

Photodynamic therapy — basic principles



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Introduction

Photosensitising drugs are quite common in nature. For instance the photosensitiser hypericin is abundantly present in the plant *Hypericum perforatum*, or St John's wort, a common plant in the temperate regions of the world. Animals are very much aware of the effects of the photosensitiser within as St John's wort remains untouched. Light is the driving force behind the therapeutic effect. When the light is off nothing happens. When the light is on effects occur at a rate we can control and only take place at the precise location that we illuminate. Light functions as the 'remote control' of the drug.

The mechanism of action of photodynamic therapy (PDT) is based on the interaction between a drug, the photosensitiser, and light. Absorption of a light particle, a photon, leads to an electronically excited state in the absorbing molecule. Commonly the energy of this excited state is transferred to vibrations of the molecule on a timescale of nanoseconds or less. Photosensitiser molecules also absorb light, but are different from normal absorbers because

they can preserve a part of the absorbed energy by forming a metastable state, a triplet state. The lifetime of the triplet state is much longer than that of the normal excited states and can be as long as microseconds to milliseconds. This extended presence of the absorbed energy in the photosensitising molecule allows it to transfer it very effectively to its environment and induce damage. Various different pathways of this energy transfer have been identified. The most commonly studied one, type II photosensitisation, acts through molecular oxygen. By collision of a photosensitiser molecule in its triplet state with molecular oxygen the energy is transferred to the oxygen that then forms singlet oxygen. The singlet oxygen then carries the energy away from the sensitiser molecule. Because of its high reactivity it usually does not get very far and the damage is done within a range of less than a micron. For this reason the type of effect that is reached by PDT is strongly dependent on the intracellular localisation on the photosensitiser.

The term photodynamic was first used in 1903 by Professor von Tappeiner, a pharmacologist from Munich, Germany. By the end of the 19th century the use of light in medicine had become very popular and in 1903 Nils Finsen received the Nobel Prize for his pioneering work in what we now call photomedicine. In that background von Tappeiner studied the effects of different substances on micelles and found out that the effectiveness of damaging the micelles was strongly dependent on the presence of oxygen [1]. Later on he performed the first clinical experiments with the photosensitiser eosin on patients with basal cell carcinoma of the skin [2].

Photodynamic therapy — basic principles is the first of two papers, the second

paper on clinical applications and the relative merits of these will be published in the forthcoming issue of *EJHP Practice*.

Drugs

The most ancient reference to human use of photosensitisers such as hypericin for therapeutic purposes is more than 4,000 years old and can be found in the book Veda, one of the oldest scriptures from ancient India. It describes the use of extracts of the plants *Psoralea corylifolia* and *Ammi majus* in combination with sunlight for the treatment of skin diseases. Similar references are found in Chinese documents from the same time and the Ebers papyrus from ancient Egypt (1550 BC). The fact that these references are found in all main cultures of that time suggests that it was common knowledge and that it has a much longer history than recorded.

Porphyrins are photosensitisers that are omnipresent in nature. Porphyrins are made inside mammalian cells as an intermediate product in the synthesis of haem. This chemical process has been designed in such a way that porphyrin levels usually remain very low. There are various diseases such as erythropoietic protoporphyria which occur when one of the critical steps in this process is disturbed which leads to severe skin photosensitisation.

Modern clinical PDT has the choice of two different approaches to photosensitisation. The first employs the haem metabolism described above. By administering the haem precursor 5-aminolevulinic acid (5-ALA) and some of its esters, the enzymatic control loop that in a normal condition keeps the porphyrin levels in the cells very low is bypassed. This results in a temporary accumulation of protoporphyrin IX (PpIX) in the cells that can be used to perform PDT. The

