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Photodynamic Therapy: An Overview

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ABSTRACT

Photodynamic therapy (PDT), also known as photoradiation therapy, phototherapy, or photochemotherapy, involves the use of a photoactive dye (photosensitizer) that is activated by exposure to light of a specific wavelength in the presence of oxygen. The transfer of energy from the activated photosensitizer to available oxygen results in the formation of toxic oxygen species, such as singlet oxygen and free radicals. These very reactive chemical species can damage proteins, lipids, nucleic acids, and other cellular components. PDT has shown potential in the treatment of oral leukoplakia, oral lichen planus, and head and neck cancer. PDT also represents a novel therapeutic approach in the management of oral biofilms. Photodynamic killing of periodontopathogenic bacteria may be an alternative to the systemic application of antibacterial drugs used in the treatment of periodontal diseases.

Introduction

The mouth is a favorable habitat for a great variety of bacteria. Microbial composition of dental plaque is the usual cause of various oral diseases in humans, including dental caries, periodontal disease and halitosis. In general, oral antibacterial agents such as antibiotics are commonly used to treat oral bacterial infection. Bacterial resistance and toxicity are unavoidable with antibiotic usage. The use of photodynamic therapy has become an alternative to antibiotic drugs. [1]

Principle

Photodynamic therapy is also known as photoradiation therapy, phototherapy or photochemotherapy. [2] Photodynamic therapy (PDT) has been suggested as an alternative to chemical antimicrobial agents to eliminate subgingival species and treat periodontitis. PDT is based on the concept that non-toxic photosensitizers can be preferentially localized in certain tissues and subsequently activated by light of the appropriate wavelength to generate singlet oxygen and free radicals that are cytotoxic to cells of the target tissue. [3]

PDT involves two stages; first, a light sensitive drug called a photosensitizer is applied to the area. Second a light or laser is shone on that area. When the light is combined with the drug, phototoxic reactions induce the destruction of bacterial cells. [1] Depending on the type of agent, photosensitizer may be injected intravenously, ingested orally, or applied topically. The relative simplicity of the mechanism of activation of photosensitizers has stimulated considerable interest in PDT. [2]

PDT has several advantages over conventional therapies. It is non-invasive and convenient for the patient. It can be performed in outpatient or day care (inpatient) settings. It can be targeted accurately and selectively in early or localized diseases. Repeated doses can be given without the need for total-dose limitations. It has excellent cosmetic results, and the healing process results in little or no scarring. [2]

Photodynamic Reaction

PDT involves three components: light, a photosensitizer and oxygen. A photosensitizer or its metabolic precursor is administered to the patient. Upon irradiation with light of a specific wavelength, the photosensitizer undergoes a transition from a low-energy ground state to an excited singlet state. Subsequently, the photosensitizer may decay back to its ground state, with emission of fluorescence, or may undergo a transition to a higher-energy triplet state. The triplet state can react with endogenous oxygen to produce singlet oxygen and other radical species, causing a rapid and selective destruction of the target tissue. [2]

There are two mechanisms by which the triplet-state photosensitizer can react with biomolecules. Type I involves electron/hydrogen transfer directly from the photosensitizer, producing ions, or electron/hydrogen removal from a substrate molecule to form free radicals. These radicals react rapidly with oxygen, resulting in the production of highly reactive oxygen species (superoxide, hydroxyl radicals, hydrogen peroxide). Type II reactions produce the electronically excited and highly reactive state of oxygen known as singlet oxygen. In PDT, it is difficult to distinguish between the two reaction mechanisms. A contribution from both Types I and II processes indicates that the mechanism of damage is dependent on both oxygen tension and photosensitizer concentration. [2]

Light Sources

PDT requires a source of light that activates the photosensitizer by exposure to low-power visible light at a specific wavelength. Human tissues transmits red light efficiently, and the longer activation wavelength of the photosensitizer results in deeper light penetration. The most photosensitizers are activated by red light between 630 and 700 nm, corresponding to a light penetration depth from 0.5cm (at 630nm) to 1.5nm (at 700nm). This limits the depth of necrosis and or apoptosis and defines the therapeutic effect. In the past, photosensitizer activation was achieved via a variety of light sources, such as argon-pumped dye lasers, potassium titanyl phosphate (KTP) or neodymium: yttrium aluminum garnet (Nd/YAG)-pumped lasers, and gold-vapor- or copper vapor-pumped dye lasers. All these laser systems are complex and expensive. At present, diode laser systems that are easy to handle, portable and cost-effective are used predominantly. For treatment of large areas, non-coherent light sources, such as tungsten filament, quartz halogen, xenon arc, metal halide and phosphor-coated sodium lamps are in use. Recently, non-laser light sources, such as light-emitting diodes (LED) have also been applied in PDT. These light sources are much less expensive and are small, light weight, and highly flexible. [2]

