Calcium Channel Blocker–Induced Gingival Hyperplasia: Case Report and Review of This Iatrogenic Disease

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Gingival hyperplasia is a common disorder associated with phenytoin and cyclosporine therapy. However, induction of this condition by calcium channel blockers is less well known. Inflammation of the gingival tissue from bacterial plaque and the subsequent development of gingival crevicular fluid may allow sequestration of the calcium channel blocker, thus predisposing the tissue to a localized toxic effect and the development of gingival hyperplasia. Calcium channel blockers have cellular effects similar to those of phenytoin and cyclosporine, including the production of a localized folic acid deficiency. All of the available calcium channel blockers have been reported to cause gingival hyperplasia. Treatment options include meticulous plaque control, and in severe cases, gingivectomy. Gingival hyperplasia can be prevented with meticulous plaque control or avoidance of the offending medication.

Key words. Gingival hyperplasia; calcium channel blockers; gingivitis; dental plaque; gingival crevicular fluid.
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Calcium channel blockers (CCBs) have become valuable and widely prescribed agents for the treatment of many health problems. Certain CCBs are effective in the management of hypertension, angina, atrial arrhythmias, diastolic heart failure, and possibly renal protection in diabetes. As the number of indications for CCBs continues to grow, so do the volume and number of CCBs available for use.

Drug-induced gingival hyperplasia (DIGH) is an iatrogenic dental disorder that is characterized by gums that are enlarged and inflamed, and bleed readily upon probing. The gums appear lobulated from papillary enlargement, and the tooth crowns may be partially covered by hyperplastic tissue. Drug-induced gingival hyperplasia is usually only cosmetically disfiguring; however, the formation of tissue pockets can interfere with proper oral hygiene, contributing to periodontal disease and dental caries. In severe cases, DIGH may even compromise the patient's ability to properly eat or speak. Patients who develop DIGH are at risk of treatment failure because of noncompliance. Those who develop severe DIGH may eventually require invasive oral surgery, such as a gingivectomy.[1]

Drug-induced gingival hyperplasia is a well-documented and widely recognized side effect of long-term phenytoin therapy. This manifestation of treatment, which occurs in approximately 50% of patients taking this medication, takes the form of a local or generalized hyperplasia.[2] The immunosuppressant cyclosporine frequently induces a similar effect in patients who have had organ transplants. In this population, the incidence of DIGH ranges from 25% to 81%.[3] Phenytoin and cyclosporine are used primarily in the treatment of epileptic and transplant patients, respectively; thus, DIGH can be anticipated and minimized with the institution of preventive oral hygiene measures.

While recognized by the dental profession, the role of CCBs in the development of gingival hyperplasia is less well known in the primary care community. In susceptible

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patients, this class of medications has been shown to induce gingival hyperplasia, which usually appears locally on the gums but can present more generally. The development of DIGH is not unique to any one agent within this class. Combining any of these agents with cyclosporine will likely produce an additive effect.

Case Report

In November 1987, a 78-year-old black female patient from our institution's family medicine clinic presented to the dental clinic for a routine checkup. Localized hyperplastic gingival tissue was found adjacent to the mandibular right canine. Her medical history included hypertension with an antihypertensive regimen of diltiazem and spironolactone with hydrochlorothiazide, both of which had been initiated in 1985. Her dental history included routine care at the dental school since 1974. Poor oral hygiene was recorded at numerous appointments; however, no hyperplastic or edematous gingival lesions had been recorded before the initiation of diltiazem in 1985.

Further examination at that time revealed a localized erythematous and raised lesion adjacent to the mandibular right canine. The lesion was initially believed to be an abscess, but this was ruled out and the tissue was removed by gingivectomy. The lesion recurred three times between March 1988 and October 1988. On each visit, the hyperplastic gingiva was excised. Each procedure included removal of plaque and calculus from the teeth and placement of the gingival tissue to a lower level to allow for more effective patient hygiene. During the October 1988 appointment, a biopsy of the lesion was done. Microscopic examination showed fibrous hyperplastic tissue with chronic inflammation. Throughout this period and for 2 years thereafter, the patient continued taking diltiazem for hypertension.

