



Photosensitizers in Photodynamic Therapy: A Current Approach

Neeraj Jain, Neelam Jain, Laxmi Mishra

Teerthankar Mahaveer College of Pharmacy, TMU, Moradabad-244102, Uttar Pradesh, India

Faculty of Pharmacy, Oriental University, Indore-452003, Madhya Pradesh, India

Faculty of Pharmaceutical sciences Rama University, Mandhana, Kanpur-209217, U.P., India.

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, foscan, 5-Aminolevulinic acid (5-ALA) etc which used in photodynamic therapy. Photosensitizers are also used to treat vitiligo, microbial infections and acne.

Keywords: Photosensitizer, Juvenile spring eruption, Photodynamic therapy, Vitiligo, Acne.

DOI Number: 10.48047/nq.2022.20.8.nq221161

NeuroQuantology 2022; 20(8): 11258-11267

11258

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 of electrons from the stable singlet state to an excited triplet state. As excited-state electrons return to a more stable configuration, they transfer their energy to

oxygen, leading to the formation of reactive oxygen intermediates. Reactive oxygen intermediates such as a singlet oxygen, superoxide anion, and hydrogen peroxide that can damage cell membranes and DNA [9]. Such functional molecules have been successfully applied in photodynamic therapy (PDT) of cancerous tumours. Signal transduction pathways that lead to the production of proinflammatory cytokines and arachidonic acid metabolites are also activated. The result is an inflammatory response that has the clinical appearance of an exaggerated sunburn reaction [10, 11].

