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# New Drugs and Future Developments in Photodynamic Therapy

D.V. Ash and S.B. Brown

**New photosensitising drugs are becoming available which should improve on some of the disadvantages of haematoporphyrin derivates for photodynamic therapy (PDT). The main features are shorter duration of systemic photosensitisation, activation by longer and more penetrating light and better tumour to normal tissue drug uptake ratios. These drugs together with better understanding of *in vivo* light dosimetry promise to improve both results and clinical acceptability for PDT in future studies.**
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## INTRODUCTION

THE PROSPECT that an innocuous drug followed by a burst of light can eradicate cancer is so arresting that it demands attention. There is obvious potential in the treatment of human malignancy and this has resulted in an explosion of interest over the past 10 years. Unfortunately the photosensitising drug which has been used for most of the clinical work is unsatisfactory in a number of ways. Many of the clinical reviews of photodynamic therapy (PDT) written in the past few years [1, 2] have concluded that this promising approach to treatment requires better drugs and better light delivery systems to activate them in order for PDT to become clinically acceptable. Consequently there has been an intensive effort to develop new drugs.

The ideal characteristics of an effective photosensitiser are:

- Single pure compound.
- Non-toxic.
- Short half life.
- Specific binding to tumour and not to normal tissue.
- High quantum yield of singlet oxygen.
- Activation spectrum with a peak between 700 and 800 nm.

Haematoporphyrin derivative (HpD) and the second generation drugs derived from it, such as photofrin have shown themselves to be effective sensitisers but do not meet many of the above criteria. The drug has a very long half life in tissue and accumulates in skin so that patients are rendered photosensitive for 6–8 weeks. Activation by 630 nm light uses a small peak of the activation spectrum which results in a relatively low yield of singlet oxygen. In human tumours there is relatively little difference between the concentration of photosensitiser in tumour compared with normal tissue [3]. While some selectivity of effect can be ensured by directing light to the tumour bearing tissue, where there is normal tissue also in the field this is damaged almost as much as the tumour tissue. Normal tissue, however, shows remarkable healing after PDT injury in contrast to that shown by the tumour [4].

Extensive clinical experience with HpD and photofrin shows that it can be successful in the treatment of superficial malignancy which is within 4 or 5 mm of the light source. Although light can be introduced by endoscopes into a substantial number of sites in the body there are still only a small number of patients who can be considered for curative treatment. For palliation there may be some advantage in achieving an effect with a single treatment, but prolonged skin photosensitisation is a significant drawback which is not shared by other alternative palliative treatments. If PDT is to become accepted as a treatment of common cancers, different drugs are needed which will overcome some of the disadvantages of photofrin. For curative treatments the drugs need to be effective for thicker tumours while for palliation they need to have less or shorter duration skin photosensitivity. There are a number of new compounds which have entered or are about to enter phase I/II studies in patients. All have potential advantages over photofrin but none is ideal and none have yet been used in enough patients to allow firm conclusions about their efficacy.

## 5-AMINOLAEVULINIC ACID (ALA)

This is a naturally occurring substance which forms part of the biosynthesis pathway for haem. An increased load of ALA causes a build up in the cells of protoporphyrin IX (PP IX) which is itself an active photosensitising drug. PP IX has a similar activation spectrum to HpD and is therefore activated with 630 nm red light. The main advantage of ALA is that it can be given topically to patients with superficial skin malignancy. A cream containing ALA is applied to the lesion and converted *in situ* after 2 or 3 h to PP IX which can then be activated by surface illumination. This treatment has shown extremely good results in patients with Bowens disease and superficial basal cell carcinoma with over 90% complete response rate [5, 6]. For Bowens disease it can almost be considered as definitive treatment for these sometimes large premalignant plaques in skin that is often fragile.

When given intravenously ALA shows selective uptake in mucosa and the duration of photosensitivity is approximately 24 h [7]. It is not quite as effective a photosensitiser as photofrin but the opportunity to use it topically and the much reduced photosensitivity after intravenous use are significant advantages. There is also a strong possibility that it is effective after oral administration.

## BENZOPORPHYRIN DERIVATIVE MONOACID (BPD MA)

This is a chlorin compound with an absorption peak at 690 nm which should almost double the effective depth of penetration compared with 630 nm.

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Because the drug is relatively insoluble it has been formulated in a unilammellar liposome [8]. The half life in plasma is approximately 6 h and skin photosensitivity returns to normal in a few days [9].

### TETRA (*m*-HYDROXYPHENYL) CHLORIN (TmHPC)

This is one of a series of tetrahydroxyphenyl porphyrin derivatives which have been prepared synthetically. It has the advantage that it can be prepared as a pure compound and the absorption spectrum shows a maximum activation at 650 nm.

Tumour to normal tissue ratios of 10–15 have been shown and the duration of skin photosensitivity seems to be less than for photofrin. TmHPC has been used intraoperatively to treat inoperable malignant mesothelioma and has shown selective necrosis at up to 1 cm depth with low doses of light (10–20 J/cm$^2$) [10].

