



## HYPERTENSION ILLUSTRATED

# Gingival hyperplasia caused by calcium channel blockers

GG Missouriis<sup>1</sup>, RG Kalaitzidis<sup>2</sup>, FP Cappuccio<sup>2</sup> and GA MacGregor<sup>2</sup>

Departments of <sup>1</sup>Cardiology, and <sup>2</sup>Blood Pressure Unit, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, UK

**Keywords:** gingival hyperplasia; calcium channel blockers

### Case report

A 49-year-old Caucasian gentleman was referred to us in 1994 with a history of essential hypertension and hypercholesterolaemia. At the time he was taking simvastatin 10 mg a day. On examination, the supine blood pressure was elevated at 180/105 mm Hg. He was treated with nifedipine LA 60 mg a day and after 4 weeks when he attended the Blood Pressure Unit the supine blood pressure was well controlled at 138/89 mm Hg. Three years later he was re-referred by his dental practitioner who noted that the patient had poor oral hygiene as well as gross gingival hyperplasia, that was likely to be due to the dihydropyridine calcium antagonist (Figure 1). Nifedipine was therefore stopped and his treatment was changed to enalapril 10 mg twice a day and bendrofluzide 2.5 mg daily with good control of blood pressure. Two months later the gingival hyperplasia had completely resolved.

### Discussion

Gingival overgrowth associated with nifedipine therapy was first reported in 1984.<sup>1,2</sup> It is now well recognized that gingival hyperplasia is a rare adverse effect of all three classes of calcium channel blockers, with the impression that it is more common with the dihydropyridine calcium antagonists. It is usually seen within a few months of starting treatment and is reversible after discontinuation of therapy.<sup>3–5</sup> Gingival hyperplasia is also seen in patients treated with diphenylhydantoin and cyclosporin.<sup>3</sup> Gingival overgrowth, however, is more commonly reported than overt hyperplasia.<sup>6</sup>

Gingival hyperplasia begins as an enlargement of the interdental papillae. Such enlargement gives the gingival tissues a lobulated or nodular appearance (Figure 1). The hyperplastic gingival tissue can

extend over the teeth and crowns, and in some cases it may interfere with eating. The above process is aggravated by gingival inflammation and poor oral hygiene. Indeed, good oral hygiene reduces but does not eliminate the gingival hyperplasia. Experimental studies in dogs using the dihydropyridine calcium antagonist oxodipine at doses 6, 24, and 73 times the intended therapeutic dosage for humans, led to dose-related gingival hyperplasia at 49 days of treatment. The severity increased with continued treatment.<sup>7,8</sup> The pathological findings were those of gingival acanthosis, parakeratosis, rete pegs proliferation, varying densities of fibroblastic and capillary proliferation, and mononuclear cell aggregations. Gingival fibroblasts contained strongly sulphated mucopolysaccharides and numerous secretory granules.

It has been postulated that the interaction between the calcium channel blockers and other drugs such as phenytoin and cyclosporin, or their metabolites, and gingival fibroblasts is calcium-dependent. These drugs which affect intracellular calcium metabolism or transport may in some patients stimulate gingival fibroblasts resulting in hyperplasia of extracellular matrix components, such as the accumulation of glycosaminoglycans resulting in gingival hyperplasia.

Our patient was also on treatment with an HMG Co reductase inhibitor (statin), when nifedipine LA 60 mg was prescribed. It is well recognised that, when calcium channel blockers which are strong inhibitors of cytochrome P450 (CYP) 3A4 are co-administered with statins that are metabolised by the same isoenzyme prior to biliary and renal excretion, may lead to reduced clearance of these drugs with an increase in side effects.<sup>9,10</sup> Indeed, in patients treated with verapamil and simvastatin the serum levels of both drugs were increased, but as yet there is little evidence for this with the dihydropyridine calcium antagonists.<sup>11,12</sup> Nevertheless, when statins and calcium channel blockers are co-prescribed, especially at high doses, there may possibly be an increase in side effects such as gingival hyperplasia. However, the exact mechanism for this remains an enigma.

Correspondence: Professor Graham A MacGregor, BP Unit, Department of Medicine, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, UK  
Received 16 July 1999; revised and accepted 25 September 1999



**Figure 1** Gross gingival hyperplasia in a hypertensive patient on treatment with a dihydropyridine calcium antagonist and an HMG Co reductase inhibitor for 3 years.

## References

- 1 Lederman D, Lumerman H, Reuben S, Freedman PD. Gingival hyperplasia associated with nifedipine therapy. *Oral Surg* 1984; **57**: 620–622.
- 2 Ramon Y, Behar S, Kishon Y, Engelberg IS. Gingival hyperplasia caused by nifedipine—a preliminary report. *Int J Cardiol* 1984; **5**: 195–204.
- 3 Seymour RA. Calcium channel blockers and gingival overgrowth. *Br Dental J* 1991; **170**: 376–379.
- 4 Colvard MD, Bishop J, Weissman D, Bargiulo AV. Cardizem-induced gingival hyperplasia. *Periodont Case Rep* 1986; **8**: 67–68.
- 5 Pernu HE, Oikarinen K, Hietanen J, Knuuttila M. Verapamil-induced gingival overgrowth: a clinical, histologic and biochemist approach. *J Oral Med Path* 1989; **18**: 422–425.
- 6 Steele RM, Schuma AA, Schreiber RT. Calcium antagonist-induced gingival hyperplasia. *Ann Intern Med* 1994; **120**: 663–664.
- 7 Nyska A, Shemesh M, Tal H, Dayan D. Gingival hyperplasia induced by calcium channel blockers: mode of action. *Med Hypotheses* 1994; **43**: 115–118.
- 8 Galliano A. Oxodipine. *Drugs of the Future* 1987; **12**: 623–624.
- 9 Azie NE et al. The interaction of diltiazem with lovastatin and pravastatin. *Clin Pharmacol Therapeut* 1998; **64**: 369–377.
- 10 Schmassmann-Suhijar D et al. Rhabdomyolysis due to interaction of simvastatin with mibefradil. *Lancet* 1998; **351**: 1929–1930.
- 11 Donahue S et al. Verapamil significantly increases serum concentrations of simvastatin but not pravastatin. *Clin Pharmacol Therapeut* 1999; **65**: 179.
- 12 Kantola T, Kivisto KT, Neuvomen PJ. Erythromycin and verapamil considerably increase serum simvastatin and semvastatin acid concentrations. *Clin Pharmacol Therapeut* 1998; **64**: 177–182.