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Association between calcium channel blockers and gingival hyperplasia

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Abstract

Aim: To study the effect of the dose and type of calcium channel blockers (CCBs) on the risk of gingival hyperplasia and to quantify this association.

Methods: The study was conducted within the Integrated Primary Care Information Project in The Netherlands. A nested case–control study was designed within a cohort of all patients who were new users of either CCBs or drugs interacting with the renin–angiotensin system (RAS). Cases were all individuals with a validated diagnosis of gingival hyperplasia. Controls were matched on age, gender and index date.

Results: Within the study population, 103 cases of gingival hyperplasia were identified and matched to 7677 controls. The risk of gingival hyperplasia was higher in current users of CCBs [adjusted odds ratio (OR_{adj}) 2.2, 95% confidence intervals (95% CI): 1.4–3.4], especially in dihydropyridines (OR_{adj} 2.1, 95% CI: 1.3–3.5) and benzothiazepine derivatives (OR_{adj} 2.9, 95% CI: 1.3–6.5) than in RAS drug users. The risk increased in patients using more than the recommended daily dose (OR_{adj} 3.0, 95% CI: 1.6–5.5) and when the duration of current use was <1 month (OR_{adj} 5.2, 95% CI: 2.1–12.6).

Conclusion: This study shows that the risk of gingival hyperplasia is twofold higher in current users of CCBs than in users of RAS drugs. The association was dose dependent and the highest for dihydropyridines or benzothiazepine derivates.

Key words: calcium channel blockers; gingival hyperplasia

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Conflict of interest and source of funding statement

As employees of Erasmus M. C., M. C. J. M. Sturkenboom, K. M. C. Verhamme and J. P. Dieleman have been involved as project leader and in analysis contracted by various pharmaceutical companies and received unconditional grants from Pfizer, Merck, Johnson & Johnson, Amgen, Roche, GSK, Boehringer, Yamanouchi, Altana and Astra Zeneca, none of which are related to the subject of this study. E. M. van Soest has been involved as project leader and received an unconditional grant from Astra Zeneca. M. C. J. M. Sturkenboom has been consultant to Pfizer, Servier, Celgene, Novartis and Lundbeck on issues not related to the subject of this paper. G. Kaur, A. Vanrolleghem and B. H. Ch. Stricker have no conflict of interest.

Gingival hyperplasia is characterized by an accumulation of extracellular matrix within the gingival connective tissue particularly the collagenous components (Yamasaki et al. 1987). It has been associated with multiple factors including systemic inflammation, adverse drug effects and cardiovascular disease (Beck & Offenbacher 2005). As gingival enlargement develops, it affects the normal oral hygiene practice and may interfere with masticator functions. It gradually becomes a source of pain and the condition often leads to disfiguration.

Drug-induced gingival overgrowth is an adverse drug reaction mainly described with three types of commonly prescribed drugs namely calcium channel blockers (CCBs) (nifedipine, diltiazem and verapamil) (Seymour 1991, Miller & Damm 1992, Nishikawa et al. 1996, Ellis et al. 1999), antiepileptic drugs (phenytoin) (Perlik et al. 1995) and immunosuppressants (cyclosporine) (McGaw et al. 1987). Drug-induced gingival hyperplasia usually occurs within the first 3 months of starting the medication and begins as an enlargement of the interdental papilla (Nishikawa et al. 1996).

Among the CCBs, it is mainly nifedipine that has been associated with gingival hyperplasia. The prevalence has been estimated to vary between 30% and 50% in nifedipine-treated patients compared with a prevalence of approximately 5% in untreated controls (Tavassoli et al. 1998, Miranda et al.

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2001). Gingival hyperplasia has also been reported following the use of amlodipine (Seymour et al. 1994, Bhatia et al. 2007), verapamil (Seymour 1991) and diltiazem (Bowman et al. 1988, Fattore et al. 1991).

CCBs are commonly prescribed and used for the treatment of cardiovascular diseases. Other drugs used to treat cardiovascular disease are diuretics, β-blockers and renin–angiotensin system affecting drugs (RAS drugs). Drug-induced gingival hyperplasia has not been reported for any of these other drugs (Torpet et al. 2004).

