Applications of Photosensitizer in Therapy

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ABSTRACT

Photosensitization can be defined as a process in which a reaction to normally harmless radiation is induced by the introduction of a specific radiation-absorbing substance (photosensitizer) that causes another component (substrate) to be changed by the radiation. Photosensitivity is characterized by phototoxic and photoallergic effects. Drugs and chemicals may interact with UV to induce photosensitivity. Photosensitive disorders may be classified as those entirely caused by solar exposure and the photoaggravated disorders. Those in the former category include polymorphic light eruption, hydroa vacciniforme, actinic prurigo, solar urticaria and chronic actinic dermatitis. Photosensitivity can be diagnosed by photo test, photo patch test and photo drug test. Recently the photodynamic therapy (PDT) is used for the treatment of cancers. There are various photosensitizers such as photofrin, foscarn, 5-Aminolevulinic acid (5-ALA) etc which used in photodynamic therapy. Photosensitizers are also used to treat vitiligo, microbial infections and acne.

Key words: Photosensitizer, Juvenile spring eruption, Photodynamic therapy, Vitiligo, Acne.

INTRODUCTION

The term photosensitivity is used to describe any cutaneous reactions to light. Photosensitivity reaction occurs when a photosensitizing agent in or on the skin reacts to normally harmless doses of UV or visible light. It is classified as phototoxic or photoallergic reaction.[1,2,3,4,5] Phototoxic reaction results from direct damage to tissue caused by a photoactivated compound. Photoallergic reactions are cell-mediated immune responses to a photoactivated compounds. Phototoxicity is much more common than photoallergic reaction. Phototoxicity is an irritation of the skin occurs after exposure to UV light. Photoallergy is an allergic reaction of the skin to UV light. Both reactions occur in sun-exposed areas of skin including the face, neck, hands and forearms. A widespread eruption suggests exposure to a systemic photosensitizer whereas a localized eruption indicates a reaction to a locally applied topical photosensitizer. Acute phototoxicity is characterized by an exaggerated sunburn reaction with erythema, edema, blistering, weeping and desquamation that occurs within minute to hours of light exposure. Photoallergic reaction resemble allergic contact dermatitis, their onset is delayed by as long as 24-72 hours after exposure to the drug and light.[6]

PHOTOSENSITIZATION MECHANISM

Phototoxicity

Various compounds especially those which have at least one resonating double bond or an aromatic ring that can absorb radiant energy cause direct damage to tissues which results in phototoxic reactions. Most compounds having those bonds and rings are activated in between wavelengths of UV-A (320-400 nm) range, although some compounds have peak absorption within the UV-B or visible range.[7] On exposure to UV rays a transient redness appears in few minutes. The major erythema response of skin to UV rays is delayed, beginning 2-6hrs after exposure and reaching a maximum in 12-24 hrs and then subsides over next few days. This delayed erythema response is sunburn and histologically it is characterized by appearance of sunburn cells (SBC). SBCs appear in 24-28 hrs after exposure and by 72 hrs, form a continuous band in stratum corneum. UV-B rays are more potent in inducing formation of SBCs than UV-A rays.[8] Sunburn is the major cause of phototoxic reactions which occurs due the formation of hyperactive species of oxygen. Photoactivation of a compound results in the excitation...
from phototoxicity histologically. Photoallergic responses are uncommon, usually manifests as a pruritic eczematous eruption and consist clinically of immediate urticarial or delayed papular lesions. The immediate urticarial lesions show very little other than some edema and vasodilatation. The delayed papular reactions present a dense perivascular round-cell infiltrate in the dermis which is characteristic though not diagnostic of these responses.[16,17,18]

**Symptoms and Diagnostic Tests**

Human body shows different symptoms that depend upon the age of the patient. There are several indications of photosensitivity which are characterized as follows depending on the age of the patient.

