Photodynamic Therapy

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Abstract:
Photodynamic therapy (PDT) is a powerful laser-initiated photochemical reaction, involving the use of a photosensitizing agent (photosensitizer) activated by light of a specific wavelength in the presence of oxygen. This leads to the formation of toxic oxygen species which can damage proteins, lipids, nucleic acids and other cellular components. Applications of photodynamic therapy in dentistry is growing rapidly for as the treatment of oral cancer, bacterial and fungal infections and photodynamic diagnosis of malignant transformation of oral lesions. PACT (photodynamic antimicrobial chemotherapy) has been efficacious in the management of peri-implantitis, endodontic infections and oral biofilms such as plaque. The absence of genotoxic and mutagenic effects, no risk of developing resistance to its antimicrobial action and increased healing process favors its long-term safety and use. Thus, PDT represents a novel therapeutic approach in the management of various dental conditions.

Key words: photodynamic therapy, photosensitizers, photodynamic antimicrobial chemotherapy, cancer therapy, oral biofilm, peri-implantitis.

INTRODUCTION
Photodynamic therapy (PDT) matured as feasible medical technology in 1980s at several institutions in the world basically as a treatment for cancer involving 3 components:

1. A photosensitizer
2. A light source
3. Tissue oxygen

The word photodynamics means the application of dynamics of photons of light on the biological molecules.¹ Employing the same principle we can describe it as a medical treatment that utilizes light to activate a photosensitizing agent in the presence of oxygen. The exposure of the photosensitizer to light results in the formation of toxic oxygen species, causing localized photodamage and cell death.

HISTORY
In strict terms photodynamic therapy is as old as life on earth and a classical example is photosynthesis by plants. German physician Friedrich Mayer-Betz performed the first study, with what was first called photoradiation therapy (PRT) with porphyrins in 1913 in humans. But it was John Toth, who acknowledged the photodynamic chemical effect of the therapy with early clinical argon dye
lasers and renamed it as photodynamic therapy (PDT). It received even greater interest as Thomas Dougherty formed the International Photodynamic Association. Its use first started in dermatology (1992), then oncology (1995), and recently in microbiology (1996).

MECHANISM OF ACTION

A photosensitizer is a chemical compound (usually a dye) that can be excited by light of specific wavelength (visible or infra-red light). The agent or its metabolic product is administered (injected or applied externally) to the patient and gets accumulated in the targeted tissues (cancer cells). The tissue is then exposed to the light activating the dye from its ground singlet state to an excited singlet state which then undergoes an intersystem crossing forming a longer lived excited triplet state. In the presence of endogenous oxygen, an energy transfer then takes place from this activated agent to the oxygen molecule forming excited singlet state oxygen or other reactive oxygen species (ROS), causing a rapid and selective destruction of the target tissues. There are two mechanisms for this last process. Type I reaction involving electron 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, and hydrogen peroxide). Type II reactions producing the electronically excited and highly reactive state of oxygen known as singlet oxygen. Usually it involves a contribution from both the mechanisms.²

It may also mediate tumor destruction indirectly by vascular damage through photochemical oxygen consumption or by stimulation of the host response.³ A massive invasion of inflammatory cells during and after PDT has been observed in murine tumor models.⁴

LIGHT SOURCE:

PDT requires a source of light that activates the photosensitizer by exposure to low-power visible light at a specific wavelength. Human tissue transmits red light efficiently, and the longer activation wavelength of the photosensitizer results in deeper light penetration. Consequently, most photosensitizers are activated by red light between 630 and 700 nm, corresponding to a light penetration depth from 0.5 cm (at 630 nm) to 1.5 cm (at ~ 700 nm).⁵

We have 3 light systems for the therapy:

1. Diode laser systems: they are easy to handle, portable and cost-effective.
2. Non-coherent light sources: preferred for treatment of larger areas and include tungsten filament, quartz halogen, xenon arc, metal halide and phosphor-coated sodium lamps.
3. Non-laser light sources include light-emitting diodes (LED). They are economical, light weight and highly flexible.⁶

PHOTOSENSITIZER:

Requirements of an optimal photosensitizer include following characteristics:

