

A clinical review of drug-induced gingival overgrowths

Roderick I. Marshall*

P. Mark Bartold*

Abstract

There is an increasing number of medications associated with gingival overgrowth. These medications are used to treat a number of common conditions in the Australian population and as such dentists can expect to manage a number of patients with medication-related gingival overgrowth. This review highlights the clinical features and management of the common overgrowths associated with anticonvulsants, immunosuppressants and the calcium channel blockers.

Key words: Gingival overgrowth, phenytoin, cyclosporin, calcium channel blockers.

(Received for publication July 1999. Revised July 1999. Accepted August 1999.)

Drug-induced gingival overgrowths

There is an ever increasing number of medications which may induce overgrowth of the gingiva, although a large range of pathological and idiopathic reactions can also result in gingival overgrowth. This review concentrates on the various overgrowths associated with pharmaceuticals, and their clinical management. The medication-induced gingival overgrowths occur as a side effect of drugs used mainly for non-dental treatment for which the gingival tissue is not the intended target organ.

'Overgrowth' is the preferred term for many of these medication-related conditions previously labelled as 'gingival hyperplasia' and 'gingival hypertrophy'. These terms do not truly reflect our current understanding of the macroscopically enlarged, histologically altered, gingiva.

Drugs associated with gingival overgrowth can be categorized broadly into three major groups according to their therapeutic actions, namely anticonvulsants, immunosuppressants and calcium channel blockers (Table 1). This review discusses the nature and use of the particular drugs which cause gingival overgrowth,

possible aetiological mechanisms and the clinical management of the affected patients.

In Australia, adverse drug reactions are reported to the Adverse Drug Reactions Advisory Committee (ADRAC). It has recently been reported that there are a total of only 114 cases of gingival overgrowth in the ADRAC database, of which 83 are due to phenytoin, cyclosporin or calcium channel blockers,¹ despite the fact that almost 8.5 million prescriptions for these drugs are filled each year in Australia.† However, this should not be interpreted as indicating that gingival overgrowth is very rare in Australia. Just as in other countries,² we are very poor at providing information under the voluntary reporting system and, indeed, it is likely that many dentists are unfamiliar with this process.

Anticonvulsants

Phenytoin

Phenytoin (PHT) was first used as an anti-epileptic drug in 1938 and it remains a drug of first choice for the treatment of epilepsy, particularly grand mal, temporal lobe and psychomotor seizures and may also be useful in the treatment of some forms neuralgia and cardiac arrhythmias. In Australia, phenytoin (PHT, 5,5-diphenylhydantoin) is sold under the name Dilantin, and is usually prescribed as capsules for chronic use. The dosage is individualized to allow effective anticonvulsant control and usually ranges between 300 and 600 mg/day. More than 250 000 prescriptions for Dilantin are written each year in Australia (Fig. 1).

When taken orally, PHT is absorbed slowly from the gastro-intestinal tract and shows marked interindividual variation. Most of the drug is bound to plasma proteins leaving about 10 per cent free and active. The side effects of PHT are usually toxic effects, due to excess, available, free drug. Common

*Department of Dentistry, The University of Queensland.

†Drug Utilisation Sub-Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee, Department of Health and Aged Care. Database information, 1999.

Table 1. Drugs commonly associated with gingival overgrowth, by class and Australian brand names

Category	Drugs	Brand names
Anticonvulsants	Phenytoin	Dilantin
	Sodium valproate	Epilim Valpro
	Phenobarbitone	Phenobarbitone
	Vigabatrin	Sabril
Immunosuppressants	Cyclosporin	Neoral Sandimmun
Calcium channel blockers Dihydropyridines	Nifedipine	Adalat Adapine Nifecard Nifehexal Nyefax
		Felodipine
Phenylalkylamine	Amlodipine	Norvasc
	Verapamil	Anpec Cordilox Isoptin Veracaps Verahexal
Benzothiazepine	Diltiazem	Auscard Cardcal Cardizem Coras Diltahexal Diltiamax Dilzem

adverse reactions include ataxia, tremor, nystagmus and diplopia.

Gingival overgrowth

The first reported cases of gingival overgrowth as a result of PHT therapy appeared soon after the drug was introduced.³ The gingival overgrowth usually begins as a diffuse swelling of the interdental papillae, which enlarge and coalesce, leaving a nodular appearance. Figure 2a shows phenytoin-induced gingival overgrowth compared with other drug-induced gingival overgrowths (Fig. 2b-2f).

The reported incidence of gingival overgrowth varies widely from 0-100 per cent and this variation can be attributed, in part, to medically versus dentally trained personnel and differing indices of overgrowth. Clinically significant overgrowth is estimated to occur in half of all patients taking PHT.⁴ However, a more recent study found clinically significant overgrowth in only 13 per cent of epileptic patients in a general medical practice.⁵ It has been suggested that earlier high prevalence figures may be due to a focus on institutionalized and/or hospital neurology out-patient populations.⁶ The incidence and severity of overgrowth is greatest on the labial surfaces of the maxillary and mandibular anterior teeth. Figure 3a shows a variation in the clinical appearance of phenytoin-induced gingival overgrowth compared with other variations of drug-induced gingival

overgrowths (Fig. 3b-3f). Some case reports have described overgrowth of edentulous ridges^{7,8} although it is thought that candidal infection may play a part in the aetiology of some cases.⁷

Dosage

While it is obvious that some minimal concentration (or dose) of PHT is required to cause gingival overgrowth, the incidence and severity do not appear to be directly related to the pharmacodynamics of the drug. Even subtherapeutic serum levels of PHT have been associated with gingival overgrowth.⁹

The situation is further complicated as many patients receive more than one anticonvulsant drug and this usually alters the pharmacodynamics of PHT, making the elucidation of dosage more complex. There are conflicting results with regard to the relationship between severity of overgrowth and daily dose. Some authors relate a positive correlation^{10,11} but most have not found this association to be significant.⁹

Oral hygiene

The association between plaque and gingival overgrowth raises a 'chicken or egg first' question. Overgrown tissue tends to aid plaque accumulation and prevents removal, thus leading to gingival inflammation. Longitudinal studies seem to indicate a role for poor oral hygiene on the severity of overgrowth^{11,12} and some plaque control studies have shown almost complete prevention or reduced severity of overgrowth.^{13,14}

Possible pathogenesis

To date there is no definitive explanation of how PHT induces gingival overgrowth. It is intriguing that not all patients taking phenytoin (even those

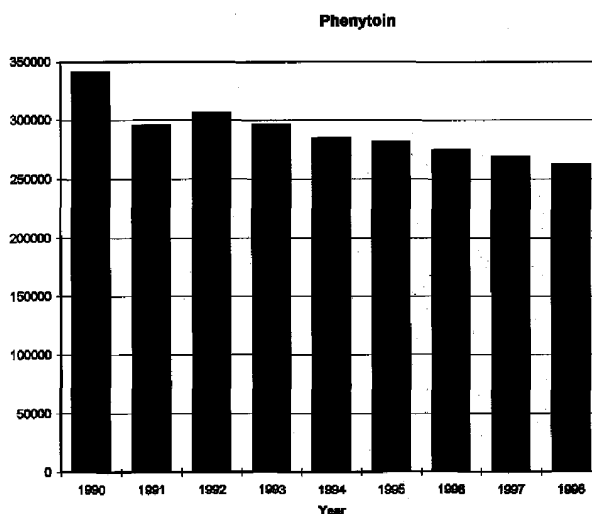


Fig. 1. - Estimated number of prescriptions for phenytoin in Australia this decade (excluding use in public hospitals).†



Fig.2. – Examples of common medication-induced gingival overgrowth.

