

# Pharmacotherapy in Periodontal Therapy

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# Pharmacotherapy in Periodontal Therapy

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## Introduction

Periodontal disease is an infection that involves the inflammatory process and the immune response. It can cause a breakdown of periodontal structures resulting in increased pocket depth, clinical attachment loss, and destruction of alveolar bone. Treatment of periodontal diseases has evolved appreciably in the last decade. Greater emphasis has been placed on nonsurgical approaches to periodontal therapy.

Nonsurgical periodontal therapy is used to delay repopulation of pathogenic microorganisms by controlling the supragingival bacterial plaque, and by disrupting or removing the subgingival gram-negative flora. The goal of this therapy is to return the tissues to a state of health that can be easily maintained by the client through periodontal debridement procedures.

In our efforts to control pathogenic microorganisms through periodontal debridement, we have learned that repopulation of the periodontal pocket of bacteria can occur after debridement within 60 days.<sup>1</sup> Additionally, certain bacteria can invade the soft tissues of the periodontal pocket, and other areas of the oral cavity, to provide a nidus for infection.<sup>2</sup> Therefore, in addition to mechanical therapy, it is sometimes necessary to administer chemical agents to

suppress the bacterial load of inflammatory periodontal diseases.

The use of chemical agents in the treatment of periodontal disease is an important adjunctive therapy. An antiseptic is a substance that prevents or inhibits the growth of microorganisms or kills microbes on contact.<sup>3</sup> An antibiotic is a substance that is synthesized by microorganisms that prevents or inhibits the growth of microorganisms by stopping reproduction of or by killing the bacteria.<sup>3</sup> The purpose of this paper is to review pharmacotherapy in periodontics as a treatment measure that may be used to ensure long-term periodontal health in clients.

## Locally Delivered Antibiotics/Antimicrobials

The use of local delivery systems to treat various medical conditions—such as the skin patch to prevent seasickness, deliver HRT, or aid in smoking cessation—is now common. When treating periodontal disease, we are faced with the challenge of bacteria not only in the periodontal pocket, but also sometimes in the soft tissue walls and exposed dentin or cementum.<sup>4</sup> Local drug delivery allows the use of concentrations of approximately 100 times higher that does

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systemic administration.<sup>5</sup> Site-specific, controlled-release delivery systems have allowed us to administer therapeutic levels of drug to the site of infection for prolonged periods of time. Agents are available in the United States and other parts of the world that incorporate the active ingredient into an agent (fibers, gels, chips, collagen film, acrylic strips, and a polymer). The active ingredient is then released over a period of days. The U.S. Food and Drug Administration (FDA) considers most of these products as adjuncts to traditional mechanical therapy, with the primary endpoint of the FDA clinical trials being reduced probing depth. One product was studied as a monotherapy with the primary endpoint of the FDA clinical trials being gains in attachment level.

A locally delivered product must remain in the pocket long enough to be effective. Considering that the gingival crevicular fluid in a 5 mm pocket is replaced about 40 times per hour, a reservoir that can release the drug continuously to offset this fluid elimination is necessary.<sup>6</sup> The goal of locally delivered products should be to eliminate the pathogenic organisms or alter the inflammatory response, and thereby minimize tissue destruction. The three criteria for achieving these goals are: the medication must reach the intended site of action; it must remain at an adequate concentration; and it must last for a sufficient amount of time.<sup>6</sup> Local delivery devices can be sustained-release devices or controlled-delivery systems. A sustained-release device provides drug delivery for less than 24 hours, and a controlled-delivery system releases the drug for more than 24 hours.<sup>6</sup>

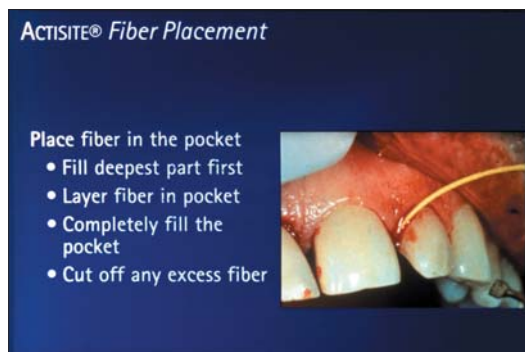
## Locally Delivered Antimicrobial Products

This section contains detailed information about Actisite, PerioChip, Atridox, and Arestin. Minocycline and

metronidazole are two products being studied in Europe that are not available in the United States; they will not be discussed in this supplement.

### Actisite: Tetracycline HCl

The first controlled-release product in the United States was (Actisite), originally marketed by Procter & Gamble. This product is no longer being sold. Actisite is an ethylene vinyl acetate fiber impregnated with 12.7 mg of tetracycline HCl, which is placed in the pocket after scaling and root planing (SRP), and sealed in



**Actisite**

place with cyanoacrylate. The client would return in 10 days for removal of the fiber.

