42 Drugs for the Control of Supragingival Plaque

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DRUG LIST

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The periodontium, which is responsible for the retention of teeth in the maxilla and mandible, consists of four tissue types. Cementum and alveolar bone are the hard tissues to which the fibrous periodontal ligament anchors the tooth into the skeleton, and the gingiva is the covering tissue of the periodontium (Fig. 42.1). The gingiva is a unique body tissue in that it allows the penetration of calcified tissue (i.e., teeth) into an intact mucosa while protecting the underlying periodontal tissues. The accumulation of microorganisms on the tooth surface along the gingival margin can alter the structure and function of the gingiva, inducing an oral inflammatory reaction. Its clinical expression is called *gingivitis*.

During adolescence gingivitis is almost universal, and in adulthood it affects approximately 50% of the population. Because of the frequent appearance of gingivitis, this disease remains a principal concern for the dentist, since it can convert to other more destructive forms of periodontal disease. Hence, the prevention or cure of gingivitis is of particular interest.

The most common method of eliminating gingivitis is by the mechanical removal of the microorganisms found in dental plaque via toothbrush and floss. However, effective mechanical removal of plaque is a tedious, time-consuming process that is affected by an individual's gingival architecture, tooth position, dexterity, and motivation. Consequently, incomplete removal of dental plaque by mechanical means allows for the induction, continued progression, or both of gingivitis. Therefore, pharmacological agents that prevent or reduce plaque can aid the dentist by effectively preventing or eliminating gingival inflammation. Accordingly, the development of safe and effective topical liquid antimicrobial agents will help in the maintenance of healthy gingival tissues. This chapter examines the relationship of supragingival dental plaque to gingivitis and the unique pharmacokinetic characteristics of common antiplaque agents.

THE ROLE OF SUPRAGINGIVAL DENTAL PLAQUE IN THE INITIATION OF GINGIVITIS

Many types of materials accumulate on teeth. By far the most widespread and important deposit is dental plaque. *Plaque consists primarily of microorganisms in an organized matrix of organic and inorganic components.* Bacteria account for at least 70% of the mass of plaque. In fact, one cubic millimeter of dental plaque contains more than 100 million bacteria consisting of more than 400 species. The organic matrix of plaque consists of polysaccharide, protein, and lipid components, while the inorganic matrix is composed primarily of calcium and phosphorous ions.

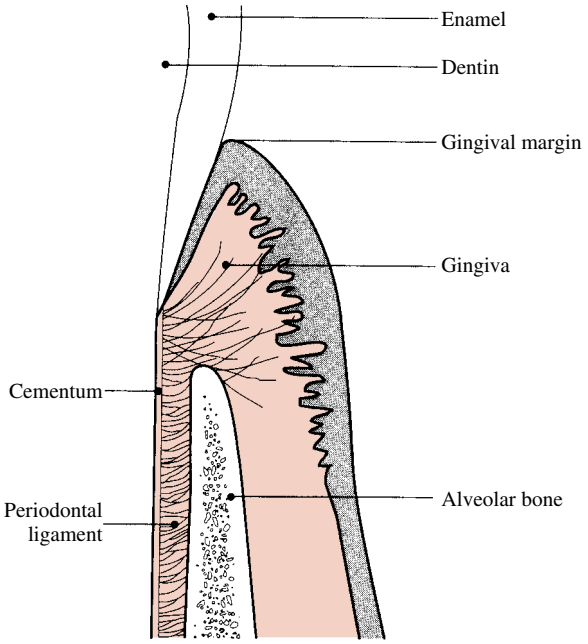

FIGURE 42.1
Anatomical landmarks in the periodontium.

The dental plaque above the gingival margin of the tooth is designated as supragingival, and the dental plaque below the gingival margin (i.e., in the gingival sulcus or pocket) is called subgingival. Gingivitis can be experimentally induced in an uninflamed periodontium by allowing the unimpeded accumulation of supragingival plaque and is reversed completely by the thorough and complete removal of supragingival plaque.