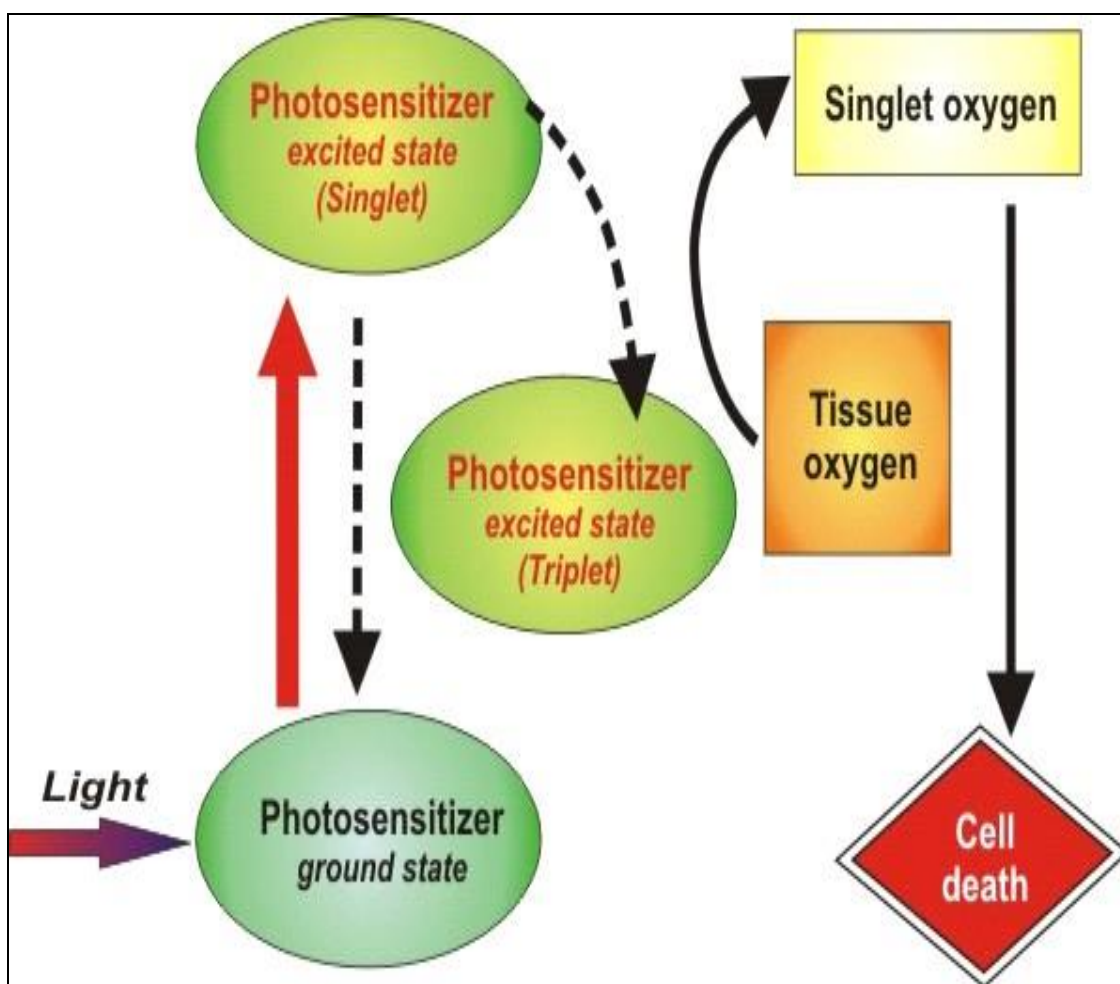


Figure 1: Mechanism of Phototoxicity [12]

Photoallergic reactions

Cell mediated immune responses are responsible for photoallergic reactions in which the antigen is a light-activated drug. Photoactivation results in the development of a metabolite that can bind to

protein carriers in the skin to form a complete antigen [13]. The reaction proceeds specifically, through langerhans cells and other antigen-presenting cells which take up the antigen and then migrate to regional lymph nodes. In those



locations, the langerhans cells present the photoallergen to T lymphocytes that express antigen-specific receptors. The T cells become activated and proliferate, and they return to the site of photoallergen deposition. In the skin, the T cells orchestrate an inflammatory response that usually has an eczematous morphology if the photoallergen is applied topically or the characteristics of a drug eruption if the photoallergen is administered systemically. These are mediated by immunological pathways and require prior sensitization to drug and UV-rays. It is usually seen in a small number of individuals. Clinical effects range from acute urticarial reactions to papular lesions appearing 24 hrs after exposure. UV radiation may react with photosensitizing agent to form a stable hapten. The photoproduct then combines with protein carrier to form an antigen. Radiation can also alter tissue protein, enabling it to act as a carrier for either the photosensitizing agent itself or its photoproduct [14, 15]. Photoallergy also differs 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 & 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 100mJ/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 [20].

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 [20].

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, acridine dye, methylene blue, quinine, buckwheat and porphyrin. These substances photo-oxidize 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 [21].

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 few hours and last several days succeeded by increased pigmentation on epicutaneous application and intradermal injection. These compounds have therapeutic value in leucoderma [21].

Metallotetrapyrrolics 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 [22].

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 [23, 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% [26].

Table 1: List of Drugs that Induces Photosensitivity [27]

Drug classifications	Drugs
Muscle relaxant	Afloqualone
Psychoactive	Chlorpromazine, promethazine, diazepam, carbamazepin, imipramine
Antifungal agent	Griseofulvin, flucytosine, itraconazole
Antibacterial agent	Nalidixic acid, enoxacin, ofloxacin, ciprofloxacin, lomefloxacin, sparfloxacin, fleroxacin, tosufloxacin, tetracycline, doxycycline
Antihistamine	Diphenhydramine, mequitazine
Antiinflammatory	Ketoprofen, tiaprofenic acid, suprofen, piroxicam, ampiroxicam, actarit, diclofenac, naproxen
Antihypertensive agent	Hydrochlorothiazide, trichlormethiazide, meticrane, clofenamide, tripamide, metolazone, furosemide, tilisolol HCl, pindolol, diltiazem HCl, nicardipine HCl, nifedipine, captopril, lisinopril
Antipodagric	Benzbromarone



Antidiabetic	Tolbutamide, chlorpropamide, glibenclamide, carbutamide, glymidine sodium
Prostatomegaly therapeutic agent	Tamsulosin
Lipid-lowering drug	Simvastatin
Antitumor agent	5-FU, tegafur, dacarbazine, flutamide
Photochemistry therapeutic agent	8-Methoxypsoralen, trioxypsoralen, hematoporphyrin derivative
Antirheumatic	Sodium aurothiomalate, methotrexate
Vitamin	Etretinate, pyridoxine, Vit. B ₁₂

