Heal Talk

Various Agents Used As Local Drug Delivery - A Periodontic Review

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Abstract

Periodontitis is an immuno-inflammatory disease of the tissues surrounding the teeth. Different treatment modalities have been proposed in the treatment of such conditions like mechanical debridement and use of antimicrobials. The main goal of antibiotic therapy is establishing the concentration of drug that inhibits the pathogenic bacteria. Administration of drug locally in the periodontal pocket is a promising therapeutic modality for achieving better clinical outcomes when used as an adjunct to conventional non surgical periodontal therapy. Intensive research efforts are now focussed on the development of new strategies for more effective treatment.

Keywords: Local drug delivery, periodontitis, antimicrobial agent.

Introduction

Periodontitis is an inflammatory disease affecting the tooth supporting structures, caused by pathogenic bacteria associated with dental plaque and resulting in progressive loss of the alveolar bone around the teeth with increased probing depth and recession or both. However, the nature of the periodontal disease caused by bacterial plaque appears to depend on the interaction among the bacterial end-product, the environment, and the response of the host's defense mechanisms to the bacterial assault[1].

Since the early 1970's, the quest to identify bacterial specificity in periodontal disease became the prominent area of investigation. Loesche (1976) proposed the specific plaque hypothesis, according to which specific bacteria caused specific forms of periodontal diseases. Increasing knowledge of anaerobic bacteria as predominant agents in the development of periodontal disease has led to new treatment strategies, aiming primarily at suppression or elimination of specific periodontal diseases[2]. Conventional therapeutic modality for treatment of periodontal disease includes mechanical scaling and root planning and surgical therapy. However, mechanical therapy itself may not always reduce or eradicate the anaerobic microflora at the base of pocket, within the gingival tissues and in both structures inaccessible to periodontal instruments[3]. Moreover, recolonization of pathogenic bacteria occurs from the residual bacterial reservoir in dentinal tubules causing reoccurrence of the inflammatory condition of gingival and periodontal tissue.[4]

To overcome this, administration of antimicrobials both systemic and locally would enhance a treatment protocol and serve as adjuncts to mechanical therapy. Systemic antimicrobial agents may reduce or eliminate bacteria that cannot be removed by scaling and root planning. However, side effects such as drug toxicity, acquired bacterial resistance, drug interaction, superimposed infections, uncertain patient compliance, nausea, vomiting and gastrointestinal disturbances limit the use of systemic antimicrobials[5].

Therefore to overrule these short comings, Dr. Max Goodson in 1979 first developed local delivery of therapeutic agents into a viable concept[6]. The term local delivery, site-specific delivery sustained release, controlled - release, prolonged release, timed release, slow release, sustained action, prolonged action or extended action are sometimes used synonymously[7]. The potential therapeutic advantage of local delivery avoids most of the problems associated with systemic therapy, limiting the drug to its target site and hence achieving a much higher concentration[8]. Local delivery devices are systems designed to deliver agents locally into periodontal pocket and periodic use of local delivery systems in reducing probing depths, stabilizing attachment levels and minimizing bleeding would allow better control of the disease[9].

Various Agents Used as Local Drug Delivery

Povidone-iodine- Elemental iodine or its derivatives [polyvinylpyrrolidone-iodine complex (PVP-iodine)] are possibly the most broad-spectrum and potent antiseptics available. Dilute PVP-iodine have ability to kill Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis and other periodontal pathogens in vitro in as slight as 15s of contact and bacteria and yeasts in vivo within 5min of contact[10]. PVP iodine is also effective against various virures present in oral cavity like herpesviruses, which show resistance to chlorhexidine, which is of interest because of the suspected significance of cytomegalovirus and Epstein–Barr virus in destructive periodontal disease. Irrigation of periodontal lesion with diluted povidone-iodine solution (final concentration 0.05% free iodine) as an adjunct to sub gingival debridement revealed reduction in gingival inflammation and 2 mm or more in gain of clinical attachment; enhanced healing pertaining to better suppression over periopathogens.[11] PVP-iodine solution can kill periodontal bacteria and decrease postoperative bacteraemia following oral surgery[12]. However, PVP-iodine is contraindicated to individuals who are allergic to iodine, suffering from thyroid dysfunction, or are pregnant or nursing.[13]

Tetracycline

In 1979 Goodson et al first proposed the concept of controlled delivery in the treatment of periodontitis. The first delivery devices involved hollow fibers of cellulose acetate filled with tetracycline.[14]Tetracyclines are a group of antibiotics classified as broad spectrum drug which are bacteriostatic antimicrobials and are effective against many Gram negative & Gram positive both aerobic and anaerobic periodontopathogens species such as Actinobacillus actinomycetemcomitans(Aa). Tetracycline-HCl in vitro displays substantivity to dentin tooth surfaces, and maintains its antimicrobial activity upon desorption.[15] Apart from antimicrobial action, a number of additional properties of this group of drug have been identified. These include collagenase inhibition, anti-inflammatory actions, inhibition of bone resorption and their ability to promote the attachment of fibroblast to root surfaces.[16]

