SUBGINGIVAL DELIVERY OF THERAPEUTIC AGENTS IN THE TREATMENT OF PERIODONTAL DISEASES

W. Aubrey Soskolne

Department of Periodontics, Hebrew University-Hadassah Faculty of Dental Medicine, Founded by the Alpha Omega Fraternity, P.O. Box 12272, Jerusalem, Israel

ABSTRACT: This article reviews the current status of controlled local delivery of antibacterial agents in the treatment of periodontitis. The principle of local intrapocket delivery of antibacterial agents and their delivery are discussed. The dosage forms include fibers, film/slabs, and injectable systems, some of which are degradable, while others are not and need to be removed at the termination of the treatment. The antibacterial agents used cover a range of antibiotics as well as antiseptics, and the composition of the delivery systems, their reported use, and the clinical results are summarized. The use of these systems in clinical practice is relatively recent, and therefore their application and integration into the dental office are not yet clearly defined. Clinical applications that have been tested are critically reviewed, and clinical situations in which controlled delivery of antibacterial agents may prove to be clinically useful are suggested for scientific evaluation.

Key words. Subgingival drug delivery, controlled release, antibacterial agents, periodontitis.

Introduction

The inflammatory periodontal diseases are widely accepted as being caused by bacteria associated with dental plaque. However, the nature of the periodontal disease resulting from dental plaque appears to depend to a large extent on the interaction among the bacterial agent, the environment, and the response of the host's defense mechanisms to the bacterial assault (Fig. 1).

Traditionally, periodontal disease therapy has been directed at altering the periodontal environment to one which is less conducive to the retention of bacterial plaque in the vicinity of the gingival tissues, in particular, the marginal attachment apparatus. Classic therapeutic regimes to achieve this aim would include some or all of the following procedures: instruction in oral hygiene techniques to achieve an adequate level of oral cleanliness, scaling, correction of inadequate restorative dentistry, root planing, and the surgical elimination of pockets or other anatomical defects which aid bacterial retention and interfere with plaque removal. With the increasing awareness of the bacterial etiology of periodontal disease (Socransky, 1970; Slots, 1979; Moore *et al.*, 1983) and in particular the hypothesis that specific bacteria are involved (Loesche *et al.*, 1985), a more direct approach using antibacterial agents has become an integral part of the therapeutic armamentarium. Influencing the third factor in the triad, the host's immune regulatory system, is another approach that is being tested to alter the disease progression. To date, the use of controlled local drug delivery to treat periodontal disease has concentrated on the use of antibacterial agents; therefore, this review will be largely limited to these agents.

The delivery of antibacterial agents to the disease site has been carried out by systemic or topical administration. There is evidence that systemic administration of antibiotics (Genco, 1981; Van Palenstein Helderman, 1986) is effective in altering the progression of certain forms of periodontitis. However, the routine use of antibiotics over long periods of time is contra-indicated because of the development of resistant bacterial strains and possible systemic side-effects. Topical administration of antibacterial agents in the form of mouthwashes has been shown to be effective in controlling supragingival plaque (Kornman, 1986). However, their access to the periodontal pocket and the subgingival flora is limited (Flotra, 1973; Pitcher *et al.*, 1980) and therefore ineffective in controlling disease progression. Local delivery of chemotherapeutic agents into the pockets *via* a syringe or irrigating device has been shown to have an effect on the subgingival flora, but, clinically, it has not been effective in halting the progression of periodontal attachment loss (Greenstein, 1987, 1995) .The lack of clinical efficacy

is probably because of the short time the irrigating solution remains in contact with the pocket environment (Soskolne *et al.*, 1997). The recent development of sophisticated, subgingivally placed delivery systems has provided the possibility of maintaining effective, intrapocket, levels of antibacterial agents for extended periods of time. These systems have provided the profession with a new tool which, in clinical trials, has been shown to alter the subgingival flora and influence the healing of the marginal attachment apparatus.

Principle of Local Intrapocket Delivery of Antibacterial Drugs

The periodontal pocket provides a natural reservoir bathed by gingival crevicular fluid which is easily accessible for the insertion of a delivery device. The gingival crevicular fluid provides a leaching medium for the release of a drug from the solid dosage form and for its distribution throughout the pocket. These features, together with the fact that the periodontal diseases are localized to the immediate environment of the pocket, make the periodontal pocket a natural site for treatment with local sustained-release delivery systems.

The goal in using an intrapocket device for the delivery of an antibacterial agent is the achievement and maintenance of therapeutic levels of the drug for the required period of time.

Studies suggest that the critical period of exposure of the pocket to an antibacterial agent is in the 7-10 days' range. Studies using chlorhexidine (Soskolne *et al.*, 1983; Stabholz *et al.*, 1986) have shown that 3 days of exposure to the agent results in an immediate and marked change in the bacterial flora, which is maintained for 7 days; however, there is a rapid return to baseline levels by 14 days. When the exposure to chlorhexidine was increased to 9 days, the effect on the microbial flora was extended to 11 weeks and more. Similarly, in studies with tetracycline as the active agent (Goodson *et al.*, 1985), the authors found that 10 days of exposure provided a long-term effect which was not obtained with exposures of shorter duration.

Types of Devices That Have Been Tested

Intrapocket devices can be divided into two broad categories, depending on whether they are degradable. Non-degradable devices have the advantage that the therapist controls the removal of the device and therefore has greater control over the time of exposure of the pocket environment to the drug. The degradable devices have the great advantage of requiring the patient to pay only a single visit to the therapist for inserting the device. This minimizes patient visits and ensures compliance in that the patient does not have to return to have the device removed. A non-degradable device left *in situ* beyond its period of therapeutic efficacy is a potential hazard in that it could result in a foreign body response. Devices have been developed in three broad dosage forms: fibers, film/slabs, and injectable systems.

