

## Informational Paper Drug-Associated Gingival Enlargement\*

This informational paper is intended to provide the dental profession with an overview of existing evidence regarding the prevalence, risk factors, pathogenesis, and clinical management of drug-associated gingival enlargement. *J Periodontol* 2004;75:1424-1431.

An increasing number of medications are associated with gingival enlargement. Currently, more than 20 prescription medications are associated with gingival enlargement,<sup>1</sup> and an estimated 5% of the elderly outpatient population in the United States is taking these medications.<sup>2</sup> "Gingival enlargement" or "gingival overgrowth" is the preferred term for all medication-related gingival lesions previously termed "gingival hyperplasia" or "gingival hypertrophy." These earlier terms did not accurately reflect the histologic composition of the pharmacologically modified gingiva.

Drugs associated with gingival enlargement can be broadly divided into three categories: anticonvulsants, calcium channel blockers, and immunosuppressants. Although the pharmacologic effect of each of these drugs is different and directed toward various primary target tissues, all of them seem to act similarly on a secondary target tissue, i.e., the gingival connective tissue, causing common clinical and histopathological findings.

### TYPES OF PHARMACOLOGIC AGENTS

#### Anticonvulsants

Phenytoin remains the drug of choice for treatment for grand mal, temporal lobe, and psychomotor seizures since it was first introduced in the 1930s.<sup>3</sup> In the U.S., about 2 million patients take phenytoin for seizure control.<sup>4</sup> The first reported cases of phenytoin-associated enlargement appeared more than 6 decades ago.<sup>3</sup> Since then, other anticonvulsant agents have been introduced that have frequently been linked to clinically significant forms of gingival enlargement. For example, gingival enlargement cases after chronic use of valproic acid, carbamazepine, or phenobarbitone in adult patients have been reported but are rare or have been poorly documented.<sup>5-7</sup> Vigabatrin is a relatively new antiepileptic agent that can cause gingival overgrowth.<sup>8</sup> However, there has been no systematic attempt to study gingival enlargement in patients taking vigabatrin.

#### Calcium Channel Blockers

Antihypertensive drugs in the calcium channel blocker group are used extensively in elderly patients who have angina or peripheral vascular disease.<sup>3,9</sup> The total number of annual prescriptions for this class of agents has continued to rise in recent years.<sup>3</sup> Gingival overgrowth associated with nifedipine was first reported in the early 1980s and was soon also described with diltiazem, verapamil, and in rare cases with amlodipine and felodipine (reviewed in reference 3).

#### Immunosuppressants

Cyclosporin A (CsA) is a powerful immunosuppressant widely used for prevention of transplant rejection as well as for management of a number of autoimmune conditions such as rheumatoid arthritis.<sup>10,11</sup> Successful use of CsA in transplant medicine has been limited by the development of prominent renal, cardiac, and gingival fibrosis.<sup>12-15</sup> Renal and cardiac lesions may be so severe as to cause transplant failure.<sup>13-15</sup> Gingival lesions were reported as soon as results of the first clinical trials of this medication were published,<sup>16</sup> and were more systematically examined in the 1980s.

### PREVALENCE

Accurate determination of prevalence rates in each drug category is extremely difficult due to differences in the reported prevalence rates. These differences may be due, at least in part, to assessment of enlargement by medical versus dental personnel, differing indices of overgrowth, focus on institutionalized versus outpatient populations, type of systemic condition being treated, age of the patients, other medications administered simultaneously, poorly controlled underlying periodontal conditions, and other factors. Although the prevalence varies greatly in different reports, the gingival enlargement prevalence in phenytoin-treated, non-institutionalized patients is about 50%.<sup>17</sup>

Gingival enlargement in adult patients treated with valproic acid is rare. However, there have been a few reported cases in children.<sup>3</sup> Earlier studies found prevalence rates for nifedipine ranging between 15% and

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**Table 1.****Estimated Prevalence of Drug-Associated Gingival Enlargement According to the Most Frequently Reported Prevalence Rates**

