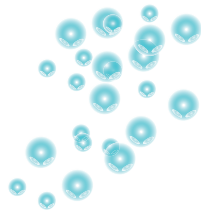


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Review Articles

Photodynamic therapy: a new antimicrobial approach to infectious disease?

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Photochem. Photobiol. Sci., 2004, 2, 436-450

Photodynamic therapy (PDT) employs a non-toxic dye, termed a photosensitizer (PS), and low intensity visible light which, in the presence of oxygen, combine to produce cytotoxic species. PDT has the advantage of dual selectivity, in that the PS can be targeted to its destination cell or tissue and, in addition, the illumination can be spatially directed to the lesion. PDT has previously been used to kill pathogenic microorganisms *in vitro*, but its use to treat infections in animal models or patients has not, as yet, been much developed. It is known that Gram-(\ominus) bacteria are resistant to PDT with many commonly used PS that will readily lead to phototoxicity in Gram-(\ominus) species, and that PS bearing a cationic charge or the use of agents that increase the permeability of the outer membrane will increase the efficacy of killing Gram-(\ominus) organisms. All the available evidence suggests that multi-antibiotic resistant strains are as easily killed by PDT as naïve strains, and that bacteria will not readily develop resistance to PDT. Treatment of localized infections with PDT requires selectivity of the PS for microbes over host cells, delivery of the PS into the infected area and the ability to effectively illuminate the lesion. Recently, there have been reports of PDT used to treat infections in selected animal models and some clinical trials: mainly for viral lesions, but also for acne, gastric infection by *Helicobacter pylori* and brain abscesses. Possible future clinical applications include infections in wounds and burns, rapidly spreading and intractable soft-tissue infections and abscesses, infections in body cavities such as the mouth, ear, nasal sinus, bladder and stomach, and surface infections of the cornea and skin.

Photodynamic Therapy of Microbial Infections: State of the Art and Perspectives

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Journal of Environmental Pathology, Toxicology, and Oncology, 25(1-2)505-519 (2006)

Photodynamic therapy (PDT) is coming of age as an efficient alternative treatment for microbial infections, a problem which is presently aggravated by the increasingly widespread diffusion of antibiotic-resistant microbial strains. In particular, the use of red light-absorbing photosensitizers as photodynamic antimicrobial agents is characterized by various favorable features, including: (a) the broad spectrum of antimicrobial action of selected phenothiazines, porphyrins, and phthalocyanines, which promote the photosensitized inactivation of Gram(+) and Gram(-) bacteria, fungi, mycoplasma, and parasites by using one phototherapeutic protocol and mild irradiation conditions; (b) porphyrins/phthalocyanines display no appreciable toxicity in the dark at photochemically active doses; (c) microbial cell death is primarily a consequence of membrane photodamage through a typically multitarget process, which minimizes the risk of both the onset of mutagenic processes and the selection of photoresistant cells; (d) such photosensitizers act with essentially identical efficiency against both wild and antibiotic-resistant strains, whereas no selection of photoresistant microbial pathogens has been observed; (e) a combination between antibiotic-based and photodynamic therapy is possible. A typical example of phthalocyanine-sensitized photoinactivation of methicillin-resistant *Staphylococcus aureus* (MRSA) is provided. At present, antimicrobial PDT appears to be especially convenient for the treatment of localized infections, such as oral candidosis, periodontitis or chronic wounds.

KEY WORDS: photodynamic therapy, microbial infections, porphyrins, phthalocyanines, photosensitization, activated oxygen, antibiotic resistance, bacteria, fungi

Photodynamic Therapy in Dentistry

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ABSTRACT

Photodynamic therapy (PDT), also known as photoradiation therapy, phototherapy, or photochemo therapy, 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. Applications of PDT in dentistry are growing rapidly: the treatment of oral cancer, bacterial and fungal infection therapies, and the photodynamic diagnosis (PDD) of the malignant transformation of oral lesions. PDT has shown potential in the treatment of oral leukoplakia, oral lichen planus, and head and neck cancer. Photodynamic antimicrobial chemotherapy (PACT) has been efficacious in the treatment of bacterial, fungal, parasitic, and viral infections. The absence of genotoxic and mutagenic effects of PDT is an important factor for long-term safety during treatment. PDT also represents a novel therapeutic approach in the management of oral biofilms. Disruption of plaque structure has important consequences for homeostasis within the biofilm. Studies are now leading toward selective photosensitizers, since killing the entire flora leaves patients open to opportunistic infections.

