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Prevalence and risk of gingival overgrowth in patients treated with diltiazem or verapamil

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Abstract

Objectives: This study was conducted to determine the prevalence and risk factors for gingival enlargement in patients treated with diltiazem or verapamil.

Material and Methods: A cross-sectional study was conducted and data from 46 patients actually taking diltiazem or verapamil were compared with 49 cardiovascular controls that never received any of these drugs. All patients were examined for the presence of gingival enlargement using two different indices, the vertical gingival overgrowth (GO) index, and horizontal Miranda & Brunet (MB) index in the interdental area. Gingival index, plaque index, and probing depth were also evaluated.

Results: The total study population was 95:32 diltiazem-treated, 14 verapamil-treated and 49 cardiovascular control subjects. Gingival enlargement occurred in 31% (GO index) and 50% (MB index) of the patients taking diltiazem. Gingival enlargement in the verapamil-treated group was 21% for the GO index and 36% for the MB index. The prevalence of gingival enlargement was higher in the diltiazem- and verapamil-treated patients than in controls for both indices. The difference between the diltiazem-treated group and control was statistically significant ($p = 0.022$ for GO and $p = 0.001$ for MB), while the difference between the verapamil-treated group and controls was not significant. The risk of gingival enlargement (OR – Odds Ratio) associated with diltiazem therapy was 4.0 (1.2–13.1) for the GO index and of 6.0 (2.1–17.3) for the MB index. When the OR were adjusted for gingival index (GI) values, the risk of gingival enlargement was 3.5 (1.0–12.4) for the GO index and 6.2 (1.9–20.0) for the MB index. In the verapamil-treated group the OR values were not significant. The level of concordance between GO and MB indices in all three groups showed a κ-value of 0.72 ($p < 0.001$).

Conclusion: Patients taking diltiazem are at high risk for gingival enlargement and gingivitis has a stronger effect than the drug treatment on gingival enlargement risk.

Key words: calcium channel-blockers; diltiazem; gingival overgrowth; risk factors; verapamil

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Calcium channel blockers are extensively used in the management of cardiovascular diseases. Chemically, the calcium antagonists can be clasified as dihydropiridines (nifedipine), benzothiazine (diltiazem) and phenylakylamine (verapamil). The main unwanted side-effects of the calcium channel blockers are attributable to vasodilatation (headache, facial flushing, dizziness and peripheral edema. Their long-term use has been associated with gingival overgrowth (GO) (Seymour 1991, Brunet et al. 1996, Dukes & Aronson 2000).

Gingival enlargement in patients treated with nifedipine (Lederman et al. 1984, Ramon et al. 1984, Lucas et al. 1985, Seymour 1991, Bullón et al. 1994, Miranda et al. 2001) and other dihydropyridines, such as nitrendipine (Brown et al. 1990), nicardipine (Nagano et al. 1985), felodipine (Lombardi et al. 1991), and amlodipine (Juncadella et al. 1994, Seymour et al. 1994), has been extensively reported. Case reports on gingival enlargement induced by diltiazem (Colvard et al. 1986, Giustiniani et al. 1987, Bowman et al. 1988) and verapamil (Cucchi et al. 1985, Smith & Glenert 1987, Pernu et al. 1989) first appeared in the mid-1980s. Since then, only a few articles, with comparative controls, have reported on the prevalence of gingival enlargement induced by these drugs. Fattore et al. (1991) reported a prevalence of 74% in a group of patients treated with diltiazem while the prevalence in the control group was 13%. There is only one report on the prevalence for diltiazem and verapamil compared with controls (Steele et al. 1994). In this article the prevalence of gingival enlargement

was 21% in a group of diltiazem-treated patients, 19% in patients treated with verapamil, and 4% in the control group. Because the reported prevalences varied widely the true prevalence is not known. (Table 1)

The clinical and pathologic features in drug-induced GO are independent of the drug administered which suggests a common pathway of induction (Akimoto et al. 1991). The pathogenic mechanisms involve different factors, such as dental plaque, gingival inflammation, presence of genetically predetermined gingival fibroblasts (named *responders*), and effect of the drug itself, with all compounds affecting the transmembrane flow of calcium (Sooriyamoorthy & Gower 1989, Brown et al. 1991, Atilla & Kütükçuler 1998, Miranda et al. 2001). Because very often drug-induced gingival enlargement involves a form of combined GO, with the effect of the drug, dental plaque and the inflammatory status, it is important to determine the contribution of each factor. Gingival inflammation has been reported to be a risk factor for gingival enlargement in a group of patients treated with nifedipine (Miranda et al. 2001), but predictors of gingival enlargement in patients treated with other calcium channel blockers have not been reported.