Fibers: The controlled release drug delivery devices are basically of two types i.e., degradable and non-degradable. The non degradable devices such as the tetracycline HCl impregnated fibers (Actisite) have been approved by the United States Food and Drug Administration (FDA) for the treatment of periodontitis. They are non-resorbable biologically inert, safe, plastic copolymer (ethylene and vinyl-acetate) loaded with 25% w/w tetracycline HCI powder packaged as a thread of 0.5 mm in diameter and 23 cm in length. It maintains constant concentrations of active drug in the crevicular fluid in excess of 1000 µg/ml for a period of 10 days. Following application of tetracycline fibres a definite reduction in the subgingival microbiota has been observed.[17] Bio-resorbable form of fibre are commercially available as Periodontal plus AB having the advantage of no second appointment for removal as it biodegrades

within 7 days, so ensures the compliance.[18] Actisite, as an adjunct to SRP, showed significantly greater reductions in probing depths, bleeding on probing and significant reduction in A. a and P. gingivalis levels than SRP alone in the treatment of chronic adult periodontitis. Also this mode of drug delivery (controlled release drug delivery system) appears to be safe for the periodontal tissues and is well tolerated by the patients.[19]

Dosage and Administration

Actisite (tetracycline hydrochloride) periodontal fiber is indicated as an adjunct to scaling and root planning for 10 days. Actisite fiber should be inserted into the periodontal pocket and the pocket is completely filled. The fiber should be inserted to closely approximate the periodontal pocket and should be in contact with the base of the pocket. Fibers are secured in position in the pocket by using cyanoacylate adhesive. When placed within a periodontal pocket, Actisite fiber provides continuous release of tetracycline for 10 days. At the end of 10 days of treatment, all fibers must be removed. Fibers lost before 7 days should be replaced.[17]

Gel: Gel is applied sublingually with the help of blunt cannula and syringe. The safety profile, longer-term retention, antimicrobial activity suggests that tetracycline containing copolymer gels represents a safe and effective therapy for periodontitis. Comparative analysis of tetracycline containing dental gels: poloxamer and monoglyceride based formulations have been done which shows that when applied subgingivally produce a significant improved outcome in moderate to deep periodontal pockets.[20] Noteworthy results were seen with Tetracycline-Serratiopeptidase-Containing Periodontal Gel Formulation along with scaling and root planing.[21] Bioerodible Injectable Poly (ortho-ester) for Tetracycline Controlled Delivery formulations loaded with tetracycline 10% or 20% showed complete in vitro degradation concomitant with drug release.[22]

A new generation of semi-synthetic tetracycline compounds called Glycylcyclines has recently been developed[23] which are effective not only against tetracycline-sensitive bacteria, but also against tetracycline-resistant gram-positive and negative microorganisms.

Subgingival Doxycycline

A gel system using a syring with 10% doxycycline is available. Doxycycline is a broadspectrum bacteriostatic agent and has the ability to downregulate MMP's a family of zinc dependent enzymes that are responsible for degradation of a variety extracellular matrix molecules including collagens.[24] The FDA approved 10% Doxycycline in a gel system ATRIDOX (42.5 mg Doxycycline), is a subgingival controlled-release product composed of a 2 syringe mixing system. Doxycycline levels in GCF peaked to 1,500 - 2000 µg/ml in 2 hours following treatment with ATRIDOX. These levels remained above 1000 µg/ml through 18 hours, at which time the levels began to decline gradually. Local levels of Doxycycline have been found to remain well above the minimum inhibitory concentration for periodontal pathogens (6.0µg/ml) through Day 7. It was reported that approximately 95% of the polymer is bio absorbed or expelled from the pocket naturally within 28 days.Several studies have reported the efficacy of 10% doxycycline hyclate as a local delivery antimicrobial agent for attaining probing depth reduction and gaining clinical attachments.[25]

Sub gingival Minocycline

Minocycline is a semisynthetic derivative of tetracycline and a very potent broad spectrum antibiotic. Minocycline works by interfering with protein synthesis in the bacterial cell wall. A Locally delivery, sustained release form of minocycline, a bacteriostatic antibiotic has been tried clinically via in three different modes i.e. film, microspheres, and ointment.[26]

Film: 30% of Minocycline incorporated in Ethyl cellulose film were tested as sustained release devices. The results indicated that the use of this device may cause complete eradication of pathogenic flora from the pocket after 14 days.[27]

