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PHENYTOIN IN EPILEPSY MANAGEMENT: EFFICACY, SAFETY, AND DRUG INTERACTIONS

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ABSTRACT

Phenytoin is a widely used antiepileptic drug that has played a significant role in the management of seizure disorders for several decades. It is primarily indicated for the treatment of focal (partial) seizures and generalized tonic–clonic seizures. Phenytoin exerts its antiepileptic effect mainly by stabilizing neuronal membranes through selective inhibition of voltage-gated sodium channels, thereby reducing repetitive neuronal firing and seizure propagation. Despite its proven efficacy, phenytoin exhibits complex pharmacokinetics characterized by nonlinear (zero-order)metabolism, narrow therapeutic index, and high plasma protein binding, which necessitate careful therapeutic drug monitoring. The drug is extensively metabolized in the liver by cytochrome P450 enzymes, making it susceptible to numerous drug–drug interactions. Long-term use of phenytoin is associated with several adverse effects, including gingival hyperplasia, hirsutism, osteomalacia, peripheral neuropathy, and hematological abnormalities. Recent studies have focused on improving phenytoin delivery systems, minimizing toxicity, and understanding pharmacogenetic influences on its metabolism and response. This review summarizes the pharmacology, mechanism of action, pharmacokinetics, clinical applications, adverse effects,

and recent advances related to phenytoin, highlighting its continued relevance and challenges in modern epilepsy management.

KEYWORDS: *Phenytoin, tonic–clonic seizures, osteomalacia, cerebraldysrhythmia, psychiatricphenomena, cytochrome P450 enzymes.*

INTRODUCTION

Phenytoin (Diphenylhydantoin) was first synthesized in 1908 as a compound similar to barbiturates, but it was not used initially because it showed weak sedative effects. Later, in 1938, its anticonvulsant activity was tested using the electroshock seizure model, after which it became an important antiepileptic drug. Unlike many antiepileptic medicines, phenytoin is not a central nervous system depressant. Mild sedation may occur at therapeutic doses, but this effect does not increase with higher doses. Instead, toxic doses cause excitation and muscle stiffness. Phenytoin is especially effective in eliminating the tonic phase of generalized tonic–clonic (maximal electroshock) seizures, while the clonic phase is either unaffected or slightly prolonged. It mainly works by preventing the spread of seizure activity in the brain. However, it does not increase the seizure threshold for PTZ-induced convulsions. Although it controls tonic–clonic seizures, focal EEG discharges and seizure aura may still persist.

CHEMICAL STRUCTURE

EPILEPSY

Epilepsies are a group of disorders of the CNS characterized by paroxysmal cerebraldysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic bodymovements (convulsions), sensory or

psychiatricphenomena These episodes occur unpredictably and vary greatly in how often they happen. Epilepsy originates from a localized area of the brain, and its clinical features depend on the location of this focus, the pathways through which the abnormal electrical activity spreads, and the temporary suppression of brain function that follows the seizure. Known since ancient times as the "disease of lightning," epilepsy was accurately characterized a little over a century ago by J. Hughlings Jackson.

TYPES OF EPILEPSY

1. Idiopathic Generalized Epilepsies

Idiopathic generalized epilepsies are relatively common and include generalized tonic–clonic seizures (23%), absence seizures (6%), and myoclonic seizures (3). Research shows that generalized tonic–clonic seizures are more likely to affect cognitive abilities than simple or complex partial seizures. The risk of cognitive impairment becomes even higher if a patient experiences status epilepticus. There is still debate about whether seizures in primary generalized epilepsy begin in the cerebral cortex or the thalamus. However, many studies suggest that the frontal lobes play an important role in generating seizure activity in generalized epilepsies. Neuropsychological testing supports this, showing problems with prefrontal functions such as working memory and mental flexibility. Brain imaging studies also reveal reduced glucose metabolism and lower N-acetyl aspartate levels in the prefrontal cortex, along with structural abnormalities in the frontal lobes seen on MRI scans. Overall, findings from EEGs, cognitive testing, and brain imaging indicate that frontal lobe structures are affected in primary generalized epilepsy. However, these frontal impairments are not unique to generalized epilepsies, as similar or even more severe deficits can also occur in focal epilepsies originating in the temporal, parietal, or frontal lobes.

