Present research status on drug-induced gingival overgrowth

Incidence of gingival overgrowth caused by calcium channel blockers

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Abstract : The incidence of gingival overgrowth caused by calcium channel blockers was determined. The overgrowth was found in patients receiving amlodipine, diltiazem, manidipine, nicardipine, nifedipine and nisoldipine. The highest rate of gingival overgrowth was obtained by nifedipine (7.6%), followed by diltiazem (4.1%), manidipine (1.8%), amlodipine (1.1%), nisoldipine (1.1%) and nicardipine (0.5%). The rate of nifedipine-induced gingival overgrowth was significantly higher than those of amlodipine, manidipine, nicardipine and nisoldipine, but not diltiazem.

Key words : calcium channel blocker, gingival overgrowth, incidence

Introduction

Gingival overgrowth induced by calcium channel blockers is a well-known adverse effect. Amlodipine1-3), diltiazem4,5), felodipine6), manidipine7,8), nicardipine9), nifedipine3,5,8,10-12), nisoldipine13), nitrendipine14) and verapamil15-17) were reported as causative drugs for gingival overgrowth. However, this evidence has come from several case reports, and there have been few prevalence studies to evaluate the magnitude of this effect. Since the incidence of gingival overgrowth induced by calcium channel blockers remains poorly defined, the rates of 15 calcium channel blockers were determined.

Patients and Methods

During a 17-year period (1991–2007), 1,467 dental patients taking a calcium channel blocker for a minimum of 3 months attended the Department of Oral Surgery, Nihon University School of Dentistry at Matsudo for treatment of their various oral diseases. The patients were surveyed to determine the calcium channel blocker-induced gingival overgrowth. The 15 kinds of calcium channel blocker and numbers of cases were as follows: amlodipine (n = 267), azelnipine (n=11), barnidipine (n=25), benidipine (n=28), diltiazem (n = 196), efondipine (n=14), felodipine (n=4), flunarizine (n = 32), manidipine (n = 111), nicardipine (n = 219), nifedipine (n = 347), nilvadipine (n = 58), nisoldipine (n = 89), nitrendipine (n = 25) or verapamil (n = 41). Patients taking other drugs known to induce gingival overgrowth such as phenytoin and cyclosporin A were excluded from this study. Clinical diagnosis of calcium channel blocker-induced gingival overgrowth was verified by disappearance or decreased severity of gingival overgrowth after withdrawal of the causative drug.

Results

Gingival overgrowth was found in patients receiving amlodipine (n = 3), diltiazem (n = 8), manidipine (n
nicardipine (n = 1), nifedipine (n = 27) and nisoldipine (n = 1), but not azelnipine, barnidipine, benidipine, efonidipine, felodipine, flunarizine, nilvadipine, nitrendipine and verapamil (Table 1). The highest rate was obtained by nifedipine (7.6%), followed by diltiazem (4.1%), manidipine (1.8%), amlodipine (1.1%), nisoldipine (1.1%) and nicardipine (0.5%). The incidence of nifedipine-induced gingival overgrowth was significantly higher than those of amlodipine, manidipine, nicardipine and nisoldipine, but not diltiazem (Table 1). Concerning amlodipine, diltiazem and nifedipine, males were 2.0-3.5 times more likely to develop overgrowth.

A typical case of gingival overgrowth is as follows: A 48-years-old man was on amlodipine (5 mg/day) for hypertension. A marked painless gingival swelling at interdental papillae on the labial side of the lower and upper anterior teeth was found at nine months following administration of amlodipine. The gingival tissues were firm and fairly hard, but bled rather easily upon probing and brushing (Fig. 1). Since 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 amlodipine was made. A gingival specimen was obtained for histological examination, which revealed gingival overgrowth (Fig. 2). Amlodipine 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 to the patient for the gingival overgrowth. Marked reduction of gingival overgrowth was evident 2 months after withdrawal of amlodipine (Fig. 3). We concluded that this gingival overgrowth was induced by amlodipine.

Discussion

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). Calcium channel blocker-induced gingival overgrowth was reported in both classes, in which

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of case</th>
<th>Gingival overgrowth (%)</th>
<th>Ratio gender (male/female)</th>
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<tbody>
<tr>
<td>Amlodipine</td>
<td>267</td>
<td>3 (1.1)</td>
<td>2.0</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>196</td>
<td>8 (4.1)</td>
<td>3.0</td>
</tr>
<tr>
<td>Manidipine</td>
<td>111</td>
<td>2 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>219</td>
<td>1 (0.5)</td>
<td>3.5</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>347</td>
<td>27 (7.6)</td>
<td></td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>89</td>
<td>1 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Azelnipine</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Barnidipine</td>
<td>25</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Benidipine</td>
<td>28</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Efonidipine</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Felodipine</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Flunarizine</td>
<td>32</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nilvadipine</td>
<td>58</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>25</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Velapami</td>
<td>41</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 Gingival overgrowth induced by calcium channel blockers

Statistical difference vs nifedipine: a. Fisher's test (two tail); b. \( \chi^2 \)-test (Yate's correlation).