Microsphere: A new, locally delivered, sustained release form of minocycline microspheres (ARESTIN) for subgingival placement is available. The 2% minocycline is encapsulated into bio-resorbable microspheres (20-60µm in diameter) in a gel carrier and has resorption time of 21 days. Hydrolysis of polymer takes place in gingival crevicular fluid and releases minocycline for a period of 14 days or longer before resorbing completely.[27]

Ointment: Minocycline ointment is a bio-absorbable sustained delivery system consisting of 2% minocycline hydrochloride in a matrix of hydroxyethyl-cellulose, aminoalkyl-methacrylate, triacetine and glycerine. DENTOMYCIN (2% Minocycline gel) has received regulatory approval for the treatment of periodontitis in the European Union. In Japan it is commercially available with name PERIOCLINE. The concentration of minocycline in the periodontal pocket is about 1300µg/ml, 1 hr after single topical application of 0.05 ml ointment (1mg of minocycline) and is reduced to 90µg/ml after 7 hrs. Results have shown that the combination of ointment with scaling and root planing was significantly better than scaling and root planing alone in pockets > 7mm.[28]

Sub gingival Metronidazole

Metronidazole is particularly attractive as an antimicrobial because of its selective efficacy against obligate anaerobes. Mechanism of action of metronidazole takes place by inhibiting DNA synthesis. Both systemic and local applications are effective against periodontal pathogens. Therefore, local application would be preferred. It is known to convert into a reactive reduced form and affects specifically anaerobic rods and spirochetes in subgingival microflora. A topical medication **ELYZOL** contains an oil-based Metronidazole 25% dental gel. It is applied in viscous consistency to the pocket, where it is liquidized by the body heat and then hardens again, and forming crystals in contact with water. The gel disintegrates in the pocket and releases Metronidazole. After application of Elyzol 25% dental gel, Metronidazole concentrations of above100 µ/ml were measurable in the periodontal pocket for at least 8 hours and concentrations above 1 µ/ml were found at 36 hours.[29] When metronidazole gel plus scaling and root planing were compared to root planing alone, the results have not been consistent. [30]One investigation suggested that there was a better result over a 9-month observation period when combined therapy was employed for probing depth reduction.[31]

Chlorhexidine (CHX)

Chlorhexidine is a gold standard[32] against which other antiplaque and antigingivitis agents are measured. The chlorhexidine digluconate (1:6-Di 4'-chlorophenyl-diguani-dohexane) is a synthetic antimicrobial drug and are widely used as a broad spectrum antiseptic in clinical and veterinary medicine since 1953.[33] Chlorhexidine was first introduced as general disinfectant with a broad antibacterial spectrum of action to the medical profession in the early 1950's. In the beginning it was used in dentistry to wash operation sites, and for use in endodontics to disinfect rood canals. Antiplaque property of chlorhexidine was initially reported by Schroeder in 1962. Loe and Schiott et al reported an entire inhibition of new plaque growth and prevention of the development of gingivitis by an aqueous solution of 0.2% chlorhexidine digluconate in the form of a mouthrinse.

Structure of Chlorhexidine

Chlorehexidine consist of two symmetric 4 chlorophenyl rings and two biguanide groups connected by a central hexamethylene chain.

Mechanism of Action of Chlorhexidine

The bacterial cell wall is negatively charged and contains sulphates and phosphates. Chlorhexidine is dicationic positively charged molecule which interacts with negatively charged bacterial cell wall by adsorption. Chlorhexidine shows different effects at different concentration; agent is bacteriostatic at low concentration, whereas at higher concentration the agent is bacteriaicidal. The chlorhexidine adsorption to the wall causes an alteration in integrity of membrane and chlorhexidine binds to the phospholipids in the inner membrane resulting in leakage of low molecular weight compounds like potassium ions and then phosphorous. By increasing the concentration of chlorhexidine there is progressive damage to the membrane. Cytoplasm of the cells is chemically precipitated Bactericidal stage which is irreversible.[34]

Effect on Microbial Ecology

Chlorhexidine is an antimicrobial agent active against a extensive spectrum of gram-positive and gram-negative organisms, yeast, fungi, facultative anaerobes and aerobes. Microorganisms which are highly susceptible to chlorhexidine digluconate include some Staphylococci, Streptococcus mutans, Streptococcus salivarius, Candida albicans, Escherichias coli, Selenomonas and anaerobic propionic bacteria.[35]

Chlorhexidine formulations

As a Mouthwash

CHX containing mouth washes are available in two concentratin: one, 0.2% CHX, which is used with a 10ml volume and the other 0.12% CHX, which is used with a 15ml volume. The rationale for lowering the concentration of CHX is to reduce side effect while maintaining comparable efficacy. The total amount of CHX is approximately the same in these 2 products: 10ml of 0.2% CHX contains 20mg and 15ml of 0.12% CHX contain 18mg per volume. The time of rinsing is 30 or 60 seconds depending on the adsorption rate of antiseptics to the oral cavity (50% of CHX binds to the receptors within 15 seconds) Chlorhexidine is recommended as a

twice daily, morning and evening, oral rinse to be used for at least 30 seconds. It is not intended for ingestion and should be expectorated after rinsing[36].