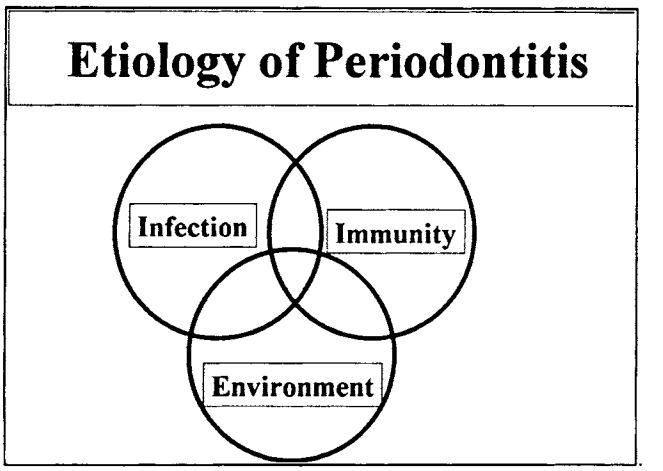

Figure. Diagrammatic representation of the triad of factors involved in the etiology of Inflammatory Periodontal Disease.

(1) Fibers

Fibers have been developed as a non-degradable dosage form only. The prototype for the use of fiber-like devices to deliver drugs to the periodontal pocket was first introduced by Goodson *et al.* (1983), using cellulose acetate dialysis tubing. Although this system was unable to sustain therapeutic levels of tetracycline hydrochloride (Goodson *et al.*, 1985), chlorhexidine gluconate (Coventry and Newman, 1982), or metronidazole (Wan Yusof *et al.*, 1984) for sufficient time to be clinically useful, it led to the development of a commercially available delivery system (Actisite®, Alza Corporation, Palo Alto, CA), based on a monolithic ethylene vinyl acetate fiber, that delivers tetracycline hydrochloride (Goodson *et al.*, 1983, 1985, 1991a,b,c; Tonetti *et al.*, 1990; Heijl *et al.*, 1991). Published data from two multicenter studies (Goodson *et al.*, 1991b; Newman *et al.*, 1994) show that the treatment of periodontal pockets with this system resulted in significant reductions in pocket probing depths and bleeding on probing and significant increases in attachment levels compared with the other treatment modalities tested.

Fibers are placed into the periodontal pocket in a manner similar to that used for a retraction cord prior to the taking of an impression of a crown preparation. A fiber can be placed around the circumference of the tooth to the depth of the pocket and folded back on itself repeatedly to fill the pocket completely. Its disadvantages are the time needed for fiber placement (from 7 to 10 min/tooth) (Goodson, 1994) and the need for use of either a periodontal pack or a cyanoacrylate glue to retain the device within the pocket for the duration of the

TABLE 1

Summary of Randomized Studies with Controlled-release Delivery Systems* as Adjuncts to Scaling and

Drug Released	Trade Name	Physical Form	Biodegradability	Reference	Study Design	Treatment Arms	(n)
Tetracycline	Actisite®	Fiber	non-degradable	Goodson *et al.* (1985)	Split-mouth	1. TCF+SRP	10
						2. TCF alone	10
						3. SRP alone	10
						4. Untreated	10
				Heijl *et al.* (1991)	Split-mouth	1. TCF+SRP	10
						2. TCF alone	10
						3. SRP alone	10
						4. Untreated	10
				Newman *et al.* (1994)	Split-mouth	1. TCF+SRP	113
						2. SRP alone	113
				Drisko *et al.* (1995)	Split-mouth (Multicenter)	1. TCF+SRP	122
						2. SRP only	122
						3. TCF alone	122
						4. TCF alone x2	122
Minocycline	Dentomycin® Periocline®	Ointment	Degradable	van Steenberghe *et al.* (1993)	Parallel arms (Multicenter)	1. Mino.+SRP	52
						2. Plac.+SRP	51
Chlorhexidine	Perio Chip®	Film	Degradable	Soskolne *et al.* (1996)	Split-mouth (Multicenter)	1. Chip+SRP	118
						2. SRP only	118

* The delivery systems mentioned in this Table are those known by the author to have approval by a regulatory authority somewhere in the world.

n = number of patients *per* treatment arm; SRP = scaling and root planing; PPD = probing pocket depth; BOP = bleeding on probing; TCF = tetracycline-Plac = placebo; Chip = chlorhexidine-containing Perio Chip; mths = months; wks = weeks; NA = not available; ND = no data; ? = significance not clear.

treatment. A fairly high risk of 23% has been reported for extrusion of these fibers from the pockets during the 10 days of treatment (Newman *et al.*, 1994). Because they are not degradable, they have the added disadvantage that the patient must make at least two visits to the therapist, one for insertion and one for removal of the device.

(2) Film/slabs

A far more widely used intrapocket delivery device has been the film or slab form. This dosage form has several advantageous physical properties for intrapocket use. The dimensions and shape of the film can be easily controlled to correspond to the dimensions of the pocket to be treated. It is easily and rapidly inserted into the pocket with minimal discomfort to the patient. It can be inserted to the base of the pocket and be totally submerged. If the thickness of the film does not exceed approximately 400 µm, and its physical properties provide it with sufficient adhesiveness, it will remain submerged without any noticeable interference to the patient's eating and oral hygiene habits.

Both degradable and non-degradable forms of films have been developed, and therefore the discussion will relate to these two forms under separate headings.