Gingivitis is due principally to the accumulation and retention of plaque at or near the gingival margin. The accumulation of supragingival plaque is also a prime influence in the development of subgingival plaque. As undisturbed plaque matures, it changes in composition and becomes more complex. A bacterial succession occurs whereby microorganisms associated with gingival health, that is, gram-positive rods and cocci, are replaced by microorganisms associated with gingivitis, that is, gram-negative rods and cocci, as well as spiral organisms and spirochetes. As a consequence of the change in microflora, the inflammation-induced changes in the gingiva cause an increase in epithelial cell turnover and connective tissue degradation, resulting in anatomical changes that tend to deepen the gingival sulcus, causing a gingival pocket to form. This change in gingival architecture and the subgingival environment provides a new and better protected niche for bacteria to grow. Here they are continually bathed by exudate from the gingival crevice and end products from the supragingival plaque. Hence, control of supragingival plaque will also have a profound influence on the developing composition of periodontitis-associated subgingival plaque.

PHARMACOKINETICS OF THE ORAL CAVITY

The therapeutic outcome of topically applied agents used to control oral infections will depend on the characteristics of drugs that take advantage of the unique physiological and anatomical circumstances in the oral cavity. This section is a broad overview of important oral pharmacokinetic principles.

Absorption

The vascularity of the oral cavity, combined with a thin epithelial lining in some areas, allows for the absorption of drugs at a rapid rate. Un-ionized drugs, such as nitroglycerin, take advantage of these tissue characteristics and diffuse rapidly across the oral mucosa into the bloodstream. Unlike most drugs, for which the principal objective is to introduce the agent into the bloodstream rapidly, the goal of oral topical agents is to be retained in the oral cavity for as long as possible. Absorption can lead to toxic effects elsewhere in the body and a significant reduction of the free drug in the oral cavity. In most instances, the drugs used to restrain plaque levels are highly ionized and therefore are generally unable to penetrate the oral mucosa.

Distribution

Once an agent is topically applied in the oral cavity, the free drug can act at the primary site (i.e., bacteria in the plaque), or it can be partitioned to compartments where the drug binds nonspecifically. These drug reservoirs include the enamel, dentin, and/or cementum of the tooth, the oral mucosa, the organic and inorganic components of plaque, and salivary proteins.

The fraction of the administered dose that is nonspecifically bound to oral reservoirs is highly dependent on the drug's concentration and chemical nature and the amount of time it remains at the site. For example, a 1-minute rinse with 0.2% chlorhexidine will result in approximately 30% of the total amount dispensed being retained, whereas a 3-minute rinse with 0.1% sodium fluoride will result in less than 1% of the administered dose being found in the oral cavity after an hour. The ability of oral agents to bind to oral reservoirs nonspecifically and reversibly is an important quality for sustained release of drugs.

Metabolism

In the oral cavity, drug metabolism occurs in mucosal epithelial cells, microorganisms, and enzymes in the saliva; metabolism also takes place in renal and hepatic tissue once the drug is swallowed. Although biotransformation of agents in the oral cavity is potentially an important aspect of reducing effective drug concentra-

tions, quantitatively it accounts for only a small percentage of drug inactivation.

Excretion

Salivary flow is extremely important in the removal of many agents from the oral cavity. Human saliva has a diurnal flow that varies between 500 and 1,500 mL in the daytime to less than 10 mL of secretion at night. The rate of clearance of a drug from the oral cavity therefore is profoundly important in determining the amount of time a drug is in contact with the tooth surface.

Substantivity

The period that a drug is in contact with a particular substrate in the oral cavity is *substantivity*. Drugs that have a prolonged duration of contact are considered to have high substantivity. In the oral cavity, substantivity depends on two important pharmacokinetic features: the degree of reversible nonspecific binding to oral reservoirs and the rate of clearance by salivary flow (Fig. 42.2).