Dentists deal with oral infections on a regular basis. The oral cavity is especially suitable for PACT, because it is relatively accessible to illumination.

Anti-microbial photodynamic therapy: useful in the future?

Tim Maisch

Lasers Med Sci (2007) 22: 83–91

Abstract

Previous chapters in this volume have focused on fundamental principles and clinical applications of PDT. This chapter will attempt to outline emerging areas of research to identify some new applications that may become useful in the future in clinical practise. The worldwide rise in antibiotic resistance has driven research to the development of novel anti-microbial strategies. Cutaneous diseases caused by MRSA are ideally suited to treatment by anti-microbial photodynamic therapy for eradicating localized infections and for modulating wound healing due to the ability to deliver photosensitizer and light with topical application. The use of photosensitizer and light as an anti-microbial agent against periodontal microbial biofilms should also represent an attractive method of eliminating oral bacteria. Suitable light sources, laser light and non-coherent light will be briefly covered. This chapter will focus on some aspects of anti-microbial photodynamic therapy that appear to be promising for dermatological indications and inactivation of pathogenic bacteria within the oral cavity.

Keywords: Anti-microbial photodynamic therapy. Oral bacteria. MRSA. Photosensitizer. Porphyrin-photosensitization

Periimplantitis

Lethal photosensitization for decontamination of implant surfaces in the treatment of peri-implantitis

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Clin. Oral Impl. Res. 12, 2001; 104–108

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Key words: photosensitization, peri-implantitis, diode laser

Abstract: Peri-implantitis is considered to be a multifactorial process involving bacterial contamination of the implant surface. A previous study demonstrated that a combination of toluidine blue O (100 mg/ml) and irradiation with a diode soft laser with a wavelength of 905 nm results in an elimination of *Porphyromonas gingivalis* (*P. gingivalis*), *Prevotella intermedia* (*P. intermedia*), and *Actinobacillus actinomycetemcomitans* (*A. actinomycetemcomitans*) on different implant surfaces (machined, plasma-flamesprayed, etched, hydroxyapatite-coated). The aim of this study was to examine the laser effect *in vivo*. In 15 patients with IMZ implants who showed clinical and radiographic signs of peri-implantitis, toluidine blue O was applied to the implant surface for 1 min and the surface was then irradiated with a diode soft laser with a wavelength of 690 nm for 60 s. Bacterial samples were taken before and after application of the dye and after lasing. The cultures were evaluated semiquantitatively for *A. actinomycetemcomitans*, *P. gingivalis*, and *P. intermedia*. It was found that the combined treatment reduced the bacterial counts by 2 log steps on average. The application of TBO and laser resulted in a significant reduction ($P,0.0001$) of the initial values in all 3 groups of bacteria. Complete elimination of bacteria was not achieved.

Our summary:

Significant reduction of *P. gingivalis*, *P. intermedia*, and *A. actinomycetemcomitans* with 15 patients with peri-implantitis

Lethal photosensitization and guided bone regeneration in treatment of peri-implantitis: an experimental study in dogs

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Clin. Oral Impl. Res. 17, 2006 / 273–281

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Key words: guided bone regeneration, histology, peri-implantitis, photodynamic therapy/ photosensitizers, reosseointegration