1. Highly selective tumor accumulation: targetibility
2. Low toxicity and fast elimination from the skin and epithelium
3. High quantum yield of singlet oxygen production in vivo
4. Cost effectiveness and commercial availability
5. High solubility in water, injection solutions, and blood substitutes
6. Storage³

The various agents can be grouped under 3 generations.⁷ First generation include photofrin (most extensively used) and hematoporphyrin derivatives (HPD). Second generation include 5-aminolevulinic acid (ALA), benzoporphyrin derivatives (BPD), temoporfin (mTHPC) and talaporphin sodium (LS11). Foscan (mTHPC) is the most potent amongst them. ALA, is an intrinsic
photosensitizer that is converted in situ to a photosensitizer, protoporphyrin IX. Topical ALA and its esters have been used to treat pre-cancer conditions, and basal and squamous cell carcinoma of the skin. Third-generation photosensitizers include currently available drugs that are modified by targeting with monoclonal antibodies or with non-antibody-based protein carriers and protein/receptor systems, and conjugation with a radioactive tag. Currently only 3 agents have been approved by FDA - Porfimer sodium, ALA and Vertoporfirin. Foscan is in used only in European countries.

ADVANTAGES OF PDT

Therapy has only localized effects as the photosensitizer is selectively absorbed at a greater rate by target tissues, can be performed in outpatient or day-case settings, is more economical than radiation and surgical therapy for cancer patients, shows faster post-op healing with no long term side effects, less invasive and can be repeated many times at the same site if needed, unlike radiation.

LIMITATIONS:

Light needed to activate photosensitizer cannot penetrate more than 1cm of tissue depth using standard laser and low powered LED technology and hence is less effective in treatment of large tumors and metastasis. It may leave many people very sensitive to light post therapy and cannot be used in people allergic to porphyrins.

CURRENT STATUS IN DENTISTRY:

It is mainly used as anticancer therapy for head and neck region including early stage cancers and early recurrences of the oral cavity and larynx (Tis/ T1/T2), oral lichen planus, leukoplakia, verrucous hyperplasia and some metastatic lesions. Now a days it is also being employed for the Photodynamic diagnosis (PDD) of malignant transformation of oral lesions and treatment of various autoimmune disorders. A new field has evolved using the principle of this therapy, the PHOTODYNAMIC ANTIMICROBIAL CHEMOTHERAPY (PACT) against various viral, fungal and bacterial infections in the oral cavity. It works not only on periodontal conditions but also on all forms of plaque associated conditions (periodontitis and peri-implantitis)

PHOTODYNAMIC ANTIMICROBIAL CHEMOTHERAPY

In recent years, the emergence of antibiotic resistant strains, such as methicillin resistant Staphylococcus aureus and vancomycin-resistant Enterococcus faecalis, stimulated a search for alternative treatments. PACT has the potential to be such an alternative, especially for the treatment of localized infections of the skin and the oral cavity. Micro-organisms that are killed by PACT include bacteria, fungi, viruses, and protozoa. 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. The photosensitizer can be delivered to infected areas by topical application, instillation, interstitial injection, or aerosol delivery.

Photosensitizers used in PACT include: (i) phenothiazine dyes [Methylene Blue (MB) and Toluidine Blue O (TBO; tolonium chloride)]; (ii) phthalocyanines [aluminum disulphonated phthalocyanine and cationic Zn(II)-phthalocyanine]; (iii) chlorines [chlorin e6, Sn(IV)chlorin e6, chlorin e6-2.5 Nmethyl- d-glucamine (BLC1010)], and polylysine and polyethyleneimine conjugates of chlorine e6; (iv) porphyrins (hematoporphyrin HCl, Photofrin®, and ALA); (v) xanthenes (erythrosin); and (vi) monoterpene (azulene).

The following bacterias can be destroyed: Total streptococcus, Actinomyces, Lactobacillus, Prevotella intermedia, Peptostreptococcus micros, Fusobacterium nucleatum and Enterococcus faecalis.

PACT can be used for disinfection of tooth cavities, root canals and periodontal therapy. It also been recently tested for the treatment of peri-implantitis.

