Research Paper

Volume : 2 | Issue : 6 | June 2013 • ISSN No 2277 - 8179

Photodynamic Therapy in Periodontology & Implantogy : a Review article

Medical Science

KEYWORDS :

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Introduction

It has been an established concept that microorganisms are the main culprits for periodontal[1,2] and endodontic diseases[3, 4, 5]. In both periodontics and endodontics the approach towards the pathology is mechanical debridement of the affected area along with local and systemic antimicrobials. The disadvantages of antimicrobial agents range from lack of patient compliance, microbial resistance in the biofilm[6,7], systemic side effects, failure on the antibiotics to act on non perfused areas, allergy and limitation of spectrum of microorganisms affected. Strategies employed by microorganisms resisting antibiotics have been thickening of their outer wall, encoding of new proteins which prevent the penetration of drugs, onset of mutants deficient in those porin channels allowing the influx of externally added chemicals, etc.[8, 9,10]. The solution to these problems is unknown till date. Treatment using light and light activated compounds is referred back from ancient times, and was used to treat a wide variety of disorders and malaise [11, 12, 13]. But the breakthrough came when first report emerged on light-absorbing properties and fluorescence of various dyes, it became clear that dye excitation by light exerts destructive action in biologic systems. This so-called "Photodynamic action" was described as a process in which light, after being absorbed by dyes, sensitizes organisms for visible light-inducing cell damage. Photodynamic therapy is based on the principle that a photoactivable substance that is photosensitizer binds to the target cell and can be activated by light of a suitable wavelength. Photodynamic is also known as Photoactivated disinfection (PAD) or Photoactivated chemotherapy (PACT).

History

German medical student Raab et al in 1900 first studied photodynamic reaction using cultures of Paramecium and acridine an organic dye. The first medical use of chemically enhanced phototherapy (other than for restoration of pigmentation) was reported by Jesionek and Tappeiner" in 1905when they treated five basal cell carcinomas by injecting eosin into the tumour and exposing it to light reporting three cures[14]. The essential involvement of light and oxygen in the process was shortly thereafter demonstrated by von Tappeiner[15], who coined the term "photodynamic." Haxthausen and Hausmann in 1908 were the first to suggest that hematoporphyrin was a photodynamic photosensitizer. In 1960, Theodore Maiman, a scientist with the Hughes Aircraft Corporation, developed the first working laser device which emitted a deep red colored beam from a ruby crystal (Coluzzi 2004). Wilson et al (1993) proved the effect of cyanide photosensitizer on gram negative and gram positive species. Ackrayd R (1999) used aminolaevulinic acid induced photodynamic therapy for treatment of adenocarcinoma. Thereafter in the recent past many combinations of lasers and photosensitizers were tried ant different parameters with varying successes.

Mechanism of Action

The 3 components of photodynamic therapy are oxygen, photosensitizer and light.

A photosensitizer is a chemical compound which when administered to the patient is taken up selectively by the diseased tissue and readily undergoes photo excitation when lased with a suitable wavelength transferring its energy to other molecules causing destruction of pathologic tissues and microorganisms. Usually the photosensitizer is excited from a ground singlet state (quantum state with zero spin angular momentum) to an excited singlet state. It then undergoes intersystem crossing to a longer-lived excited triplet state. In this state, two reactions are possible as mentioned in the previous article. For optimum results some properties are desired in these photoactive compounds.

Ideal requisites of photosensitizers

1. No dark toxicity.
2. Preferential uptake & retention in diseased tissue.
3. Minimal or no skin sensitivity.
4. Rapid clearance
5. Limited in vivo stability for rapid clearance from normal tissue.
6. High absorption in the red region of the visible spectrum with high extinction coefficient ($E \geq 50\,000\ M^{-1}\ cm^{-1}$) is also an important criterion to increase the number of photons absorbed and to take advantage of the increase in the penetration depth of light into tissue at longer wavelengths.
7. The absorption band of the sensitizer should not overlap the absorption bands of other chromophores present in the tissues.

More than 400 compounds have shown photosensitizing properties, either in vitro or in vivo.

