Photodynamic therapy

Photodynamic therapy (PDT) is a selective therapeutic approach involving uptake of a sensitizer by the target cells followed by their destruction on light-induced activation of the chemical. Although the technique was discovered at the turn of the 20th century, its widespread use has awaited the development of suitable drugs and light sources (Brown, 1999). It is now being applied to a range of malignant and non-malignant disorders, with a continual expansion in its licensed indications.

WHAT IS PDT?

For PDT to occur, a combination of factors are needed, i.e. substrate (tissue) together with sensitizer, light and oxygen. Activation of the sensitizer by light (usually red) results in the release of reactive oxygen species which destroy the target tissue. Sensitizers show preferential accumulation in diseased tissue, hence there is little damage to surrounding healthy tissue and minimal scarring (Stewart et al, 1998).

WHY IS PDT AN ATTRACTIVE THERAPEUTIC OPTION?

- Selective localization of drug in target tissue relative to healthy tissue
- Excellent healing and minimal scarring
- Several lesions may be treated simultaneously
- Subclinical lesions can be detected
- Applicable to a wide range of disorders.

WHY HAS PDT TAKEN SO LONG TO DEVELOP?

At the turn of the 20th century, Raab described light activation of a dye and its lethal effect on bacteria. Von Tappeneimer in 1904 discovered that oxygen was essential for the process, and coined the phrase 'photodynamic', while Hausmann in 1911 used haematoporphyrin to photosensitize mice. Shortly afterwards, Meyer-Betz injected himself with haematoporphyrin, producing a severe phototoxic reaction which persisted for several weeks.

However, it wasn't until 1993 that haematoporphyrin derivative (HPD) was approved for clinical use. Many improved sensitizers are in development, but only HPD is presently licensed. Factors contributing to the delays in PDT development include the previous lack of suitable light sources and the complexity of the treatment parameters that need to be established.

WHAT PARAMETERS NEED TO BE SPECIFIED?

- Sensitizer: identity, dose, formulation, route
- Light source and delivery system
- Light characteristics: wavelength, dose, dose rate, possible fractionation
- Drug–light time interval.

WHICH LIGHT SOURCE TO USE?

Non-laser light sources, e.g. filtered xenon arc lamps or light-emitting diodes, are cheap and easy to use for superficial lesions. However, the high output of lasers is required when using fibreoptic delivery, i.e. for internal use. Delivery systems include interstitial fibres which take the light into the substance of the lesion, and a balloon to facilitate even light distribution in hollow organs, e.g. uterus, bladder. Until recently, lasers have been bulky and expensive, but diode lasers are now available, which are portable (the size of a briefcase), convenient and easy to operate (Bown, 1998).

Red light (broadband or coherent) is usually used for activation of sensitizers. Porphyrin-based sensitizers such as HPD have several absorption peaks throughout the visible wavebands, including strong absorption at 400 nm and a much smaller peak at 630 nm. However, 630 nm is the chosen activation wavelength since there is better tissue penetration by red light, as a result of less scattering and less absorption by melanin and haemoglobin.

WHICH DRUG TO USE?

The first generation drug HPD and its partly purified form Photofrin® (Quadra Logics Technologies, Vancouver) cause prolonged photosensitivity. Numerous second generation drugs are under development and many offer the following advantages (Kreimer-Birnbaum, 1989):

- Pure compounds
- Absorb light of longer wavelengths, enabling deeper tissue penetration
- Faster tissue clearance.

An elegant form of PDT employs aminolevulinic acid (ALA), a precursor of haem (Kennedy and Pottier, 1990). When excess ALA is applied, the haem pathway is overloaded and the sensitizer protoporphyrin IX (PpIX) builds up, which is then activated at 630/635 nm. Conveniently, residual PpIX is metabolized away in 24–48 hours.

WHAT IS THE CURRENT STATUS OF CLINICAL PDT?

Many thousands of patients have now been effectively treated, and Photofrin® has been approved in several countries for the treatment of both early and advanced pulmonary and oesophageal cancer. Phase III clinical trials are ongoing with meta-tetrahydroxyphenylchlorin (mTHPC, 652 nm), benzoporphyrin derivative (BPD, 690 nm), tin etiopurpurin

($SnEt_2$, 660 nm), ALA and ALA esters. Mono-l-aspartyl chlorin (NPe6, 675 nm) and lutetium texaphyrin (Lu-Tex, 732 nm) are also promising. Current PDT trials include those for malignancies of the skin, head and neck, breast and bladder, and a range of non-oncological disorders including menorrhagia, age-related macular degeneration, vascular disease and psoriasis (Dougherty et al, 1998).

WHAT ARE THE FUTURE DIRECTIONS?

Within the next year or two, we can expect approval for further clinical indications for Photofrin® and approvals for ALA and mTHPC, and possibly other drugs, in oncology. The use of PDT in ophthalmology may become newsworthy, since the approval for PDT of age-related macular degeneration with BPD is likely soon, and may be followed by the approval of $SnEt_2$ (Brown, 1999).

Progress depends on effective interaction of specialized clinicians, photochemists, photobiologists and physicists. PDT will be used for an increasing number of niche applications, perhaps in association with other modalities. In the longer term, third generation highly targeted drugs are predicted, with linkage to monoclonal antibodies or peptide targeting sequences. HM

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KEY POINTS

- Photodynamic therapy (PDT) involves a photochemical interaction of sensitizer, light and oxygen.
- PDT is selective, producing minimal damage to surrounding tissue.
- Side-effects are minor compared with alternative therapies.
- A wide range of non-malignant and malignant disorders may be treated.
- Improved light sources make PDT a practical proposition.
- An 'ideal' sensitizer shows high selectivity, activation at long wavelengths of light, and rapid clearance.
- Prolonged skin photosensitivity can be a problem with older systemic sensitizers.
- Licensed indications are growing.