Prevalence of Manidipine-Induced Gingival Overgrowth

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Introduction

Drug-induced gingival overgrowth has been described as an adverse effect associated with three types of drugs: anticonvulsants (phenytoin), immunosuppressive agents (cyclosporine A), and various calcium channel blockers for cardiovascular diseases (1, 2).

Manidipine hydrochloride (manidipine) is a long-acting dihydropyridine calcium antagonist, which causes systemic vasodilation by inhibiting the voltage-dependent calcium inward currents in vascular smooth muscle cells. It has been well tolerated in clinical trials, with most adverse effects related to vasodilation. Commonly reported events include ankle edema, headache, palpitation, flushing, dizziness, rash, and fatigue (3, 4). Recently, gingival overgrowth has also been indicated as an adverse effect of manidipine (5). However, this evidence has come from several case reports (6–9) and there have been no prevalence studies to evaluate the magnitude of this effect. Due to uncertainty regarding the prevalence of gingival overgrowth, we aim to determine the incidence as induced by manidipine. Herein we describe a case of manidipine-induced gingival overgrowth, together with a review of the literature regarding the pathogenesis and clinical management of drug-induced gingival overgrowth.

Abstract

We studied the prevalence of manidipine-induced gingival overgrowth. The incidence of such overgrowth was 1%, and was found in only one case among the surveyed patients. Together with a review of the literature regarding the pathogenesis and clinical management of drug-induced gingival overgrowth, we describe a case of manidipine-induced gingival overgrowth.

Patients and Methods

Dental patients (n=101) who received manidipine for more than three months were surveyed to determine the incidence of drug-induced gingival overgrowth. Patients taking other drugs known to induce gingival overgrowth, such as phenytoin and cyclosporine A, were excluded from this study. Clinical diagnosis of manidipine-induced gingival overgrowth was verified by the disappearance or decreased severity of gingival overgrowth after withdrawal from manidipine.

Results

The gingival overgrowth was discovered in only one patient receiving manidipine (n=101), an incidence of 1.0%.

Case

A 69-year-old man with hypertension was referred to the Oral Surgery Department with a complaint of painless gingival swelling. Intraoral examination revealed marked gingival swelling of the interdental papillae on the labial side of the lower anterior teeth (Fig. 1). The gingival tissues were fairly hard, but bled rather easily upon probing and brushing. Thus, it was determined that oral hygiene had been inadequate. The patient had been receiving manidipine 10
mg/day for 10 months. As the clinical findings of gingival overgrowth were similar to those of other calcium channel blockers such as nifedipine and diltiazem, a tentative diagnosis of gingival overgrowth induced by manidipine was made. A gingival specimen was obtained for histological examination, which revealed gingival overgrowth.

Manidipine was discontinued after consultation with the patient's physician and was replaced with an ACE- (angiotensin converting enzyme) inhibitor. No specific periodontal treatment was provided for the gingival overgrowth. A marked reduction of gingival overgrowth was evident 2 months after the withdrawal of manidipine (Fig. 2). Consequently, we concluded that this gingival overgrowth was induced by manidipine. Oral cleaning, scaling, and monitoring of the gingival status were followed up by the patient's dentist.

**Histological findings**

On histopathological examination, it was discovered that the surface of the tissue was covered by parakeratotic and acanthotic stratified squamous epithelium, with irregular elongation and fusion of rete ridges. In the subepithelial connective tissue, bundles of collagen fibers with a normal density of fibroblasts were noted, and increased vascularity and mild lymphocyte infiltration were recognized (Fig. 3).

**Discussion**

Manidipine is occasionally used for the treatment of hypertension, ranking fifth among the calcium channel blockers used in Japan (10). There are two main classes of calcium channel blockers: dihydropyridines (amlodipine, felodipine, manidipine, nifedipine, nicardipine, and nisoldipine) and nondihydropyridines, which include a benzothiazepine (diltiazem) and a phenylalkylamine (verapamil) (1, 2, 11). Calcium channel blocker–induced gingival overgrowth has been reported from both classes; the first report of gingival overgrowth among calcium

![Fig. 1. Manidipine-induced gingival overgrowth at the interdental papillae.](image1)

![Fig. 2. Manidipine-induced gingival overgrowth at the interdental papillae. Marked reduction was evident 2 months after the withdrawal of manidipine.](image2)

![Fig. 3. Histological view of gingival overgrowth (hematoxylin and eosin, original magnification: X4).](image3)
channel blockers involved nifedipine (12). Since then, many cases concerning nifedipine (13, 14, 15) as well as other calcium channel blockers, such as amlodipine (13, 16), diltiazem (13), felodipine (17), manidipine (6–9), nicardipine (18, 19), nisoldipine (20), nitrendipine (21), and verapamil (22, 23) have been reported as causative drugs for gingival overgrowth.

Previous reports concerning the prevalence of calcium channel blocker-related gingival overgrowth with sample sizes of more than 100 have been summarized in Table 1. The highest incidence of gingival overgrowth was found with nifedipine and varied from 6.3% to 43.6% (14, 16, 19). The incidence in regards to amlodipine varied from 1.7% to 3.3% (13, 16) and that of diltiazem was reported to be 2.2% (13). The incidence documented for manidipine was lower than those of amlodipine, diltiazem, and nifedipine. However, with respect to several case reports (6–9), manidipine has also been implicated as a causative drug for gingival overgrowth.

