

CALCIUM CHANNEL ANTAGONIST-INDUCED GINGIVAL HYPERPLASIA

RESPONSE

One of the common adverse effects associated with calcium channel blockers is drug-induced gingival hyperplasia, although gingival overgrowth is perhaps more frequent than overt hyperplasia ^[1]. Nifedipine has caused the most cases of gingival hyperplasia, but other calcium channel blockers have also induced this adverse effect. In a single-blind, case controlled study of 115 geriatric males, the incidence of gingival hyperplasia was 38% for nifedipine, 21% for diltiazem, and 19% for verapamil ^[2]. In adult and pediatric renal transplant patients exposed to nifedipine as well as other agents potentially contributing, an overall gingival hyperplasia incidence of 44% in adults and 27% in children was noted ^[3]. The combination of cyclosporine and calcium channel blockers frequently leads to gingival hyperplasia in renal transplant recipients. Another factor contributing to its development might be class I and II histocompatibility antigens. In a study of 76 renal transplant recipients with similar immunosuppressive and antihypertensive regimens, the major histocompatibility complex (MHC) class II antigen HLA-DR2 was present in 63% with gingival hyperplasia versus 34% without gingival hyperplasia ($p=0.03$). In contrast, the class I antigen HLA-A3 was found in 0% versus 24% ($p=0.01$) of those with and without gingival hyperplasia, respectively ^[4]. Analysis of hyperplastic gingival tissue from 5 nifedipine-treated and 7 phenytoin-treated patients showed c-Myc oncoprotein expression in 80% of the nifedipine cases and 71% of the phenytoin cases. Epithelial cells expressing bcl-2 oncoprotein were present in all 12 cases. Expression of c-Myc oncoprotein augments active cellular proliferation of growing tissue, while bcl-2 oncoprotein confers an apoptosis-resistance ^[5]. Nifedipine was more commonly associated with gingival hyperplasia than other antihypertensive agents (p less than 0.05) ^[4].

Review of statistical data available concerning calcium channel antagonist-induced gingival hyperplasia shows most of the reported cases have involved patients over the age of 50 years who took these drugs for postmyocardial infarction, angina pain, essential hypertension, and Raynaud's syndrome. Gingival hyperplasia has occurred as early as 1 month after initiation of therapy and as delayed as 2 to 3 years from the onset of therapy ^{[1][6]}. In one case, overgrowth first appeared with a dosage increase after 12 years of nifedipine therapy ^[7].

TREATMENT

The treatment varies, with discontinuation of the drug being the most effective, although it is not yet known whether discontinuation of the drug is essential to control the symptoms of gingival overgrowth. Gingivectomy and use of chlorhexidine rinses have been used but have not been consistently effective in preventing recurrence of symptoms with continued drug use; meticulous dental hygiene with plaque control through proper brushing and flossing is basic to control ^{[8][9]}; (Wynne, 1991) ^[10]. Dental hygiene alone will reduce but not prevent the extent of gingival hyperplasia induced by calcium channel blockers ^[11], but aids in determining if surgical reduction will be required as well as reducing the hemorrhagic field present for any subsequent surgical intervention ^[12]. The 18-month recurrence rate after periodontal surgery for severe drug-induced gingival overgrowth was 44% of 16 patients maintained on nifedipine. Other variables significantly associated with recurrence were attendance at recall appointments, age, and 18-month papilla bleeding index ^[13].

CLINICAL REPORTS

AMLODIPINE

Three patients on amlodipine 5 to 10 mg daily developed gingival problems within 2 to 3 months after starting therapy. Plasma and gingival crevicular fluid (GCF) drug levels were determined. Two patients showed GCF:plasma ratios greater than 200:1, while the third had a ratio of 23:1 ^[14]. In another series of 3 patients with significant gingival hyperplasia after 4 to 8 months, amlodipine therapy had GCF levels ranging from 260 to 4000 mcg/L, and 2 patients had plasma: GCF ratios greater than 1:200. A fourth patient without evidence of gingival hyperplasia had no detectable GCF amlodipine levels. Gingivectomy revealed hyperplasia characterized by a stroma of loose collagen, active fibroblast activity, abundant ground substance, and acantholytic changes in the overlying epithelium, consistent with histology seen in other drug-induced gingival hyperplasias ^[15]. No increased prevalence of hyperplasia was noted among 150 patients with 6-month follow up ^[12].

