Photosensitizers in dentistry

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_Photodynamic therapy (PDT), also known as photoradiation therapy, phototherapy, or photochemotherapy, involves the use of a photoactive dye (photosensitizer) that is activated by exposure to light of a specific wavelength in the presence of oxygen (Konopka et al.). The transfer of energy from the activated photosensitizer to available oxygen results in the formation of toxic oxygen species, such as singlet oxygen and free radicals. These very reactive chemical species can damage proteins, lipids, nucleic acids, and other cellular components. Depending on the type of agent, photosensitizers may be injected intravenously, ingested orally, or applied topically.

Although a number of different photosensitizing compounds such as methylene blue, rose bengal, and acridine are known to be efficient singlet oxygen generators (and therefore potential photodynamic therapy agents), a large number of photosensitizers are cyclic tetrapyrroles or structural derivatives of this chromophore; in particular porphyrin, chlorin, bacteriochlorin, expanded porphyrin, and phthalocyanine (PC's) derivatives.

This is possibly because cyclic tetrapyrrolic derivatives have an inherent similarity to the naturally occurring porphyrins present in living matter consequently they have little or no toxicity in the absence of light (Leanne et al.).

Photosensitizers can be categorized by their chemical structures and origins. In general, they can be divided into three broad families:

_Porphyrin-based photosensitizer (e.g., Photofrin, ALA/PpIX, BPD-MA),
_Chlorophyllbased photosensitizer (e.g., chlorins, purpurins, bacteriochlorins), and
_Dye (e.g., phthalocyanine, naphthalocyanine) (Zheng Huan et al.).
_Photosensitizer families (Allison et al.)

_Porphyrin platform
_HpD (hematoporphyrin derivative)
_HpD-based
_BPD (benzoporphyrin derivative)
_ALA (5-aminolevulinic acid)
_Texaphyrins

_Chlorophyll platform
_Chlorins
_Purpurins
_Bacteriochlorins

_Dyes
_Phtalocyanine
_Naphthalocyanine.

_Generations of photosensitizers

Most of the currently approved clinical photosensitizers belong to the porphyrin family. Traditionally, the porphyrins and those photosensitizers developed in the 1970s and early 1980s are called first generation photosensitizers (e.g., Photofrin). Photofrin® (di-

hematoporphyrin ether), available for 30 years in its commercial form, and hematoporphyrin derivatives (HPDs) are referred to as first-generation sensitizers. Photofrin® is the most extensively studied and clinically used photosensitizer.

Porphyrin derivatives or synthetics made since the late 1980s are called second generation photosensitizer (e.g., ALA). Second-generation photosensitizers include 5-aminolevulinic acid (ALA), benzoporphyrin derivative (BPD), lutetium texaphyrin, temoporfin (mTHPC), tinethyletiopurpurin (SnET2), and talaporfin sodium (LS11). Foscan® (mTHPC), the most potent second-generation photosensitizer, has been reported to be 100 times more active than Photofrin® in animal studies. These photosensitizers have a greater capability to generate singlet oxygen; however, they can cause significant pain during therapy, and, because of their high activity, even dim light (60 Watt bulb) can lead to severe skin photosensitivity (Dougherty et al.).

The third agent, ALA, is an intrinsic photosensitizer that is converted in situ to a photosensitizer, protoporphyrin IX. Topical ALA and its esters have been used to treat pre-cancer conditions, and basal and squamous cell carcinoma of the skin.

Third generation photosensitizers generally refer to the modifications such as biologic conjugates (e.g., antibody conjugate, liposome conjugate) and built-in photo quenching or bleaching capability. Third-generation photosensitizers include currently available drugs that are modified by targeting with monoclonal antibodies. These terms are still being used although not accepted unanimously and dividing photosensitizing drugs into such generations may be very confusing. In lot of cases, the claim that newer generation drugs are better than older ones is unjustified. The premature conclusions on novel or investigational photosensitizers may send a misleading message to researchers or clinicians by suggesting that the older drugs should be replaced by the newer ones or wrongly imply to patients that newer photosensitizing drugs are superior to older ones.

Currently, only four photosensitizers are commercially available: Photofrin, ALA, Visudyne™ (BPD; Verteporfin), and Foscan. The first three have been approved by the FDA, while all four are in use in Europe.

_Indications for photosensitizers

_ALA-based PDT for the treatment of oral pre-malignant lesions
_as an adjunctive in treatment of chronic periodontitis and periimplantitis
_for disinfection of root canals in endodontic therapy
_treatment of early head and neck carcinomas
_palliative treatment for refractory head and neck cancer
_as an intra-operative adjuvant therapy, for recurrent head and neck cancer.

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