Photochemical predictive analysis of photodynamic therapy in dermatology

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ABSTRACT

Photodynamic Therapy is a recent treatment modality that allows malignant tissue destruction. The technique provides a localized effect and good cosmetic results. The application of Photodynamic Therapy is based on the inoculation of a photosensitizer and the posterior irradiation by an optical source. This radiation chemically activates the drug and provokes reactions that lead to tissue necrosis.

Nowadays there are fixed clinical Photodynamic Therapy protocols that make use of a particular optical dose and photosensitizer amount. These parameters are independent of the patient and the lesion. In this work we present a Photodynamic Therapy model that tries to predict the effect of the treatment on the skin. First the results of a clinical study in the Dermatology Department of the Marqués de Valdecilla University Hospital are presented. The most common lesions and some unsuccessful cases are stated. The predictive model proposed is based on a 3D optical propagation of radiation by a Monte Carlo approach. Once the optical energy is obtained, a complex photochemical model is employed. This model takes into account the electronic transitions between molecular levels and particles concentrations. As the process of generation of photosensitizer is not homogeneous, the photosensitizer distribution is also taken into account. The optical power of the source, the exposition time and the optochemical characteristics of the tissue can be varied. This implies that these parameters could be adjusted to the particular pathology we are dealing with, so the unsuccessful cases could be better treated.

Keywords: PDT, basocelullar carcinoma, skin pathology, optical dose, photochemical model

1. INTRODUCTION

The use of light for treatment and diagnosis is an important area of biophotonics. Among light activated therapies, Photodynamic Therapy (PDT) has emerged as a promising treatment of several types of cancer (eg. endobronchial lung tumor, esophageal cancer with Barrett's esophagus, skin cancer, brain tumors, breast cancer, gynecologic malignancies) and other diseases (eg. macular degeneration, rheumatoid arthritis, psoriasis, endometriosis, etc), [1]. It is based in the use of light to activate a photosensitizer (PS) that eventually leads to the destruction of malignant cells. In the case of disease in an internal organ such as a lung, light is administered using a flexible fiber-optic delivery endoscopic system. The PS is administered either intravenously or topically.

PDT is based in the interaction among a photosensitizing drug, the light of appropriate wavelength and the cellular oxygen. These three elements are necessary to induce the photochemical reactions in the malignant tissue in order to cause the reactive oxygen species involved in the malignant cell killing, [2]. Therefore it is necessary to emphasize that all these elements have to be taken into account to obtain an accurate PDT model which permits to know a priori the photodynamic effect in the tissue.

The PS distribution in the target tissue plays an important role in determining the evolution and effectiveness of PDT. The common modeling of PDT processes using systemic PSs assumes a uniformly distribution. However, this statement is not valid in the case of topical PS that present an inhomogeneous distribution. This aspect is important to know the

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Photonic Therapeutics and Diagnostics VI, edited by N. Kollias, B. Choi, H. Zeng, R. S. Malek, B. J.-F. Wong, J. F. R. Ilgner, K. W. Gregory, G. J. Tearney, L. Marcu, H. Hirschberg, S. J. Madsen, A. Mandelis, A. Mahadevan-Jansen, E. D. Jansen, Proc. of SPIE Vol. 7548, 754809 · © 2010 SPIE · CCC code: 1605-7422/10/$18 · doi: 10.1117/12.842235

spatial accumulation of PS after the incubation period and the initial concentration when the irradiation period begins. Therefore, an accurate modeling of the photochemical procedure should consider the biophysical distribution of the cromophore in the target tissue.

This work provides a PDT predictive model applied to skin disorders with a topically applied PS. The basic principles utilized in PDT are introduced in section 2. Section 3 describes the 3D optical propagation of radiation by means of the Radiation Transport Theory via a Monte Carlo numerical approach. The time-dependent distribution of the PS is calculated by diffusion due to concentration gradients (Fick's law). This is shown in section 4. In section 5, the spatial optical energy is introduced in a photochemical model for the PDT process. The different molecular reactions are modelled by means of a differential equations system. This system is solved via a numerical method, taking into account its stiff nature. Prior predictive analysis was based on a simplified model for the photochemical processes involved. The model is applied to the skin and some results appear in the next section. PDT process can be predicted for different PS concentration taking into account its inhomogeneous distribution in the tissue and optical source parameters.