Plaque has also been identified as a risk factor for drug–induced gingival overgrowth. The severity of gingival overgrowth in patients taking calcium channel blockers correlates well with poor plaque control and is commensurate with the degree of plaque-induced inflammation (13, 24). The importance of plaque as a cofactor in the etiology of drug–associated gingival overgrowth has been recognized in the most recent classification system for periodontal diseases (25). Another factor affecting the occurrence of gingival overgrowth may include gender, with males being three times as likely to develop overgrowth (26). Although there are conflicting data with respect to the relationship between severity of overgrowth and daily dose of medication, most studies have not reported a significant association with dosage (15, 27, 28).

Clinical manifestation of gingival overgrowth frequently appears from one to three months after the initiation of treatment with associated medications (29). Gingival overgrowth normally begins at the interdental papillae and is more frequently found in the anterior segment of the labial surfaces (27, 30, 31), as in the present case. 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 is normally confined to the attached gingiva but may extend coronally and interfere with esthetics, mastication, or speech (27, 30, 31). Disfiguring gingival overgrowth triggered by the medications is not only esthetically displeasing, but often impairs nutrition and access for oral hygiene, resulting in an increased susceptibility to oral infection, caries, and periodontal diseases. Most drug–associated gingival overgrowth appears to be clinically indistinguishable among the causative drugs (32).

An ultrastructural study demonstrated that the increase in gingival tissue volume is primarily due to a connective tissue response rather than epithelial cell layer involvement (33, 34). The histopathology of the lesions in all drug categories (phenytoin, cyclosporine A, and calcium channel blockers) is similar and is characterized by excessive accumulation of extracellular matrix proteins, such as collagen, or amorphous ground substance (27, 30, 34, 35). Varying degrees of inflammatory infiltrate exist, while an increase in the number of fibroblasts remains controversial (35–37). The predominant type of infiltrating inflammatory cell is the plasma cell. Parakeratinized epithelium of variable thickness covers the connective tissue stroma and epithelial ridges may penetrate deep into the connective tissue, creating irregularly arranged collagen fibers (33).

The mechanism through which medication triggers a connective tissue response in the gingiva is still
poorly understood. Because only a subset of patients treated with the medications will develop gingival overgrowth, it has been hypothesized that these individuals have fibroblasts with an abnormal susceptibility to the drug treatment. Indeed, it has been shown that fibroblasts from overgrown gingiva in phentoin–treated patients are characterized by elevated levels of protein synthesis, most of which is collagen (38). However, results of a study comparing intraoral lesions with the presence of fibrosis at extraoral sites failed to show that the severity of gingival overgrowth correlates well with the formation of fibrotic lesions elsewhere in the body (39). Such gingival overgrowth cannot be considered a consequence of systemic and/or genetic fibroblast hyperactivity. A limitation of this study was that the conclusions were based on examination of extraoral tissues at the macroscopic level only (39). It also has been proposed that susceptibility or resistance to pharmacologically induced gingival enlargement may be governed by the existence of differential proportions of fibroblast subsets in each individual that exhibit a fibrogenic response to these medications (38, 40). In support of this hypothesis, it has been shown that functional heterogeneity exists in gingival fibroblasts.

The most effective treatment of drug-related gingival overgrowth is the withdrawal or substitution of medication. When this treatment approach is taken, as demonstrate in our case report, it can take from 1 to 8 weeks for resolution of gingival lesions (16). Unfortunately, not all patients respond to this mode of treatment, especially those with longstanding gingival lesions. Substitution of phentoin with a different anticonvulsant has long been suggested as the treatment of choice for severely affected gingiva. Recently, the feasibility of phentoin substitution has increased with the addition of a new generation of anticonvulsants such as lamotrigine, gabapentin, sulthiame, and topiramate. Changes from nifedipine to diltiazem or verapamil are an option for physicians. Changing hypertensive therapy from nifedipine to an antihypertensive in the same class, such as isradipine, may result in regression of gingival overgrowth (41). Professional debridement with scaling and root planing as needed has been shown to offer some relief of gingival overgrowth (42). Another non–surgical treatment, tenidap (an antiinflammatory drug) has also been indicated as having a possible role in the prevention of drug–related gingival overgrowth (43).

Because the anterior labial gingiva is frequently involved, surgery is commonly performed for esthetic reasons before any functional consequences are present. The classical surgical approach has been the external bevel gingoectomy. However, total or partial internal gingivectomy has been suggested as an alternative approach (27). This more technically demanding approach has the benefit of limiting the large, denuded connective tissue wound that results from external gingivectomy, thereby minimizing postoperative pain and bleeding.

The recurrence rate of severe gingival enlargement in cyclosporine A– or nifedipine–treated patients after surgical periodontal therapy was found to be about 40% within 18 months after active treatment (41). Significant determinants of recurrence were found to be younger age, gingival inflammation, and poor compliance with maintenance visits (44).

Conclusions
Gingival overgrowth induced by manidipine was found with low incidence in surveyed patients. The clinical findings of gingival overgrowth were similar to those of other calcium channel blockers.

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