Although some studies have addressed the risk of gingival hyperplasia during the use of CCBs, it was often based on case reports (Bowman et al. 1988, Seymour et al. 1994, Bhatia et al. 2007) or on a cross-sectional study (Meisel et al. 2005). Ellis et al. (1999) conducted a community-based cohort study to compare the prevalence of gingival overgrowth in patients using either nifedipine, amlodipine or diltiazem with the prevalence in patients with arterial hypertension (medically treated or not). In this study, the prevalence of gingival hyperplasia was the highest for patients using nifedipine.

To our knowledge, the association between the use of CCBs and the risk of gingival hyperplasia, compared with other drugs that are used for the same indication, has not yet been studied. In addition, the effect of dose and the different types of CCBs has not yet been established. To address these issues, we designed a nested case–control study within a cohort of new users of CCBs and/or drugs interacting with the RAS.

Methods

Settings

This study was conducted in the Integrated Primary Care information (IPCI) database in the Netherlands. The IPCI database is a general practice research database containing data from electronic patient records of a group of about 150 general practitioners (GPs) in the Netherlands (van der Lei et al. 1993). The database contains the complete medical records of approximately 800,000 patients. In the Dutch health care system, each person is registered with a single GP, who acts as gatekeeper to medical care (Schrijvers 1997). Electronic records contain coded and anonymous data on patient demographics, reasons for GP visits (free text), symptoms and diagnosis [using the International Classification for Primary Care (ICPC) and free text], specialist referrals and discharge letters, laboratory findings, hospitalizations (Lamberts et al. 1992, van der Lei et al. 1993) and drug prescriptions. Information on drug prescriptions comprises the brand name, quantity, strength, prescribed daily dose, the Anatomical Therapeutic Chemical Classification (ATC) code and the physician-linked indications (WHO 2010). To maximize the completeness of the data, GP participating in the IPCI projects are not allowed to maintain paper-based records in addition to the electronic medical records. The system complies with European Union guidelines on the use of medical data for medical research and has proven valid for pharmacoepidemiologic research (Vlug et al. 1999). The study was approved by the Scientific and the ethical Advisory Board of the IPCI project. The source population comprised all subjects 18 years and older, who were registered with GPs participating in the IPCI project for at least 1 year. The study period started on 1 January 1996 and ended on 31 September 2006.

Study cohort

From the source population, we selected a cohort of new users of either CCBs (dihydropyridine derivatives, phenylalkylamine derivatives and benzothiazepine derivatives) or RAS drugs (ACE inhibitors or angiotensin II receptor blockers) during the study period. Patients using RAS drugs were chosen as a reference group as these drugs are used for similar indications as CCBs such as arterial hypertension and ischaemic heart disease but have not been associated with gingival hyperplasia. All individuals were followed until one of the following events: gingival hyperplasia, death, transferring out of the GP practice, date of last data collection or end of the study period, whichever came first.

Case definition

Cases were defined as patients developing gingival hyperplasia during follow-up. The computerized medical data were screened for potential gingival hyperplasia based on both free text (''gingivitis'', ''gingival hyperplasia'' and ''gingival overgrowth'') and ICPC code (D19 and D20) search. A patient was classified as having gingival hyperplasia if symptoms were present and a dentist and/or a GP had confirmed the diagnosis. The review of all potential cases was conducted by two medically trained persons blinded to the exposure. The index date was defined as the date of the first symptoms of gingival hyperplasia.

Nested case–control study

Within the cohort of new RAS drug or CCB users, a nested case–control study was designed. For each case, potential controls were selected and matched on gender, age (year of birth) and index date (calendar time). Matching means that cases and controls have the same gender, the same year of birth and that controls are present in the cohort at the index date (date of the diagnosis of gingival hyperplasia) of the cases. To increase the power of the study, we choose to take the maximum number of controls as possible. This implies that a person could function as a control for more than one case (repeatedly sampling according to the incidence density sampling approach) and therefore represent control moments rather than persons. Exposure and risk factors were assessed at the time of the index date, both for cases and for controls.