2. PDT

PDT is an optical treatment technique applied in several clinical areas such as gynecology, dermatology, ophthalmology, urology and so on. In dermatology has been widely used due to the facility that offers the direct irradiation of the diseased area without employing invasive methods. Nowadays, it is suitable to treat several types of skin cancers and other chronic skin pathologies. In clinical practice, if offers good response results in the majority of the patients however it cannot achieve an optimal efficiency in all of them, specially in certain types of lesions. Figure 1 shows the type of skin diseases that have been treated with PDT in the Dermatology Department of Marqués de Valdecilla University Hospital in the time period between April 2006 and January 2009. A total of 71 skin pathologies were treated, most of them were actinic keratosis and basocelullar carcinoma. It was detected a recidivism index of approximately 10%, of which the 60% of the cases corresponds to nodular basocelullar carcinoma, whose lesions penetrate deeply in skin.

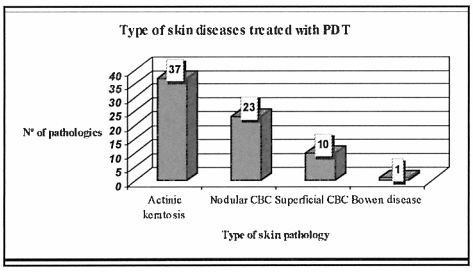

Figure 1. Number and type of skin diseases treated with PDT.

There is a fixed clinical PDT protocol that make use of a particular optical dose and PS amount. These parameters are independent of the patient and the type of disease, however there are differences in the treatment response depending on the type of pathology and patient.

3. OPTICAL MODEL

There are different optical models for using in biological tissue. Modeling a biological tissue implies dealing with an heterogeneous medium, which does not allow an analytic exact approach of the radiation pattern with Maxwell equations. For the problem we are dealing with, the distribution of light in a three-dimensional tissue must be obtained. This objective is reached by means of the Radiation Transport Theory (RTT) [3]. The model assumes that the scattering events are sufficiently numerous as to the light to be considered incoherent, in such a way that polarization or interference effects can be neglected. As a consequence, the basic parameter of light is the specific intensity, $I(\vec{r},\hat{s},t)$ (W/m^2sr), that is, the light power per unit area per unit solid angle. The radiation is expected to be at point $\vec{r}$, and to follow the $\hat{s}$ direction. The scattering events are treated according to the scattering phase function, $p(\hat{s},\hat{s}')$, which contains the probabilities of light to be scattered in the different directions. Light comes from direction $\hat{s}'$ and is redirected to $\hat{s}$. The basic idea in order to write the differential radiation transport equation is that radiation from a particle attenuates due to absorption and scattering and also gains power because another particle can scatter light in the direction of the particle of interest. This, with no sources inside the tissue and a steady-state situation can be written as

$$\hat{s}\cdot\overline{\nabla}I(r,\hat{s}) = -(\mu_a+\mu_s)I(r,\hat{s}) + \frac{\mu_a+\mu_s}{4\pi}\int_{4\pi} p(\hat{s}\cdot\hat{s}')I(r,\hat{s}')d\Omega' \quad (1)$$

Where μ_a is the absorption coefficient, μ_s is the scattering coefficient, Ω refers to the solid angle and $Q(r(t),\hat{s},t)$ represents a source placed at the point of interest.

Numerical analysis has been widely applied to a great variety of problems governed by differential equations. In the particular topic of the radiation transport equation, the Monte Carlo method has demonstrated its applicability and accuracy, compared with exact solutions. Perhaps the most used implementation of the Monte Carlo method applied to the RTT model is the one by Wang and Jacques. They programmed the Monte Carlo method in standard C. The key point is the inclusion of the random character on a computer, by means of a mathematical probability analysis, in such a way that numbers with any probability distribution can be obtained from numbers that follow a uniform distribution between 0 and 1. Light is treated as a sequence of photons, whose number is intended to be representative of the accuracy of the solution obtained. One photon is launched and its trajectory, affected by the scattering, and loss of energy are calculated, while the absorption in each point is stored. Cylindrical symmetry is assumed, because laser beams usually show this kind of symmetry, so in fact the data can be interpreted as coming from a 3-D analysis. The complete tissue is divided in a two-dimensional grid in the r and z directions of the cylindrical coordinates system. As usual, more accurate results require a smaller grid, but the need of a reduced time of computation imposes a limit. The Monte Carlo program assumes that the optical beam is infinitely narrow, and that it has perpendicular incidence. The second assumption is reasonable, but the former can provoke serious disappointments with the reality, specially if the dimensions of the optical spot and the tissue are of the same order. In order to correct this limitation, another program by the same authors [4] implements the convolution of the results. In this way, the solution of the Monte Carlo analysis can be later transformed for taking into account cylindrical or gaussian geometry of the laser beam.