Oral reservoirs are an important source for the continued release of drugs. The oral compartments that accumulate a drug must reversibly bind large portions of the administered dose and release therapeutic concentrations of free drug to the site of action over long periods. Therefore, effective agents with high substantivity ideally would not bind irreversibly, nor would they bind with high affinity to oral reservoirs.

Salivary flow also will significantly affect the substantivity of topically applied liquid agents. The clearance of an agent from the oral cavity is directly proportional to the rate of salivary flow. Hence, during periods of high salivary flow, a greater release of drug from oral reservoirs is necessary to maintain therapeutic concentrations. Strategies that use natural or drug-induced periods of low salivary flow can increase the substantivity of an oral agent.

ANTIPLAQUE AGENTS

Bisbiguanides

Chlorhexidine is a symmetrical cationic molecule that is most stable as a salt; the highly water-soluble digluconate is the most commonly used preparation. Because of its cationic properties, it binds strongly to hydroxyapatite (the mineral component of tooth enamel), the organic pellicle on the tooth surface, salivary proteins, and bacteria. Much of the chlorhexidine binding in the mouth occurs on the mucous membranes, such as the alveolar and gingival mucosa, from which sites it is slowly released in active form.

Pharmacokinetics

The rate of clearance of chlorhexidine from the mouth after one mouth rinse with 10 mL of a 0.2% aqueous solution follows approximately first-order kinetics, with a half-life of 60 minutes. This means that following application of a single rinse with a 0.2% chlorhexidine solution, the concentration of the compound exceeds the minimum inhibitory concentration (MIC) for oral streptococci (5 mg/mL) for almost 5 hours. The pronounced substantivity, along with the relative susceptibility of oral streptococci, may account for the great effectiveness of chlorhexidine in inhibiting supragingival plaque formation.

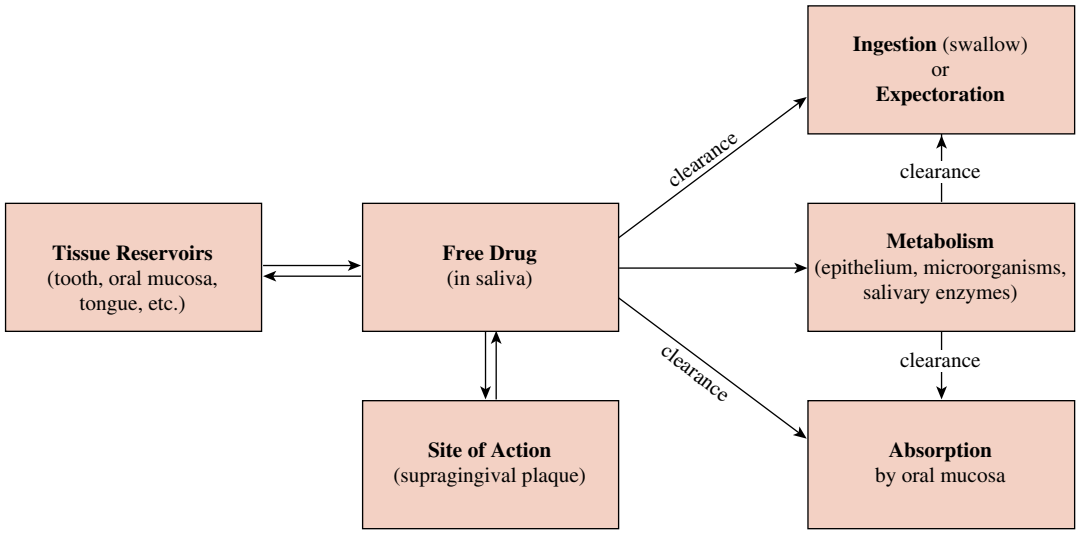

FIGURE 42.2
Pharmacokinetic factors that affect substantivity of rinsing agents.

