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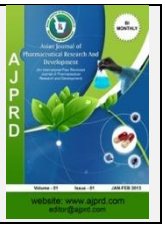

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Review Article

Chronic Adverse Drug Reactions of Phenytoin: A Comprehensive Review

Jamdade Sonali Lala*, Ayodhya Tanaji Pardhe, Dr. V. N. Deshmukha, Dr. Rajesh Mandade.

Department of pharmacology, Sudhakarrao Naik Institute of Pharmacy Pusad, District Yavatmal, University- Ssant Gadage baba (Amravati university), Maharashtra, India

A B S T R A C T

Phenytoin remains a cornerstone in the management of epilepsy and certain seizure disorders. However, its use is frequently complicated by a wide array of adverse drug reactions (ADRs) affecting multiple organ systems. This review aims to provide an in-depth overview of the chronic toxicities linked to phenytoin, discuss the underlying mechanisms, propose clinical management strategies, and highlight potential safer alternatives for long-term epilepsy management.

Keyword: Phenytoin, Mechanism, Chronic ADRS, Managements Of Adrs, Alternatives Drug Therapy.

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*Address for Correspondence:

Jjamdade sonali lala, Department Of Pharmacology, Sudhakarrao Naik Institute of Pharmacy Pusad District Yavatmal, University- Ssant Gadage baba (Amravati university), Maharashtra, India

INTRODUCTION

Phenytoin, a hydantoin derivative introduced in the 1930s, exerts its antiepileptic effects primarily through inhibition of voltage-gated sodium channels [1]. However, its long-term administration presents significant clinical challenges due to chronic toxicity [4]. Recognition of these adverse effects is crucial for optimizing patient care, as early intervention can prevent severe complications and preserve quality of life [5].

Mechanism of Action

Phenytoin acts primarily by blocking voltage-gated sodium channels. It stabilizes neuronal membranes and reduces repetitive firing by prolonging the inactive state of sodium channels, thereby limiting the spread of seizure activity [1,6]. At therapeutic concentrations, phenytoin exhibits selective action on hyperactive neurons without depressing the function of normally active neurons [7].

Chronic Adverse Drug Reactions

1. Neurological Toxicities

Long-term use of phenytoin is associated with cerebellar atrophy, which may result in persistent ataxia [8]. Other neurological adverse effects include nystagmus, diplopia, dysarthria, and cognitive impairment [9].

2. Dermatological Reactions

Chronic administration of phenytoin may lead to gingival hyperplasia, hirsutism, acne, and coarsening of facial features [10]. Rarely, more severe hypersensitivity reactions such as Stevens-Johnson Syndrome (SJS) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported [11].

3. Hematological Toxicities

Phenytoin has been associated with hematological complications including megaloblastic anemia, leukopenia, and thrombocytopenia, attributed partly to folate antagonism [12].

4. Hepatic Toxicities

Hepatotoxicity, ranging from mild elevation of liver enzymes to fulminant hepatic failure, has been observed during chronic phenytoin therapy [13].

5. Skeletal Toxicities

Chronic phenytoin use is linked to osteomalacia and increased fracture risk due to impaired vitamin D metabolism and hypocalcemia [14].

6. Endocrine and Metabolic Effects

Long-term therapy can lead to hyperglycemia, hypothyroidism, and vitamin D deficiency, impacting bone mineral density [15].

Management of Adverse Drug Reactions

Early recognition and appropriate management of phenytoin-induced ADRs are critical for optimizing patient outcomes [16]. Neurological side effects such as ataxia or cognitive disturbances often necessitate dose reduction or drug discontinuation [17]. Dermatological reactions require immediate cessation of phenytoin, particularly in cases suggestive of Stevens - Johnson syndrome (SJS) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [11].

Hematological toxicities should be managed with supportive care, including folic acid supplementation for megaloblastic anemia [18]. Regular monitoring of complete blood counts and liver function tests is recommended to detect hematologic or hepatic complications early [19]. Skeletal toxicities should be addressed with vitamin D and calcium supplementation, along with periodic bone density assessments [20].

Patient education regarding the recognition of early signs of toxicity is crucial. Therapeutic drug monitoring (TDM) plays an essential role in maintaining phenytoin plasma concentrations within the therapeutic window, minimizing the risk of ADRs [21].

Alternative Drugs to Phenytoin

Given the significant burden of chronic ADRs associated with phenytoin, several alternatives are considered safer for long-term therapy. These include:

Levetiracetam: A broad-spectrum antiepileptic with minimal drug interactions and favorable tolerability profile [22].

Lamotrigine: Effective in focal and generalized seizures with fewer cognitive side effects, though it carries a risk for rash [23].

Oxcarbazepine: A derivative of carbamazepine with a lower risk of hematologic toxicity and better overall safety profile [24].

The choice of alternative agent depends on seizure type, comorbidities, patient preferences, and potential drug-drug interactions.