Abstract: The purpose of this study was to evaluate the effect of lethal photosensitization and guided bone regeneration (GBR) on the treatment of ligature-induced peri-implantitis in different implant surfaces. The treatment outcome was evaluated by clinical and histometric methods. A total of 40 dental implants with four different surface coatings (10 commercially pure titanium surface (cpTi); 10 titanium plasma-sprayed (TPS); 10 acid-etched surface; 10 surface-oxide sandblasted) were inserted into five mongrel dogs. After 3 months, the animals with ligature-induced peri-implantitis were subjected to surgical treatment using a split-mouth design. The controls were treated by debridement and GBR, while the test side received an additional therapy with photosensitization, using a GaAlAs diode laser, with a wavelength of 830nm and a power output of 50mW for 80 s (4 J/cm²), and sensitized toluidine blue O (100 mg/ml). The animals were sacrificed 5 months after therapy. The control sites presented an earlier exposition of the membranes on all coating surfaces, while the test group presented a higher bone height gain. Re-osseointegration ranged between 41.9% for the cpTi surface and 31.19% for the TPS surface in the test sites; however differences were not achieved between the surfaces. The lethal photosensitization associated with GBR allowed for better re-osseointegration at the area adjacent to the periimplant defect regardless of the implant surface.

Our summary:

PAD together with guided bone regeneration (GBR) allowed for better re-osseointegration (higher bone height gain) than GBR alone

Periodontitis

In Vivo Killing of *Porphyromonas gingivalis* by Toluidine Blue-Mediated Photosensitization in an Animal Model

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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY,
Mar. 2003, p. 932–940, Vol 47, 3

Porphyromonas gingivalis is one of the major causative organisms of periodontitis and has been shown to be susceptible to toluidine blue-mediated photosensitization in vitro. The aims of the present study were to determine whether this technique could be used to kill the organism in the oral cavities of rats and whether this would result in a reduction in the alveolar bone loss characteristic of periodontitis. The maxillary molars of rats were inoculated with *P. gingivalis* and exposed to up to 48 J of 630-nm laser light in the presence of toluidine blue. The number of surviving bacteria was then determined, and the periodontal structures were examined for evidence of any damage. When toluidine blue was used together with laser light there was a significant reduction in the number of viable *P. gingivalis* organisms. No viable bacteria could be detected when 1 mg of toluidine blue per ml was used in conjunction with all light doses used. On histological examination, no adverse effect of photosensitization on the adjacent tissues was observed. In a further group of animals, after time was allowed for the disease to develop in controls, the rats were killed and the level of maxillary molar alveolar bone was assessed. The bone loss in the animals treated with light and toluidine blue was found to be significantly less than that in the control groups. The results of this study show that toluidine blue-mediated lethal photosensitization of *P. gingivalis* is possible in vivo and that this results in decreased bone loss. These findings suggest that photodynamic therapy may be useful as an alternative approach for the antimicrobial treatment of periodontitis.

Our summary:

Rats inoculated with *P. gingivalis* and treated with LAD:

1. No surviving bacteria in the group treated
2. On histological examination no negative effects
3. Significant less bone resorption after 90 days in the treated group compared to control group

Efficacy of Photodynamic Therapy on Inflammatory Signs and Two Selected Periodontopathogenic Species in a Beagle Dog Model

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J Periodontol 2005;76:1100-1105

Background: Current research aims to find alternatives to conventional methods for suppressing periodontopathogenic bacteria. Photodynamic therapy (PDT) could be a suitable treatment procedure of periodontal infections.

Methods: In the present study, the PDT method was tested with two photosensitizers, chlorine e6 and BLC1010, in an experiment on beagle dogs. The animals were infected with *Porphyromonas gingivalis* (*Pg*) and *Fusobacterium nucleatum* (*Fn*) in all subgingival areas. After infection, we observed clinical signs of gingival inflammation, including an increase of redness and bleeding on probing. Microbiological monitoring before and after treatment was performed using polymerase chain reaction (PCR). PDT was conducted with a diode laser with a wavelength of 662 nm using a power of 0.5 W and the photosensitizers.