(a) Non-degradable films

The first descriptions of film- or slab-form intrapocket delivery devices appeared in 1982 (Addy *et al.*, 1982; Friedman and Golomb, 1982). Addy and co-workers (Addy *et al.*, 1982) described the use of slabs of methylmethacrylate for the intrapocket delivery of tetracycline, metronidazole, and chlorhexidine. A self-polymerizing mixture of the polymer, monomer, and the appropriate drug were cured, as sheets, under high pressure and then

Root Planing

Length of Study	Significant Reduction Compared w/ SRP Control: PPD	Significant Reduction Compared w/ SRP Control: BOP
12 mths	? (0.39 mm)	ND
2 mths	No (0.37 mm)	No
6 mths	Yes (0.73 mm)	Yes (13%)
12 mths	NA	No
12 wks	Yes (0.3 mm)	No
6 mths	Yes (0.33 mm @ 3 mths; 0.46 mm @ 6 mths)	Yes @ 3mths

containing Actisite fibers; Mino = Dentomycine minocycline-containing ointment;

cut into films of suitable sizes. Studies showed that the release of drugs from acrylic films measuring 10 x 1 x 0.5 mm was dependent on the nature of the drug and its concentration in the delivery device. Addy *et al.* (1982) described formulations which delivered, *in vitro*, therapeutic levels of all three drugs over a 14-day period. In later studies (Yeung *et al.*, 1983; Addy and Langeroudi, 1984; Addy *et al.*, 1988), they showed various degrees of clinical efficacy, but this system has not been developed for clinical use.

In the same year, an ethylcellulose film, cast from ethanol or chloroform solutions of the polymer, was described (Friedman and Golomb, 1982). The appropriate drug and plasticizing agent were incorporated into the solution prior to casting. The dried films (200-300 µm thick) were then cut into the required shapes. Films containing chlorhexidine (Friedman and Golomb, 1982; Soskolne *et al.*, 1983; Stabholz *et al.*, 1986, 1991), metronidazole (Golomb *et al.*, 1984), minocycline (Elkayam *et al.*, 1988), and tetracycline (Elkayam *et al.*, 1989; Stabholz *et al.*, 1989) have been developed and tested. The release of the therapeutic agent from these films is dependent on the solvent used, the presence of a plasticizer, the nature and concentration of the drug in the film, and the physical dimensions of the film. The most extensive studies have been carried out using films that release chlorhexidine. Pockets exposed to chlorhexidine for nine consecutive days after scaling and root planing had significantly better clinical results than controls for up to 11 weeks post-treatment (Stabholz *et al.*, 1986). The use of this formulation has also been shown to provide significantly better results than routine therapy in the maintenance of periodontal pockets over a two-year period (Stabholz *et al.*, 1991). A formulation releasing tetracycline over a seven-day period (Elkayam *et al.*, 1989) also produced significantly better results than scaling and root planing alone over 12 weeks (Stabholz *et al.*, 1989).

(b) Degradable devices

Many degradable devices in the form of a film have been tested experimentally. Resorbable hydoxypropylcellulose-based devices for the delivery of tetracycline and chlorhexidine (Noguchi *et al.*, 1984) and ofloxacin (Higashi *et al.*, 1990; Kimura *et al.*, 1991) have been tested clinically. The first report on a degradable intrapocket sustained-release delivery system was the study by Noguchi *et al.* (1984) using hydoxypropylcellulose films. In this study, a rapid release of the drugs from the film within 2 hrs was demonstrated *in vitro*, with maximum dissolution of the film occurring after 3 hrs. *In vivo*, retention of tetracycline in the pockets could be detected 24 hrs after insertion of the device, and significant clinical and microbiological advantages over the control group were described. Although this was a pioneering study in the development of a degradable system, the rapid degradation of the device and the short duration of drug exposure were distinct disadvantages. Using a modification of this system by incorporating slowly soluble methacrylic acid copolymer particles into the hydoxypropylcellulose films (Higashi *et al.*, 1990; Kimura *et al.*, 1991), investigators prolonged the release of the drug ofloxacin from the device such that 70% was released in the first 8 hrs *in vitro*. *In vivo* levels above 2 µg/mL of ofloxacin were maintained for 7 days after treatment with the device. Two applications of this device, one week apart, resulted in significant reductions in the number of spirochetes and motile organisms in the pockets, as identified by darkfield microscopy. Similar shifts were not seen in the placebo-treated or untreated control pockets. Re-treatment of these same pockets with films after scaling and root planing showed further reductions in the pathological flora, but the changes

TABLE 2

Summary of Randomized Control Studies Comparing the Use of Controlled-release Delivery Systems*

Drug Released	Trade Name	Physical Form	Biodegradability	Reference	Study Design	Treatment Arms	(n)
Metronidazole	Elyzol®	Gel	degradable	Pedrazzoli *et al.* (1992)	Split-mouth	1. Metro. only 2. SRP only	24 24
				Ainamo *et al.* (1992)	Split-mouth (Multicenter)	1. Metro. only 2. SRP only	206 206
				Stelzel & Flores-de-Jacoby (1996)	Split-mouth	1. Metro. only 2. SRP only	30 30
Tetracycline	Actisite®	Fiber	non-degradable	Goodson *et al.* (1991)	Split-mouth (Multicenter)	1. TCF only 2. SRP only 3. Plac. Fiber 4. Untreated	113 113 113 113

* The delivery systems mentioned in this Table are those known by the author to have approval by a regulatory authority somewhere in the world.

n = number of patients *per* treatment arm; SRP = scaling and root planing; PPD = probing pocket depth; BOP = bleeding on probing; TCF = tetracycline-placebo; mths = months.

were not significantly different from controls.

Deasy *et al.* (1989) studied the effects of tetracycline hydrochloride and metronidazole released from 0.5-mm-thick films formed by the compacting of a 15-mg mixture of the drug and polyhydroxybutyric acid in an infrared press. The *in vitro* release rate of the drug depended on the drug load and the drug used. *In vitro*, the films, although intact after 5 days in a buffer solution, became progressively more fragile, with loss of mechanical strength. Clinically, films containing 25% of either drug were placed into pockets at four-day intervals for 16 days and their effects compared with untreated control pockets. In general, improvement in the clinical and microbiological parameters measured were noted over the 16 days of treatment, with a return to control levels on cessation of treatment. No information was provided on the *in vivo* survival time of the film.