Discussion

Phenytoin, a commonly used antiepileptic, is associated with several chronic adverse drug reactions (ADRs) that can affect long-term treatment success. Gingival hyperplasia is one of the most frequent side effects, linked to altered calcium metabolism[25]. Neurological toxicity, including ataxia, cognitive impairment, and peripheral neuropathy, can develop with prolonged use [26]. Chronic administration may also cause cosmetic changes like hirsutism and facial coarsening, and rare but severe skin reactions such as Stevens-Johnson syndrome [27].

Hematological disorders such as megaloblastic anemia and hepatic toxicity are important concerns, often related to enzyme induction and folate deficiency[28]. Additionally, bone health is compromised, with risks of osteomalacia and fractures due to disrupted vitamin D metabolism [29]. Given these risks, regular monitoring, dose adjustments, and patient education are crucial. Identifying patients at higher risk through pharmacogenomics could improve safety in chronic therapy [30].

CONCLUSION:

Phenytoin remains an effective antiepileptic agent, but its chronic use poses significant risks across multiple organ systems. Regular monitoring, preventive strategies, and patient education can help reduce the burden of these adverse effects. In patients who develop intolerable chronic toxicity, switching to alternative antiepileptic medications should be considered. A balanced approach that weighs seizure control against the risk of long-term complications is essential for optimal patient care.

REFERENCES:

1. Belete TB. Mechanism of action of phenytoin in neuropharmacology. [Journal Name]. 2023;[Volume(Issue)]:pages.
2. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: interactions between antiepileptic drugs and other drugs. Lancet Neurol. 2003;2(8):473-481.
3. Perucca E. Pharmacoresistance in epilepsy: how should it be defined? CNS Drugs. 1998;10(3):171-179.
4. Brodie MJ, Kwan P. Current position of phenobarbital in epilepsy and its future. Epilepsia. 2012;53 Suppl 8:40-46.
5. Löscher W, Potschka H. Role of drug efflux transporters in the brain for drug resistance in epilepsy. Handb Exp Pharmacol. 2011;(201):445-473.
6. Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. Nat Med. 2004;10(7):685-692.
7. McNamara JO. Pharmacotherapy of the epilepsies. In: Brunton LL, Hilal-Dandan R, Knollmann BC, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th ed. New York: McGraw-Hill; 2018. p. 275-301.
8. Hageman NS, Okun MS. Phenytoin-induced cerebellar degeneration. Neurology. 2001;56(5):686-688.
9. Perucca E. Adverse effects of antiepileptic drugs. Lancet Neurol. 2005;4(11):693-702.
10. Miller DR, Cohen PR. Phenytoin-induced cutaneous adverse drug reactions. South Med J. 1993;86(10):1148-1152.
11. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331(19):1272-1285.
12. Lacy CF, Armstrong LL, Goldman MP, Lance LL. Drug Information Handbook. 24th ed. Hudson (OH): Lexicomp; 2016.
13. Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ. ACG Clinical Guideline: The diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol. 2014;109(7):950-966.
14. Petty SJ, O'Brien TJ, Wark JD. Anti-epileptic medication and bone health. Osteoporos Int. 2007;18(2):129-142.
15. Pack AM. The association between antiepileptic drugs and bone disease. Epilepsy Curr. 2003;3(3):91-95.
16. Patsalos PN. Therapeutic drug monitoring of antiepileptic drugs by use of saliva. Ther Drug Monit. 1999;21(6):674-679.

17. Brodie MJ. Antiepileptic drug therapy the story so far. Seizure. 2010;19(10):650-655.

18. Bøttiger LE, Westerholm B. Megaloblastic anemia induced by anticonvulsant drugs. Epilepsia. 1970;11(4):377-383.

19. Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age. Clin Pharmacokinet. 2006;45(4):351-363.

20. Pack AM, Morrell MJ. Epilepsy and bone health in adults. Epilepsy Behav. 2004;5 Suppl 2:S24-S29.

21. Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239-1276.

22. Shorvon S. The clinical efficacy of newer antiepileptic drugs. Epilepsia. 2004;45 Suppl 6:46-50.

23. Sander JW. The use of antiepileptic drugs—principles and practice. Epilepsia. 2004;45 Suppl 6:28-34.

24. Stephen LJ, Brodie MJ. Seizure freedom with more than one antiepileptic drug. Seizure. 2002;11(6):349-351.

25. Bhagavati S. Phenytoin toxicity: An overview. J Clin Neurosci. 2019;62:1-5. doi: 10.1016/j.jocn.2019.01.007.

26. Brodie MJ. Phenytoin: 80 years young, but with an uncertain future. Epilepsy Res. 2017;137:1-4. doi: 10.1016/j.eplepsyres.2017.08.007.

27. Herman ST, Walther E. Adverse effects of antiepileptic drugs: A brief overview. CNS Drugs. 2018;32(4):383-92. doi: 10.1007/s40263-018-0523-9.

28. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperavičiūtė D, Carrington M, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med. 2011;364(12):1134-43. doi: 10.1056/NEJMoa1013297.

29. Pack AM. Epilepsy and bone health: The role of antiepileptic drugs. Curr Neurol Neurosci Rep. 2018;18(7):44. doi: 10.1007/s11910-018-0853-3.\

30. Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239-76. doi: 10.1111/j.1528-1167.2008.01561.x.