### *N*-ASPARTYLCHLORINE e6 (NPe6)

This is a chlorin compound which has been derived directly from naturally occurring chlorophyll. The maximum absorption is at 664 nm. Early results suggest that it is effective as a photosensitiser and that skin photosensitivity is minimal one week after drug administration. The drug is maximally effective when light is given 2 h after dosing and seems to have a predominantly vascular effect *in vivo* [11, 12].

### TIN ETIOPURPURIN (SnEt2)

This is a synthetic drug which is a chlorin with a fused ring. Its absorption maximum is 700 nm with a quantum singlet yield of 0.6–0.7. The drug appears to be maintained at fairly constant levels for 24 h but clears from the skin over several days rather than several weeks as for photofrin. Extensive animal trials have been performed and the drug is due to enter phase I clinical studies in 1993 [13].

### ZINC PHTHALOCYANINE DERIVATES (ZnPc)

Phthalocyanines have been studied as potential PDT drugs for several years and in animal studies aluminium and zinc phthalocyanine compounds have shown advantages over photofrin. Zinc phthalocyanine is being considered for clinical trial by delivery in a liposomal system. Its absorption maximum is 680 nm. There is potentially a slight disadvantage in that the drug may impart a grey or green–blue tinge to the skin of patients for a time after intravenous injection [14].

Some of the above drugs have different modes and sites of action and it is possible to envisage combining photosensitisers in order to enhance overall response. This has been tried in a mammary tumour where a combination of photofrin and tetraphenylporphyrin produced a syngergistic effect with a 100% cure rate [15].

The wide range of new compounds makes it necessary to have sensitive and appropriate experimental models against which to test new drugs. The first requirement is an *in vitro* test of photosensitising ability but after that there is a need to have systems which will assess:

- Uptake in tumour and normal tissue.
- Direct cellular sensitivity.
- Vascular effects.
- Depth of penetration of PDT effect in tissue.

Magnetic resonance imaging (MRI) seems to be a promising test for screening new drugs. The rapid induction of hypoxia by most PDT drugs can be detected by MRI scanning and there is sufficient spatial resolution to measure the depth of effect [16]. MRI also demonstrates early changes in intracellular pH and phosphate metabolism which may be a sensitive means of predicting efficacy. It can also be used to rapidly assess the effect of adjusting the treatment parameters.

## COMBINATION OF PDT WITH BIOREDUCTIVE DRUGS

One of the striking features of the response of tissues to PDT is vascular shutdown which rapidly results in tumour hypoxia. Bioreductive drugs are metabolised under hypoxic conditions to produce cytotoxic species *in situ*. There is, therefore, a good theoretical basis for combining PDT with bioreductive drugs in order to take advantage of both mechanisms at the site of tumour. *In vitro* experiments have shown enhancement of PDT effect when given with mizonidazole [17] and even greater enhancement has been shown *in vitro* with new bioreductive compounds [18]. None of these combinations have yet been tested clinically but it may be an interesting area for future study.

## LIGHT DELIVERY

A useful PDT effect can only be achieved if enough light reaches tumour tissue containing sufficient drug to produce a lethal phototoxic reaction. The penetration of light into tissue is therefore a major limiting factor to extending the range of treatment. If drugs with a high quantum yield and high tumour specificity can be developed, however, it is possible that only 1% of incident light is sufficient to produce an effect and that the depth of effect would be greater than the small increment that can be expected by using a less efficient photosensitiser that is activated by slightly longer wavelengths of light. The ideal of course would be to have a drug which combines both properties and would then allow activation at between 700 and 800 nm where it becomes more feasible to use simpler and cheaper diode lasers. In the meantime poor light penetration has been overcome by interstitial light delivery. Using techniques similar to those developed for afterloading interstitial brachytherapy, optical fibres can be introduced into tumours through pre-implanted transluscent plastic tubes so that light can be carried 2 or 3 cm below the skin surface. In some instances this has allowed up to 60 cc of tumour to be destroyed by a single PDT treatment [3]. In order to achieve consistent and reproducible effects it is necessary to ensure that adequate doses of light are received at the tumour margins. This requires more information about the absorption and scattering properties of light in different tissues and knowledge of the threshold of drug and light combination required to ensure a cytotoxic effect. *In vivo* dosimetry will be necessary to collect enough information to accurately predict, plan and deliver PDT in the future.

PDT is at an exciting stage of development and there is an opportunity to build on the considerable experience which has been gained with first and second generation photosensitisers. What should not be lost sight of, however, in the search for new compounds is that for certain well selected cases PDT using HpD or photofrin has already shown itself to be curative and can provide effective palliation for some more advanced cases.

1. Ash D, Brown SB. Photodynamic therapy achievements and prospects. *Br J Cancer* 1989, **60**, 151–152.
2. Manyak MJ. Photodynamic therapy: present concepts and future applications. *The Cancer J* 1990, **32**, 104–109.