Category	Pharmacologic Agent	Trade Name	Prevalence
Anticonvulsants	Phenytoin	Dilantin	50% <sup>6,17,23</sup>
	Sodium valproate (valproic acid)	Depakene, Depacon, Epilim, Valpro	Rare <sup>3,5,23</sup>
	Phenobarbitone	Phenobarbital, Donnatal	<5% <sup>7</sup>
	Vigabatrin	Sabril	Rare <sup>8</sup>
	Carbamazepine	Tegretol	None reported
Immunosuppressants	Cyclosporin	Neoral, Sandimmune	Adults 25-30% <sup>13,21,24</sup> Children >70% <sup>22</sup>
Calcium channel blockers	Nifedipine	Adalat, Nifecard, Procardia, Tenif	6-15% <sup>18-20</sup>
	Isradipine	DynaCirc	None reported
	Felodipine	Agon, Felodur, Lexxel, Plendil	Rare <sup>3,20</sup>
	Amlodipine	Lotrel, Norvasc	Rare <sup>3,20</sup>
	Verapamil	Calan, Covera, Isoptin, Tarka, Verelan	<5% <sup>25</sup>
	Diltiazem	Cardizem, Dilacor, Diltimax, Tiazac	5-20% <sup>26</sup>

85%;<sup>18,19</sup> however, a community-based, well-controlled epidemiological study found that only about 6% of subjects taking nifedipine had clinically significant overgrowth.<sup>20</sup> The prevalence with verapamil, diltiazem, felodipine, or amlodipine was significantly smaller.<sup>3,20</sup> With respect to CsA, although reported rates vary, a review of the few well-controlled studies indicated that the overall rate is 25% to 30%.<sup>21</sup> However, pediatric heart-lung transplant recipients on CsA appear to be more susceptible to CsA-associated enlargement, with up to 97% of these children developing some degree of overgrowth.<sup>22</sup>

A summary of estimated prevalence rates for drug-associated gingival enlargement is shown in Table 1.

**RISK FACTORS****Plaque**

The severity of gingival enlargement in patients taking these medications correlates well with poor plaque con-

trol<sup>17</sup> and is commensurate with the degree of plaque-induced inflammation.<sup>20,27</sup> The importance of plaque as a cofactor in the etiology of drug-associated gingival enlargement has been recognized in the most recent classification system for periodontal diseases.<sup>28</sup> In this classification, “drug-influenced gingival enlargements” are categorized as plaque-induced gingival diseases modified by medications. In support of this classification system, plaque accumulation was strongly associated with the occurrence of gingival overgrowth both in an animal model of CsA-induced gingival enlargement,<sup>29</sup> and in a large group of CsA-treated allograft patients using a multivariate regression analysis model.<sup>30</sup> In addition, it was shown that patients with evidence of inflammatory gingival overgrowth prior to initiation of CsA treatment are more likely to develop severe gingival enlargement.<sup>31</sup>

**Other Factors**

As with most periodontal diseases, a multifactorial model appears to best explain the occurrence and distribution of gingival overgrowth in patients, receiving medications associated with this condition. This has been illustrated in a large study of CsA-treated patients, which failed to fully explain the distribution of gingival overgrowth based solely on the level of plaque and gingivitis.<sup>32</sup> Other factors affecting the occurrence of gingival enlargement may include gender, with males being three times as likely to develop overgrowth,<sup>20</sup> and age, which is inversely correlated.<sup>17,22,27</sup> Although there are conflicting data with respect to the relationship between severity of enlargement and daily phenytoin, CsA, or nifedipine dose, most studies have not reported a significant association with dosage.<sup>3,33,34</sup> Examination of tissue typing data in transplant recipients has shown that HLA B37-positive patients are significantly more likely to show severe gingival enlargement, whereas the opposite is true about HLA DR1-positive patients.<sup>35,36</sup>

Donor-host HLA mismatching was not correlated to the degree of gingival enlargement.<sup>30</sup>

Interactions between simultaneously administered medications affecting gingival enlargement have also been reported. Chronic comedication with phenytoin and other anticonvulsant agents does not affect the degree of gingival enlargement in adult epileptic patients.<sup>37</sup> However, CsA-treated patients are often on prednisolone or azathioprine as well, which can modify the severity of gingival enlargement.<sup>38</sup> In contrast, patients on CsA who are also receiving a calcium channel blocker present with a greater severity of the gingival lesions than patients medicated with CsA alone.<sup>39</sup> The choice of the calcium channel blocker used in conjunction with CsA can also affect the prevalence or severity of gingival enlargement. It has been reported that the prevalence of gingival overgrowth in renal transplant recipients maintained on CsA and amlodipine is higher than those receiving CsA and nifedipine.<sup>40</sup> In addition, when effects of a combined treatment of CsA and nifedipine or diltiazem were tested in an animal model, CsA was found to synergistically enhance gingival growth with nifedipine and to a lesser degree with diltiazem.<sup>41</sup>