- (a) Phenytoin-associated gingival overgrowth.
- (b) Cyclosporin-associated gingival overgrowth.
- (c) Nifedipine-associated gingival overgrowth.
- (d) Verapamil-associated gingival overgrowth.
- (e) Diltiazem-associated gingival overgrowth.
- (f) Felodipine-associated gingival overgrowth.

taking high dosages, with and without inflammation) develop gingival overgrowth.

Most theories of pathogenesis have centred on the gingival fibroblast and its interaction with phenytoin and/or its metabolites.¹⁵ It has been suggested that PHT selects for a subpopulation of fibroblasts that have increased protein synthesis and collagen production.¹⁶ However, it was concluded that the lesion ‘represents neither hypertrophy, hyperplasia nor

fibrosis’; it is just an overgrowth of apparently normal cell and fibre composition.¹⁷ Others have suggested a role for a lack of collagen breakdown,^{18,19} or a decrease in the volume of the collagenous matrix due to an increase in the non-collagenous component.^{20,21} A number of authors have postulated a role for intracellular calcium (Ca^{++}) in the pathogenesis of the gingival overgrowth.^{22,23} PHT has been reported *in vitro* to increase the release of various growth factors



Fig. 3. – Examples of the variation in clinical appearance of gingival overgrowth associated with:
 (a) Phenytoin.
 (b) Nifedipine.
 (c) Nifedipine.
 (d) Nifedipine.
 (e) Verapamil.
 (f) Diltiazem.

and cytokines which may promote connective tissue growth.²⁴⁻²⁶

A role for relative folate deficiency has also been investigated but has not been a consistent finding.^{27,28} Other possible aetiologic factors include relative immunosuppression, decreased adrenocortico-tropic hormone (ACTH) production and cellular damage from PHT metabolites, but these have received little support.²⁹

Sodium valproate

Gingival overgrowth following sodium valproate administration is rare in adult patients.³⁰ There have been only two reported cases of gingival overgrowth following sodium valproate therapy and these most likely represent idiosyncratic hypersensitivities rather than variants of the PHT-like overgrowth. The first involved a 15 month old child³¹ and the second a 15 year old child.³² In the latter case, gingival

overgrowth was observed 18 months after initiating drug treatment (600 mg/day) and regressed within three months of stopping the therapy. (This individual had never received PHT.)

Phenobarbitone

Most reported cases of phenobarbitone-induced gingival overgrowth have been poorly documented, however, a recent description of two cases of monotherapy with phenobarbitone is much more precise.³³ In both cases the patients were profoundly mentally retarded teenage males who had received phenobarbitone for most of their lives. The gingivae were enlarged uniformly without lobulation of the interdental papillae and the overgrowth was more severe in the posterior regions compared with the anterior, which is contrary to most other medication-induced gingival overgrowth. The histological and clinical appearance was similar to familial forms of gingival fibromatosis and, although there was no family history in these cases, it is possible that the gingival signs are part of a syndrome and the phenobarbitone therapy just happens to be common to both. The cases responded well to surgical excision and good oral hygiene appeared to prevent recurrence at six months.

Vigabatrin

Recently a single case report was published of gingival overgrowth attributed to vigabatrin therapy. Vigabatrin is a relatively new anticonvulsant drug, which acts as a selective, irreversible inhibitor of the acid transaminase of gamma-aminobutyric acid (GABA) which is the primary inhibitory neurotransmitter in the brain. The gingival overgrowth was first noted two months after initiating vigabatrin therapy and histological examination revealed epithelial thickening with elongated rete pegs and moderately dense foci of chronic inflammatory cells in the connective tissue. The gingival overgrowth did not respond to conservative periodontal therapy and it recurred following gingivectomy.³⁴ There appears to be no other reports of this form of overgrowth, so it possible that this reaction was an idiosyncratic hypersensitivity.

Immunosuppressants

Cyclosporin

Cyclosporin (Cs) has been used almost universally in the prevention of organ transplant rejection. Since its initial use in renal transplant recipients³⁵ it has been used effectively alone and in combination with other immunosuppressant drugs and has been used to prevent rejection in hepatic, pancreatic, bone marrow, cardiac and lung transplants, as well as in the management of a number of autoimmune conditions such as rheumatoid arthritis.

Cs absorption from the gut is quite variable and bio-availability and time to peak serum concentration varies greatly between individuals. In Australia many patients now receive a new micro-emulsion of Cs (Neoral), designed to give better absorption, and it is expected to eventually supersede the old formulation. The use of Cs continues to increase in Australia (Fig. 4). It is usually prescribed as a capsule or oral solution for long-term use. The drug is bound mostly to both cells and lipoproteins with approximately 5 per cent free in the plasma. Common adverse reactions include nephrotoxicity, hypertension, hepatotoxicity and neurotoxicity. The oral side effects of Cs include the rare lingual fungiform papillae hypertrophy (LFPH) and gingival overgrowth.^{36,37}

Gingival overgrowth

Gingival overgrowth was first noticed with Cs therapy in the initial human trials of the drug^{36,38} but was described in the dental literature in 1983 by both Rateitschak-Plüss and coworkers³⁷ and Wysocki *et al.*³⁹ Cs gingival overgrowth is clinically indistinguishable from that associated with PHT. The overgrowth, which normally begins at the interdental papillae, is more common in the anterior segments of the mouth and on labial surfaces of the teeth (Fig 2b).⁴⁰ Overgrowth is usually confined to the attached gingiva but may extend coronally and interfere with the occlusion, mastication and speech without necessarily altering the underlying periodontium (Fig. 5a, 5b). The incidence of Cs gingival overgrowth ranges from 13 per cent⁴¹ to 81 per cent.⁴² As with PHT overgrowth, the reasons for this range are many and include the nature of the disease being treated, the age of the patient, the method of assessment, the dosage and duration of Cs and additional medications.⁴³ Cs overgrowth

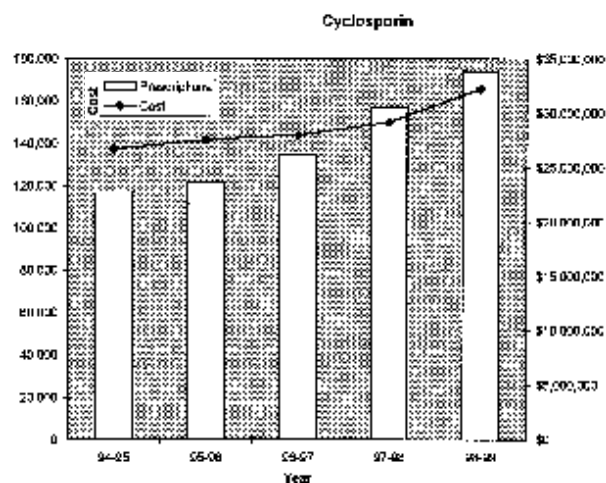


Fig. 4. – Estimated number and cost of prescriptions for cyclosporin in Australia, 1994-99.†



Fig. 5. – Examples of the variation in clinical appearance of cyclosporin-induced gingival overgrowth.
 (a) Gross overgrowth covering almost 100 per cent of the teeth.
 (b) Radiographic appearance of the patient in (a). Note the absence of any significant bone loss.
 (c) Mild overgrowth.
 (d) Inflamed moderate overgrowth.
 (e) Mildly inflamed and fibrotic overgrowth.
 (f) Fibrotic overgrowth.

has not been described in edentulous patients.⁴² The severity of overgrowth may range from none to a very mild swelling of the interdental papilla, to marked excess gingiva covering at least three-quarters of the tooth (affecting 17 per cent of patients)⁴⁴ (Fig. 5c-5f).