Exposure definition

From the prescription database, we calculated the duration of each prescription based on the prescribed quantity and dosing regimen. For cases and controls, we assessed the use of CCBs and RAS drugs at the index date. Exposure at the index date was categorized into 3 mutually exclusive groups, namely current, past and no use. A person was currently exposed if the index date fell within the period of use or if the person had stopped for a maximum of 30 days before the index date. A person was classified as past user if the last date of use ended >30 days before the index date. If the patient had no prescription for a CCB, they were considered non-exposed to CCB; similarly, if they had no prescription for RAS drugs, they were considered as non-exposed to RAS drugs. For current users of CCBs, the effect of daily dose and treatment duration was studied. To aggregate doses of different drugs, daily dosages were expressed as defined daily dose (DDD) equivalents. The DDD is the

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recommended maintenance dosage of a drug for an adult for the main indication, as defined by the World Health Organization (Vlug et al. 1999). To evaluate dose–response effects, the current daily dose of CCBs was categorized into three categories: <1 DDD, 1 DDD and >1 DDD. To study the effect of different types of CCBs, current exposure of CCBs was classified into three categories namely dihydropyridine derivatives (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, lacidipine, nilvandipine, manidipine, barnidipine, lercanidipine, clinidipine and benidipine); phenylalkylamine derivatives (verapamil, gallopamil); and benzothiazepine derivatives (diltiazem).

Covariates

Information on potential confounders was retrieved from the medical records by electronic searches on both ICPC codes and free text. As potential confounders, we considered known risk factors for gingival hyperplasia (pregnancy, diabetes and smoking) in addition to cardiovascular risk factors (hypertension, angina pectoris, congestive heart failure, hypercholesterolaemia, prior myocardial infarction, transient ischaemic attack, dyslipidaemia and stroke). To study confounding by severity of hypertension, the highest blood pressure measured in the year before the index date was taken into account.

As co-medication, we evaluated current use of drugs (use at index date or stopped at most 30 days before the index date) that have been associated with gingival hyperplasia (antiepileptic drugs, immunosuppressant drugs and oral contraceptives) or with underlying conditions that have been associated with gingival hyperplasia (e.g. cardiovascular drugs as a proxy for underlying cardiovascular disease).

To study the effect of confounding by indication, the analysis was repeated in those patients receiving a CCB or an RAS drug for the treatment of hypertension only (Kimmel & Storm 2006). Confounding by indication may arise when the indication for the treatment is a risk factor for the outcome of the study. If indeed the indication for the use of CCBs, namely cardiovascular diseases, is a risk factor for gingival hyperplasia, this could spur the association between CCBs and gingival hyperplasia.

Statistical analysis

Conditional logistic regression analyses were performed to estimate unadjusted and adjusted matched odds ratio (OR_{adj}) and 95% confidence intervals (95% CI). To evaluate which factors were confounders, we first included, one by one, risk factors for gingival hyperplasia into the model. All covariates that were univariately associated with the outcome ($p<0.05$) and that changed the OR of a gingival hyperplasia in any of the exposure categories by $>10\%$ were retained in the final model (Greenland 1989). As a sensitivity analysis, we repeated the analysis, including all known risk factors for gingival hyperplasia as well as all confounding factors in the final model. All statistical analyses were performed using the statistical software packages SPSS 12.0 (SPSS Inc.).

Results

Within the study cohort of 20,636 persons who started with a CCBs or an RAS during the study period, we identified 103 patients with definite gingival hyperplasia. To these cases, we matched 7677 controls on gender, birth date and index date. Cases might have up to 70 controls as we decided to take the maximum number of controls as possible to increase the power of the study. The median age of the cases was 60.9 years (SD 15.2), and the majority were female (58.3%). The characteristics of the cases and controls are provided in Table 1. Smoking, use of diuretics and myocardial infarction were associated with gingival hyperplasia in the univariate analysis. Although not statistically significant, there seemed to be an association between the use of antiepileptic drugs and gingival hyperplasia.

To investigate the association between the use of CCBs and/or RAS drugs and the risk of gingival hyperplasia, we first examined associations by separating out the timing of use of both RAS drugs and CCBs (Table 2). Because the risk of gingival hyperplasia was rather homogeneous for current use of CCBs compared with the various RAS drug user categories (current and past use), the RAS drug users were grouped for further comparisons. Current use of CCBs (compared with no use of CCBs regardless of RAS use) doubled the risk of gingival hyperplasia (OR_{adj} 2.2, 95% CI: 1.4–3.4). No association between past use of CCBs and gingival hyperplasia could be observed.

