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# The management of drug-induced gingival overgrowth

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***Abstract***

**Objectives:** This review critically evaluates the different therapies that are available to manage drug-induced overgrowth (DIGO).

**Material and Methods:** This review is based on literature identified using the online databases MEDLINE and PUB MED. It is not a systematic review, but a conventional review of the relevant literature.

**Results:** Patients benefit from a non-surgical approach if this can be delivered before commencement of medication although in many instances this may not be practicable. Systemic antibiotic usage has been evaluated in the management of ciclosporin-induced gingival overgrowth. Efficacy appears to be equivocal and long-term use is undesirable. Surgical excision remains the main treatment option especially for patients with severe overgrowth. Few studies have compared different techniques with respect to recurrence rate or post-operative sequelae.

**Conclusion:** DIGO is a common clinical problem that often requires intervention. Non-surgical techniques can limit the occurrence of this unwanted affect, reduce the extent of plaque-induced gingival inflammation and reduce the rate of recurrence. Wherever possible this management strategy should be adopted first. Surgical treatment is often the most reliable option and scalpel gingivectomy remains the treatment of choice. Further investigations are required to develop appropriate management strategies to prevent recurrence of DIGO.

Key words: gingival overgrowth; gingivectomy; lasers; management; non-surgical treatment; systemic antibiotics

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Gingival overgrowth is well recognized unwanted effect associated with three major drugs/drug groups – phenytoin, ciclosporin and the calcium channel blockers. The prevalence of this unwanted effect varies between drugs, and a variety of risk factors have been identified in relation to the expression of drug-induced gingival overgrowth (DIGO) (Seymour et al. 2000). Severe gingival overgrowth is often disfiguring and can interfere with both speech and mastication. Despite our greater understanding of the pathogenesis of DIGO, its treatment still remains a challenge for the Periodontist. The problem is compounded by the high recurrence rate arising from chronic usage of the listed medications and persistence of other risk factors. In this review, we consider different treatment options that have been explored in the management of DIGO. Such management strategies can most simply be categorized as either non-surgical or surgical approaches.

## Non-Surgical Approaches

The primary aim of non-surgical approaches is to reduce the inflammatory component in the gingival tissues and thereby avoid the need for surgery (Somacarrera et al. 1997). A variety of non-surgical approaches have been proposed. Ideally preventative programmes should be instituted before the initiation of drug therapies implicated in DIGO (Modeer & Dahllof 1987). However, for prospective transplant patients, this is often impractical as such patients are frequently too unwell for such measures to be instituted. Despite this reservation, improving the patient's standard of self-maintained oral hygiene in the absence of other therapeutic measures can influence the development of gingival overgrowth. Gingival enlargement may regress with time in patients undergoing a vigorous oral hygiene programme (Montebugnoli et al. 2000).

The nature of the relationship between plaque and the expression of gingival overgrowth is unclear, and, controversy exists as to whether plaque accumulation is the cause of the gingival changes or the consequence of it. The effect of improved oral hygiene on the development of ciclosporin-induced gingival overgrowth has been investigated in a 6-month longitudinal study (Seymour & Smith 1991). Significant gingival overgrowth changes were observed in two groups of patients post-transplant. One group received oral hygiene therapy while the second

acted as a control. In the 6-month post-transplant observation period the magnitude of change in the oral hygiene group was less marked than in the control. Oral hygiene therapy, while of some benefit to the patients, failed to completely prevent the development of overgrowth.

Individual case reports have shown that meticulous self-administered oral hygiene, alongside professionally delivered oral hygiene and scaling and root planing can result in complete resolution of both ciclosporin (Ciantar 1996) and nifedipine-induced gingival overgrowth (Hancock & Swan 1992). However, it should be emphasized that these were only case reports and lacked controls. They do help to illustrate what can be achieved in certain patients by non-surgical means.

