Photodynamic Antimicrobial Chemotherapy in the General Dental Practice

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INTRODUCTION

Laser photonic energy can be absorbed by target tissue and molecular elements. In the surgical excision of tissue, such energy is rapidly converted into thermal energy that causes physical disruption and possible vaporization. Relative to each target tissue and corresponding incident laser wavelength exists a thermal threshold, below which the incident photonic energy values are insufficient to initiate disruption, resulting in reversible warming.[1]

At much lower incident energy levels, intracellular structures such as cell mitochondria can absorb incident photonic energy, resulting in stimulation of adenosine triphosphate and ultimately in an increase in cell respiration.[2] Such "low-level laser" action has been well documented,[3] reflecting a general process of energy transfer within such structures. A procedure used in cancer treatment called photodynamic therapy (PDT) utilizes this energy transfer.[4]

Allied to investigations into low-level laser effects, it has been shown that certain chemotherapeutic agents possess similar capacity for electron transfer in the presence of photonic energy.[5] Where this occurs in close proximity to host tissue and in particular tissue oxygen, reactive oxygen species can be formed simultaneously with singlet oxygen. Ultimately, these reactions will kill cells through apoptosis or necrosis.[4, 6-7]

The major outcome of such knowledge has been seen in the general principles of photodynamic therapy in the treatment of neoplastic tumors.[8-9] However, similar effects have been demonstrated *in vitro,* using low-level photonic energy on selected bacterial species with some success. This has led to the emergence of photodynamic antimicrobial chemotherapy (PACT) in treating a broad range of bacterial infections in the mouth.

This paper reviews the process of energy transfer in PACT, the development of clinical protocols, and the applications of PACT in clinical dentistry.

COMPONENTS AND MECHANISMS

Light has been used for therapeutic purposes for several centuries. Initially, ultraviolet radiation was applied in the treatment of acne vulgaris, skin tuberculosis, and rickets.[10-11] With the development of light-absorbing properties and fluorescence of various dyes, it was realized that these chemicals, when photoexcited, were capable of exerting destructive effects on target cells. This process was termed photodynamic action and further research[12-13] into the mechanisms involved gave rise to an understanding of "dye-sensitized photo-oxidation of molecular oxygen."

A photosensitizer is a chemical compound that readily undergoes photoexcitation and then transfers its energy to other molecules.[5] 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 above.[4] When the photosensitizer and an oxygen molecule are in proximity, an energy transfer can take place that allows the photosensitizer to relax to its ground singlet state and create an excited singlet-state oxygen molecule. Singlet oxygen is a very aggressive chemical species and will very rapidly react with any nearby biomolecules.[7]

GLOSSARY

Various acronyms have been used to describe the processes whereby incident low-level laser radiation might provide energy to aid diagnosis and therapy.

PDT: Photodynamic therapy. The use of subablative incident laser radiation to activate a chosen photosensitizer and effect a predetermined photochemical change in surrounding host tissue.

PAD: Photo-activated disinfection. A descriptive term adopted by certain manufacturers to suggest the elimination of target bacteria, using a suitable photosensitizer, such as tolonium chloride or methylene blue.

PACT: Photodynamic antimicrobial chemotherapy. A more precise descriptive term that reflects the use of photonic energy to drive a chemotherapeutic action resulting in antimicrobial action.

There are more than 400 compounds that have been shown to exhibit photosensitizing properties, either *in vitro* or *in vivo.*[14] Some of the more significant may be summarized as follows:

- phenothiazine dyes – e.g., methylene blue (MB) and toluidine blue O (TBO; tolonium chloride)[15-16]
- phthalocyanines[17-18]
- chlorines[19]
- porphyrins – e.g., hematoporphyrin HCl, Photofrin®, 5-ALA (aminolevulinic acid)[20-21]
- xanthenes – e.g., erythrosine.[22]

The basic principle of PACT is to utilize a photosensitizer in combination with a light source to activate it.[23] Wilson and Pratten reported that neither the light source alone in the absence of the photosensitizer nor the photosensitizer alone in the absence of the light source had any significant effect on the simulated antibacterial therapy.[18] In contrast, Dörtbudak *et al.* demonstrated that application of toluidine blue O alone resulted in significant reduction of some, but not all, bacterial species tested.[24] In the above studies,[15-22] all of the compounds except erythrosine were activated by visible red light in the wavelength range of 630 to 662 nm produced by a laser; an ordinary tungsten lamp was used in a study of erythrosine's effectiveness,[22] but that compound has a maximum absorption in the 500 to 550-nm range, which is blue and green light. Wilson and Patterson have suggested a 700 to 850-nm range of energy for an 'ideal' photosensitizer. Nonetheless, a diode laser is usually used for photodynamic procedures.[23]