**Childhood symptoms**

Lesions on ears in spring (juvenile spring eruption), itchy lesions on V area of neck or elsewhere (polymorphous light eruption), burning pain, increased protoporphyrin levels in red blood cell (Erythropoietic protoporphyria), lesions on bridge of nose (Actinic prurigo), scar formation (Hydroa vacciniforme).[19]

**Adulthood symptoms**

Females with itchy lesions in V area of neck (Polymorphous light eruption), all sun-exposed areas, positive phototest results (Drug-induced photosensitivity), (lesions appear within 5-10 min and disappears within 1-2 h, urticaria on phototesting (Solar urticaria), anti−RO/SS-A antibodies, skin immunofluorescence, phototesting with late readings (Lupus erythematosus), porphyrin determinations (Porphyria cutanea tarda).[19]

**Old age symptoms**

There are various old age symptoms such as persistent redness of face in elderly man (Chronic actinic dermatitis), all sun-exposed areas, positive phototest results (Drug-induced photosensitivity), CD4+ cells on histological examination (Cutaneous T-cell lymphoma), creatine level in 24-h urine (Dermatomyositis).[19]

**Diagnostic tests**

Various photosensitivity tests are conducted to determine the level of photosensitivity. These tests are performed after various symptoms of photosensitivity are observed. Ultraviolet radiation is divided into ultraviolet A (UVA) (operative wavelength of 320 to 400 nm), ultraviolet B (UVB) (operative wavelength of 290 to 320 nm) and ultraviolet C (UVC) (operative wavelength of 100 to 290 nm). UVA, UVB and visible light are most frequently used for the diagnosis purpose.

1) **Photo test:** The most widely conducted photo test is exposure to UVB irradiation in the minimal dose that causes...
erythema in 24 hours (minimal erythema dose; MED). The average dose for ethnic Japanese is 60 to 100 mJ/cm². When the MED is low, involvement of a photosensitive disease is suspected.[20]

2) Photo-patch test: The photo-patch test is conducted to examine the influence of rays when a chemical substance is placed on the skin. 24 to 48 hours after a material that is suspected of causing photosensitive disease is applied on the skin, the site is exposed to UV rays. If reddening or swelling occurs within 24 hours, the test is considered to be positive for such disease.[24]

3) Photo-drug test: The influence of radiation in the presence of a chemical substance can also be examined by photo-drug test. A drug that is suspected of causing a photosensitive disease is taken orally instead of topically. The photo-drug test is generally used for diagnosis of drug-induced hypersensitive diseases.[23]

**Photosensitizers**

Photosensitizers are the agents that may leave skin vulnerable to UV exposure causing erythema, itching, scaling, rashes or inflammation. These substances combined with UV light also may contribute to other health problems including skin cancer, photoaging and allergic reactions. It can be divided into following main groups:

**Photodynamic Agents**

Photodynamic agents are naturally occurring or may be synthetic pigments and dyes, which require oxygen for their action e.g. erythrosin, rhodamin, hypericine, Bengal rose, anthracene, acidine dye, methylene blue, quinine, buckwheat and porphyrin. These substances photoxidize terpenene, blood serum protein and cause haemolysis. They are topically inactive but on intradermal injection cause immediate photoreaction of short durations. Erythema produced by photodynamic compound appears immediately after irradiation and disappear after a few hours.[23]

**Photosensitizing Agents**

Photosensitizing agents do not require oxygen for reaction. These photosensitizing agents include furanocoumarins and their derivatives e.g. psoralen, xanthotoxin, bergapten, isobergapten and imperatorin. These compounds neither cause photo-oxidation of terpenene or haemolysis, nor photooxidize blood serum protein to any appreciable extent, but provoke dermatitis characterized by erythema after latent period of a few hours and last several days succeeded by increased pigmentation on epicutaneous application and intradermal injection. These compounds have therapeutic value in leucoderma.[21]

Metalloctetrapyrolics particularly porphyrins, azaporphyrins that includes gallium in central pyrrolic core have phototherapeutic application in photodetection and phototherapy of target tissues. These compounds are also used for treatment and detection of cardiovascular disorder.[21]

**Drug Induced Photosensitivity**

Cutaneous drug eruptions are one of the most common types of adverse reaction to drug therapy, with an overall incidence rate of 2-3% in hospitalized patients.[24,25] Almost any medicine can induce skin reactions, and certain drug classes, such as non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and antiepileptics, have drug eruption rates approaching 1-5%.[24]

**Photosensitivity Management**

Prevention of photosensitivity reactions is mainly based upon patient education. Patients should be well educated