There is no doubt that patients at risk from, or who have developed drug-induced gingival overgrowth will benefit from effective oral hygiene measures, professional tooth cleaning, scaling and root surface instrumentation. Such treatment, in the presence of good plaque control will reduce the inflammatory component in the gingival tissues (Kantarci et al. 1999). For some patients these measures alone could reduce the gingival overgrowth to acceptable levels, for others, it could make surgical correction easier. Local environmental factors that enhance plaque accumulation such as faulty restorations, broken teeth or carious lesions should be eliminated and any fixed or removable prostheses should be designed to minimize plaque retention. We would advocate such a course of treatment in the first instance, unless the overgrowth was severe enough to impact upon eating, tooth brushing or appearance.

### Antiseptic Mouthwashes

Adjunctive chemical plaque removal has also been used in the management of DIGO. Animal studies have shown that regular application of a chlorhexidine solution to rats medicated with ciclosporin resulted in significantly less overgrowth than in control animals (Pilatti & Sampaio 1997). In humans chlorhexidine has, to date, only been evaluated in the management of phenytoin-induced gingival overgrowth, when regular use of this mouthwash helps to reduce the recurrence rate after surgery (O'Neil & Figures 1982). However, the unwanted effects of chlorhexidine of bacterial resistance and taste disturbance limit its long-term use. Other antiseptic mouthwashes have not been investigated in either the prevention of DIGO or reducing the rate of recurrence after surgery.

### Systemic Antibiotics

Short courses of azithromycin and metronidazole have been evaluated in the management of DIGO in organ transplant patients. However, the results of these studies are conflicting. There is evidence to suggest that a combination of oral hygiene reinforcement and systemic antibiotics may be beneficial in the management of DIGO (Glaude & Snyder 1990).

Complete remission of ciclosporin-induced gingival overgrowth has been reported in four renal transplant patients after a 7-day course of metronidazole (Wong et al. 1994). No details were provided of the patient's periodontal condition before medication with metronidazole and the small number of patients and lack of a control group somewhat limits the significance of these findings. Furthermore, in a larger study of 13 children, no improvement in overgrowth were seen at the end of a 3-month period (Aufricht et al. 1997). In addition, metronidazole is known to reduce the hepatic metabolism of ciclosporin leading to the potential risk of nephrotoxicity (Herzig & Johnson 1999). Benefits of metronidazole on the gingival tissues may have resulted simply from a change in the subgingival biofilm and an associated reduction in tissue inflammation.

Azithromycin has also been evaluated in the management of ciclosporin-induced gingival overgrowth. A review of clinical trials suggest that there are some benefits associated with the use of systemic azithromycin in the management of gingival overgrowth (Strachan et al. 2003) and that systemic administration of the drug appears more effective in reducing overgrowth than a local delivery preparation (Nafar et al. 2003). Azithromycin appears to be more effective than metronidazole in the management of this unwanted effect (Chand et al. 2004). There are two suggested mechanisms by which azithromycin may act in this context. Firstly by reducing concomitant bacterial infection and hence inflammation (Mesa et al. 2003), or secondly by increasing the phagocytic activity of gingival fibroblasts, thereby reversing the ability of ciclosporin to decreases collagen degradation (Paik et al. 2004). This second phenomena has only been demonstrated in rats.

The benefits of azithromycin or metronidazole in the management of DIGO remain to be determined in a series of well constructed RCTs. Most studies to date have used small numbers of patients, and appropriate controls have not always been employed. All studies have used short-term courses, which may have brought about some reduction in overgrowth, however, as DIGO is a recurrent and continuous problem, there are concerns regarding the use of repeated doses of antibiotics in the long-term management of this unwanted effect, especially in immunosuppressed patients.

### Other Agents

Phenytoin has been shown to inhibit folic acid metabolism although the mechanism by which this occurs is uncertain (Vogel 1977). There is some evidence that a folic acid mouthwash (1 mg/ml) may be efficacious in reducing the recurrence of phenytoin-induced gingival overgrowth and that a mouthwash is more effective than systemic administration (Poppell et al. 1991). It has been suggested that topical folate may reduce gingival inflammation by binding to the plaque-derived endotoxins. This action may, in turn, reduce gingival overgrowth. It has also been shown that patients with a low baseline plasma and red blood cell folate levels show a greater gingival response to topical folic acid than patients with normal levels (Drew et al. 1987).

