Prevalence and Severity of Amlodipine Induced Gingival Overgrowth

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ABSTRACT

Introduction: Amlodipine, a long-acting CCB, is a commonly used hypertension drug. Dihydropyridines are the agents most frequently implicated. All of them seem to act similarly on secondary target tissue, i.e., the gingival connective tissue, causing common clinical histo-pathological findings. This study was carried out with an aim to determine the prevalence of Amlodipine Induced Gingival Overgrowth (AIGO). It is also a concern for both the patient and the clinician due to its unaesthetic appearance and formation of new niches for periodontopathogenic bacteria.

Material and methods: Prospective clinical study to assess prevalence and severity of Amlodipine induced Gingival Overgrowth in hypertensive patients attending Hypertension OPD in Government Stanley Medical College Hospital receiving amlodipine singly or in combination with other drugs not known to cause this effect.

Results: It is interesting to note the incidence of ankle edema which is more known fact about the side effects of this calcium channel blocker was only 32percent as against 68percent of AIGO

Conclusion: In this study 76% of the patients were found to have gingival overgrowth, of which there was a 68% incidence in females, 66% of patients were found to be over 50 years of age. No significant correlation was observed between age, gender, drug dosage and prevalence of gingival overgrowth.

Keywords: Calcium Channel Blockers, Amlodipine, Gingival Overgrowth.

INTRODUCTION

Amlodipine was first reported for causing gingival overgrowth as side effect, by Seymour et al in 1994. Clinical manifestation of gingival enlargement frequently appears within 1 to 3 months after initiation of treatment with the associated medication. Gingival overgrowth normally begins at the interdental papillae and is more frequently found in the anterior segment of the labial surfaces.[3] Gradually gingival lobulations are formed that may appear inflamed or more fibrotic in nature, depending on the degree of local factor induced inflammation. The fibrotic enlargement normally is confined to the attached gingival but may extend coronally and interfere with esthetics, mastication, or speech.[4]

Gingival enlargement was graded according to the index originally described by Angelopoulos and Goaz 1972 and later modified by Miller and Damn 1992: GO index. The height of gingival tissue was measured from the cementoenamel junction to the free gingival margin. The following grades were scored in 6 points around each tooth: Grade 0, normal; 1, minimal enlargement (≤2 mm in size, with gingiva covering the cervical third or less of anatomic crown); 2, moderate enlargement (2–4 mm in size and/or gingiva extending into middle third of anatomic crown); and 3, severe enlargement (nodular gingiva >4 mm and/or gingiva covering more than two-thirds of tooth crown). GO was also measured in the buccal-lingual direction in all interdental papilla according to the index described by Seymour et al. 1985 and modified by Miranda et al. 1998: Miranda-Brunet (MB) index. The increase in size of papilla was measured from the enamel surface, at interdental contact point to the outer papillary surface.[5] Two scores were obtained, one for the buccal papilla and another for lingual/palatal papilla, according to the following criteria: Grade 0, papillary thickness of <1 mm; 1, papillary thickness between 1 and 2 mm; and 2, papillary thickness >2 mm.[6]

For both indices an average mean was calculated for whole mouth, anterior and posterior areas. GO was considered to be present when grades other than zero were recorded in one or in both GO and MB indices.[7]

Other measures included the Loe and Silness gingival index (GI), plaque index (PI) by Silness and Loe and probing pocket depth (PD).These indices were measured in 6 points around each tooth. All measurements were done by the same examiner.[8] This study was carried out with an aim to determine the prevalence of Amlodipine Induced Gingival Overgrowth (AIGO). It is also a concern for both the patient and the clinician due to its unaesthetic appearance and formation of new niches for periodonto pathogenic bacteria.

MATERIAL AND METHODS

Patients known to have hypertension and who have received amlodipine either singly or in combination with other antihypertensive drugs for a variable period were screened for the presence of gingival overgrowth and graded for severity based on Carranza's clinical score. Study was conducted in

Grade 0 – No signs of gingival enlargement.

Grade 1 – Enlargement confined to interdental papillae.

