

DOSIMETRY FOR PHOTODYNAMIC THERAPY OF ENDOMETRIAL TISSUE.

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ABSTRACT

Hysterectomy is the most common major operation performed in the United States with dysfunctional uterine bleeding as one of the major indications. The clinical needs for simple and safe endometrial destruction are essential. Photodynamic therapy (PDT) may offer a simple and cost effective solution for the treatment of dysfunctional uterine bleeding. The dosimetry is discussed for the case of topical application of the photosensitizer. This technique might be the method of preference because undesired side effects such as skin photosensitization that is typical for systemically injected photosensitizers, can be avoided. Effective PDT requires a sufficient amount of light delivered to the targeted tissue in a reasonable period of time. A trifurcated optical applicator consisting of three cylindrical diffusing fibers has been constructed, and this applicator can deliver a typical required optical dose of about 50-100 J/cm² to the full depth of the endometrium for an exposure time of 10-20 min.

Key words: Tissue optics, photodynamic therapy, uterus, endometrium, dosimetry

INTRODUCTION

Photodynamic therapy (PDT) of the endometrium implies the introduction of a light delivery system through the uterine cervix following administration of a photosensitizer. The human endometrium has unique proliferation and neovascularization characteristics. Depending on the phase in the menstrual cycle its thickness varies between 1-5 mm [1]. From the structural standpoint, the thick myometrium surrounding the thin endometrial layer can serve as a "barrier" to protect vital pelvic organs during illumination. Several experiments in rats and rabbits support the thesis that high uptake and retention of various photosensitizers by the endometrium following topical application [2-4] is feasible.

The clinical needs for a simple and safe endometrial destruction are essential. Hysterectomy is the most common major operation performed in the United States with dysfunctional uterine bleeding as one of the major indications leading to surgery.

Photodynamic therapy may offer a simple and cost effective solution for dysfunctional endometrial bleeding and could avoid a significant number of more invasive surgical procedures.

The present study was designed to analyze the cytotoxic dose for topically administered photosensitizers [5] The drug is installed in the uterine cavity for a period of a few hours before irradiation. The irradiation is performed with the use of a specially designed trifurcated applicator that enables a sufficient optical dose to be delivered to the full depth of the endometrium without inducing hyperthermic effects.[6-8]

OPTICAL DISTRIBUTION

The optical distribution in tissues can for most PDT applications be adequately described by the diffusion approximation of the more general equation of radiative transfer, [6]

This approximation can be expressed,

$$\nabla^2 \varphi - \frac{\varphi}{\delta^2} = -\frac{q}{D} c \quad (1)$$

where φ is the optical fluence rate, q is the source density of diffuse photons, D is the optical diffusivity, δ is the optical penetration depth and c is the velocity of light. The optical diffusivity D can be expressed,

$$D = \frac{c}{3(\mu_a + (1-g)\mu_s)} = \frac{c}{3(\mu_a + \mu_s^1)} \quad (2)$$

where μ_a and μ_s are, respectively, the optical absorption coefficient and the optical scattering coefficient. The parameter g is the average cosine of the scattering angle and the quantity $\mu_s^1 = (1-g)\mu_s$ is the reduced scattering coefficient.

The optical penetration depth is given by ,

$$\delta = \sqrt{\frac{D}{c\mu_a}} \quad (3)$$

Multiple reflections will build up the fluence rate in the cavity until the radiation transmitted through the cavity wall is equal to the light coupled into the cavity. A relationship between the optical power coupled into the cavity and the optical fluence rate can be obtained by taking the photon flux vector at the surface of the cavity equal to the direct unscattered irradiation from the applicator. The expression for fluence rate in the cylindrical symmetrical case where a long cylindrical applicator is positioned coaxially in a uterine cavity, e.g., in the murine uterine horn, will be

$$\varphi = \frac{P\delta c}{2\pi a D K_1\left(\frac{a}{\delta}\right)} K_0\left(\frac{r}{\delta}\right) \quad (4)$$

where P is the optical power per unit length of the applicator and a is the radius of the cylindrical cavity. The functions K_0 and K_1 are, respectively, the modified Bessel functions of zero and first order.