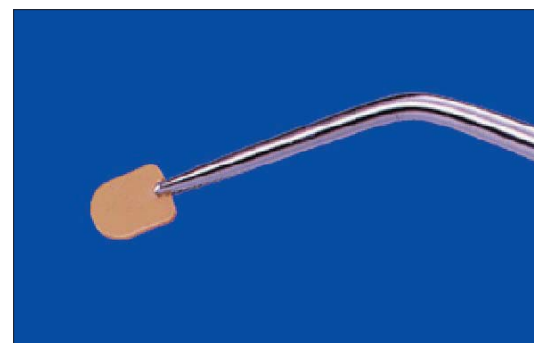
When Actisite was first available, the difference between the local delivery system of Actisite and systemic antibiotic delivery was stressed, as this was the first product of its kind in the United States. A 10-day dose of Actisite was 12.7 mg of tetracycline, or one fiber. The systemic dose was 10,000 mg (1,000 mg/day for 10 days). The concentration in crevicular fluid was 1,590 mg/mL, vs. 4–8 mg/mL. The concentration in blood was not detectable with the fiber, and was 2 mg/mL or less with systemic delivery.<sup>7</sup>

\*(footnote: Dexcel Pharma <<http://dexcelpharma.com/>>)

In a six-month, randomized, single-blind study, Actisite, as an adjunct to SRP, showed significantly greater reductions in probing depths and bleeding on probing than SRP alone.<sup>8</sup> Actisite was the first generation of locally delivered products for the treatment of periodontitis in the United States.

### PerioChip: 2.5 mg Chlorhexidine Gluconate

PerioChip\* (chlorhexidine gluconate) is a small, orange-brown, tombstone-shaped chip for insertion into periodontal pockets that was approved by FDA in the spring of 1998. Each PerioChip weighs approximately 7.4 mg and contains 2.5 mg of chlorhexidine gluconate in a biodegradable matrix of hydrolyzed gelatin cross-linked with glutaraldehyde.<sup>9</sup> PerioChip also contains glycerin and purified water. The purpose of this biodegradable delivery system is



**PerioChip**

to reduce pocket depth in chronic periodontitis, as an adjunctive therapy to SRP.

Chlorhexidine gluconate is active against a broad spectrum of microbes. The chlorhexidine molecule, due to its positive charge, reacts with the microbial

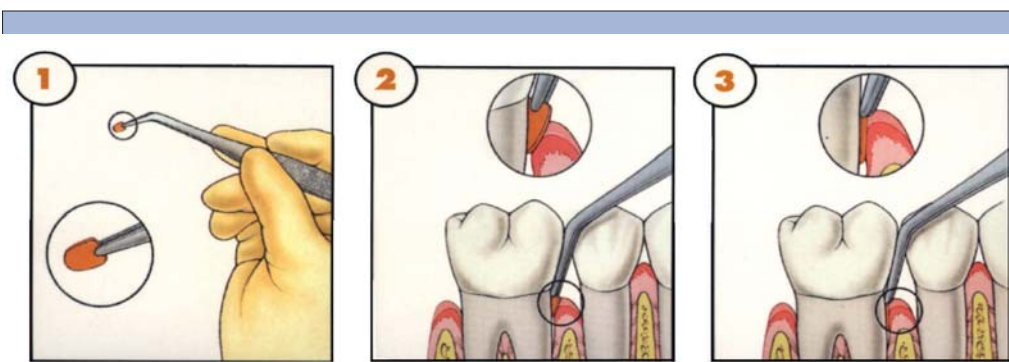
cell surface, destroys the integrity of the cell membrane, penetrates the cell wall and precipitates the cytoplasm so that the cell dies.<sup>10</sup> Studies with PerioChip showed reductions in the numbers of the putative periodontopathic organisms *Porphyromonas (Bacteroides) gingivalis*, *Prevotella (Bacteroides) intermedia*, *Bacteroides forsythus*, and *Campylobacter rectus (Wolinella recta)* after placement of the chip.<sup>9</sup>

No overgrowth of opportunistic organisms or other adverse changes in the oral microbial ecosystem were noted.

The product is inserted directly into periodontal pockets that are 5 mm or greater in depth, following SRP. PerioChip releases chlorhexidine in vitro in a biphasic manner, initially releasing approximately 40% of the

chlorhexidine within the first 24 hours, and then releasing the remaining chlorhexidine in an almost linear fashion for 7–10 days.<sup>11</sup> This release profile may be explained as an initial burst effect, dependent on diffusion of chlorhexidine from the chip, followed by a further release of chlorhexidine as a result of enzymatic degradation.<sup>11</sup>

Results of two large multicenter clinical studies in the U.S. indicates that the adjunctive use of PerioChip with SRP results in significantly greater reduction of periodontal pockets than does SRP alone.<sup>12</sup> Included in the double-blind, randomized, controlled clinical trials, were 447 adult clients with periodontitis who had at least 4 pockets with probing depth of 5–8 mm that bled on probing. Clients



**1. Grasp PerioChip® at flat end with forceps.**

**2. Insert PerioChip®, curved end first, into the pocket to its maximum depth.**

**3. Further maneuver PerioChip® into position, if necessary.**

The goal of this therapy is to return the tissues to a state of health that can be easily maintained by the client through periodontal debridement procedures.

studied were in good general health. At the end of the nine-month study period, clients who received PerioChip in addition to SRP showed a .95 mm reduction in pocket depth compared to a .65 mm improvement with SRP alone.<sup>12</sup>

In the SRP group the main reduction in pocket depth occurred between baseline and three months, after which point it stabilized. In the PerioChip group, the reduction was statistically the same as the SRP alone group after three months, but then it continued to improve.<sup>12</sup> Because a decrease of 2 mm or more in pocket depth may have a significant impact on a client's treatment plan, including the possibility of treating a client nonsurgically rather than surgically, researchers also looked at the proportion of clients who

experienced a 2 mm or more reduction in pocket depth.