The biodegradable polyester poly(ϵ-caprolactone) has been tested, *in vitro*, as a matrix for sustained-release delivery, both as a fiber for the delivery of tetracycline (Dunn *et al.*, 1983; Goodson *et al.*, 1983) and as a film for the delivery of chlorhexidine (Medlicott *et al.*, 1992). Clinically, the fibers released their tetracycline content very rapidly, with a half-life of 11 hrs (Goodson *et al.*, 1983). No clinical studies could be found in which the films containing chlorhexidine had been tested in periodontal pockets.

Different types of collagen-based membranes have also been tested for local drug delivery. A degradable controlled-release device based on a formaldehyde-cross-inked Byco protein matrix containing chlorhexidine has been described by Steinberg *et al.* (1990). Byco protein is a hydrolyzed gelatin of bovine origin. The release of chlorhexidine from this device and its dissolution *in vitro* were shown to be dependent on the degree of protein cross-linking. The nature of the chlorhexidine salt used also affected the release rate. Based on this study, the Perio Chip® (Perio Products Ltd., Jerusalem, Israel) has been developed for the controlled subgingival delivery of chlorhexidine. This is a 5 mm x 4 mm x 0.3 mm film containing 2.5 mg of chlorhexidine gluconate. When the chip is placed subgingivally, it releases its chlorhexidine content and degrades, maintaining chlorhexidine gingival crevicular fluid levels of ≥ 100 ppm over a 7-10-day period. Recently, a split-mouth, multicenter, clinical trial was carried out on 118 patients with moderate periodontitis to examine the efficacy of the Perio Chip when used as an adjunct to scaling and root planing for the

Instead of Scaling and Root Planing

Length of Study	Significant Reduction Compared w/ SRP Control: PPD	Significant Reduction Compared w/ SRP Control: BOP
6 mths	No (Metro = 1.14 mm; SRP = 0.88 mm)	No (Metro = 16%; SRP = 13%)
6 mths	No (Metro = 1.3 mm; SRP = 1.5 mm)	No (Metro = 32%; SRP = 39%)
6 mths	No (Metro = 1.3 mm; SRP = 1.5 mm)	No (Metro = 32%; SRP = 39%)
60 days	Yes (TCF = 1.05 mm; SRP = 0.74 mm)	Yes (TCF = 45.8%; SRP = 19.7%)

containing Actisite fibers; Metro = Elyzol metronidazole-containing gel; Plac =

treatment of periodontal pockets. The results clearly demonstrated a significantly greater reduction in probing pocket depths in the Perio Chip-treated pockets than in the pockets treated with scaling and root planing only, both at 3 (diff. = 0.28 mm, $p \leq 0.01$) and 6 months (diff. = 0.46 mm, $p \leq 0.01$) post-treatment. The gain in attachment was also greater in the Perio Chip-treated pockets, reaching significant levels in deep pockets at both 3 (diff. = 0.51 mm, $p \leq 0.01$) and 6 (diff. = 0.65 mm, $p \leq 0.001$) months (Soskolne *et al.*, 1997).

Using a 2% glutaraldehyde cross-linked atelocollagen, Minabe *et al.* (1989a) developed a degradable delivery system to deliver tetracycline. Intrapocket levels of tetracycline greater than 8 µg/mL were reported 10 days after insertion of the film into pockets. Two clinical studies were carried out to test the efficacy of the system. The effects of 4 applications of these films to pockets with probing depths of 4 mm or more, at one-week intervals, were compared with the effects of placebo films. The tetracycline-containing films resulted in a significant improvement in bleeding on probing and a reduction in the percentage of spirochetes and black-pigmented *Bacteroides* species one and four weeks after the last application. The placebo-treated pockets showed no change (Minabe *et al.*, 1989c). A seven-week follow-up of pockets treated with a single application showed significant improvements in plaque index, gingival index, pocket depth, and bleeding on probing, at various time points, compared with the baseline measurements and with the results obtained with placebo films (Minabe *et al.*, 1989b). The device was reported to dissolve in the pocket in about 1 week.

A collagen film containing 5% metronidazole was evaluated as an adjunct to scaling and root planing in a three-month clinical trial (Hitzig *et al.*, 1994). Other than the dimensions of the device (5 mm x 5 mm), no information was provided about the nature of the matrix, the release kinetics of the device, or its degradability. These authors reported a significant adjunctive effect for the local metronidazole therapy on gingival index, bleeding on probing, probing pocket depth, and attachment level measurements, compared with scaling and root planing alone.

(3) Injectable Systems

The possibility of injecting a delivery system into the pocket has a number of advantages. It is a relatively simple procedure with little or no discomfort associated with the insertion of the dose form. The initial fluid nature of the formulations, which is necessary for its use with a syringe, would theoretically allow the formulation to gain access to the entire pocket. In order to be retained in the pocket, the formulation would need to undergo a change into a sticky semi-solid or solid phase so as to prevent it from being washed out of the pocket by the gingival crevicular fluid (GCF) flow. All injectable systems can be considered as degradable.

Different systems have been described in the literature, two of which are commercially available. A 2% minocycline-containing ointment (Dentomycin®, Cyanamid International, Lederle Division, Wayne, NJ, and SunStar, Osaka, Japan) does not appear to have any sustained-release properties. In a study using this ointment as an adjunct to scaling and root planing, van Steenberghe *et al.* (1993) made 4 applications of the ointment into the pocket at two-week intervals, starting immediately after completion of the scaling and root planing. This resulted in a significant, 0.3-mm greater improvement in pocket depth than did the placebo gel at 12 weeks post-scaling and root planing and 6 weeks after the last application of the gel. The changes in the bleeding index and probing attachment levels were not significantly different. In the minocycline-treated pockets, there was a significant increase in the number of pockets, with undetectable levels of *P. gingivalis* and *P. intermedius* compared with the controls, throughout the study. The effect of minocycline on *A. actinomycetemcomitans* became significant only after the third application of the oint-

ment and remained significant for 6 weeks.