2. Symptomatic Focal Epilepsies

According to the International Classification of Epilepsies, focal epilepsies are divided into four main types based on their location: temporal, frontal, parietal, and occipital lobe epilepsies. In most cases, there are no specific causes identified for these localization-related epilepsies, except for hippocampal sclerosis. Temporal lobe epilepsy associated with hippocampal sclerosis is widely recognized as a distinct and common syndrome, which is why its neuropsychological features are discussed separately.

3. Mesial Temporal Lobe Epilepsy

Temporal lobe epilepsy is the most common type of focal epilepsy, and about 70% of patients show hippocampal sclerosis on histopathological examination. Mesial temporal lobe epilepsy (MTLE) often does not respond well to antiepileptic medication, making many patients suitable candidates for epilepsy surgery. As a result, MTLE has been extensively studied from a neuropsychological perspective.

The most common symptoms of MTLE are impairments in episodic memory, either material-specific or more general, due to damage to the hippocampus. Patients with MTLE affecting the language-dominant hemisphere frequently experience word-finding difficulties, likely caused by the spread of epileptic activity to lateral temporal regions. MTLE is also associated with moderate difficulties in intelligence, academic performance, language skills, and visuospatial abilities.

In many cases, attention and executive functions related to the prefrontal cortex remain relatively intact. However, patients with MTLE who also experience secondary generalized tonic–clonic seizures are at higher risk of broader intellectual decline and specific impairments in prefrontal functioning. These patients may show metabolic disturbances in the prefrontal regions, which are believed to be linked to the spread of seizure activity beyond the temporal lobe.

Here is the same content rewritten in simple words, as if explained by you:
Phenytoin works by stabilizing the neuronal cell membrane. It prevents repeated and excessive firing of neurons that happens during seizures. In epilepsy, neurons undergo a “depolarization shift,” which is an abnormally large and synchronized depolarization with repeated action potentials. Phenytoin controls this by prolonging the inactivated state of voltage-gated sodium (Na^+) channels, which increases the refractory period of the neuron.

Because of this action, phenytoin selectively blocks high-frequency neuronal firing while allowing normal low-frequency firing to continue, since sodium channels get enough time to recover. At therapeutic doses, it mainly acts on sodium channels. Other effects such as reduced calcium (Ca^{2+}) entry, decreased glutamate activity, and increased GABA responses occur only at high or toxic doses.

Phenytoin also prevents intracellular accumulation of sodium that normally occurs during repeated neuronal firing. At therapeutic levels, it does not change the resting membrane potential and therefore does not interfere with normal synaptic transmission. Unlike phenobarbitone and valproate, phenytoin does not affect the process of kindling. Its ability to suppress rapid firing of neurons makes it useful not only in epilepsy but also in conditions like trigeminal neuralgia and certain cardiac arrhythmias.

MECHANISM OF ACTION PHENYTOIN

Phenytoin works by stabilizing the neuronal cell membrane. It prevents repeated and excessive firing of neurons that happens during seizures. In epilepsy, neurons undergo a "depolarization shift," which is an abnormally large and synchronized depolarization with repeated action potentials. Phenytoin controls this by prolonging the inactivated state of voltage-gated sodium (Na^+) channels, which increases the refractory period of the neuron.