While it appears that some patients are more susceptible to gingival overgrowth than others, the relationship to drug dosage and serum concentration

is contentious. Plasma and salivary concentrations, plaque and gingival indices have all been correlated to the severity of overgrowth but there is wide individual variation. Whole saliva concentrations of Cs are higher in patients taking the liquid form of the drug compared with the capsule form,⁴⁵ but salivary concentrations correlate poorly with blood levels. Gingival overgrowth is thought to develop in patients within three months of taking Cs.⁴⁶

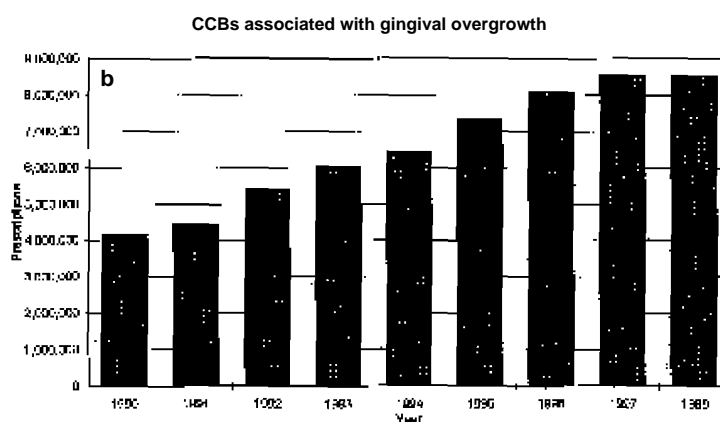
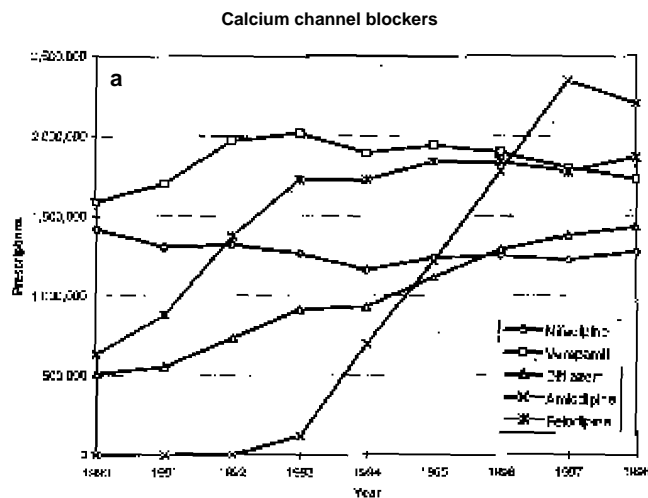


Fig. 6. - (a) Estimated number of prescriptions for selected calcium channel blockers in Australia this decade (excluding use in public hospitals).† (b) Estimated number of prescriptions for calcium channel blockers associated with gingival overgrowth in Australia this decade (excluding use in public hospitals).†

However, others have reported overgrowth only in patients taking Cs for more than three months.³⁹ A randomized placebo controlled study⁴⁷ found that patients with gingival overgrowth were significantly younger than those without overgrowth. This finding was in agreement with others^{44,48} and is consistent with anecdotal reports. A recent report in children indicated a 100 per cent prevalence of overgrowth in subjects taking Cs for longer than three months.⁴⁹

Oral hygiene

The role of plaque in Cs-induced gingival overgrowth is uncertain. It has been shown that oral Cs can concentrate locally in plaque,⁵⁰ however, an intensive course of plaque control and removal of gingival irritants has been shown to have little effect on the development of gingival overgrowth.⁵¹ In a recent large study the distribution of plaque and gingivitis was unable to fully explain the distribution of gingival overgrowth.⁵²

Possible pathogenesis

The pathogenesis of gingival overgrowth due to Cs remains enigmatic but, as for PHT, is probably associated with both direct and indirect effects of Cs on fibroblasts and the extracellular components of the lamina propria.^{53,54} *In vitro* studies of gingival fibroblast responses to Cs have found much variation in their collagenase activity.⁵⁵ Up-regulation of collagenolysis in response to Cs has been shown to be due to effects on both collagenase and TIMP (tissue inhibitor of metalloproteinase) levels.

Tissue typing of transplant recipients has shown that HLA B37 positive patients are significantly more likely to show severe gingival overgrowth⁵⁶ and conversely HLA DR1 positive patients are less likely to develop gingival overgrowth.⁵⁷

Calcium channel blockers

The widespread use of calcium channel blockers (CCBs) began in the 1980s. CCBs are a group of

drugs which have different chemical structures and actions but are all thought to be agonists of the slow Ca^{++} channel into cells. They are used for the treatment of many cardiovascular disorders including angina, hypertension, supraventricular arrhythmias and some forms of acute myocardial infarction. The CCBs are very widely prescribed. A survey of 1645 elderly patients in Australia⁵⁸ found almost 18 per cent were taking a CCB‡ and they are considered an antihypertensive of first choice in elderly patients also exhibiting angina or peripheral vascular disease. While the use of some CCBs has remained constant over this decade (Fig. 6a), the total number of prescriptions for CCBs associated with gingival overgrowth continues to rise (Fig. 6b).

The common side effects of CCBs include, headache, dizziness, facial flushing and oedema. Gingival overgrowth was first reported in association with nifedipine in 1984^{59,60} and was soon also described with verapamil⁶¹ and diltiazem⁶² usage. A number of other CCBs not available in Australia (nitrendipine and oxodipine) have also been associated with gingival overgrowth.

Gingival overgrowth

Nifedipine

Nifedipine-induced gingival overgrowth (Fig. 2c) has been described by many authors, with a prevalence ranging between 14.7 per cent⁶³ and 83 per cent.⁶⁴ The real prevalence is unknown as it is mostly presented in the literature as case reports. It seems probable that the actual prevalence is toward the lower end of the range as the drug is widely prescribed around the world. A small, controlled (but not randomized) study of 47 patients indicated a prevalence of approximately 20 per cent which the authors considered abnormally high.⁶⁵

A recent large study has reported a prevalence of 43.6 per cent (compared with 4.2 per cent in controls).⁶⁶ Differing indices of overgrowth, differing populations, dosage and duration of medication are possible explanations for the differences between studies. A single study had shown overgrowth in five cases was associated with higher doses of nifedipine⁶³ but others have been unable to show any relationship between dose and overgrowth.⁶⁶

It has been reported in one study that nifedipine concentrates in the gingival crevicular fluid up to 90 times the serum concentration and, of the nine patients examined, nifedipine could be found in the crevicular fluid of all five of the patients with gingival overgrowth and two of the 'non-responders'.⁶⁷ While a male predominance has been reported⁶⁸ it should be remembered that most studies in this area have

not been randomized. The variability of the clinical appearance of this gingival overgrowth is probably related to the level of oral hygiene (Fig. 3b-3d).

