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CASE REPORT : PHENYTOIN INDUCED-GINGIVAL OVERGROWTH

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Abstract: Phenytoin Induced-Gingival Overgrowth. Phenytoin is an antiepileptic drug that primarily used for the treatment of tonic-clonic and partial seizures. The narrow therapeutic index of phenytoin and its ubiquitous daily use pose a high risk of side effect. The incidence of phenytoin-induced gingival overgrowth is the highest among drugs that induce gingival overgrowth. This condition is associated with multiple factors, and the pathogenesis of phenytoin-induced connective tissue responses in the gingiva is associated with several factors such as fibroblasts, inflammatory cytokines, and matrix metalloproteinase (MMP) synthesis. To prevent such serious adverse consequences, it is necessary that phenytoin is used reasonably in clinical practice.
Keyword: gingival overgrowth, drug-induced gingival overgrowth, phenytoin

Abstrak: Pembesaran Gingiva yang Diinduksi Fenitoin
Fenitoin merupakan obat anti-epilepsi yang umum digunakan sebagai terapi bangkitan tonik-klonik dan parsial. Indeks terapeutik yang sempit dan penggunaannya yang luas meningkatkan risiko terjadinya efek samping. Insiden pembesaran gingiva yang diinduksi fenitoin ditemukan paling banyak dibandingkan penggunaan obat antiepilepsi lain. Kondisi ini berhubungan dengan banyak faktor dan patogenesis pembesaran jaringan ikat disebabkan oleh beberapa faktor seperti fibroblas, sitokin inflamasi dan sintesis matriks metalloproteinase (MMP). Penggunaan fenitoin secara tepat harus diperhatikan dalam praktik klinis guna mencegah efek samping yang serius.
Kata kunci: pembesaran gingiva, pembesaran gingiva diinduksi fenitoin, fenitoin

INTRODUCTION

Phenytoin, introduced in 1938, is one of anticonvulsant agent that commonly used for epilepsy treatment. Phenytoin used to treat acute repetitive seizures, partial-onset and generalized tonic-clonic seizures, and status epilepticus. However, phenytoin treatment is associated with several side effects, and toxicity plays a key role in these issue (Awasthi, Agrawal, Chakraborty et al., 2022). Previous studies show that gingival hypertrophy was common adverse effect of phenytoin. Drug-induced gingival overgrowth, previously known as drug-induced gingival hyperplasia or hypertrophic gingivitis, is a condition where the gingival tissue increase in the size due to side-effect of certain drugs. This condition causes problems with chewing, aesthetics, and pronunciation, and leads to the decrease the quality of life of the patients (Farook et al 2019).

The prevalence of phenytoin-induced gingival hyperplasia showed variations ranging from 13% to 50%, in community-based studies in treated patients. The onset of excessive gingival growth may occur after first month of treatment. However, it usually occurs more than 3 months after the start of phenytoin use. The enlargement of the gingival tissue generally begins in the around the lip and the surfaces of the mandibular anterior. Clinically, the expansion of the gingival tissues begins in the region of interdental papillae, which gradually increase in size. Some studies suggest that phenytoin-induced gingival hyperplasia is more common in younger age groups (Candotto et al., 2019). To prevent such serious adverse consequences, it is necessary that phenytoin is used reasonably in clinical

practice. This review article focuses on overgrowth gingival as a side effect of phenytoin used.

CLINICAL USE OF PHENYTOIN

Phenytoin first demonstrated in 1938 by Tracy Putnam and H. Houston Merritt, when they discovered that it could be used to control seizures, while avoiding the sedation that was typical to phenobarbital (Patocka et al, 2020). Phenytoin was the first effective antiepileptic drug (AED) used to treat acute repetitive seizures, partial-onset and generalized tonic-clonic seizures (Gupta, M. and Tripp, J, 2023). A number of publications have reviewed the efficacy of phenytoin relative to other, mainly newer, AEDs used in monotherapy in patients with epilepsy. Experience has also established that phenytoin is ineffective for treating myoclonic seizures (irrespective of the age of onset), absence and atonic seizures of primary generalized epilepsy, infantile spasms and seizures in the Lennox–Gastaut syndrome. Phenytoin was later used as an antiarrhythmic drug in cardiology. However, currently, its usage as antiarrhythmic purpose is abandoned, but still reserves their importance in the treatment of epilepsy (Eadie, 2015).