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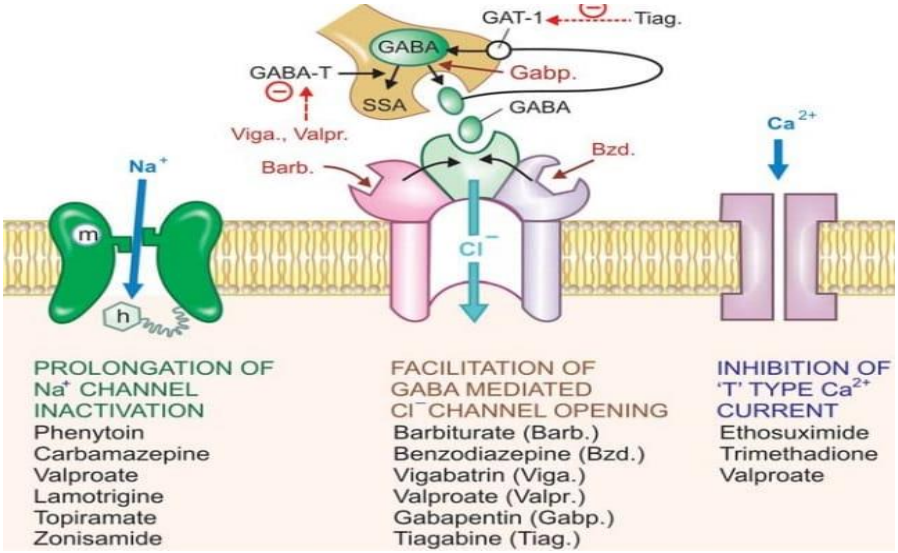


MEASURES OF EFFICACY

The primary goal of antiepileptic drug (AED) therapy is to achieve effective seizure control with minimal adverse effects. Therefore, one of the most important measures of efficacy is the proportion of patients who attain seizure freedom for a defined period. The feasibility of achieving remission depends on the type of epilepsy and the characteristics of the study population. In newly diagnosed adult patients, complete seizure control is often achievable, making seizure freedom from the start of treatment or after dose titration a meaningful and sensitive outcome measure. However, this end point may not be appropriate for severe epilepsy syndromes such as Lennox–Gastaut syndrome, where complete seizure control is less realistic. Seizure control can be evaluated at specific time points, such as 1, 2, or 3 years after initiation of therapy. These long-term assessments provide clinically relevant information regarding the sustained efficacy of an AED. Another useful outcome measure is the time taken to achieve a continuous seizure-free period, such as one year. This approach directly reflects the main therapeutic objective and allows inclusion of patients who experience seizures initially but later achieve control. Despite their clinical relevance, these outcome measures may lack sensitivity because they require total seizure freedom to demonstrate efficacy. Patients who experience even a single seizure due to poor compliance or intercurrent illness may be classified as treatment failures.

EFFICACY IN PREVENTION OF POST TRAUMATIC SEIZURES:

This cross-sectional study was carried out in the Department of Neurosurgery, Ayub Medical College, Abbottabad, from April to October 2015. Approval for the study was obtained from the institutional ethical review board prior to commencement.

Patients of either gender presenting with moderate to severe head injury within 48 hours of trauma were included consecutively. Patients younger than 5 years or older than 50 years, those with penetrating head injuries, known epilepsy, or deranged electrolyte, liver, or renal profiles were excluded. Individuals who had already experienced a seizure after the injury were also not included. A sample size of 163 patients per group was calculated using the WHO software for sample size determination, based on the formula for estimating a proportion with absolute precision and standard assumptions. Patients were recruited through the OPD and Emergency Department. After obtaining informed written consent, all eligible patients were admitted to the Neurosurgery department and ICU for further assessment. A detailed history along with complete general, systemic, and neurological examination was performed. All patients received phenytoin prophylaxis at admission. A loading dose of 20 mg/kg IV over 60 minutes was administered, followed by a maintenance dose of 5 mg/kg/day in two divided doses. Patients were monitored clinically for the development of seizures during the first seven post-traumatic days. Patients presenting within 12 hours of injury were grouped as early presenters, while those presenting after 12 hours were categorized as late presenters. Data collected included demographic details (name, age, gender), mechanism of injury, severity of trauma, and any seizure occurrence within the first week. All information was recorded using a structured proforma. Data analysis was performed using SPSS version 14.0. Mean and standard deviation were calculated for quantitative variables such as age and GCS at presentation. Categorical variables such as gender and efficacy were presented as frequencies and percentages. Efficacy was further stratified by age, gender, and severity of head injury to assess effect modification. The Chi-square test was applied at a 5% significance level to compare outcomes between patients presenting within and after 12 hours of injury.