Verapamil

Verapamil is a phenylalkylamine derivative CCB. The early reports of gingival overgrowth associated with this drug began in the mid 1980s⁶¹ (Fig. 2d, 3e). The prevalence of verapamil-induced overgrowth appears to be very low. Miller and Damm could only find three cases in the literature and their review of 5000 dental patients seen over three years found only 24 patients taking verapamil for more than a year. Only one of these patients showed gingival overgrowth.⁶⁹

Diltiazem

Few cases of overgrowth due to diltiazem appear to have been reported. In one case a patient initially developed overgrowth after 15 days of verapamil therapy.⁷⁰ Discontinuation of the verapamil led to resolution of the gingival overgrowth but when diltiazem (240 mg/day) was started the overgrowth returned over a period of 24 days, being more prominent around the labial surfaces of anterior teeth (Fig. 2e, 3f).

Amlodipine

Amlodipine is yet another CCB which, unlike other dihydropyridines, has a long half-life (35-50 hours). It has been reported as the cause of gingival overgrowth in three patients and is likely to be a rare condition.⁷¹ A recent small observational study was unable to show an increased prevalence of gingival overgrowth in 150 patients taking amlodipine at 5 mg/day for at least six months.⁷² Gingival overgrowth began two to three months after starting the medication at 5-10 mg/day and the authors felt these changes were compounded by the patients' existing periodontal condition.⁷³ The crevicular fluid concentrations were found to be up to 292 times those found in plasma.

Felodipine

Only two cases of gingival overgrowth ascribed to felodipine are reported in detail in the literature.^{74,75} In both cases the gingival overgrowth began soon after the patients commenced felodipine (Fig. 2f). Given the wide prescription of this drug it is assumed that the prevalence of gingival overgrowth associated with this drug is low.

Possible pathogenesis

Nifedipine

Little is known about the pathogenesis of the gingival overgrowth associated with this medication.

‡Thomson WM. Personal communication.

It has been speculated that some alteration to Ca⁺⁺ metabolism is involved,⁶³ but others have suggested that nifedipine may act indirectly by stimulating either production of IL-2 by T cells⁷⁶ or metabolites of testosterone.⁷⁷ Still other work suggests a role for TGFβ, bFGF and heparan sulphate glycosaminoglycan.⁷⁸

Regrettably, none of these theories explain why only some patients develop nifedipine gingival overgrowth. It seems possible that a number of mechanisms could act synergistically to produce the overgrowth.

Verapamil

It has been postulated that the apparent lack of potency of verapamil in causing gingival overgrowth may be due to its more complex mechanism of action. In a manner akin to Cs gingival overgrowth it has been suggested that verapamil may select for a subpopulation of fibroblasts, thus altering the balance of regeneration and degradation. Most cases were associated with high doses (480 mg/day) of verapamil, including two cases reported recently in children, who only experienced the overgrowth after their daily dose was increased.⁷⁹

Diltiazem, amlodipine, felodipine

Because of the paucity of reports of gingival overgrowth associated with these drugs there has been little speculation of the possible pathogenesis other than to say that it is likely to be similar to the other calcium channel blockers.

Other drugs

Erythromycin

A single case of gingival overgrowth has been associated with the use of erythromycin in a young boy.⁸⁰ The condition resolved on withdrawal of the drug and returned upon repeat challenge. The authors were unable to suggest any possible mechanism for the phenomenon.

Treatment

Drug substitution

One of the foundations of treatment of all drug-induced gingival overgrowths is drug substitution. Substitution of PHT with a different anticonvulsant drug has long been advocated as treatment of gingival overgrowth. The feasibility of drug substitution has increased in recent times with the addition a new generation of anticonvulsant drugs such as vigabatrin (Sabril), lomatrigine (Lamictal), gabapentin (Neurontin), sulthiame (Ospolot) and topiramate (Topamax). Reduction of gingival overgrowth after withdrawal of PHT has been reported⁸¹ and complete regression after six months has been described in a small group of children.⁸²

Reduction in the dose of Cs has been shown to be beneficial,⁸³ however, the nature of organ transplants often means that alternative therapy or dose reduction is not available. Some patients can use more conventional immunosuppressants such as steroids and azothioprine but survival rates are not as good. New immunosuppressants such as tacrolimus (FK506) (Prograf), rapamycin and mycophenolate mofetil (MMF) (CellCept) may offer some hope, as to date these have not been reported in association with gingival overgrowth. Recent case reports indicate 'improvement' in gingival overgrowth when patients were changed to tacrolimus therapy.⁸⁴

Withdrawal and substitution of the drug along with improved oral hygiene has been successful in many cases of nifedipine gingival overgrowth.^{85,86} Unfortunately, not all cases respond to this treatment, particularly patients with long-standing overgrowth.⁶⁸ In a similar manner, drug substitution has been effective in some cases of gingival overgrowth due to verapamil,^{61,79} amlodipine⁷³ and felodipine.⁷⁵

It should be remembered that the conditions for which patients are taking these drugs can be very difficult to control and physicians may be very reluctant to modify an effective drug regime 'just for the gums'. Thus, while it is worth asking if drug substitution is possible, the dentist should understand that a negative response is not necessarily a disregard for the gingival problem, but rather a concern for the debilitating effects of the underlying condition.

Oral hygiene

Although the role of plaque has not been clearly defined in most medication-induced gingival overgrowth, there is no doubt that the resulting gingival inflammation can contribute an additional level of enlargement due to oedema, regardless of any initiating or contributing effect it may have on gingival overgrowth. Control of this inflammatory component of the gingival overgrowth, while important in itself, also aids in determining if surgical reduction is necessary and, additionally, allows for a less haemorrhagic field in any subsequent surgical intervention.

A programme of intense oral hygiene failed to prevent the onset of Cs-induced gingival overgrowth⁴⁶ nor was it particularly effective at reducing existing overgrowth,⁴² but was of some benefit for general periodontal health, as expected. Chlorhexidine (0.12 per cent) mouthrinse has been reported to reverse recurrent Cs overgrowth following gingivectomy⁸⁷ and a study in rats indicates it may have a role in limiting but not preventing gingival overgrowth,⁸⁸ however, the side effects of long-term chlorhexidine have to be considered. Pernu and others⁸⁹ have shown that gingival bleeding increases the relative risk of gingival overgrowth in patients taking Cs.



Fig. 7. – Treatment of gingival overgrowth.

(a) Nifedipine-associated gingival overgrowth, subsequently treated with conservative plaque control.

(b) Same patient as (a), following treatment.

(c) Cyclosporin- and nifedipine-associated gingival overgrowth in a renal transplant patient.

(d) Same patient as (c) after combined external and internal bevel gingivectomy.

(e) Postoperative appearance, one week following surgical treatment in (d).

(f) Three month postoperative appearance after (d). Note evidence of overgrowth recurrence and less than ideal plaque control.

Patients receiving nifedipine do not respond to conventional treatment as well as patients not taking the drug.⁹⁰ The role of plaque in nifedipine-induced gingival overgrowth is uncertain as no convincing longitudinal studies have investigated its role. Some role can be inferred from a case study⁹¹ where improvement in oral hygiene together with thorough scaling resulted in significant reduction in gingival overgrowth without substitution of the drug (Fig. 7a,7b). This is

in contrast to others^{92,93} who found that conservative scaling and improved oral hygiene was unable to limit the overgrowth.