In January 1991, the patient presented with localized gingival inflammation and hyperplasia in the area of the mandibular left canine. Her medication had been changed in October 1990 to nifedipine to better control her hypertension. The gingiva was reflected (gingiva pulled away from the tooth surface for the purpose of debriding), the tooth surface debrided, and a biopsy performed. Microscopic examination again revealed chronic hyperplastic tissue.

One year later, the hyperplastic tissue recurred in the areas of both mandibular canines (Figure 1). It was treated as before, and again a biopsy was obtained. At this time, the patient had been taking felodipine since July 1991. Microscopic examination again showed hyperplastic tissue with inflammation. No recurrence of the hyperplastic tissue in this area has been noted since this treatment.

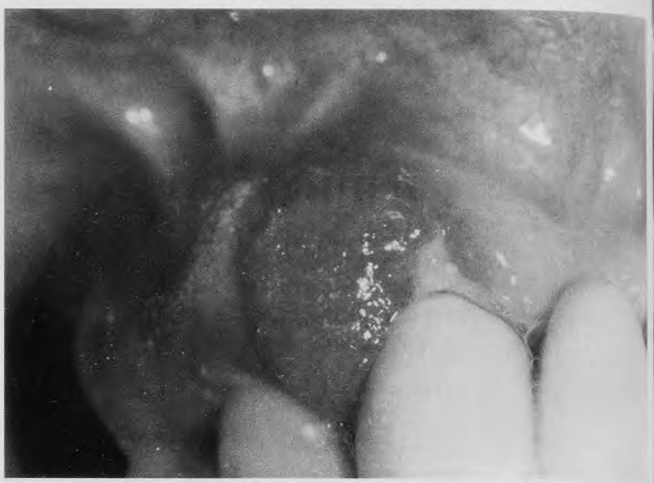

Figure 1. Hyperplastic tissue of the mandibular canine (January 1992) in a patient who had been taking felodipine since July 1991. Note calcification due to poor dental hygiene.

In September 1993, examination revealed localized erythematous hyperplasia on the gingiva adjacent to her maxillary central incisors. Her medication had been changed to enalapril maleate in December 1992, with verapamil added in May 1993. In August 1993, verapamil was discontinued, and benazepril monotherapy was begun for control of her hypertension. She was seen again in the dental clinic in April 1994. The lesion adjacent to her maxillary central incisors was still present even though she had not taken a CCB since August 1993 (Figure 2). Signs of local chronic periodontal destruction were also present. Clinically, the tissue appeared consistent with the previous hyperplastic lesions.

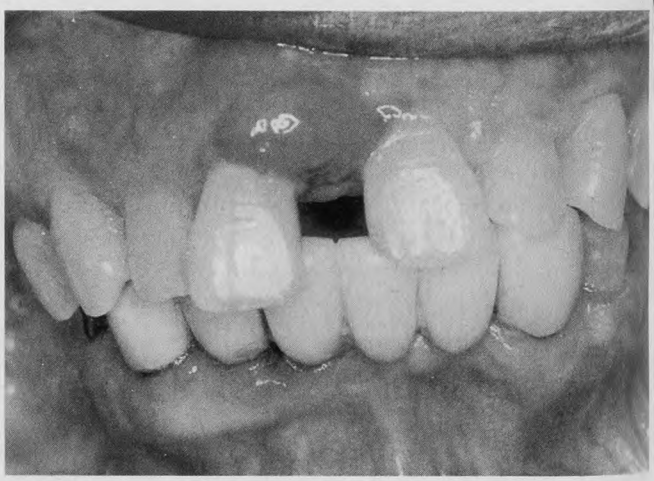

Figure 2. Lesion adjacent to the maxillary central incisors (April 1994) consistent with previously occurring hyperplastic tissue. Eight months earlier, verapamil had been discontinued and benzapril monotherapy begun.