DRUG INTERACTION

What is a drug interaction?

A drug interaction happens when a patient takes two or more medicines at the same time and one drug affects the action of another drug. This effect may increase or decrease the drug's normal action in the body. Sometimes, drug interactions can be beneficial, such as when one drug increases the therapeutic effect of another. However, interactions can also be harmful if they cause more side effects, toxicity, or reduced effectiveness of the medicine.

When two drugs act together in a synergistic manner (both enhancing each other's effects), the interaction may still become harmful if the doses are not properly reduced, leading to increased side effects. On the other hand, if a drug interaction reduces the effect of one or more drugs, the dose of the affected drug may need to be increased to achieve the desired effect.

Drug interaction are mainly classified into two types:

1. Pharmacokinetic interactions

These interactions occur when one drug affects the way another drug is absorbed, distributed, metabolized, or eliminated from the body. As a result, the amount of drug present at the site of action changes. Such interactions usually lead to an increase or decrease in the plasma concentration of the drug, its metabolites, or both.

2. Pharmacodynamic interactions

mechanisms of action. They take place at the cellular or receptor level, where the drugs produce their effects. Unlike pharmacokinetic interactions, plasma drug levels do not change in pharmacodynamic interactions These interactions occur when two drugs act on the body through similar or opposite.

DRUG-DRUG INTERACTION

PHENYTOIN-DIAZEPAM INTERACTION

Phenytoin is known to interact with several medications, mainly those that inhibit the CYP2C9 enzyme, such as amiodarone, cimetidine, fluvoxamine, and fluconazole. Other interactions have also been linked to inhibition of CYP2C19, including omeprazole, felbamate, fluoxetine, and topiramate. Diazepam itself is not an enzyme inhibitor, but since it is metabolized by CYP2C19, a possible interaction with phenytoin cannot be ruled out. To investigate this interaction, a literature search was carried out using MEDLINE, Embase, Health Star, and Web of Science databases for studies published between 1966 and December 2002. The search included the terms phenytoin, diazepam, and drug interactions and was limited to English-language studies in adult humans. Relevant tertiary sources were also reviewed, and Health Canada's Adverse Drug Reaction Monitoring Program was contacted, although no additional information was obtained. The available case reports and clinical studies examining the interaction between phenytoin and diazepam showed mixed and sometimes unclear results. Two case reports suggested that phenytoin blood levels may increase when diazepam is given at the same time. In contrast, one observational study

reported lower phenytoin levels in patients taking both phenobarbital and diazepam. However, these studies did not provide sufficient details regarding patient compliance, use of other medications, or the effects of stopping diazepam. Two controlled pharmacokinetic studies also produced conflicting findings. One study involving 124 patients taking phenytoin with a benzodiazepine found that phenytoin concentrations increased in a small group of patients whose doses remained unchanged, with an average increase of 67% after six weeks. Some patients experienced marked increases, although the results were not statistically significant. Another study involving eight patients found a mean decrease of 16% in phenytoin levels after one month of benzodiazepine therapy. Based on this, the authors concluded that diazepam does not inhibit phenytoin metabolism and may act as a weak enzyme inducer.