It is difficult to draw conclusions regarding the role of plaque in verapamil gingival overgrowth. Two of the reported cases^{69,94} had significant levels of plaque but many patients taking verapamil have high levels of plaque and no overgrowth. Good oral hygiene failed to reduce such overgrowth reported in

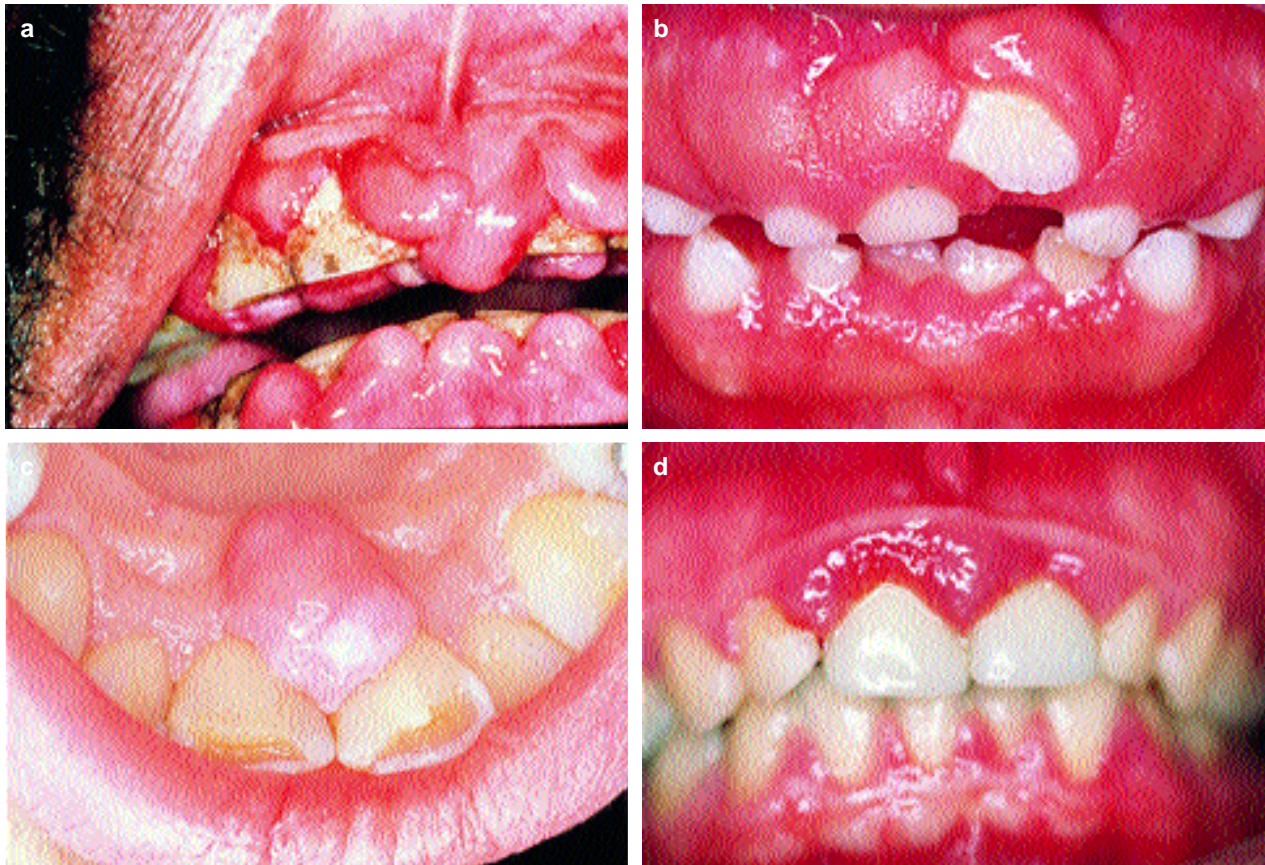


Fig. 8. – Non-drug-induced gingival overgrowth due to:
 (a) Poor plaque control.
 (b) Hereditary gingivofibromatosis.
 (c) Myxofibroma.
 (d) Iatrogenic, poor subgingival crown margins.

children.⁷⁹ Little information is available regarding plaque control and the other CCBs but it is assumed that the situation would be similar to those mentioned.

Surgical treatment

The need for, and timing of, any surgical intervention needs to be carefully assessed. Surgery is normally performed for cosmetic/aesthetic needs before any functional need is manifested. In cases where drug therapy is likely to continue for many years, psychosocial considerations need to be considered in an effort to reduce the frequency and extent of any surgical intervention. While classical external bevel gingivectomy is still a viable treatment option, the large denuded connective tissue wound that results can be painful and requires careful postoperative care to prevent infection. There is a tendency towards the use of either a total or partial internal bevel gingivectomy approach. This technically more demanding approach has the benefit of allowing ‘primary closure’ thus reducing the chances of postoperative complications, however, it requires more time and skill to accomplish (Fig. 7c-7f).

Surgical treatment of PHT-, Cs- and CCB-induced gingival overgrowth has centred on gingivectomy by conventional methods and, more recently, the use of CO₂ lasers.^{95,96} The CO₂ laser has been advocated because of the decreased surgical time, rapid postoperative haemostasis and the fact that often the underlying medical conditions are relative contraindications for conventional surgery.

Surgical excision has been tried in non-responding nifedipine cases⁹⁷ and it has been successful when combined with good oral hygiene.⁹⁸ Similar results have been found with verapamil^{79,94} and diltiazem gingival overgrowth, although it does recur.⁹⁹ Most reports of amlodipine gingival overgrowth have also required surgical intervention. The only other reported case of felodipine gingival overgrowth received careful plaque control and surgical excision of the most prominent gingival tissue, however, the authors did not state how effective this therapy was.⁷⁴

Combinations of medications associated with gingival overgrowth

The most common combination of drugs that cause gingival overgrowth is Cs and nifedipine.

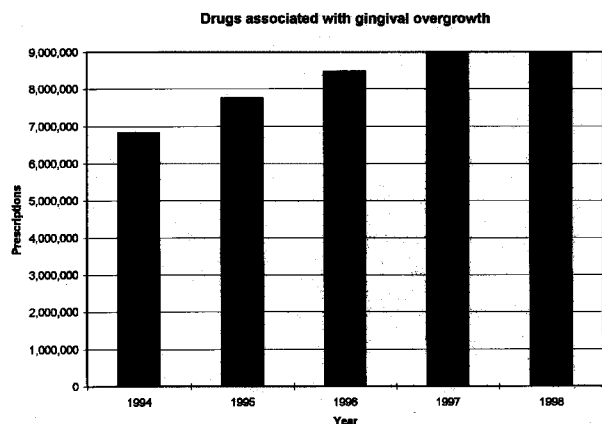


Fig.9. – Estimated number of prescriptions for all drugs commonly associated with gingival overgrowth in Australia, 1994-98.†

Nifedipine is used frequently to treat hypertension which may be primary or secondary to Cs nephrotoxicity. A significant increase in the incidence of gingival overgrowth has been described in renal transplant patients taking nifedipine as well as Cs compared with those taking Cs alone (51 per cent compared with 8 per cent).¹⁰⁰ Other investigators have reported an increased prevalence and severity in renal patients taking both drugs (Fig. 7c). They concluded that local factors and pharmacological parameters were unrelated to overgrowth and indicated a trend for HLA A19-positive patients to show signs of gingival overgrowth, suggesting an underlying genetic susceptibility.¹⁰¹

Further studies of renal and cardiac transplant patients have suggested that while the incidence of clinically significant gingival overgrowth may be similar, the severity of overgrowth appears to be significantly greater in those receiving both Cs and nifedipine.¹⁰² Patients taking both drugs had significantly higher gingival overgrowth scores, probing depths and a greater need for surgery.

