Prevalence of Amlodipine-induced Gingival Overgrowth

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Abstract
The prevalence rate of amlodipine-induced gingival overgrowth was determined in patients taking amlodipine for three months. Gingival overgrowth was found in four cases among the 301 patients surveyed; a prevalence rate of 1.3%. The clinical findings of amlodipine-induced gingival overgrowth were similar to those induced by other calcium channel blockers.

Introduction
Many terms have been used to describe medication-related abnormal growth of gingiva, including gingival overgrowth, hyperplasia, hypertrophy, and enlargement. However, the general term that best describes this iatrogenic condition is gingival overgrowth (1–17). Drugs associated with gingival overgrowth can be categorized broadly into three major groups according to their therapeutic actions: anticonvulsants (phenytoin), immunosuppressive agents (cyclosporine A), and calcium channel blockers (18–20).

Amlodipine is a long-acting calcium channel blocker used as an anti-hypertensive and for the treatment of angina (9). In conjunction with an increase in the usage of amlodipine, however, an adverse effect of gingival overgrowth has been reported (1–17). Evidence regarding gingival overgrowth has come from several case reports (1–8, 11–17), although there have been only two studies on the prevalence to evaluate the magnitude of this effect (9, 10). Because the prevalence of amlodipine-associated gingival overgrowth remains poorly defined, we determined the prevalence rate of amlodipine-associated gingival overgrowth. A typical case of amlodipine-induced gingival overgrowth is also described herein, together with a review of the literature regarding calcium channel blocker-induced gingival overgrowth.

Patients and Methods
Dental patients (n=301) who received amlodipine for more than three months were surveyed to determine the rate 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 amlodipine-induced gingival overgrowth was verified by the disappearance or decreased severity of gingival overgrowth after the withdrawal of amlodipine. This study was approved by the Ethics Committee of Nihon University School of Dentistry at Matsudo (No. EC08–005).

Results
Gingival overgrowth was found in four patients among the 301 patients receiving amlodipine that were surveyed. The prevalence rate of gingival overgrowth was 1.3%, of which the extent and severity varied among the patients. The clinical findings of amlodipine-induced gingival overgrowth were similar to those seen with use of other calcium channel blockers, such as nifedipine and diltiazem.
Case report of amlodipine associated gingival overgrowth

A 48-year-old man was taking amlodipine (5 mg/day) for hypertension. A marked painless gingival swelling at the interdental papillae on the labial side of the lower and upper anterior teeth was found nine months after the start of amlodipine treatment. The gingival tissues were firm and fairly hard, but bled rather easily upon probing and brushing (Fig. 1). Because the clinical findings of gingival overgrowth were similar to those seen with use of other calcium channel blockers, such as nifedipine and diltiazem, a tentative diagnosis of amlodipine-induced gingival overgrowth was made. A gingival specimen was obtained for histological examination, of which the findings were the epithelium with irregular elongation and fusion of rete ridges and bundles of collagen fibers in the subepithelial connective tissue (Fig. 2). Thus, we concluded that this gingival overgrowth was induced by amlodipine. Amlodipine was discontinued after consultation with the patient’s physician and was replaced with an angiotensin converting enzyme (ACE) inhibitor. No specific periodontal treatment, brushing instruction, or oral care was provided to the patient for the gingival overgrowth. Marked reduction of gingival overgrowth was evident two months after the withdrawal of amlodipine (Fig. 3). Thus, we concluded that this gingival overgrowth was induced by amlodipine. Oral cleaning, scaling, and monitoring of the gingival status were being followed up by the patient’s dentist.

Discussion

Amlodipine is a dihydropyridine calcium antagonist that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine is frequently used as an anti-hypertensive and for the treatment of angina (9). However, various adverse effects of amlodipine have been reported, including headache, edema, dizziness, flushing, palpitations, and gingival overgrowth (21, 22).

