Gingival Hyperplasia Induced by Nifedipine

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Abstract

We describe 4 cases of gingival hyperplasia induced by nifedipine, together with clinical and histological findings. Hyperplasia of the interdental papillae was observed in all cases. Histologic examination showed multilayered epithelial parakeratosis with variations in the width, proliferation, reticulation and elongation of the rete pegs. Substitution of another drug and improvement of oral hygiene led to reduction of the gingival overgrowth without gingivectomy. These treatments are essential for gingival hyperplasia induced by nifedipine.

Introduction

Nifedipine is a calcium channel-blocking agent commonly used for treatment of ischemic and hypertensive heart diseases. The side effects of nifedipine include hypotension, headaches, weakness, muscle cramps, flushing, dizziness, tremor, joint stiffness, peripheral edema, dermatitis, pruritus and urticaria[1]. Recently, nifedipine has also been implicated as the causative agent of gingival hyperplasia[2–10]. The present article describes 4 cases of gingival hyperplasia induced by nifedipine, along with the clinical and histological findings.

Case Reports

Case 1

A 51-year-old man with systemic vascular hypertension was referred to us with gingival overgrowth. He had been regularly receiving nifedipine 40 and 20 mg/day for 3 years and for the last 2 years, respectively. He had first noticed gingival
overgrowth approximately 6 months after the start of nifedipine administration, and the gingiva had gradually continued to increase in size. Although he had undergone gingivectomy 5 or 6 times, recurrences of the overgrowth persisted.

Oral examination revealed marked gingival overgrowth on the buccal and palatal sides of the upper posterior teeth and on the buccal side of the lower posterior teeth (Figs. 1, 2). Overgrowth was also found on the labial side of the lower anterior teeth (Fig. 3). The gingival tissues were firm and fairly hard, but bled rather easily upon probing and brushing. Thus, oral hygiene had not been adequate. A gingival specimen was obtained for histological examination, which revealed gingival hyperplasia.

Fig. 1  Case 1. A 51-year-old man with gingival hyperplasia on the buccal side of the upper posterior molar teeth

Fig. 2  Case 1. Gingival hyperplasia on the palatal side of the upper posterior molar teeth
Nifedipine was discontinued after consultation with the patient’s physician. Oral cleaning and scaling were started, and gradual improvement was observed thereafter without gingivectomy. Marked reduction of inflammation and overgrowth was evident 2 months after withdrawal of nifedipine (Figs. 4a, 4b). Monitoring of the gingival status is now being followed up.

Figs. 4a and 4b  Case 1. Two months following withdrawal of nifedipine. Marked regression of hyperplasia is evident.
Case 2

A 50-year-old man was referred for extraction of teeth. He had been suffering from essential systemic hypertension for 10 years, and had been treated with nifedipine 30 mg/day for 2 years. He had not noticed the presence of gingival overgrowth on the labial side of the lower anterior teeth (Fig. 5). Since the teeth associated with the gingival overgrowth were extracted, gingivectomy was also performed. The histological diagnosis was gingival hyperplasia.

Fig. 5 Case 2. A 50-year-old man with gingival hyperplasia on the labial side of the lower anterior teeth

Case 3

A 74-year-old man with essential systemic hypertension was referred for bleeding from the gingiva. He had been receiving nifedipine 20 mg/day for 5 years. The bleeding was easily controlled by compression with oxidized cellulose. He had been unaware of gingival overgrowth on the buccal sides of the upper posterior teeth (Fig. 6). A biopsy specimen was found to consist of gingival hyperplasia. However, he did not return after treatment of the bleeding, and was lost to follow-up.

Fig. 6 Case 3. A 74-year-old man with gingival hyperplasia (arrow) on the buccal side of the upper posterior teeth
**Case 4**

A 46-year-old woman with systemic vascular hypertension was found to have gingival overgrowth to the labial side of the lower anterior teeth. She had been receiving nifedipine 40 mg/day for 4 years, and had first noticed the overgrowth 1 month after the start of nifedipine administration. Repeated gingivectomy had not produced any improvement (Fig. 7). The histological diagnosis was gingival hyperplasia. Nifedipine was discontinued after consultation with the patient's physician. However, since the hypertension could not be controlled with other drugs, nifedipine was restarted. Although slight regression of hyperplasia was observed 1 month after withdrawal of nifedipine, recurrence occurred after further

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**Fig. 7** Case 4. A 46-year-old woman with gingival hyperplasia on the labial side of the lower anterior teeth

**Fig. 8** Epithelial hyperplasia with acanthosis (original magnification, x125)
nifedipine treatment. Oral cleaning and scaling were then continued without discontinuation of nifedipine, and thereafter marked and slight reduction of inflammation and overgrowth were observed, respectively. The gingival status is now being followed up.