Verapamil and Cs interactions have also been investigated in renal transplant patients. While there was an increased prevalence and severity of gingival overgrowth in patients taking both drugs, this was not significant. The dosage of either drug was unrelated to overgrowth. The authors concluded that verapamil was having no augmenting effect on either the severity or the prevalence of the gingival overgrowth.¹⁰³

Concluding comments

The authors have noted that the common drug-induced gingival overgrowths have a similar clinical appearance (particularly when fully established) and their histological appearances are also very alike. The gingival overgrowth appears to develop from enlarged interdental papillae which coalesce, unlike other forms of gingival overgrowth (hereditary, iatrogenic,

etc.) which usually involve an enlargement of the entire gingival apparatus. At a cellular level, although a little more variable, the general presentation is of an excess of fairly normal tissue often with an overlying chronic inflammation. The selectivity of the overgrowth towards the anterior region of the mouth in some patients suggests a number of factors (including a genetic predisposition) may interact with the local environment resulting in overgrowth. The possible pathogenesis of gingival overgrowth is the subject of an excellent review by Seymour *et al.*¹⁰⁴ With such a broad range of medications it seems likely that a number of different molecular changes can result in similar cellular and tissue appearances. The dentist should always be conscious that many non-medication-induced overgrowths may have a similar appearance, without the drug history (Fig. 8).

Treatment is generally centred on drug substitution, if possible, and effective plaque control. When these measures fail to resolve the overgrowth to a satisfactory level, then surgical intervention, usually by internal bevel gingivectomy, provides a good short-term outcome. The use of lasers to provide a sealed conventional gingivectomy wound is also suggested, particularly when substantial haemorrhage is expected. It should be emphasised that these treatment options do not necessarily prevent recurrence and patients should be made aware of this fact.

It seems likely that the use of medications with the potential to cause gingival overgrowth will increase (Fig. 9). Even accepting the lowest reported prevalence figures, it can be assumed that most dentists will have a number of patients in their care (approximately 10) who will suffer from gingival overgrowth. A clear understanding of the drugs that cause this phenomenon and the management of these cases is important for all dentists.

References

1. Adverse Drug Reaction Advisory Committee. Drug induced gingival overgrowth. Australian Adverse Drug Reactions Bulletin 1999;18:6-7.
2. Lokken P, Skomedal T. Gingival hyperplasia induced by calcium channel blockers. Rare or frequent in Norway? Tidsskr Nor Laegeforen 1992;112:1978-1980.
3. Kimball O. The treatment of epilepsy with sodium diphenylhydantoinate. JAMA 1939;112:1244-1245.
4. Hassell T. Epilepsy and the oral manifestations of phenytoin therapy Basel: Karger, 1983.
5. Thomason J, Seymour R, Rawlins M. Incidence and severity of phenytoin-induced gingival overgrowth in epileptic patients in general medical practice. Community Dent Oral Epidemiol 1992;20: 288-291.
6. Hassell T, O'Donnell J, Pearlman J, Tesini D, Murphy T, Best H. Phenytoin-induced gingival overgrowth in institutionalised epileptics. J Clin Periodontol 1984;11:242-253.
7. Darling M, Arendorf T, Shaikh A, Stephen L. Gingival hyperplasia of an edentulous alveolar ridge in an epileptic – a case report. N Z Dent J 1988;84:114-116.
8. McCord J, Sloan P, Quayle A, Hussey D. Phenytoin hyperplasia occurring under complete dentures: a clinical report. J Prosthet Dent 1992;68:569-572.