Since the true prevalence and associated risk factors for gingival enlargement induced by diltiazem and verapamil is not known, the aim of the present study was to determine the prevalence, severity, and risk factors of gingival enlargement in: (1) a population of patients treated with diltiazem alone; (2) in patients treated with verapamil alone, and (3) to compare the results with those from a cardiovascular control group.

Material and Methods

Study population

A cross-sectional study was carried out at the ''CAP-Rambla'' primary care center serving a population of 170,000 inhabitants, in Terrassa, Barcelona (Spain). All patients over 18 years of age treated with diltiazem or verapamil who were consecutively visited by his/her general practitioner or cardiologist were eligible. Patients were included if they were actually taking diltiazem or verapamil and using regular doses during at least the last 6 months. The presence of at least 16 permanent teeth, with a minimum of 10 anterior teeth was required. Patients who had periodontal treatment within the 6 months prior to the initiation of the study, patients with concomitant systemic disorders known to affect the gums (such as diabetes, endocrine disorders, leukemia, thrombocytopenic purpura, immunodeficiency states), and patients taking anticonvulsant drugs, calcium antagonists other than diltiazem or verapamil, cyclosporine A, oral contraceptives, and sexual hormones were excluded from the study. Patients included in the diltiazem- or verapamil-treated groups were not treated with other calcium-channel blockers. Control group included patients not treated with diltiazem or verapamil, or any other drugs known to cause GO, who fulfilled the same inclusion and exclusion criteria. All patients agreed to participate in the study and gave their written informed consent.

Gingival enlargement was graded according to the index originally described by Angelopoulos & Goaz (1972) and later modified by Miller & Damm (1992) (GO index). The height of gingival tissue was measured from the cemento–enamel junction to the free gingival margin. The following grades were scored in six dental points around each tooth: Grade 0, normal gingiva. Grade 1, minimal enlargement = less than 2 mm increased in size and gingiva covered the cervical third or less of the anatomic crown. Grade 2, moderate enlargement = 2–4 mm increased in size, and/or gingiva extended into middle third of anatomic crown. Grade 3, severe enlargement = nodular growth greater than 4 mm increased in size, and/or gingiva covered more than two-thirds of the tooth crown. Gingival overgrowth was also measured in the buccal–lingual direction in all inter-dental papilla according to the index described by Seymour et al. (1985) and modified by Miranda & Brunet (MB) index (Brunet et al. 2001, Miranda et al. 2001). The increase in size of the papilla was measured from the enamel surface, at the inter-dental contact point, to the outer papillary surface. Two scores were obtained, one for the buccal papilla and another for the lingual/palatal papilla, according to the following criteria: Grade 0, papillary thickness

Table 1. Prevalence of gingival enlargement

Authors	Year	Cases	Prevalence of gingival enlargement (total number patients taking the drug/% with gingival overgrowth)					Comments
			DTZ	VML	NFD	CsA	Control	
Cuchi et al.	1985	1	–	1	–	–	–	–
Colvard et al.	1986	2	2	–	–	–	–	–
Giustiniani et al.	1987	1	1	–	–	–	–	–
Smith & Glenert	1987	1	–	1	–	–	–	–
Bowman et al.	1988	1	1	–	–	–	–	–
Pernu et al.	1989	1	–	1	–	–	–	–
Fattore et al.	1991	93	35/74%	4/NR%	23/83%	–	31/13%	–
Miller & Damm	1992	24	–	24/4%	–	–	–	–
Steele et al.	1994	115	33/21%	26/19%	29/38%	–	27/4%	No risk assesment*
Bullón et al.	1995	35	13/NR%	–	–	–	22/NR%	No risk assesment†
Bullón et al.	1996	55	13/NR%	–	18/NR%	–	24/NR%	No risk assesment
Cebeci et al.	1996	51	–	29/51%	–	22/40%	–	No risk assesment
Ellis et al.	1999	911	186/2.2%	–	442/6.3%		102/0%	Risk assesment‡

