension or arrhythmias.

Pharmacokinetics of Phenytoin

Pharmacokinetics means "what the body does to the drug."

It describes ADME: Absorption, Distribution, Metabolism and Excretion.

A. Absorption

Phenytoin is administered mainly by the oral route in several formulations.

Oral phenytoin is absorbed from the gastrointestinal tract.

Absorption can vary depending on the formulation.

Food and gastrointestinal factors may influence absorption.

Phenytoin has relatively low aqueous solubility, which is an important pharmaceutical consideration.

The injectable form is used when rapid parenteral therapy is required.

B. Distribution

After absorption, phenytoin enters the systemic circulation.

Phenytoin is highly bound to plasma proteins, mainly albumin.

Approximately 90% of circulating phenytoin is protein-bound.

Only the unbound/free fraction is pharmacologically active and able to cross biological membranes.

Phenytoin crosses the blood–brain barrier, allowing it to reach its principal site of anticonvulsant action.

In patients with low albumin, the free fraction may increase even when total plasma phenytoin appears within the usual therapeutic range.

Important for review:

Total phenytoin concentration = bound phenytoin + free phenytoin

The free concentration is particularly important when protein binding is altered.

C. Metabolism

Phenytoin is metabolized mainly in the liver.

Major enzymes involved include:

- CYP2C9
- CYP2C19

The drug undergoes hepatic metabolism to inactive metabolites, which are subsequently eliminated.

One important characteristic is capacity-limited metabolism.

At lower concentrations, metabolism can approximate first-order behavior. As metabolic enzymes become saturated, relatively small increases in dose can produce disproportionately large increases in plasma concentration.

This is why phenytoin has a narrow therapeutic range and requires careful dose adjustment.

D. Excretion

Most phenytoin is eliminated after hepatic metabolism.

Metabolites are primarily eliminated through the urine.

Only a small proportion of unchanged phenytoin is excreted.

Renal disease can indirectly affect interpretation of phenytoin concentrations, particularly through changes in protein binding.

Pharmacodynamics of Phenytoin

Pharmacodynamics means "what the drug does to the body."

For phenytoin, pharmacodynamics mainly concerns its effects on neuronal voltage-gated sodium channels.

Mechanism of action

• During neuronal activity:

Depolarization → Voltage-gated Na^+ channels open → Na^+ enters neuron → Action potential

Phenytoin preferentially binds to the inactivated state of voltage-gated sodium channels.

It thereby:

1. Stabilizes sodium channels in the inactivated state.
2. Delays their return to the resting/available state.
3. Reduces the ability of neurons to fire repeatedly at high frequency.
4. Limits abnormal electrical activity.
5. Reduces propagation of seizure activity.

Adverse Effects

Phenytoin can cause adverse effects involving the central nervous system, skin, gastrointestinal system, gums, liver, blood, bones, and cardiovascular system. The risk generally depends on dose, duration of treatment, serum concentration, and individual susceptibility.

1. **Central Nervous System Effects**

- These are among the most important concentration-related adverse effects.
- Nystagmus: involuntary, usually side-to-side movement of the eyes.
- Ataxia: difficulty maintaining coordination and balance.
- Diplopia: double vision.
- Dizziness and vertigo
- Drowsiness
- Slurred speech (dysarthria)
- Tremor
- Headache
- Confusion, particularly with excessive concentrations.

These effects are often associated with excessive phenytoin exposure and may improve after appropriate dose adjustment.

2. Gingival Hyperplasia

- Gingival hyperplasia means abnormal enlargement/overgrowth of the gums.
- It is particularly associated with long-term phenytoin therapy
- Poor oral hygiene can increase the problem.
- The enlarged gums may bleed more easily and can interfere with eating or oral hygiene.
- Good dental hygiene and regular dental care are important.

3. **Hirsutism and Cosmetic Effects**

- Long-term treatment may cause:
- Hirsutism — increased growth of coarse hair.
- Acneiform skin changes
- Coarsening of facial features in some patients.

These effects can be particularly troublesome for patients receiving prolonged therapy.

4. Skin Reactions

Phenytoin can cause various skin reactions, ranging from mild to potentially severe.