Mechanisms of Action

Although chlorhexidine affects virtually all bacteria, gram-positive bacteria are more susceptible than are gram-negative organisms. Furthermore, *Streptococcus mutans* and *Antinomies viscosus* seem to be particularly sensitive. *S. mutans* has been associated with the formation of carious lesions in fissures and on interproximal tooth surfaces and has been identified in large numbers in plaque and saliva samples of subjects with high caries activity.

Low concentrations of chlorhexidine are bacteriostatic, while high concentrations are bactericidal. Bacteriostasis is the result of chlorhexidine binding to the negatively charged bacterial cell wall (e.g., lipopolysaccharides), where it interferes with membrane transport systems. Oral streptococci take up sugars via the phosphoenolpyruvate-mediated phosphotransferase (PEP-PTS) system. The PEP-PTS is a carrier-mediated group translocating process in which a number of soluble and membrane-bound enzymes catalyze the transfer of the phosphoryl moiety of PEP to the sugar substrate with the formation of sugar phosphate and pyruvate. Chlorhexidine is known to abolish the activity of the PTS at bactericidal concentrations. High chlorhexidine concentrations cause intracellular protein precipitation and cell death. Despite its pronounced effect on plaque formation, no detectable changes in resistance of plaque bacteria were found in a 6-month longitudinal study of mouth rinses.

Clinical Uses

The previous routine treatment for cases of severe gingival disease consisted of calculus and plaque removal and oral hygiene instructions. Subsequent resolution of the gingival inflammation was largely dependent on daily plaque control by the patient. However, the use of a 0.1 to 0.2% chlorhexidine mouthwash supplementing daily plaque control will facilitate the patient's effort to fight new plaque formation and to resolve gingivitis. Consequently, use of chlorhexidine is indicated in the following situations: in disinfection of the oral cavity before dental treatment; as an adjunct during initial therapy, especially in cases of local and general aggressive periodontitis; and in handicapped patients.

Adverse Effects and Toxicity

The most conspicuous side effect of chlorhexidine is the development of a yellow to brownish extrinsic stain on the teeth and soft tissues of some patients. The discoloration on tooth surfaces is extremely tenacious, and a professional tooth cleaning using abrasives is necessary to remove it completely. The staining is dose dependent, and variation in severity is pronounced between individuals. This side effect is attributed to the cationic nature of the antiseptic. Desquamative soft tissue lesions have also been reported with use of drug concentrations exceeding 0.2% or after prolonged application. A frequently observed side effect is impaired taste sensation. It was reported that rinsing with a 0.2% aqueous solution of chlorhexidine digluconate resulted in a significant and selective change in taste perception for salt but not for sweet, bitter, and sour.

In vitro, chlorhexidine can adversely affect gingival fibroblast attachment to root surfaces. Furthermore, protein production in human gingival fibroblasts is reduced at chlorhexidine concentrations that would not affect cell proliferation. Such findings corroborate earlier studies showing delayed wound healing in standardized mucosal wounds after rinsing with 0.5% chlorhexidine solution.

As an oral rinsing agent, to date chlorhexidine has not been reported to produce any toxic systemic effects. Since chlorhexidine is poorly absorbed in the oral cavity and gastrointestinal tract, little if any enters the bloodstream. A summary of chlorhexidine oral rinses is given in Table 42.1.

Nonionic Bisphenols

Triclosan is a broad-spectrum antimicrobial compound. It was originally used in soaps, antiperspirants, and cosmetic toiletries as a germicide. Today, triclosan is incorporated into toothpaste because of its wide spectrum of antimicrobial activities and low toxicity.

