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Pharmacology and Dental Therapeutics

Third Edition

Pharmacology and Dental Therapeutics

Third Edition

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This book is dedicated to

Gayle, Tom, and Oliver (R.A.S)

Janice, Robert, and Simon (J.G.M)

Nicola, Matthew, and Jonathan (M.S.Y)

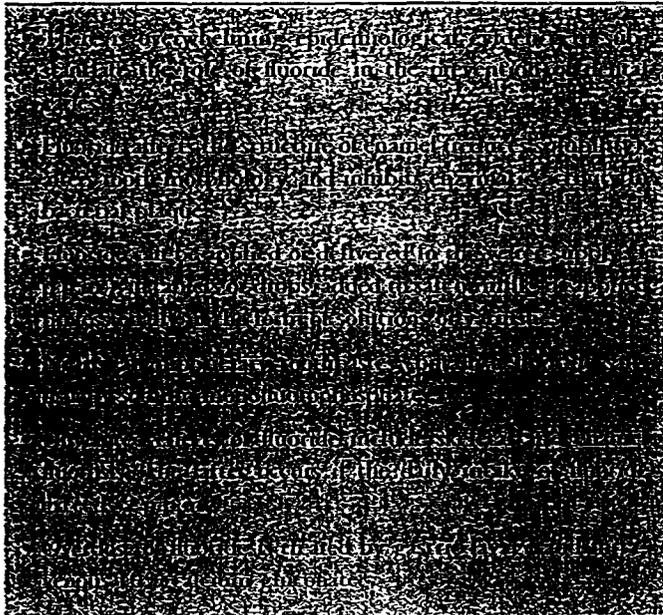
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Key facts

Dental caries and fluoride



Periodontal disease

The periodontal diseases are caused by bacterial plaque, although systemic disorders can modify the response of the periodontal tissues to bacterial toxins and enzymes. In essence, the diseases are a result of an interaction between the bacterial products and the host's immune and inflammatory responses. Periodontal disease is broadly classified as: gingivitis, where inflammatory changes are confined to the gingival connective tissue; and periodontitis, which involves loss of connective-tissue attachment to the root surface, apical migration of the junctional epithelium, pocket formation, and/or gingival recession and bone loss. The common form of periodontitis is the chronic adult type. Rarer types include prepubertal, juvenile, and rapidly progressive periodontitis. These conditions are now collectively referred to as early-onset periodontitis. A further form of periodontitis is now recognized and known as refractory periodontitis. As the name suggests, this type of periodontal disease does not respond to conventional treatment and appears to be associated with a specific microflora. Refractory periodontitis can only be diagnosed retrospectively and frequently requires systemic antimicrobial therapy to resolve the condition.

Pathogenesis of periodontal disease

There is overwhelming evidence that periodontal diseases are caused by bacterial plaque. However, several additional mechanisms may contribute towards the degradation of the gingival and periodontal connective tissues.

Activation of the host's immune cells (macrophages as well as

T and B lymphocytes) by plaque toxins and enzymes can cause the release of a variety of cellular and biochemical mediators. Some of these mediators have the potential to cause degradation of gingival and periodontal connective tissue and alveolar bone resorption. The exact mechanism of plaque-induced periodontal destruction is uncertain. Interleukin-1, prostaglandins of the E series, and tumour necrosis factor released from macrophages and polymorphonuclear leucocytes can all modulate tissue destruction. In turn, these mediators activate metalloproteinases (i.e. collagenases) that degrade the connective tissue matrix.

Longitudinal studies in adults have shown that periodontal destruction is episodic and is characterized by bursts of activity, followed by periods of quiescence. Such bursts may be synchronous or occur at random times. There is uncertainty over the site specificity of such bursts and the initiating factors. Certain bacterial species, the so-called periodontopathogens (see later), are associated with active disease. *In-vitro* studies confirm the pathogenicity of these bacteria and the ability of their enzymes and toxins to destroy the periodontal tissues. However, it remains to be confirmed whether these bacteria are the initiators or the consequence of the burst of activity. It could also be argued that bursts are related to a localized failure of the host's response. An obvious cause for such a failure is a change in antigenic challenge arising from the subgingival microflora.

The pathogenesis of periodontal disease remains an area of intensive research. Perhaps the only fact that can be stated with confidence is that the disease is caused by the accumulation of bacterial plaque. The subsequent interaction between bacteria and their products with the host's immune and inflammatory responses probably leads to tissue breakdown and the progression of the disease. A thorough understanding of the disease process is mandatory since this will lead to more appropriate methods of control.

Dental plaque

Dental plaque is a bacterial aggregation on the teeth or other solid structures in the mouth. It is an uncalcified, soft material which is so tenaciously adherent to the tooth surface that it resists removal by salivary flow or a gentle spray of water across its surface. The dense bacterial masses are enveloped in a matrix that originates either from the host (salivary glycoproteins), or from the bacteria themselves (extracellular polysaccharides).

Composition of plaque

Approximately 70% of the volume of plaque is bacterial cells. The rest is made up of extracellular polysaccharides that act as a matrix for the cellular component. The carbohydrates include dextran, which is a predominantly α 1-6-linked variety of glucan (a polymer of glucose), and mucan, which is a predominantly α 1-3-linked glucan. These glucans are produced primarily by *Streptococcus mutans* and *Actinomyces* species during initial plaque formation.

In addition to the bacteria and matrix, plaque contains small

ers of epithelial cells and white blood cells probably derived from crevicular fluid.

Development of plaque

Each tooth surface is vigorously cleaned of all soft deposits, then a new pellicle, distinct from dental plaque, begins to form within only a few minutes. This so-called pellicle is an amorphous layer, 0.1–0.5 μ m thick, composed of salivary glycoproteins that have become covalently adsorbed on to the tooth surface. The adsorbed molecules of glycoprotein may penetrate the enamel surface and this leads to difficulty in completely removing the pellicle (and eventually plaque) from the tooth by normal brushing. The molecules of glycoprotein eventually undergo a biochemical modification to produce a highly insoluble surface coating that serves as a base on which supragingival plaque formation occurs.

The first bacteria to colonize the pellicle are *Streptococcus sanguis* and *Streptococcus mitis*, followed by *Actinomyces* species. As the plaque continues to form, the number of bacteria increases by further adsorption from saliva and by multiplication of bacteria which have already colonized the teeth. There are several qualitative changes in its bacterial composition. The proportions of Gram-negative cocci and Gram-positive and Gram-negative rods increase gradually and the percentage of Gram-positive cocci is reduced.

Small, pleomorphic and fusiform bacteria are seen in 2–4-day-old plaque and they eventually grow in to replace the coccal forms. The maturation of the plaque matrix increases the proportion of Gram-negative organisms to Gram-positive organisms, and the metabolic characteristics of the bacteria become predominantly anaerobic. These changes in metabolism usually coincide with the features of gingivitis.

As inflammation develops in the marginal gingival tissues, the gingiva becomes oedematous and swollen. The primary source of bacteria of the microbial flora changes as the increased flow of gingival fluid continuously bathes the subgingival bacteria. The apical portion of the previously supragingival plaque becomes protected in the clinically deepened gingival sulcus, and may now be regarded as a subgingival deposit. The growth of supragingival plaque is enhanced by the downgrowth of bacteria from the supragingival location. This occurs partly by the movement of discrete colonies of pioneer bacteria by the migration of motile forms, and predominantly by the migration of bacteria through the continuous layer of plaque. The environment changes to favour the colonization and growth of Gram-negative anaerobic bacteria. The subgingival plaque is protected from the cleansing mechanisms of the oral cavity. A more loosely attached bacterial layer can exist on the surface of the plaque.

The contents of a periodontal pocket are now rightly referred to as plaque.

Plaque is a biologically derived fluid that contains a suspension of either cells or bacteria. The major constituents of this fluid are the Gram-negative bacteria of the subgingival plaque. The bulk of the mass of the biofilm is derived from gingival crevicular

fluid. Other constituents include immunoglobulins, PMNs and other white blood cells, epithelial squames, and various proteolytic enzymes. The subgingival biofilm has a dynamic composition and its physicochemical properties have an important influence on local drug delivery that is sometimes used in the treatment of periodontal diseases.

Mechanisms of bacterial adherence to tooth surfaces

The bacteria that initially colonize the pellicle or tooth surface must possess a specific mechanism by which they adhere either to glycoprotein or to the hydroxyapatite. Many oral bacteria have ultrastructural appendages or fimbriae radiating from their surface. It is likely that such structures are important in the process of early bacterial attachment. The fimbriae have distinct lectin-like properties, which may be able to recognize specific sites within the pellicle or hydroxyapatite. One example is the ability of *Streptococcus mutans* to recognize β -galactoside residues of salivary glycoproteins in the pellicle. Similarly, bacterial co-aggregation can occur involving surface lectins on one micro-organism and carbohydrate-containing receptors on another cell. Such mechanisms would be responsible for the observation that several different types of bacteria are seen on a tooth surface after only a few days of abstaining from tooth cleaning.