## CLINICAL MANIFESTATIONS OF GINGIVAL ENLARGEMENT

Clinical manifestation of gingival enlargement frequently appears within 1 to 3 months after initiation of treatment with the associated medications.<sup>42</sup> Gingival overgrowth normally begins at the interdental papillae and is more frequently found in the anterior segment of the labial surfaces.<sup>3,9</sup> Gradually, gingival lobulations are formed that may appear inflamed or more fibrotic in nature, depending on the degree of local factor-induced inflammation. The fibrotic enlargement normally is confined to the attached gingiva but may extend coronally and interfere with esthetics, mastication, or speech.<sup>3,9</sup> Disfiguring gingival overgrowth triggered by these medications is not only esthetically displeasing but often impairs nutrition and access for oral hygiene, resulting in an increased susceptibility to oral infection, caries, and periodontal diseases.<sup>11</sup>

Most drug-associated gingival enlargements appear to be clinically indistinguishable, with the possible exceptions of phenobarbitone<sup>7</sup> and CsA.<sup>5</sup> In phenobarbitone-treated patients, the gingiva may be enlarged uniformly without lobulations of the interdental papillae, and severity of the clinical lesions has been reported to be greater in the posterior as compared to the anterior regions.<sup>7</sup> In individuals immunosuppressed with CsA, sometimes pebbly or papillary lesions appear on the

surface of larger lobulations,<sup>43</sup> which have been associated with the presence of *Candida* hyphae invading the gingival epithelium.<sup>43,44</sup> Other investigators have reported that tissues affected by CsA are generally more hyperemic and bleed more readily upon probing than tissues affected by phenytoin.<sup>5</sup>

## HISTOPATHOLOGY OF THE LESION

An ultrastructural study demonstrated that the increase in gingival tissue volume is primarily due to a connective tissue response rather than epithelial cell layer involvement.<sup>45</sup> The histopathology of the lesions in all drug categories is similar and is characterized by excessive accumulation of extracellular matrix proteins, such as collagen, or amorphous ground substance.<sup>3,4,9</sup> Varying degrees of inflammatory infiltrate exist, while an increase in the number of fibroblasts remains controversial.<sup>46-48</sup> The predominant type of infiltrating inflammatory cell is the plasma cell. Parakeratinized epithelium of variable thickness covers the connective tissue stroma, and epithelial ridges may penetrate deep into the connective tissue, creating irregularly arranged collagen fibers.<sup>45</sup>

## PATHOGENESIS

### *Role of Fibroblasts*

The mechanism through which these medications trigger a connective tissue response in the gingiva is still poorly understood. Because only a subset of patients treated with these medications will develop gingival overgrowth, it has been hypothesized that these individuals have fibroblasts with an abnormal susceptibility to the drug. Indeed, it has been shown that fibroblasts from overgrown gingiva in phenytoin-treated patients are characterized by elevated levels of protein synthesis, most of which is collagen.<sup>49</sup> However, results of a study comparing intraoral lesions with the presence of fibrosis at extraoral sites failed to show that the severity of gingival enlargement correlates well with the formation of fibrotic lesions elsewhere in the body.<sup>50</sup> Such enlargement cannot be considered a consequence of systemic and/or genetic fibroblast hyperactivity. A limitation of this study was that the conclusions were based on examination of extraoral tissues at the macroscopic level only.<sup>50</sup>

It also has been proposed that susceptibility or resistance to pharmacologically induced gingival enlargement may be governed by the existence of differential proportions of fibroblast subsets in each individual which exhibit a fibrogenic response to these medications.<sup>49,51</sup> In support of this hypothesis, it has been shown that functional heterogeneity exists in gingival

fibroblasts in response to various stimuli.<sup>49,52</sup> It was further demonstrated that CsA could react with a phenotypically distinct subpopulation of gingival fibroblasts to enhance protein synthesis.<sup>53,54</sup>