This implementation of the Monte Carlo model is also multi-layered, so it is possible to define several layers of different materials, with their borders always perpendicular to the laser beam, which is very useful due to tissues usually can be divided in different strata. For the appropriate definition of the model, the characteristics and dimensions of each layer are required. The optical parameters needed are the index of refraction, n, the absorption coefficient, μ_a, the scattering coefficient, μ_s, and the anisotropy of scattering, g. This last parameter is called average cosine of scatter (dimensionless), and is related with the scattering phase function. The average cosine of scatter gives an idea about the probability of being scattered in a particular direction. For instance, $g=0$ implies that all directions all equally probable. If $g>0$ the radiation tends to be scattered forward, and vice versa. The albedo tries to illustrate the predominance of absorption or scattering in a particular tissue.

4. PS DISTRIBUTION

The affinity of the PDT PS for malignant cells is an indispensable condition to achieve the effectiveness of the PDT process. When a PDT drug is administered (systemically or topically), both normal and malignant cells absorb the drug. However, after an incubation period, the concentration of the PS in the normal cells is significant reduced while the malignant cells retain it producing a selective localization in cancerous tissue and precancerous cells.

In dermatology, PDT with topical 5-aminolevulinic acid or methyl aminolevulinate (MAL) is widely extended due to their effectiveness in the treatment of basal cell carcinomas, actinic keratoses or Bowen's disease. MAL, is a metabolic precursor in the biosynthesis of hemo, which generates endogenously a photoactive PDT sensitizer known as protoporphyrin IX (PpIX). Light activation of accumulated PpIX generates a photochemical reaction to produce the cytotoxic agent.

The assumption of a uniformly PS distribution is not valid in the case of topically administered PDT drugs which distributes no uniformly in the target tissue. This is taken into account to calculate the spatial accumulation of PS after the incubation period and the initial concentration when the irradiation period begins. The modeling of the biophysical distribution of MAL in the skin must take into account the precursor diffusion and the conversion to PpIX.

The time dependent distribution of PS is described by Fick's first law of mass flow which assumes that the diffusion of drug molecules occurs from areas of high concentration to those where the concentration is lower.

$$\vec{j} = -\kappa \cdot gradN \tag{2}$$

where $\vec{j}$ is the flux vector, N is the concentration of PS and κ is the diffusivity. In the skin this distribution is dependent on drug permeability through the stratum corneum, on the diffusivity of dermis and epidermis, on the drug clearance time, and on the conversion rate from MAL to PpIX, [5]. When the incubation time of PS is much lower than its relaxation time, the PS concentration can be calculated as

$$N(t) = N_o\left(erfc\left(\frac{x}{2\sqrt{\kappa t}}\right) - e^{\frac{K}{\kappa}x}e^{\frac{K^2}{\kappa}t}erfc\left(\frac{K}{\sqrt{\kappa}}\sqrt{t} + \frac{x}{2\sqrt{\kappa t}}\right)\right) \tag{3}$$

where N_o is the PS concentration in the skin surface at time t=0 and x is the distance from the stratum corneum, which is located at x=0 and is characterized by its permeability K.