Pharmacokinetics

Triclosan is retained in dental plaque for at least 8 hours, which in addition to its broad antibacterial property could make it suitable for use as an antiplaque agent in oral care preparations. However, the compound is rapidly released from oral tissues, resulting in relatively poor antiplaque properties as assessed in clinical studies of plaque formation. This observation is further corroborated by a poor correlation between minimal inhibitory concentration values generated in vitro and clinical plaque inhibitory properties of triclosan. Improvement of substantivity was accomplished by incorporation of triclosan in a polyvinyl methyl ether maleic acid copolymer (PVM/MA, *Gantrez*). With the combination of PVM/MA copolymer and triclosan, the substantivity of the triclosan was increased to 12 hours in the oral cavity.

Mechanism of Action

Triclosan is active against a broad range of oral gram-positive and gram-negative bacteria. The primary target of its antibacterial activity is the bacterial cell membrane. High concentrations cause membrane leakage and ultimately lysis of the bacterial cell. Effects at lower

TABLE 42.1 Comparison of Antiplaque Agents in Oral Rinses

Rinse	Active Agent	Concentration (%)	Pharmacological Actions	Effect on Plaque	Effect on Gingivitis	Dispensed	Side Effects
PerioGard[a] Peridex[a]	Chlorhexidine	0.12	Interferes with sugar transport Disrupts cell membranes Precipitates intracellular proteins	↓↓↓	↓↓↓	P	Extrinsic tooth staining Altered taste sensation Enhanced calculus formation Oral ulcers
Viadent	Sanguinarine	0.01	Suppresses bacterial enzymes	↓	↓	OTC	Burning sensation
Listerine[a]	Essential oils[b]	0.25	Inhibits bacterial enzymes	↓	↓/o	OTC	Bitter taste
	Alcohol	26.90	Reduces amount of endotoxin Denatures bacterial cell walls				Bitter taste Burning sensation Desiccation of mucous membranes
Act[c]	Fluoride	0.23	Inhibits bacterial glycolysis	o	o	OTC	Mild tooth staining
Plax[a]	Sodium benzoate	Unknown	Dissolves plaque?	o	o	OTC	None reported
	Sodium lauryl sulfate	Unknown					

↓, decrease; o, no change; P, prescription; OTC, over the counter.
[a]*PerioGard, Peridex, Listerine,* and *Plax* are trade name examples; other similar generic rinsing agents are commercially available.
[b]Essential oils contain eucalyptol, methyl salicylate, thymol, and menthol.
[c]Suggested use of fluoride rinses at these concentrations is for control of carious lesions.

concentration are more subtle. Triclosan has been shown to bind to cell membrane targets and inhibit enzymes associated with the phosphotransferase and proton motive force systems.

Clinical Effects

Triclosan plus copolymer is available in toothpaste. Commercially available dentifrice concentrations contain 0.3% triclosan and 2.0% PVM/MA copolymer. This product (*Total*) was tested in a large number of short-term controlled clinical trials, from which a statistically significant but clinically modest 15 to 20% plaque reduction was reported. The same toothpaste composition also exhibited significant anticalculus properties. Typically, the reported reductions in calculus formation ranged from 25 to 35%. Finally, of considerable interest is the observation that triclosan inhibits gingivitis by a mechanism independent of its antiplaque activity. In a clinical study, minimal plaque effects accompanied an average 50% reduction in gingivitis. An explanation of this surprising effect stems from research conducted using a gingival fibroblast cell culture model. These experiments revealed that triclosan could inhibit the IL-1-induced production of prostaglandin E_2.

Essential Oils

A mixture of essential oils consisting of thymol 0.06%, eucalyptol 0.09%, methyl salicylate 0.06%, and menthol 0.04% in an alcohol-based vehicle (26.9%) provides the plaque-inhibiting properties of rinsing agents such as *Listerine*.