Another mechanism of bacterial adherence involves the enzyme glucosyl transferase (GTF), which converts dietary sucrose to glucan polymers. GTF binds strongly to saliva-coated hydroxyapatite and may be able to bind bacteria directly to the surface. Alternatively, indirect mechanisms may involve GTF interactions with α 1–3 glucose chains produced by the adsorbed enzyme on cell surfaces. This would explain why bacterial adherence to tooth surfaces is not improved by premade or commercially available glucans, as the active GTF enzyme is only available during bacterial production of glucan molecules.

Other factors such as electrostatic or electrodynamic forces can influence bacterial–tooth and bacterial–bacterial adherence, but evidence suggests it is the lectin–carbohydrate interaction that is of primary importance for bacterial adhesion to the tooth surface and the subsequent development of plaque.

The management of periodontal diseases

Periodontal diseases can be prevented by either inhibiting the formation of plaque on the tooth surface, or by completely removing plaque before inflammatory changes occur in the periodontal tissues. Complete plaque removal by mechanical means may be possible in well-motivated individuals, but most people leave plaque on some part of the tooth surface after brushing. It can be argued, of course, that a completely plaque-free dentition and absolute periodontal health are not just unattainable, but are unnecessary for many of the population. However, in certain types of particularly destructive forms of periodontal disease (for example in the early-onset periodontal conditions), even very thin, undetectable films of plaque may predispose to excessive periodontal destruction in a short period. In such cases, high standards of plaque

control are essential if tooth loss in later life is to be avoided. Furthermore, certain physically or mentally handicapped patients are unable either to clean their teeth effectively or to attend a dentist regularly. These patients may also suffer from extensive periodontal disease.

A need exists for means of plaque control as adjuncts or alternatives to the time-honoured mechanical methods (Tables 12.1 and 12.2). There has been considerable research into developing plaque inhibitory agents and anticalculus agents that can be used in the management of periodontal disease. In addition, the role of bacterial plaque in the pathogenesis of periodontal disease is well established, and there is increasing evidence that specific bacteria may be more directly involved in the aetiology of the early-onset periodontal conditions (Table 12.3). Thus the development of specific antimicrobial agents directed towards such bacteria is an important advance in the management of this type of periodontal disease.

Prostaglandins of the E series are important mediators of the tissue destruction and bone loss seen in periodontal disease. Various studies have shown that non-steroidal anti-inflammatory

drugs (NSAIDs) may help stop bone loss and connective tissue breakdown (see later).

Properties and aims of antiplaque agents

The principles of chemical plaque control are based on certain criteria. Chemical agents should inhibit the microbial colonization of tooth surfaces and prevent the subsequent development of plaque. They should also eliminate or reduce the pathogenicity of already existing plaques, and prevent calculus formation.

A large number of compounds, including enzyme preparations, antibiotics, antiseptics, and surface-active substances, have been evaluated as antiplaque agents (see Table 12.1). The ideal properties of an antiplaque agent are listed in Table 12.2 above. No substance currently fulfils all these criteria.

First- and second generation agents

Antiplaque compounds have been categorized primarily according to their antimicrobial efficacy and relative substantivity. The term substantivity refers to the ability of a compound to be adsorbed on to a surface (or binding site) and then subsequently released from that surface over a period of time. When the compound is bound, it is in an inactive form.

First-generation compounds include antibiotics, phenols, quaternary ammonium compounds, and sanguinarine. They can reduce plaque scores by about 20–50%, and their efficacy is limited by their poor retention in the oral cavity.

Second-generation agents are more effectively retained by oral tissues and their slow-release properties reduce plaque scores by 70–90%. The bisbiguanides are examples. Using first-generation agents 4–6 times daily produces a similar effect to using the second-generation compounds once or twice a day.

Enzymes

Various enzymes have been used as antiplaque agents (see Table 12.1), on the basis of the theory that they would break down the matrix of already formed plaque and calculus. Furthermore, it was supposed that certain proteolytic enzymes would be bactericidal

Table 12.1 Classification of antiplaque agents

Cationic surfactants

Bisbiguanides, e.g. chlorhexidine digluconate, alexidine
Quaternary ammonium compounds, e.g. cetylpyridinium chloride, benzalkonium chloride, benzalkonium chloride, domiphen bromide
Pyrimidine derivatives, e.g. hexetidine
Bispyridine derivatives, e.g. octenidine hydrochloride

Phenolic compounds

Listerine (thymol 0.06%, eucalyptol 0.09%, methyl salicylate 0.06%, methanol 0.04%)
Triclosan

Herbal extracts

Sanguinarine

Heavy metal salts

Zinc chloride and citrate
Stannous fluoride
Copper sulfate

Enzymes

Mucinase
Mucanase
Dextranase
Amyloglucosidase/glucose oxidase

Anionic surfactants

Aminoalcohols, e.g. octapinol, decapinol
Plax
Sodium dodecyl sulfate
Sodium lauryl sulfate

Table 12.2 Ideal properties of antiplaque agents

1	Eliminate pathogenic bacteria only
2	Prevent the development of resistant bacteria
3	Exhibit substantivity
4	Be safe to the oral tissues at the concentrations and dosages recommended
5	Significantly reduce plaque and gingivitis
6	Inhibit the calcification of plaque to calculus
7	Not stain teeth or alter taste
8	Have no adverse effects on the teeth or dental materials
9	Be easy to use
10	Be inexpensive

Based on Bral and Brownstein 1988

Table 12.3 Pathogens which have been associated with different forms of periodontal disease

Disease	Associated micro-organisms
Localized juvenile periodontitis	<i>Actinobacillus actinomycetemcomitans</i> , <i>Prevotella intermedia</i> , <i>Capnocytophaga</i> spp., <i>Eikenella corrodens</i> , <i>Fusobacterium</i> spp., <i>Peptostreptococcus micros</i> , <i>Selenomonas</i> spp., Spirochaetes (<i>Treponema</i> spp.)
Rapidly progressive periodontitis	<i>Actinobacillus actinomycetemcomitans</i> , <i>Prevotella intermedia</i> ,
Early-onset/generalized juvenile periodontitis	<i>Eubacterium</i> spp., <i>Fusobacterium</i> spp., <i>Peptostreptococcus micros</i> , <i>Selenomonas</i> , Spirochaetes (<i>Treponema</i> spp.), <i>Wolinella recta</i>
Adult periodontitis	<i>Actinobacillus actinomycetemcomitans</i> , <i>Bacteroides forsythus</i> , <i>Eikenella corrodens</i> , <i>Fusobacterium</i> spp., <i>Peptostreptococcus micros</i> , <i>Selenomonas</i> , Spirochaetes (<i>Treponema</i> spp.), <i>Wolinella recta</i> <i>Prevotella intermedia</i>
Refractory periodontitis	<i>Actinobacillus actinomycetemcomitans</i> , <i>Porphyromonas gingivalis</i> , <i>intermedius</i> , and <i>forsythus</i> , <i>Eikenella corrodens</i> , <i>Fusobacterium</i> spp., <i>Peptostreptococcus micros</i> , Spirochaetes (<i>Treponema</i> spp.), <i>Wolinella recta</i> , <i>Candida</i> spp.
Periodontal abscess	<i>Porphyromonas gingivalis</i> and <i>Prevotella intermedia</i> , <i>Peptostreptococcus micros</i> , <i>Staphylococcus</i> spp., <i>Candida</i> spp.
Acute necrotizing ulcerative gingivitis (NUG)	<i>Porphyromonas gingivalis</i> and <i>Prevotella intermedia</i> , Spirochaetes (<i>Treponema</i> spp.)

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to plaque organisms and so act as 'disinfectants' when applied topically in the oral cavity

Enzymes that have been used to destroy plaque include mucinases, extracts from dried pancreas (containing trypsin, chymotrypsin, carboxypeptidase, amylase, lipase, and nuclease), dextranase, and mutanase. These have been incorporated into chewing gum and toothpastes. However, although *in-vitro* findings showed promise, clinical trials produced indifferent results and a high incidence of unwanted effects. These enzymes are thus of little value in the control of periodontal disease.

A more effective enzymatic system for reducing plaque growth is based upon the production of an intrinsic salivary inhibitor by a series of humoral factors and biochemical pathways. This system is known as the lactoperoxidase-hypothiocyanite system, and is the basis for the pharmacodynamics of the commercially available dentifrice Zendium (Oral-B Laboratories).