3. Lowdell C, Ash D, Driver I, Brown SB. Interstitial photodynamic therapy in man. *Br J Cancer* 1993 (in press).
4. Gilson D, Ash D, Driver I, Feather JW, Brown SB. Therapeutic ratio of photodynamic therapy in the treatment of superficial tumours of skin and subcutaneous tissues in man. *Br J Cancer* 1988, **58**, 665–667.
5. Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. *Photochem Photobiol* B 1990, **6**, 143–148.
6. Cairnduff F, Ash D, Brown SB. Treatment of superficial basal cell carcinoma and Bowen's disease with topical PDT using ALA cream. Br J Cancer 1993 (in press).
7. Loh CC, Dodwell J, MacRobert AJ, Krasner N, Phillips D, Bown SG. The kinetics of 5-aminolaevulinic acid photosensitisation in the rat stomach. In Spinelli P, Dal Fante M, Marchesini R, eds. *Photodynamic Therapy and Biomedical Lasers*. Excerpta Medica 1992, 286–291.
8. Lui H, Kollias N, Wimberley J, Anderson RR. Photosensitising potential of benzoporphyrin derivative monoacid ring A (BPD-MA) in patients undergoing photodynamic therapy. *Photochem Photobiol* 1992, **55**, 30A Abstract.
9. Sternberg E, Dolphin D. An overview of second generation drugs for photodynamic therapy including BPD-MA. In Spinelli P, Dal Fante M, Marchesini R, eds. *Photodynamic Therapy and Medical Lasers*. Excerpta Medica 1993, 470–474.
10. Lofgren L, *et al.* Transthoracic endoscopic photodynamic treatment of malignant mesothelioma. *The Lancet* 1991, 337, 9737, 359.
11. Roberts WG, Smith KM, McCullough JL, *et al.* Skin photosensitivity and photodestruction of several potential photodynamic sensitisers. *Photochem Photobiol* 1989, **49**, 431–438.
12. Nelson JS, Roberts WG, Berns JW. *In vivo* studies in the utilisation of mono-L-aspartize chlorin (NPe6) for photodynamic therapy. *Cancer Res* 1987, **47**, 4681–4685.
13. Morgan AR, Garbo GM, Keck RW, Eriksen LD, Selman SH. Metallopurpurins and light: effect on transplantable rat bladder tumours and murine skin. *Photochem Photobiol* 1990, **51**, 589–592.
14. Cruse-Sawyer J, Dixon B, Dawson L, Wainwright M, Griffiths S, Brown SB. Zinc phthalocyanine: a new photosensitiser for PDT. In Spinelli P, Dal Fante M, Marchesini R, eds. *Photodynamic Therapy and Biomedical Lasers*. Excerpta Medica 1992.
15. Nelson JS, Liaw LH, Lahlum RA, *et al.* Use of multiple photosensitisers and wavelengths during photodynamic therapy. A new approach to enhance tumour eradication. *J Natl Cancer Inst* 1990, **82**, 868–873.
16. Dodd NJ, Moore JV, Poppitt DG, Wood B. Magnetic resonance evaluation of PDT by various sensitisers. *Br J Cancer* 1989, **60**, 164–167.
17. Evanson JF, Moan J. Photodynamic therapy of C3H tumours in mice: effect of drug/light dose fractionation and misonidazole. *Lasers in Med Sci* 1988, **3**, 1–6.
18. Bremner JCM, Adams GE, Pearson JK, *et al.* Increasing the effect of photodynamic therapy in the RIF-1 murine sarcoma, using the bioreductive drugs RSU 1069 and RB6145. *Br J Cancer* 1992, **66**, 1070–1076.

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# Childhood Cancer Mortality in the European Community, 1950–1989

**M. Carmen Martos and Jørgen H. Olsen**

**A descriptive study on childhood cancer mortality was carried out in the European Community (EC) covering the period 1950–1989. An annual total of 3392 cancer deaths were seen among children in the EC during the period 1979–1988, yielding an age-standardised cancer mortality rate of 50 per $10^6$. Leukaemia was the most prevalent cause of death among children with cancer (39%). Excess mortality was observed among boys for cancers at all sites combined and for cancers at specific sites, exclusive of malignant tumours of the kidney. This excess is presumed to be due mainly to sex differences in incidence. Markedly higher mortality rates of childhood cancer were seen in southern countries of the EC than in central and northern countries. This difference appeared to be due mainly to differences in cancer incidence among the countries and to a lesser degree to differences in treatment and survival. An overall decline in mortality from childhood cancer in the EC occurred from the early 1960s. In spite of the improvements in survival, however, childhood cancer remains a major cause of death in the EC, affecting about 15% of children between the ages of 1 and 14.**
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## INTRODUCTION

CHILDHOOD CANCER is relatively rare; nevertheless, in nearly all developed countries, it has become the second most frequent cause of death in children after the first year of life [1].

A decrease in mortality from cancer in childhood has been observed in recent decades [2–4] while the incidence has remained stable [5–7]. The decline is attributed to improved survival rates for several tumour types [8–10]. Thus, geographical and temporal comparisons of mortality rates can be used to assess differences in the adoption, application and effectiveness of control programmes between countries.

In spite of the inherent limitations in mortality data, they have the advantages of uniformity and availability at a national level. Comparable incidence data, however, can be obtained only for a few countries and for certain regions, counties and districts [1]. A data bank on deaths by sex, age and cause was set up by the World Health Organization (WHO), which is updated annually.

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