As outlined above, the photosensitizer compound in its ground state is activated by light and transformed into a high energized triplet state. Two mechanisms of action explain the effectiveness of PACT:[25]

- The triplet compound interacts with the cell's organic substrate molecule, producing free radicals and radical ions. These in turn react with endogenous oxygen and reactive oxygen species (ROS) such as hydrogen peroxide and hydroxyl radicals which irreversibly damage the cell's membrane. ROS compounds can also damage subcellular organelles and enzymes as well as DNA.[26]
- The triplet compound interacts directly with the molecular oxygen to produce a singlet oxygen, which is highly reactive. It also causes irreparable cellular damage, including the cell wall.

Although both mechanisms exist in relation to each other, singlet oxygen generally produces the lethal bacterial effects of PACT. The interaction is extremely rapid, since the radius of action of singlet oxygen is estimated to be on the order of 0.01 to 0.02 µm, corresponding to a lifetime of 0.01 to 0.04 µs in cells.[27] There is limited migration of the molecule from its formative site, thus its effect is very localized. The advantage is that surrounding structures can be preserved;[25] however, the placement of the photosensitizer should be as close to the infection as possible.

CLINICAL APPLICATIONS

The majority of the common disorders within the oral cavity are due either to bacterial causes or are exacerbated by secondary bacterial contamination. Notwithstanding the need for the clinician to correctly diagnose the condition and address all local and systemic contributory factors, the elimination of pathogenic bacteria has represented a core objective. In addition to the presence of bacterial colonies, the existence of a biofilm can constitute a formidable barrier to many local applied therapies[28-29] and systemic antibiotic use has led to inconsistent results. Of significance to the latter, antibiotic resistance and systemic side effects may present a challenge and deter the casual use of such therapies.[30-33]

The consequence of risk associated with concomitant bacteremia during periodontal and restorative treatment has been the subject of a recent review.[34] Over more than 40 years, prophylactic administration of systemic antibiotics has been considered best practice in those patients at risk of bacterial endocarditis and, despite recommendations to the contrary, the controversy remains.[35]

Mechanical instrumentation, including scaling and root planing and the use of ultrasonics, has been advocated to provide adjunctive debridement in periodontal and periimplantitis treatment. The efficacy of such treatment may be compromised by lack of direct access to the treatment site and the possible risk to underlying healthy tissue.

The photothermal interaction of lasers, using supra-ablation threshold values, can produce tissue temperatures to aid in bacterial reduction.[36]

With regard to the sole use of ablative laser energy in bactericidal effects, the following phenomena may be considered as limiting factors:

- Primary bactericidal action linked to absorption characteristics
- Primary interaction coaxial with laser beam
- Risk of collateral damage associated with nontarget absorption and thermal rise
- Other difficulties – access, limitations of delivery tip design, etc.

Conversely, the use of a nonablation, low-level laser wavelengths to initiate photodynamic antimicrobial chemotherapy in a suitably administered photosensitizer may be seen to have the following advantages over "conventional" laser use:

- Nonsurgical (subablative) photonic energy values employed
- Primary (indirect) interaction through chemical mediator (photosensitizer)
- Little risk of collateral damage within confined target sites. Methylene blue as a photosensitizer should be used with caution and in dilute doses, to avoid possible toxicity[37]
- The use of noncollimated light through a diffuser tip can overcome limited access and be further compensated by scatter through the body of the liquid sensitizer.

Local infections such as those that occur within the oral cavity may be potential targets for antibacterial photodynamic therapy, in addition to other mechanical debridement techniques. The supra- and subgingival plaque biofilm on tooth surfaces is often easily accessible for flushing with the dye and activation with the low-level laser light.