DTZ, diltiazem; VML, verapamil; NFD, nifedipine ; CsA, cyclosporin A; NR, non-reported.

*NFD *versus* Control ($p < 0{,}006$); DTZ *versus* Control ($p = 0.12$); VML *versus* Control ($p = 0.21$).

†DTZ *versus* Control ($p = 0.005$).

‡NFD *versus* Control ($p = 0.012$); DTZ *versus* Control ($p > 0.05$); males three times as likely to develop overgrowth than females.

of less than 1 mm. Grade 1, papillary thickness between 1 and 2 mm. Grade 2, papillary thickness greater than 2 mm.

A standard periodontal probe (Michigan 8/11) was used to assess the extent of enlargement. For both indices an average mean was calculated for whole mouth, anterior and posterior areas, and buccal and lingual/palatal surfaces. Gingival enlargement was considered to be present when grades other than zero were recorded in one or in both GO and MB indices.

Other measures included the GI as described by Löe & Silness (1963), plaque index (PI) as described by Quigley & Hein (1962), and periodontal probing depth (PD) (32). These indices were measured at six points around each tooth. The same examiner (J.M.), unaware of the drugs status of the subjects, did all measurements.

Statistical analysis

The statistical analysis was directed to comparing either diltiazem- or verapamil-treated patients with controls, using the Chi-square (χ^2) test or Fisher's exact test for category variables and the Student ''*t*''-test for continuous ones. The influence of confounding or risk factors on periodontal enlargement and the association between the different periodontal indices were explored by χ^2 or Fisher's exact test. Adjusted gingival enlargement risk associated with diltiazem or verapamil treatment was estimated by logistic regression. Two models were constructed, with gingival enlargement assessed by either GO or MB indices, in which treatment was initially entered and adjusted by forward stepwise inclusion of covariates.

Results

The total study population was 95:32 diltiazem-treated, 14 verapamil-treated and 49 cardiovascular control subjects. The gender and age distribution was similar among the three groups, although cardiovascular controls were slightly younger than the diltiazem or verapamil-treated patients. (Table 2). All three groups had been taking similar coadjuvant medications (nitroglycerin, digoxin, aspirin, diuretics, Angiotensin Converting Enzyme Inhibitors (ACEI), β-blockers, benzodiazepines, coumadins, statins). Patients in the diltiazem-treated group had been taking the drug at doses between 120 and 360 mg/day (mean ± SD = 186 ± 5 mg) for a mean period of 22 months (range = 6–36 months). Patients in the verapamil-treated group had been taking 40–240 mg/day (mean ± SD = 189 ± 7 mg) for a mean period of 30 months (range = 9–36 months).

Gingival enlargement occurred in 31% (GO index) and 50% (MB index) of the patients taking diltiazem. Gingival enlargement in the verapamil-treated group was 21% for the GO index and 36% for the MB index. The prevalence of gingival enlargement was higher in the diltiazem and verapamil-treated patients than in controls for both indices. The difference between the diltiazem-treated group and control was statistically significant ($p = 0.022$ for GO and $p = 0.001$ for MB), while the difference between the verapamil-treated group and controls was not significant. (Table 3). Other clinical indices GI, PI, PD were slightly higher among diltiazem-and verapamil-treated patients, but this difference did not reach statistical significance.

The bivariate analysis in all three groups with respect to quantitative (GI, PI, PD) and qualitative variables (gender, age smoking, bruxism, oral breathing pattern, and the presence of dental prosthesis) only showed a significant association between gingival enlargement (GO and MB indices) and GI ($p < 0.001$).