Phenytoin is well absorbed following oral administration (Patocka et al, 2020). The recommendation initial dose of phenytoin ranges from 200-300 mg per day and maintenance dose 200-400 mg per day in adults or 4-10mg/kg/day in children (Kusumartuti et al, 2019; Gupta and Trip, 2023; Awasthi, 2022). The intramuscular administration is not recommended because its absorbed very slowly and inconsistently. Intravenous phenytoin is fully bioavailable, but the highly alkaline pH of the solution, and its content of polyethylene glycol, require very slow administration to minimize side effects. The drug may crystallize out if injected into an intravenous fluid reservoir containing a solution at a more physiological pH. Intravenous phenytoin known effective in treating neonatal seizures and convulsive status epilepticus (Eadie, 2015). Phenytoin cannot be given to patients with a history of hypersensitivity to phenytoin or other hydantoins, and injection preparations are contraindicated in sinus bradycardia, sinoatrial block, 2nd or 3rd degree heart block (Gupta, M. and Tripp, J, 2023).

MECHANISM OF ACTION

Phenytoin can be administered by oral delivery or parenteral delivery. Phenytoin has a consistent and complete, or nearly complete (~95%), oral bioavailability. The distribution of the drug is widespread throughout the body with the distribution volume in the range of 0.5 - 0.8 L/kg. Phenytoin easily crosses the blood – brain barrier and it is extensively bound (90%) to plasma protein, mainly albumin (Patocka, et al. 2020, Eadie, 2015). Phenytoin will produce metabolites in the form of inactive p-hydroxyphenytoin, is formed via a postulated short-lived arene oxide intermediate in a reaction catalysed by the CYP450 isoforms CYP2C9 and CYP2C19 (Gupta and Trip, 2023).

Phenytoin has a highly selective inhibitory effect on the motor area of cerebral cortex. Phenytoin is a voltage-gated, sodium channel blocker. It exerts its effect by stabilizing the inactive state of the Na+ channels and extending the refractory period of the neuron. Importantly, phenytoin inhibits or eliminates abnormal electrical activity in nerve and muscle cells without affecting normal bioelectrical production and conduction. The electrophysiological basis of these effects involves regulation of transmembrane movement and intracellular distribution of Na+, K+, and Ca2+. Phenytoin has a highly significant blocking effect on the Na+ channels of neurons with abnormal high-frequency discharges, where it inhibits these repeated high-frequency discharges; conversely, phenytoin has no significant effect on normal low-frequency discharge. In addition, phenytoin blocks Ca2+ (T-type) neuronal channels that inactivate quickly and inhibits Ca2+ influx (Patocka et al, 2020).

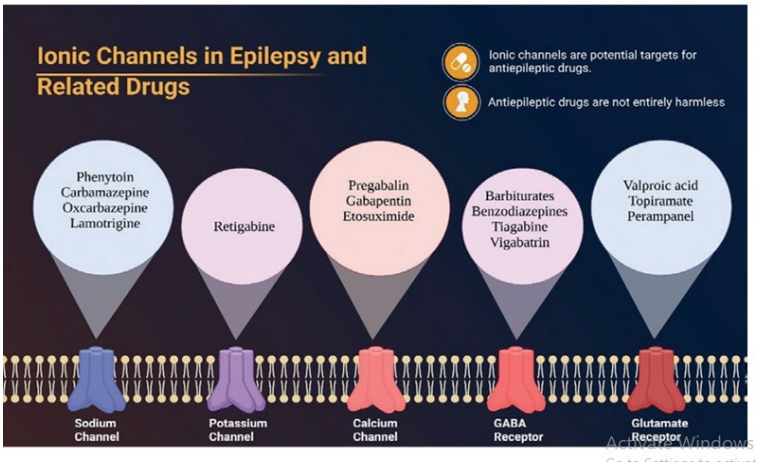

Figure 1. Mechanism of action phenytoin (Rubio *et al.*, 2023)

Phenytoin also regulates neurotransmitter including, acetylcholine, serotonin, norepinephrine, dopamine, GABA and endorphins. At high concentrations, phenytoin inhibits GABA uptake at nerve endings, the end result is an increase in Cl− influx and hyperpolarisation, and subsequent inhibition of the incidence and spread of abnormal high-frequency discharge (Eadie, 2015).

ADVERSE EFFECT OF PHENYTOIN

Phenytoin has a narrow therapeutic index and adversely affects multiple organ systems. Due to its long half-life, it may be administered in a less frequent daily dosage. Thus, a small increment in dose above the required maintenance dose often results in side effects (Awasthi, 2022). The side effects related to phenytoin can be seen in table 1.