### Change in Medication

One obvious solution in the management of DIGO is to change medication. For many years, this was not an option for ciclosporin. However, with the advent of new immunosuppressant (e.g. tacrolimus) alternatives are now available. The prevalence and severity of DIGO in adult transplant patient immunosuppressed with tacrolimus has been shown to be approximately half that of ciclosporin, however, like ciclosporin concomitant use of calcium channel blockers increases both severity and prevalence of DIGO (Ellis et al. 2004). While it may be possible to alter immunosuppressant regimen, a high proportion of organ transplant recipients

require medication with a calcium channel blocker in order to ameliorate the nephrotoxicity of ciclosporin or tacrolimus (Freehally et al. 1987). Persistence of gingival overgrowth after a change from ciclosporin to tacrolimus may at least in part be due to the patients ongoing medication with calcium channel blockers. Nonetheless, it has been shown that switching from ciclosporin to tacrolimus does reduce the severity of overgrowth and the need for surgical intervention (Hernandez et al. 2003). Although such a change in medication may improve the gingival tissues, it does not necessarily lead to the complete resolution of the overgrowth (Ellis et al. 2004). Reduction in gingival overgrowth has been reported where a different calcium channel blocker, such as verapamil has been substituted for nifedipine (Lederman et al. 1984), but more usually where substitution is made by a structurally different antihypertensive drug, such as the angiotensin-converting enzyme inhibitor, enalapril (Puolijoki et al. 1988), the β-blocking drug, atenolol (Mohapatra et al. 1991, Bhatia 1992, James & Linden 1992), or thiazide diuretics (Nishikawa et al. 1991, Ellis et al. 1993, Seymour et al. 1994). On some occasions, where ciclosporin substitution is inappropriate, a reduction in gingival overgrowth has been reported coinciding with a reduction of calcium channel blocker dosage (Bezan 1987, Smith 1993).

Phenytoin usage is now declining, partly due to its adverse effect profile and also the introduction of new antiepileptics. However, changing antiepileptic medication can be a challenge, and a gradual staged approach is required. This may take 2–3 months during which time serum levels of the antiepileptics requires monitoring along with the frequency and severity of seizures occurrence. Carbamazepine, ethosuximide and sodium valproate are alternatives to phenytoin which have been shown not to cause DIGO (Seymour et al. 1985).

For the calcium channel blockers, there is a greater range of alternative medications which achieve the same therapeutic goals. Prevalence and severity of overgrowth has been shown to be very different even with drugs of a similar chemical structure. For example nifedipine and amlodipine are both dihydropyridines and yet amlodipine has a prevalence of severe gingival overgrowth of half that of nifedipine (3.3% compared with 6.3%) (Ellis et al. 1999). Change in medication should only be considered for those patients where the new medication can offer some advantage for control of their hypertension, who present with clinically significant overgrowth and are at high risk from either corrective surgery or recurrence after gingvectomy. Reduction in the size of the gingival overgrowth has been reported within a week of drug withdrawal (Raman et al. 1988), and may lead to full resolution. If such a strategy is considered then the dentist must liaise with the patient's physician to review their current medication. All drugs have unwanted effects and the morbidity of gingival overgrowth needs to be compared with other possible unwanted effects arising from alternative medication.

### Surgical Management of DIGO

Although a variety of non-surgical measures have been shown to be of some value in the management of DIGO, surgical correction of gingival overgrowth is still the most frequent treatment. Such treatment is only advocated when overgrowth is severe. The use of clinical indices such as the gingival overgrowth index (Seymour et al. 1985) in research have suggested that surgical intervention is warranted when scores in excess of 30% are apparent (Thomason & Seymour 1990). However, in the day-to-day management of individual patients it is perhaps more important to consider the impact that gingival changes may have on the patients quality of life or their ability to maintain a healthy periodontium. From the patient's prospective, surgical correction of DIGO should result in little or no post-operative pain or sequelae, good aesthetics and a reduced risk of recurrence. Currently, the surgical management of DIGO includes the scalpel gingivectomy, overgrowth flap surgery, electrosurgery and laser excision.