Table 1: Approved photosensitisers in Europe and their primary use

Drug	Compound (INN/IUPAC name)	Registration	Indication
Photofrin	porfimer sodium	Canada, Japan, The Netherlands, USA	Lung cancer, oesophageal cancer
Photobarr	porfimer sodium	EU, USA	Ablation of high-grade dysplasia (HGD) in patients with Barrett's oesophagus
Foscan	temoporfin	EU	Foscan is indicated for the palliative treatment of patients with advanced head and neck squamous cell carcinoma failing prior therapies and unsuitable for radiotherapy, surgery or systemic chemotherapy
Visudyne	verteporfin	Canada, EU, USA ≤24 countries	Age-related macular degeneration
Metvix	methyl aminol-evulinate HCl	Australia, Brazil, EU, New Zealand, USA	Treatment of actinic keratosis, Bowen's disease and basal cell carcinoma (BCC)
Hexvix	hexaminolevulinate HCl	EU	Detection of bladder cancer, such as carcinoma <i>in situ</i> , in patients with known bladder cancer or high suspicion of bladder cancer
Gliolan	5-aminolevulinic acid HCl	EU	Gliolan is indicated for visualisation of malignant tissue during surgery for malignant glioma (WHO grade III and IV)

second approach uses the classical route: to administer a photosensitiser directly.

Various routes of administration of photosensitisers of precursors are possible, intravenous, oral and topical. Topical administration is effective only for drugs with a high tissue penetration such as ALA and its esters. In humans this leads to local photosensitisation only.

The first commercially available photosensitiser was Photofrin, developed by QLT (Canada) and first registered in Canada in 1993. It was registered in the United States in 1995 and subsequently in Europe in countries such as The Netherlands and France in 1996 for treatment of cancer. The compound was later registered for treatment of high grade dysplasia in Barrett's oesophagus in Europe in 2004 under the brand name Photobarr.

As Photofrin is regarded as a first-generation photosensitiser, with prolonged skin photosensitivity as the main side effect, the search for more active compounds with less or no skin photosensitivity resulted in several second-generation photosensitisers. The first of these to be approved was Visudyne (verteporfin), also developed by QLT, for the treatment of age-related macular degeneration. Another photosensitiser which gained approval in 2001 in Europe was

Foscan (temoporfin). This drug has been approved for treatment of advanced head and neck cancer in patients not suitable for radiotherapy, chemotherapy or surgery.

Next to the above-mentioned exogenous photosensitisers, administered intravenously, ALA was developed as endogenous photosensitiser. The first ALA-based compound to be approved was Levulan, in 1999 by the FDA, for the skin disease actinic keratosis (AK). The compound is applied topically and in this case activation is accomplished by blue light. Table 1 lists the photosensitisers currently approved for clinical use in Europe.

There are many other photoactive drugs. For instance, 8-methoxypsoralen is commonly used as an oral photosensitiser in PUVA therapy. The photo action of these drugs does not employ oxygen and hence this therapy is not considered a photodynamic therapy. The more details we learn about the action mechanisms however, the vaguer this separation becomes.

Light

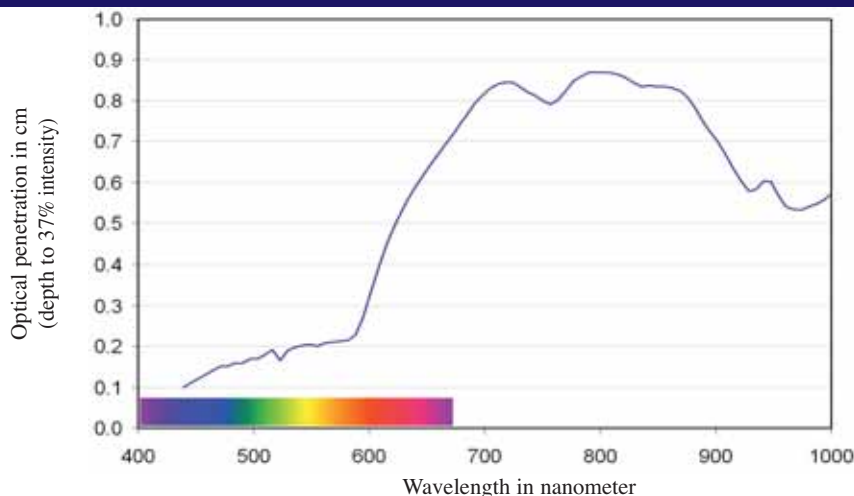
Light does not penetrate tissue as deep as ultrasound or X-rays. Depending on the wavelength (see Figure 1) penetration depths range from 100 micrometer to 1.5 cm. Light transport through tissue

is influenced by two dominant processes: light scattering and light absorption. In Caucasians light attenuation is mainly due to absorption by haemoglobin, which absorbs strongly in the blue-green region, and much less in the red, near infrared. As a result we have a 'therapeutic window', between 630 and 800 nm. Although all photosensitisers also absorb in the green and blue or UVA range, we usually use the red and near infrared absorption bands because of the deeper penetration of light, although in some experimental applications blue and green light was used to intentionally induce a very superficial effect only.