Grade 2 – Enlargement involves papilla and marginal gingivae.

Grade 3 – Enlargement covering three quarters or more of the crown.

Selection criteria

Inclusion criteria

- Patients taking Amlodipine Besylate tablets, without interruption for a minimum period of atleast 3 weeks at a variable dosage, either singly or in combination with other drugs, except Nifedipine and Diltiazem.

Exclusion criteria

- Peripubertal patients

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- Pregnant women
- Patients on other drugs known to cause gingival overgrowth, viz., Phenytoin, Mesantoin, Ethosuximide, Methosuximide, Valproic acid.
- Patients on immune suppressant drug cyclosporine.
- Patients on other calcium channel blockers Nifedipine, Diltiazem.
- Patients who discontinued therapy for more than 4 weeks.
- Patients with poor oral hygiene.
- Patients known to have systemic diseases like Leukemia, Granulomatous diseases like Wegeners and Sarcoidosis.
- Patients on orthodontic appliances or implants.

RESULTS

Table-1 shows the side effects observed in the patients due to Amlodipine. Amlodipine-induced gingival overgrowth was the most common side effect observed in the patients. Table-2 shows the Correlation between duration of Amlodipine and Amlodipine induced gingival hypertrophy (AIGO). The patients who were for first three years on Amlodipine developed AIGO at a high rate. Table -3 shows correlation between dosage of Amlodipine and gingival overgrowth. 10 mg of Amlodipine induced AIGO in most patients and at a high rate. Grade 2 hypertrophy was most commonly found (table-4).

Side effects	Profile of side effects	Percentage
AIGO	68	61.8
Ankle edema	37	28.1
Bleeding gums	5	4

Table-1: Profile of side effects

Index	On Amlodipine	Developed AIGO	Percentage
1-3 Years	44	34	77.3
3-6 Years	20	18	90
6-9 Years	18	14	77.8
> 9 Years	18	10	55.6

Table-2: Correlation between duration of Amlodipine and Amlodipine induced gingival hypertrophy (AIGO)

Dose of Amlodipine	Study population	Developed AIGO	Percentage
2.5 MG	20	11	55
5 MG	51	41	80.4
7.5MG	9	4	44.4
10MG	20	18	90

Table-3: Correlation between dosage of Amlodipine and gingival overgrowth

Grades of hypertrophy	Percentage of population
Grade 1	26
Grade 2	43
Grade 3	6

Table-4: Grades of gingival hyperplasia in study population

DISCUSSION

Many studies have been conducted and case reports showed that amlodipine is commonly prescribed antihypertensive and high potential in causing gingival hypertrophy and whenever there is associated risk factors like poor oral hygiene the propensity increases.The risk of recurrence of drug-induced gingival enlargement has been reported in both surgical and nonsurgical methods—especially if cessation of the offending drug was not an option or was temporary. Recurrence could occur as early as 3–6 months following the surgical intervention, and could affect as many as 40% of the patients. It appears that the risk of recurrence is higher in patients with poor oral hygiene or lack of dental care. Our study nearly 68% of the study population had gingival hypertrophy and regardless og age, sex, duration and dose.

Pharmacological Profile (Amlodipine)[8-10]

- Long acting dihydropyridine (other members:- nifedipine, nicardipine, isoradipine, nitrendipine and felodipine)
- Mechanism of action:- coronary and peripheral arterial vasodilatation
- Dosage: 2.5 or 5 grams, single dose (alone or in combination with Atenolol)
- Adverse effects:- headaches, facial flushing, dizziness, oedema, gingival hyperplasia

Risk factors

Dental plague and oral hygiene level

The oral bacterial biofilm is a common risk factor for all forms of inflammatory periodontal diseases and its presence exacerbates CCB-induced gingival enlargement. The severity of gingival enlargement is well correlated with poor oral hygiene. The importance of the microbial plaque as a cofactor in the etiology of drug-associated gingival enlargement has been recognized in a recent classification system of periodontal diseases by the American Academy of Periodontology.[11] The finding that the gingival overgrowth is almost exclusively related to dentate areas suggests that factors attached to the dentition, such as bacterial dental plaque, have a role in gingival enlargements. Whether these lesions are preventable by professional tooth cleaning and installation of good oral hygiene habits before prescribing this class of drug is unknown and requires clinical trial.[11,12]