PHENYTOIN–RIFAMPICIN INTERACTION

Dr F. J. Abajo and colleagues from Hospital del Insalud "La Paz," Madrid, reported a clinically significant interaction between rifampicin and phenytoin. An 82-year-old man receiving rifampicin (600 mg/day) and ethambutol (1200 mg/day) for pulmonary tuberculosis was admitted with generalized seizures. He had a previous history of idiopathic focal seizures, which had been well controlled for many years with phenytoin and phenobarbitone. Since he had remained seizure-free for over 10 years, antiepileptic therapy had been stopped nine months earlier. After admission, phenytoin monotherapy was restarted. A relatively high dose of 400 mg/day was needed to control seizures. During rifampicin therapy, serum phenytoin levels remained within the therapeutic range (17.3–18.2 mg/L). Eight weeks later, the phenytoin dose was reduced to 375 mg/day. Just before stopping rifampicin and ethambutol, the phenytoin level was 14.4 mg/L. One week after stopping antitubercular therapy, the level slightly decreased to 13 mg/L, but by the second week, it rose sharply to 22 mg/L, exceeding the therapeutic range. Despite further reductions in phenytoin dose (to 350 mg and later 325 mg/day), serum concentrations continued to rise and remained high for several weeks. Only after nine weeks did stable therapeutic levels (13.6–15.3 mg/L) return. Blood samples were consistently taken 10–12 hours after dosing, and patient compliance was good. This case clearly demonstrates that rifampicin increases the metabolism of phenytoin, leading to lower serum levels during combined therapy. When rifampicin was withdrawn, enzyme activity gradually returned to normal, resulting in dangerous elevation of phenytoin levels. Rifampicin is a strong hepatic microsomal enzyme inducer, while phenytoin is metabolized by these enzymes. The delayed and prolonged rise in phenytoin concentration

after rifampicin withdrawal supports this mechanism. Ethambutol does not induce liver enzymes and was unlikely to contribute to this interaction. This report highlights the importance of close monitoring of phenytoin levels during and after rifampicin therapy to prevent toxicity.

FOOD-DRUG INTERACTION

Most clinically important food–drug interactions occur because food alters a drug's bioavailability, with the greatest concern being reduced absorption that can lead to treatment failure, often due to chelation or food-induced physiological changes such as altered gastric acid secretion. In a study of six healthy volunteers, sodium phenytoin taken with a high-protein meal was absorbed more slowly than in the fasting state, but the total amount absorbed remained unchanged, as indicated by similar AUC values and comparable urinary excretion of its main metabolite, HPPH.

HERB-DRUG INTERACTION

Phenytoin (PHT) is a widely used antiepileptic drug for the treatment of both generalized and partial seizures. It has a narrow therapeutic range (10–20 µg/mL), poor water solubility, and a slightly acidic nature, which contribute to irregular and slow oral absorption. To improve its solubility, several prodrugs such as fosphenytoin have been developed. However, PHT still tends to precipitate in the gastrointestinal environment, leading to variable absorption. The usual daily dose of PHT ranges from 400–600 mg. It has a long and variable half-life (12–36 hours), resulting in significant inter-patient variability. Due to its extended elimination, steady-state levels may take 1–4 weeks to achieve, and most patients require once-daily dosing. Because of its narrow therapeutic index, therapeutic drug monitoring is essential to maintain efficacy while avoiding toxicity.

Pharmacokinetics and pharmacodynamics of PHT can be influenced by factors such as age, pregnancy, nutritional status, and drug interactions. Herbal medicines, which contain multiple active constituents, may interact with conventional drugs by inducing or inhibiting cytochrome P450 enzymes. Such herb–drug interactions can alter drug effectiveness or safety and are often difficult to detect due to underreporting and lack of awareness. Therefore, evaluating potential interactions between herbal products and conventional drugs remains an important clinical concern.