Results: The PDT procedure carried out with either of the photosensitizers caused a significant reduction in the clinical inflammation signs of redness and BOP, compared to the controls (laser only and no treatment). Furthermore, PDT with chlorine e6 caused a significant reduction in *P. gingivalis*-infected sites, whereas there was a lack in suppression after PDT with BLC1010. *F. nucleatum* could hardly be reduced with chlorine e6, and only to a certain extent with BLC 1010 and laser only. In the control groups, the *Pg*-infected test sites did not change.

Conclusions: This study demonstrated that the photodynamic therapy using photosensitizer and a 662 nm laser light source is distinctly advantageous in reducing the periodontal signs of redness and bleeding on probing. The procedure also appears to significantly suppress *P. gingivalis*.

KEY WORDS

Animal studies; bacterial infections/therapy; periodontal; diseases/therapy; photochemotherapy.

Our summary:

Significant reduction of periodontal signs of redness and bleeding on probing after infection with *Porphyromonas gingivalis* (*Pg*) and *Fusobacterium nucleatum* (*Fn*)

Endodontics

Endodontic photoactivated disinfection using a conventional light source. An *in vitro* and *ex vivo* study.

Sebastian Schlafer, Aarhus Universitet Danmark

International Endodontic Journal, submitted for publication

Abstract

Aim. The present study investigated the antimicrobial effect of endodontic photoactivated disinfection (PAD) using a conventional LED lamp emitting 1 J/s in the red spectrum and toluidine blue (TBO). Treatment was performed on endodontic pathogens in planktonic suspension and in extracted human molars with a limited irradiation time of 30 seconds.

Methodology. The first part of the study analysed the effect of four treatment regimes (PAD, TBO without light, light without TBO, negative control treatment) on planktonic suspensions of *Escherichia coli*, *Candida albicans*, *Enterococcus faecalis*, *Fusobacterium nucleatum* and *Streptococcus intermedius*. In the second part, the most curved root canals of extracted molars were prepared, sterilized and inoculated with cultures of *S. intermedius*. PAD was performed either immediately after inoculation or after overnight incubation. The treatment outcome was compared to negative control treatment.

Results. PAD yielded significant reductions ($p < 0,001$) in the viable counts of all organisms in planktonic suspension. *E. coli* and *S. intermedius* showed the highest, *C. albicans* the lowest susceptibility. No or small reductions could be achieved using TBO or light alone. PAD treatment of *S. intermedius* in root canal treated molars yielded a mean reduction of 99.7% ($p < 0,001$) immediately after inoculation and of 95.82% ($p < 0,001$) after overnight incubation.

Conclusions. PAD using an LED lamp with high energy output for 30 seconds strongly reduces the number of viable endodontic pathogens in planktonic suspension and in root canals and might be an efficient and affordable adjunct to endodontic therapy. Clinical trials are required to investigate the treatment outcome *in vivo*.

Our summary:

FotoSan killing 99,7% of *S. intermedius* (*ex-vivo* study)

Microbiological evaluation of photo-activated disinfection in endodontics (An *in vivo* study)

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BRITISH DENTAL JOURNAL VOLUME 200 NO. 6
MAR 25 2006

Objective To determine the microbiological effect of photoactivated disinfection (PAD) as an adjunct to normal root canal disinfection *in vivo*.

Design A randomised trial carried out in general dental practice.

Subjects and methods Patients presenting with symptoms of irreversible pulpitis or periradicular periodontitis requiring endodontic therapy were selected at random. A microbiological sample of the canal was taken on accessing the canal, after conventional endodontic therapy, and finally after the PAD process (photosensitiser and light) had been carried out on the prepared canal. All three samples from each canal were plated within 30 minutes of sampling and cultured anaerobically for five days. Growth of viable bacteria was recorded for each sample to determine bacterial load.