Table 1. Common and/or serious adverse effects of phenytoin (Eadie, 2015)

System	Adverse effects
Nervous system	Nystagmus, gait ataxia, diplopia, dyskinesias, dizziness, headache, mood and cognitive changes, sedation, diplopia, depressed consciousness, cerebellar degeneration
Skin	Morbilliform rash in 5–10%, Stevens–Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, hirsutism, acne
Gums	Hypertrophy
Bone	Osteomalacia
Haematological	Lymphadenopathy (pseudolymphoma), megaloblastic anaemia, suppression of individual blood cell lines
Other hypersensitivity reactions	Aromatic anticonvulsant hypersensitivity syndrome, systemic lupus erythematosus
Cardiovascular	Cardiac conduction defects, arrhythmias, hypotension (intravenous therapy), cardiac depression
Biochemical alterations	Increased: γ-glutamyl transpeptidase, alkaline phosphatase, sex hormone-binding globulin Reduced: folate, thyroid hormones, sex hormones
Teratogenesis	Various malformations reported but little convincing statistical evidence of major teratogenic effects Fetal hydantoin syndrome

McLaughlin WS et al found that high plasma phenytoin levels were a significant risk factor for gingival overgrowth. Brunet L et al in 2004 reported that inflammation of the gingiva is also a significant risk factor for gingival overgrowth (Mardiana, Kartini and Widjasena, 2012). Study Asadi-Pooya, et al found that phenytoin is the most notorious antiepileptic drug with regard to the cosmetic adverse effects and is often associated with gingival hyperplasia. Phenytoin-induced gingival hyperplasia can occur within 3 months of drug use, and more severe after 12-18 months (Hatahira et al, 2017; Chacko and Abraham, 2014). Research conducted by Mardiana et al found that oral phenytoin doses and phenytoin levels in the blood were significant risk factors for the incidence of gingival hyperplasia, while the duration of phenytoin administration was not. Patients with oral phenytoin doses of ≥300 mg have a 21 times greater risk of developing gingival hyperplasia than patients with oral phenytoin doses (Mardiana, Kartini and Widjasena, 2012).

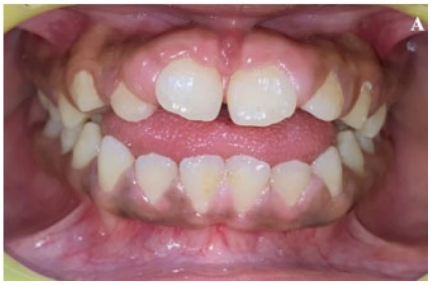

Figure 2. Gingival overgrowth due to adverse effect of phenytoin (Awasthi, 2022)

MECHANISM OF PHENYTOIN-INDUCED GINGIVAL OVERGROWTH

Gingival enlargement is associated with multiple factors, including inflammatory (acute and chronic), idiopathic, drug-induced, neoplasia (benign and malignant tumor), hormonal disturbance, ascorbic acid deficiency, changes in gingival connective tissue homeostasis, and pre-existing dental plaque. Poor oral hygiene may also predispose patients to gingival hyperplasia and keeping a good oral hygiene should be considered seriously by all patients who are taking any antiepileptic drug (Hatahira et al, 2017). Phenytoin in the saliva is absorbed or diffused via the sulcular epithelium into the serum causing a double exposure to phenytoin via two pathways, mainly from the systemic circulation and partly from the reabsorption pathway of the saliva. Thus, gingival sulcular tissue is more susceptible to the effects of phenytoin causing gingival overgrowth (Farook et al, 2019).

The mechanism mediating the pathogenesis of medication-induced connective tissue responses in the gingiva is still poorly understood. Some hypotheses have suggested the role of factors such as 1) fibroblasts, 2) inflammatory cytokines, and 3) matrix metalloproteinase (MMP) synthesis. The increase of gingival connective tissue in gingival overgrowth due to the accumulation of extracellular matrix proteins in gingival fibroblasts associated with varying degrees of chronic inflammation (Sharma et al., 2020). Drug - induced gingival overgrowth has been proposed to result from an increase in cell growth, a decrease in cell apoptosis, inflammation in the periodontal tissue, an abnormal immune response, modulation of the function of the extracellular matrix (i.e. the synthesis or degradation of collagen) and/or interactions between the cells and the drugs (Takeuchi, 2021).