During the last decade, an increasing number of studies have been published that describe the effect on periodontal pathogenic bacteria by photodynamic methods. These investigations have underlined the introduction of PACT into the practice of periodontology.[38-42]

Other investigations have shown the use of PACT in the treatment of a number of pathogenic bacterial and fungal infections, summarized as follows:

- Tooth surface disinfection prior to dental treatment[43]

Figure 1: Periowave™, a low-level laser device, capable of use with a photosensitizer

- Disinfection of infected root canals[44]
- Periodontology[45-46]
- Peri-implantitis[47]
- Antifungal[48]
- Antiviral.[49]

Current developments in commercial low-level laser emission have given rise to several devices which emit light in the visible red region of the electromagnetic spectrum. One such instrument (PAD™ Plus, Denfotex Light Systems Ltd., Inverkeithing, Fife, UK) uses tolonium chloride solution as the supplied photosensitizer and is designed primarily for antibacterial action within the tooth (cavity preparation and endodontics). Another device (Periowave™, Ondine Biopharma Corp., Vancouver, British Columbia, Canada, shown in Figure 1) supplies a methylene blue solution for use in periodontology, para-implantology, and oral mucosal infection sites. The author's experience has been with the latter instrument. Figure 2 shows the device's fiber-optic delivery system, and Figure 3 shows the laser activated with emission through the diffuser tip.

Use of PACT is seen as adjunctive to the reduction of bacterial pathogens and is part of the overall treatment necessary to address causative factors and repair, remodel, or restore the tissue site as required. Safety regulations must be applied as per National statutes and guidance and the Class III classification of the laser defines the use of wavelength-specific protective eyewear for patient and operator. The photosensitizer solution is supplied in single-use disposable vials, onto which a blunt, side-release cannula is fitted; the cannula is applied to the tissue site and a small amount of photosensitizer expelled. The laser unit is configured by the manufacturer to deliver a fixed cycle of continuous-wave light emission, enabled through a foot switch, with the following power parameters: 220 mW / 60 seconds / 13 joules. The nature of the diffuser delivery tip helps ensure that laser photonic energy is applied evenly throughout a volumetric zone of photosensitizer and is considered effective within a 1 to 2-mm distance from the diffuser tip. Therefore, in the periodontal pocket disinfection of a single root tooth site, the tip is applied at four sites (mesial, distal, facial, palatal), with additional application at bifurcation sites for molar teeth; each site is exposed to the fixed cycle of light emission.

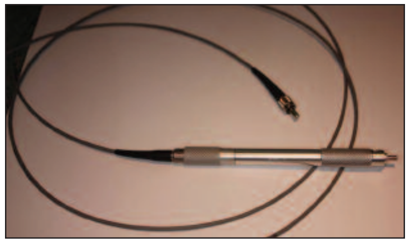

Figure 2: A fiber delivery system is connected to a disposable, single-use, plastic diffuser, which allows even distribution of light within the target area

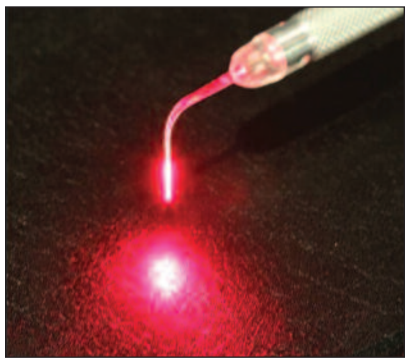

Figure 3: Diffuser tip with emitted laser radiation. This allows an even distribution of photonic energy thru 360°

CLINICAL CASES

The following clinical cases present examples of PACT. Figures 4 to 7 show adjunctive treatment of a periodontal pocket during the placement of a new crown.

Figures 8 to 11 also present the use of PACT for adjunctive treatment of periodontitis.

Figures 12 to 16 illustrate a case of peri-implantitis adjunctively treated with PACT.

Figures 17 to 20 portray treatment of candidal cheilitis of the lip using methylene blue photosensitizer.

Figures 21 to 23 depict a similar candidiasis-type lesion on the palate, treated with PACT.

Figures 24 to 31 show the adjunctive use of PACT during osseous surgery as part of the treatment to resolve periodontal breakdown associated with failed fixed bridgework.

Figure 4: Upper left bicuspid requiring replacement porcelain-fused-to-metal (PFM) crown. Associated gingival hyperplasia and inflammation are visible in preoperative left image. Right image shows the application of methylene blue solution, prior to exposure to laser energy

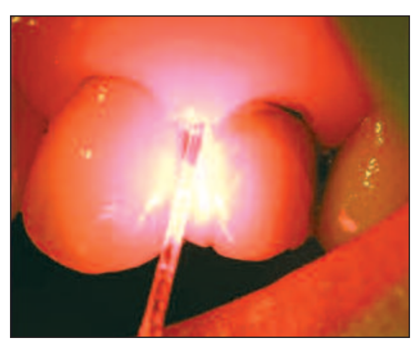

Figure 5: Periodontal sulcus being exposed to laser photonic energy

Figure 6: Single-use photosensitizer syringe, blunt needle cannula, and diffuser tip