Certain oral bacteria are known to produce hydrogen peroxide by the oxidation of the glycolytic enzyme NADH₂ oxidase. Normally, hydrogen peroxide is used to oxidize another NADH₂ molecule, or is inactivated by the enzyme catalase. However, when the level of hydrogen peroxide is increased it assists lactoperoxidase in the oxidation of thiocyanate to produce the hypothiocyanite ion (OSCN⁻), which is the hypochlorite of thiocyanogen. Hypothiocyanite ions interfere with cellular oxidation-reduction mechanisms, by upsetting the NADH₂-NADPH₂ balance. Lactoperoxidase and thiocyanate are essential to this reaction, and are both normal constituents of saliva.

The optimal level of hydrogen peroxide required for hypothiocyanite production is achieved by a further enzyme system involving amyloglucosidase and glucose oxidase. Both are constituents of Zendium toothpaste (Fig. 12.1).

In clinical trials, this toothpaste has been shown to inhibit plaque formation when compared with either placebo pastes containing no enzymes or other commercially available pastes.

Antibiotics as antiplaque agents

The bacterial nature of dental plaque and its primary role in the aetiology of periodontal disease has stimulated a considerable amount of research into the use of antibiotics to try to control the disease. Agents that have been evaluated include penicillin, vancomycin, erythromycin, and kanamycin. In all instances the drugs are used topically. However, since the mid-1970s, interest in this approach has waned. The potential problems of bacterial resistance, disturbances in the gut and oral flora, and the increased risks of hypersensitivity reactions are of more clinical significance than the antiplaque effects of these drugs. Furthermore, there are now many alternative antiplaque agents available for use instead of antibiotics.

Although the topical use of antibiotics has now ceased, the systemic use of these drugs is of benefit in the management of certain types of periodontal disease. This application is discussed later.

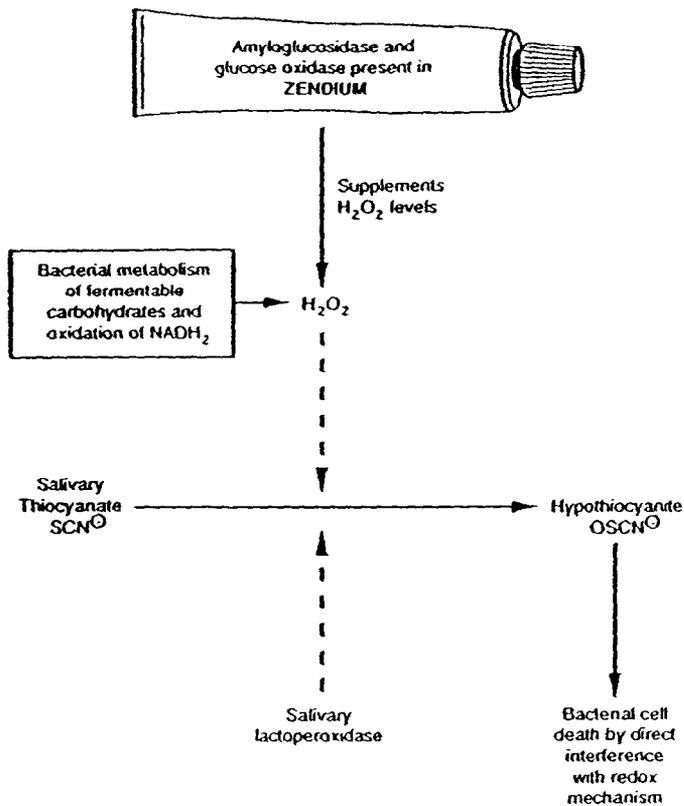


Fig. 12.1 Mechanism of Zendium in the lactoperoxidase-hypothiocyanite system.

Phenols

The phenols are a group of antiseptic compounds that have been used in medicine for over 100 years. Preparations of phenols and their derivatives have had widespread application as disinfectants and antiseptics (see Chapter 10). Most phenols exert a non-specific antibacterial action, which is dependent on the ability of the non-ionized form of the drug to penetrate the lipid component of the cell walls of Gram-negative organisms. The resulting structural damage affects the permeability control of the organisms. In addition, several metabolic processes that depend on enzymes in the cell membrane are also disrupted. Phenolic compounds also exhibit anti-inflammatory properties. This may result from their ability to inhibit neutrophil chemotaxis, neutrophil superoxide ion generation, and prostaglandin synthetase production.

Phenols have been incorporated into mouthrinses for topical use as antimicrobial/antiseptic agents to inhibit plaque formation. Listerine is an over-the-counter phenol preparation that contains thymol (0.06%), eucalyptol (0.09%), methyl salicylate (0.06%), and methanol (0.04%), i.e. in a hydroalcoholic vehicle.

The antiplaque activities of Listerine are well established. When compared to the vehicle or to water alone, Listerine was found to reduce both the wet and dry weights of plaque by more than 50% after 9 months' use. It also reduced the protein content

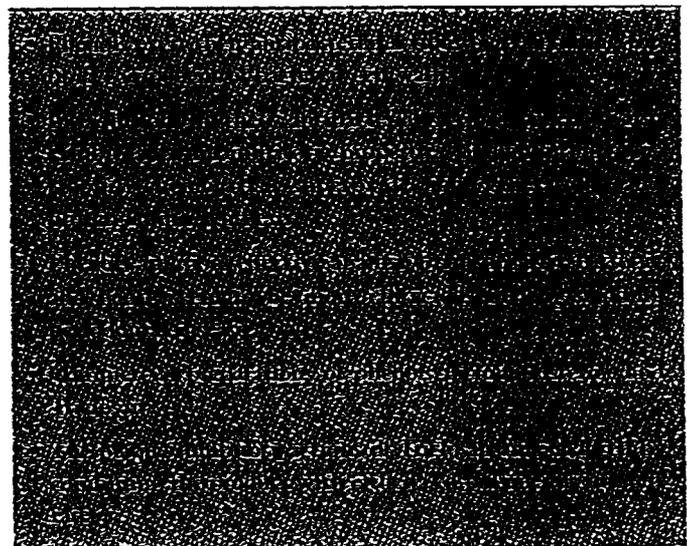
of plaque by about 60% and its toxicity by 75%. This suggests that the active agents in Listerine affect the pathogenicity of plaque by reducing its overall endotoxin activity.

TRICLOSAN

This compound is a non-ionic bisphenol with a broad spectrum of activity against both Gram-positive and Gram-negative bacteria as well as fungi. The compound exhibits poor substantivity and can be formulated into a mouthrinse or a toothpaste. The mechanism of Triclosan's antibacterial effect is uncertain. Due to its hydrophobic and lipophilic nature, it adsorbs on to the lipid portion of the bacterial cell membrane. At low concentrations, Triclosan interferes with vital transport mechanisms within the bacteria. When used alone, Triclosan possesses a moderate plaque-inhibitory effect. This activity is enhanced when the compound is combined with zinc citrate or incorporated into a co-polymer of methoxyethylene and maleic acid. These combinations are used extensively in proprietary toothpastes. The co-polymer increases the substantivity of Triclosan and acts as a reservoir. The combination of Triclosan and zinc citrate does not appear to be associated with the development of resistant strains, and long-term use has no adverse effects on the oral flora. No other unwanted effects have been reported with the long-term use of these combinations.

The clinical benefits of Triclosan and zinc citrate are small, but measurable. The impact of these compounds on the periodontal health of the population remains to be determined.

Key facts Phenols



Quaternary ammonium compounds

Quaternary ammonium compounds are cationic antiseptics and surface-acting agents. The basic chemical structure is a central nitrogen atom linked to four alkyl groups by covalent bonds. An

covalent bond connects the anion to the nitrogen atom (Fig 12.2). The molecules have a net positive charge and react with the negatively charged, cell-membrane phospholipids, disrupting its structure and so increasing permeability. Quaternary ammonium compounds tend to be more effective against Gram-positive than Gram-negative micro-organisms. This may suggest that these agents would be more beneficial as antiplaque agents when used against early developing plaque, which contains predominantly Gram-positive bacteria. Indeed, these compounds are used extensively as prebrushing rinses, that is they are rinsed around the mouth before toothbrushing. Prebrushing rinses are thought to disrupt plaque and thus facilitate its removal by mechanical means. Quaternary ammonium compounds used as antiplaque agents include benzethonium chloride, benzalkonium chloride, and cetylpyridinium chloride.