Candotto et al found that phenytoin alters the inflammatory

response to gingival fibroblast gene expression with 13 inflammatory genes (CXCL5, CXCL10, CCR1, CCR4, CCR5, CCR6, IL-1A, IL-1B, IL-5, IL-7, IL-6R, BMP-2, and TNFSF-10) were statistically significant. All but one gene resulted downregulated after 24h of treatment with phenytoin. BPM2 was the only, although weakly, up-expressed gene. Study by Takeuchi found that treatment with phenytoin decreased the number of apoptotic cells compared with the control. Phenytoin also increased the percentage of viable cells and decreased the percentage of dead cells compared with the control, and increased the cyclin D mRNA expression level compared to the control. Phenytoin causes the inhibition of collagen degradation via MMPs/TIMP-1, where MMP are involved in tissue remodelling of ECM especially tissue degradation. Thus, inhibition of MMPs causes excessive accumulation of connective tissues in the ECM. Phenytoin also reduces intracellular folic acid and induces the production of mediators such as TGF-β and TNF-α. The antiepileptic action of phenytoin is mainly through the inhibition of sodium channels. However, phenytoin also inhibits the calcium channels, including in the gingival fibroblasts (Farook et al, 2019).

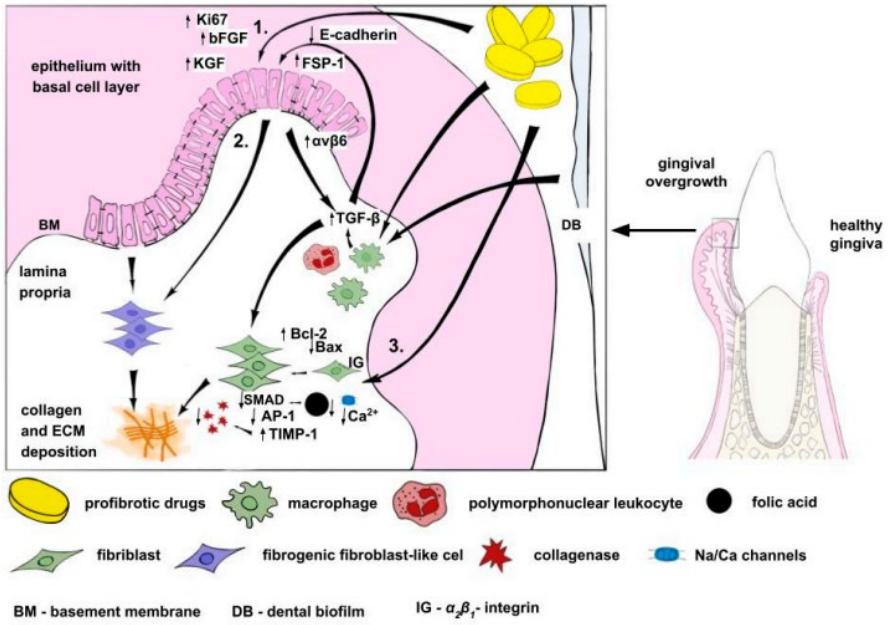

Figure 3. Pathophysiology of drug-induced gingival overgrowth (Droździk and Droździk, 2023).

Pathophysiology of drug-induced gingival overgrowth can be seen in Figure 3. (1) Profibrotic drugs increase keratinocyte proliferation and decrease keratinocyte apoptosis characterized by increased levels of proliferative markers (Ki67), basic fibroblast growth factor (bFGF) or keratinocyte growth factor (KGF). Tumor growth factor (TGF)-β1, a key mediator in mesenchymal epithelial transition (EMT) in gingival epithelial cells, initiates decreased E cadherin expression and increases regulation of fibroblast-specific protein-1 (FSP-1) and αvβ6 integrine levels. (2) Drugs impact intracellular Ca2+ homeostasis (via action on calcium and sodium channels or targeting calcineurin). The decrease in intracellular Ca2+ results in reductions in folic acid (FA) uptake and, in turn, reduced intracellular levels of FA, which leads to changes in the activity of matrix metalloproteinases and failure to activate collagenase. TGF-β, apart from the role in EMT, stimulates fibroblastic population activity and increases the relative proportion of sulfated glycosaminoglycans. Decreased cellular FA levels result in reduced expression of SMAD (SMAD), which in

turn downregulates the expression of the AP-1 gene. Reduced AP-1 leads to tissue inhibition of metalloproteinase (TIMP)-1 gene expression. An increase in TIMP-1 activity, which is involved in the activation of collagenase, produces a reduction in the amount of activated collagenase. Intracellular collagen processing is reduced via decreased a2b1-integrin, which is a specific receptor for collagen type I in fibroblasts, and determines the initial step of collagen phagocytosis (Droździk and Droździk, 2023).

CONCLUSION

Phenytoin induced gingival overgrowth is a side effect with multifactorial aetiology. Several mechanisms have been proposed addressing the pathophysiological mechanism of phenytoin induced gingival overgrowth both at a cellular and molecular level. To prevent such serious adverse consequences, it is necessary that phenytoin is used reasonably in clinical practice.

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