PerioChip treatment resulted in greater percentages of both pockets and clients who showed pocket depth reductions of 2 mm or more, compared with SRP alone at nine months. In the SRP alone group, about 13.5% of clients had more than a 2 mm reduction at the end of the 9-month study period. When PerioChip was added to the regimen, that number more than doubled to 30.3%, a significant difference, statistically and clinically.<sup>12</sup> Smokers and nonsmokers were enrolled in these studies. Although nonsmokers using PerioChip demonstrated significant improvement in probing depths, smokers demonstrated a trend toward improvement that did not reach statistical significance.<sup>9</sup> This finding is consistent with the consensus that smoking is a risk factor in periodontal diseases.

PerioChip should not be used in any client who is hypersensitive to chlorhexidine, and has not been studied for its effects on pregnant or lactating women, or on children. It is FDA pregnancy Category C. The use of PerioChip in an acutely abscessed periodontal pocket has not been studied and therefore is not recommended.<sup>9</sup>

Placement is as follows: Remove the chip(s) from the refrigerator. The peri-

## Systemic Antibiotics

Systemic antibiotics have been used since 1929 to kill (bactericidal) or suppress (bacteriostatic) bacteria. Systemic drug delivery, where a tablet or capsule is taken orally, disperses the drug through the circulatory system. In addition to the beneficial effects of antibiotics, there are unwelcome events such as toxicity, allergic reactions, interactions with other medications, superinfection with resistant organisms, and opportunistic overgrowth of viral and fungal organisms.<sup>42</sup>

By far the most serious of these unwanted events is bacterial resistance. Although bacterial resistance has been present for many years, it has become a serious global problem that has reached the dental community. Excessive and improper use of systemic antibiotics by both health care practitioners and clients has contributed to the problem. This very serious global dilemma has given rise to “super infections” that are killing many individuals throughout the world. Microorganisms are becoming increasingly more adept at circumventing the most potent antibiotics, as they adapt to survive.

It is not desirable to eradicate all oral bacteria, as some aid in the digestive process and fend off pathogenic organisms. A certain balance must be maintained to prevent the opportunistic overgrowth of viral and fungal organisms. It would be ideal to eliminate the disease-causing microbes by targeting them specifically, but this is not always possible given the broad-spectrum power of certain antibiotics. Systemic drug delivery provides only small-to-moderate amounts in the periodontal pocket area, and is not the best choice to treat chronic periodontal infection.<sup>43</sup>

Dental hygienists see antibiotic prescriptions written for appropriate oral uses, such as acute periodontal abscesses, peri-implantitis, and the treatment of refractory or rapidly progressing periodontitis. Another example of appropriate use of antibiotics is using the premedication guidelines issued by the American Heart Association for the prevention of bacterial endocarditis. Also, certain immunocompromised clients are premedicated to prevent primary and secondary infections.

However, indiscriminate use in the dental office has contributed to the resistance problem.<sup>44</sup> Using antibiotics to prevent lawsuits, as analgesics, as prophylaxis for clients not “at risk,” in lieu of mechanical therapy, or to treat chronic periodontitis, are all considered inappropriate uses of systemic antibiotics.<sup>45</sup> It is common knowledge that many prescriptions are written for courses of antibiotics ranging from 10–30 days for treatment of periodontitis.<sup>46</sup> While considering the potential effects of systemic antibiotics, their use for the treatment of most chronic periodontitis cases cannot be currently justified.<sup>47</sup> “The emerging resistance among oral and medical pathogens to common antibiotics dictates a restrictive and conservative use of systemic antibiotic therapy.”<sup>48</sup> When necessary, proper selection, dosing, and usage can help minimize problematic reactions. Common systemic antibiotics/antimicrobials used in periodontal therapy are tetracyclines, penicillins (some with beta-lactamase inhibitors), nitroimidazoles, and lincomycins. Cephalosporins and macrolides are not often used, as the periodontal pathogens are not sensitive to these drugs.<sup>3</sup>

Systemic tetracyclines have antibacterial and non-antibacterial properties. The non-antibacterial properties include anticollagenase characteristics and the ability to inhibit bone resorption.

odontal pocket should be isolated and the surrounding area dried before chip insertion. The PerioChip should be grasped by the square end using non-serrated forceps, so that the rounded end points into, and is inserted into, the periodontal pocket to its maximum depth. It should be placed at the base of the pocket. If necessary, the chip can be further maneuvered into position using the tips of the forceps or a flat instrument. The PerioChip does not need to be removed since it biodegrades completely.<sup>12</sup>

According to clinical studies, it takes less than one minute to insert PerioChip into the periodontal pocket and no anesthesia is required. PerioChip stays in place, releasing chlorhexidine gluconate, and is fully bioabsorbable in 7 to 10 days.<sup>12</sup> PerioChip may be inserted at the time of SRP and every three months thereafter as part of a periodontal maintenance program if pockets remain 5 mm or greater. Up to eight chips can be placed at each visit.<sup>9</sup>

Most oral pain or sensitivity occurred within the first week of the initial chip placement, was mild to moderate in nature, and resolved within days. These reactions were observed less frequently with subsequent chip placement at three and six months.<sup>12</sup>