Discussion

Mechanism of Disease

There are many theories about the pathogenesis of DIGH at the molecular level, and specific risk factors have been identified.[1] The use of CCBs in the presence of gingivitis or inflammation of the gingival tissue from bacterial plaque may predispose patients to DIGH. Inflammation from bacterial plaque causes a natural increase in connective tissue production, leading to gingival enlargement.[1] With regard to phenytoin and cyclosporine therapy, a number of reports have demonstrated that a bacterial inflammatory component is necessary for the expression of DIGH.[3-6] The use of a CCB in beagles led to the observation that gingival overgrowth begins in areas displaying signs of previous inflammation.[7] These medications, along with bacterial plaque and the subsequent onset of gingivitis, are now clearly believed to be cofactors in the development of DIGH.

Inflammation and gingivitis may play an important role in DIGH through the production of gingival crevicular fluid (GCF), a serum-derived transudate produced within the gingiva in direct relationship to the extent of inflammation.[8] Gingival crevicular fluid may be important because of its ability to accumulate high concentrations of CCBs within the gingival tissue when inflammation is present, predisposing tissue to the toxic effects of the sequestered agent.[8,9] Concentrations of GCF in patients receiving nifedipine with signs of gingival enlargement have ranged from 15 to 88 times that of plasma. Concentrations of amlodipine besylate within the GCF have been shown to be 25 to 250 times that of plasma.[9] Although research related to this phenomenon is limited, sequestration of CCBs in the GCF is thought to be linked to gingivitis, localized toxic drug effects, and the development of DIGH.

A common feature of phenytoin, cyclosporine, and CCBs is their ability in some way to influence calcium metabolism. Calcium channel blockers have effects on cellular calcium influx, and phenytoin has been shown to stabilize neuronal membranes by affecting Ca^{2+}/Na^{+} flux and decreasing intracellular calcium uptake.[10] Cyclosporine has the ability to inhibit interleukin-2–dependent T-cell proliferation by preventing a change in the intracellular uptake of calcium ions. This lowering of cytosolic-free calcium ions by cyclosporine is actually indistinguishable from that of calcium antagonists.[11,12] The reduction in free cytosolic calcium may impair collagen resorption, possibly by interfering with T-cell proliferation and collagenase synthesis in fibroblasts.[13] The disruption of collagen homeostasis may significantly influence the development of DIGH.

Another hypothesis regarding the development of DIGH is the influence of folic acid deficiency. Systemic and localized folic acid deficiency can be found with the use of all the agents known to induce gingival hyperplasia, including CCBs.[1] The alteration of calcium and sodium ion exchange in turn affects folic acid uptake into cells. Gingival tissue has a naturally high turnover rate, which leads to increased demand for folic acid.[14] It has been hypothesized that localized folic acid deficiency limits the amount of collagenase activator protein produced in the gingival tissues. This deficiency results in less efficient catabolism of the excessive connective tissue produced by the inflammation.[3]

CCBs and DIGH

There are many case reports of CCB-induced gingival hyperplasia in the literature. All of the dihydropyridine CCBs, including the newer formulations, have a reported association with DIGH development. Cases of DIGH with nifedipine therapy are the most frequently reported, which may reflect the widespread use of this popular CCB rather than an intrinsic characteristic of the drug. Evaluation of various case reports of DIGH with the use of nifedipine suggests that the incidence is in excess of 10%, with small retrospective studies reporting rates as high as 20% to 25% in isolated populations.[13,15,16] A recent report found that 38% of patients receiving nifedipine for at least 3 months had significant gingival hyperplasia.[17]