A. Mild:

- Skin rash
- Itching
- Morbilliform/maculo-papular rash

B.**Serious**:

- Stevens–Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)
- DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)
- Warning signs such as a widespread rash, blistering, skin peeling, facial swelling, fever, or involvement of the mouth/eyes require urgent medical assessment.

5. Hepatotoxicity

- Phenytoin can rarely cause significant liver injury.
- Possible manifestations include:
- Increased liver enzymes
- Loss of appetite
- Nausea
- Abdominal discomfort
- Jaundice

Liver function should be considered when clinically indicated, especially if symptoms suggest hepatic injury.

6. Hematological Effects

Rare but potentially serious blood-related reactions include:

- Leukopenia
- Thrombocytopenia
- Agranulocytosis
- Aplastic anemia
- Other blood dyscrasias

Symptoms such as unusual infections, persistent fever, unusual bruising, or bleeding should be medically evaluated.

7. Gastrointestinal Effects

Possible effects include:

- Nausea
- Vomiting
- Abdominal discomfort
- Constipation
- Loss of appetite

These are generally less serious than the neurological or hypersensitivity reactions.

8. **Bone and Vitamin D Effects**

Long-term phenytoin treatment can affect vitamin D metabolism and bone health.

Possible consequences include:

- Reduced vitamin D availability
- Reduced bone mineral density
- Osteomalacia
- Increased risk of fractures in susceptible patients

This is related partly to phenytoin's enzyme-inducing effects on vitamin D metabolism.

9. Peripheral Neuropathy

Prolonged treatment, particularly with excessive exposure, has been associated with:

Tingling or numbness

- Altered sensation
- Weakness in severe cases

10. Cardiovascular Effects

These are particularly important with intravenous phenytoin.

Rapid IV administration can cause:

- Hypotension
- Bradycardia
- Cardiac arrhythmias
- Conduction abnormalities
- In severe cases, cardiovascular collapse

Therefore, IV phenytoin must be administered carefully with appropriate cardiovascular monitoring.

11. **Local Effects of IV Administration**

Phenytoin injection can cause local complications such as:

- Pain
- Inflammation
- Tissue injury
- Purple glove syndrome, a rare complication involving swelling, discoloration, and pain around the injection site.

12. Hypersensitivity Reactions

Phenytoin can cause systemic hypersensitivity reactions.

Features may include:

- Fever
- Rash
- Lymphadenopathy
- Facial edema
- Liver involvement
- Kidney involvement
- Blood abnormalities

DRESS is particularly important because it can involve multiple organs.

13. Pregnancy-Related Concerns

Phenytoin crosses the placenta and has been associated with fetal abnormalities and developmental effects. Pregnancy planning and treatment decisions should therefore be discussed with a healthcare professional rather than stopping phenytoin abruptly.

14. Concentration-Related Toxicity

A useful way to present phenytoin toxicity in your review is:

- Increasing phenytoin exposure → nystagmus → ataxia/diplopia → dysarthria/confusion → severe CNS toxicity
- However, serum concentration and clinical toxicity do not always correlate perfectly, particularly when protein binding is altered

Phenytoin – Dosage Forms

Phenytoin is available in oral and parenteral dosage forms. The choice of dosage form depends on the patient's condition, required onset of action, swallowing ability, and clinical situation.

1. Phenytoin Tablets

- Type: Solid oral dosage form
- Phenytoin tablets contain phenytoin or, commonly, phenytoin sodium.

Characteristics:

- Intended for oral administration.
- Convenient for long-term maintenance therapy.
- Available in different strengths depending on the manufacturer and country.
- The formulation should provide consistent drug release and absorption.

Advantages:

- Easy to administer.
- Convenient for outpatient treatment.
- Good stability compared with liquid formulations.
- Suitable for long-term therapy.

Limitations:

- Absorption can vary between formulations.
- Dose changes require careful monitoring because phenytoin has nonlinear pharmacokinetics.
- Not suitable when the patient cannot swallow.

2. Phenytoin Capsules

Type: Solid oral dosage form

Phenytoin is also available as extended-release capsules in some markets.

Purpose of extended-release formulation:

Provides slower release of drug.

Helps maintain drug concentrations over a longer period.

Can reduce the number of daily doses compared with some immediate-release preparations.