Results of multivariate analysis showed that the risk (odds ratio – OR) for gingival enlargement associated with diltiazem treatment was 4.0 (1.2–13.1) for GO index and 6.0 (2.1–17.3) for the MB index. When the OR were adjusted for GI values, the risk of gingival enlargement was 3.5 (1.0–12.4) for the GO index and 6.2 (1.9–20.0) for the MB index. In the verapamil-treated group the OR values were not significant. (Table 4).

The level of concordance between GO and MB indices in all three groups showed a κ-value of 0.72 ($p < 0.001$).

Discussion

In our sample, patients treated with diltiazem showed a prevalence of gingival enlargement of 31% and 50% according to the GO and MB indices, respectively. Patients in the verapamil-treated group showed a prevalence of 21% (GO index) and 36% (MB index). Although the prevalence (with respect to cardiovascular controls) was higher for diltiazem and verapamil, the differences were only statistically significant for diltiazem. Steele et al. (1994) showed a prevalence of gingival enlargement of 21% in a group of diltiazem-treated patients, 19% in patients treated with verapamil, and 38% in a nifedipine-treated group. The prevalence respect to the control group (4% of patients in this control group had gingival enlargement) was significantly higher for the nifedipine group of patients (Steele et al. 1994). Similarly, we have previuosly reported a significantly higher prevalence of gingival enlargement in 65 cardiovascular patients treated with nifedipine than in 147 controls (Miranda et al. 2001).

Cebeci et al. (1996) investigated the effect of verapamil treatment on the severity and prevalence of cyclosporin A-induced gingival enlargement in 51 renal transplant recipients. Although the prevalence of GO was more pronounced

Table 2. Demographic characteristics of patients

Data	Cardiovascular control patients ($n = 49$)		Diltiazem-treated patients ($n = 32$)			Verapamil-treated patients ($n = 14$)		
	n	%	*n*	%	*p* value*	*n*	%	*p* value
Male/female ratio	21/28	43/57	15/17	47/53	NS	6/8	43/57	NS
Mean age (SD) years	59 (10)		64 (9)		NS	66 (8)		0.036
Age					NS			NS
<56	20	41	6	18		3	21	
57–66	16	33	13	41		3	21	
67–80	13	26	13	41		8	58	
Smokers (>20 cigarette/day)	4	8	2	6	NS	0	0	NS
Bruxism	13	27	6	19	NS	3	21	NS
Oral breathing pattern	9	18	3	9	NS	1	7	NS
Dental prosthesis	14	29	11	34	NS	7	50	NS

*Diltiazem- or verapamil-treated patients *versus* cardiovascular control patients.
NS, non-significance.

Table 3. Periodontal evaluations of control and diltiazem- or verapamil-treated patients

Data	Cardiovascular control patients ($n = 49$)		Diltiazem-treated patients ($n = 32$)			Verapamil-treated patients ($n = 14$)		
	n	%	*n*	%	*p*-value*	*n*	%	*p*-value
Vertical gingival enlargement (GO index)					0.022			NS
$= 0$	44	90	22	69		11	79	
> 0	5	10	11	31		3	21	
Horizontal nodullary-papilla enlargement (MB index)					0.001			NS
$= 0$	42	86	16	50		9	64	
> 0	7	14	16	50		5	36	
Gingival index (GI)					NS			NS
$\leqslant 1.5$	26	53	12	38		7	50	
> 1.5	23	47	20	62		7	50	
Plaque index (PI)					NS			NS
$\leqslant 2.5$	20	41	8	25		4	29	
> 2.5	29	59	24	75		10	71	
Probing depth					NS			NS
$\leqslant 3$	41	84	21	66		11	79	
> 3	8	16	11	34		3	21	

Chi-square analysis collapsing categories: GO = 0, >0; MB = 0, >0; GI = ⩽1.5, >1.5; PI = ⩽2.5, >2.5; PS = ⩽3, >3.
*Diltiazem- or verapamil-treated patients *versus* cardiovascular control patients.
NS, non-ignificance.