9. Peñarrocha-Diago M, Bagán-Sebastián J, Vera-Sempere F. Diphenylhydantoin-induced gingival overgrowth in man: A clinico-pathological study. *J Periodontol* 1990;61:571-574.
10. Panuska H, Gorlin R, Bearman J, Mitchell D. The effect of anti-convulsant drugs upon the gingiva – a series of analyses of 1048 patients II. *J Periodontol* 1961;31:15-28.
11. Addy V, McElnay J, Eyre D, Campbell N, D'Arcy P. Risk factors in phenytoin-induced gingival hyperplasia. *J Periodontol* 1983;54:373-377.
12. Steinberg S, Steinberg A. Phenytoin-induced gingival overgrowth in severely retarded children. *J Periodontol* 1982;53:429-433.
13. Pihlstrom B, Carson J, Smith Q, Bastien S, Keenan K. Prevention of phenytoin associated gingival enlargement – a 15 month longitudinal study. *J Periodontol* 1980;51:311-317.
14. Modéer T, Dahllöf G. Development of phenytoin induced gingival overgrowth in non-institutionalised epileptic children subject to different plaque control programs. *Acta Odontol Scand* 1987;45:81-85.
15. Seymour R. Drug-induced gingival overgrowth. *Adverse Drug React Toxicol Rev* 1993;12:215-232.
16. Hassell T, Gilbert G. Phenytoin sensitivity of fibroblasts as the basis for susceptibility to gingival enlargement. *Am J Pathol* 1983;112:218-223.
17. Hassell T, Page R, Lindhe J. Histologic evidence for impaired growth control in diphenylhydantoin gingival overgrowth in man. *Arch Oral Biol* 1978;23:381-384.
18. Goultshin J, Shoshan S. Inhibition of collagen breakdown by diphenylhydantoin. *Biochim Biophys Acta* 1980;631:188-191.
19. May L, Tan E, Holness R, Vitto J. Phenytoin modulates connective tissue metabolism and cell proliferation in human skin fibroblast cultures. *Arch Dermatol* 1985;121:79-83.
20. Kantor M, Hassell T. Increased accumulation of sulfated glycosaminoglycans in cultures from human fibroblasts from phenytoin-induced gingival overgrowth. *J Dent Res* 1983;62:383-387.
21. Suresh R, Puvanakrishnan R, Dhar S. Alterations in human gingival glycosaminoglycan pattern in inflammation and phenytoin induced overgrowth. *Mol Cell Biochem* 1992;115:149-154.
22. Brunius G, Modéer T. Effect of phenytoin on intracellular ⁴⁵Ca²⁺ accumulation in gingival fibroblasts *in vitro*. *J Oral Pathol Med* 1989;18:485-489.
23. Marshall R, Bartold P. Medication induced gingival overgrowth. *Oral Dis* 1998;4:130-151.
24. Modéer T, Dahllöf G, Karsten J, Otteskog P. Potentiation of fibroblast DNA synthesis by a phenytoin-induced mononuclear cell derived factor *in vitro*. *Scand J Dent Res* 1989;87:186-187.
25. Dill R, Miller E, Weil T, Lesley S, Farmer G, Lacopino A. Phenytoin increases gene expression for platelet derived growth factor B chain in macrophages and monocytes. *J Periodontol* 1993;64:169-173.
26. Soory M, Kasasa S. The effects of epidermal growth factor, interleukin-1, and phenytoin, alone and in combination on C₁₉ steroid conversions in fibroblasts. *J Periodontol* 1997;68:819-826.
27. Inoue F, Harrison J. Folic acid and phenytoin hyperplasia. *Lancet* 1981;2:86.
28. Poppell T, Keeling S, Collins F, Hassell T. Effect of folic acid on recurrence of phenytoin-induced gingival overgrowth following gingivectomy. *J Clin Periodontol* 1991;18:134-139.
29. Seymour R, Heasman P. *Drugs, diseases, and the periodontium*. Oxford: Oxford University Press, 1992.
30. Seymour R, Smith D, Turnbull D. The effects of phenytoin and sodium valproate on the periodontal health of adult epileptics. *J Clin Periodontol* 1985;12:413-419.
31. Syrjanen S, Syrjanen K. Hyperplastic gingivitis in a child receiving sodium valproate. *Proc Finn Dent Soc* 1979;75:95-98.
32. Behari M. Gingival hyperplasia due to sodium valproate. *J Neurol Neurosurg Psychiatry* 1991;54:279-280.
33. Gregoriou A, Schneider P, Shaw P. Phenobarbital-induced gingival overgrowth? Report of two cases and complications in management. *J Dent Child* 1996;63:408-413.
34. Katz J, Givol N, Chaushu G, Taicher S, Shemer J. Vigabatrin-induced gingival overgrowth. *J Clin Periodontol* 1997;24:180-182.
35. Calne R, Thiru S, McMaster P, *et al.* Cyclosporin-A in patients receiving renal allografts from cadaver donors. *Lancet* 1978;1:1323-1327.
36. Starzl T, Weil R, Iwatsuki S, *et al.* The use of cyclosporin A and prednisone in cadaver kidney transplantation. *Surg Gynecol Obstet* 1980;151:17-26.
37. Rateitschak-Plüss E, Hefti A, Lörtscher R, Thiel G. Initial observation that cyclosporin-A induces gingival enlargement in man. *J Clin Periodontol* 1983;10:237-246.
38. Calne R, Rolles K, White D, *et al.* Cyclosporin-A in clinical organ grafting. *Transpl Proc* 1981;13:349-358.
39. Wysocki G, Gretzinger H, Laupacis A, Ulan R, Stiller C. Fibrous hyperplasia of the gingiva: A side effect of cyclosporin A therapy. *Oral Surg Oral Med Oral Pathol* 1983;55:274-278.
40. Tyldesley W, Rotter E. Gingival hyperplasia induced by cyclosporin-A. *Br Dent J* 1984;157:305-309.
41. Wondimu B, Dahllöf G, Berg U, Modéer T. Cyclosporin-A-induced gingival overgrowth in renal transplant children. *Scand J Dent Res* 1993;101:282-286.
42. Friskopp J, Klintman G. Gingival enlargement. A comparison between cyclosporine and azathioprine treated renal allograft recipients. *Swed Dent J* 1986;10:85-92.
43. Seymour R, Jacobs D. Cyclosporin and the gingival tissues. *J Clin Periodontol* 1992;19:1-11.
44. Daley T, Wysocki G, Day C. Clinical and pharmacological correlations in cyclosporin-induced gingival hyperplasia. *Oral Surg Oral Med Oral Pathol* 1986;62:417-421.
45. Modéer T, Wondimu B, Larsson E, Jonzon B. Levels of cyclosporin-A (CsA) in saliva in children after oral administration of the drug in mixture or in capsule form. *Scand J Dent Res* 1992;100:366-370.
46. Seymour R, Smith D, Rogers S. The comparative effects of azathioprine and cyclosporin on some gingival health parameters of renal transplant patients. *J Clin Periodontol* 1987;14:610-613.
47. The Multiple Sclerosis Study Group. Efficacy and toxicity of cytosporine in chronic progressive multiple sclerosis: A randomized, double blinded, placebo controlled clinical trial. *Ann Neurol* 1990;27:591-605.
48. Thomason J, Seymour R, Ellis J, Kelly P, Parry G, Dark J, Idle J. Iatrogenic gingival overgrowth in cardiac transplantation. *J Periodontol* 1995;66:742-746.
49. Karpinia K, Matt M, Fennell R III, Hefti A. Factors affecting cyclosporine-induced gingival overgrowth in pediatric renal transplant recipients. *Pediatr Dent* 1996;18:450-455.
50. Niimi A, Tohnai I, Kaneda T, Takeuchi M, Nagura H. Immunohistochemical analysis of the effects of cyclosporin A on gingival epithelium. *J Oral Pathol Med* 1990;19:397-403.
51. Seymour R, Smith D. The effect of a plaque control programme on the incidence and severity of cyclosporin-induced gingival changes. *J Clin Periodontol* 1991;18:107-110.
52. Thomason J, Kelly P, Seymour R. The distribution of gingival overgrowth in organ transplant patients. *J Clin Periodontol* 1996;23:367-371.
53. Bartold P. Regulation of human gingival fibroblast growth and synthetic activity by cyclosporine-A *in vitro*. *J Periodont Res* 1989;24:314-321.
54. Barber M, Savage N, Seymour G. The effect of cyclosporin and lipopolysaccharide on fibroblasts: Implications for cyclosporin-induced gingival overgrowth. *J Periodontol* 1992;63:397-404.
55. Tipton D, Stricklin G, Dabbous M. Fibroblast heterogeneity in collagenolytic response to cyclosporine. *J Cell Biochem* 1991;46:152-165.
56. Thomason J, Seymour R, Ellis J, *et al.* Determinants of gingival overgrowth severity in organ transplant patients: An examination of the role of HLA phenotype. *J Clin Periodontol* 1996;23:628-634.
57. Cebeci I, Kantarci A, Firatli E, *et al.* Evaluation of the frequency of HLA determinants in patients with gingival overgrowth induced by cyclosporine-A. *J Clin Periodontol* 1996;23:737-742.