Clinical Features

Clinical manifestation of gingival enlargement frequently appears within 1 to 3 months after initiation of treatment with the associated medication.[13] Gingival over growth normally begins at the interdental papillae and is more frequently found in the anterior segment of the labial surfaces. Gradually, gingival lobulations are formed that may appear inflamed or more fibroticinnature, depending on the degree of local factor-induced inflammation. The fibrotic enlargement normally is confined to the attached gingival but may extend coronally and interfere with esthetics, mastication, or speech. Disfiguring gingival over growth triggered by this medication is not only aesthetically displeasing but often impairs nutrition and access for oral hygiene, resulting in an increased susceptibility to oral infection, caries, and periodontal diseases.[14]

Histological Features

Histologically, slight to moderate hyperkeratosis, thickening of the spinous layer, fibrosis of underlying connective tissue with fibroblastic proliferation, increase in the number of capillaries with slight chronic perivascular inflammation is seen.

Pathogenesis

Role of Fibroblasts

Because only a subset of patients treated with this medication

will develop gingival overgrowth, it has been hypothesized that these individuals have fibroblasts with an abnormal susceptibility to the drug. It has been showed that fibroblast from over grown gingival in these patients are characterized by elevated levels of protein synthesis, most of which is collagen.[14,15]

Role of Inflammatory Cytokines

A synergistic enhancement of collagenous protein synthesis by human gingival fibroblasts was found when these cells were simultaneously exposed to nifedipine and interleukin-1b (IL-1b), apro inflammatory cytokine that elevated in inflamed gingival tissues. In addition to IL-1b, IL-6 may play role in the fibrogenic responses of the gingival to these medications.

Role of Matrix Metalloproteinase (MMP) Synthesis and Function

Because most types of pharmacological agents implicated in gingival enlargement have negative effects on calcium ions influx across cell membranes, it was postulated that such agents may interfere with the synthesis and function of collagenases.

Prevention

In the susceptible patient, drug-associated gingival enlargement may be ameliorated, but not prevented by elimination of local factors, meticulous plaque control, and regular periodontal maintenance therapy. Each recall appointment should include detailed oral hygiene instruction and complete periodontal prophylaxis, with supra-and subgingival calculus removal as needed. In some instance orthodontic bands and/or appliances should be removed.[15]

Treatment

Drug Substitution/withdrawl: The mosteffectivetreatment of drug-related gingival enlargement is withdrawl or substitution of medication. When this treatment approach is taken as suggested by another case report, it may take from 1 to 8 weeks for resolution of gingival lesions. Unfortunately, not all patients respond to this mode of treatment especially those with long standing gingival lesions.

Non-Surgical treatment: Professional debridement with scaling and root planning as needed has been to shown to offer some relief in gingival over growth patients.

Surgical Periodontal treatment: Because the anterior labial gingivalis frequently involved, surgery is commonly performed for esthetic reasons before any functional consequences are present. The classical surgical approach has been the external bevel gingivectomy. However a total or partial internal gingivectomy approach has been suggested as an alternative. This more technically demanding approach has the benefit of limiting the large denuded connective tissue wound that result from the external gingivectomy, there by minimizing postoperative pain and bleeding.

CONCLUSION

CCBs are important components of managing patient populations with hypertension, angina or supraventricular cardiac arrhythmias. However, a serious and often overlooked side effect of this class of drugs affects some patients. Gingival overgrowth is a common oral finding in these patients. Drug cessation and a substitution to other class of antihypertensive medications is the best treatment option. Otherwise, these lesions could be managed by nonsurgical or surgical techniques that only provide a short-time relief, as recurrence is to be expected if the offending drug is continued.Prevalence of Amlodipine Induced Gingival Overgrowth was noted to be significant in this study population, no clear association could be found between age, gender, duration and dosage.

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