The ratio between the actual fluence rate in the inner layer of the lumen wall and the incident unscattered radiation can be expressed,

$$\frac{\varphi(r=a)}{\frac{P}{2\pi a}} = \frac{\delta c}{D} \frac{K_0\left(\frac{a}{\delta}\right)}{K_1\left(\frac{a}{\delta}\right)} \quad (5)$$

This ratio is dependent on the radius of the lumen (or with the radius of the applicator for applicators embedded in the tissue) and the optical properties of the tissue. The optical penetration depth of uterine tissue at 630 nm wavelength is in the range of 2.6-4 mm. [8-9] The ratio is about 2.8 in the case of a typical size cylindrical applicator of 1 mm diameter is embedded in uterine cavity with a typical optical penetration depth and diffusivity of, respectively, 4 mm and $8.7 \cdot 10^4$ m²/s. [8]

TOPICAL APPLICATION

The drug solution will be instilled into the uterine cavity and the drug will be allowed to diffuse into the endometrium. The optical radiation will be carried out when an adequate drug concentration has been established over the full thickness of the endometrium.

The transport of drugs with small molecular weight in the endometrium can be expressed by a diffusion process of the form [5],

$$\nabla^2 N - \frac{1}{\kappa} \frac{\partial N}{\partial t} - \frac{N}{\kappa \tau} = 0 \quad (5)$$

where N, κ , and τ are, respectively, the density, the diffusivity and the relaxation time.

The operator ∇^2 is the Laplacian operator and t is the time.

The drug distribution at time t after exposing the endometrial surface to a constant concentration can, provided that a possible diffusion barrier at the surface can be neglected, be expressed, Eq.5,

$$N(x,t) = \int_0^t \frac{N_0 x}{2\sqrt{\pi \kappa t^3}} e^{-\frac{x^2}{4\kappa t}} e^{-\frac{t}{\tau}} dt \Rightarrow_{\tau \Rightarrow \infty} N_0 \operatorname{erfc}\left(\frac{x}{2\sqrt{\kappa t}}\right) \quad (6)$$

where N_0 is the concentration at the endometrial surface and N(x,t) is the concentration at depth x at time t.

When depletion of the drug due to decomposition and clearance can be neglected, i.e., the relaxation times $\tau \Rightarrow \infty$, the expression simplifies to the term on the right hand side of the Eq.6.

The diffusivity of a typical photosensitizer such as 5-aminolevulinic acid (5-ALA) in tissue has not been reported. However, an order of magnitude estimate can be obtained by using the diffusivities for compounds with approximately the same molecular weight. (5-ALA HCl mol.wt. 168) The diffusivity for oxygen, acetic acid (mol.wt. 60) and sucrose (mol.wt. 342) in water at 20 °C are, respectively, $1.8 \cdot 10^{-9}$, $0.88 \cdot 10^{-9}$ and $0.45 \cdot 10^{-9}$ m²/s. [10] An example of the drug distribution for a value of the diffusivity equal to $\kappa = 10^{-9}$ m²/s is shown in Fig.1 . The drug concentration at the surface is normalized to unity, i.e., $N_0 = 1$.

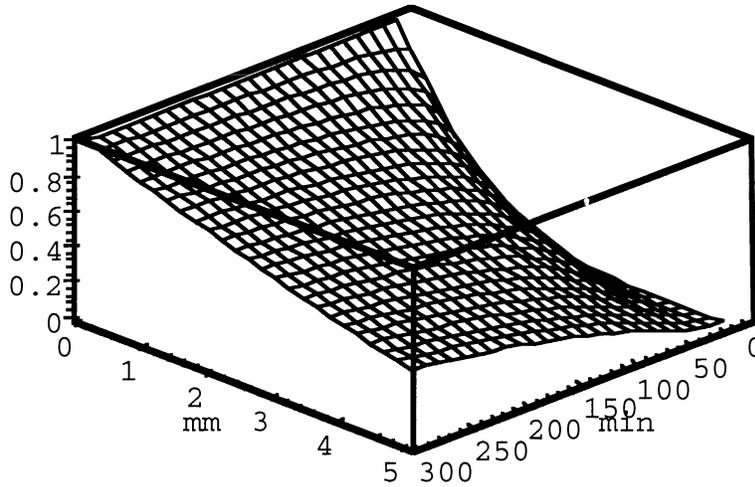


Fig.1 Drug distribution versus distance from the uterine cavity (mm) and time after instillation (min.).

The graph demonstrates that 5-ALA distribution to a depth of 4-5 mm is within 50% of the surface value after about 5 hours of diffusion.