In these studies and one additional study involving a total of 619 clients, there were no reports of visible staining or altered taste perception after the use of PerioChip. No serious adverse events were reported. The most frequently observed adverse events in the two pivotal trials (PerioChip versus placebo group) were toothache (51% versus 41%), upper respiratory tract infection (28% versus 26%), headache (27% versus 28%) and sinusitis (14% versus 13%), respectively.<sup>9</sup> PerioChip treatment maintained probing attachment level compared with baseline or with SRP alone at nine months.<sup>13</sup>

Clients should avoid dental floss at the site of PerioChip insertion for 10 days after placement, because flossing might dislodge the chip. All other oral hygiene may be continued as usual, and dietary habits need not be modified. Dislodging of the PerioChip is uncommon; however, clients should be instructed to notify the dental hygienist or dentist promptly if it occurs. If the chip is dislodged seven days or more after placement, it should be considered that the client has received a full course of treatment. If dislodgement occurs within 48 hours after placement, a new PerioChip should be inserted. If dislodgement occurs more than 48 hours after placement, the chip should not be replaced, but the client should be reevaluated at 3 months. A new PerioChip may be placed at that time if the pocket depth has not been reduced to less than 5 mm.<sup>9</sup>

Clients should also be advised that, although some mild to moderate sensitivity is normal during the first week after placement of PerioChip, they

should notify the dental hygienist or dentist promptly if pain, swelling, or other problems occur. PerioChip must be stored in a refrigerator; 2°–8°C (36°–46°F), and has a shelf life of 2 years.<sup>9</sup> Although some clinicians have reported placing this product in the freezer; this has not been studied and is not recommended.

## Atridox: Doxycycline

Atridox\* (doxycycline) 10% is indicated for use in the treatment of chronic

adult periodontitis to gain clinical attachment, and reduce probing depth and bleeding on probing. It was approved by FDA in the fall of 1998, and received the American Dental Association Seal of Acceptance in the fall of 1999. In the spring of 1999, Atrix Laboratories, Inc. received approval of Atridox (doxycycline) 8.5%, a site-specific antibiotic therapy for the treatment of periodontal disease, from the Medicines Control Agency in the United Kingdom.

Atridox is a controlled-release product for subgingival use composed of a two-syringe mixing system. Syringe A contains 450 mg of the Atrigel Delivery System, which is a bioabsorbable, flow-

of the drug for a period of seven days.<sup>15</sup>

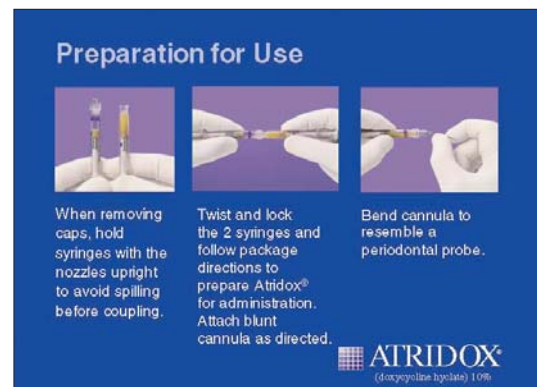
Doxycycline is a broad-spectrum antibiotic synthetically derived from oxy-tetracycline. It is bacteriostatic, inhibiting bacterial protein synthesis due to disruption of transfer RNA and messenger RNA at ribosomal sites.<sup>16</sup> In vitro testing has shown that *Porphyromonas gingivalis*, *Prevotella intermedia*, *Campylobacter rectus*, and *Fusobacterium nucleatum*, which are associated with periodontal disease, are susceptible to doxycycline at concentrations  $\leq 6.0 \mu\text{g/mL}$ .<sup>17</sup>

Two controlled, multicenter, parallel-design, nine-month clinical trials involved 831 subjects (study 1=411; study 2=420) with chronic adult periodontitis charac-

Site-specific, controlled-release delivery systems have allowed us to administer therapeutic levels of drug to the site of infection for prolonged periods of time.

able polymeric formulation composed of 36.7% poly (DL-lactide) dissolved in 63.3% N-methyl-2-pyrrolidone. Syringe B contains doxycycline hydrochloride that is equivalent to 42.5 mg of doxycycline.<sup>14</sup> Each Atridox syringe system is intended for use in only one client. The constituted product, which ranges in color from pale yellow to yellow, is a viscous liquid with a concentration of 10% of doxycycline hydrochloride. Upon contact with the crevicular fluid, the liquid product solidifies, allowing for controlled release

terized by mean probing depths of 5.9 to 6.0 mm. Subjects received one of four treatments: 1) Atridox, 2) SRP, 3) vehicle control, or 4) oral hygiene. Treatment was administered to sites with probing depths 5 mm or greater that bled on probing. Subjects with detectable subgingival cal-



**Atridox**

\*Distributed by CollaGenex Pharmaceuticals, Inc. <<http://www.collagenex.com/>>

## The FDA considers most of these products as adjuncts to traditional mechanical therapy, with the primary endpoint of the FDA clinical trials being reduced probing depth.

culus on greater than 80% of all tooth surfaces were excluded from enrollment.<sup>18</sup> All subjects received a second administration of the initially randomized treatment four months after their baseline treatment. Changes in efficacy parameters, attachment level, pocket depth, and bleeding on probing, between baseline and month nine showed that: 1) Atridox was superior to vehicle control and oral hygiene, and 2) Atridox met the decision rule of being at least 75% as good as SRP (the standard required for any product approved as a stand-alone therapy for periodontitis).<sup>18</sup> Clinicians should note that the studies were of nine months' duration; additional research would be necessary to establish long-term comparability to SRP.