In a cross-sectional study of 135 patients maintained on cyclosporine plus either amlodipine or nifedipine since renal transplantation (average of 46.5 and 52.2 months, respectively), the choice of calcium channel blocker and age were independent predictors of gingival overgrowth. The prevalences of gingival overgrowth among amlodipine and nifedipine recipients were 72% and 53%, respectively ($p=0.03$). Multivariate regression analysis determined that the odds ratio for developing gingival overgrowth was 3 (confidence interval, 1.3 to 6.9) with amlodipine versus nifedipine use ^[16].

DILTIAZEM

A case of hyperplastic gingivitis occurred within 24 days during diltiazem therapy in a 58-year-old male with angina at a dose of 60 mg twice a day. The patient had previously developed gingivitis within 15 days after starting verapamil ^[17]. Similarly, persistent gingival hyperplasia between 1985 and 1993 was noted in an elderly black woman who variously received treatment with diltiazem, nifedipine, felodipine, and verapamil; at her last recorded visit, hyperplastic tissue was still present even though she had been off all calcium antagonist therapy for approximately 8 months ^[8]. Gingival hyperplasia has been identified in 76% of those receiving diltiazem in geriatric patients ^[18].

FELODIPINE

In the first case of gingival hyperplasia due to felodipine, a 42-year-old man associated the onset of painful gingivae with the start of felodipine therapy ^[10]. Dental treatment consisted of elimination of plaque accompanied

by detailed oral hygiene instructions. Furthermore, the most prominent hyperplastic tissue was excised by gingivectomy. Tissue samples were obtained, and the most significant components were lymphocytes, plasma cells, fibroblasts, and an increased amount of collagen bundles. The review concluded that in view of the large number of patients taking calcium channel blockers, gingival hyperplasia may be considered relatively uncommon; however, clinicians must be aware of this pathology.

FLUNARIZINE

Two of 14 pediatric patients developed gingival hyperplasia during 3 months of flunarizine add-on therapy at doses between 0.1 to 0.3 mg/kg daily. Mean peak serum levels were 65 ng/mL ^[19].

MANIDIPINE

The first reported case of gingival hyperplasia due to manidipine occurred in a 43-year-old woman being treated for hypertension, with other drug therapies including carteolol and bromhexine (for associated Sjogren syndrome). Periodontal exam revealed an exaggerated probing depth (4.83 mm), extensive plaque and bleeding on probing, with a gingival overgrowth index (GOI) of 2.42. Drug therapies were continued, but extensive periodontal treatment was given, including oral hygiene, root planing, and surgical removal of remaining gingival pockets. Probing depth was reduced to 1.93 mm, GOI improved to 0.02, and bleeding on probing improved from 100% at baseline to less than 5%. Histology showed features similar to nifedipine-induced gingival overgrowth ^[20].

NIFEDIPINE

Nifedipine dosage was directly related to gingival overgrowth scores in both adult and pediatric renal transplant patients. Other concomitant drugs (cyclosporine) and clinical variables in this population contributed to an overall gingival hyperplasia incidence of 44% in adults and 27% in children ^[3]. Others, however, showed dosage and duration of therapy were not significant predictors of nifedipine-induced gingival hyperplasia (n=35 adults).

Positive associations with overgrowth were noted for plaque index, bleeding index, and inflammation, while age was an inverse predictor ^[21]. Genetic susceptibility (HLA A-19 positive) may be involved ^[12].