Drug-induced gingival hyperplasia has been reported infrequently in postmarketing surveillance of felodipine,[18] nicardipine hydrochloride (personal communication, Syntex Laboratories, Inc, Palo Alto, Calif, August 4, 1993), and isradipine (personal communication, Sandoz Pharmaceuticals, East Hanover, NJ, August 4, 1993). Amlodipine, the most recently approved CCB, has not been spared association with this condition. Recently, three cases of amlodipine-induced gingival hyperplasia were reported in the medical literature.[9] The infrequent reporting of this condition probably does not mean that the newer dihydropyridines have a lower incidence of DIGH. It is more likely a reflection of their smaller share of the CCB market. However, the association between amlodipine and gingival hyperplasia has not been adequately evaluated in clinical studies, primarily because of the short time this CCB has been available. An overall dihydropyridine class effect may be assumed at this point until further evaluation is done. The decision to use any one dihydropyridine CCB over another in anticipation of avoiding or reducing the likelihood of this side effect is probably not warranted.

The nondihydropyridine CCBs, diltiazem and verapamil, are also considered to induce gingival hyperplasia.

Both have been reported to be associated with DIGH in a number of case studies.[19–24] A small retrospective chart review of 24 patients concluded that verapamil has a lower incidence of DIGH than nifedipine; however, this conclusion needs further confirmation.[24] In a retrospective study, DIGH was reported to be present in 21% (7/33) of patients taking diltiazem and 19% (5/26) of those taking verapamil.[17] Both medications are known to induce DIGH in susceptible patients, but until adequately investigated, they should not be assumed to have a lower incidence than dihydropyridines.

Calcium channel blockers, particularly nifedipine, are often used in the treatment of cyclosporine-induced hypertension in the organ transplant population. Among these patients, DIGH is a common occurrence. Although it is unknown whether the combination of nifedipine and cyclosporine has additive or synergistic effects in promoting DIGH, there are reports suggesting that it produces an additive increase in gingival hyperplasia.[25] It is currently unknown whether other CCBs in combination with cyclosporine would have a similar or a smaller effect. A recent retrospective study of 66 renal transplant patients addressed these issues.[26] Patients receiving cyclosporine alone or in combination with nifedipine or diltiazem were evaluated for hyperplastic development. The authors of this study concluded that there was no difference between the nifedipine and diltiazem groups, although there was a trend toward increased gingival overgrowth in the nifedipine group. The addition of a calcium antagonist also did not appear to potentiate the effect of cyclosporine in this small study. In contrast, a recent study showed a significant increase in the degree of hyperplasia in children receiving cyclosporine and nifedipine as compared with children receiving cyclosporine alone.[27] Although it is inconclusive whether CCBs potentiate the effect in combination with cyclosporine, alternative antihypertensives may prevent additive hyperplasia in transplant patients.

Other Causes of Gingival Hyperplasia

Non–drug-induced gingival hyperplasia has been reported secondary to vitamin deficiencies, particularly deficiencies in vitamins A and C. Endocrine imbalances, such as those that occur in diabetes mellitus or during puberty or pregnancy, have been reported to cause gingival hyperplasia. In addition, Crohn's disease and leukemia have been implicated as a contributing factor in the development of this form of hyperplasia.[28] Gingival fibromatosis is an enlargement that may be familial or idiopathic. Familial gingival fibromatosis may be either a separate finding or connected to one of many hereditary syndromes.[29]

Treatment of Drug-Induced Gingival Hyperplasia

The treatment of DIGH is limited to meticulous plaque control and, if necessary, surgical removal of the hyperplastic tissue by means of gingivectomy. Because of the progressive nature of this condition, surgical removal of the tissue may need to be repeated unless the medication is discontinued. Although withdrawing the offending medication generally reverses hyperplasia, this course of action may be less effective following prolonged exposure.[1,30,31]

The administration of folic acid has some theoretical merit in the treatment of DIGH. Although oral folic acid supplementation has not shown efficacy in reversing phenytoin-induced gingival hyperplasia,[32] a topical solution of folic acid (1 mg/mL solution, with 5 mL rinse for 2 minutes twice daily) has resulted in significant regression of gingival hyperplasia as compared with both oral folic acid and placebo. It has been postulated that topical folic acid may reduce hyperplasia by affecting pathogenic flora or reducing inflammation.[33] Further investigation into this potential treatment of DIGH is needed.