Atridox should not be used by clients who are hypersensitive to doxycycline or any other tetracycline. The use of drugs in the tetracycline class during tooth development may cause permanent discoloration of the teeth; therefore, they should not be used in pregnant women, unless other drugs are not likely to be effective or are contraindicated. Atridox

is FDA Pregnancy Category D. Because of the potential for serious adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking doxycycline or other tetracycline products. Clients exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs.<sup>14</sup>

Product packaging provides detailed information on how to prepare and apply Atridox. First, the clinician removes the pouched product from refrigeration at least 15 minutes before mixing. Syringe A (liquid delivery system) and Syringe B (drug powder) are coupled and the liquid contents of Syringe A (indicated by purple stripe) injected into Syringe B (doxycycline powder). The clinician then pushes the contents back into Syringe A. This entire operation is one mixing cycle. The clinician then completes 100 mixing cycles at a pace of one cycle per second, using brisk strokes. (At this point, the coupled syringes can be stored in the resealable pouch at room temperature for a maximum of three days. After storage, an additional 10 mixing cycles should be performed just prior to use.) After mixing, the contents will be in Syringe A (indicated by purple stripe). The coupled syringes should be held vertically for several seconds. The two syringes and the blunt cannula attached to Syringe A.

Application of Atridox does not require local anesthesia. The clinician bends the cannula to resemble a periodontal probe and uses it in a similar manner to explore the periodontal pocket. The cannula tip should remain near the base of the pocket while the product is expressed into the pocket until it reaches the top of the gingival margin.

The clinician removes the cannula tip from the pocket, turning it towards the tooth, pressing it against the tooth surface, and pinching the string of formulation. Variations on this technique may be needed to separate the Atridox formulation and the cannula.

An appropriate dental instrument can be used to pack Atridox into the pocket. Dipping the edge of the instrument in water before packing will help keep the formula from sticking to the instrument, and will help speed its coagulation. A few drops of water dripped onto the surface of the product once it is in the pocket also will aid in coagulation, and more Atridox may be necessary.

Either Coe-Pak periodontal dressing or Octyldent dental adhesive can be used to cover the pockets containing Atridox. Application may be repeated four months after initial treatment.

In clinical trials, Atridox was generally well tolerated. Side effects were similar to those of placebo. The most common were headache, common cold, gum discomfort, pain, soreness, toothache, and tooth sensitivity.

Mechanical oral hygiene procedures, such as tooth brushing and flossing, should be avoided on any treated areas for seven days postoperatively. The client should be advised to avoid excessive sunlight or artificial ultraviolet light while the doxycycline is in the system, and that doxycycline may decrease the effectiveness of birth control pills. Atridox must be stored in a refrigerator, 2°–8°C (36°–46°F).<sup>14</sup>

## Arestin: Minocycline HCl

Arestin (minocycline HCl 1mg) is indicated as adjunctive therapy to SRP for reduction of pocket depth in clients with chronic periodontitis. Arestin "microspheres" contain the antibiotic minocycline, a member of the tetracycline class

\*Distributed by OraPharma, Inc. [www.orapharma.com](http://www.orapharma.com), [<arestin.com>](mailto:<arestin.com>)

of antibiotics that has been shown to be effective in eradicating the periodontal pathogens implicated in chronic periodontitis.

Minocycline hydrochloride is a bacteriostatic, broad-spectrum, semisynthetic tetracycline derivative. Its antimicrobial activity inhibits protein synthesis.<sup>16</sup> In vitro susceptibility testing has shown that the organisms *Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*, *Eikenella corrodens*, and *Actinobacillus actinomycetemcomitans*, which are associated with periodontal disease, are susceptible to minocycline at concentrations of  $\geq 8 \mu\text{g/mL}$ , and qualitative and quantitative changes in plaque microorganisms have not been demonstrated in clients with periodontitis using this product.<sup>17</sup>

Serum and saliva levels of minocycline were determined after 1 mg minocycline was administered to a mean of 51.94 sites. The mean dose normalized saliva AUC (total area under the plasma concentration-time curve) and  $C_{\text{max}}$  (maximum plasma drug concentration) were found to be approximately 125 and 1,000 times higher, respectively, than those of serum parameters.<sup>19</sup> Saliva levels were far higher than serum levels, and were still present in some study subjects after 14 days.<sup>19</sup> Minocycline is considered one of the most potent antibiotics in the tetracycline family and has been proven very effective in eradicating periodontal pathogens implicated in periodontitis.<sup>20</sup>

Arestin (minocycline HCl 1 mg) microspheres studies were conducted at 22 universities and dental schools across the United States in over 920 clients with chronic periodontitis.<sup>20</sup> More than 27,000

sites  $\geq 5$  mm were treated in two single-blind (N=748) and one open-label (N=173) trial. More than 60% of the pockets that responded to Arestin + SRP had reductions of  $\geq 2$  mm, and 65% of clients treated with Arestin + SRP had pocket reductions from  $\geq 6$  mm to  $< 5$  mm. These clients were 286% more likely to become maintainable under 5 mm. In the two controlled, multicenter, investigator-blind, vehicle-controlled, parallel-design studies (three arms), 748 clients with generalized moderate to advanced chronic periodonti-

depths greater than or equal to 7 mm had a mean reduction of 2 mm (vs. 1 mm with SRP alone). Arestin + SRP had statistically significant greater pocket depth reduction over SRP alone ( $p \geq 0.05$ ). Arestin + SRP was proven very effective in clients with cardiovascular disease.<sup>21</sup>