### Scalpel Gingivectomy

The surgical treatment of choice is the gingivectomy, which was first advocated for drug-induced gingival overgrowth in 1941 (Thompson & Gillespie 1941). The soft tissue wall of the pocket is excised (Wang & Greenwell 2001). As there is, in nearly all circumstances, adequate attached gingiva, there is little fear of creating mucogingival problems with this technique. Conventionally the excess tissue is released by means of a long bevel incision which should ideally allow the complete removal of pocket tissue as part of the excised tissue mass, particularly in the inter-dental region. If the tissue is greatly thickened in the horizontal plane, a shallower initial incision may be required to gain access to the inter-dental area, followed by a separate re-contouring of the remaining tissue to reduce its bucco-lingual width, if necessary. With this approach the increased bulk of the tissue can be removed, the soft tissue pockets are eliminated and the crowns of the teeth exposed. This procedure improves access to any faulty restorations or calculus deposits, facilitating their elimination. The procedure is used extensively and the technique is straight-forward, accurate and causes minimal damage to the surrounding tissues. As it may be regarded as the ''standard treatment'', it is often compared with other techniques, however, there are few studies on recurrence rates, patient satisfaction with aesthetics and incidence of post-operative complications after such surgery. Peri-operative haemorrhage is the main disadvantage of scalpel excision, and this can be significant in highly vascularized and inflamed overgrown gingival tissues (Liboon et al. 1997).

Aesthetic outcomes have also been poorly evaluated after scalpel gingivectomy and again the only evidence comes from a comparative study (Pilloni et al. 1998). Patients with overgrowth were treated by either flap surgery or gingivectomy. Those treated by the latter method appeared to have a ''smoother'' gingival surface than when treated by a flap procedure. Numbers in this study were small and long-term benefits need to be considered. Further work in this area is required.

### Electrosurgery

Electrosurgery techniques have been used in dentistry for the past 70 years. Although such techniques produce adequate haemostasis, they have the disadvantage of causing a surrounding zone of thermal necrosis, which may impede wound healing. Reports in the literature have confirmed delayed healing of electrosurgery wounds when compared with scalpel wound healing (Liboon et al. 1997). This is probably due to the production and accumulation of

excessive latent heat, which can be significant if electrosurgery is performed inappropriately. The amount of latent heat produced is dependant upon instrumentation variables, such as type of waveform, size of cutting electrode, time required for incision and the energy produced at operating site (Krejci et al. 1987). Nevertheless, surgical intervention using conventional means (scalpel) may sometimes be technically difficult and/or impractical for example in children or mentally handicapped, or in patients suffering from impaired haemostasis. In these situations the use of electrosurgery may be advantageous (Walker et al. 1980).

### Laser Gingivectomy

The dental laser may be another useful alternative treatment to conventional gingivectomy techniques. The use of laser surgery to remove excess gingival tissue has been described by a number of authors (Barak & Kaplan 1988, Gold 1991, Hattler et al. 1992, Roed-Petersen 1993). Lasers have remarkable cutting ability and they also generate a coagulated tissue layer along the wall of the laser incision which promotes healing (Goharkhay et al. 1999). Other advantages of the use of laser in correcting DIGO include a relative bloodless operative and post-operative field, greater accuracy in making incisions, sterilization of the operating field, minimal swelling and scarring, vaporization and cutting with much less post-operative pain (Barak & Kaplan 1988, Roed-Petersen 1993, Mavrogiannis et al. 2004). The haemostasis provided by the laser may also avoid the need for a periodontal dressing (Russo 1997). Lasers can also be used for re-countouring the gingiva, for tissue welding, and to minimize the need for sutures. The laser gingivectomy may be particularly useful in patients on anticoagulant therapy or for whom problems with haemostasis are anticipated.