<table>
<thead>
<tr>
<th>Table 1: List of Drugs that Induces Photosensitivity[27]</th>
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<td><strong>Drug classifications</strong></td>
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<tr>
<td>Muscle relaxant</td>
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<tr>
<td>Psychoactive</td>
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<tr>
<td>Antifungal agent</td>
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<td>Antibacterial agent</td>
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<td>Antihistamine</td>
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<td>Antiinflammatory agent</td>
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<td>Prostatomegaly therapeutic agent</td>
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<td>Lipid-lowering drug</td>
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<td>Antitumor agent</td>
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<td>Photochemistry therapeutic agent</td>
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<td>Antirheumatic</td>
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to minimize sun exposure. Additional light protection can be provided by the use of UV-A protective sunscreens and physical barriers such as clothing. Sunscreens that provide UV-A coverage are dioxybenzone, avabenzene, titanium dioxide, zinc oxide. Patients should be counseled to avoid sources of high-intensity light like tanning beds. Some reactions may be dose related, a decrease in dose may be considered to help minimize the reaction. A mild reaction like sunburn may be easily handled with skin protectants and topical or systemic analgesics. Patients may also be benefited from application of cooling creams or gels. Antibacterial creams may be necessary to prevent infection, if patients have blisters that are broken. Oral or topical corticosteroids are used to handle severe reactions. Drugs like antihistamines may also prevent pruritus associated with reactions.

Role of Photosensitizers in the Therapy

Vitiligo
Vitiligo is an idiopathic acquired pigmentary disorder characterized by loss of melanin formation which is the main pigment in mammalian skin, hair and eyes with subsequent development of white patches. Photocchemotherapy is one of the most successful treatment of vitiligo.[31,32,33,34,35] El Mofy in 1948 introduced modern photocchemotherapy of vitiligo with psoralen and UVA (PUVA).[36] 8-methoxy psoralen (8-MOP) and 4, 5, 8-trimethylpsoralen (TMP) are the most commonly used psoralens, both systemically as well as topically. TMP produces fewer side effects and better pigmentation than 8- MOP. Oral psoralen photocchemotherapy requires longer UV-A exposures than those required for topical therapy.[37]

Photodynamic Therapy (PDT)
Photodynamic therapy (PDT) is an emerging modality for the treatment of neoplastic and non-neoplastic diseases.[38,39] It is based on the concept that light irradiation can change an inert substance into an active one. PDT involves the interaction of a specific light sensitive agent, so-called photosensitiser and a particular type of light. The photosensitising agent is injected into the bloodstream is absorbed by cells all over the body but remains in or around the tumour cells for a longer time than it does in normal cells. Approximately 24-72 hours after injection, when most of the agent has left normal cells but remains in cancer cells, the tumour is exposed to laser light which can be directed through fiber optic to deliver the proper amount of light to areas inside the body. The light energy is absorbed by the photosensitising agent that causes a chemical reaction and produces an active form of excited singlet oxygen.[40] These reactive oxygen species (ROS) have a very short lifetime but are extremely reactive and usually induce a phototoxic reaction that kills nearby tumour cells. In addition to directly killing tumour cells (cell death by necrosis or by apoptosis), PDT appears to shrink or destroy tumors by damaging blood vessels in the tumor (vascular shutdown), thereby preventing the cancer from receiving necessary nutrients or may activate the immune system to attack the tumor cells.

Advantages
- Selective tumor destruction with normal tissue preservation.
- Limited damage to surrounded tissue.
- Lack systemic toxicity.
- It can be targeted very precisely.
- It is less invasive approach than surgery.
- Unlike radiation, it can be repeated several times at the same site if necessary.
- Usually performed in an outpatient procedure.
- It may result in less scarring.
- Well accepted cosmetic results.