### **Role of Inflammatory Cytokines**

A synergistic enhancement of collagenous protein synthesis by human gingival fibroblasts was found when these cells were simultaneously exposed to nifedipine and interleukin-1 $\beta$  (IL-1 $\beta$ ), a proinflammatory cytokine that is elevated in inflamed gingival tissues.<sup>55</sup> In addition to IL-1 $\beta$ , IL-6 may play a role in the fibrogenic responses of the gingiva to these medications.<sup>56</sup> A reported histologic feature of CsA-induced gingival lesions is a dramatic elevation in the expression of IL-6 by cells within the gingival connective tissue.<sup>56</sup> IL-6 appears to target connective tissue cells such as fibroblasts both by enhancing proliferation<sup>57</sup> and by exerting a positive regulation on collagen and glycosaminoglycan synthesis.<sup>58</sup> Therefore, this cytokine has been proposed to play a pathogenic role in fibrotic diseases such as pulmonary and gingival fibroses.<sup>7,51</sup> Fibroblasts derived from CsA-influenced overgrown gingiva “spontaneously” secreted higher IL-6 levels than from inflamed or normal gingiva *in vitro*.<sup>59</sup> In addition, CsA, nifedipine, and phenytoin were found to synergize with IL-1 $\beta$  to further enhance secretion of this cytokine by gingival fibroblasts *in vitro*.<sup>51</sup>

### **Role of Matrix Metalloproteinase (MMP) Synthesis and Function**

Because most types of pharmacological agents implicated in gingival enlargement have negative effects on calcium ion influx across cell membranes, it was postulated that such agents may interfere with the synthesis and function of collagenases.<sup>60</sup> In support of this hypothesis, a recent *in vitro* study has shown that human gingival fibroblasts treated with clinically relevant CsA doses exhibit significantly reduced levels of MMP-1 and MMP-3 secretion; these reduced levels may contribute to the accumulation of extracellular matrix components.<sup>61</sup> These findings were further supported by an animal study that showed lower collagenase mRNA levels *in situ* accompanied by a decrease in collagen phagocytosis and degradation.<sup>62</sup>

## **PREVENTION AND TREATMENT OF GINGIVAL ENLARGEMENT**

### **Prevention**

In the susceptible patient, drug-associated gingival enlargement may be ameliorated, but not prevented, by elimination of local factors, meticulous plaque con-

trol, and regular periodontal maintenance therapy. A 3-month interval for periodontal maintenance therapy has been recommended for patients taking drugs associated with gingival enlargement.<sup>63</sup> Each recall appointment should include detailed oral hygiene instructions and complete periodontal prophylaxis, with supra- and subgingival calculus removal as needed. In pediatric patients, it is recommended that parents also receive oral hygiene instructions. In some instances, orthodontic bands and/or appliances should be removed.<sup>64</sup> An animal study has shown that topically applied 0.12% chlorhexidine can reduce the severity of gingival enlargement triggered by CsA administration<sup>65</sup> and thus may be a valuable tool in the prevention and overall management of gingival enlargement in humans.

### **Treatment**

**Drug substitution/withdrawal.** The most effective treatment of drug-related gingival enlargement is withdrawal or substitution of medication. When this treatment approach is taken, as suggested by a case report, it may take from 1 to 8 weeks for resolution of gingival lesions.<sup>43</sup> Unfortunately, not all patients respond to this mode of treatment, especially those with longstanding gingival lesions.<sup>3</sup>

Substitution of phenytoin with a different anticonvulsant has long been suggested as the treatment of choice for the severely affected gingiva. Recently, the feasibility of phenytoin substitution has increased with the addition of a new generation of anticonvulsants such as lometrigine, gabapentin, sulthiame, and topiramate. Changes from nifedipine to diltiazem or verapamil by the patient's physician are an option. Changing hypertensive therapy from nifedipine to an antihypertensive of the same class, such as isradipine, may result in regression of gingival enlargement.<sup>66</sup> Tacrolimus (FK506) is an alternative immunosuppressant for renal transplant recipients that has not been associated with gingival enlargement. Switching from CsA to tacrolimus can cause significant resolution or complete regression of the gingival enlargement in renal transplant recipients.<sup>67</sup> However, in heart transplant patients, if the patient is medically stable and side effects of immunosuppression with CsA are well controlled, the cardiology team will frequently be disinclined to alter the therapeutic regimen.<sup>43</sup>