The distribution of the photodynamically active compound will be the case of 5-ALA, be dependent on the conversion rate to protoporphyrin IX. The PpIX distribution can, provided that diffusion is negligible, be expressed,

$$\frac{dP}{dt} = \alpha N - \frac{P}{\tau_p} \quad (7)$$

where α expresses the conversion rate. The protoporphyrin distribution is P and τ_p is its relaxation time. When clearance of PpIX as well as depletion of 5-ALA due to the conversion process both are negligible, the protoporphyrin distribution can be expressed,

$$P(x,t) = \int_0^t \alpha N(x,t) dt = \alpha N_0 \left(\left(t + \frac{x^2}{2\kappa} \right) \operatorname{erfc} \left(\frac{x}{2\sqrt{\kappa t}} \right) - \frac{x\sqrt{t}}{\sqrt{\kappa\pi}} e^{-\frac{x^2}{4\kappa t}} \right) \quad (8)$$

The distribution at the surface where the concentration of 5-ALA is constant and equal to N_0 , increases then linearly with time, i.e., $P(x=0,t)=\alpha N_0 t$. The generation of PpIX at deeper layer will, however, be delayed because time is required for 5-ALA to diffuse to these regions.

The distribution of PpIX versus depth and time is shown in Fig.2. The diffusivity of 5-ALA is the same as used in Fig.1, i.e., $\kappa=10^{-9} \text{ m}^2/\text{s}$. The concentration is normalized to the value at the surface after 5 hours .

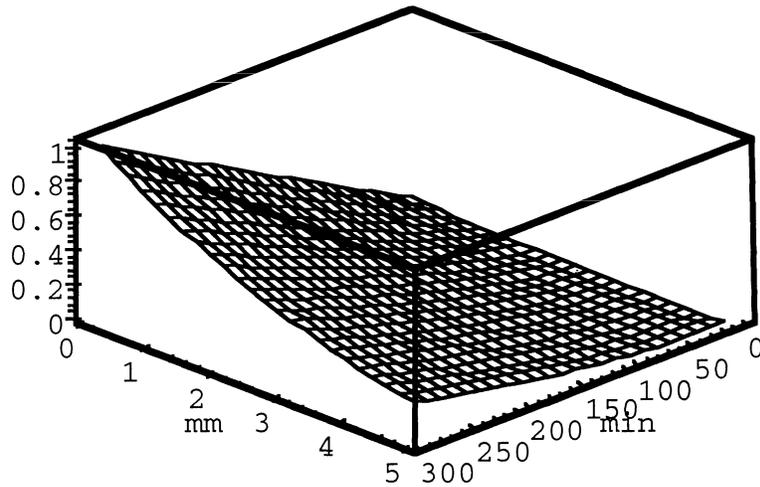


Fig.2 Protoporphyrin IX distribution versus distance from the uterine cavity (mm) and time after instillation (min.). Normalized to concentration at surface after 300 min. of diffusion.

The corresponding distribution when it is normalized to the value at the surface at same instant of time is shown in Fig.3

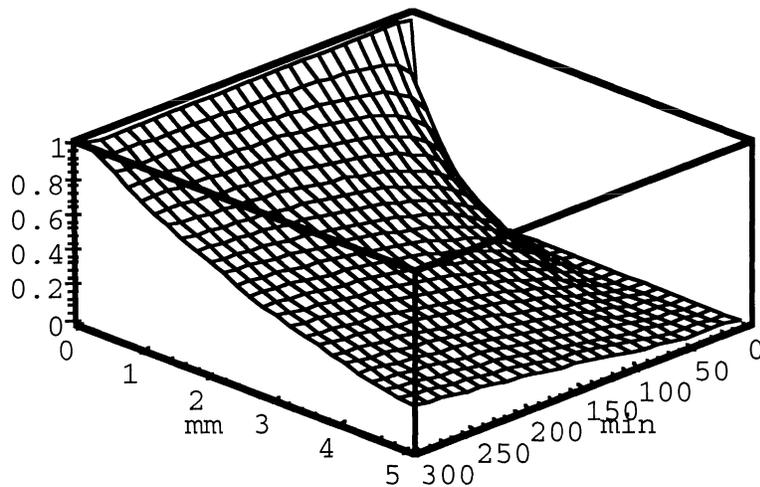


Fig.3 Protoporphyrin IX distribution versus distance from the uterine cavity (mm) and time after instillation (min.). Normalized to the concentration at the surface at the same time.

The depletion with depth of the PpIX concentration will, under the specified conditions, be more pronounced than for 5-ALA. The reason for this is the delay of the conversion

process due to the time required for the diffusion of 5- ALA. The concentration of PpIX at a depth of 4-5 mm is, however, 20-25% of the value at the surface after 5h.

If , on the other hand, the relaxation time of PpIX is fast enough to establish a local equilibrium almost instantaneously, the distribution will be given by,

$$P(x,t) = \tau_p \alpha N(x,t). \quad (9)$$

The PpIX distribution is in this case always proportional to the 5-ALA distribution. The depletion of the PpIX concentration with distance will be smaller than in the case discussed in Eq.8. However, the absolute value of the concentration will also be smaller.