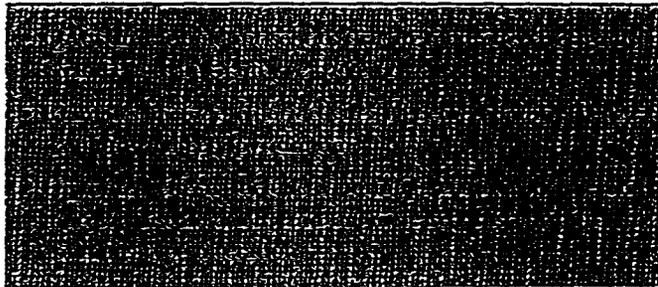
Many clinical trials support the effectiveness of quaternary ammonium compounds as antiplaque agents. However, comparison with chlorhexidine preparations (see later), suggests their clinical usefulness is somewhat limited. The oral retention of quaternary ammonium compounds is about twice that of chlorhexidine,

when assessed by their release into water rinses. However, the absorption of quaternary ammonium compounds into saliva is much more rapid. Factors in saliva could influence the relative absorption of these compounds. *In vitro*, calcium ions displace cetylpyridinium chloride from carboxyl groups at lower concentrations than those needed to displace chlorhexidine. Furthermore, the doubly charged chlorhexidine may bond more effectively to oral sites than the monovalent quaternary ammonium compounds. Such differences in physicochemical properties may account for the poorer efficacy of these compounds.

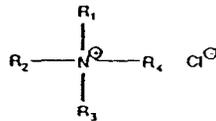
Quaternary ammonium compounds are not without unwanted effects and these include a burning sensation of the oral mucosa, brownish discoloration of the teeth and tongue, and a recurrent aphthous-type ulceration.

Key facts

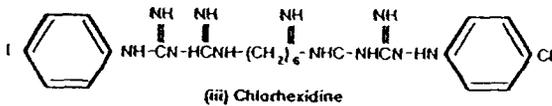
Quaternary ammonium compounds (QACs)



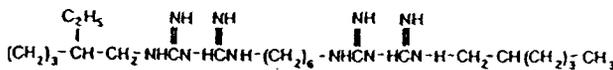
(i) Phenols



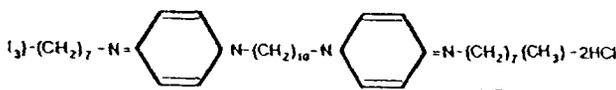
(ii) Quaternary ammonium compounds



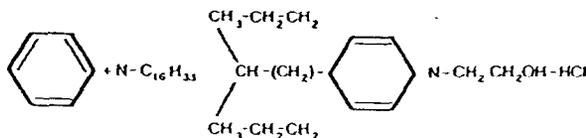
(iii) Chlorhexidine



(iv) Alexidine



(v) Octenidine



(vi) Cetylpyridinium chloride

(vii) Aminoalcohols

Fig. 12.2 Structures of antiplaque agents.

Bisbiguanides

The bisbiguanide compounds, which include chlorhexidine gluconate and alexidine, are the most effective antiplaque agents currently in use. Bisbiguanides are the primary second-generation antiplaque agents and exhibit considerable substantivity, and they also have very broad antibacterial properties.

CHLORHEXIDINE DIGLUCONATE

Chlorhexidine is a cationic chlorophenyl bisbiguanide (Fig 12.2) with outstanding bacteriostatic properties. It was synthesized by ICI in 1954 after extensive investigations of the biological properties of polydiguanide compounds.

Chlorhexidine is a well-tolerated and long-lasting antiseptic which is not neutralized by soaps, body fluids, or other organic compounds. Other medical uses of chlorhexidine are discussed in Chapter 10. Its application as an antiplaque agent was first proposed in 1969, and it is now available as a 0.2% or 0.12% aqueous solution, as a toothpaste gel (0.5–1%), and a local delivery device (a gelatin chip—the Periochip) for placement into periodontal pockets after root surface debridement.

PHARMACOKINETICS OF CHLORHEXIDINE When chlorhexidine is used as an antiplaque mouthrinse, its mode of action is purely topical. The drug does not penetrate through oral epithelium, and if some solution is inadvertently swallowed, the drug binds to the

mucosal surfaces of the alimentary tract. These cells are desquamated and together with any unbound chlorhexidine are excreted in the faeces. The small amount of chlorhexidine that may be absorbed is metabolized in the liver.

BACTERICIDAL ACTION OF CHLORHEXIDINE The action of chlorhexidine in killing bacterial cells depends initially on the drug having access to the cell walls. This is facilitated by electrostatic forces between the negatively charged cells and the net positively charged, chlorhexidine molecules. Having gained access to the cell membrane, chlorhexidine disorients its lipoprotein structure, destroying the osmotic barrier of the bacteria. Cell permeability increases and intracellular components such as potassium ions leak through the damaged membrane.

A secondary action of chlorhexidine is to cause intracellular coagulation, which effectively slows down the rate of cell-content leakage. This cytoplasmic coagulation is responsible for the bactericidal effect of chlorhexidine and is directly dependent on the concentration of the drug.

EFFECT OF CHLORHEXIDINE ON ORAL BACTERIA The short-term use of chlorhexidine causes a striking reduction in the number of oral micro-organisms. In the absence of other oral hygiene measures, chlorhexidine has been shown to reduce the number of bacteria in saliva by 85% after only 24 hours. A maximum reduction of 95% occurred after around 5 days. After this the numbers of bacteria gradually increased, but an overall reduction of 70–80% was maintained at 40 days. Cessation of chlorhexidine mouth rinses results in a rapid return of normal salivary bacterial counts.

Some bacteria are more susceptible to chlorhexidine than others. *Staphylococci* spp., *Strep. mutans*, *Strep. salivarius*, and *E. coli* are susceptible to chlorhexidine at a low minimum inhibitory concentration (MIC), whereas certain Gram-negative cocci resembling *Veillonella* spp. are the least susceptible.

The long-term use of any antimicrobial agent can be associated with increased microbial resistance and reduced sensitivity. Long-term studies of chlorhexidine are inconclusive in this respect. It has been suggested that the prolonged use of chlorhexidine tends to be more bactericidal towards strains of the more resistant bacteria in the oral flora. In effect, therefore, there is no change from susceptible organisms to resistant ones, so the effect on long-term plaque inhibition is negligible.

RETENTION OF CHLORHEXIDINE IN THE ORAL CAVITY Chlorhexidine is the most effective antiplaque agent. This is primarily due, not to its ability to destroy micro-organisms, but rather to the specific pharmacodynamics associated with the retention of the drug in the oral cavity.

After rinsing with 10 mL of a 0.2% aqueous solution of chlorhexidine for 1 minute, approximately 30% of the drug is retained in the mouth. The drug is believed to bind electrostatically to acidic protein groups such as phosphates, sulfates, and carboxyl ions which exist extensively on the oral tissues. Calcium ions in saliva are able to displace chlorhexidine from the carboxyl

binding sites. This displacement is comparatively slow and may help to explain the prolonged bacteriostatic effect of the drug in the mouth. Further, chlorhexidine can displace calcium ions that are bound to the sulfated glycoproteins of bacterial plaque. These findings suggest three possible mechanisms for the inhibition of plaque by chlorhexidine:

1. The blocking of acidic groups of salivary glycoproteins will reduce their adsorption to hydroxyapatite and the formation of the acquired pellicle.
2. The ability of bacteria to bind to tooth surfaces may be reduced by the adsorption of chlorhexidine to the extracellular polysaccharides of bacterial capsules or glycocalyxes.
3. Chlorhexidine may compete with calcium ions for acidic agglutination factors in plaque.

Laboratory studies have also shown that chlorhexidine can bind to hydroxyapatite. However, the conditions under which this occurs are not usually comparable to those *in vivo*. Thus, it is now considered that the affinity of chlorhexidine for the acidic proteins in pellicle, plaque, and calculus and on the surfaces of bacteria and oral mucosa is of greater clinical significance than its affinity for hydroxyapatite.

FACTORS AFFECTING THE RETENTION OF CHLORHEXIDINE A number of factors have been demonstrated to affect the binding capacity and plaque-inhibitory effect of chlorhexidine *in vivo*. After an oral rinse, the concentration of the drug in saliva falls rapidly and logarithmically during the first 4–8 hours, although the drug may still be detected after 24 hours. The proportion of chlorhexidine retained depends directly on both the concentration and the volume of the rinse solution. Approximately half of the chlorhexidine retained during a 60-second rinse will have bonded to receptor molecules in the first 15 seconds.