Figure 7: Completed new PFM crown with healthy tissue (right) at three weeks post-treatment

Figure 8: Preoperative probing demonstrating presence of periodontal disease

Figure 9: After methylene blue solution had been applied to post-scaling treatment sites, the pockets are exposed to laser photonic energy

Figure 10: Immediate postoperative view

Figure 11: One-month postoperative view. Clinical appearance shows lack of inflammation and bleeding

Figure 12: Probing of a diseased area of peri-implantitis. PACT will be used adjunctively with an open flap procedure that will also employ an Er:YAG laser for debridement

Figure 13: Debridement of implant fixtures using an Er:YAG laser

Figure 14: Treatment site immediately prior to application of the photosensitizer

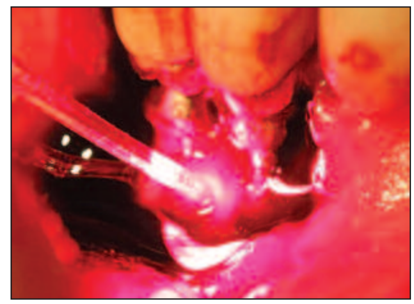

Figure 15: Photosensitizer exposed to laser photonic energy, delivered through diffuser tip. After PACT is completed, guided bone regeneration (GBR) is employed in the defect

Figure 16: Postoperative clinical appearance at three months

Figure 17: Close-up view of a persistent candidal cheilitis lesion of the lower lip

Figure 18: Application of methylene blue solution to the lesion

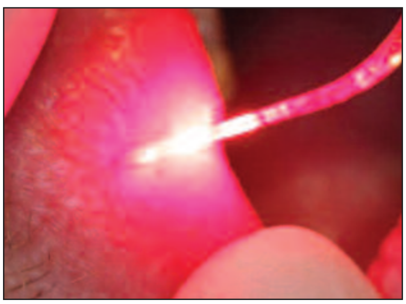

Figure 19: Exposure of treatment site to activated diffuser tip. The tip is placed alongside the lesion to allow intimate exposure

Figure 20: Healing of lesion at two weeks, showing appearance of resolution of the fungal infection

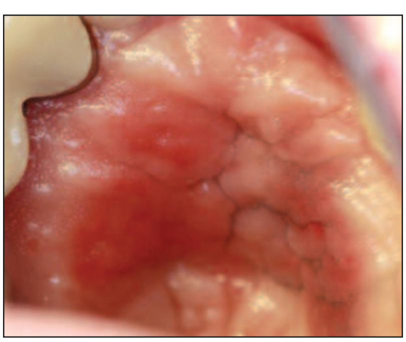

Figure 21: Pretreatment view of candidal denture stomatitis, showing characteristic epithelial hyperplasia and inflammation

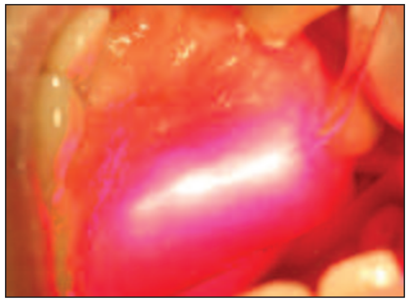

Figure 22: Application of laser photonic light diffuser tip

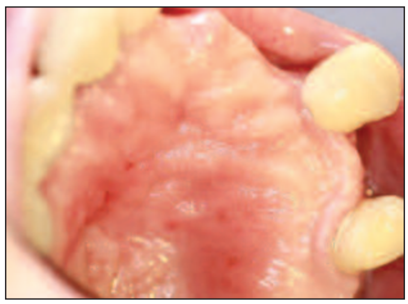

Figure 23: Follow-up view at two weeks post-treatment, showing appearance of resolution of inflammatory changes in epithelium

Figure 24: View of probing of the periodontal defect, which is an infrabony defect associated with teeth #11 and 12 (upper left canine, first premolar). Tooth #11 is a distal abutment for a failing fixed bridge and the defect is considered secondary to an open tooth contact. PACT will be used adjunctively to an open flap procedure, in which an Er:YAG laser will also be employed

Figure 25: Pretreatment radiograph showing bone loss

Figure 26: The bridge has been removed and the periodontal defect is debrided using a surgical Er:YAG laser application

Figure 27: Additional use of an Er:YAG laser allows selective removal of subgingival calculus from root surfaces