Photosensitivity Management

Prevention of photosensitivity reactions is mainly based upon patient education. Patients should be well educated 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 [28]. 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 [29]. Oral or topical corticosteroids are used to handle severe reactions [30]. 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. Photochemotherapy is one of the most successful treatment of vitiligo [31, 32, 33, 34, 35]. El Mofty in 1948 introduced modern photochemotherapy of vitiligo with psoralen and UVA (PUVA) [36]. 8-methoxy psoralens (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 photochemotherapy 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 photosensitizer and a particular type of light. The photosensitizing 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 photosensitizing 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 [41] 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 [42]. 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 [43]. 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 photosensitizer 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 porphyrin sodium or photofrin for use in PDT to treat or relieve symptoms of esophageal cancer [44]. When the cancer obstructs the esophagus or when the cancer cannot be satisfactorily treated with laser therapy. Porphyrin sodium can also used to treat non-small lung cancer in patients for whom the usual treatments are not appropriate [45]. It is

mainly activated by diode laser light at 630nm. The irradiation dose is 100-200 J/cm² [46].

Foscan (temoporfin)

Foscan is a more potent photosensitizer than photofrin and ALA. It has been approved for the treatment of head and neck cancer [47]. It is activated at 652 nm wave length. The irradiation dose is as low as 10 J/cm².

5-Aminolevulinic acid (5-ALA)

5-amino levulinic acid (ALA) is a second generation photosensitizer which is hydrophilic zwitter ion at physiological pH. ALA was approved for treatment of actinic keratosis and basal cell carcinoma of skin. Recently, it was introduced as a new drug for PDT of bladder cancer [48] and to be used in a diagnostic procedure (photodynamic diagnosis [PDD] or ALA-induced fluorescence endoscopy, [AFE]) [49, 50]. It has an advantage of possibility of topical administration [49]. 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 [51]. 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 [52, 53, 54].

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 [55]. 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^[56, 57].

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)^[58, 59]. ALA can be administered both topically as well as orally^[60]. Kimura et al performed an experiment in which the total number of acne patients was 51. A 10mg/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^[61].

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^[62]. Garcez et al^[63] 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 polyethylenimine 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 (foscan) 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

11264



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 inducing apoptosis and necrosis of keratinocytes which in turn 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.

Acknowledgements

The authors are thankful to the Principal of Teerthankar Mahaveer College of Pharmacy, Teerthankar Mahaveer University, Moradabad for their kind support and providing all the necessary facilities and encouragement for successful completion of this work.

References

1. Nayak P. Commonly used photosensitizing medications: their adverse effects and precautions to be considered. *International Journal of Pharmaceutical Sciences Review and Research*. 2010; 4: 135-140.
2. Epstein JH. Actinic manifestations: Cutaneous diseases induced by the sun. *Clin Pharmacol Ther*. 1974; 16: 959-963.
3. Jarratt M. Drug photosensitization. *Int J Dermatol*. 1976; 15: 317-323.
4. Blaylock WK. Common drug reactions: Their mechanisms and management. *virginia medical journal*. 1981; 108: 529-533.
5. Todd B. Photosensitizing medications. *Geriatr Nurs*. 1984; 5: 263.
6. Kaplan AP. Drug-induced skin disease. *J Allergy Clin Immunol*. 1984; 74: 573-579.
7. Parrish JA, Anderson RR, Urbach F, Pittis D. UV-A: Biological effects of ultraviolet radiation with emphasis on human responses to longwave ultraviolet rays. New York: Plenum Press, p. 262; 1978.
8. Parrish JA, White HAD, Pathak MA. Photomedicine. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, AustenKF, Editors. *Dermatology in general medicine*. New York: McGraw-Hill, p. 942-994; 1979.
9. Blum HF. *Photodynamic Action and Diseases Caused by Light*. New York: Rhinehold Publishing Corporation, p. 309; 1941.
10. Epstein S. Chlorpromazine photosensitivity: Phototoxic and photoallergic reactions. *Arch Derm*. 1968; 98: 354-363.
11. Epstein S. Photoallergy versus phototoxicity. In: Rees RB, Editor. *Dermatoses due to environmental and physical factors*. Springfield, p. 119-135; 1962.
12. http://os.tnw.utwente.nl/images_new/proj4_0_1.jpg
13. Pichler WJ. Immune mechanism of drug hypersensitivity. *Immunol Allergy Clin North Am* 2004; 24: 373-397.
14. Harber LC, Boet RL. Pathogenic mechanisms of drug induced photosensitivity. *J Invest Dermatol*. 1972; 58: 327-342.
15. Dutta SN, Roy CL, Sen P, Dhanda PC. Adverse reactions after prolonged use of chlorpromazine. *J Indian Med Assoc*. 1967; 49: 542-543.
16. Allen JE. Drug-induced photosensitivity. *Clin Pharm*. 1993; 12: 580-587.
17. Emmett EA. Drug photoallergy. *Int J Dermatol*. 1978; 17: 370-379.
18. Targovnik SE, Targovnik JH. Cutaneous drug reactions in porphyrias. *Clin Dermatol*. 1986; 4: 110-117.
19. Roelandts R. The Diagnosis of Photosensitivity. *Arch Dermatol*. 2000; 136: 1152-1157.
20. Gary A, Wasserman MD, Herbert F, Haberman MD. Photosensitivity: results of investigation in 250 patients. *Canadian Medical Association Journal*. 1975; 113: 1055-1060.