**Histological examination**

The gingival specimens from these 4 patients showed identical histological findings except for inflammatory reactions (Fig. 8). Epithelial hyperplasia with acanthosis and parakeratosis was found, and elongation of the rete pegs was evident. The connective tissue showed large bundles of dense collagenous fibers with a moderate increase of fibroblasts. Inflammatory reactions with lymphocytes and plasma cells, located perivascularly, showed various degrees from mild to severe.

**Discussion**

With the increasing use of nifedipine, more cases of gingival hyperplasia caused by this drug have been reported[2-10]. The principal action of nifedipine is to inhibit the influx of extracellular calcium ions across the membranes of cardiac and vascular smooth muscle cells, without changing the serum calcium concentration. The process of contraction of cardiac and vascular smooth muscle is dependent on the movement of extracellular calcium ions into the cells through specific ion channels (mostly voltage-dependent L-channels). By inhibiting this calcium influx, nifedipine inhibits contraction, thereby dilating the main coronary and systemic arteries. The mechanism of relief of angina includes relaxation and prevention of coronary artery spasm, as well as reduction of oxygen utilization by the myocardium[4,7]. The mechanism of nifedipine-induced hyperplasia is still unclear, but may be related to the drug's ability alter calcium metabolism[3,5].

Nifedipine-induced gingival hyperplasia was first reported by LEDERMAN et al.[2] in 1984 and has since been confirmed by others[3-10]. The incidence of gingival hyperplasia induced by nifedipine is reported to be 6.5-14.7%[6,8,10], which is lower than that due to diphenylhydantoin (32% to over 70%)[11-14]. Since the incidence of that due to cyclosporin A varies among reports (8% to over 70%)[15-17], no comparison can be made.

BUTLER et al.[7] reported that gingival hyperplasia induced by nifedipine was histologically and clinically similar to that associated with diphenylhydantoin and cyclosporin. Thus, histologically the overlying stratified squamous epithelium was parakeratotic, with elongated, thin rete ridges. Numerous fibroblasts were also present. LUCAS et al.[4] compared nifedipine- and diphenylhydantoin-induced hyperplasia, and reported that both displayed an increase of extracellular ground substance and fibroblasts.

In the present patients, withdrawal of nifedipine, improvement of oral hygiene, and gingivectomy were applied for the treatment of gingival hyperplasia induced by nifedipine. Nifedipine had been discontinued in case 1 and captopril substituted instead. Subsequently, marked regression of the hyperplasia was observed without gingivectomy. However, in case 4, since the hypertension was not
controlled by other drugs, nifedipine was restarted. Slight regression of the hyperplasia was observed 1 month after the withdrawal of nifedipine and improvement of oral hygiene, but recurrence occurred after further nifedipine treatment. Thus, the hyperplasia increased with further nifedipine treatment, but was reduced when nifedipine was discontinued. Accordingly, when hyperplasia develops, nifedipine should be discontinued and an alternative drug should be prescribed in consultation with the patient's physician\textsuperscript{[2,3]}. If discontinuation is not possible, oral cleaning and scaling must be performed and continued with symptomatic treatment. Improvement of oral hygiene is essential, and should be applied first. Gingivectomy should then be performed after oral hygiene has improved. However, since there are several reports of regression of hyperplasia without gingivectomy\textsuperscript{[2,4,9]}, gingivectomy should be applied only in severe cases. Thus, gingivectomy may not be essential for treatment of gingival hyperplasia induced by nifedipine.

**Conclusions**

Four cases of gingival hyperplasia induced by nifedipine were presented, in which regression of hyperplasia without gingivectomy was observed when nifedipine treatment was discontinued. Thus, substitution of the drug for another, and improvement of oral hygiene are essential for the treatment of gingival hyperplasia induced by nifedipine.

**References**