CYTOTOXIC DOSE

The sensitizer will photo decompose during irradiation. The bleaching effect is characterized by the bleaching parameter θ that expresses the amount of optical fluence required to photobleach the drug concentration to 1/e, i.e., to 37 % of the initial concentration. The amount of singlet oxygen Q generated by a total optical dose Ψ can thus be expressed, [11,12]

$$Q = \int_0^{\Psi} kC d\Psi = \int_0^{\Psi} kC_0 e^{-\frac{\Psi}{\theta}} d\Psi = kC_0 \theta \left(1 - e^{-\frac{\Psi}{\theta}} \right) \quad (10)$$

where k is a parameter characterizing the efficiency of the singlet oxygen generation process and $C=C(x,t)$ is the local concentration of the photodynamically active drug during the irradiation. The corresponding drug concentration before the irradiation is C_0 . Further on, it is assumed that the change in the concentration during the irradiation period only is due to bleaching and that depletion due to other mechanism is negligible.

The optical dose Ψ can when the light level is kept constant during the irradiation, be expressed,

$$\Psi = \varphi \Delta t_{irr} \quad (11)$$

where Δt_{irr} is the radiation time and the fluence rate φ is given by Eq.1

The drug concentration before irradiation can be expressed, Eqs.6,8,9

$$C_0 = P(x, \Delta t_{diff}) \quad (12)$$

where Δt_{diff} is the diffusion time, i.e., the time between injection of the drug in the uterus and the irradiation.

CLINICAL APPLICATORS

The positioning of the trifurcated applicator based on three cylindrical diffusely emitting fibers is shown in Fig.4. The collapsed uterine cavity has a triangular shape.

The geometrical dimensions can vary individually, but 30 mm long sides represent a typical sized uterus. The middle fiber is installed along the uterine axis whereas the two other fibers are positioned along the two sides of the triangle.

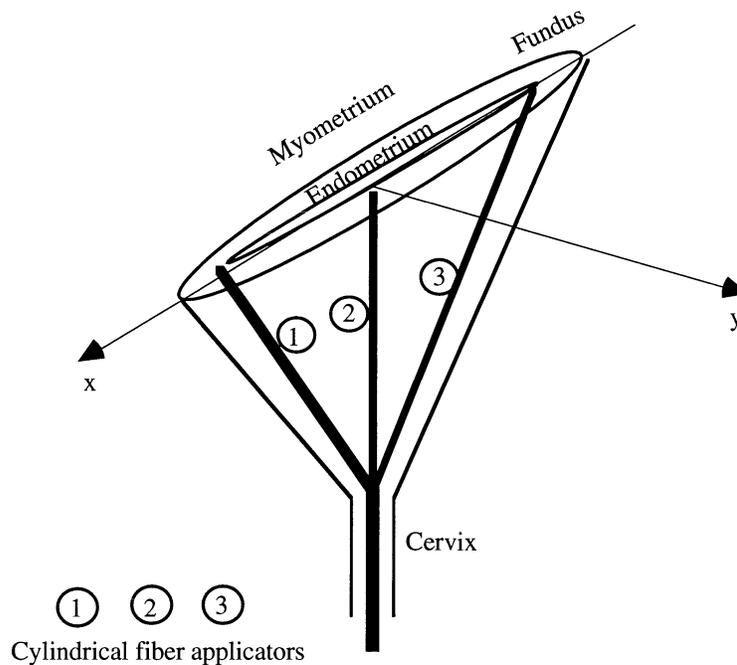


Fig.4 Fiber applicator installed in the collapsed uterine cavity.

The most critical difficult region to obtain an adequate light distribution is in the upper part of the uterine cavity, i.e., the fundus, where the distances between the individual fibers are maximal.