A dosage form for the sustained-release subgingival delivery of minocycline hydrochloride has been described in the literature (Okuda *et al.*, 1992; Jones *et al.*, 1994). This dosage form consists of the antibiotic microencapsulated in a biodegradable polymer, poly(glycolide-co-dl-lactide), that is delivered subgingivally in powder form by means of a syringe. In these studies, some significant changes in the subgingival microflora were noted in the minocycline-treated pockets when compared with control-treated pockets. In one study, significant reductions in black-pigmented *Bacteroides* species for up to 3 months were noted (Okuda *et al.*, 1992). In a later study, significant reductions from baseline levels of *Porphyromonas gingivalis* were noted in pockets one month post-treatment with minocycline alone and minocycline as an adjunct to scaling and root planing (Jones *et al.*, 1994). Scaling and root planing supplemented with minocycline also resulted in significantly greater reductions in probing pocket depths than scaling and root planing alone, or no treatment, at one and three months post-treatment (Jones *et al.*, 1994).

The second commercially available system (Elyzol®, Dumex, Copenhagen, Denmark) is a formulation consisting of a water-free mixture of melted glycerol monooleate and metronidazole benzoate to which a triglyceride, sesame oil, has been added to lower the melting point in order to improve the flow properties of the gel in the syringe. When the mixture comes into contact with water, it sets in a liquid crystalline state. The formulation contains 25% metronidazole as 40% wt/wt metronidazole benzoate. The solubility of the drug and its concentration in the formulation influence its release profile. The matrix is degraded by neutrophil and bacterial lipases present in the GCF (Norling *et al.*, 1992). Concentrations of 103-1297 µg/mL of metronidazole were recorded in inflamed pockets treated with this device, with effective doses being maintained for 24-36 hr (Stoltze, 1992). Systemic levels of between 0.2 and 1.3 µg/mL of metronidazole were measured after the administration of 29-103 mg of the gel (Stoltze and Stellfeld, 1992). The recommended therapy is two separate applications in each pocket, one week apart (Klinge *et al.*, 1992). The results of clinical studies comparing this therapeutic approach alone with scaling and root planing indicate that the metronidazole gel results in a reduction in probing pocket depth and bleeding on probing which is not significantly different from the results obtained with scaling and root planing (Ainamo *et al.*, 1992; Pedrazzoli *et al.*, 1992; Stelzel and Flores-de-Jacoby, 1996).

Human clinical trials where an injectable polymer matrix formulation was used, containing 10% doxycycline hyclate as the active ingredient, have been reported in abstract form only (Polson *et al.*, 1995). These authors indicate that subgingival treatment with this formulation improved and maintained periodontal health better than their control treatments.

Clinical Applications of Subgingival Sustained-release Delivery Formulations

Although research on the development and clinical testing of subgingivally placed dosage forms for the treatment of periodontitis has been in progress for almost 20 years, it is only recently that these devices have been made generally available to the dental community as part of their armamentarium for treating patients. It is therefore only natural that clinical experience in using these devices is just beginning to tell us in what situations these devices will prove to be useful and how they should be integrated into daily clinical practice.

The most widely studied application of subgingivally placed dosage forms is their use as an adjunct to scaling and root planing. This application is generally considered as primary therapy for patients presenting with untreated periodontitis. In the majority of studies which have been carried out on pockets with probing pocket depths (PPD) $\geq$ 5 mm, an adjunctive effect has been demonstrated when compared with scaling and root planing alone (Goodson *et al.*, 1985, 1991b; Heijl *et al.*, 1991; van Steenberghe *et al.*, 1993; Drisko *et al.*, 1995; Soskolne *et al.*, 1996). The mean improvement in PPD resulting from the adjunctive effect compared with the scaling and root planing (SRP) controls ranged between 0.28 mm and 0.46 mm over a clinical follow-up time of 2-12 months (for summary, see Table 1).

A second application that has been studied is the use of subgingivally placed dosage forms as an alternative to SRP (for summary, see Table 2). This therapeutic approach has been used in studies with the injectable gel formulation with metronidazole (Elyzol) as the effective agent (Ainamo *et al.*, 1992; Klinge *et al.*, 1992; Pedrazzoli *et al.*, 1992; Stelzel and Flores-de-Jacoby, 1996). This approach has several problems associated with it, since it challenges the routine, proven, and highly effective treatment of SRP. To this purpose, it has to be shown either to be significantly better than SRP in affecting periodontitis or to be "at least as good as" SRP. This effect would have to be over both the short as well as the long term, with definite application advantages. None of the studies designed to compare the two therapies has been able to show that Elyzol produces significantly better reductions in PPD than SRP. A recent study, published only in abstract form, examines whether Elyzol therapy is "at least as good as" SRP and concludes that Elyzol is 90% as good as SRP at the 85% confidence level or 82% as good at the 95% confidence level (Pihlstrom *et al.*, 1995). This approach was also explored in a multicenter study with tetracycline fibers (Goodson *et al.*, 1991b).

These authors showed greater pocket depth reduction, attachment level gain, and reduction in bleeding on probing with the fibers than was obtained with SRP alone. However, they go to great lengths to try to explain this result as extraordinary, due to the minimal response obtained in the SRP-only group, and stress that these results should not be interpreted as detracting from the importance of SRP. It would seem that substantially more evidence is required, especially over the long term, before the dental profession could be persuaded to discard the established therapy of scaling and root planing and leave subgingival deposits of calculus for these new treatment forms.