When studying the different types of CCBs, we observed that the use of dihyropyridine and benzothiazepine derivatives was associated with an increased risk of gingival hyperplasia with an OR_{adj} of 2.1 (95% CI: 1.3–3.5) and 2.9 (95% CI: 1.3–6.5), respectively

Table 1. Patient characteristics, comorbidities and use of concomitant medication in cases and controls

	Cases $n=103$ (%)	Controls $n=7677$ (%)	*$OR_{matched}$	95% CI
Median age (SD)	60.9 (15.2)	63.0 (10.6)	NA	NA
Male gender	43 (41.7)	3315 (43.2)	NA	NA
Comorbidities				
Diabetes mellitus	24 (23.3)	1530 (19.9)	1.5	0.9–2.4
Hypertension	61 (51.2)	4460 (58.1)	1.0	0.7–1.6
Transient ischaemic attack	4 (3.9)	252 (3.3)	1.3	0.5–3.7
Heart failure	10 (9.7)	415 (5.4)	1.9	0.9–4.0
Stroke	2 (1.9)	210 (2.7)	0.8	0.8–3.1
Angina	14 (13.6)	929 (12.1)	1.3	0.7–2.4
Myocardial Infarction	10 (9.7)	382 (5.0)	2.3	1.1–4.5
Dyslipidaemia	25 (24.3)	2375 (30.9)	0.9	0.6–1.5
Smokers	27 (26.2)	1303 (17.0)	2.3	1.4–3.8
Pregnancy	0 (0)	4 (0.1)	NA	NA
Use of concomitant medication				
Anti epileptic drugs	3 (2.9)	110 (1.4)	2.6	0.8–8.4
Anticoagulants drugs	10 (9.7)	497 (6.2)	0.4	0.3–1.2
Immunosuppressant drugs	0	27 (0.4)	NA	NA
β-blockers	24 (23.3)	2422 (31.5)	0.7	0.5–1.2
Diuretics	30 (29.1)	1593 (20.8)	1.8	1.3–2.7
Oral contraceptives	1 (1)	27 (0.4)	1.6	0.2–11.9

*Matched on age, gender and index date.
CI, confidence interval; OR, odds ratio; NA, not assessable.

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Table 2. Risk of gingival hyperplasia between CCBs/RAS drugs users

RAS	CCB	Cases $n = 103$ (%)	Controls $n = 7677$ (%)	$OR_{matched}$* (95.0% CI)	$OR_{adjusted}$† (95.0% CI)
Current	No	33 (32.0)	2704 (35.2)	Reference	Reference
	Past	1 (1.0)	227 (3.0)	NA	NA
	Current	8 (7.8)	372 (4.8)	2.0 (0.9–4.4)	2.0 (0.9–4.3)
Past	No	18 (17.5)	1861 (24.2)	0.8 (0.4–1.5)	0.8 (0.4–1.5)
	Past	5 (4.9)	379 (4.9)	1.3 (0.5–3.3)	1.3 (0.5–3.3)
	Current	10 (9.7)	372 (4.8)	2.7 (1.3–5.7)	2.7 (1.3–5.5)
No	Past	8 (7.8)	840 (10.9)	0.7 (0.3–1.6)	0.7 (0.3–1.6)
	Current	20 (19.4)	922 (12.0)	1.9 (1.1–3.4)	1.8 (1.0–3.2)

*Matched on age, gender and index date.
†Adjusted for smoking.
CI, confidence interval, OR, odds ratio; CCB, calcium channel blockers; RAS, renin–angiotensin system affecting drugs, NA; not assessable.