Important point:

Different phenytoin formulations may not have identical bioavailability. Therefore, changing between formulations should be done carefully with appropriate clinical monitoring.

3. Phenytoin Oral Suspension

Type: Liquid oral dosage form

Phenytoin oral suspension is particularly useful when swallowing tablets or capsules is difficult.

Composition generally includes:

Phenytoin/phenytoin sodium

Suspending agent

Vehicle

Sweetening/flavoring agents

Preservatives or other formulation excipients as required

Advantages:

Easier administration in patients who have difficulty swallowing.

Dose can be measured according to the prescribed amount.

Useful in pediatric or certain geriatric patients.

Limitations:

Requires thorough shaking before administration.

Drug distribution can become non-uniform if the suspension is not mixed properly.

Measuring devices should be used accurately.

Formulation changes can affect bioavailability.

4. Phenytoin Sodium Injection

Type: Parenteral dosage form

Injectable phenytoin sodium is used when rapid parenteral administration is clinically required.

It may be administered by the IV route under appropriate medical supervision.

Important pharmaceutical issue:

Phenytoin sodium has poor aqueous solubility, so the injectable formulation requires specialized formulation approaches to keep the drug in solution.

The injection may contain excipients such as:

Propylene glycol

Alcohol

Sodium hydroxide or other pH-adjusting components

The exact composition depends on the specific marketed formulation.

Advantages:

Useful when oral administration is not possible.

Provides systemic drug delivery without relying on gastrointestinal absorption.

Limitations:

Requires careful administration.

Rapid IV administration can cause hypotension and cardiac arrhythmias.

Appropriate cardiovascular and respiratory monitoring may be required.

Local tissue injury can occur if the solution is improperly administered.

5. Fosphenytoin Injection

Fosphenytoin is a water-soluble prodrug of phenytoin.

It was developed mainly to overcome some formulation and administration problems associated with injectable phenytoin.

After administration:

Fosphenytoin → conversion by phosphatases → Phenytoin → anticonvulsant effect

Advantages:

Much more water-soluble than phenytoin.

Suitable for parenteral administration.

Can be administered IV and, depending on the product, IM.

Generally easier to administer than phenytoin sodium injection.

Important point:

Fosphenytoin is not a different therapeutic class; it is converted into phenytoin and ultimately produces the pharmacological effect of phenytoin.

Therapeutic Effects of Phenytoin

Phenytoin is an antiseizure (antiepileptic) drug that mainly produces its therapeutic effects by reducing excessive electrical activity in the brain. Its primary molecular action is use-dependent blockade of voltage-gated sodium (Na^+) channels.

1. Anticonvulsant Effect

The major therapeutic effect of phenytoin is the prevention and control of seizures.

During a seizure, neurons undergo repeated and uncontrolled action potentials. Phenytoin stabilizes neuronal membranes by prolonging the inactive state of voltage-gated sodium channels.

Mechanism:

Phenytoin → Na^+ channel inactivation → ↓ repetitive neuronal firing → ↓ seizure propagation → anticonvulsant effect

It particularly limits high-frequency repetitive firing, while having relatively less effect on normal neuronal activity.

2. Effect on Focal-Onset Seizures

Phenytoin is effective in controlling focal-onset seizures, in which abnormal electrical activity begins in a localized area of the brain.

It can reduce:

Abnormal neuronal discharge

Spread of seizure activity

Frequency and severity of seizures

Focal seizures may occur with or without impairment of awareness.

3. Effect on Generalized Tonic-Clonic Seizures

Phenytoin can be used for generalized tonic-clonic seizures.

Its action prevents the rapid spread and sustained repetitive neuronal firing associated with seizure activity.

It is not generally useful for typical absence seizures and may sometimes worsen certain generalized seizure types.

4. Prevention of Seizure Propagation

An important therapeutic effect is the prevention of spread of abnormal electrical activity from one group of neurons to surrounding areas.

Phenytoin:

Reduces repetitive action potentials

Limits propagation of abnormal electrical impulses

Helps stabilize neuronal excitability

This contributes to its ability to control seizure activity.

5. Effect in Status Epilepticus

Phenytoin/fosphenytoin can be used as part of the treatment of status epilepticus, particularly for preventing recurrence after initial seizure termination.