11265



21. Sen P, Mediratta PK, Bhaduri J. Light, skin and drugs. *Indian Journal of Pharmacology*.1992; 24: 82-89.
22. Robinson BC, Leitch IM, Greene S, Rychnovsky S. Metallotetrapyrrolic photosensitizing agents for use in photodynamic therapy. US Patent 0105669 A1; 2003.
23. Breathnach SM, Hintner H. Adverse Drug Reactions and the Skin. Oxford: Blackwell Scientific, p. 72; 1992.
24. Crowson AN, Brown TJ, Magro CM. Progress in the understanding of the pathology and pathogenesis of cutaneous drug eruptions. *Am J Clin Dermatol*. 2003; 4: 407-428.
25. Wolkenstein P, Revuz J. Drug-induced severe skin reactions. *Drug Safety*. 1995; 13: 56-68.
26. Bigby M. Rates of cutaneous reactions to drugs. *Arch Dermatol*. 2001; 137: 765-770.
27. Warnock JK, Morris DW. Adverse cutaneous reactions to mood stabilizers. *Am J Clin Dermatol*. 2003; 4: 21-30.
28. Moore DE. Drug-induced cutaneous photosensitivity. *Drug Safety*. 2002; 25: 345-372.
29. Berbari RR. Handbook of nonprescription drugs, 14th ed. Washington DC: American Pharmacists Association; 2004.
30. Morison WL. Photosensitivity. *N Engl J Med*. 2001; 350: 1111-1117.
31. Al-Khawajah MM, Photochemotherapy for vitiligo: Seven years experience at a university hospital. *Ann Saudi Med*. 1997; 17: 175-178.
32. Parrish JA, Fitzpatrick TB, Shea C. Photochemotherapy of vitiligo. *Arch Dermatol*. 1976; 112: 1531-1534.
33. Lassus A, Halme K, Eskelinen A. Treatment of vitiligo with oral methoxsalen and UVA. *Photodermatology*. 1984; 1: 170-173.
34. Pathak MA, Mosher DB, Fitzpatrick TB. Safety and therapeutic effectiveness of 8-methoxypsoralen, 4,5,8-trimethylpsoralen, and psoralen in vitiligo. *Natl Cancer Inst Monogr*. 1984; 66: 165-173.
35. Honigsmann H, Fitzpatrick TB, Pathak MA. Oral photochemotherapy with psoralens and UVA (PUVA): Principles and Practice. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al, Editors. *Dermatology in general medicine*. 4th ed. New York: McGraw- Hill, p.1728-1754; 1993.
36. El-Mofty AM. A preliminary clinical report on the treatment of leukoderma with Ammi majus Linn. *J Egypt Med Assoc*. 1948; 31: 651-665.
37. Ortel B. Vitiligo treatment. In: Honigsmann H, Stingl G, Editors. *Therapeutic photomedicine, Current problems in dermatology*. Basel: Karger, p. 265-279; 1986.
38. Wilson BC, Jeeves WP. Photodynamic therapy of cancer. In: Ben-Hur E, Rosenthal I, Editors. *Photomedicine*, Boca Raton, FL: CRC Press, p. 127-177; 1987.
39. Gomer CJ, Rucker N, Ferrario A, Wong S. Properties and applications of photodynamic therapy. *Radial Res*. 1989; 120: 1-18.
40. Moan J, Berg K. The photodegradation of porphyrins in cells can be used to estimate the life time of singlet oxygen. *Photochem Photobiol*. 1991; 53: 549-553.
41. Henderson BW, Dougherty TJ. How does photodynamic therapy work. *Photochem Photobiol*. 1992; 55: 145-157.
42. Eljamel MS. New light on the brain: The role of photosensitizing agents and laser light in the management of invasive intracranial tumors. *Tech Canc Res Treat*. 2003; 2: 303-309.
43. Kaye AH, Morstyn G, Brownbill D. Adjuvant high-dose photoradiation therapy in the treatment of cerebral glioma: A Phase 1-2 Study. *J Neurosurg*. 1987; 67: 500-505.
44. Chopp M, Mereski MO, Madigan L. Sensitivity of 9L gliosarcomas to photodynamic therapy. *Radiation Research*, 1996; 146: 461-465.
45. Stummer W, Gotz C, Hassan A. Kinetics of photofrin II in perifocal brain edema. *Neurosurg*. 1993; 33: 1075-1081.
46. Whelan HT, Schmidt MH, Segura AD. The role of photodynamic therapy in posterior fossa brain tumors: A preclinical study in a canine glioma model. *J Neurosurg*. 1993; 79: 562-568.
47. Berenbaum M, Bonnett R, Cheoretan E. Selectivity of meso-tetra-(hydroxyphenyl) porphyrins and chlorins and photofrin in causing photodamage in tumor, skin, muscle and bladder. *Laser Med Sci*. 1993; 8: 235-243.
48. Waidelich R, Stepp H, Baumgartner R. Clinical experience with 5-aminolevulinic acid and photodynamic therapy for refractory