Metronidazole is an interesting prospect for future treatment. Four patients with cyclosporine-induced gingival hyperplasia who were treated with a 7-day course of metronidazole 400 mg three times per day showed improvement or resolution of the hyperplasia.[34] Further study of this treatment option and expanded investigation of phenytoin-induced and calcium channel blocker–induced gingival hyperplasia are desirable.

Prevention of Drug-Induced Gingival Hyperplasia

A key to preventing DIGH is recognizing which patients have a potential for developing this condition and instituting early intervention. Several studies have demonstrated that proper dental prophylaxis and good oral hygiene can reduce or prevent the development of phenytoin-induced gingival hyperplasia.[4,35,36] In subsequent investigations, a clear correlation was established between three variables and an increased risk of developing DIGH in patients receiving phenytoin therapy: gingivitis, a visible plaque index, and the duration of phenytoin therapy.[37]

A number of interventions have been attempted to prevent recurrence of DIGH following surgical removal of the hyperplastic tissue. Chlorhexidine mouthwash has been used as secondary prevention of DIGH in patients receiving phenytoin after gingivectomy. The use of 0.1% chlorhexidine gluconate mouthwash three times daily along with aggressive plaque control reduced the inci-

dence of recurrent hyperplasia.[38] Oral folic acid supplementation as secondary prevention following gingivectomy also has been attempted but has not proven clinically effective.[39] Meticulous plaque control through frequent brushing and flossing seems to be the most effective method of reducing the chance of development of DIGH. There has been no evaluation of the association between gingivitis and CCBs or of prevention and treatment methods. However, findings regarding prevention and treatment with phenytoin and cyclosporine can likely be extrapolated to patients taking CCBs.

Conclusions

Calcium channel blockers are effective in the treatment of many clinical conditions, including hypertension and angina pectoris. The indications for use of this class of drugs continue to increase, and cumulatively, the use of CCBs exceeds that of all other drugs known to cause DIGH. Therefore, the reported incidence of patients experiencing DIGH also may continue to rise.

The case described demonstrates the effect of CCBs on the development of gingival hyperplasia in a patient with poor dental hygiene. The patient's lesions had not been present before the initiation of treatment with diltiazem, even though she had a history of poor dental hygiene. No other causes of gingival hyperplasia were readily identified. Hyperplastic tissue developed during therapy with diltiazem, nifedipine, verapamil, and felodipine. It is not known whether the lesions will cease to develop now that CCBs have been discontinued.

Hyperplastic tissue may initially go unrecognized, and conditions other than hyperplasia may be suspected. In the case described, the lesion was initially thought to be either edema or an abscess, both of which were ruled out on further examination. On microscopy, the biopsied lesions clearly showed hyperplastic tissue with inflammatory infiltrates.

There are three entities that appear necessary for the development of DIGH: (1) bacterial plaque causing inflammation and increased connective tissue production, (2) the presence of sequestered drug leading to a localized folic acid deficiency and decreased connective tissue catabolism, and (3) sulcular gingiva.[1] Indigent patients in particular may be at the highest risk for development of this side effect because of poor dental hygiene and limited access to dental care. The possibility of DIGH in this population, as well as for any patient with inadequate dental care, must be considered. When CCB therapy is started, the patient should be evaluated for gingivitis, properly educated about dental hygiene, encouraged to floss and brush properly, and advised to see a dental hygienist on a regular basis. Furthermore, to rule out the development of gingival hyperplasia, physicians should perform a visual oral examination of all patients undergoing follow-up evaluation for conditions treated with CCBs.

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