EFFECTS OF PACT ON ORAL BIOFILMS:

A wide range of persistent human infections are due to microbial biofilms. Dental plaque can be
defined as the diverse community of microorganisms found on the tooth surface as a biofilm, embedded in an extra-cellular matrix of polymers (EMP) of host and microbial origin. Microorganisms grow in biofilms stuck to a solid surface where they multiply and form microcolonies. Periodontal diseases result from accumulation of subgingival bacterial biofilms on tooth surfaces. Although mechanical removal of the periodontal pathogens is the current gold standard of treatment, antibiotics are also known to be effective. However, development of resistance in the target organisms is a problem associated with the use of such drugs. Additionally, concerns regarding systemic antibiotics use include side effects such as pseudomembranous enterocolitis, superinfection, other gastrointestinal disorders, and emergence of antibiotic resistance. Locally delivered antibiotics are an acceptable alternative for efficacy and are less likely to cause systemic side effects. However, disadvantages include inconvenience (because of required change in oral hygiene habits), cost (repeated treatments), and usability in relatively small areas in oral cavity which is not convenient for management of a generalized disease. The use of photoactivatable compounds or photosensitizers (PS) to cause photodestruction of oral bacteria has been demonstrated, indicating that photodynamic therapy (PDT) could be a useful alternative to mechanical means as well as antibiotics in eliminating periopathogenic bacteria. The antimicrobial activity of photosensitizers is mediated by singlet oxygen, which, because of its high chemical reactivity, has a direct effect on extracellular molecules. Thus, the polysaccharides present in EMP of a bacterial biofilm are also susceptible to photodamage. Such dual activity, not exhibited by antibiotics, represents a significant advantage of PACT. Breaking down biofilms may inhibit plasmid exchange involved in the transfer of antibiotic resistance, and disrupt colonization.

An example is Periowave™, a photodynamic disinfection system developed by Ondine Biopharma Corporation that utilizes low intensity lasers and wavelength-specific, light-activated compounds to specifically target and destroy microbial pathogens and reduce the symptoms of disease. The photosensitive compounds are topically applied in the gingival sulcus and the laser is used to activate the compounds and complete the disinfection.

Activity of PACT against oral biofilms include in vitro studies by, and few in vivo studies (in animal model) are available. All these studies found PDT to be effective in reducing bacterial load in the biofilm. Studies done by Braun et al., 2008 in patients with chronic periodontitis showed better clinical outcomes when PDT was used along with conventional therapy. However, Oliveira et al., 2009 could not find any statistical differences between PDT and scaling and root planning in patients with aggressive periodontitis.

**PERSPECTIVE AND FUTURE DIRECTIONS**

In general, however, PDT remains on the periphery of the treatment options for head and neck cancer. Thus far, the lack of accurate dosimetry and appropriate illumination devices, coupled with poorly defined treatment parameters, has diminished the success of PDT. The development of new, more tumor-specific photosensitizers and light delivery systems, and well-designed, randomized, and standardized controlled trials should improve the efficacy of PDT and accelerate the FDA’s approval of its use for the treatment of head and neck cancers. A moderate enhancement of photosensitizer accumulation in tumor tissues provides a first level of selectivity, while further selectivity may be provided by the homogenous illumination of the target area with a custom-size fiber optic. Developing such devices would be a much-needed future direction for PDT. The LED devices that can be shaped into numerous forms and sizes, and are cost-effective, may replace laser light sources and their fiber optics. Recent concept include (i) a metronomic PDT that uses a continuous delivery of photosensitizer and light at low rates for extended periods of time, (ii) implantable light sources, and (iii) the attachment of bioluminescent material to photosensitizers.

PACT will not replace antimicrobial chemotherapy, but the photodynamic approach may improve the treatment of oral infections, accelerating and lowering the cost of the treatment. Development
of new photosensitizers, more efficient light delivery systems, and further animal studies are required to establish the optimum treatment parameters before investigators can proceed to clinical trials and eventual clinical use.

Major controversies in PDT includes: (i) the difficulty in establishing the optimum conditions for a treatment that has several components, (ii) clinician and hospital resistance to a new approach, (iii) the cost of setting up a PDT center, (iv) the previous lack of inexpensive and convenient light sources, and (v) difficulty in obtaining FDA approval.2

CONCLUSION:

Thus to summarize PDT may have a significant potential for the treatment of oral cancer and oral dysplastic lesions, as well as PACT for the treatment of oral infections, but its future depends on interactions between clinical applications and technological innovations.

REFERENCES