SIDE EFFECTS

Common Side Effects

Phenytoin commonly causes skin-related side effects, especially with long-term use. The most frequent is gingival hyperplasia, affecting about 50% of patients. Around one-third may also develop coarse facial features, enlarged lips, and thickened scalp or facial skin, particularly with prolonged treatment. Another common effect is hirsutism, seen in about 12% of children, usually within the first three months; it often improves after stopping the drug. Studies in children and adolescents with epilepsy show higher rates of hirsutism, acne (especially in females), leukonychia, and small hand scars compared with healthy controls, though some research found no clear link between phenytoin and acne or increased skin oil. Regarding cardiovascular safety, oral phenytoin toxicity with high blood levels rarely causes serious heart problems, so routine cardiac monitoring is usually unnecessary. With intravenous phenytoin, cardiac side effects such as hypotension, bradycardia, or arrhythmias can occur, particularly in older patients, at high doses, or with rapid infusion rates. These effects are generally reversible when the infusion is stopped or slowed, and fatalities are rare but have been reported with extremely rapid administration.

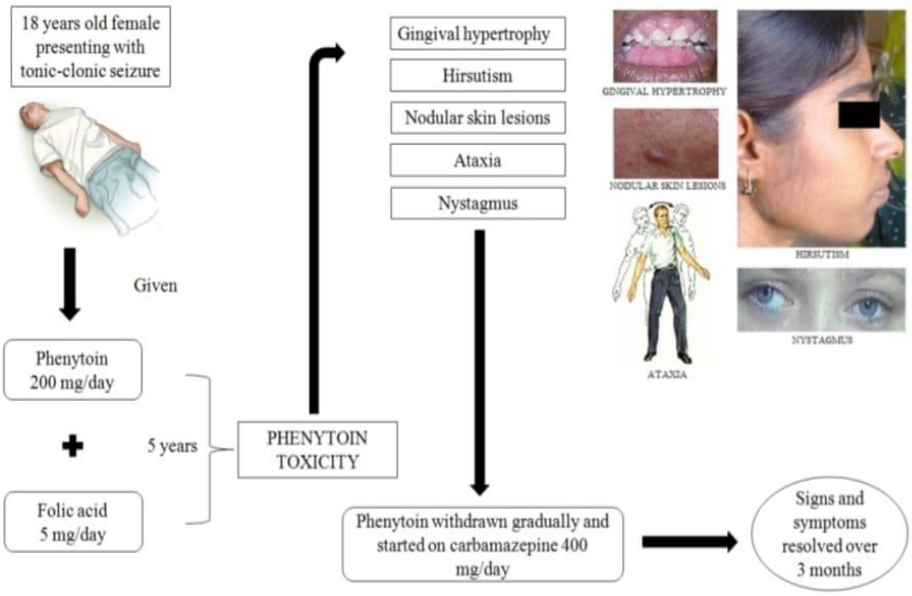
SEVERE ADVERSE EFFECTS

Cardiovascular-Clinical studies of oral phenytoin toxicity showed that even when serum levels were almost twice the therapeutic limit, patients did not develop significant cardiovascular or ECG abnormalities, suggesting that routine cardiac monitoring is unnecessary in oral overdose.

Large prospective studies evaluating IV phenytoin found that cardiovascular adverse effects were uncommon and usually related to high doses and rapid infusion rates. Hypotension and bradycardia occurred mainly in elderly patients or those with pre-existing cardiac disease and resolved after stopping or slowing the infusion. Most cardiac effects appeared when doses exceeded 800 mg and infusion rates were greater than 40 mg/min. Another study reported hypotension as the most frequent adverse effect, especially in patients over 60 years old, but symptoms resolved when infusion rates were reduced. Arrhythmias and conduction abnormalities were rare, no deaths occurred, and severe complications were associated with excessively rapid administration. Overall, cardiovascular toxicity from phenytoin is uncommon when appropriate dosing and infusion rates are used.