If the relaxation mechanism of PpIX is fast compared to the diffusion time of the PS ($\tau_p << t$), the concentration of PpIX, $P(t)$, is proportional to the instantaneous value of MAL concentration and can be calculated by expression in (4), where ε_p is the yield of the conversion process and $\tau_{a\to p}$ is the amount of time inverted in the generation of PpIX.

$$P(t) = \varepsilon_p \frac{\tau_p}{\tau_{a\to p}} N(t) \tag{4}$$

5. PHOTOCHEMICAL MODEL

The photochemical reactions that take place during PDT can be model resolving a differential equations system, (5) to (10), that takes into account the transitions between states of the particles involved, like the PS or the oxygen, [6, 7]. Its solutions permit to observe the temporal evolution of the molecular concentrations of the principal compounds involved in the process. The stiff differential equations system was solved by means of a differential equation solver (ode15s) within the Matlab® platform. In order to obtain coherent results, we had to adjust relative and absolute error tolerances and solve on a time interval from 0 to 4000 s with an initial condition vector at time 0.

$$\frac{d[S_0]}{dt} = -\nu\rho\sigma_{psa}[S_0] - kpb[{}^1O_2][S_0] + \frac{\eta_{10}}{\tau 1}[S_1] + \frac{\eta_{30}}{\tau 3}[T] + \frac{\alpha s}{\tau 3}[T][{}^3O_2] \tag{5}$$

$$\frac{d[S_1]}{dt} = -\frac{1}{\tau 1}[S_1] + \nu\rho\sigma_{psa}[S_0] \tag{6}$$

$$\frac{d[T]}{dt} = -\frac{\eta_{30}}{\tau 3}[T] - \frac{\alpha s}{\tau 3}[T][{}^3O_2] + \frac{\eta_{13}}{\tau 1}[S_1] \tag{7}$$

$$\frac{d[{}^3O_2]}{dt} = -\frac{\alpha s}{\tau 3}[T][{}^3O_2] + \frac{\eta_0}{\tau 0}[{}^1O_2] + P \tag{8}$$

$$\frac{d[{}^1O_2]}{dt} = -kpb[S_0][{}^1O_2] - kcx[R][{}^1O_2] - ksc[C]i[{}^1O_2] - \frac{\eta_0}{\tau 0}[{}^1O_2] + \frac{\alpha s}{\tau 3}[T][{}^3O_2] \tag{9}$$

$$\frac{d[R]}{dt} = -kcx[{}^1O_2][R] + U \tag{10}$$

In these equations, $[S_0]$ is the concentration of the PS in ground state, $[S_1]$ is the concentration of the PS in singlet excited state; $[T]$ is the concentration of PS in triplet excited state; $[{}^3O_2]$ the concentration of oxygen in ground state; ${}^1O_2$ is the concentration of singlet oxygen; $[R]$ the concentration of singlet oxygen receptors; $[C]_i$ is the scavenger concentration; τ_1 is the relaxation time from state S_1 to S_0; τ_3 is the relaxation time from state T to S_0; τ_0 the relaxation time from state ${}^1O_2$ to ${}^3O_2$; η_{10} is the quantum yield of the transition from state S_1 to S_0; η_{13} is the quantum yield of the transition S_1 to T; η_{30} is the quantum yield of T transition to S_0; η_0 is the quantum yield of

$^1O_2$ transition to $^3O_2$; α_s is the efficiency factor for energy transfer from T to $^3O_2$; kpb stands for the biomolecular photobleaching rate; kcx is the biomolecular cytotoxicity rate; ksc is the rate of reaction of $^1O_2$ with various oxygen scavengers; ν is light speed in tissue; ρ is the photon density; σ_{psa} is the absorption cross-section of S_0 molecules; P is the rate of oxygen diffusion and perfusion; and U is the cell damage repair rate.

6. RESULTS

We have obtained the spatial and temporal distribution of the PS in the case of healthy skin with a permeability of an intact stratum corneum and a damaged tissue sample which presents a strongly reduced diffusion barrier. The effect of a reduced diffusion barrier in the case of a damaged tissue sample produces a higher PS accumulation than in normal skin due to an intact barrier blocks the diffusion during the first part of the PS incubation process as can be observed in Fig. 2.

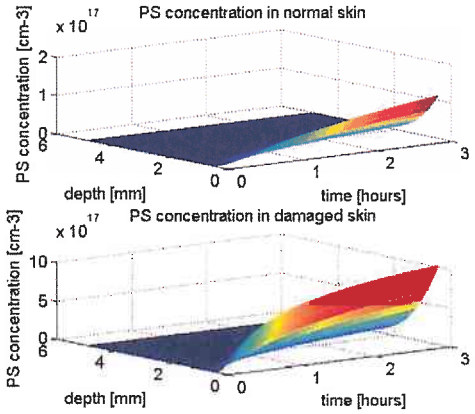

Figure 2. PS concentration distribution a) in normal skin ($k=10^{-8}$ m/s), b) in damaged skin ($k=10^{-6}$ m/s)