Arestin was shown to be effective in eradicating certain pathogens implicated in periodontal disease. It maintains minocycline levels in crevicular fluid well above the following minimal inhibitory

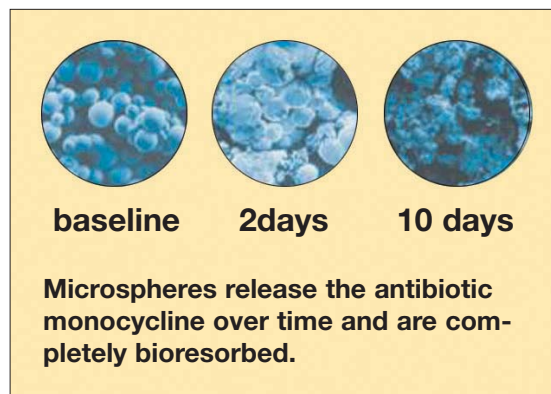


**Arestin**



tis characterized by a mean probing depth of 5.90 and 5.81 mm, respectively, were enrolled.<sup>20</sup> In these two studies, an average of 29.5, 31.7, and 31 sites were treated at baseline in the SRP alone, SRP + vehicle, and SRP + Arestin groups, respectively. When these studies are combined, the mean pocket depth change at nine months was -1.18 mm, -1.10 mm, and -1.42 mm for SRP alone, SRP+ vehicle, and SRP + Arestin, respectively. The trials showed Arestin, as adjunct therapy to SRP, to be significantly more effective in reducing pocket depth than SRP alone.

In clinical studies, Arestin with SRP demonstrated 27% greater pocket-depth reduction in molars than did SRP alone. Arestin with SRP also was effective in furcation sites. Clients with average pocket



concentration (MIC) levels of common periodontal pathogens for at least 14 days. The following MIC levels represent the minimum concentration of antibiotic needed to eradicate the particular pathogen:

- *P. gingivalis*: 0.06  $\mu\text{g/ml}$
- *P. intermedia*: 0.25  $\mu\text{g/ml}$
- *actinomycetemcomitans*: 2.00  $\mu\text{g/ml}$

In two studies, the following subgroups were prospectively analyzed: smokers, patients over and under 50 years of age, and patients with a previous history of cardiovascular disease. The results of the combined studies showed that, in smokers, the mean reduction in pocket depth at nine months was less in all treatment groups than in nonsmokers, but the reduction in mean pocket depth at nine months with SRP + Arestin was significantly greater than with SRP + vehicle or SRP alone.<sup>22</sup>

A recent 9-month study showed pocket depth reductions of  $1.82 \pm 0.73$  mm ( $p < 0.0001$ ), and a gain in clinical attach-

ment level of 1.58 mm ( $\pm 1.01$ ). No appreciable oral soft tissue changes or adverse events were noted.<sup>23</sup> An additional six-month study was conducted to evaluate changes in alveolar bone height and standard clinical measures of periodontitis (clinical and radiographic measurement including probing depth, clinical attachment level, and interproximal bone height) during conventional periodontal maintenance, compared to isolated root planing and multiple doses of subgingival minocycline.<sup>24</sup> Isolated root planing and subgingival minocycline added little additional time to the treatment regimen, but resulted in more pocket depth reduction and less bone loss than conventional periodontal maintenance.<sup>24</sup>

Previous studies using minocycline encapsulated in a biodegradable polymer, poly (glycolide-co-dl-lactide) noted significant changes in the subgingival microflora compared with controls. One showed significant reductions in black-pigmented *Bacteroides* for up to three months.<sup>25</sup> Jones et al. noted significant reductions from baseline levels of *P. gingivalis* in pockets one month after treatment with minocycline alone and with minocycline as an adjunct to SRP.<sup>26</sup>

A recent study evaluated the effect of Arestin + scaling and root planing (SRP) on crevicular fluid levels (GCF) of ICTP, a bone resorptive marker. Subjects were randomly assigned to three treatment groups: SRP, SRP + Arestin, or SRP + vehicle. The SRP + Arestin group showed significant reductions in both ICTP and IL-1 levels after one month.<sup>27</sup>

Arestin should not be used in pregnant or lactating women, or in children. It is FDA Pregnancy Category D. Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Clients that will be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema. Arestin has not been stud-

ied in abscessed pockets or implants. The most frequently reported adverse events, unrelated to dental treatment, in the three multicenter U.S. trials were headache, infection, flu syndrome, and pain. Adverse events were reported in  $\geq 3\%$  of the combined clinical trial population of three multicenter U.S. trials. The change in clinical attachment levels was similar across all study arms, suggesting that neither the vehicle nor Arestin compromise clinical attachment.<sup>21</sup>