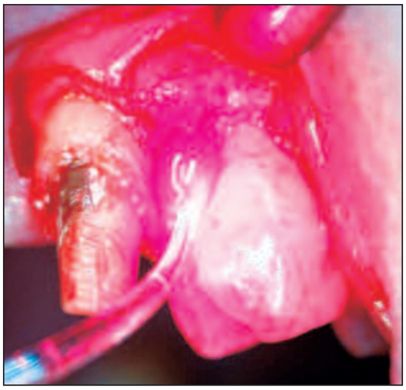

Figure 28: Infrabony pocket debridement and calculus removal is followed immediately by PACT, using methylene blue solution and laser diffuser tip

Figure 29: Use of a guided bone regeneration technique, employing hydroxyapatite matrix and membrane to augment bone defect

ADVANTAGES AND ADVISORIES

In the author's clinical experience, the benefits to be derived from the adjunctive use of PACT in providing treatment of conditions of a bacterial origin may be summarized as follows:

- Straightforward clinical technique
- Nonsurgical protocol required for application of photosensitizer
- Topical / systemic antibiotics not required
- Useful as an adjunct to restorative / endodontic / surgery site pathogen reduction
- PACT can disrupt plaque biofilm, thus making it an adjunctive for use with ultrasonics, surfactant

Figure 30: Healing at three months, at the time of final bridge fabrication

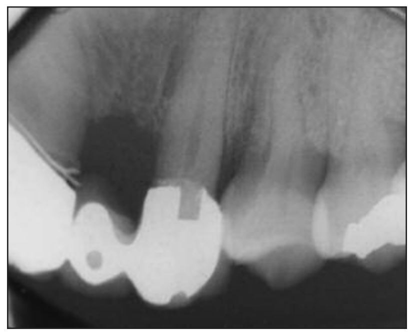

Figure 31: Radiograph at three months showing early bone in-fill

- Facilitates access into deep / limited-access sites (furcations, invaginations)
- Reduced need for surgery / direct flap approach. Patient comfort enhanced
- Reduced risk of bacteremia. Useful in patients with "at-risk" medical history
- Useful in treatment of mucosal pathologies – candida, herpes, cheilitis
- GBR success enhanced following PACT.

Potential drawbacks to PACT include:

- Possible impairment of benign oral flora which may lead to an overgrowth of a single resistant species. Staining the target selectively is seen as a way to help avoid this unwanted, potentially phototoxic reaction.[38]
- Photosentizers can adhere strongly to the soft tissue of the periodontal pocket and may affect periodontal attachment during wound healing. Routine removal of the dye solution after photosensitization procedures will mitigate this concern.[25]
- Photosensitizers can compromise patient esthetics by producing temporary pigmentation of the periodontal tissues. Excess dye should be removed with water spray.[25] The use of photosensitizers in a paste base rather than liquid may facilitate removal through irrigation with a saline solution.[50]
- Should higher-powered diode lasers be used to irradiate the photosensitizer, extended duration of exposure at the same spot should be avoided to prevent thermal accumulation or injury to deeper tissues, such as bone or dental pulp.[25]

CONCLUSION

The majority of pathologies treated in everyday general dental practice can be considered to be primary bacterial infections or are complicated by secondary bacterial contamination. Many techniques have been advocated to address the need for elimination of bacterial pathogens as part of treatment and one of the claimed advantages of surgical laser use is a bacterial reduction of target sites in both hard and soft tissue management. However, the limitations of the coaxial emission of the laser beam and difficulty in accessing all sites may compromise the desired outcome.

The use of laser photonic energy to activate an intermediate chemical and achieve bacterial destruction through secondary effect has been shown to offer advantages over surgical laser use.

This paper has presented the underlying principles of PACT action and considered some of the areas of clinical treatment where PACT has been shown to be of benefit. Potential drawbacks are described, along with suggested measures to mitigate concerns.

Differing regulatory policies have restricted a more widespread uptake of this treatment modality in dental practice. However, the general principles and instrumentation of photodynamic therapy in general medicine have been long-accepted globally and it is hoped that the opportunity to integrate PACT into general dental practice will allow this modality to gain in popularity.

AUTHOR BIOGRAPHY

Dr. Steven Parker is in private practice in Harrogate, United Kingdom, and a visiting professor in laser dentistry at the University of Genoa, Italy. He has been active in the use and teaching of laser applications in dentistry since 1990 and has lectured extensively on all aspects of laser use. He is a past president of the Academy of Laser Dentistry and currently is chair of the Academy's Education Committee.

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