The pH in the oral cavity significantly affects both the binding and the release of chlorhexidine. Reducing the pH of the rinsing solution from 6.4 to 3 greatly reduces drug retention. The mechanism probably involves a reduction in the available negatively charged receptor sites for chlorhexidine when the environment becomes more acidic. Increasing the pH, however, does not appear to affect retention. Reducing the pH of the oral cavity by using acidic after-rinses also reduces retention of the drug and the subsequent plaque-inhibition. Free calcium ions also reduce the oral binding of chlorhexidine and increase its release from protein binding sites. The mechanism is likely to involve direct competition between the ions and the drug for available carboxyl groups on oral tissues. This finding has an important implication with respect to the use of chlorhexidine mouthrinses and the use of toothpastes. Most proprietary toothpastes contain calcium salts as filler agents. Thus if chlorhexidine is used soon after toothbrushing, there will be a high concentration of calcium ions present in the mouth. This will affect the binding of chlorhexidine and reduce its substantivity. Patients should be advised to use chlorhexidine at least 30 minutes after toothbrushing to avoid an

reaction between the calcium ions in toothpaste and the mouthwash.

UNWANTED EFFECTS OF CHLORHEXIDINE Chlorhexidine has been used for 30 years and its unwanted effects are of a local nature. Many patients find its initial taste unpleasant and repeated use often produces a disturbance in taste, which may last for several hours. Occasional cases of desquamative lesions of the oral mucosa and parodontal swelling have been reported, but the incidence is low. The main unwanted effect of chlorhexidine mouthwash or gel is a brown staining of the teeth. Three possible mechanisms may all contribute to this problem:

Non-enzymatic browning reactions (Maillard reactions): Carbohydrates and amino acids can act as substrates for the Maillard reaction. These food substances undergo a series of condensation and polymerization reactions leading to the formation of brown-pigmented substances known as melanoids. Melanoid production is catalysed by a high pH and chlorhexidine. The glycoprotein of the acquired pellicle covering the tooth surface may serve as a substrate for the Maillard reaction.

Formation of pigmented metal sulfides: The glycoprotein molecules of the tooth pellicle contain many disulfide bridges. When the glycoprotein is denatured, the disulfide bridges split yielding free sulfhydryl groups, which react with ferric stannous ions in the diet to form brown or yellow metallic sulfides. Chlorhexidine causes denaturation of the pellicle glycoprotein, and this may contribute towards the staining potential.

Reaction between chlorhexidine and factors in the diet: Many factors may be involved in the reaction between chlorhexidine and constituents of the diet to produce staining. It has been shown that aldehydes and ketones react with chlorhexidine to form coloured products and that these products would attach to a tooth surface. Staining from chlorhexidine is accentuated if there is a heavy consumption of tea, coffee, and red wine, these all contain tannin, which denatures the pellicle glycoprotein. Red wine also contains a high amount of iron.

Regular use of chlorhexidine causes thickening of the pellicle, providing a larger than usual surface area for stain absorption. The thickened pellicle also predisposes towards supragingival calculus formation and this may counteract the benefit of chlorhexidine.

The efficacy of chlorhexidine appears to be less in the presence of blood. The compound binds to various proteins found in blood and the bound substance is inactive. There are obvious implications with the use of chlorhexidine in the subgingival environment where the tissues are inflamed and blood may be present. The use of chlorhexidine in these circumstances will be more successful once the inflammation is brought under control.

In-vitro studies have also shown that chlorhexidine is cytotoxic

to gingival fibroblasts and inhibits their ability to bind to surfaces such as dentine. This finding could have an impact upon the healing of periodontal defects after regenerative procedures.

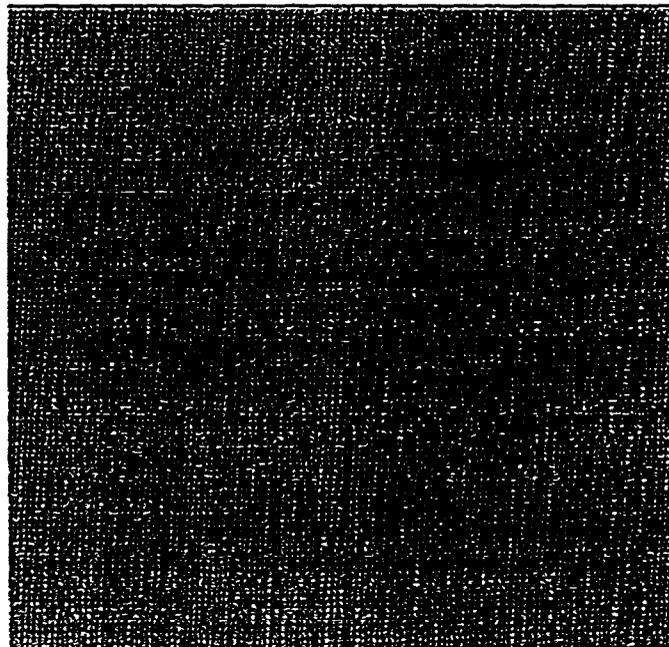
ALEXIDINE AND OTHER BISBIGUANIDES

Alexidine (2-ethylhexylbisbiguanide dihydrochloride) is structurally related to chlorhexidine and has very similar properties. In alexidine, the *p*-chlorophenyl groups of chlorhexidine are replaced by alkyl terminal groups (Fig. 12.2). The antiplaque activity of alexidine has been demonstrated following the use of 0.035% and 0.05% mouthwashes.

A number of other alkyl bisbiguanides, including hexocitidine, heptahexidine, hexidecicine, and hexhexidine, also have activity against oral micro-organisms comparable to that of chlorhexidine. The activity appears to be related to the structure of the molecules. For example, agents with branched terminal alkyl groups are more active against *Actinomyces* spp than those with unbranched groups. Similarly, increasing the length of the methylene bridge increases the activity against species of *Bacteroides* and *Fusobacterium*.

From a clinical viewpoint, the structure modification of antiplaque agents to optimize their activity against specific bacterial species may prove a valuable field for future research. Such agents will become particularly useful if the precise roles of the periodontopathogens are clearly identified.

Key facts Bisbiguanides



Bispyridines

Ocetinidine hydrochloride is the main bispyridine used as an antiplaque agent. Twice-daily rinsing with a 0.1% solution in a

glycerol base almost completely inhibits plaque formation. As with chlorhexidine, staining of the teeth and occasional epithelial desquamation are the main unwanted effects associated with octenidine.

Metallic salts

The salts of certain heavy metals can inhibit the growth of dental plaque and calculus formation. Salts of zinc and tin have received most attention and a number of commercial toothpastes now include these compounds in their formulation.

ZINC SALTS

Zinc citrate is the main zinc salt used for its antiplaque and anticalculus activity. Toothpastes containing up to 4% zinc citrate significantly inhibit plaque growth. The antiplaque activity of zinc salts appears to be a direct inhibitory action against streptococci. These micro-organisms are the first to colonize the tooth surface and are thus important in plaque formation.

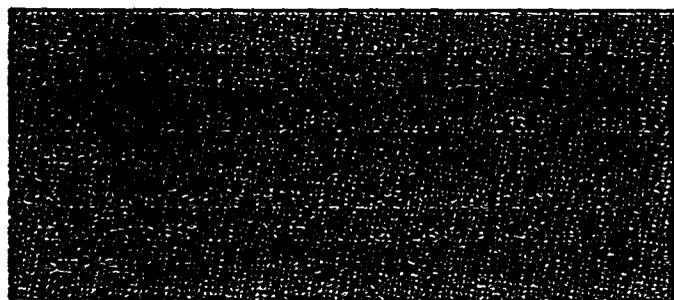
TIN SALTS

The ability of tin ions to inhibit plaque formation has been studied, primarily using stannous fluoride mouthrinses. Daily rinsing with a 0.1% stannous fluoride solution significantly reduces bacterial accumulation on the teeth.

The action of stannous ions is mediated through their ability to bind to lipoteichoic acid on the surface of Gram-positive bacteria. The surface net charge of the organism is therefore reversed and the adsorption of the cells on to teeth is consequently reduced. Furthermore, the effectiveness of a stannous fluoride solution in reducing bacterial adhesion is related to the stability of the stannous ions in aqueous solution and the rate at which they are taken up and retained by specific bacteria. The accumulation of tin in bacteria may alter their metabolism and other physicochemical characteristics.

Key facts

Metallic salts



Herbal extracts

Sanguinarine is the main herbal extract used for its antiplaque activity. It is a benzophenanthridine alkaloid derived from the plant *Sanguinaria canadensis*. It is structurally related to the alkaloids found in the plant *Fagura zanthoxyloides*—in Third World

countries this plant is chewed as a method for cleaning teeth. Sanguinarine, in its quaternary iminium form, has antimicrobial properties that have led to its introduction as an antiplaque agent. *In-vitro* analysis of minimum inhibitory concentration (MIC) values of sanguinarine has determined that, in the range of 1 to 16 $\mu\text{g mL}^{-1}$, the drug can inhibit the growth of a wide range of oral bacteria.

In addition to its antimicrobial properties, a further important feature of sanguinarine is its retention in dental plaque when used as a mouthrinse. The levels in plaque can exceed the MIC values for up to 2 hours after rinsing.