Treatment of Intracranial Cancers
Malignant gliomas are one of the most invasive intracranial tumors which are difficult to eradicate surgically and carry a dismal prognosis. Their cure is mainly dependent on radical and complete local excision. The main causes of failure to eradicate them are their inability to visualize and detect them, the presence of the blood brain barrier and the low tolerance of brain tissue to ionizing radiation. Photodynamic detection and photodynamic therapy offers an excellent chance of visualizing tumor nests and targeted destruction of the remaining tumor cells safely followed by surgical excision which may results in the survival of patients suffering from these invasive tumors. PDD/ PDT is safe treatment for invasive intracranial tumors and well tolerated by most patients. Intracavity irradiation after surgical excision of high grade gliomas is the most favored method of brain tumor PDT. PDD maximizes surgical tumor resection leading to better prognosis and prolonged survival while, PDT gives significant improvement in survival of patients with malignant gliomas who have dismal prognosis. Therefore, the majority of patients treated so far had recurrent malignant disease with very poor prognosis.

Photosensitizers used in PDT of Cancer

Photofrin
Photofrin is a first generation photosensitiser which is a hematoporphyrin derivative (HPD) are used most commonly for the treatment of bladder cancer, esophageal cancer, gastric cancer and cervical cancer. U.S. food and drug administration (FDA) has approved the porfirmer sodium or photofrin for use in PDT to treat or relieve symptoms of esophageal cancer. When the cancer obstructs the esophagus or when the cancer cannot be satisfactorily treated with laser therapy. Porfirmer sodium can also used to treat
non-small lung cancer in patients for whom the usual treatments are not appropriate. It is mainly activated by diode laser light at 630 nm. The irradiation dose is 100-200 J/cm².46

**Foscan (temoporfin)**

Foscan is a more potent photosensitiser than photofrin and ALA. It has been approved for the treatment of head and neck cancer. It is activated at 652 nm wave length. The irradiation dose is as low as 10 J/cm².

**5-Aminolevulinic acid (5-ALA)**

5-aminolevulinic acid (ALA) is a second generation photosensitizer which is hydrophilic zwitter ion at physiological pH. ALA was approved for treatment of actinic keratoses and basal cell carcinoma of skin. Recently, it was introduced as a new drug for PDT of bladder cancer and to be used in a diagnostic procedure (photodynamic diagnosis [PDD] or ALA induced fluorescence endoscopy, [AFE]). It has an advantage of possibility of topical administration. ALA is an initial substrate of heme biosynthesis. 5-ALA formed in vivo in mitochondria by condensation of glycine and succinyl CoA (catalyzed by ALA synthase). Subsequent reactions produce protoporphyrin IX (PpIX) which is converted to heme using ferrochelatase and Fe. Heme inhibits synthesis of 5-ALA. Excess administered 5-ALA passes through abnormal epidermis and converts to PpIX which is then accumulates with minimized amount of ferrochelatase. Protoporphyrin IX (PpIX), is an active compound, which accumulates in tumor cells and can be activated by violet-blue light (375-440 nm) for PDD and diode laser light (635 nm) for PDT. Depth of tissue penetration is 7-15 mm and the irradiation dose required for PDT is 100 J/cm² and skin photosensitivity continues for 7-10 days after ingestion. It can be given 3-4 hours before induction of anaesthesia in a mixture of non-fizzy orange juice at 15-20 mg/Kg bodyweight in PDD/PDT of brain tumors.

**Recent Trends in Therapy**

**PDT Acne Treatment**

Acne vulgaris commonly called acne is a common human skin disease characterised by plugged pores (blackheads and whiteheads), pimples, follicular papules or comedones, pustules and even deeper lumps (cysts or nodules) that occurs on the face, neck, chest, back, shoulders and the upper arms. The term nodulocystic have been used to describe severe cases of inflammatory acne. Cystic acne affects deeper skin tissue than does common acne. When severe, acne can lead to serious and permanent scarring. It can occur most commonly during adolescence, affecting more than 96% of teenagers and often continues into adulthood. Acne develops as a result of blockages in follicles, enlargement of sebaceous glands and an increase in sebum production occurs with increased androgens (male sex hormones). In these conditions the naturally occurring largely commensal bacteria i.e. Propionibacterium acnes can cause inflammation, leading to inflammatory lesions (papules, infected pustules, or nodules) in the dermis around the microcomedo or comedone, which results in redness and may result in scarring or hyperpigmentation.