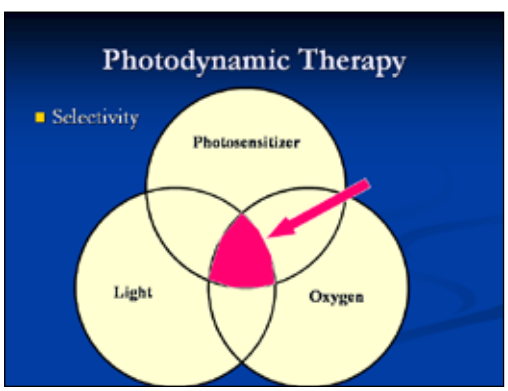
Classification of photosensitizers -:

Photosensitizers can be grouped as follows (Mark Wainwright 1998)

- Cationic-azinephotosensitizers- Phenothiazinium
- Macrocyclic photosensitizers- Porphyrin

- Natural product photosensitizers
- Naturally occurring photosensitizers
- Acridines
- Cyanines and merocyanine

Photosensitizer	Wavelength of activation
Methylene blue	633
Toluidine blue	660
Porfimer sodium	630
Temeporfin	652
Verteporfin	690
ALA	635
Chlorin e6	665
Phthalocynine	660-700
Cyanine	500-600
Acridine	400-500
Psoralen	300-380

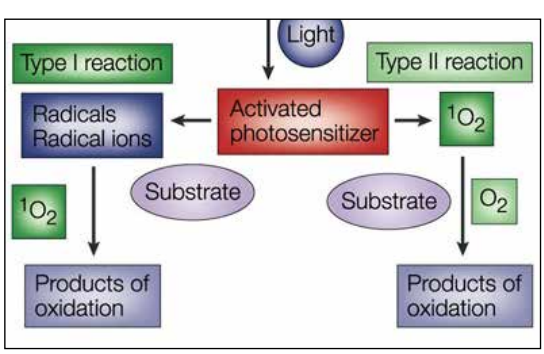


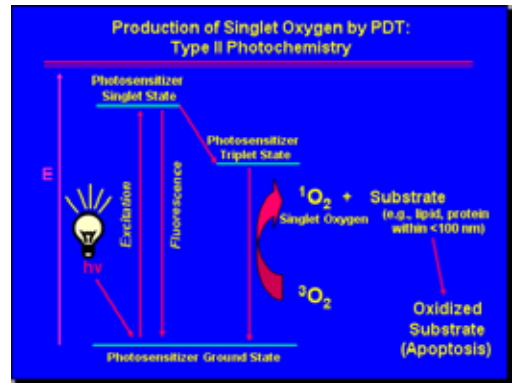
When a photosensitizer is administered to the patient and irradiated with a suitable wavelength then it goes to an excited state from its ground state. This excited state can then decay back to its ground state or form the higher energy triplet state[16, 17]. The interaction between biomolecules and triplet state photosensitizers can be of 2 types -

Type I: It involves electron/hydrogen transfer directly from the photo-sensitizer, 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: The reactions produce electronically excited and highly reactive state of oxygen known as singlet oxygen. In PDT, it is difficult to distinguish between the two reactions mechanisms.

A contribution from both Types I and II processes indicates that the mechanism of damage is dependent on both oxygen tension and photo-sensitizer concentration.





In this process free radicals are formed which then produce an effect that is toxic to the cell[18, 19]. The half-life of oxygen radicals is only about a few nanoseconds hence this cytotoxic molecule can diffuse only up to 20 nm in cells (Moan et al., 1991). Thus these photosensitizers localize in the mitochondria, plasma membrane, endoplasmic reticulum and Golgi complex at concentrations sufficient for mediating cytotoxicity. Due to the very short half-life of oxygen radicals, measured in nanoseconds, this cytotoxic molecule can diffuse only up to 20 nm in cells (Moan et al., 1991). Also the reactive end products of this pathway results in a rapid cyto and vasculo toxicity which are the basis of photodynamic therapy[20]. Research in a number of laboratories has demonstrated the potential of PDT as a treatment for localized microbial infections [21, 22, 23]. PDT has shown to be active against both gram positive and gram negative organisms [23].
Tim Maisch et al (2004) studied the general photobiological and

photochemical aspects and stated:
The photodynamic activity to induce cell damage or death is determined by five important photophysical / photochemical properties including

1) An overall lipophilicity and ionization of the photoreactive dyes,
2) The molecular extinction coefficient,
3) Quantum yield of the triplet state formation UT,
4) Redox potentials of the excited states of the P^S_{red} or PS^T_{red}, if the reaction follows the type I mechanism or
5) The quantum yield of the singlet oxygen generation, if the reaction occurs by a type II photosensitization.