Sanguinarine has been incorporated into mouthrinses and toothpastes and 0.03% is the most frequently tested concentration. Few unwanted effects are associated, but many patients find the taste unacceptable.

Surfactants

Surfactants or 'wetting agents' were introduced as an alternative method of plaque inhibition. Agents with low surface tension and lipophilic-hydrophilic properties can interfere with plaque growth by preventing bacterial adhesion to both the pellicle and within the plaque mass. Thus a plaque inhibitory effect occurs without affecting the ecological balance of the oral flora. A number of antimicrobial agents, including chlorhexidine, possess surfactant properties. This section, however, is concerned primarily with products whose effects are mediated mainly through their wetting abilities. Examples include the aminoalcohols and the proprietary mouthwash Plax.

AMINOALCOHOLS

The substituted aminoalcohols have comparatively low antibacterial properties. They also have a lower surface tension than the tooth surface and so the low antimicrobial effect may be compensated by a high local concentration on the enamel surface. Early studies have shown that a 1% octapinol solution causes complete plaque inhibition for between 3 and 12 days. Octapinol also prevented further plaque growth and was able to partly dissolve the plaque that had already formed on teeth. Similar efficacy has also been demonstrated with 1% decapinol.

The unwanted effects of aminoalcohols include a slight local anaesthetic effect on soft tissues, a slightly bitter taste, and light brown staining of the teeth, fortunately this is easily removed with a toothbrush.

PLAX

Plax is a commercial mouthrinse with surfactant properties. The rinse comprises a combination of anionic and ionic surfactants, including sodium lauryl sulfate, polysorbate 20, triclosan 0.3%, and a co-polymer of methoxyethylene and maleic acid. These ingredients act on already formed plaque to loosen and remove the deposits. The manufacturers recommend it is used before daily toothbrushing. It must be emphasized that, although Plax may be a useful adjunct to toothbrushing, it is not a substitute for daily mechanical plaque removal.

Application of antiplaque agents

The efficacy of any antiplaque agent depends not only on its activity but also on the length of contact time between tooth surface and agent. Furthermore, it is essential that the agent gains access to the specific sites on the teeth where the maximum antiplaque effects will be achieved. In health, these sites are primarily interproximally and at the gingival margins. Where there is periodontal disease, subgingival application is required.

The most frequently used modes of application for antiplaque agents are mouthrinses and toothpastes. The main problem with both these methods is the relative short contact time between the active agents and the teeth. Consequently, the well-proven success of chlorhexidine as a plaque inhibitor is related to its substantivity rather than to any unique action upon the oral flora.

Mouthrinses are unable to penetrate subgingivally and so where periodontal pockets exist, direct subgingival irrigation is required. Toothpastes may, to some extent, be applied directly into pockets using a crevicular brushing technique. However, it is doubtful that such methods can satisfactorily introduce antiplaque agents to the bases of deep periodontal pockets.

Some of the plaque inhibitory agents listed in this section are used as prebrushing rinses, that is they are used just before toothbrushing or other mechanical methods of plaque control. The manufacturers of these prebrushing mouthrinses advocate that such an application will 'loosen' plaque and perhaps facilitate its removal. At the same time, the antibacterial actions of the mouthrinses may help to reduce the pathogenicity of the bacterial plaque. Whilst some patients may find a cosmetic benefit from using prebrushing rinses, there is little evidence to support their efficacy in the application suggested. Furthermore, there is the very real risk that patients may rely solely on such mouthrinses as their only means of plaque control. This will certainly be detrimental to their dental and periodontal health.

Interproximal applications of chlorhexidine can be made by using the gel preparation together with floss, woodsticks, or interproximal brushes. In attempts to increase their contact time with the tooth surface, drugs have been incorporated into chewing gum, lozenges, and periodontal dressings. Further, a number of so-called slow-release devices have been used to increase the length of time the drugs spend in the gingival crevice or periodontal pocket. Antiplaque agents have been incorporated into pieces of dialysis tubing, hollow cellulose acetate fibres, acrylic strips, and ethyl cellulose films to prolong delivery time. Clinically and microbiologically, the effects of such systems have been promising.

Anticalculus agents

Dental calculus is an ectopic mineralized structure that arises as a result of the calcification of bacterial plaque. Many toothpastes contain active ingredients that attempt to reduce calculus formation. These are referred to commercially as tartar-control toothpastes. The active ingredients of such preparations are:

- soluble pyrophosphates;
- zinc salts (chloride and citrate);
- diphosphonates;
- Triclosan with either a polymer system or zinc citrate.

The active ingredients have several mechanisms of action that can lead to a reduction in calculus formation. These include active retention within saliva and plaque, an inhibition of the phase transformations within developing calculus, and an inhibitory effect on the accumulative factors affecting the rate of supragingival plaque mineralization.

The efficacy of commercially available antitartar toothpastes in reducing supragingival calculus formation has been demonstrated in both short- and long-term studies. Whether this reduction in calculus formation has any clinical significance with respect to periodontal health remains to be determined.

Antimicrobials in the management of periodontal diseases

Antimicrobials are typically used in medicine to eliminate infections caused by foreign pathogenic micro-organisms (see Chapter 11). The microbial aetiology of inflammatory periodontal diseases has provided the basis for the introduction of antimicrobials in the management of these diseases. This section will assess the ability of specific antimicrobial agents to reduce the pathogenicity of the subgingival microflora, and affect the clinical signs of disease.

Rationale for the use of antimicrobials in periodontal diseases

There is little doubt that specific micro-organisms are closely associated with some forms of periodontal disease (see Table 12.3). Between 6 and 12 microbial species may be responsible for most cases of periodontitis, or be causative in active episodes of the disease process. Unlike the majority of general infections, all the suspected periodontal pathogens are indigenous to the oral flora. Consequently, long-term and total elimination with antimicrobials will be very difficult to achieve. On cessation of the drug, repopulation of the indigenous bacteria will occur. Antimicrobial agents should only be considered as an adjunct to conventional periodontal therapy.

Nevertheless, in certain forms of periodontitis, the loss of connective tissue attachment is rapid. Extremely virulent Gram-negative organisms populate the deep pockets and can actually invade the gingival connective tissue. Under these circumstances, antimicrobials provide a useful adjunct to root planing; this, by itself, may not remove all subgingival deposits and certainly would not affect any invading organisms which had already penetrated the soft tissues. The micro-organisms listed in Table 12.3 are sensitive to a number of antimicrobials, especially the tetracyclines and metronidazole, hence these drugs are extensively used in the management of periodontal disease.

Routes of administration

The aim of using an antimicrobial is to achieve a concentration of the drug in the periodontal environment sufficient either to kill or arrest the growth of pathogenic micro-organisms. The most effective and reliable method is systemic administration, which enables the drug to bathe the subgingival flora by passing into the crevicular fluid. Indeed, certain drugs such as tetracycline have been found to concentrate in crevicular fluid at higher levels than those found in serum following oral administration. The drug can then bind to the tooth surfaces, from where it is released in active form.

In an attempt to minimize the risks of adverse reactions, antimicrobials have been applied topically to periodontal pockets by techniques such as subgingival irrigation, acrylic strips, gels, and fibres filled with drug. Such methods permit lower doses of antimicrobials to be administered than for oral dosing, although the extent to which the drugs penetrate the pockets is less predictable. Furthermore, the insertion and removal of multiple acrylic strips and fibres is time-consuming and this may preclude their widespread clinical use. It is now accepted that the use of local antimicrobial delivery into a periodontal pocket is an adjunct to root surface debridement and not an alternative to such treatment. Moreover, debridement will also serve to disrupt the subgingival biofilm and permit better contact between the antimicrobial agent and the subgingival flora. With some of the subgingival antimicrobials, it is recommended that they be administered up to a week after root planing. This allows for resolution of the inflammatory response and a concomitant reduction in the flow of gingival crevicular fluid. Both changes will reduce drug clearance from the pocket and prevent the delivery device from blocking the natural drainage from the periodontal defect.

Tetracyclines

The tetracyclines comprise a group of closely related bacteriostatic antibiotics that provide a broad spectrum of activity against both Gram-positive and Gram-negative micro-organisms. Tetracyclines are effective against many anaerobic and facultative anaerobic bacteria, which is a particularly important consideration when they are used in the management of periodontal diseases. Tetracyclines are also active against most spirochaetes. The general pharmacology of these drugs is discussed in Chapter 11

TETRACYCLINES AND PERIODONTAL DISEASES

Cases of moderately severe and advanced periodontal disease are usually treated with oral hygiene instruction, scaling, and root surface debridement. This usually results in a reduction in plaque scores and gingival inflammation, a decrease in periodontal pockets, and the establishment of a periodontal microbial flora compatible with the maintenance of periodontal health. In such cases, the adjunctive use of tetracycline therapy is not indicated because it is unlikely to achieve any short-term or long-lasting clinical effects not provided by mechanical debridement alone. Occasionally, a case of chronic adult periodontitis will show no

clinical improvement after routine therapy and the periodontal flora will continue to be a mixture of spirochaetes and Gram-negative anaerobic rods. These refractory cases of periodontitis can benefit from a 2-week course of systemic tetracycline therapy of 1 g daily.