The minocycline product is packaged in a box with 2 trays, each containing 12 cartridges. Each cartridge contains 1 mg of minocycline microencapsulated in 3 mg of poly (glycolide-co dl-lactide) dry powder.<sup>21</sup> The product is in a specially designed unit-dose cartridge, which is inserted into an autoclavable cartridge handle to administer the product. Each cartridge contains enough Arestin for one periodontal pocket. The minocycline is delivered in a powdered microsphere delivery system that is premeasured and premixed, and which requires no preparation or refrigeration. It is stored at room temperature: 20° to 25°C (68° to 77°F). Dentists and dental hygienists were

presses down on a thumb ring to expel the powder, while gradually withdrawing the tip from the base of the pocket. After the Arestin has been administered, the clinician pulls back on the thumb ring to remove the cartridge. Local anesthesia is not required, and the bioadhesive microspheres activate and adhere on contact with moisture. There was no slippage in the clinical trials, and no dressings or adhesives are required to keep it in the pocket. Once inserted, the product immediately adheres to the periodontal pocket. Crevicular fluid hydrolyzes the polymer, causing water-filled channels to form inside the microspheres. These openings provide a drainage system for the encapsulated antibiotic, providing for sustained release delivery. The active drug dissolves and diffuses out of the microspheres through the channels into the surrounding tissues. Eventually, the microspheres themselves are fragmented through polymer hydrolysis and are completely bioresorbed.<sup>21</sup>

Arestin is a variable dose product, and one cartridge is used for each pocket. In the U.S. clinical trials, up to 121 unit-dose cartridges were placed in a sin-

## The concept of full-mouth disinfection to minimize reinfection of periodontal pockets has become popular in the last few years.

able to treat as many as 30 sites in less than 10 minutes in the FDA clinical trials.<sup>20</sup> The microspheres are a bioadhesive and bioresorbable polymer in powder form, produced by a micro encapsulation process.

Placement is as follows: The clinician removes a disposable cartridge from the tray and connects it to the handle by twisting it into place. The tip is removed and the cartridge inserted into the base of the periodontal pocket. The clinician

gle treatment. Up to 3 treatments, at 3-month intervals, were administered in pockets 5 mm or greater. There is no limit to the number of cartridges that can be placed at each visit. The handle must be sterilized after each client.

After treatment, clients should avoid eating hard, crunchy, or sticky foods for one week and postpone brushing for a 12-hour period, as well as avoid touching treated areas. Clients should also postpone the use of interproximal cleaning

devices for 10 days after administration of Arestin. Clients should be advised that although some mild to moderate sensitivity is expected during the first week after SRP and administration of Arestin, they should notify the dental hygienist or dentist promptly if pain, swelling, or other problems occur.<sup>21</sup> No major adverse events were recorded.<sup>20</sup>

Arestin maintains therapeutic drug concentrations for at least 14 days, and the localized delivery provides an effective drug concentration at the site of infection. Arestin should not be used in pregnant or lactating women, children, or any client who has a known sensitivity to minocycline or tetracyclines.<sup>21</sup>

## Placement of Locally Delivered Agents by Dental Hygienists

Individual state boards of dentistry or dental hygiene have inconsistent rules/regulations regarding the use of locally delivered pharmaceuticals by dental hygienists. Thirty-three states have specific language regarding use of the agents within the dental hygiene portion of the practice act. Most recently, the Dental Board of California voted to allow this duty as a function of a dental hygienist under direct supervision of a dentist, and the Florida Board of Dentistry made a similar ruling for all products that do not require removal. In New York, the placement and removal of local therapeutic agents for treatment of periodontal pockets may be assigned to a New York licensed dental hygienist, but only under the personal supervision of a New York licensed dentist. "Local Therapeutic Agents" means any agent approved for use by the FDA utilized in controlled drug delivery systems in the course of periodontal pocket treatment. This was passed unanimously, has been reviewed by the legal department, and is awaiting submission to the board of regents.

## Full-Mouth Disinfection

The concept of full-mouth disinfection to minimize reinfection of periodontal pockets has become popular in the last few years. The essence of the concept requires that mechanical instrumentation and full-mouth disinfection be completed in 24–48 hours.<sup>28</sup> In addition to instrumentation, the full-mouth disinfection in Quirynen et al. study included rinsing with chlorhexidine, brushing the tongue with chlorhexidine gel, spraying the pharynx with chlorhexidine, and irrigating all pockets with chlorhexidine. It seems reasonable to assume that a variation of the suggested protocol might achieve similar results. Mechanical instrumentation with hand and powered instruments within 24–48 hours, disinfection of the oral cavity with a chlorhexidine rinse, and cleaning of the tongue with a tongue scraper and an antimicrobial agent might be a rational approach to treatment. Placement of a controlled-release antibiotic/antimicrobial into the periodontal pockets will disinfect the pockets as well as achieve a salivary spillover effect. One study indicated that subgingival administration of locally delivered minocycline achieved saliva levels far higher than serum levels, and were still present in some of the subjects after 14 days.<sup>29</sup>

## Periostat

One systemic product currently available to treat periodontal disease should be mentioned. Research has shown that even though bacteria initiate the periodontal disease process, periodontal tissue destruction is caused not by the bacteria, but by endogenous enzymes produced by the host in response to the presence of bacteria.<sup>30</sup> The pathogenic bacteria release endotoxins that evoke a host response by stimulating cells present in the periodontal tissues to release the chemical messengers

known as cytokines. Cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , and PGE<sub>2</sub> play a significant role in periodontal disease, and are implicated in a number of other inflammatory disease states, such as rheumatoid arthritis.<sup>31</sup> Cytokines induce cells—such as polymorphonuclear leukocytes (PMNs), macrophages, fibroblasts, and other resident and migrating inflammatory cells, located in the periodontium and in other areas of the body—to begin to manufacture, secrete, and activate enzymes known as matrix metalloproteinases (MMPs).<sup>32</sup>