There are three types of calcium channel blockers in common use from three distinct chemical classes:

Fig. 1. Clinical appearance of amlodipine-associated gingival overgrowth. Gingival lobulations at the interdental papillae in the anterior segment of the labial surfaces of both lower and upper gingiva.

Fig. 2. Histological view of gingival overgrowth (hematoxylin and eosin, original magnification: ×4). The surface 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 normal density of fibroblasts were noted, and increased vascularity and mild lymphocyte infiltration were also recognized.

Fig. 3. Clinical appearance two months after the withdrawal of amlodipine. Marked reduction of gingival overgrowth was evident.
phenylalkylamines (e.g., verapamil), benzothiazepines (e.g., diltiazem), and dihydropyridines (e.g., amlovidine, felodipine, manidipine, nifedipine, nicardipine, and nisoldipine) (18–20). Calcium channel blocker–associated gingival overgrowth has been reported in all three types (19, 20). The first report of gingival overgrowth among calcium channel blockers, in 1984, was induced by nifedipine (23, 24). Since then, many cases involving nifedipine as well as other calcium channel blockers have been reported. In fact, amlovidine (1–17, 25), diltiazem (25, 26), felodipine (27), manidipine (28, 29), nicardipine (30, 31), nifedipine (10, 20, 25, 26, 29, 32, 33), nisoldipine (34), nitrendipine (35), and verapamil (36, 37) have been reported as causative drugs for gingival overgrowth.

Of the many calcium channel blockers in use since the 1980s, amlovidine (Norvasc®) is the drug of choice among calcium channel blockers currently used in Japan (38, 39).

The first case of amlovidine–associated gingival overgrowth was reported by Ellis in 1993 (1). Like other calcium channel blockers, clinical manifestation of gingival overgrowth frequently appears within two to three months after starting treatment with amlovidine (3, 40).

There are two previous reports concerning the prevalence of amlovidine–associated gingival overgrowth (9, 10), which, together with the present results, are summarized in Table 1. The prevalence rates of the two previous reports (1.7% and 3.3%) showed a small difference. The present result (1.3%) was the lowest, but the difference was slight.

Compared with prevalence rates in previous reports of calcium channel blockers with more than 50 samples, the rate of amlovidine (1.4% to 3.3%) (9, 10) was lower than those of manidipine (1.8%) (25), nifedipine (6.3% to 43.6%) (3, 25, 26, 32), and diltiazem (1.7% to 4.1%) (3, 25), but higher than those of nicardipine (0.5%) (25, 30) and nisoldipine (1.1%) (25, 34).

Gingival overgrowth normally begins at the interdental papillae and is frequently found in the anterior segment of the labial surfaces (41, 42), as in the present case. Gradually, gingival lobulations form that may appear inflamed or fibrotic in nature, depending on the degree of local factor–induced inflammation. The fibrotic enlargement is typically confined to the attached gingiva but may extend coronally and interfere with esthetics, mastication, or speech (41, 42). Disfiguring gingival overgrowth triggered by medication 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 cases of drug–associated gingival overgrowth closely resemble each other among the causative drugs (43).

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 (10, 33). 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 (44). Another factor affecting the occurrence of gingival overgrowth may include sex, with males being three times as likely to develop overgrowth (45). Although there are conflicting data with respect to the relationship between severity of overgrowth and daily medication dose, most studies have not reported a significant association with dosage (32, 38, 45, 46).

In conclusion, amlovidine–associated gingival overgrowth was found at a low prevalence rate of 1.3%. The clinical findings of gingival overgrowth were similar to those seen with use of other calcium channel blockers.

Table 1. Present results and previous reports on the prevalence of amlovidine–associated gingival overgrowth

<table>
<thead>
<tr>
<th>Author</th>
<th>Gingival overgrowth/samples (%)</th>
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<tbody>
<tr>
<td>Jorgensen (1997)</td>
<td>5/150 (3.3)</td>
</tr>
<tr>
<td>Ellis (1999)</td>
<td>3/181 (1.7)</td>
</tr>
<tr>
<td>Present results</td>
<td>4/301 (1.3)</td>
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