The effects of tetracycline therapy on the subgingival flora associated with periodontitis have been well documented. A 2-week course of 1 g tetracycline daily produces a shift from an essentially complex Gram-negative flora to one which is essentially Gram-positive and associated with healthy tissues. Bacterial resistance amongst the indigenous flora is not uncommon, both before and following tetracycline therapy. Species of *Streptococcus* and *Actinomyces* have been found to be resistant. However, the association between these bacteria and gingival health may negate the importance of this resistance. In refractory cases of periodontitis, a short course of systemic tetracycline will reduce spirochaetes and Gram-negative rods to low or undetectable levels.

Tetracycline is of considerable value in the treatment of the early-onset periodontal conditions. The prime pathogen in this unusual destructive form of periodontal disease is *Actinobacillus actinomycetemcomitans* (*A.a.*). This is very susceptible to tetracycline. *A.a.* is difficult to eliminate by mechanical debridement alone, presumably because of its ability to invade the gingival connective tissue. Systemic administration of tetracycline 1 g daily for 3–6 weeks in conjunction with supragingival plaque control can halt the progression of juvenile periodontitis. However, it is more usual to give a 2-week course of tetracycline as an adjunct to surgical management.

In addition to the antimicrobial effects of tetracyclines, a further mechanism has been proposed to explain their efficacy in the management of periodontal diseases. In laboratory experiments and clinical trials on patients with diabetes, it has been shown that tetracycline, doxycycline, and minocycline can all suppress the activity of collagenases, especially those derived from PMNs (also referred to as MMP-8). Collagenases are also produced by fibroblasts which maintain collagen and gingival connective tissue homeostasis. Mammalian collagenases are calcium-dependent enzymes and, as tetracyclines bind to calcium ions, this may be the mechanism of inhibition. The conversion of tetracycline to a non-antimicrobial analogue, de-dimethylaminotetracycline, does not reduce the anticollagenolytic action of the drug. This suggests that this action is independent of antimicrobial activity. A further mechanism may be associated with the ability of the tetracyclines to scavenge oxygen radicals (e.g. hydroxyl groups or hypochlorous acid) produced by PMNs. These oxygen radicals activate latent collagenases, and their inhibition may result in further antiproteolytic effects such as inactivation of α -1 proteinase inhibitor and neutrophil elastase. These antiproteolytic properties of the tetracyclines may contribute to the general anti-inflammatory effects attributed to these drugs, and also their ability to inhibit bone resorption.

A further important property of the tetracyclines in the

management of periodontal diseases is their ability to enhance fibroblast attachment to root surfaces. This will facilitate regenerative procedures that attempt to create new periodontal attachment.

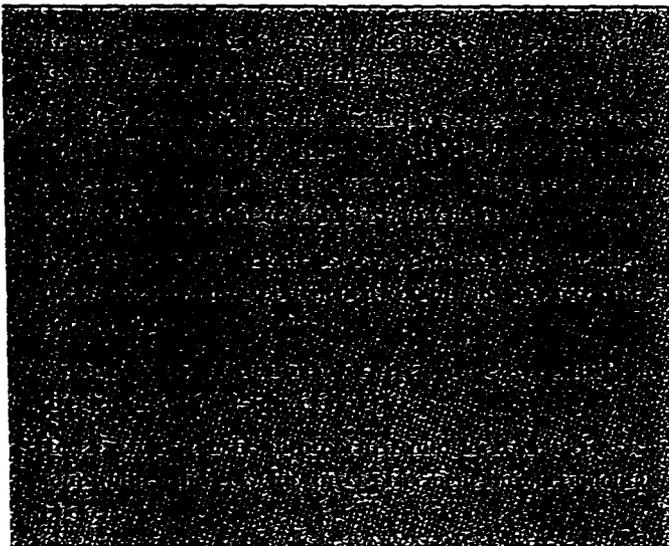
LOCAL DELIVERY

A number of slow-release devices have been used to facilitate the local delivery of tetracyclines (and other antimicrobials) into periodontal sites. Monolithic, ethylene vinyl acetate fibres have been found to be the most efficacious in achieving prolonged delivery of the drug from the entire length of the fibres. Furthermore, the concentrations of tetracyclines achieved in crevicular fluid by controlled local delivery are up to 100 times those obtained following systemic dosing ($1500\mu\text{g mL}^{-1}$ vs. $15\mu\text{g mL}^{-1}$). Thus, the chances of complete suppression of bacterial growth (and/or collagenase activity) are increased. Local application of fibres impregnated with tetracycline (Actisite) has been shown to be as effective as root surface debridement in reducing bleeding on probing and probing pocket depth. However, the fibre may be difficult to apply and be retained within the pocket.

Minocycline has also been incorporated into a local delivery system (Dentomycin gel). This gel is used as an adjunct to root surface debridement and is applied three to four times over an 8-week period. The gel is easy to apply and appears to be more effective in the treatment of deep periodontal pockets.

Key facts

Tetracyclines in periodontal disease



Metronidazole

Metronidazole is a nitroimidazole that has a broad spectrum of activity against protozoa and anaerobic bacteria. The antimicrobial activity of this drug against anaerobic cocci, and anaerobic Gram-negative and Gram-positive bacilli has led to its extensive use in the management of periodontal diseases. Its general pharmacology is discussed in Chapter 11

METRONIDAZOLE AND PERIODONTAL DISEASES

The rationale for the use of metronidazole in the treatment of periodontal diseases and other oral infections has revolved around the drug's specificity for anaerobes and the apparent inability of susceptible organisms to develop resistance. However, the plasma (or crevicular fluid) levels of metronidazole required for the drug to be effective against the majority of anaerobes have not been clearly established. Plasma levels of $6\mu\text{g mL}^{-1}$ are adequate to deal with most anaerobic infections, and these levels can be achieved by a regimen of 200 mg three times a day. However, another study showed that a concentration of $8\mu\text{g mL}^{-1}$ was inhibitory to more than 90% of bacteria in subgingival plaque. Crevicular fluid levels of $15\mu\text{g mL}^{-1}$ would be necessary for maximal inhibition. Such levels may be achieved following the administration of metronidazole 400 mg twice a day.

Many studies have shown that metronidazole has a clinical, histopathological, and microbiological benefit to the periodontal tissues. This benefit is enhanced when drug therapy is combined with conventional treatment. Metronidazole has been shown to be particularly useful in the management of advanced cases of periodontal destruction, and in the management of the early-onset periodontal conditions.

LOCAL DELIVERY OF METRONIDAZOLE

A commercially available local metronidazole preparation (Elyzol) is now available for direct application into a periodontal pocket. The product contains 25% metronidazole in a delivery vehicle containing glyceryl mono-oleate and sesame oil. Efficacy studies suggest that two applications of the gel (1 week apart) are as effective as conventional non-surgical management in reducing probing depths and bleeding on probing. Furthermore, the clinical benefit of such local drug delivery was evident up to 18 months after treatment. In this instance, the local application of metronidazole is being used as an alternative to conventional therapy, not as an adjunct.

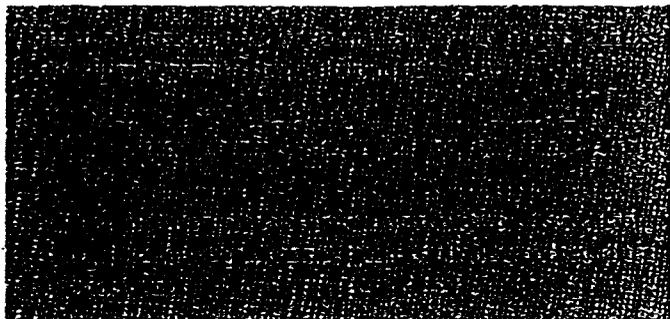
METRONIDAZOLE AND ACUTE ULCERATIVE NECROTIZING GINGIVITIS (ANUG)

Metronidazole is the treatment of choice for ANUG. Gingival ulceration, bleeding, pain, and halitosis usually resolve rapidly within about 48–72 hours of starting metronidazole treatment (200 mg, three times a day). These clinical changes are accompanied by the rapid disappearance of the spirochaete–fusobacteria complex, which is a feature of this acute disease. However, it is essential that once the acute phase of the disease has been controlled, mechanical debridement should be carried out immediately. Failure to do so will result in the recurrence of infection.