\*\*p < 0.01 \*p < 0.05
Incidence of calcium channel blocker-induced gingival overgrowth

the first report of gingival overgrowth among calcium channel blockers was nifedipine\(^8\). Since then, many cases concerning nifedipine as well as other calcium channel blockers have been reported. Amlodipine\(^1\)\(^-\)\(^3\), diltiazem\(^4\)\(^-\)\(^5\), felodipine\(^6\), manidipine\(^7\)\(^,\)\(^8\), nicardipine\(^8\), nifedipine\(^3\)\(^,\)\(^8\)\(^,\)\(^9\)\(^-\)\(^12\), nisoldipine\(^13\), nitrendipine\(^14\), and verapamil\(^3\)\(^-\)\(^5\),\(^15\)\(^,\)\(^16\) were reported as the causative drug for gingival overgrowth. However, felodipine, nitrendipine and verapamil were not found in the present study. The number of felodipine samples was small in the study. The low incidence with nitrendipine and verapamil, might be also found in future studies.

Previous reports concerning the incidence of calcium channel blocker-related gingival overgrowth with sample size of more than 100 are summarized in Table 2. The highest rate was found with nifedipine and varied from 6.3 to 43.6\%\(^3\)\(^,\)\(^4\)\(^,\)\(^11\). Those of amlodipine and diltiazem were 1.7, 3.3 and 2.2\%, respectively\(^2\)\(^,\)\(^3\). Compared with the present results, amlodipine showed a lower rate, but diltiazem and nifedipine higher rates. Since the patients of the present study were not well controlled and community-based, these differences might be observed. Ellis et al. reported that males were 3 times as likely to develop overgrowth. The present results identified the same tendency.

As mentioned, there are many kinds of calcium channel blockers, and usage of the drug has changed with the times. In the 1980s and 1990s, nifedipine (Adalat\(^8\)) was common, but the recently used drug is amlodipine (Norvasc\(^8\)).

Gingival overgrowth induced by phenytoin and cyclosporine A is also a well-known adverse effect. The
incidence was reported to be about 50\(^{18-19}\) and 30-70\(^{20-22}\), respectively, which were higher than those of calcium channel blockers.

Plaque is a well-known 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\(^3,12\). 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\(^23\). Another factor affecting the occurrence of gingival overgrowth may include gender, with males being three times as likely to develop overgrowth\(^24\). 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\(^11,25,26\).

Clinical manifestation of gingival overgrowth frequently appears within 1 to 3 months after initiation of treatment with the associated medications\(^26\). Gingival overgrowth normally begins at the interdental papillae and is more frequently found in the anterior segment of the labial surfaces\(^27,28\), as was found 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\(^27,28\). 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 is similar in characteristics among the causative drugs\(^29\).

The most effective treatment for drug-related gingival overgrowth is withdrawal or substitution of medication. When this treatment approach is taken, as suggested by a case report, it may take from 1 to 8 weeks for resolution of gingival lesions\(^2\). Unfortunately, not all patients respond to this mode of treatment, especially those with longstanding gingival lesions. Substitution of phenytoin with a different anticonvulsant has long been suggested as the treatment of choice for the severely affected gingiva. Recently, the feasibility of phenytoin 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 by the patient’s physician are an option. Changing hypertensive therapy from nifedipine to an antihypertensive of the same class, such as isradipine, may result in regression of gingival overgrowth\(^30\). Professional debridement with scaling and root planing as needed has been shown to offer some relief in gingival overgrowth patients\(^31\). Another non-surgical treatment, tenidap (an anti-inflammatory drug), was suggested as a possible way to prevent drug-related gingival overgrowth\(^32\).

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 gingivectomy. However, a total or partial

<table>
<thead>
<tr>
<th>Author</th>
<th>Gingival overgrowth/sample (%)</th>
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<tbody>
<tr>
<td></td>
<td>amlodipine</td>
</tr>
<tr>
<td>Katsumi(^4)</td>
<td>7/108 (6.5)</td>
</tr>
<tr>
<td>Nery(^11)</td>
<td>79/181 (43.6)</td>
</tr>
<tr>
<td>Jorgensen(^21)</td>
<td>5/150 (3.3)</td>
</tr>
<tr>
<td>Ellis(^21)</td>
<td>3/181 (1.7)</td>
</tr>
<tr>
<td>Present result</td>
<td>3/267 (1.1)</td>
</tr>
</tbody>
</table>
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 results from the external gingivectomy, thereby minimizing postoperative pain and bleeding.

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

Conclusions

Gingival overgrowth induced by amlodipine, diltiazem, manidipine, nicardipine, nifedipine and nisoldipine was found in surveyed patients, and the incidence of overgrowth varied among the drugs. Calcium channel blocker-induced gingival overgrowth, especially by nifedipine, appears more frequently and is now not a rare adverse effect.

Acknowledgement

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References


薬物性歯肉増殖症に関する研究の現状

カルシウム拮抗薬の歯肉増殖症発生頻度

小野 Ursue 1, 大野奈穂子 1, 長谷川一弘 1
田中 茂男 1, 小宮 正道 1, 松本 裕子 2
藤井 彰 2, 秋元 芳明 1

15 種類のカルシウム拮抗薬による歯肉増殖症発生頻度を検討した。歯肉増殖症は amlodipine, diltiazem, manidipine, nicardipine, nifedipine および nisoldipine 服用者に認められたが, azelnipine, barnidipine, benidipine, efonidipine, felodipine, flunarizine, nilvadipine, nitrendipine および verapamil 服用者にはみられなかった。最も高い発生頻度は nifedipine (7.6%) であり, diltiazem (4.1%), manidipine (1.8%), amlodipine (1.1%), nisoldipine (1.1%), nicardipine (0.5%) の順であった。Nifedipine による歯肉増殖症発生頻度は, amlodipine, manidipine, nicardipine, nisoldipine の発生頻度と比較して有意に高かった。

キーワード：カルシウム拮抗薬, 歯肉増殖症, 発生頻度