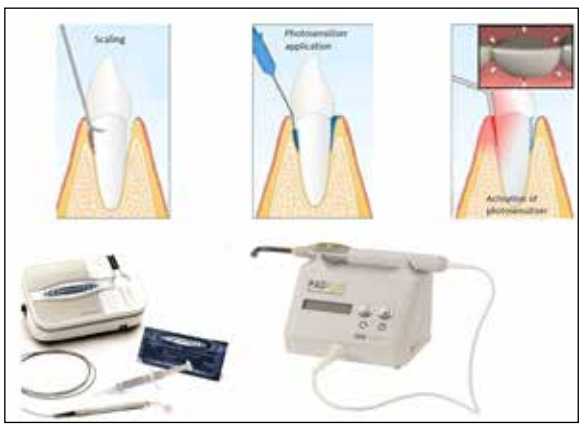
APPLICATIONS OF PHOTOACTIVATED DISINFECTION (Based on Wilson & Wilson)

- Treating periodontal pockets.
- Plaque infected cervical regions of teeth & implants.
- Disinfecting carious dentin prior to restoration.
- Destroying cariogenic microbes for caries treatment and prevention.
- Disinfecting root canals.
- Disinfecting oral tissues prior to and during surgery.
- Treating oral candidiasis in immunocompromized patients.
- Treating denture stomatitis

Applications in periodontics and implants
It has been proven that cells in biofilm are in physiological state that differs from their planktonic counterparts & tend to be less susceptible to antimicrobial agents [24]. It also explains why systemically and locally delivered antimicrobials have always been proven unsuccessful, even when they were targeted at specific microorganisms. Successful periodontal therapy is still based on the concept of elimination of the microorganisms from the infected site [25]; lasers only make it easy, non invasive and efficient. Phenothiazinium photosensitizers have shown to be safe and highly effective for periodontal infections. Scaling and root planning is to be carried out before PDT. While doing the PDT the photosensitizer is first injected in the periodontal pocket and allowed to pigment for 2 minutes. Then the fiber is inserted 1mm short of the pocket and lased by moving in a sinusoidal manner from side to side towards the coronal third. It has been

Volume : 2 | Issue : 6 | June 2013 • ISSN No 2277 - 8179

proven that photodynamic therapy has found an adjunctive role in periimplantitis[26].



Advantages of photodynamic therapy

1. Minimally invasive technique with least collateral damage to normal cells enhances results and superior healing.
2. Exceedingly efficient broad spectrum of action, since one photosensitizer can act on bacteria, virus, fungi, yeasts, and parasitic protozoa.
3. Efficacy independent of the antibiotic resistance pattern of the given microbial strain.
4. The therapy also causes no adverse effects such as ulcers, sloughing or charring of oral tissues.
5. Lesser chance of recurrence of malignancy.
6. Economical to use.

Limitations of Photodynamic therapy

Systemic administration of photosensitizer causes a period of residual skin photosensitivity due to accumulation of photosensitizers under the skin. Therefore photosensitizers can be activated by daylight causing 1st or 2nd degree burns. Hence direct sunlight must be avoided for several hours until the drug is completely eliminated from the body.

Summary and Conclusion

1) Lethal photosensitization may be an effective means of eliminating periodontopathogenic bacteria from dental plaque / biofilm.
2) PDT is efficient & safe tool for treatment of chronic and aggressive periodontitis and can prove adjunctive to mechanical debridement .
3) Development of resistance among the target organism to the PDT is unlikely. Lack of mutagenicity topical and selective action, no harm to eukaryotic / host cells are the characteristic advantages of PDT.
4) Antimicrobial Photodynamic Therapy is an efficient method for bacterial load reduction in periodontal therapy. The treatment is non invasive and can be repeated without the risk of allergies and resistance in comparison to antibiotic therapy.
5) PDT is effective even in presence of blood (C R Rovaldi 2000)

'Photodynamic Therapy' (PDT) may be an effective way to treat the bacteria linked to periodontal diseases, and could provide a better option than antibiotics or other mechanical methods for treating periodontal diseases and may prove to be a promising alternative to conventional periodontal therapy in near future.

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