Table 3. Type of CCBs use and the risk of gingival hyperplasia

	Cases $n = 103$ (%)	Controls $n = 7677$(%)	$OR_{matched}$* (95% CI)	$OR_{adjusted}$† (95% CI)
No CCBs	51 (49.5)	4665 (59.5)	Reference	Reference
Current use of				
Dihyropyridine Derivatives	26 (25.2)	1228 (16.0)	2.2 (1.4–3.6)	2.1 (1.3–3.5)
Amlodipine	12 (11.7)	694 (9.0)	1.9 (0.99–3.5)	1.8 (0.9–3.4)
Nifedipine	13 (12.6)	435 (5.7)	3.0 (1.6–5.7)	2.9 (1.6–5.5)
Felodipine	1 (1.0)	30 (0.4)	2.8 (0.4–21.1)	2.8 (0.4–21.3)
Others	0 (0)	69 (0.9)	NA	NA
Phenylalkalamine Derivatives				
Verapamil	4 (3.9)	193 (2.5)	1.6 (0.6–4.6)	1.6 (0.6–4.5)
Benzothiazepine Derivatives				
Diltiazem	8 (7.8)	244 (3.2)	3.1 (1.4–6.7)	2.9 (1.3–6.5)
Other CCBs	0	1 (0.0)	NA	NA
Past use of CCB	14 (13.6)	1446 (18.8)	0.9 (0.5–1.6)	0.8 (0.5–1.6)

Reference group: no use of CCBs but anytime RAS drugs use.
*Matched on age, gender and index date.
†Adjusted for smoking.
CI; confidence interval, OR; odds ratio; CCB, calcium channel blockers; RAS, renin–angiotensin system.

Table 4. Use of CCBs and risk of gingival hyperplasia

	Cases $n = 103$ (%)	Controls $n = 7677$ (%)	$OR_{matched}$* (95% CI)	$OR_{adjusted}$† (95% CI)
No use of CCBs	52 (50.5)	4565 (59.5)	Reference	Reference
Current use of CCBs	37 (35.9)	1666 (21.7)	2.2 (1.4–3.3)	2.1 (1.4–3.2)
Dosage				
<1 DDD	5 (4.9)	336 (4.4)	1.3 (0.5–3.3)	1.2 (0.5–3.1)
1 DDD	18 (17.5)	865 (11.3)	2.1 (1.2–3.6)	2.0 (1.2–3.5)
>1 DDD	14 (13.6)	465 (6.1)	3.0 (1.6–5.4)	2.9 (1.6–5.3)
Duration (current)				
<1 month	6 (5.8)	96 (1.3)	5.5 (2.3–13.2)	5.2 (2.1–12.6)
1–6 months	17 (16.5)	435 (5.7)	3.3 (1.9–5.8)	3.2 (1.8–5.7)
$\geq$ 6 months	15 (14.6)	1135 (14.8)	1.4 (0.8–2.5)	1.3 (0.7–2.4)
Past use of CCB	14 (13.6)	1446 (18.8)	0.9 (0.5–1.6)	0.8 (0.5–1.5)

Reference group: no use of CCBs but anytime RAS drugs use.
*Matched on age, gender and index date.
†Adjusted for smoking.
n, number; CI, confidence interval; CCB, calcium channel blockers; OR, odds ratio; DDD, defined daily dose; RAS, renin–angiotensin system.

(Table 3). Further, we observed that it was mainly the current use of nifedipine (OR_{adj} 2.9, 95% CI: 1.6–5.5) and diltiazem (OR_{adj} 2.9, 95% CI: 1.3–6.5) that was associated with an increased risk of gingival hyperplasia compared with no CCBs but anytime use of RAS drugs (Table 3). Current use of felodipine was also associated with an increased risk of gingival hyperplasia but this was not statistically significant due to low numbers.

Finally, we studied the effect of treatment duration and dosage for current users of CCBs. A significant dose

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response was observed in current users of CCBs (Table 4). A current daily dosage of <1 DDD was not associated with an increased risk of gingival hyperplasia, whereas this risk doubled for doses equal to 1 DDD (OR_{adj} 2.2 95% CI: 1.3–3.7) and tripled for daily dosages above 1 DDD (OR_{adj} 3.0, 95% CI: 1.6–5.5). Long-term current use of CCBs was not associated with an increased risk of gingival hyperplasia whereas current use between 1 and 6 months and especially short-term current use (use of <1 month) was (OR_{adj} 5.2, 95% CI 2.1–12.6) (Table 4).

