DOSIMETRY METHODS IN PHOTORADIATION THERAPY

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I. INTRODUCTION

It is important to be able to specify the effective dose in photoradiation therapy (PRT) or photodynamic therapy (PDT) in order to compare results and to assure that the dose is sufficient to achieve the desired therapeutic effect while not damaging nonmalignant tissues excessively. The effective absorbed dose depends on the energy flux density or "space irradiance" at the dose point, the concentration of photosensitizing drug, and the concentration of molecular oxygen. Up to now, the clinician has not been able to specify the true, effective absorbed dose, although such terms as "light dose" (which is really an energy flux density, not a dose) have been used. The energy flux density at the dose point within the tumor is seldom known; instead the source power or irradiance is given. The dosage (mg drug per kg body weight) and the time delay after intravenous injection are specified, but the concentrations of the drug in tumor and normal tissue are not measured or even reproducible with the same dosage and time delay. The concentration of molecular oxygen is usually unknown, although a hypoxic region of a tumor would be protected from photodynamic cytotoxicity. Methods have to be developed to measure or calculate the contributions to the effective absorbed dose.

The dose formulation should apply to any photosensitizer, but the results and methods discussed here are intended specifically for hematoporphyrin derivative (HpD) and dihematoporphyrin ether (DHE), the photosensitizers now approved and used in treatment of tumors in human patients.

This paper has been updated from previous discussions of dosimetry in photodynamic or photoradiation therapy\textsuperscript{1-5}.

II. DEFINITION OF DOSE

The effective absorbed dose is defined as

\[ D^\star (J/kg) = (a/\rho) \cdot C \cdot \phi \cdot K \cdot t \]  

(1)
where

\[ a = \text{specific absorbance of photosensitizer at source wavelength, m}^{-1}(\mu g/g)^{-1} \]
\[ \rho = \text{tissue density, about 1030 kg m}^{-3} \]
\[ C = \text{concentration of photosensitizer in tissue, } \mu g/g \]
\[ \phi = \text{energy flux density of light, W m}^{-2} \]
\[ K = \text{relative photodynamic effectiveness, ratio of absorbed dose required to achieve a specified biological endpoint under reference conditions, to the absorbed dose required to achieve the same endpoint under the prevailing conditions} \]
\[ t = \text{duration of irradiation, s} \]

If the light is not monochromatic, the effective absorbed dose has to be integrated over the spectrum. (The relative photodynamic effectiveness, as well as the specific absorbance and energy flux density, are in general functions of wavelength.) If the energy flux density or concentration is not constant, the dose rate has to be integrated over the duration of the irradiation. Note that any thermal effects are excluded from the photochemical dose defined, but could be included by means of a time and temperature dependent factor if desired. Methods of determining the specific absorbance spectrum, concentration, energy flux density throughout the tumor and neighboring normal tissue, and the relative photodynamic effectiveness factor, are discussed in this paper.

III. SPECIFIC ABSORBANCE

Photocemistry is not possible unless light photons are absorbed. The specific absorbance of a substance (absorption coefficient per unit concentration) depends on wavelength and chemical form hence on bonding as influenced by solvent, pH, etc. For PRT, the specific absorbance is desired for physiological conditions. Apparently, for HpD or DHE, the photosensitizer is not active until bound in the cell, perhaps in mitochondrial membrane. Thus the absorbance should be measured in cells or a suspension of cells. This introduces a complication, because the scattering from cells interferes with the measurement of the absorption coefficient as a function of wavelength in a spectrophotometer. Using a like suspension of cells (but without photosensitizer) in a cuvette in the reference beam only partially alleviates the problem. Corrections have to be made, as in other turbid samples. It is also necessary to measure or control the concentration. Results obtained by our group for HpD are reproduced in Ref. 5. More measurements should be performed, especially for cells containing DHE. Our tentative value for the specific absorbance at the standard irradiation wavelength of 630 nm is 0.48 m\(^{-1}\) per \(\mu g/g\).

IV. CONCENTRATION

There is little information available on the concentration of HpD or DHE in human tumors and its dependence on dosage, time after injection, and physiological state or type of tumor. Some experiments have been performed in animal tumor models. The concentration is usually related to fluorescence, although a few experiments have been done with HpD