Photodynamic therapy

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The therapeutic use of light in medicine has increased during the latter half of the century with the development of laser and fibreoptic technology. Laser-mediated photocoagulation is now an established treatment for many disorders. Photodynamic therapy—or the harnessing of non-thermal light energy via a photosensitizing drug with consequent localized tissue necrosis—is a rapidly expanding technique that has already undergone clinical trial in some ten thousand patients with malignant, inflammatory and degenerative conditions. Development of the technology has required a convergence of scientific expertise from many areas including optical physics, engineering, biochemistry, and pharmacology in addition to clinical medicine. Here we review the current position of photodynamic therapy and speculate on its likely impact in the near future.

PRINCIPLES

The photodynamic effect requires the presence of a chemical photosensitizer, light of appropriate wavelength and oxygen. The principle of the therapy is that energy (absorbed as light via the intracellular photosensitizer) is transferred to oxygen molecules which then form highly reactive intermediaries (Figure 1). The short half-life of such reactive oxygen species ($<1\,\mu s$) explains the very localized nature of the effect; and the modest energy requirement means that hyperthermia, and hence damage to adjacent organs, is unlikely.

Photodynamic therapy has several potential advantages over conventional treatments. The main attraction is the lack of scarring since connective tissues, including collagen and elastin, tend to be unaffected[1] (Figure 2). The mechanical and functional integrity of the organ is thus left intact. Photodynamic therapy also allows more selective tissue necrosis than, say, hyperthermic ablation, for reasons including localization of drug to hyperproliferating tissue, selective uptake of some photosensitizers to specific tissue layers, the very localized cytotoxic effect and the precision

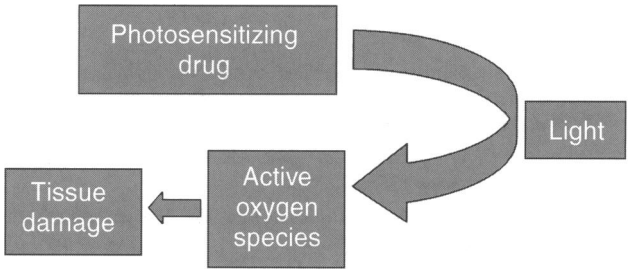

Figure 1 **Principle of photodynamic therapy**

with which the laser light can be directed via optical fibres. In addition, resistance to treatment does not seem to develop with repeated use[2].

Each photosensitizer has its action spectrum and light should be applied at the wavelength of maximum absorption. For clinically used sensitizers this wavelength varies from 420 nm (blue) to 780 nm (deep red). Light-waves of greater length penetrate tissue further: blue light attenuates greatly within 1–2 mm whereas red light can penetrate more than 5 mm. The treatment of deeper lesions therefore requires a photosensitizer that is activated at a long wavelength. In addition, light of shorter wavelength is more likely to be absorbed by melanin and haemoglobin. Thus, most of the newer photosensitizers are excited by long wavelengths.

In addition to light, the photodynamic effect depends on adequate tissue levels of photosensitizer. The drug can be given systemically, topically or directly into the organ, and clearly the risk of drug-associated systemic effects is lowest in patients who receive topically applied photosensitizers for the treatment of superficial lesions. Selectivity for hyperproliferating tissue varies between photosensitizers: some (such as Photofrin) are distributed to connective tissue and the vasculature; others (such as 5-aminolaevulinic acid) are localized to the mucosal layers. The choice of photosensitizer thus depends on the nature of the lesion to be treated.

Photodynamic therapy in its current form has several limitations. It is an ablative treatment that yields no biopsy material, so a definitive diagnosis must be made before treatment. It is more complex than other treatment modalities since optimal delivery of light (usually by laser) and drug requires collaboration between scientists and