Further, to study the potential of confounding by indication, we conducted a stratified analysis in those patients receiving CCBs/RAS drugs for the treatment of hypertension only (50.2% of all patients), and in patients receiving these drugs for other indications (Kimmel & Storm 2006). These analyses yielded results similar to our primary analysis (data not shown). Furthermore, confounding by severity of hypertension was not observed, as adjusting for the severity of hypertension in the model had no effect on the estimate (data not shown).

Finally, we conducted a sensitivity analysis in which all known risk factors for gingival hyperplasia as well as the confounding factors were entered into the final model. This analysis yielded similar results (data not shown).

Discussion

This population-based nested case–control study shows that the current use of CCBs is associated with an increased risk of gingival hyperplasia when compared with persons treated with RAS drugs. The effect was dose-dependent and decreased after cessation of drug use. When studying the effect of different classes of CCBs, an increased risk of gingival hyperplasia was observed for the current use of dihydropyridine and benzothiazepine derivates compared with no use. In addition, we confirmed known risk factors for gingival hyperplasia such as smoking and the use of concomitant medication such as antiepileptic drugs (not statistically significant due to low numbers).

Gingival hyperplasia is a well-known adverse effect of CCBs (Seymour 1991, Ellis et al. 1999). All three classes of CCBs have been associated with gingival hyperplasia but mainly the dihydropyridine calcium antagonists. The prevalence of nifedipine-induced gingival hyperplasia ranges between 6.3% and 83% within users (Barak et al. 1987, Tagawa et al. 1990, Akimoto et al. 1991, Fattore et al. 1991, Burkes et al. 1992, Ellis et al. 1999). This large range in prevalence can be explained by the differences in the populations that have been studied, differences in used dosages or oral hygiene practice and differences in case ascertainment. Fewer data are available on the association between the use of diltiazem and gingival hyperplasia (Bowman et al. 1988, Fattore et al. 1991, Seymour 1991). In contrast to Seymour (1991), we did not observe an association between the current use of amlodipine and verapamil and gingival hyperplasia. Because of low exposure to isradipine in the Netherlands, we could not confirm the findings of Westbrook et al. (1997) on the association between the use of isradipine and the risk of gingival hyperplasia.

Onset of drug-induced gingival overgrowth mostly appears within the first month of CCB administration (Tam & Wandres 1992), and most changes will occur within the first 9 months of treatment (Tagawa et al. 1990). In our study, we found that the risk of gingival hyperplasia was mainly observed in current users of CCBs who used the drug for <1 month. Furthermore, we observed that the increased risk of gingival hyperplasia appeared to be related to drug dosage. Barak et al. (1987) also reported an increased incidence of gingival hyperplasia with higher doses of nifedipine. In contrast, other studies found that gingival hyperplasia is not associated with drug dosage or duration of the therapy (Akimoto et al. 1991, James & Linden 1992, Tam & Wandres 1992).

The exact mechanism behind the use of CCBs and the increased risk of gingival hyperplasia is not completely understood. Several pathophysiologic mechanisms have been suggested. Gingival hyperplasia is a calcium-dependent process. Because CCBs affect calcium ion cellular flux; it thus seems plausible that CCBs increase the risk of gingival hyperplasia (Barak et al. 1987, Akimoto et al. 1991, Seymour 1991, Harel-Raviv et al. 1995). CCBs inhibit the intercellular uptake of calcium and this inhibitory action may affect the secretory properties of gingival fibroblasts or the production of collagenases (Seymour 1991). This may result in overstimulated gingival fibroblasts.

As for all observational data, some caution is warranted when interpreting our data, as issues such as bias and confounding might influence our results. We considered selection bias but believe it is unlikely because cases and controls were derived from the same population-based cohort and controls were gender, age and index date matched and randomly drawn from the source population. Misclassification of gingival hyperplasia is likely because our disease assessment was based on the longitudinally collected GP records, rather than dentist records. Also, cases of gingival hyperplasia were identified based on a scrutinous review of the patient's medical file rather than on a periodontal examination of the patients by the researcher as done by Ellis et al. (1999). Using this approach, we were only able to pick up symptomatic gingival hyperplasia, and thus missed asymptomatic patients with mild to moderate gingival hyperplasia. However, we do believe that this misclassification is probably non-differential as review of potential cases was performed by two medical doctors who were blinded to drug exposure. If indeed the misclassification is non-differential, this would imply that we underestimated the risk of gingival hyperplasia in patients treated with CCBs. As our exposure assessment was based on longitudinally collected GP prescriptions rather than on dispensing or patient-reported intake, we might have misclassified at least some of the exposure to CCBs. Here as well, we believe that this exposure misclassification will be non-differential, which implies that the reported risk estimate is an underestimate of the true risk.