Essential oils may reduce plaque levels by inhibiting bacterial enzymes and by reducing pathogenicity of plaque via reduction of the amount of endotoxin; the alcohol is probably responsible for denaturing bacterial cell walls. The substantivity of Listerine appears to be quite low, and therefore, it must be used at least twice a day to be effective. A variety of clinical studies have demonstrated that Listerine is capable of reducing plaque and gingivitis over extended periods; however, the degree of reduction is variable. Listerine will reduce plaque and gingivitis anywhere from 14.9 to 20.8% and 6.5 to 27.7%, respectively (Table 42.1). Adverse reactions include a bitter taste and burning sensation in the oral cavity. Regular use of high-alcohol rinses can aggravate existing oral lesions and desiccate mucous membranes. In addition to Listerine, a huge number of American Dental Society (ADA) approved generic equivalents available over the counter.

Fluorides

Fluorides are widely used in caries prevention, for which they have been highly effective. Systemic administration of fluorides for caries prevention is available via drinking water (1 mg/ L), tablets (0.25–1 mg), drops (0.125–0.5 mg), topical application by mouthwashes (200–1,000 mg/L), gels for home use (900 mg/kg) and professional use (9,000–19,000 mg/kg), and dentifrices (1,000 mg/kg). In contrast to the efficacy of fluorides in preventing carious lesions, these formulations have relatively poor antibacterial properties (Table 42.1). The weak therapeutic benefit of fluorides on gingivitis is due to a modest inhibition of glycolysis in plaque bacteria. Sodium fluoride, monofluorophosphate, and stannous fluoride are the compounds used in topically applied agents.

A few well-controlled clinical studies suggested a potential plaque-inhibiting effect for dentifrices containing stannous fluoride. However, these results were most likely due to the stannous ion rather than to fluoride; the positive charge of the stannous ion may interfere with bacterial membrane function, bacterial adhesion, and glucose uptake, thereby inhibiting the formation of plaque.

Mild tooth staining has been observed after use of stannous fluoride products. The ADA Council on Dental Therapeutics endorses fluorides for their caries-inhibiting effect but not for plaque inhibition.

Prebrushing Rinses

The topical application of a liquid rinse before brushing as an aid in the mechanical removal of supragingival plaque is a novel idea. Since the introduction of the first prebrushing rinse there has been a rapid increase in the number of generic products that claim to physically loosen or remove plaque. Prebrushing rinses usually contain a plethora of ingredients, and it is not known which constituent is the active chemical. It has been suggested that sodium lauryl sulfate acts as a detergent to dislodge or loosen the plaque on teeth (Table 42.1). When prebrushing rinses were tested against placebo rinses, prebrushing rinses appeared to have no effect on plaque reduction.

FUTURE DIRECTIONS

Today gingivitis and periodontitis are prevented principally through mechanical plaque control; however, dentition free of supragingival and subgingival plaque is extremely difficult to accomplish and maintain. On an annual basis, Americans spend more than $750 million on oral rinsing agents, although few effective plaque-inhibiting oral rinses are available and many are associated with side effects that prohibit long-term use.

The goal of future product development is not so much an improvement in the antiplaque performance of the existing effective compounds but rather lessening of their side effects and development of better delivery systems. Products that combine various known com-

pounds with well-established plaque-inhibiting properties are under investigation. Among the most promising products are amine fluoride plus stannous fluoride and copper sulfate plus hexetidine. In the future, chemoprevention of supragingival plaque will depend on products that are effective, substantive, and safe.

Study Questions

1. The period during which a drug is in contact with a substrate in the oral cavity is
   (A) Excretion
   (B) Absorption
   (C) Distribution
   (D) Substantivity
   (E) Drug clearance
2. Yellow or brownish extrinsic stain of teeth is a frequently observed side effect of
   (A) Fluoride
   (B) Triclosan
   (C) Essential oils
   (D) Chlorhexidine
   (E) Sodium lauryl sulfate
3. The LEAST effective chemical agent for reduction of dental plaque is
   (A) Triclosan
   (B) Essential oils
   (C) Chlorhexidine
   (D) Stannous fluoride
   (E) Sodium lauryl sulfate
4. Which of the following agents was combined with the PVM/MA polymer to improve substantivity?
   (A) Fluoride
   (B) Triclosan
   (C) Essential oils
   (D) Chlorhexidine
   (E) Sodium lauryl sulfate
5. Which commercial product would you prescribe for a recovering alcoholic?
   (A) Act
   (B) Plax
   (C) Total
   (D) Peridex
   (E) Listerine