In an earlier examination of 9 patients on nifedipine (5 of whom suffered gingival hyperplasia), GCF:plasma ratios averaged 84:1. The maximum GCF level of nifedipine measured was 9300 mcg/L with a GCF:plasma ratio of 316:1, a level not seen even in toxic overdose and approaching maximum solubility of nifedipine. Although these data were from 1 of the 4 patients who did not exhibit hyperplasia, the authors speculate that since the GCF levels of both nifedipine and amlodipine are so concentrated, a local toxic effect may be involved ^[22].

A 58-year-old man presented to the emergency department with pain in his right molar area and generalized gingival swelling. The patient had been taking nifedipine for 18 months for angina. The patient was managed with extensive oral hygiene instructions. Meticulous removal of daily plaque was stressed. The patient also received chlorhexidine rinses for one month and then was followed monthly. During the treatment, the nifedipine dose was not changed, and gingival overgrowth had not returned for 18 months (Hancock et al, 1992). Previously, the treatment of gingival hyperplasia consisted of reduction or elimination of the drug or surgical excision of the affected areas. Most reports documented have shown continued overgrowth of the gingiva with just plaque control treatment, so well-designed studies with significant numbers of patients are needed to determine the effectiveness of oral hygiene measures in preventing or treating gingival overgrowth that occurs due to calcium channel blocker therapy.

Concurrent use of an HMG CoA reductase inhibitor ("statin") simvastatin was postulated as contributory to the development of gingival hyperplasia in a 49-year-old man being treated for hypertension and hypercholesterolemia. After three years treatment with both agents, he was noted to have gross gingival hyperplasia complicated by generally poor oral hygiene. Nifedipine LA 60 mg daily was stopped and enalapril 10 mg twice daily along with a thiazide diuretic substituted. Two months later the hyperplasia was completely resolved. The potential drug-drug interaction between calcium antagonists and statins (inhibition of cytochrome P450 3A-mediated metabolism of statins) which may lead to concurrent elevations of the serum concentrations of both drugs (verapamil and simvastatin in one example cited) was suggestive but not investigated specifically ^[1].

In a cross-sectional study of 135 patients maintained on cyclosporine plus either amlodipine or nifedipine since renal transplantation (average of 46.5 and 52.2 months, respectively), the choice of calcium channel blocker and age were independent predictors of gingival overgrowth. The prevalences of gingival overgrowth among amlodipine and nifedipine recipients were 72% and 53%, respectively (p=0.03). Multivariate regression analysis determined that the odds ratio for developing gingival overgrowth was 3 (confidence interval, 1.3 to 6.9) with amlodipine versus nifedipine use ^[16]. [Insert as new paragraph]? The 18-month recurrence rate after periodontal surgery for severe drug-induced gingival overgrowth was 44% of 16 patients maintained on nifedipine. Other variables significantly associated with recurrence were attendance at recall appointments, age, and 18-month papilla bleeding index ^[13].

NITRENDIPINE

A 68-year-old man reporting for routine dental examination was diagnosed with nitrendipine-induced gingival hyperplasia, and subsequently gingivectomy was performed. He was given chlorhexidine mouth rinse, and normal healing was observed. The mechanism of this effect appeared to involve sodium/calcium flux dynamics, folate uptake, collagenase activation and bacterial inflammation ^[23].

There are currently several proposed mechanisms of action for this adverse effect. These include inflammation from bacterial plaque and increased sulfated glycosaminoglycans, immunoglobulins, and folic acid, or perhaps a local toxic effect from the extremely high concentrations of some agents found in the GCF ^{[8][14][22][24]}. A common feature for drugs causing gingival hyperplasia is direct effects on calcium metabolism, perhaps leading to changes in collagenase to an inactive form allowing for an increase in extracellular matrix ^[25].

VERAPAMIL

A 31-year-old woman developed gingival hyperplasia after a 2-year history of verapamil use. Treatment was careful elimination of plaque and detailed oral hygiene instructions. Overgrowth recurred in 1 month despite

proper oral hygiene. Verapamil was then discontinued, and the gingival overgrowth regressed ^[26]. Rapid onset within 15 days has also been reported ^[17].

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