

Drug-Induced Gingival Hyperplasia

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Abstract: *This article has summarized observations and results of controlled laboratory and clinical studies of drug-induced gingival hyperplasia associated with phenytoin, cyclosporine, and nifedipine use. Furthermore, information regarding the pharmacologic aspects of these medications is presented. More information is needed for a greater understanding of drug-induced gingival hyperplasia. It appears that the primary preventive measure is to maintain a high standard of oral hygiene and the elimination of gingival irritation. Most of the drugs have side effects and drugs such as phenytoin, cyclosporine, and nifedipine induced gingival hyperplasia. Pathophysiology epidemiology, pathogenesis and management of gingival hyperplasia is reviewed here. Gingival hyperplasia: an overgrowth of the gum tissue.*

Keywords: Cyclosporine, Gingival hyperplasia, Nifedipine, Phenytoin

1. Introduction

An overgrowth of the gum tissue, often in patients treated with phenytoin, used to control epileptic seizures. Numerous other medications have also been associated with gingival hyperplasia. gingival enlargement due to proliferation of fibrous connective tissue.

Certain anticonvulsants, cyclosporine, and a variety of calcium channel blockers have been shown to produce clinically and histologically similar gingival enlargements in certain susceptible patients. These drugs appear to be similar with respect to their pharmacologic mechanism of action at the cellular level. The primary target tissue is the most essential difference among them. Therefore it is tempting to speculate that these agents may act similarly on a common secondary target tissue, such as gingival connective tissue, and cause a hyperplastic response. This tissue reaction may involve a disturbance of calcium ion influx into specific cell populations with a resulting alteration in collagen metabolism and other host cell response mechanisms. A connection between ion exchange, folate uptake, collagenase activation, and bacterial inflammation may exist. Until a more effective approach can be developed from future research results, treatment should continue to emphasize plaque control, professional debridement, and resective gingival procedures to improve function, esthetics, and access for home care.(1)

2. Background

- Drug induced gingival hyperplasia remains a serious aesthetic problem both for patient and periodontologist. Current management involves repeated periodontal surgery, plaque control and maintenance of good oral hygiene. Unfortunately not all patients respond to this treatment and recurrences can occur even after surgery.(2)
- Several causes of gingival hyperplasia are known, and the most recognized is drug-induced gingival enlargement. Furthermore, causes of congenital gingival enlargement include hereditary and metabolic disorders, such the fetal valproate syndrome.[3]
- Gingival overgrowth, also known as gingival hyperplasia secondary to drugs, was first reported in the

dental literature in the early 1960s in institutionalized epileptic children who were receiving therapy with phenytoin (Dilantin) for the treatment of seizures. Cyclosporine, a potent immunosuppressant widely used since the early 1980s in organ transplant recipients and for psoriasis, and numerous calcium channel blocker agents, including nifedipine and amlodipine, have also been associated with gingival overgrowth.[4]

- Nifedipine appears to have an additive effect when used together with cyclosporine in transplant recipients with hypertension. In addition, phenobarbital-induced gingival overgrowth has been reported but is rare and needsBecause not all patients on phenytoin, cyclosporine, and/or calcium antagonists develop gingival overgrowth, identifying patients at risk is important in order to take all the necessary measures to minimize the onset and severity of this condition.
- Currently, the etiology of drug-induced gingival overgrowth is not entirely understood but is clearly multifactorial. Debate is ongoing regarding whether drug-induced gingival overgrowth is due to hyperplasia of the gingival epithelium or of submucosal connective tissue, and/or both. Furthermore, the effect of age, sex, and duration and dosage of the drug in the pathogenesis of gingival overgrowth is not clearly understood. One of the main reasons is that clinical and epidemiologic studies are primarily retrospective, and they are unable to fully clarify this association further evaluation.(5)
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Some of the risk factors known to contribute to gingival overgrowth include the presence of gingival inflammation (ie, gingivitis) resulting from poor oral hygiene. Furthermore, the presence of dental plaque may provide a reservoir for the accumulation of phenytoin or cyclosporine. In orthodontic patients, gingival overgrowth has been suggested to be due to nickel accumulation and epithelial cell proliferation.[6]

Other intrinsic risk factors include the susceptibility of some subpopulations of fibroblasts and keratinocytes to phenytoin, cyclosporine, and/or nifedipine, and the number of Langerhans cells present in oral epithelium.[7, 8]The latter appears to be related to the presence of inflammation and dental plaque.