The results obtained with the photochemical model during the irradiation period have been calculated for both PS distributions, in normal and damaged skin. Fig.3 shows the time dependence of the concentrations of the PS, oxygen in ground state, singlet oxygen and singlet oxygen receptors in the case of damaged and normal skin respectively. As it can be observed, the concentration of ground state molecules of PS, oxygen in ground state and receptors vary slowly in response to the activation light. The time needed to reach the maximum singlet oxygen concentration is supposed as the time required to reach the desired cytotoxic effect and varies depending on the type of skin sample.

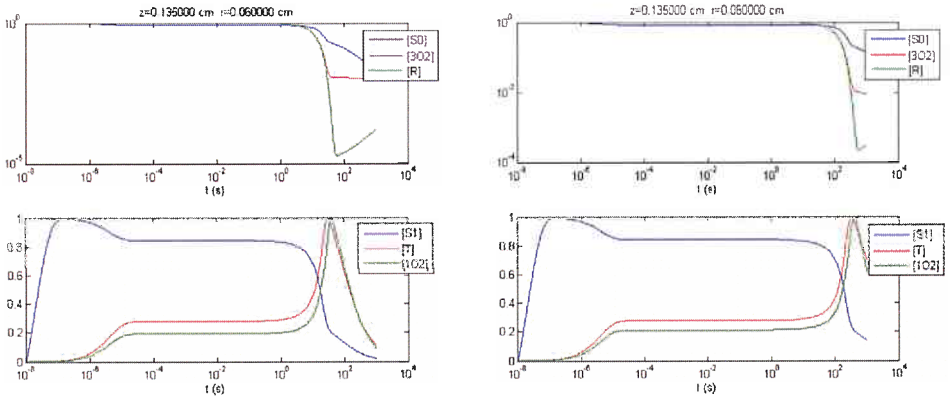

Figure 3. Time dependence of the PDT elements concentrations in damaged (graphic on the left) and normal skin (graphic on the right).

These results are calculated at the same position in the tissue sample and under the same irradiation conditions (I=100 mW/cm^2). The maximum singlet oxygen concentration is reached faster in the case of damaged skin due to its reduced

diffusion barrier. Therefore, reduced diffusion barrier produce an improvement in the PS's accumulation and consequently, a reduction in the radiation time to achieve the desired cytotoxic effect.

The time to reach the maximum singlet oxygen concentration increases with depth as is resumed in table 1 for the case of a systemic PS which distributes uniformly in the tissue using an irradiance of 150 mW/cm^2, so this type of modeling can be used to estimate the radiation time to treat a pathology localized at a specific depth.

Table 1. Time of radiation to reach the maximum singlet oxygen concentration at different depths in the tissue (I=150 mW/cm^2).

z (mm)	0.5	1.1	1.6	2.2	2.7	3.3	3.8
t (s)	29.24	40.34	66.07	123.2	249.6	527.6	1106

7. CONCLUSIONS

PDT is an optical therapeutic modality widely used in dermatology to treat several types of skin pathologies. There are fixed clinical PDT protocols that make use of a particular optical dose and PS amount, however the treatment response is not optimal for all the patients. In order to adapt PDT dosimetry to each specific case, modeling all the process involved plays an important role.

A complete model of PDT was presented. Light propagation in tissue is described by a numerical Monte Carlo model. The inhomogeneous distribution of the topical PS used is characterized by means of Fick´s law which permits to know the PS accumulation at different positions in healthy and damaged tissue. Finally a photochemical model shows the temporal evolution of the different molecular concentrations involved in the photoreactions that take place during the process.

The results obtained constitute an approach to predict the temporal and spatial evolution of the different components involved in PDT. The graphics shown in this work permit to know the time that is necessary to achieve the desired cytotoxic effect in malignant tissue and normal skin for different parameters related with irradiation or photosensitizer in order to improve actual clinical results. However, these results must be interpreted carefully due to the great amount of parameters involved in the modeling of this complex process. Subsequently future research works are required to improve the results obtained and to continue developing new accurate models.

ACKNOWLEDGMENTS

This work has been partially carried out under the project TEC2006-06548/TCM of the Spanish Ministry of Science and Innovation.

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