The development of clinical PDT has been strongly accelerated by the developments in modern electro-optics. At present low cost diode lasers and light emitting diode sources are available delivering sufficient amounts of light in the narrow absorption bands of the photosensitisers. These devices are easy to operate and very reliable. In addition, modern fibre optics allows the transport of large amounts of laser light via thin optical fibres through endoscopes deep into the body.

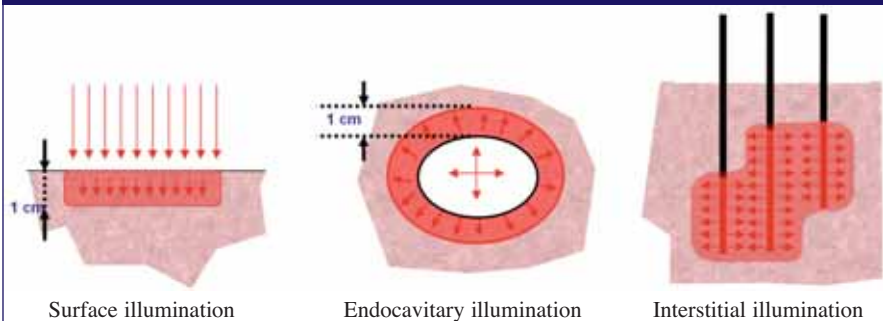
There are three basic geometries for light delivery (see Figure 2). The first and simplest one is superficial illumination. Here we shine a broad beam on a surface, usually the skin. Depending on

Figure 1: Penetration of light into human breast tissue



The color bar indicates the visible wavelengths. The range above 700 nm, near infrared, is not visible to the eye.

Figure 2: Three illumination geometries



Left: surface illumination reaching roughly 1 cm below the surface; middle endocavitary illumination where a light source is placed inside a body cavity. Here the therapeutic range is up to 1 cm below the cavity surface; interstitial illumination: multiple linear light diffusers are placed through needles inside the tissue. Around each fibre a sausage shaped area with a diameter of 2 cm is treated. Using several fibres any size volume can be treated at any depth.

the photosensitiser we can treat up to 1 cm deep. Using fibre optics we can guide light through an endoscope into hollow organs such as the bladder or the oesophagus. Again depending on the photosensitiser we can treat up to 1 cm deep. Larger and deep-seated volumes can be treated by placing optical fibres inside the tissue. This approach, referred to as interstitial PDT or iPDT, is used for instance for the prostate or for large tumours of the base of the tongue.

Selectivity

In the early days PDT was considered to be the magic bullet: PDT was supposed to kill tumour cells selectively and spare

normal tissue. This has somewhat overstretched our expectations and led to disappointments early on. A certain degree of selective retention of the photosensitiser in diseased tissue was observed, but the level of selectivity is several orders of magnitude away from what we would like it to be. Yet in some cases the selective accumulation of the photosensitiser is sufficient to enable diagnostic use based on the emission of light (fluorescence) by the photosensitiser. The not very selective distribution of photosensitiser is the cause of one of the main side effects of PDT: systemic photosensitisation. Skin photosensitisation is an issue with all systemically-administered photo

sensitisers, but yet its severity is very different for the different drugs used. With the 'old' photosensitiser Photofrin skin reactions to daylight have been documented for several weeks to months. With the more recently introduced sensitisers Foscan and Visudyne skin photosensitisation lasts a few weeks. For the endogenous sensitisers ALA and MAL the sensitisation occurs through endogenously produced PpIX. The same haem metabolism that creates the porphyrins also destroys them rapidly and skin photosensitisation is limited to 24 or maximum 48 hours.

For superficial basal cell carcinoma a depth of action of a millimetre is sufficient to eradicate the disease. For these applications topical applications are preferred, because photosensitisation is limited to the area to which the drug is applied. For many other oncological applications 1 or 2 cm depth of therapeutic action can be considered problematic. Nevertheless, we regard the limited penetration of light a virtue of PDT rather than a limitation. Using the illumination strategies described it enables us to treat any tissue volume without damaging underlying structures.

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