PHENYTOIN TOXICITY

This cross-sectional study was carried out in the Department of Neurosurgery, Ayub Medical College, Abbottabad, from April to October 2015. Approval for the study was obtained from the institutional ethical review board prior to commencement. Patients of either gender presenting with moderate to severe head injury within 48 hours of trauma were included consecutively. Patients younger than 5 years or older than 50 years, those with penetrating head injuries, known epilepsy, or deranged electrolyte, liver, or renal profiles were excluded. Individuals who had already experienced a seizure after the injury were also not included. A sample size of 163 patients per group was calculated using the WHO software for sample size determination, based on the formula for estimating a proportion with absolute precision and standard assumptions. Patients were recruited through the OPD and Emergency Department. Afterobtaining informed written consent, all eligible patients were admitted to the Neurosurgery department and ICU for further assessment. A detailed history along with complete general, systemic, and neurological examination was performed. All patients received phenytoin prophylaxis at admission. A loading dose of 20 mg/kg IV over 60 minutes was administered, followed by a maintenance dose of 5 mg/kg/day in two divided doses. Patients were monitored clinically for the development of seizures during the first seven post-traumatic days. Patients presenting within 12 hours of injury were grouped as early presenters, while those presenting after 12 hours were categorized as late presenters. Data collected included demographic details (name, age, gender), mechanism of injury, severity of trauma, and any seizure occurrence within the first week. All information was recorded using a structured proforma. Data analysis was performed using SPSS version 14.0. Mean and standard deviation were calculated for quantitative variables such as age and GCS at presentation. Categorical variables such as gender and efficacy were presented as frequencies and percentages. Efficacy was further stratified by age, gender, and severity of head injury to assess effect modification. The Chi-square test was applied at a 5% significance level to compare outcomes between patients presenting within and after 12 hours of injury.



SAFE AND EFFECTIVE USE OF PHENYTOIN REQUIRES CAREFUL ATTENTION AT FOUR KEY STAGES OF TREATMENT

1. Loading
2. Starting maintenance therapy
3. Adjusting the dose
4. Monitoring, follow-up, and patient education

1. Loading Phase

A loading dose of phenytoin is used when there is a high and immediate risk of seizures and therapeutic blood levels must be achieved quickly. Situations where loading is appropriate include:

- Status epilepticus
- Frequent new-onset seizures (excluding most withdrawal-related seizures)
- Breakthrough seizures associated with low anticonvulsant blood levels
- A first seizure that has a high chance of recurring, such as when a focal brain lesion is present
- Depending on urgency, loading may be done using:
- Intravenous phenytoin (infused at a rate not exceeding 50 mg per minute)
- Intravenous or intramuscular fosphenytoin
- Oral phenytoin

To calculate an initial loading dose, or an additional booster dose to raise a low serum level, a standard loading formula based on phenytoin's distribution in the body is used. This formula estimates how much drug is required to increase the blood level by a desired amount. After intravenous loading, the peak phenytoin level depends mainly on how the drug distributes in body tissues, not on how quickly it is eliminated. While metabolism and elimination may later be influenced by factors such as liver disease or drug interactions, these factors generally do not affect the calculated loading dose itself. Giving too much phenytoin during loading can cause early toxicity. For example, using the loading formula shows that a 60-kg patient with no measurable phenytoin level who needs a target level of 15 µg/mL would require approximately 675 mg not the routinely given 1000 mg.

The same formula is useful for supplemental loading when:

- The initial loading dose failed to reach the desired level, or
- The achieved level was insufficient to control seizures

In these situations, simply increasing the daily maintenance dose is not effective because phenytoin levels rise too slowly. Additionally, if the low level is due to poor medication adherence, increasing the maintenance dose may be dangerous. Once compliance improves, the higher dose could result in toxic blood levels.