Light is delivered via fiber-optic catheters terminated with cylindrical diffusers or lenses for flat-field applications. Modern fiber-optic systems and different types of endoscopes are more flexible and reliable and can target light more accurately to obtain more homogenous illumination. [2]

Photosensitizers

An ideal photosensitizer should be non-toxic and should display local toxicity only after activation by illumination. It should have highly selective accumulation and fast elimination from skin and epithelium, should be able to generate singlet oxygen, should be cost-effective and easily available, should be soluble in water, injection solutions and blood substitutes, should have storage and application light stability. Natural and synthetic photoactive compounds having photosensitizing potential include degradation products of chlorophyll, polyacetylenes, thiophenes, quinones (cercosporin), antraquinones (fagopyrin, hypericin) and 9-methoxypsoralen. Acridine orange, methylene blue, rose bengal, toluidine blue O, sulphonated metallo-phthalocyanines (photosense), porphyrin derivative (HPD- Photofrin), 5-aminolevulinic acid (ALA), benzoporphyrin derivative (BPD), lutetium texaphyrin, mono-L-aspartyl chlorine (NPe6), temoporfin (foscan), talaporfin sodium (LSII), tinethyletiopur-

purin (SnET2) and psoralen have been used as photosensitizers. [2] Toluidine blue O (TBO), azure B chloride and methylene blue are effective photosensitizers for killing of Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans and Fusobacterium nucleatum following exposure to laser light. Moreover, oral bacteria in multi-species biofilms can be killed by red light in the presence of TBO. Furthermore, the use of light-emitting diode and TBO promotes cellular death and prevents the formation of biofilms of streptococcus mutans in a noninvasive way. The anaerobic bacteria Porphyromonas gingivalis, Fusobacterium nucleatum and Capnocytophaga gingivalis can also be completely photo-inactivated by illumination in the presence of chlorine e6 and N-methyl-d-glucamine (BLC1010) photosensitizers. [1]

Photodynamic antimicrobial therapy (PACT)

Like PDT, PACT utilizes photosensitizers and visible or ultraviolet light in order to give a phototoxic response, normally via oxidative damage. Currently, the major use of PACT is in the disinfection of blood products, particularly for viral inactivation, although more clinically-based protocols are being developed, e.g. in the treatment of oral infection. The technique has been shown to be effective in vitro against bacteria (including drug-resistant strains), yeasts, viruses and parasites. PACT is proposed as a potential, low-cost approach to the treatment of locally occurring infection. [4] The development of resistance to PACT appears to be unlikely, since in microbial cells, singlet oxygen and free radicals interact with several cell structures and different metabolic pathways. PACT is equally effective against antibiotic-resistant and antibiotic-susceptible bacteria and repeated photosensitization has not induced the selection of resistant strains. [2]

de Oliveira RR, Schwartz-Filho HO, Novaes Jr AB, Taba Jr M (2007) tested the applicability of photodynamic therapy as an alternative for the treatment of aggressive periodontitis. They reported that PDT may be important in dealing with aggressive periodontitis because the photosensitizer is capable of penetrating through the epithelium and connective tissue, as are the periodontopathogens, especially Actinobacillus actinomycetemcomitans, which can infiltrate through the epithelial barrier into the periodontal tissues. They reported that PDT has advantages such as reducing the treatment time, no need for anesthesia, destruction of bacteria in a very short period of time (<60 seconds), unlikely development of resistance by the target bacteria and avoidable damage to the adjacent host tissues. [5]

Photodynamic killing of periodontopathogenic bacteria may be an alternative to the systemic application of antibacterial drugs used in the treatment of periodontal diseases. Even though the method is still in the experimental stage, increasing bacterial resistance problems may promote the introduction of photodynamic therapy (PDT) into periodontal practice. Even though PDT is still in experimental stages of development and testing, the method may be an adjunct to conventional antibacterial measures in periodontology. [6]

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