MMPs, such as collagenases, gelatinases, and stromelysins, destroy particular proteins, one being collagen. In periodon-

A part of being a professional is to perform evidenced-based care that is focused on the client's desires and needs, and tailor treatment to each person on an individual basis.

tal disease, we see low levels of tissue inhibitors of metalloproteinases (TIMP) and high levels of MMPs. Collagen damage is greater than regeneration in these sites of infection. Destruction of the periodontal ligament, gingiva, and alveolar bone result, leading to gingival recession, pocket formation, tooth mobility, and possible tooth loss.

While we realize that it is necessary to minimize bacteria in the pocket by

mechanical and chemical means, we now know that modulating the host response can minimize tissue damage. The classes of drugs being studied for this action include the nonsteroidal antiinflammatory drugs (NSAIDs), tetracyclines, and bisphosphonates. The tetracyclines have been shown, in low doses, to inhibit several MMPs by a mechanism independent of their antimicrobial activity.<sup>32-34</sup> One of the newer tetracyclines, doxycycline, has been found to be a potent inhibitor of collagenase (MMP-8), the MMP most plentiful in tissues with active periodontal disease.<sup>32,35</sup> Additional studies have shown that doxycycline reduces the elevated collagenase activity in the gingival crevicular fluid of patients with adult periodontitis.<sup>36,37</sup>

Currently, Periostat\* is the only FDA- and ADA-approved drug to treat the host response. It is indicated as an adjunct to SRP to promote attachment level gain and to reduce pocket depths in clients with chronic periodontitis. The daily dosing regimen of Periostat (20 mg twice daily) has been studied and has been shown to produce plasma levels of doxycycline which are substantially lower than those required to induce an antimicrobial effect, a subantimicrobial dose. When administered according to the dosage regimen prescribed in the labeling, Periostat has been shown to have no detrimental effect on the susceptibility of the microflora to doxycycline and other common antibiotics.<sup>38,39</sup> The adjunctive use of Periostat with SRP is more effective than SRP alone and represents a new method in the long-term management of chronic periodontitis.

Periostat should not be given to pregnant or nursing women, infants, children, or those who have shown hypersensitivity to any of the tetracyclines. It is FDA Pregnancy Category D. Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, magnesium, and bismuth subsalicylate; and by iron-containing preparations. Clients should be

warned that oral contraceptives may not be effective while using Periostat, and that they should avoid sunlight. If photosensitivity occurs, manifested by a sunburn-like effect, the product should be discontinued. A client on anticoagulant therapy should consult the physician for a possible downward adjustment of the medication. As tetracyclines may interfere with the bactericidal effects of the b-lactam class of antibiotics, such as penicillin, it is not advisable to administer these drugs concurrently. The concurrent use of a tetracycline and Penthrane, methoxy-fluorane, has been reported to result in fatal renal toxicity. Adverse events were nonremarkable and similar to placebo.<sup>40</sup>

The product is prescribed as Periostat twice daily, for three, six, or nine months, depending on the severity of the periodontal condition, and mitigating circumstances, such as smoking. It should be administered at least one hour before morning and evening meals.

## Clinical and Statistical Significance

The results of clinical trials help determine if a new treatment or product is better than one that is currently available. Statistical significance means that the differences found in a study did not happen by chance. Clinical significance could signify the need to adopt new treatment methods. Both statistical and clinical significance are required for decision making. Table I shows some of the characteristics that one author has stated to be of value in the area of clinical significance.<sup>42</sup>

## Summary

New products and treatment regimens will continue to be developed. A part of being a professional is to per-

form evidenced-based care that is focused on the client's desires and needs, and tailor treatment to each person on an individual basis. This involves evaluating the clinical data and assessing whether products and procedures can be beneficial to our clients. The studies on locally delivered antibiotics/antimicrobials, and

## Table I

### Index of Clinical Significance<sup>41</sup>

1. Absolute criteria: percentage of sites with 2 mm changes in probing depth or gain in clinical attachment
2. Cut-off point: percentage of sites reduced to 5 mm or less
3. Frequency distribution: percentage of sites changes 1 mm, 2 mm, or 3 mm at specific initial probing depths
4. Reduction of the incidence of disease progression (threshold for disease progression being defined as 2 mm loss of clinical attachment)
5. Percentage of osseous fill in bony defects
6. Percentage of sites and percentage of patients returned to health (no inflammation)
7. Percentage of sites/patients still needing therapy
8. Percentage change of the defect using a novel therapy compared to root planning
9. Percentage improvement of any parameter in light of the magnitude of severity of the defect being treated
10. Mean changes in pocket depth and attachment level for the patient

\* There are statistical techniques that can take into account changes in multiple sites in one patient so that they are not treated as independent events.<sup>41</sup>

\*Marketed by CollaGenex Pharmaceuticals, Inc., Newtown, PA 18940. www.periostat.com, <www.collagenex.com>

low-dose antibiotics, provide evidence that these products could be of value in treating chronic periodontitis.

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