Pathophysiology:

Several studies have shown that the interaction of phenytoin, cyclosporine, and nifedipine with epithelial keratinocytes, fibroblasts, and collagen can lead to an overgrowth of gingival tissue in susceptible individuals. Phenytoin has been shown to induce gingival overgrowth by its interaction with a subpopulation of sensitive fibroblasts. Cyclosporine has been suggested to affect the metabolic function of fibroblast (eg, collagen synthesis, breakdown), whereas nifedipine, which potentiates the effect of cyclosporine, reduces protein synthesis of fibroblasts. A review of existing literature shows that a cofactor clearly is needed to induce gingival overgrowth.[7, 9, 10, 11, 12, 13, 14] In fact, several lines of evidence point to a modulation of inflammatory processes.

Epidemiology:

Frequency:

-Among adults, 50% to 90% have gingivitis (surrounding 3 or 4 teeth)
-Only up to 13% of the population is susceptible to severe periodontal disease(18)

Mortality/Morbidity:

-No mortality is associated with gingival enlargement. Morbidity can be severe in some cases because of gross overgrowth of gingival tissue, which can lead to gingival bleeding, pain, teeth displacement, and periodontal disease.

Race:

-No racial predilection exists for the onset of drug-induced gingival overgrowth.

Sex:

-No sexual predilection exists for drug-induced gingival overgrowth, although in one study, males were 3 times more likely than females to develop gingival overgrowth with calcium antagonists.

Age:

-No age predilection exists for the onset of drug-induced gingival overgrowth; however, phenytoin-induced gingival overgrowth appears to be more frequent in young patients with epilepsy. Most likely, this may be related to the age of the population, the nature of the disease, and poor oral hygiene.

Pathogenesis of drug-induced gingival overgrowth-A review of studies in the rat model:

-Drug-induced gingival overgrowth is a side effect associated principally with 3 types of drugs: anticonvulsant (phenytoin), immunosuppressant (cyclosporine A), and various calcium channel blockers (nifedipine, verapamil, diltiazem). In this review, we describe the features of phenytoin-, cyclosporine A- and nifedipine-induced gingival overgrowth in rats and discuss factors influencing the onset and severity of these disorders

There are several features common to the gingival overgrowth induced by these drugs:

-->gingival overgrowth is more conspicuous in the buccal than in the lingual gingiva and less severe in the maxilla than in the mandible;

--> once the blood concentration of the drug reaches a certain level as a result of increasing the dose, the incidence of gingival overgrowth is 100% and its severity is dependent on the blood level, the most severe overgrowth being induced by cyclosporine A; -->the duration of drug administration for maximal gingival overgrowth to develop is about 40 days;

-->the gingival overgrowth regresses spontaneously after discontinuing the drug;

-->accumulation of dental plaque is not essential for the onset of overgrowth, but plays a role in its severity; and

-->more severe overgrowth is induced in young than in old rats(15)

Management of gingival enlargement:

-In addition to plaque control and medical management, periodontal surgical treatment and multidisciplinary dental care are key strategies in managing gingival enlargement.

-Mild gingival enlargement may only require local management as improvement in oral hygiene, together with professional cleaning of the teeth, can lead to resolution of inflammation and reduction in gingival enlargement. Treatment planning becomes more complex where there is periodontitis plus gingival enlargement that is a cosmetic or functional problem. Periodontitis can be treated using conventional clinical care, but the gingival enlargement may require changes to the medication regimen, periodontal surgery to remove excess tissue, or a combination of the two.(16)

3. Conclusion

Drug induced gingival overgrowth is a serious aesthetic and psychologically disturbing side effect of some

particular class of drugs. Therefore, physician and dentist should be well aware to such drugs or they should prescribe alternative drug regimens having minimal or free form this unwanted side effect of drug

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