58. Thomson W, Slade G, Spencer A. Dental caries experience and use of prescription medications among people aged 60+ in South Australia. *Gerodontology* 1995;12:104-110.
59. Lederman D, Lumerman H, Reuban S, Freeman P. Gingival hyperplasia associated with nifedipine therapy. *Oral Surg Oral Med Oral Pathol* 1984;57:620-622.
60. Ramon Y, Behar S, Kishon Y, Engelberg I. Gingival hyperplasia caused by nifedipine – a preliminary report. *Int J Cardiol* 1984;5:195-204.
61. Cucchi G, Giustiniani S, Robustelli F. Gengivite ipertrofica da verapamil. (Gingival hyperplasia caused by verapamil.) *G Ital Cardiol* 1985;15:556-557.
62. Colvard M, Bishop J, Weissman D, Bargiulo A. Cardizem-induced gingival hyperplasia. *Periodontal Case Rep* 1986;8:67-68.
63. Barak S, Engelberg I, Hiss Z. Gingival hyperplasia caused by nifedipine: histopathological findings. *J Periodontol* 1987;58:639-642.
64. Fattore L, Stablein M, Bredfeldt G, Semla T, Moran M, Doherty-Greenburg J. Gingival hyperplasia: a side effect of nifedipine and diltiazem. *Spec Care Dent* 1991;11:107-109.
65. Barclay S, Thomason J, Idle J, Seymour R. The incidence and severity of nifedipine-induced gingival overgrowth. *J Clin Periodontol* 1992;19:311-314.
66. Nery E, Edson R, Lee K, Pruthi K, Watson J. Prevalence of nifedipine-induced gingival hyperplasia. *J Periodontol* 1995;66:572-578.
67. Ellis J, Seymour R, Monkman S, Idle J. Disposition of nifedipine in plasma and gingival crevicular fluid in relation to drug-induced gingival overgrowth. *J Periodontol Res* 1993;28:373-378.
68. Harel-Raviv M, Eckler M, Lalani K, Raviv E, Gornitsky M. Nifedipine-induced gingival hyperplasia. *Oral Surg Oral Med Oral Pathol* 1995;79:715-722.
69. Miller C, Damm D. Incidence of verapamil-induced gingival hyperplasia in a dental population. *J Periodontol* 1992;63:453-456.
70. Giustiniani S, Robustelli della Cuna F, Marieni M. Hyperplastic gingivitis during diltiazem therapy. *Int J Cardiol* 1987;15:247-249.
71. Ellis J, Seymour R, Thomason J, Monkman S, Idle J. Gingival sequestration of amlodipine and amlodipine-induced gingival overgrowth. (Letter.) *Lancet* 1993;341:1102-1103.
72. Jorgensen M. Prevalence of amlodipine-related gingival hyperplasia. *J Periodontol* 1997;68:676-678.
73. Seymour R, Ellis J, Thomason J, Monkman S, Idle J. Amlodipine-induced gingival overgrowth. *J Clin Periodontol* 1994;21:281-283.
74. Lombardi T, Fiore Donno G, Belser U, Di Felice R. Felodipine induced gingival hyperplasia: a clinical and histologic study. *J Oral Pathol Med* 1991;20:89-92.
75. Young P, Turiansky G, Sau P, Liebman M, Benson P. Felodipine induced gingival hyperplasia. *Cutis* 1998;62:41-43.
76. Glefand E, Cheung R, Grinstein S, Mills G. Characterization of the role of calcium influx in mitogen-induced triggering of human T cells. Identification of calcium-dependent and calcium independent signals. *Eur J Immunol* 1986;16:907-912.
77. Sooriyaamoorthy M, Gower D, Eley B. Androgen metabolism in gingival hyperplasia induced by nifedipine and cyclosporin. *J Periodont Res* 1990;25:25-30.
78. Saito K, Mori S, Iwakura M, Sakamoto S. Immunohistochemical localization of transforming growth factor beta, basic fibroblast growth factor and heparan sulphate glycosaminoglycan in gingival hyperplasia. *J Periodont Res* 1996;31:545-555.
79. Mehta A, Chidambaram B, O'Riordan A. Verapamil-induced gingival hyperplasia in children. *Am Heart J* 1992;124:535-536.
80. Valsecchi R, Cainelli T. Gingival hyperplasia induced by erythromycin. *Acta Derm Venereol (Stockh)* 1992;72:157.
81. Brunsvold M, Tomasovic J, Reumping D. The measured effect of phenytoin withdrawal on gingival hyperplasia in children. *J Dent Child* 1985;13:845-849.
82. Dahllöf G, Axiö E, Modéer T. Regression of phenytoin-induced gingival overgrowth after withdrawal of medication. *Swed Dent J* 1991;15:139-143.
83. Daly C. Resolution of cyclosporin A (CsA)-induced gingival enlargement following reduction in CsA dosage. *J Clin Periodontol* 1992;19:143-145.
84. Budde K, Fritsche L, Mai I, *et al.* Clinical pharmacokinetics of tacrolimus in rescue therapy after renal transplantation. *Int J Clin Pharm Ther Toxicol* 1996;34:493-497.
85. Puolijoki H, Siitonen L, Saha H, Suojanen I. Gingival hyperplasia caused by nifedipine. *Proc Finn Dent Soc* 1988;84:311-314.
86. Westbrook P, Bednarczyk E, Carlson M, Sheehan H, Bissada N. Regression of nifedipine-induced gingival hyperplasia following switch to a same class calcium channel blocker, isradipine. *J Periodontol* 1997;68:645-650.
87. Ciancio S, Bartz N, Lauciello F. Cyclosporine-induced gingival hyperplasia and chlorhexidine: A case report. *Int J Periodontics Restorative Dent* 1991;11:241-245.
88. Pilati G, Sampaio J. The influence of chlorhexidine on the severity of cyclosporin A-induced gingival overgrowth. *J Periodontol* 1997;68:900-904.
89. Pernu H, Pernu L, Huttunen K, Nieminen P, Knuutila M. Gingival overgrowth among renal allograft recipients related to immunosuppressive medication and possible local background factors. *J Periodontol* 1992;63:548-553.
90. Bullon P, Machuca G, Martinezsahuquillo A, Rios J, Velasco E, Rojas J, Lacalle J. Evaluation of gingival and periodontal conditions following causal periodontal treatment in patients treated with nifedipine and diltiazem. *J Clin Periodontol* 1996;23:649-657.
91. Hancock R, Swan R. Nifedipine-induced gingival hyperplasia. *J Clin Periodontol* 1992;19:12-14.
92. Zlotogorski A, Nyska M, Sela M, Nyska A, Gotsman M. Nifedipine-induced gingival hyperplasia: Case reports and literature review. *Isr J Med Sci* 1989;25:453-455.
93. Barak S, Kaplan I. The CO₂ laser in the excision of gingival hyperplasia caused by nifedipine. *J Clin Periodontol* 1988;15:633-635.
94. Pernu H, Oikarinen K, Hietanen J, Knuutila M. Verapamil-induced gingival overgrowth: a clinical, histologic, and biochemic approach. *J Oral Pathol Med* 1989;18:422-425.
95. Pick R, Pecaro B, Silberman C. The laser gingivectomy. The use of CO₂ laser for the removal of phenytoin hyperplasia. *J Periodontol* 1985;56:492-496.
96. Hylton R. Use of CO₂ laser for gingivectomy in a patient with Sturge-Weber disease complicated by dilantin hyperplasia. *J Oral Maxillofac Surg* 1986;44:646-648.
97. Abitbol T, Rosenfeld-Abitbol M. Surgical treatment of nifedipine-induced gingival hyperplasia. A case report. *N Y State Dent J* 1996;62:34-37.
98. Nishikawa S, Tada H, Hamasaki A, *et al.* Nifedipine-induced gingival hyperplasia: A clinical and *in vitro* study. *J Periodontol* 1991;62:30-35.
99. Bowman J, Levy B, Grubb R. Gingival overgrowth induced by diltiazem. *Oral Surg Oral Med Oral Pathol* 1988;65:183-185.
100. Slavin J, Taylor J. Cyclosporin, nifedipine and gingival hyperplasia. *Lancet* 1987;2:739.
101. Margiotta V, Pizzo I, Barbaro A. Cyclosporin and nifedipine induced gingival overgrowth in renal transplant patients: Correlations with periodontal and pharmacological parameters, and HLA antigens. *J Oral Pathol Med* 1996;25:128-134.
102. Thomason J, Seymour R, Rice N. The prevalence and severity of cyclosporin and nifedipine induced gingival overgrowth. *J Clin Periodontol* 1993;20:37-40.
103. Cebeci I, Kantarci A, Firatli E, Carin M, Tuncer Ö. The effect of verapamil on the prevalence and severity of cyclosporine-induced gingival overgrowth in renal allograft recipients. *J Periodontol* 1996;67:1201-1205.
104. Seymour R, Thomason R, Ellis J. The pathogenesis of drug-induced gingival overgrowth. *J Clin Periodontol* 1996;23:165-175.

Address for correspondence/reprints:

Dr Rod Marshall,
The University of Queensland,
Dental School,
Turbot Street,
Brisbane, Queensland 4000.