To control for confounding by indication, we designed a case–control study in a cohort of new CCBs or RAS users (Kimmel & Storm 2006). In addition, we conducted a stratified analysis in patients with hypertension only and found similar results.

Smoking was an important confounder in our study. From the literature, we know that smoking is an important risk factor for cardiovascular diseases and several studies have suggested that smoking is related to periodontal diseases (Calsina et al. 2002).

Conclusion

This nested case–control study, in a cohort of patients newly treated with CCBs and/or RAS drugs, showed that

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current use of CCBs was associated with an increased risk of gingival hyperplasia. As the prevalence of CCB use is relatively high in the population, especially among patients with cardiovascular disease, it is important that medical professionals are aware of this association.

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References

Akimoto, Y., Tanaka, S., Omata, H., Shibutani, J., Nakano, Y., Kaneko, K., Kawana, T., Teshigawara, H., Nakao, S. & Fujii, A. (1991) Gingival hyperplasia induced by nifedipine. *Journal of Nihon University School of Dentistry* **33**, 174–181.

Barak, S., Engelberg, I. S. & Hiss, J. (1987) Gingival hyperplasia caused by nifedipine. Histopathologic findings. *Journal of Periodontology* **58**, 639–642.

Beck, J. D. & Offenbacher, S. (2005) Systemic effects of periodontitis: epidemiology of periodontal disease and cardiovascular disease. *Journal of Periodontology* **76**, 2089–2100.

Bhatia, V., Mittal, A., Parida, A. K., Talwar, R. & Kaul, U. (2007) Amlodipine induced gingival hyperplasia: a rare entity. *International Journal of Cardiology* **122**, e23–e24.

Bowman, J. M., Levy, B. A. & Grubb, R. V. (1988) Gingival overgrowth induced by diltiazem. A case report. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* **65**, 183–185.

Burkes, E. J. Jr., Jacoway, J. R., Stevens, D. T. & Braddock, M. E. (1992) Nifedipine-induced gingival hyperplasia. *The Journal of the Tennessee Dental Association* **72**, 35–37.

Calsina, G., Ramon, J. M. & Echeverria, J. J. (2002) Effects of smoking on periodontal tissues. *Journal of Clinical Periodontology* **29**, 771–776.

Ellis, J. S., Seymour, R. A., Steele, J. G., Robertson, P., Butler, T. J. & Thomason, J. M. (1999) Prevalence of gingival overgrowth induced by calcium channel blockers: a community-based study. *Journal of Periodontology* **70**, 63–67.

Fattore, L., Stablein, M., Bredfeldt, G., Semla, T., Moran, M. & Doherty-Greenberg, J. M. (1991) Gingival hyperplasia: a side effect of nifedipine and diltiazem. *Special Care in Dentistry* **11**, 107–109.

Greenland, S. (1989) Modeling and variable selection in epidemiologic analysis. *American Journal of Public Health* **79**, 340–349.

Harel-Raviv, M., Eckler, M., Lalani, K., Raviv, E. & Gornitsky, M. (1995) Nifedipine-induced gingival hyperplasia. A comprehensive review and analysis. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* **79**, 715–722.

James, J. A. & Linden, G. J. (1992) Nifedipine-induced gingival hyperplasia. *Dental Update* **19**, 440–441.

Kimmel, S. E. & Storm, B. L. (eds). (2006) *Textbook of Pharmacoepidemiology*. Chichester, England: John Wiley & Sons.

Lamberts, H., Wood, M. & Hofmans-Okkes, I. M. (1992) International primary care classifications: the effect of fifteen years of evolution. *Family Practice* **9**, 330–339.

McGaw, T., Lam, S. & Coates, J. (1987) Cyclosporin-induced gingival overgrowth: correlation with dental plaque scores, gingivitis scores, and cyclosporin levels in serum and saliva. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* **64**, 293–297.