Results Thirty of the 32 canals were included in the results. Cultures from the remaining two did not reach the laboratory within the target time during which viability was sustained. Of the remaining 30, 10 canals were negative to culture. These were either one of the canals in multi-rooted teeth where the others were infected or where a pre-treatment with a poly-antibiotic paste had been applied to hyperaemic vital tissue. Sixteen of the remainder were negative to culture after conventional endodontic therapy. Three of the four which had remained infected cultured negative after the PAD process. In the one canal where culturable bacteria were still present, a review of the light delivery system showed a fracture in the fibre reducing the effective light output by 90%.

Conclusions The PAD system offers a means of destroying bacteria remaining after using conventional irrigants in endodontic therapy.

Our summary:

20 root canals out of 30 were infected, 3 root canals were infected after conventional endodontic therapy, but showed no infectious cultures after PAD treatment.

Other studies

Advanced Noninvasive Light-activate Disinfection: Assessment of Cytotoxicity on Fibroblast Versus Antimicrobial Activity Against *Enterococcus faecalis*

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Abstract

Recent interest in light-activated disinfection demands insight on the selectivity towards bacterial cells compared with mammalian cells. This study was aimed to evaluate the cytotoxicity and selectivity of an advanced noninvasive light-activated disinfection (ANILAD) developed in our laboratory. The extent of cytotoxic effect of methylene blue activated by visible light of wavelength 664 nm was tested and compared with sodium hypochlorite (NaOCl) under in vitro and ex vivo conditions on fibroblast L929 cells. Simultaneous evaluation of cytotoxicity and antibacterial effect was also conducted to study the specificity of lightactivated therapy (LAT) toward prokaryotic cells (*Enterococcus faecalis*). The cytotoxicity was evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay and trypan blue viability test, whereas colony-forming units were determined to evaluate bacterial viability.

Data from both in vitro and ex vivo experiments showed that cytotoxicity was significantly less in LAT compared with NaOCl ($p < 0.001$). *E faecalis* cells were killed at a faster rate than fibroblasts. An irradiation dose producing 97.7% bacterial killing showed only 30% fibroblast dysfunction. This study indicated that ANILAD produced an insignificant effect on mammalian cells. (*J Endod* 2007;33:599–602).

Our summary:

Significantly less cytotoxicity of LAD compared to Sodiumhypochlorite

Treatment of oral candidiasis with methylene blue–mediated photodynamic therapy in an immunodeficient murine model

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Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002; 93: 155–60

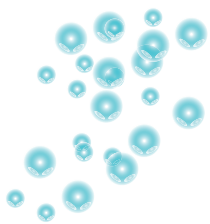
Objective. The purpose of this study was to evaluate the efficacy of using methylene blue (MB)–mediated photodynamic therapy to treat oral candidiasis in an immunosuppressed murine model, mimicking what is found in human patients.

Study design. Seventy-five experimental mice with severe combined immunodeficiency disease were inoculated orally with *Candida albicans* by swab 3 times a week for a 4-week period. On treatment day, mice were cultured for baseline fungal growth and received a topical oral cavity administration of 0.05 mL MB solution at one of the following concentrations: 250, 275, 300, 350, 400, 450, or 500 $\mu\text{g}/\text{mL}$. After 10 minutes the mice were recultured and underwent light activation with 664 nm of diode laser light with a cylindrical diffuser. After photodynamic therapy the mice were cultured again for colonyforming units per milliliter and then killed, their tissue harvested for histopathology.

Results and conclusions. The results indicate an MB dose-dependent effect. Concentrations from 250 to 400 $\mu\text{g}/\text{mL}$ reduced fungal growth but did not eliminate *Candida albicans*. MB concentrations of 450 and 500 $\mu\text{g}/\text{mL}$ totally eradicated *Candida albicans* from the oral cavity, resulting in reductions from 2.5 log₁₀ and 2.74 log₁₀ to 0, respectively. These results suggest that MB-mediated photodynamic therapy can potentially be used to treat oral candidiasis in immunodeficient patients.

Our summary:

PAD can potentially be used to treat oral candidiasis in immunodeficient patients.



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