The use of subgingivally placed dosage forms as part of maintenance therapy for adult periodontits patients on recall after definitive therapy is a third application. There are two different clinical approaches that have been tested. Stabholz *et al.* (1991) reported a split-mouth study which compared the use of controlled local chlorhexidine delivery with routine maintenance therapy of pockets with PPD ≥ 5 mm, at three-month intervals, over a two-year period. This approach did not attempt to select pockets according to their clinical behavior post-definitive treatment. Their results indicate that the use of controlled subgingival chlorhexidine release provides significantly greater improvements in both PPD and probing attachment levels (PAL) over the entire study period. The other, slightly different, approach compares the effect of subgingival controlled release of antibacterial agents to SRP in pockets which were identified as bleeding on probing or as unresponsive to previous therapy. Newman *et al.* (1994) used maintenance patients to compare the adjunctive effect of Actisite® fibers with SRP in pockets which were identified as being unresponsive to previous therapy. They found that the adjunctive use of tetracycline fibers resulted in a mean improvement advantage in PPD of 0.29 mm after 3 months and 0.73 mm after 6 months over SRP alone. In two recent abstracts (Garrett *et al.*, 1996; Killoy *et al.*, 1996), the effect of substituting subgingival controlled release of doxycycline hyclate and tetracycline hydrochloride for mechanical debridement in periodontal maintenance patients was examined. Pockets that bled on probing were selected for these studies. Garrett *et al.* (1996) showed that doxycycline delivered subgingivally in a bioresorbable polymer, at baseline and 4 months, produced significantly better PAL, PPD, and bleeding on probing (BOP) results than a placebo polymer over a six-month period. No comparison was made with routine maintenance therapy, however. Killoy *et al.* (1996) reported that the subgingival placement of tetracycline fibers either at baseline only, or at baseline and 6 months, also gave significantly better results in PPD, PAL, and BOP than routine mechanical maintenance therapy.

We recognize that our present ability to diagnose ongoing active periodontitis or to predict future disease activity is, at best, very poor. We use PPD as our most reliable predictor of future disease, and on that basis, after we have controlled the infection, we carry out definitive treatment at sites remaining over a certain PPD. It is assumed that the reason that deep pockets are more prone to further breakdown is that it is difficult to gain access to their deeper aspects for personal (Flotra, 1973; Pitcher *et al.*, 1980) and professional (Waerhaug, 1978; Fleischer *et al.*, 1989) cleaning. Definitive therapy is therefore usually directed at reducing PPD by the use of resective or regenerative surgical procedures. Soskolne *et al.* (1996)) have shown that the subgingival use of controlled-release chlorhexidine as an adjunct to scaling and root planing in pockets with PPD ≥ 5 mm reduces the number of pockets losing attachment by 50% over the six-month follow-up period. A similar~50% reduction in pockets losing attachment has been reported (Michalowicz *et al.*, 1995) when the controlled release of tetracycline was used subgingivally as an adjunct to scaling and root planing. This significant reduction in the percent of losing pockets suggests that it may be advantageous to our patients to have controlled delivery of antibacterial agents as an adjunct to initial therapy (which is aimed at infection control) in all pockets ≥ 5 mm, followed up with subgingival controlled-release anti-infective therapy, in pockets remaining ≥ 5 mm in PPD, at regular periodic maintenance visits. If increasing PPD (interpreted as loss in PAL) were used as the criterion for instituting surgical therapy, then controlled subgingival antibacterial therapy should reduce the sites needing surgery by 50%.

There are several clinical situations in which controlled delivery of antibacterial agents may prove to be clinically useful but for which no clinical studies are yet available. These include the treatment of furcation involvement, pericoronitis, and dry sockets. Another area of possible application is their use in periodontal surgery to reduce infection, particularly when guided tissue regenerative procedures are used. Their use in conjunction with anti-inflammatory agents to control periodontal disease and to stimulate bone regeneration may also prove to be a useful line of pursuit. The development of systems to be used in these clinical situations and testing their efficacy will provide a very fruitful line of research for years to come.

Conclusion

The controlled-release subgingival delivery of antibacterial agents for the treatment and control of periodontitis is a fast-growing field. Its clinical use is in its infancy, and results are promising. It seems that the nature of the antibacterial agent is of less importance than the length

of time that the subgingival environment needs to be exposed to the agent. The acceptance of controlled drug delivery in clinical practice will be heavily influenced by the ease of application of these systems and their economical viability. Among the directions that future studies will take are the use of drugs other than antibacterial agents to control the inflammatory process and the development of clinical protocols to make the clinical use of these drug delivery systems simple and economically viable.

Acknowledgment

The author wishes to acknowledge that he was involved in the development of one of the delivery systems (Perio Chip®) described in this review and in the clinical trials to test its efficacy. He continues to act as a consultant to the company, Perio Products Ltd., Jerusalem, Israel, which manufactures the Perio Chip®.

References

Addy M, Langeroudi M (1984). Comparison of the immediate effects on the sub-gingival microflora of acrylic strips containing 40% chlorhexidine, metronidazole or tetracycline. J *Clin Perio* 11:379-386.

Addy M, Rawle L, Handley R, Newman HN, Coventry JF (1982). The development and *in vitro* evaluation of acrylic resin strips and dialysis tubing for local drug delivery. J *Periodont* 53:693-699.

Addy M, Hassan H, Moran J, Wade W, Newcombe R (1988). Use of antimicrobial containing acrylic strips in the treatment of chronic periodontal disease. A three month follow-up study. J *Periodont* 59:557-564.

Ainamo J, Lie T, Ellingsen BH, Hansen BF, Johansson LA, Karring T, *et al.* (1992). Clinical responses to subgingival application of a metronidazole 25% gel compared to the effect of subgingival scaling in adult periodontitis. J *Clin Perio* 19:723-729.

Coventry J, Newman HN (1982). Experimental use of a slow release device employing chlorhexidine gluconate in areas of acute periodontal inflammation. J *Clin Perio* 9:129-133.

Deasy PB, Collins AEM, Maccarthy DJ, Russell RJ (1989). Use of strips containing tetracycline hydrochloride or metranidazole for the treatment of advanced periodontal disease. J *Pharm Pharmacol* 41:694-699.

Drisko CL, Cobb CM, Killoy WJ, Michalowitz BS, Pihlstrom BL, Lowenguth RA, *et al.* (1995). Evaluation of periodontal treatments using controlled-release tetracycline fibers: clinical response. J *Periodont* 66:692-699.

