Light and Drug Distribution with Topically Administered Photosensitizers

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Abstract. Photodynamic therapy (PDT) based on topical application of photosensitizers is currently in clinical use for the treatment of basal cell carcinoma of the skin, and it has been evaluated in animal models for photo-ablation of the endometrium. This paper presents a dosimetry model which indicates that a limiting factor in treating thick tumours will be the transport of the drug into the tumour rather than depletion of the optical distribution. The model predicts that an optical irradiation of 100 mW cm\(^{-2}\) at 635 nm for 20 min, i.e. well below the threshold for hyperthermic reaction, will give an adequate light dose to a depth of 3 mm. The time required for photosensitizers to diffuse to this depth is in the range of 3–15 h, dependent on the diffusion properties of the tissue.

INTRODUCTION

Effective photodynamic therapy (PDT) requires the generation of cytotoxic products by excited-state photosensitizers (1–3). Most photosensitizers, e.g. haematoporphyrin derivatives, chlorins and phthalocyanines, have traditionally worked best when administered systemically. In recent years, however, very promising results have been obtained with topical application of 5-aminolaevulinic acid (5-ALA). This compound, a precursor in the biosynthesis of haem, stimulates the production of the photodynamically active compound, protoporphyrin IX (PpIX). Topically administered sensitizers have been used clinically in photodynamic treatment of basal cell carcinomas, and experimentally in animal models for destruction of the endometrium.

In PDT with systemically administered sensitizer, it is usually appropriate to assume a uniformly distributed drug dose in the target tissue (4, 5). The decay of the cytotoxic dose with distance from the irradiated surface is therefore primarily due to depletion of the light.

The situation is almost the opposite when the sensitizer is applied topically. The distribution of the drug with distance from the surface is dependent on molecular diffusion properties and tissue vascularity (6). Since the penetration depth of the drug is usually smaller than the optical penetration depth, drug transport properties, rather than tissue optical properties, can limit the treatment of thick, deep lesions.

OPTICAL DISTRIBUTION

The optical absorption and scattering coefficients of skin are quite different from those of other tissues. One of the characteristics of skin is the very high scattering coefficient, i.e. the effective (reduced) scattering coefficients of dermis and epidermis are typically a factor of 5–10 larger than the values found in muscle tissue and in many tumours. The effective back-scattering of light in skin results in a high reflection coefficient together with an elevated optical fluence rate in epidermis and in upper dermis. However, the high scattering...
Fig. 1. Light dose distribution in fair Caucasian skin. Incident fluence normalized to unity. (a) Wavelength 635 nm, (b) wavelength 514 nm. Epidermal thickness 100 μm. Dermal blood fraction 1% (---) and 2% (-----). Optical properties at 635 nm: dermal scattering coefficient \( \mu_s = 23 \cdot 10^3 \text{ m}^{-1} \), epidermal scattering coefficient \( \mu_s = 45 \cdot 10^3 \text{ m}^{-1} \), average cosine of scattering angle \( \langle g \rangle = 0.8 \), dermal absorption coefficient (in absence of blood) \( \mu_a = 25 \text{ m}^{-1} \), epidermal absorption coefficient (melanin) \( \mu_a = 570 \text{ m}^{-1} \). Optical properties at 514 nm: dermal scattering coefficient \( \mu_s = 28 \cdot 10^3 \text{ m}^{-1} \), epidermal scattering coefficient \( \mu_s = 56 \cdot 10^3 \text{ m}^{-1} \), average cosine of scattering angle \( \langle g \rangle = 0.8 \), dermal absorption coefficient (in absence of blood) \( \mu_a = 25 \text{ m}^{-1} \), epidermal absorption coefficient (melanin) \( \mu_a = 1.33 \cdot 10^3 \text{ m}^{-1} \).

reduces the optical penetration depth, and the optical fluence rate at depths larger than 1–2 mm in skin will be smaller than in the case of most other tissues. The detailed optical distribution in skin is very complex, but mathematical modelling based on numerical Monte Carlo calculations or analytical models based on diffusion theory give a fairly good description (7, 8).

The optical distribution in fair Caucasian skin is given in Fig. 1 (8). Figure 1(a) shows that the distribution for 635 nm light peaks in the upper dermis at a level of about four times the incident fluence. The in situ fluence level remains above the incident unscattered fluence to a depth of about 2.5 mm (it is assumed here that the optical properties of any tumour and/or the subcutaneous fat are approximately the same as those of the dermis). The major absorber in epidermis is melanin, whereas the predominant chromophore in dermis is haemoglobin. The corresponding results at 514 nm are shown in Fig. 1(b). The enhanced absorption in both haemoglobin and melanin at 514 nm compared to 635 nm reduces the peak in situ fluence to about three times the incident fluence. It is also noteworthy that at 514 nm, the fluence now peaks in the stratum corneum rather than in the upper dermis. The fluence remains above incident to about 0.5–0.7 mm depth, but falls off substantially at depths larger than 1–1.5 mm.

The corresponding optical distributions in tissues with more typical optical properties, such as would be expected for many tumours, are shown in Fig. 2. The melanin content of epidermis is kept unchanged, but the epidermal scattering coefficient is taken to be equal