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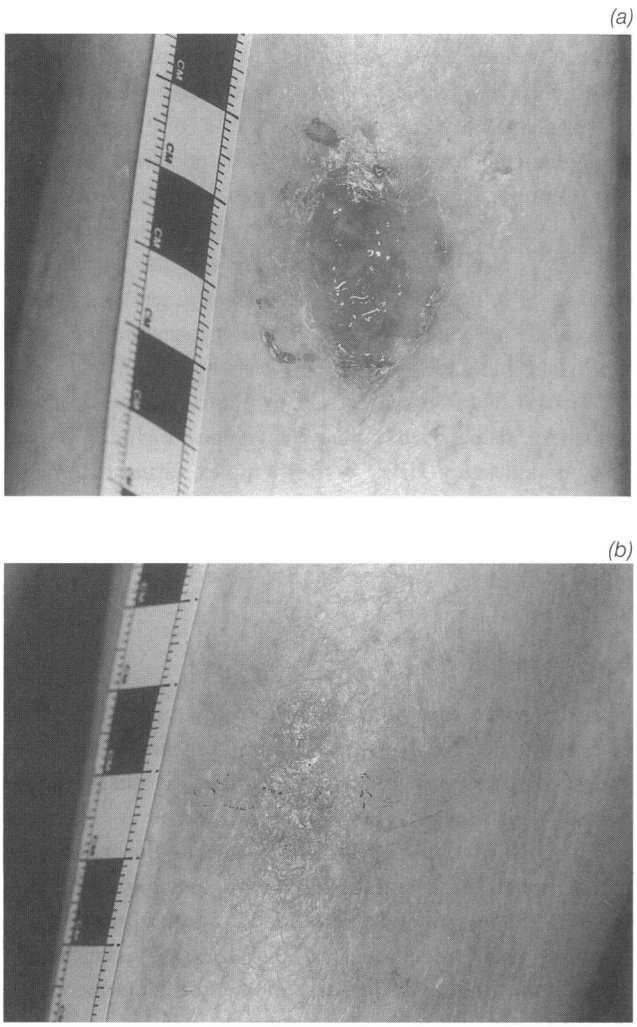

Figure 2 **Ulcerating basal cell carcinoma of the shin: (*a*) before photodynamic therapy, (*b*) two months after photodynamic therapy**

clinicians. In addition, with earlier sensitizers, skin photosensitivity lasting several weeks limited its acceptability. Newer photosensitizers and improvements in light delivery have simplified therapy, and a major advance has been the development of powerful, low-cost, portable non-laser light sources[3]. Although at present these cannot be directed into monofilament optical fibres (< 1 mm), they are replacing lasers for photodynamic therapy of skin lesions.

PHOTODYNAMIC DETECTION

For detection of disease, the use of short wavelength light (i.e. blue or ultraviolet) allows the identification of abnormal areas by fluorescence. 5-aminolaevulinic acid (ALA), a precursor of the haem biosynthetic pathway, is increasingly being used for photodynamic detection because of its local conversion into natural photosensitizers. ALA is selectively taken up by dysplastic and malignant mucosa[4] and this property has been exploited in the diagnosis of non-visible carcinoma-*in-situ* of the bladder[5], the detection of early stage lung cancer[6], the intraoperative assessment of resection margins in glioma surgery[7] and nephron-sparing surgery for renal cell carcinoma[8].

PHOTODYNAMIC THERAPY

Superficial epidermal/mucosal lesions

For treatment of *skin lesions* the sensitizer is usually ALA, because this agent can be given topically and localizes to mucosal and epidermal layers. Photodynamic therapy is an attractive option because conventional surgery and radiotherapy can cause troublesome skin contraction, scarring and ulceration, especially in multiple or extensive disease; moreover, areas with low skin laxity and poor vascularity (e.g. the bridge of the nose and the anterior tibial area) often require skin grafting. ALA photodynamic therapy for superficial lesions including basal cell carcinoma[9] and pre-invasive Bowen's disease has yielded excellent cosmetic results[10].

Another potential application is *urothelial disease*, again because of the limitations of conventional treatments, with which over half of patients with superficial bladder tumours will have recurrences and one-third with carcinoma-*in-situ* do not respond. The bladder can be accessed easily by cystoscopy, and laser light can be delivered down flexible optical fibres. Photosensitizers can be given either systemically (Photofrin) or intravesically (ALA). Results with photodynamic therapy as a salvage treatment have been very promising so far[11,12].

Existing treatments for *lower-genital-tract intraepithelial neoplasia* (cervical and vaginal) involve excision or ablation, recurrence and scarring being common sequelae. Topical ALA photodynamic therapy with a portable light source, under local anaesthesia, has given encouraging results. Only a small minority of patients reported serious discomfort[13].

Since ALA is selectively taken up by the mucosa rather than the deeper layers, underlying muscle is spared; thus, even if dosage of ALA photodynamic therapy is excessive, a tubular organ is unlikely to become stenosed. In theory, therefore, such treatment should be valuable in *Barrett's oesophagus*, and promising initial results have indeed been obtained[14]. *Early-stage lung cancer* is another area where ALA photodynamic therapy is being tried.