Gels

Chlorhexidine digluconate has also been incorporated in gels. CHX gels are available in concentration of 1%, 0.2% and 0.12%. CHX Gel that is applied once a day has proved to be effective in the treatment of denture stomatitis and oral candidiasis reducing oral malodour and also reduces staining[37]

Chlo-Site

CHLO-SITE is an agent (Xanthano GEL) used for topical application, which contains a mixture of chlorhexidine digluconate and dihydrochloride, in a ratio of 1:2. Xanthan gel is a saccharide polymer, which constitutes of a three-dimensional mesh mechanism, which is biocompatible with chlorhexidine. Both chlorhexidine and gel matrix are mucoadhesive so that they stick inside the pockets and are not easily washed out by gingival fluid or saliva. The gel gets vanished from the pocket within l0-30 days of injection and effective concentration of gel lasts for at least 15 days in the region. It degrades spontaneously at the site of application, is well tolerated and is efficient in treatment of periodontal disease & peri-implantitis.[38] Its mechanism of action includes reduction pellicle formation, alteration of bacterial adherence to teeth, and alteration of bacterial cell walls which causes cell lysis.[39]

Chlorhexidine Dentifrices

The utilization of chlorhexidine dentifrices means a more direct application of chlorhexidine in the areas where it is needed. More recently, some toothpaste have been specifically formulated to ensure a high availability of the contained antiseptic. A1% chlorhexidine toothpaste of this type has been investigated in a 19- day, randomized double blind, placebo-controlled, cross-over experimental gingivitis clinical trial. The toothpastes were used as slurries which were rinsed around the mouth twice per day for 1 minute during the experimental period. Plaque and gingivitis scores were- significantly reduced and stain scores were significantly increased in the active toothpaste period with respect to those in the placebo period. CHX in dentifrices gained little attention because of its interaction with anionic ingredients present in toothpaste and competition for oral retention sites[40].

Spray

Sprays (0.2% CHX) could well be used as a replacement for, or an adjunct to, mechanical tooth-brushing. This is especially true in situations in which mechanical tooth cleaning is impossible and the use of a mouthwash is difficult or not possible at all.

Indications: Mentally handicapped patients, elderly persons in nursing homes, patients in intensive care units in hospitals, intermaxillary fixation.[41]

Perio-Chip: 2.5 mg Chlorhexidine Gluconate PerioChip, the controlled subgingival delivery of chlorhexidine gluconate, is a small, orange-brown, tombstone-shaped chip (4.0 x 5.0 x 0.35mm) in a biodegradable matrix of hydrolyzed gelatine and has been approved by FDA.[42] Effects of Perio Chip on oral microorganism showed reduction in the numbers of the putative periodontopathic organisms specially Porphyromonas gingivalis, Prevotella intermedia, Aggregatibacter actinomycetemcomitans (Aa), and Fusobacterium nucleatum (Fn) after placement of the chip. Perio Chip releases chlorhexidine in vitro in two phases, approximately 40% of the chlorhexidine is releasing within the first 24 hours, and then releasing the remaining chlorhexidine in an almost linear fashion for 7–10 days. Adverse effects of chlorhexidine mouth rinses such as staining, alteration in taste perception, and mouth irritation are not expected with the perio-chip treatment, since possible contact with the oral mucosa and gingiva is minimal.

Periocol-CG: Periocol CG (4x5 mm, 0.25 - 0.32 mm thick and 10 mg wt) is prepared by incorporating 2.5mg chlorhexidine from a 20% chlorhexidine solution in collagen membrane. Collagen is a natural protein, having chemotactic property for fibroblasts and its high affinity to fibroblast is via its scaffold like fibrillar structure which stimulates platelet degranulation, thereby accelerating fibers and clot attachment. It has been shown to completely resorb after 30 days; however their coronal edge degrades within 10 days. [42]

Conclusion

Current data suggest that local delivery of antimicrobials into a periodontal pocket can simprove the periodontal health. Nevertheless these drug systems do not provide a higher result when compared to mechanical scaling and root planning. In combination with scaling and root planning, the adjunctive use of local drug delivery may enhance the results in sites that don't respond to conventional therapy. Local drug delivery systems with controlled release properties have the potential to be used as a therapeutic component in the management of periodontal diseases. Therefore the clinician will need to make decisions based on the desired outcomes of the therapy.

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