The optical dose distribution in this region is calculated as the sum of contributions from three semi-infinite long fibers. See Eq.4. An example of the optical distribution is shown in Fig.5. The orientation of the x and y axis in Fig 5 corresponds to the corresponding axis in Fig.4. The diameter of the fibers is 0.8 mm, the optical power per unit length of each fiber is $P=100 \text{ mW/cm}$ and the exposure time is $\Delta t_{irr}=600 \text{ s}$. The optical penetration depth of uterine tissue is taken $\delta=4 \text{ mm}$ and the reduced scattering coefficient is $\mu_s^1=0.8 \text{ mm}^{-1}$. [7]

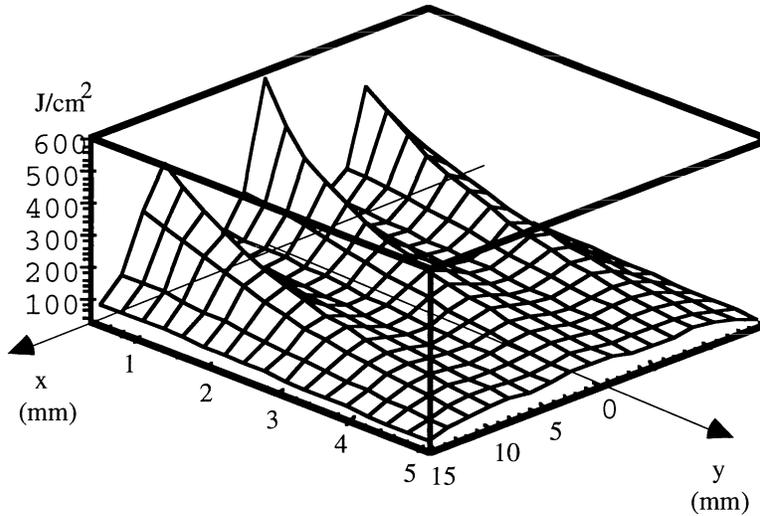


Fig. 5 Optical dose in J/cm^2 vs. distances from uterine axis.

The corresponding distribution of the cytotoxic dose is shown in Fig.6. The diffusivity of the drug is $\kappa=10^{-9} m^2/s$, the diffusion time is $\Delta t_{diff}=5$ hours and the bleaching fluence is $75 J/cm^2$. This bleaching fluence corresponds to the value reported for Photofrin II and corresponding values for PpIX have been reported in the range of 30-50 J/cm^2 . [5,11]. The drug distribution is calculated in accordance with Eq.9 and the drug concentration at the surface of the endometrium is taken to correspond to a threshold damage fluence of $30 J/cm^2$. The maximum obtainable cytotoxic dose will, since the bleaching fluence is $75 J/cm^2$, be 2.5 times the threshold value.

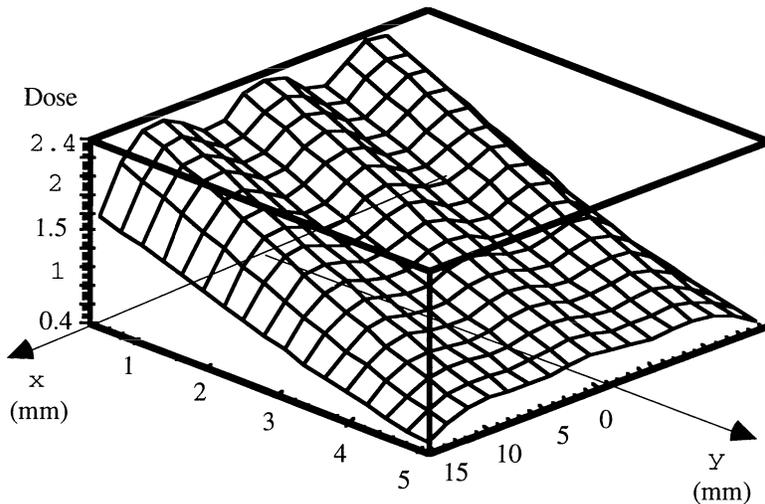


Fig.6 Cytotoxic dose vs. distances from uterine axis. Dose normalized to a threshold dose equal to unity.

These calculations thus demonstrate that the selected set of parameters will give a cytotoxic dose above the threshold for tissue necrosis to a depth of 2-3 mm. This depth of necrosis is limited by the drug concentration rather than the optical fluence; the optical fluence is above 100 J/cm² to a depth of 4-5 mm as shown in Fig.5. The drug concentration can in principle be increased by increasing the diffusion time. However, necrosis to a depth of 2-3 mm can be adequate if the treatment is carried out at an optimal time during the menstruation cycle.

CONCLUSIONS

The analysis indicates that irradiation of the endometrium by a trifurcated optical applicator inserted into the human uterus can deliver a sufficiently large light dose to initiate a photodynamic destruction of the entire layer. An emitted optical power per unit length of the applicator of 100 mW/cm can deliver a sufficient fluence to the full thickness of the endometrium and the myometrium after 10- 20 min. of exposure. The cytotoxic drug can be administered systemically, but the analysis indicates that the drug can be applied topically if a time of 4-5 hours is allowed for the drug to diffuse into the tissue before irradiation.

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