Meisel, P., Schwahn, C., John, U., Kroemer, H. K. & Kocher, T. (2005) Calcium antagonists and deep gingival pockets in the population-based SHIP study. *British Journal of Clinical Pharmacology* **60**, 552–559.

Miller, C. S. & Damm, D. D. (1992) Incidence of verapamil-induced gingival hyperplasia in a dental population. *Journal of Periodontology* **63**, 453–456.

Miranda, J., Brunet, L., Roset, P., Berini, L., Farre, M. & Mendieta, C. (2001) Prevalence and risk of gingival enlargement in patients treated with nifedipine. *Journal of Periodontology* **72**, 605–611.

Nishikawa, S., Nagata, T., Morisaki, I., Oka, T. & Ishida, H. (1996) Pathogenesis of drug-induced gingival overgrowth. A review of studies in the rat model. *Journal of Periodontology* **67**, 463–471.

Perlik, F., Kolinova, M., Zvarova, J. & Patzelova, V. (1995) Phenytoin as a risk factor in gingival hyperplasia. *Therapeutic Drug Monitoring* **17**, 445–448.

Schrijvers, A. (1997) *Health and Health Care in the Netherlands. A Critical Self-Assessment of Dutch Experts in Medical and Health Sciences*. Utrecht: De Tijdstroom.

Seymour, R. A. (1991) Calcium channel blockers and gingival overgrowth. *British Dental Journal* **170**, 376–379.

Seymour, R. A., Ellis, J. S., Thomason, J. M., Monkman, S. & Idle, J. R. (1994) Amlodipine-induced gingival overgrowth. *Journal of Clinical Periodontology* **21**, 281–283.

Tagawa, T., Nakamura, H. & Murata, M. (1990) Marked gingival hyperplasia induced by nifedipine. *International Journal of Oral and Maxillofacial Surgery* **19**, 72–73.

Tam, I. M. & Wandres, D. L. (1992) Calcium-channel blockers and gingival hyperplasia. *The Annals of Pharmacotherapy* **26**, 213–214.

Tavassoli, S., Yamalik, N., Caglayan, F., Caglayan, G. & Eratalay, K. (1998) The clinical effects of nifedipine on periodontal status. *Journal of Periodontology* **69**, 108–112.

Torpet, L. A., Kragelund, C., Reibel, J. & Nauntofte, B. (2004) Oral adverse drug reactions to cardiovascular drugs. *Critical Reviews in Oral Biology and Medicine* **15**, 28–46.

van der Lei, J., Duisterhout, J. S., Westerhof, H. P., van der Does, E., Cromme, P. V., Boon, W. M. & van Bemmel, J. H. (1993) The introduction of computer-based patient records in The Netherlands. *Annals of Internal Medicine* **119**, 1036–1041.

Vlug, A. E., van der Lei, J., Mosseveld, B. M., van Wijk, M. A., van der Linden, P. D., Sturkenboom, M. C. & van Bemmel, J. H. (1999) Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods of Information in Medicine* **38**, 339–344.

WHO. (2010) Guidelines for ATC classification and DDD assignment 2010, Oslo, Norway.

Yamasaki, A., Rose, G. G., Pinero, G. J. & Mahan, C. J. (1987) Ultrastructure of fibroblasts in cyclosporin A-induced gingival hyperplasia. *Journal of Oral Pathology* **16**, 129–134.

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Clinical Relevance

Scientific rationale for the study: Drug-induced gingival overgrowth is an adverse drug reaction mainly described with three types of commonly prescribed drugs namely CCBs, antiepileptic drugs and immunosuppressants. Whether CCBs increase the risk of gingival hyperplasia compared with other cardiovascular drugs or the effect of dose and types of CCBs on the risk of gingival hyperplasia has not yet been established

Principal findings: The current users of CCBs were at a higher risk of gingival hyperplasia compared with users of RAS drugs. The association was dose dependent and the highest for current users of dihydropyridines or benzothiazepine derivates.

Practical implications: MDs should be vigilant for the potential of gingival hyperplasia when prescribing CCBs, especially when prescribing high doses and/or CCBs from the dihydropyridines or the benzothiazepine class.

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