**Non-surgical treatment.** Professional debridement with scaling and root planing as needed has been shown to offer some relief in gingival overgrowth patients.<sup>68</sup> In chronically immunosuppressed patients, papillary lesions present on the surface of the enlarged gingiva have been reported to resolve using topical



antifungal medications (e.g., nystatin lozenges).<sup>43,44</sup> Slight to moderate gingival enlargement following CsA treatment has also been treated with a short course of azithromycin (3 to 5 days, 250 to 500 mg/day),<sup>69,70</sup> a semisynthetic macrolide derived from erythromycin that does not affect cyclosporin blood levels.<sup>70</sup> Findings from several case reports, two non-randomized prospective clinical trials, and one randomized double-blind cross-over trial in CsA-treated renal transplant recipients suggest that if gingival overgrowth is treated early with azithromycin, amelioration or complete regression of the lesions is possible (reviewed in reference 70). The overall duration of the effects of azithromycin ranges between 3 months and 2 years.<sup>70</sup> Another study contradicts these findings, showing that a 7-day course of azithromycin (or metronidazole) does not induce remission of CsA-induced gingival overgrowth, although it acts on concomitant bacterial overinfection and gingival inflammation.<sup>71</sup>

**Surgical periodontal treatment.** Because the anterior labial gingiva is frequently involved, surgery is commonly performed for esthetic reasons before any functional consequences are present. The classical surgical approach has been the external bevel gingivectomy. However, a total or partial internal gingivectomy approach has been suggested as an alternative.<sup>3</sup> This more technically demanding approach has the benefit of limiting the large denuded connective tissue wound that results from the external gingivectomy, thereby minimizing postoperative pain and bleeding.

The use of carbon dioxide lasers has shown some utility for reducing gingival enlargement, an approach which provides rapid postoperative hemostasis. Consultation with the patient's physician prior to surgical treatment regarding antibiotic and steroid coverage should take place in the immunosuppressed patient.<sup>3</sup> Another eminent complication is primary high blood pressure or high blood pressure secondary to CsA treatment. If blood pressure is poorly controlled, surgical reduction of the overgrown gingiva should be postponed because of the risk of postoperative hemorrhage. Sudden unnecessary changes in dental chair position should also be avoided to prevent postural hypotension.<sup>43</sup>

**Treatment outcomes and recurrence rate.** The recurrence rate of severe gingival enlargement in CsA- or nifedipine-treated patients after surgical periodontal therapy was found to be about 40% within 18 months after active treatment.<sup>72</sup> Significant determinants of recurrence were found to be younger age, gingival inflammation, and poor compliance with maintenance visits.<sup>72</sup> Chlorhexidine (0.12%) oral rinse twice daily has been

reported to prevent recurring overgrowth following surgical treatment.<sup>23</sup>

## MOLECULAR BIOLOGY: POTENTIAL SOLUTIONS TO AN AGE-OLD PROBLEM?

Clearly, our understanding of the pathogenesis of gingival overgrowth is incomplete at best; however, the development of novel preventative and therapeutic approaches to gingival overgrowth requires a systematic approach. This should include the development and use of animal models of gingival overgrowth<sup>24,25</sup> and organotypic<sup>26,73</sup> and single-cell culture systems,<sup>74</sup> which can be cross-correlated with human gingival tissue studies.<sup>75,76</sup> The complexity of the events that contribute to gingival overgrowth have yet to be fully realized, but will require molecular and high throughput approaches, such as reverse transcription-polymerase chain reaction (RT-PCR), quantitative real-time PCR, and DNA microarray technologies.<sup>75,76</sup>

## CONCLUSION

The use of medications with the potential to contribute to the development of gingival overgrowth will likely increase in the years to come. Among the old and relatively newer pharmacologic agents involved in gingival enlargement, overall, phenytoin still has the highest prevalence rate (approximately 50%), with calcium channel blockers and CsA-associated enlargements about half as prevalent. Current studies on the pathogenetic mechanism of drug-associated enlargement are focusing on the direct and indirect effects of these drugs on gingival fibroblast metabolism. If possible, treatment is generally targeted on drug substitution and effective control of local inflammatory factors such as plaque and calculus. When these measures fail to cause resolution of the enlargement, surgical intervention is recommended. These treatment modalities, although effective, do not necessarily prevent recurrence of the lesions. Newer molecular approaches are needed to clearly establish the pathogenesis of gingival overgrowth and to provide novel information for the design of future preventative and therapeutic modalities.

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