Dunn RL, Perkins BH, Goodson JM (1983). Controlled release of tetracycline from biodegradable fibres (abstract). J *Dent Res* 62:289.

Elkayam R, Friedman M, Stabholz A, Soskolne AW, Sela MN, Golub L (1988). Sustained release device containing minocycline for local treatment of periodontal disease. J *Control Rel* 7:231-236.

Elkayam R, Friedman M, Stabholz A, Soskolne AW, Azoury R (1989). Sustained release device of tetracycline for dental use, structure and kinetics of drug release *in vitro* and *in vivo*. *Proc Int Conf Pharm Tech* 2:346-354.

Fleischer HC, Mellonig JT, Brayer WK, Gray JL, Barnett JD (1989). Scaling and root planing in multirooted teeth. J *Periodont* 60:402-409.

Flotra L (1973). Different modes of chlorhexidine application and related local side effects. J *Periodont Res* 8(Suppl 12):41-44.

Friedman M, Golomb G (1982). New sustained release dosage form of chlorhexidine for dental use. J *Periodont Res* 17:323-328.

Garrett S, Polson AM, Stoller N, Bandt C, Killoy W, Hanes P, *et al.* (1996). Periodontal maintenance substituting 10% doxycycline hyclate delivered in a bioresorbable polymer (Atrigel) for mechanical debridement (abstract). J *Dent Res* 75(Spec Iss):159.

Genco RJ (1981). Antibiotics in the treatment of human periodontal diseases. J *Periodont* 52:545-588.

Golomb G, Friedman M, Soskolne A, Stabholz A, Sela MN (1984). Sustained release device containing metronidazole for periodontal use. J *Dent Res* 63:1149-1153.

Goodson JM (1994). Antimicrobial strategies for treatment of periodontal diseases. *Periodontology* 2000 5:142-168.

Goodson JM, Holborow D, Dunn RL, Hogan P, Dunham S (1983). Monolithic tetracycline-containing fibres for controlled delivery to periodontal pockets. J *Periodont* 54:575-579.

Goodson JM, Offenbacher S, Farr DH, Hogan PE (1985). Periodontal disease treatment by local drug delivery. J *Periodont* 56:265-272.

Goodson JM, Cugini MA, Kent RL, Armitage GC, Cobb CM, Fine D, *et al.* (1991a). Multicenter evaluation of tetracycline fiber therapy: I. Experimental design, methods, and baseline data. J *Periodont Res* 26:361-370.

Goodson JM, Cugini MA, Kent RL, Armitage GC, Cobb CM, Fine D, *et al.* (1991b). Multicenter evaluation of tetracycline fiber therapy. II. Clinical response. J *Periodont Res* 26:371-379.

Goodson JM, Tanner A, McArdle S, Dix K, Watanabe SM (1991c). Multicenter evaluation of tetracycline fiber therapy: III. Microbiological response. J *Periodont Res* 26:450-451.

Greenstein G (1987). Effects of subgingival irrigation on periodontal status. J *Periodont* 58:827-836.

Greenstein G (1995). The role of supra- and subgingival irrigation in the treatment of periodontal diseases. Position paper published by The American Academy of Periodontology, pp. 1-18.

Heijl L, Dahlén G, Sundin Y, Wenander A, Goodson JM (1991). A 4-quadrant comparative study of periodontal treatment using tetracycline-containing drug delivery fibers and scaling. J *Clin Perio* 18:111-116.

Higashi K, Morisaki K, Hayashi S, Kitamura M, Fujimoto N, Kimura S, *et al.* (1990). Local ofloxin delivery using a controlled-release insert (PT-01) in the human periodontal pocket. J *Periodont Res* 25:1-5.

Hitzig C, Charbit Y, Bitton C, Fosse T, Teboul M, Hannoun L, *et al.* (1994). Topical metronidazole as an adjunct to subgingival debridement in the treatment of chronic periodontitis. J *Clin Perio* 21:146-151.

Jones AA, Kornman KS, Newbold DA, Manwell MA (1994). Clinical and microbiological effects of controlled-release locally delivered minocycline in periodontitis. J *Periodont* 65:1058-1066.

Killoy WJ, Rapley JW, Drisko CL, Yonke ML, Ridenhour LS (1996). Single and repeated tetracycline fiber treatment vs. periodontal maintenance (abstract). J *Dent Res* 75(Spec Iss):159.

Kimura S, Toda H, Shimabukuro Y, Kitamura M, Fujimoto N, Miki Y, *et al.* (1991). Topical chemotherapy in human periodontitis using a new controlled release insert containing ofloxacin. 1. Microbiological observations. J *Periodont Res* 26:33-41.

Klinge B, Attström R, Karring T, Kisch J, Lewin B, Stoltze K (1992). 3 regimens of topical metronidazole compared with subgingival scaling on periodontal pathology in adults. J *Clin Perio* 19:708-714.

Kornman KS (1986). The role of supragingival plaque in the prevention and treatment of periodontal diseases. A review of current concepts. J *Periodont Res* 21(Spec Suppl 16):5-22.

Loesche WJ, Syed SA, Schmidt E, Morrison EC (1985). Bacterial profiles of subgingival plaques in periodontitis. J *Periodont* 56:447-456.

Medlicott NJ, Jones DS, Tucker IG, Holborow D (1992). Preliminary release studies of chlorhexidine (base and diacetate) from poly(ge-caprolactone) films prepared by solvent evaporation. *Int J Pharm* 84:85-89.

Michalowicz BS, Pihlstrom BL, Drisko CL, Cobb CM, Killoy WJ, Caton JG, *et al.* (1995). Evaluation of periodontal treatments using controlled-release tetracycline fibers: maintenance response. J *Periodont* 66:708-715.

Minabe M, Uematsu A, Nishijima K, Tomomatsu E, Tamura T, Hori T, *et al.* (1989a). Application of a local drug delivery system to periodontal therapy: 1. Developement of collagen preparations with immobilized tetracycline. J *Periodont* 60:113-117.