PDT is a procedure that treats active and resistant acne that combines a special light activated solution which targets and destroys acne activity. This treatment can also diminish older acne scars, leaving the skin with a much smoother appearance. Intractable acne on the body can be extensively treated by ALA based PDT (ALA-PDT). It can be administered both topically as well as orally. Kimura et al performed an experiment in which the total number of acne patients was 51. A 10 mg/kg B.W. of ALA was administered orally to the patients then, after 4 hours acne lesions were exposed to polychromatic visible light from a metal halide lamp. The wavelength of a light ranges from 540 to 800nm. In one session, the total light energy dose was 60-80 J/cm² for the body. All patients undergo two sessions of PDT and no other treatments received after PDT or during the follow-up period. The study concluded that PDT-ALA was considered to be effective for the treatment of moderate to severe acne.

**Antimicrobial Photodynamic Therapy**

Bacterial infection plays an important role in the development of necrosis in the dental pulp and the formation of periapical lesions, therefore, the main goal of endodontic treatment is the elimination of bacterial infection and associated inflammation in the pulpal tissue and also the mechanical removal of damaged tissue found inside the root canal that acts as a growth medium for microbes. Garcez et al performs an experiment in which ten single rooted freshly extracted human teeth were inoculated with stable bioluminescent Gram-negative bacteria (Proteus mirabilis and Pseudomonas aeruginosa) to produce 3-day biofilms in prepared root canals. Bioluminescence imaging was used to quantify bacterial burdens. A conjugate between polyethyleneimide and chlorin(e6) as the photosensitizer (PS) can be employed in PDT and diode laser light (660-nm) delivered into the root canal via a 200-m fiber, and this was compared and combined with standard endodontic treatment using mechanical debridement and antiseptic irrigation. After the success of experiment, they concluded that endodontic therapy alone can reduced bacterial bioluminescence by 90% while, PDT alone can reduced bioluminescence by 95%. The combination can reduced bioluminescence by >98%, and the bacterial re-growth observed 24 hours after treatment was much less for the combination than for either single treatment.
Future Prospects of PDT

Recently new photosensitizers are being developed by several pharmaceutical companies that increases the number of choices for the treatment of cancers that are previously treated with photofrin but extend the indications as well. An example is the application of PDT with Benzoporphyrin Derivative-Monoacid Ring A (BPD-MA) for treatment of age-related macular degeneration and possibly for rheumatoid arthritis, the possible use of Tin Etiopurpurin (SnET2) and mTHPC (foscarnet) for prostatic diseases, the topical use of ALA or its methyl ester for dermatologic superficial lesions and perhaps the application of PDT for treatment of coronary artery diseases. However, the real challenge in the future is gaining physician acceptance of PDT as a viable treatment modality.[64]

CONCLUSION

Photosensitivity is a skin reaction (i.e. rash) that occurs after exposure to ultraviolet (UV) radiation from the sun or an artificial light source. Photosensitivity can be caused by various agents including cosmetics, perfumes, certain medications, and even the sunscreen that is meant to protect your skin. Phototoxic reaction results from direct damage to tissue caused by compounds that are activated by light. Photoallergic reactions are cell-mediated immune responses to a photoactivated compounds. Phototoxicity is much more common than photoallergic reaction. Cutaneous lupus erythematosus represents an autoimmune disease characterized by photosensitivity, apoptosis of keratinocytes and an inflammatory infiltrate in superficial and/or deep compartments of the skin. Recent findings in cutaneous LE study suggest an amplification cycle with UV-injury results in the production and release of a first set of chemokines and the presence of extracellular self-DNA. Subsequently, a first wave of effector memory T cells as well as PDC is recruited to sites of UV injury and may be activated via different pathways.

Drugs which are essentially used for treatment of various ailments have various side effects one of the major side effects is photosensitization that further induces phototoxicity and photo allergy. The diagnosis of the toxic effects of UV rays can now be easily detected by various types of tests. Photosensitizers that induce photosensitivity are now being used in PDC therapy for treating cancers. The efficacy of photosensitizers is also utilized in the Antimicrobial therapy and treatment of acne and vitiligo. The PDT is going to be the futuristic trend for treatment of various disorders like rheumatoid arthritis and to treat certain diseases like prostatic diseases, dermatologic superficial lesions and coronary artery diseases.

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