Various *head and neck malignancies* have been successfully treated with early systemic porphyrin photosensitizers[15] and research continues with newer less phototoxic drugs. In addition, good initial results are reported in early gastrointestinal cancer, particularly *stomach cancer*[16].

Solid-organ cancer

For the treatment of neoplasia in solid organs, systemic photosensitizers are required. The light is delivered by placing several interstitial light fibres in the diseased area by means of

radiological imaging. m-THPC (meso-tetra-hydroxyphenyl chlorin, Foscan) has been used in recurrent *prostate* cancer and inoperable cancer of the *pancreas*[17]. With pancreatic photodynamic therapy the surrounding tissues, in particular the bowel, blood vessels and the common bileduct, were undamaged. When *brain* tumours recurring after surgery and radiation were treated by use of a haematoporphyrin derivative[18], survival lengthened though no cures were obtained. One of the main drawbacks of interstitial placement of fibres is bleeding, which can lead to unequal light distribution within the tissue. Solid tumours of the *eye* are suitable for photodynamic therapy because the organ's optical properties obviate the need for such fibres; preliminary clinical studies show success with small ocular tumours[19].

BENIGN CONDITIONS

The uptake of some photosensitizers by hyperproliferating tissue and the observation that photodynamic therapy can cause vascular stasis have prompted applications in benign conditions.

Senile macular degeneration, associated with macular neovascularization, is the leading cause of blindness in the UK. Currently, the accepted treatment is laser photocoagulation but this causes adjacent thermal damage to the retina. Benzoporphyrin derivative (BPD-MA, Verteporfin) photodynamic therapy offers selectivity since at the time of illumination the photosensitizer is still predominantly within the neovasculature. Light is delivered via a slit-lamp to the eye shortly after systemic injection of BPD-MA. The light dose is usually delivered within one minute and only topical anaesthesia is required[20].

Restenosis after coronary angioplasty arises from fibrocellular intimal hyperplasia and no drugs have been clinically effective in reducing its incidence. The possible value of photodynamic therapy (with ALA or BPD-MA) is now being explored in clinical trials after success in rat models[21].

Psoriasis is commonly treated with ultraviolet light after administration of a psoralen, but an alternative is photodynamic therapy with a topical photosensitizer[22]. There is some evidence that photodynamic therapy can lessen the pain of psoriatic arthritis as well as improving the skin lesions, perhaps by reducing the number of activated T cells and thereby the autoimmune response[23].

After intrauterine instillation ALA is localized selectively in the endometrium[24], and clinical trials are now underway to evaluate the use of ALA photodynamic therapy with transcervical administration of red light, as a treatment for *menorrhagia*.

INFECTION CONTROL

With the increase in bacterial resistance to antibiotics, new ways to treat infection must be explored. Photodynamic antimicrobial chemotherapy has been shown effective *in vitro* against bacteria (including drug-resistant strains), yeasts, viruses and parasites. By means of various photosensitizers and light doses this technique can be used to disinfect blood products and cell suspensions with negligible cellular damage[25]. Localized superficial infections (for example, skin ulcers infected with multiply resistant *Staphylococcus aureus*) could in theory be treated with ease. The photolysis of oral bacteria could also offer new treatments for caries and peridontal disease[26]; and even *Helicobacter pylori* can be eradicated by sensitization with methylene blue and exposure to laser light[27].

Viruses that are susceptible to photodynamic death by oxidative damage to their envelope include human immunodeficiency virus, herpes simplex virus, cytomegalovirus and measles virus. Studies are planned to evaluate photodynamic therapy, by extracorporeal treatment of blood, as a way to reduce the body burden of HIV.

PROSPECTS

There is much optimism that photodynamic therapy will offer effective local-anaesthetic day-case procedures for various lesions now requiring inpatient treatment under general anaesthesia. In conditions such as Barrett's oesophagus it might even improve on the results of conventional management. However, existing techniques leave much room for improvement. Photosensitizers that localized more specifically to the diseased tissue would allow better sparing of the surrounding normal tissue. Trials are just starting with the texaphyrin group of photosensitizers (which are tumour selective) in conjunction with gadolinium enhancement. The logical extension would be use of the technique for both visualization and treatment of complex tumours, and even distant metastases.

With certain lesions we are at present unable to illuminate the key area adequately. Infrared, with its long lightwaves, should offer better penetration; so we should be able to apply non-visible radiation in deep anatomical sites without the need for interstitial light fibres.

In short, photodynamic therapy has the potential to become an important modality in the treatment of a broad spectrum of conditions in the twenty-first century.

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