ANSWERS

1. **D.** Excretion (A) and drug clearance (E) are factors involved in drug elimination, while absorption (B) describes the ability of a drug to cross membranes and enter the blood stream. Distribution (C) describes the ability of a drug to enter a variety of body compartments during its circulation in the blood.
2. **D.** It is due to the ability of this cation to strongly bind to tooth surfaces, requiring strong abrasives to remove the stain. The other four compounds are not cationic and do not bind strongly to tissues.
3. **E.** Triclosan (A) is active against a broad range of oral gram-positive and gram-negative bacteria. Essential oils (B) are effective in reducing plaque levels by inhibiting bacterial enzymes. Chlorhexidine (C) is generally effective against all bacteria, but *Streptococcus mutans* and *Actinomyces viscosus,* two bacteria particularly associated with dental lesions, are especially susceptible to its action. Stannous fluoride (D) is widely used in caries prevention, and many studies have proven its effectiveness.
4. **B.** None of the other compounds listed has been shown to decrease supragingival plaque in combination with the polymer in a commercial preparation.
5. **C.** All of the other preparations contain alcohol.

SUPPLEMENTAL READING

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CASE Study Drug Research and Periodontal Disease

A 21-year old white woman who works as a research analyst for the Food and Drug Administration was evaluating the results of a new drug for the treatment of periodontal disease. Her review of the phase III clinical data caused her to visit her dentist, since she was concerned that her oral cavity exhibited many of the signs of the subjects who were participants in the clinical study. A review of her periodontium by her dentist revealed swollen and tender gingiva that were accompanied by erythema and bleeding upon mild provocation. Her dental radiographs revealed no abnormalities, and her physician found her to be healthy at her last physical examination. She reports taking no medications and denies allergies to any medicine. She is concerned about her health because her gingiva will bleed when she eats fibrous foods (e.g., apples) and affects her appearance.

1. What do you think is the most likely cause of her periodontal disease?
2. Should she be referred to a physician for further physical examination for a systemic alteration that was overlooked at her last physical examination? If so, what problem should be considered, and what tests should be ordered?
3. Should an oral chemotherapeutic agent be prescribed for her periodontal disease? If so, which one would you prescribe and what would be the benefit and disadvantage of using this agent for this patient?

ANSWER:

1. In most instances, dental plaque can cause erythema and gingival bleeding, but the gingival response can also be exacerbated by a variety of systemic conditions, including diabetes mellitus, leukemia, malnutrition, puberty and pregnancy.
2. An examination by the dentist should eliminate many of the potential systemic issues that can affect the periodontium of this patient. For example, the age of the patient, her appearance, and questions about her diet should be enough to rule in or out issues concerning puberty and malnutrition. However, if systemic conditions cannot be ruled out, an additional physical examination by a physician may be necessary. Additional tests to be requested could include oral glucose tolerance test for diabetes mellitus, human chorionic gonadotropin levels for pregnancy, and/or qualitative and quantitative evaluation of bone marrow cells and blood cells for leukemia.
3. If the patient's periodontal disease is the result of a leukemia or diabetes mellitus, the first response should be to treat the disease that is exacerbating the oral response to plaque. In these cases, an intensive oral physiotherapy program using over-the-counter toothpastes with triclosan would be warranted for home care. If the patient is pregnant, a thorough review of oral hygiene combined with over-the-counter toothpaste with triclosan would be appropriate. If persistent inflammation and gingival enlargement continue, the use of a prescription antiplaque rinse, such as chlorhexidine, would be warranted.