There are now many different types of lasers available to the Periodontist. The ND:YAG laser has been used for a variety of intaoral soft tissue procedures and can be used without anaesthesia (White et al. 1991). The $CO_2$ laser has been used for the removal of phenytoin-induced gingival overgrowth, and has been reported to have all the previously mentioned advantages of lasers together with minimal post-operative discomfort and prompt healing of the gingival tissues (Pick et al. 1985).

Comparison of laser to scalpel excision in the management of DIGO using a split-mouth crossover design study demonstrated a significantly lower rate of recurrence for laser gingivectomy over a 6-month follow-up period (Mavrogiannis et al. 2006). The study employed the diode laser at a wavelength of 810 nm. Post-operative pain scores were similar for the two treatments. The laser gingivectomy was also preferred by the patients.

Lasers do have advantages in the management of DIGO, but they are expensive and long-term benefits of laser gingivectomy need to be established.

In a comparative study scalpel, electrosurgery, and $CO_2$ laser were evaluated for mucosal incisions and excisions (Liboon et al. 1997). The scalpel was quicker to use for both incision and excision, followed by electrosurgery and the $CO_2$ laser. There is also a significant cost element to be considered in addition to the advantage of the scalpel over other techniques.

### Flap Surgery

The recurrence rate after various surgical techniques has only recently been evaluated (Mavrogiannis et al. 2006). Using a split mouth design, organ transplant patients with clinically significant gingival overgrowth were treated with both flap surgery and scalpel gingivectomy. All patients were followed up for a period of 6 months. There was no difference between the treatments with respect to recurrence of the gingival overgrowth. Patients after flap surgery reported more pain than after gingivectomy. Flap surgery may be complicated by excessive gingival enlargement, especially in the inter-proximal space. It would seem to be more suited for those cases of mild to moderate overgrowth associated with both bone and attachment loss.

When gingival overgrowth is extensive, then it may be better to manage its removal under general anaesthesia as this allows all the areas to be addressed at one time, but in most cases surgery can be managed under local anaesthesia. Experience would suggest that a more profound level of local anaesthesia and control of bleeding is achieved by the use of local anaesthetic solutions containing adrenaline. This may present a potential problem in cardiac transplant patients which needs to be addressed. As a consequence of the transplantation procedure, the new heart is no longer affected by vagal control and the heart rate in these patients appears to be sensitive to exogenous catecholamines to a larger extent than patients with a normally innervated heart.

A rapid increase in heart rate may be observed in some patients following the use of adrenaline containing local anaesthetic solutions, especially if the solution is inadvertently injected into a blood vessel. Fortunately, the induced tachycardia is usually of short duration, as adrenaline is rapidly metabolized. At present, and until firm evidence regarding the specific effects of adrenaline containing local anaesthetic solution in cardiac transplant patients are known, the patient's pulse rate and blood pressure should be monitored throughout the surgical procedure (Meechan et al. 2002).

### Conclusion

In this review we have evaluated a variety of methods used in the management of DIGO. There are obvious benefits arising from subjecting all patients on the listed drugs to a course of non-surgical management. The aim of such treatment is to reduce the inflammatory components in the gingival tissues and hopefully reduce the overgrowth to more aesthetically acceptable or manageable levels. Ideally, all patients about to be medicated with ciclosporin, phenytoin or a calcium channel blocker, should go through a full periodontal assessment and any disease presented treated appropriately. Unfortunately, for many of these patients this is impractical and such patients often present to the Periodontologist with existing gingival overgrowth. For many patients, surgery is the main option and the scalpel gingivectomy is still the treatment of choice. Preventing recurrence of overgrowth is a significant challenge to the Periodontist and members of the dental team. Change in medication is an option, but there may be medical or financial reasons why this cannot be expedited.

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