PDT Study Using a Model Incorporating Initial Oxygen Concentration and Blood Flow Increase

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Abstract

Introduction: Type II photodynamic therapy (PDT) is an experimental modality for cancer treatment based on the combined action of a photosensitizing drug (photosensitizer), a special wavelength of light and singlet oxygen ($^1O_2$) generation; the cell killing is caused by the reaction of cellular acceptors with $^1O_2$. A mathematical model has been previously developed to incorporate the macroscopic kinetic equations for $^1O_2$ generation, photosensitizers in ground and triplet states, oxygen, and tissue acceptors along with the diffusion equation for the light transport in tissue. Initial oxygen concentration ($[^3O_2]_0$) and the changes of the blood flow during PDT might affect the treatment efficacy. In this study, the effects of $[^3O_2]_0$, as well as the blood flow increase during PDT, on the magnitude of $^1O_2$ generation is studied.

Methods: By simplifying and combining the energy transfer processes in PDT, a set of equations are produced, which describes the creation of $^1O_2$. These equations are dependent on various parameters such as the light source (LS), optical absorption and scattering coefficients (μ_a and μ_s') and photochemical parameters of the photosensitizer. In this model, the spatial distribution of light fluence (ϕ) in the tumor is calculated via Eq. (1), based on the diffusion approximation. Spatial and temporal photosensitizer distribution (S_0), $^3O_2$ and $^1O_2$ concentrations are obtained by solving a set of coupled time-dependent differential equations [1].

The symbol $\Gamma_s = g\,(1-[^3O_2]/[^3O_2]_0)$, where g is the maximum oxygen supply rate and δ is the correction parameter for low photosensitizer concentration; $[^1O_2]_{rx}$ is defined as the $^1O_2$ effectively leading cell death. The initial conditions are: $\phi^{=} = 0$, $[^1O_2]_{rx} = 0$, $[^3O_2] = [^3O_2]_0$, and $[S_0] = [S_0]_0 = 5\ \mu M$.

Application of COMSOL Multiphysics® software: The forward calculation of the macroscopic kinetic equations was done in COMSOL Multiphysics® software for the modeling of $^3O_2$ and $^1O_2$ generation. The finite-element calculation was implemented within COMSOL software by varying the input parameters, such as $[^3O_2]_0$ and ϕ. Based on our mice study, $[^3O_2]_0$ was varying between 5-60 µM. The blood flow was considered by making g to be time dependent based on the published results [2-3].

Results: Using the obtained results, one can correlate the tissue oxygenation with the macroscopic quantity measured in the blood vessel. Moreover, the effects of the blood flow changes during PDT on $^1O_2$ generation, $[^3O_2]$ as well as photosensitizer photobleaching is

obtained. This model also shows that $[^3O_2]_0$ has no effect on the long term 1O2 generation.

Conclusion: Several improvements of the model formulations have been made to consider $[^3O_2]_0$ for both tumor and normal tissues during PDT. In the well-oxygenated tissue, the exact $[3O_2]$ will have little influence on treatment efficacy. When $[3O_2]$ becomes limiting, small changes in ϕ or $[3O_2]0$ have large effects.

Reference

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Figures used in the abstract

$$\mu_a\phi - \nabla\cdot\left(\frac{1}{3\mu_s'}\nabla\phi\right) = LS \quad (1)$$

$$\frac{d[S_0]}{dt} + \left(\xi\sigma\frac{\phi[S_0] + \delta[^3O_2]}{[^3O_2] + \beta}\right)[S_0] = 0 \quad (2)$$

$$\frac{d[^3O_2]}{dt} + \left(\xi\frac{\phi[S_0](1 + \sigma([S_0 + \delta]))}{[^3O_2] + \beta}\right)[^3O_2] = \Gamma_s \quad (3)$$

$$\frac{d[^1O_2]_\infty}{dt} - f\cdot\left(\xi\frac{\phi[S_0][^3O_2])}{[^3O_2] + \beta}\right) = 0 \quad (4)$$

The symbol $\Gamma_s = g\,(1\text{-}[^3O_2]/[^3O_2]_0)$, where g is the maximum oxygen supply rate and δ is the correction parameter for low photosensitizer concentration; $[^1O_2]_\infty$ is defined as the $^1O_2$ effectively leading cell death. The initial conditions are: $\phi = 0$, $[^1O_2]_\infty = 0$, $[^3O_2] = [^3O_2]_0$, and $[S_0] = [S_0]_0 = 5\ \mu M$.

Figure 1