Key facts

Metronidazole in periodontal disease





Combination antimicrobial therapy

There is increasing evidence that a combination of 375 mg amoxicillin (amoxycillin) and 250 mg metronidazole, three times a day for a week, is of value in the management of refractory and other rapidly progressive forms of periodontitis. This combination therapy has also been shown to be effective in treating refractory cases of localized juvenile periodontitis where patients still harboured *Actinomyces actinomycetemcomitans* after treatment with a systemic tetracycline. Before such a combination of antimicrobials is prescribed, it is essential that the periodontal diagnosis is correct, and that some attempt has been made to identify the microorganisms and their sensitivity.

NSAIDs in the management of periodontal diseases

NSAIDs are a heterogeneous group of compounds whose analgesic, anti-inflammatory, and antipyretic properties are due to the inhibition of eicosanoid synthesis (see Chapters 4 and 6). The eicosanoids are important mediators of inflammation in periodontal disease, and prostaglandins of the E series are potent stimulators of osteoclasts. This latter activity is one of the factors contributing towards bone loss, a major feature of periodontal disease. Further evidence that prostaglandins may be important in the pathogenesis of periodontal disease came from cross-sectional studies on patients on long-term NSAID therapy. These patients had less alveolar bone loss and gingival inflammation than age-matched, otherwise healthy controls.

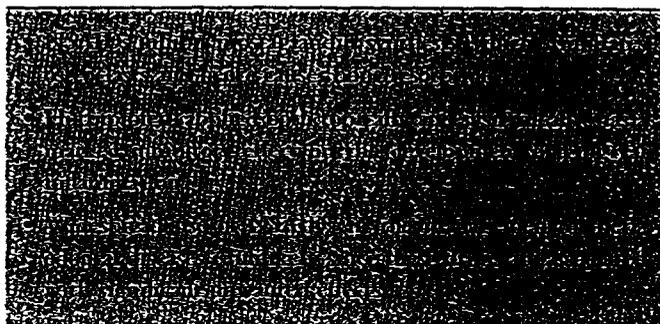
Other studies have shown that topical and systemic flurbiprofen have a marked inhibitory effect on the development of gingival inflammation in the experimental gingivitis model. Systemic flurbiprofen (50 mg twice daily for 2 months) has been evaluated on patients with refractory periodontitis. The rate of bone loss was considerably reduced and some sites actually gained bone. Long-term systemic flurbiprofen (3 years) reduced bone loss for 12–18 months of treatment. This benefit does not extend beyond 2 years, although this may be due to lack of compliance by patients taking the flurbiprofen therapy, or to a true loss of the effect of flurbiprofen such that other pathways of bone resorption became active.

The precise mechanism of the action of NSAIDs in preventing periodontal bone loss needs to be established. Subsequently, the

dose, frequency of dosing, and the most suitable method of administration of the drug can be determined. It would be unrealistic to expect patients with periodontal disease to undertake regular and prolonged systemic NSAID therapy, especially as periodontal disease is not outwardly disabling. However, if relatively small, but active, amounts of an NSAID such as flurbiprofen could be incorporated into a gel or toothpaste for topical application, then compliance would be better.

Studies of NSAIDs and periodontitis over the next few years should provide new methods for preventing and controlling the onset and progression of a disease which is currently the major cause of tooth loss in adults.

Key facts NSAIDs in periodontal diseases



Oxygen-releasing agents

Hydrogen peroxide and sodium peroxyborate (Bocasan) are the main oxygen-releasing agents used in the treatment of periodontal disease. Both are restricted to the treatment of acute necrotizing ulcerative gingivitis, which is thought to be caused by anaerobic bacteria. It is doubtful if the oxygen released has a significant action on the metabolism of anaerobic organisms during the short period of exposure. This painful gingival condition is more appropriately treated with metronidazole.

Conclusion

There is little doubt that antiplaque agents and antimicrobials are of significant value in the management of periodontal diseases. The antiplaque agent of choice is chlorhexidine. This agent can be applied in a variety of ways. Subgingival irrigation or other means of direct placement of the drug into the periodontal pocket is a useful adjunct to conventional periodontal treatment. Rinsing the mouth with a 0.2% solution is of value after periodontal surgery and in the management of oral mucosal lesions such as aphthous ulceration and stomatitis secondary to radiotherapy and chemotherapy.

Tetracycline is of proven benefit as an adjunct to surgery in the treatment of juvenile periodontitis. It is also useful in cases of

fractory and rapidly progressive periodontitis. A 2–4-week course is usually advocated. Tetracycline concentrates in the gingival fluid and inhibits collagenase. These two properties make it of particular value in the management of periodontal disease.

Dentine sensitivity

Painful symptoms arising from exposed dentine are a common problem in the adult population, with an incidence of 1/7. Exposure of dentine can arise from either the removal of enamel or abradement of the root surface. Loss of enamel occurs in attrition, erosion, toothbrush abrasion, or caries. Several factors can cause abradement of the root surface including gingival recession with increasing age, chronic periodontal disease, periodontal surgery, incorrect toothbrushing, and trauma.

Dentine sensitivity (erroneously termed hypersensitivity) is characterized by pain, elicited by various stimuli, that disappears when the stimulus is removed. Some people are sensitive to cold alone; others to touch, sweet, or sour foods; and some to a combination of any of these stimuli. The pain may be so severe that they find eating difficult.

Theories of dentine sensitivity

Exactly how external stimuli are transmitted through dentine to the pulp is not established and, although evidence suggests that dentine is innervated, the extent of this innervation is uncertain. There are three theories of dentine sensitivity:

- the dentinal receptor mechanism;
- the hydrodynamic mechanism; and
- the modulation of nerve impulses by polypeptides.

Dentinal receptor mechanism

This theory suggests that the odontoblast has a sensory function, perhaps serving as a transducer between external stimuli and the nearby pulpal nerve plexus. Certainly, when there is disruption of odontoblasts, the dentine becomes very sensitive. However, pain-relieving substances, such as potassium chloride, 5-hydroxytryptamine, and histamine, have failed to evoke pain when applied to exposed dentine. This finding would question the nociceptive role of the odontoblast.

Hydrodynamic mechanism

This is the most widely accepted theory. Dentine tubules contain fluid, so a blast of air, or hot and cold stimuli will cause a rapid movement of this fluid within the tubules. This movement will cause deformation of both the odontoblastic process and adjacent nerve fibres. Nerve deformation causes pain.

Modulation of nerve impulses by polypeptides

Dentine tissue contains a number of polypeptides that can act as modulators of neural transmission. These include substance P and bradykinin, which may alter the permeability of the odontoblast

cell membrane (depolarization). Such depolarization could make the pulp more sensitive to various external stimuli. Thus, substance P and bradykinin may act as modulators of nerve impulses in the pulp.

Desensitizing agents

Ideally, a desensitizing agent should:

- be non-irritant to the pulp;
- be relatively painless on application;
- be easily applied;
- have a rapid onset of action;
- be permanently effective;
- not stain the teeth;
- be consistently effective.

Many agents have been used to treat dentine sensitivity, and some are discussed below.

Sodium fluoride

This is conveniently applied as a paste, for example Lukomsky's paste, which contains equal parts by weight of sodium fluoride, kaolin, and glycerin. The paste is burnished into the previously dried sensitive area, and left on for about 3 minutes before the patient is allowed to rinse. Occasionally, application may cause a marked but transitory pain. Fluoride from the sodium salt will be taken up by the dentine thus making it more resistant to acid decalcification. The fluoride may also lead to an increase in secondary dentine formation, thus blocking dentinal tubules. Sodium fluoride either in pastes, gels, or mouthwashes has to be applied frequently for maximum effectiveness.

Stannous fluoride

This also reduces dentine sensitivity. In solution it undergoes spontaneous hydrolysis and oxidation, so it is applied in the form of a gel mixed with carboxymethylcellulose or glycerine. Stannous fluoride acts as an enzyme poison and may inactivate enzymatic activity in the odontoblastic process. Like sodium fluoride, stannous fluoride induces mineralization within the dentinal tubules, thus creating a calcific barrier on the dentine surface.

Sodium monofluorophosphate

This fluoride salt is widely used in toothpastes, but is of uncertain efficacy as a desensitizing agent. It is suggested that monofluorophosphate is hydrolysed by hydroxyapatite on the surface of enamel and dentine. The hydrolysis releases fluoride ions, which are then incorporated into the lattice work of the apatite crystal.

Calcium hydroxide

Although this compound occludes dentinal tubules, its use as a desensitizing agent is uncertain, probably because of its poor adhesion to exposed dentine.