Table 4. Risk of gingival enlargement – odds ratio (OR)

Data	Diltiazem		Verapamil	
	GO	MB	GO	MB
Drug	4.0 ($p = 0.023$) (1.2–13.1)	6.0 ($p < 0.001$) (2.1–17.3)	2.4 (NS) (0.5–11.6)	3.3 (NS) (0.9–12.9)
Drug	3.5 (NS) (1.0–12.4)	6.2 ($p < 0.002$) (1.9–20.0)	2.5 (NS) (0.5–13.5)	4.0 (NS) (0.9–18.1)
GI-adjusted	9.5 ($p < 0.005$) (2.0–44.9)	9.9 ($p < 0.001$) (2.9–33.9)	9.5 ($p < 0.005$) (2.0–44.9)	9.9 ($p < 0.001$) (2.9–33.9)

NS, non-significance; GO, gingival overgrowth; MB, Miranda & Brunet;GI, gingival index.

in cyclosporin A+verapamil group compared with the cyclosporin A group (51,72% *versus* 40,91%) the difference was not statistically significant, showing that verapamil, in this group of patients, had no effect on the prevalence and severity of cyclosporin A-induced GO. Ellis et al. (1999) in a group of 911 patients treated with calcium channel blockers, showed a prevalence lower than in previous studies, with marked differences between the different drugs (6.3% for nifedipine, 1.7% for amlodipine and 2.2% for diltiazem) and with higher risk for developing clinically significant GO in the patients treated with nifedipine, than in those taking either amlodipine or diltiazem (Ellis et al. 1999).

In our study although prevalence of gingival inflammation (GI > 1.5), poor plaque control (PI > 2.5) and probing depth (PD > 3) were globally higher among diltiazem and verapamil treated patients, differences in GI, PI and PD with the cardiovascular control group were not significant. Often drug-induced gingival enlargement involves a form of combined GO, with the effect of the drug and the inflammatory status and, therefore, it is difficult to determine the contribution of each factor. Some authors have reported a relationship of GO with both GI and PI (Seymour 1991, Bullón et al. 1994, Nery et al. 1995, Atilla & Kütükçuler 1998).

In the present study, risk estimates of gingival enlargement (OR) induced by diltiazem and verapamil were higher for MB than for GO index, and higher for diltiazem than for verapamil treatment. In all cases, risk estimates varied slightly but significantly when adjusted for GI. In fact, GI index had a stronger effect than the drug treatment on gingival enlargement risk. The results of the present study suggest that gingival inflammation has a stronger effect than drug treatment itself in patients treated with diltiazem. The complete model showed a non-significant effect for verapamil, because of a lack of statistical power in relation to a small sample size. Although calcium channel blockers are extensively used in the management of cardiovascular diseases, only a few articles, with comparative controls, have reported on the prevalence of gingival enlargement induced by diltiazem and verapamil. Similarly, sample size in groups treated with diltiazem and verapamil have been smaller that those of patients treated with nifedipine. This could be the result of a reduced prescription of these drugs for cardiovascular treatment or reflect a true lower prevalence of gingival enlargement associated to its intake. To the best of our knowledge, the risk of gingival enlargement attributable to diltiazem treatment has not been previously documented. The risk of gingival enlargement related to nifedipine (Miranda et al. 2001) and phenytoin (Brunet et al. 2001) treatment has been previously reported.

The present study used two indices that recorded vertical–GO and horizontal–MB gingival enlargement. The MB Index (Miranda et al. 2001) evaluates the nodullary papilla enlargement and results from a modification of the index described by (Seymour et al. 1985). There were differences in the prevalence of gingival enlargement according to the index used (vertical *versus* horizontal registers). One possible explanation is that the MB index detects GO at earlier stages of enlargement than the

GO index. The concordance between both measurements confirmed the reliability of the indices.

Seymour et al. (2000) indicate that risk factors for drug-induced GO are: drug variables, concomitant medications, periodontal variables, age, gender and genetic factors. We have reported on the weight of periodontal variables as risk factors associated to GO because of a pharmacological agent. Although these are variables that we cannot modify, factors such as age, gender and genetics, are to be taken into account to predict individual chances of gingival enlargement.

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