CONCLUSION

Phenytoin continues to play an important role in the management of epilepsy, particularly in focal seizures and generalized tonic–clonic seizures. Its well-established efficacy is mainly due to stabilization of neuronal membranes through inhibition of voltage-gated sodium channels, which helps in controlling seizure activity effectively in many patients. Despite its proven effectiveness, the clinical use of phenytoin is limited by a narrow therapeutic index and wide inter-individual variability in pharmacokinetics. Safety concerns arise from its dose-dependent side effects such as nystagmus, ataxia, dizziness, and cognitive impairment, as well as long-term adverse effects including gingival hyperplasia, hirsutism, osteomalacia, and peripheral neuropathy. Serious adverse reactions like hypersensitivity syndromes, hepatic dysfunction, and blood dyscrasias, though less common, require careful monitoring. Drug interactions remain a major challenge with phenytoin therapy, as it is a potent inducer of hepatic enzymes and is itself affected by several drugs, leading to altered plasma concentrations and potential loss of seizure control or toxicity. Phenytoin toxicity, characterized by neurological, gastrointestinal, and systemic manifestations, emphasizes the

need for therapeutic drug monitoring and individualized dosing. In conclusion, while phenytoin is an effective and time-tested antiepileptic drug, its use demands careful patient selection, regular monitoring, and awareness of drug interactions and adverse effects. When used judiciously, with appropriate dose adjustments and monitoring, phenytoin remains a valuable option in epilepsy management.

REFERENCE

1. H_Jokeit, M Schacher - Epilepsy & Behavior, 2004 Elsevier.
2. FJ Abajo BMJ: British Medical Journal, 1988 pmc.ncbi.nlm.nih.gov
3. A. Murphy. K Wilbur Annals of Pharmacotherapy, 2003; journals.sagepub.com
4. B Guldiken. J Remi, Noachtar Journal of neurology. 2016; Springer.
5. K. D. Tripathi. Essentials of Medical Pharmacology, JAYPEE Brothers Medical Publishers (P) Ltd, New Delhi.
6. Thomas H. Glick, MD, Tom P. Workman, MD, and Slava V. Gaufberg, MD Cambridge Health Alliance, Cambridge, Mass; Harvard Medical School, Boston, Mass.
7. PN Patsalos, W Froscher, F Pisani, CM Van Rijn Epilepsia, 2002.
8. The effect of food on the absorption of phenytoin. M. C. Kennedy and D. N. Wade, Aust. N.Z. J. Med., 1982; 12: 258–261.
9. Keigbley MRB. Burdon DW. Mogg GAG, George RH, Alexander-Williams I. Thompson H. Pseudomembranous colitis. Lancet, 1979; i: 55940.
10. Perucca E. Pharmacologic advantages of antiepileptic drug monotherapy. Epilepsia, 1997; 38: S6–8.
11. Chadwick D. Monotherapy clinical trials of new antiepileptic drugs: design, indications, and controversies. Epilepsia, 1997; 38: S16–20.
12. Meierkord H, Boon P, Engelsen B, Go¨cke K, Shorvon S, Tinuper P, Holtkamp M (2010) EFNS guideline on the management of status epilepticus in adults. Eur J Neurol., 17: 348–355.
13. Zoneraich S, Zoneraich O, Siegel J (1976) Sudden death following intravenous sodium diphenylhydantoin. Am Heart J.
14. Rausch R, Le M-T, Langfitt JT. Neuropsychological evaluation. In: Engel J, Pedley Jr TA, editors. Epilepsy: a comprehensive textbook, vol. 1. Philadelphia: Lippincott–Raven, 1997; 977–87.
15. Dikmen S, Matthews CG. Effect of major motor seizure frequency upon cognitive-intellectual functions in adults. Epilepsia, 1977; 18: 21–9.

16. Manon-Espaillat R, Burnstine TH, Remler B, et al. Antiepilepticdrug intoxication: factors and their significance. Epilepsia, 1991; 32: 96–100.
17. Morris RG, Black AB, Lam E, et al. Clinical study of lamotrigine and valproic acid in patients with epilepsy: using a drug interaction to advantage? Ther Drug Monit., 2000; 22: 656–60.
18. Hansten PD. Understanding drug interactions. Sci Med., 1998, Jan/Feb; 16–25.