For urgent treatment, fosphenytoin is often used because of its formulation and administration advantages.

Treatment of status epilepticus requires emergency medical management and appropriate monitoring.

6. Anticonvulsant Effect Without General Anesthesia

At therapeutic concentrations, phenytoin suppresses excessive neuronal activity without producing the degree of generalized CNS depression associated with some older antiseizure drugs.

Therefore, its therapeutic action is primarily suppression of abnormal electrical activity rather than complete suppression of normal brain function.

7. Cardiac Therapeutic Effect

Phenytoin also affects cardiac voltage-gated sodium channels.

Historically, it has been investigated/used in selected situations for certain digitalis-induced cardiac arrhythmias, although this is not its primary modern therapeutic use.

This cardiac sodium-channel effect is also important for understanding its toxicity and IV administration precautions.

8. Effect on Neuronal Excitability

Overall, phenytoin decreases neuronal excitability by:

Stabilizing neuronal membranes

Reducing repetitive action potentials

Limiting sodium influx during repeated depolarization

Reducing propagation of abnormal electrical discharges

Simple Flow Diagram

Phenytoin

↓

Blocks voltage-gated Na^+ channels

↓

Prolongs Na^+ channel inactivation

↓

Decreases repetitive neuronal firing

↓

Limits seizure propagation

↓

Reduces seizure frequency/severity

CONCLUSION

Phenytoin is a well-established hydantoin-class antiseizure drug that has played an important role in the management of epilepsy for many decades. Its primary anticonvulsant action is associated with the inhibition of voltage-gated sodium channels, which reduces repetitive neuronal firing and limits the spread of abnormal electrical activity in the brain. Because of this mechanism, phenytoin is particularly useful in the management of focal-onset seizures and generalized tonic-clonic seizures.

Despite its established therapeutic efficacy, the clinical use of phenytoin presents several challenges. It has a relatively narrow therapeutic range and exhibits nonlinear pharmacokinetics, meaning that a small increase in dose can sometimes produce a disproportionately large increase in plasma drug concentration. Therefore, therapeutic drug monitoring and individualized dose adjustment can be important, particularly in patients with altered protein binding, hepatic dysfunction, drug interactions, or suspected toxicity.

Phenytoin is also associated with several adverse effects, including neurological effects such as nystagmus and ataxia and long-term effects such as gingival hyperplasia and alterations in bone health. Rare but potentially severe hypersensitivity reactions can also occur. In addition, its ability to induce hepatic drug-metabolizing enzymes contributes to numerous clinically important drug interactions. These characteristics emphasize the importance of careful prescribing, monitoring, and patient-specific treatment.

Pharmacogenomic research has further improved understanding of individual susceptibility to phenytoin-associated adverse reactions. Genetic variants such as HLA-B15:02 and HLA-A31:01 have been investigated in relation to severe cutaneous adverse

reactions in susceptible populations. Incorporating pharmacogenetic information, where clinically appropriate and supported by guidelines, may contribute to safer and more individualized therapy.

The development of fosphenytoin has addressed some pharmaceutical limitations of conventional parenteral phenytoin by providing a more water-soluble prodrug for parenteral administration. In parallel, current research is exploring precision dosing, population pharmacokinetic modeling, therapeutic drug monitoring, pharmacogenomics, and novel drug-delivery systems to improve the safety and effectiveness of phenytoin therapy.

Overall, phenytoin remains an important antiseizure medication, but its benefits must be balanced with its pharmacokinetic complexity, adverse-effect profile, and potential for drug interactions. Future advances in personalized medicine, pharmacogenomics, therapeutic monitoring, and formulation technology may help optimize phenytoin treatment and improve outcomes for patients with seizure disorders.

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HOW TO CITE: Aditya Nagnath Bokke, Anuradha Tukaram Biradar, Ravishankar Varma, Payal Kailash Matke, Phenytoin: A Comprehensive Review of Pharmacology, Pharmacokinetics, Therapeutic Applications, Adverse Effects, Drug Interactions and Pharmacogenomics, Int. J. Sci. R. Tech., 2026, 3 (11), 554-564. https://doi.org/10.5281/zenodo.24213978