Minabe M, Takeuchi K, Tamura T, Hori T, Umemoto T (1989b). Subgingival administration of tetracycline on a collagen film. J *Periodont* 60:552-556.

Minabe M, Takeuchi K, Tomomatsu E, Hori T, Umemoto T (1989c). Clinical effects of local application of collagen film-immobilized tetracycline. J *Clin Perio* 16:291-294.

Moore WEC, Holdeman LV, Cato EP, Smibert RM, Burmeister JA, Ranney RR (1983). Bacteriology of moderate (chronic) periodontitis in mature adult humans. *Infect Immun* 42:510-515.

Newman MG, Kornman KS, Doherty FM (1994). A 6-month multicenter evaluation of adjunctive tetracycline fiber therapy used in conjunction with scaling and root planing in maintenance patients: Clinical results. J *Periodont Res* 65:685-691.

Noguchi T, Izumizawa K, Fukuda M, Kitamura S, Suzuki Y, Ikura H (1984). New method for local drug delivery using resorbable base material in periodontal therapy. *Bull Tokyo Med Dent Univ* 31:145-153.

Norling T, Lading P, Engström S, Larsson K, Krog N, Nissen SS (1992). Formulation of a drug delivery system based on a mixture of monoglycerides and triglycerides for use in the treatment of periodontal disease. J *Clin Perio* 19:687-692.

Okuda K, Wolff L, Oliver R, Osborn J, Stoltenberg J, Bereuter J, *et al.* (1992). Minocycline slow release formulation effect on subgingival bacteria. J *Periodont* 63:73-79.

Pedrazzoli V, Kilian M, Karring T (1992). Comparative clinical and microbiological effects of topical subgingival application of metronidazole 25% dental gel and scaling in the treatment of adult periodontitis. J *Clin Perio* 19:715-722.

Pihlstrom B, Michalowicz B, Aeppli D, Genco R, Walker C, Howell H, *et al.* (1995). Equivalence in clinical trial (abstract). J *Dent Res* 74(Spec Iss):530.

Pitcher GR, Newman HN, Strahan JD (1980). Access to subgingival plaque by disclosing agents using mouthrinsing and direct irrigation. J *Clin Perio* 7:300-308.

Polson AM, Garrett S, Stoller N, Bandt C, Hanes P, Killoy W, *et al.* (1995). Multicenter study of doxycycline in treatment of periodontitis (abstract). J *Dent Res* 74(Spec Iss):26.

Slots J (1979). Subgingival microflora and periodontal disease. J *Clin Perio* 6:351-382.

Socransky SS (1970). The relationship of bacteria to the etiology of periodontal disease. J *Dent Res* 49(Suppl 2):203-222.

Soskolne A, Golomb G, Friedman M, Sela MN (1983). New sustained release dosage form of chlorhexidine for dental use. II. Use in periodontal therapy. J *Periodont Res* 18:330-336.

Soskolne WA, Heasman PA, Stabholz A, Smart GJ, Palmer M, Flashner M, *et al.* (1997). Sustained local delivery of

chlorhexidine in the treatment of periodontitis: A multicenter study. J *Periodont* 68:32-38.

Stabholz A, Sela MN, Friedman M, Golomb G, Soskolne A (1986). Clinical and microbiological effects of sustained release chlorhexidine in periodontal pockets. J *Clin Perio* 13:783-788.

Stabholz A, Elkayam R, Friedman M, Sela MN, Azoury R, Soskolne AW (1989). Clinical and microbiological evaluation of sustained release device of tetracycline in periodontal pockets. *Proc Int Conf Pharm Tech* 2:336-345.

Stabholz A, Soskolne WA, Friedman M, Sela MN (1991). The use of sustained release delivery of chlorhexidine for the maintenance of periodontal pockets: 2-year clinical trial. J *Periodont* 62:429-433.

Steinberg D, Friedman M, Soskolne A, Sela MN (1990). A new degradable controlled release device for treatment of periodontal disease: *In vitro* release study. J *Periodont* 61:393-398.

Stelzel M, Flores-de-Jacoby L (1996). Topical metronidazole application compared with subgingival scaling. J *Clin Perio* 23:24-29.

Stoltze K (1992). Concentration of metronidazole in periodontal pockets after application of a metronidazole 25% dental gel. J *Clin Perio* 19:698-701.

Stoltze K, Stellfeld M (1992). Systemic absorption of metronidazole after application of a metronidazole 25% dental gel. J *Clin Perio* 19:693-697.

Tonetti M, Cugini MA, Goodson JM (1990). Zero-order delivery with periodontal placement of tetracycline-loaded ethylene vinyl acetate fibres. J *Periodont Res* 25:243-249.

Van Palenstein Helderman WH (1986). Is antibiotic therapy justified in the treatment of human chronic inlammatory periodontal disease? J *Clin Perio* 13:932-938.

van Steenberghe D, Bercy P, Kohl J, DeBoever J, Adriaens P, Vanderfaeillie A, *et al.* (1993). Subgingival minocycline hydrochloride ointment in moderate to severe chronic adult type periodontitis: a randomized, double blind, vehicle-controlled, multicenter study. J *Periodont* 64:637-644.

Waerhaug J (1978). Healing of the dento-epithelial junction following subgingival plaque control II: as observed on extracted teeth. J *Periodont* 49:119-134.

Wan Yusof WZA, Newman HN, Strahan JD, Coventry JF (1984). Subgingival metronidazole in dialysis tubing and subgingival chlorhexidine irrigation in the control of chronic inflammatory periodontal disease. J *Clin Perio* 11:166-175.

Yeung FIS, Newman HN, Addy M (1983). Subgingival metronidazole in acrylic resin *vs.* chlorhexidine irrigation in the control of chronic periodontitis. J *Periodont* 54:651-657.