- superficial bladder cancer. *J Urol.* 2001; 165: 1904–1907.
49. Kriegmair M. Fluorescence photodetection of neoplastic urothelial lesions following intravesical instillation of 5-aminolevulinic acid. *J Urol.* 1994; 44: 836–840.
50. Kriegmair M, Baumgartner R, Knuchel R. Detection of early bladder cancer by 5-aminolevulinic acid induced porphyrin fluorescence. *J Urol.* 1996; 155: 105–110.
51. Tsai JC, Hsiao YY, Teng LJ. Comparative study on the ALA photodynamic effects of human glioma and meningioma cells. *Lasers Surg Med.* 1999; 24: 296-305.
52. Stummer W, Stocker S, Novotny A. In Vitro and In Vivo porphyrin accumulation by C6 glioma cells after exposure to 5-aminolevulinic acid. *J Photochem Photobio.* 1998; 45: 160-169.
53. Lilge L, Wilson BC. Photodynamic therapy of intracranial tissues: A preclinical comparative study of four different photosensitizers. *J Clin Laser Med Surg.* 1998; 16: 81-91.
54. Frisoli JK, Tudor EG, Flotte TJ. Pharmacokinetics of a fluorescent drug using laser-induced fluorescence. *Cancer Research.* 1993; 53: 5954-5961.
55. Thiboutot M, Strauss D, John S. Diseases of the sebaceous glands in Burns. 6th ed. New York: McGraw- Hill, p. 672–687; 2003.
56. Norris JF, Cunliffe WJ. A histological and immunocytochemical study of early acne lesions. *Br J Dermatol.* 1988; 118: 651–659.
57. Leyden JL, McGinley KJ, Mills OH, Kligman AM. Propionibacterium levels in patients with and without acne vulgaris. *J Invest Dermatol.* 1975; 65: 382–384.
58. Itoh Y, Ninomiya Y, Tajima S, Ishibashi A. Photodynamic therapy for acne vulgaris with topical 5-aminolevulinic acid. *Arch Dermatol.* 2000; 136: 1093-1095.
59. Itoh Y, Ninomiya Y, Tajima S, Ishibashi A. Photodynamic therapy of acne vulgaris with topical 5-aminolevulinic acid and incoherent light in Japanese patients. *Br J Dermatol.* 2001; 144: 575-579.
60. Kennedy JC, Marcus SL, Pottier RH. Photodynamic therapy (PDT) and photodiagnosis (PD) using endogenous photosensitization induced by 5-aminolevulinic acid (ALA): Mechanisms and clinical results. *J Clin Laser Med Surg.* 1996; 14: 289-304.
61. Kimura M, Itoh Y, Tokuoka Y, Kawashima N. Delta-aminolevulinic acid based photodynamic therapy for acne on the body. *The Journal of Dermatology.* 2004; 31: 48-51.
62. Siqueira JF. Endodontic infections: Concepts, paradigms, and perspectives. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2002; 94: 281–293.
63. Garcez AS, Riberio MS, Tegos GP, Nunez SC, Jorge AOC, Hamblin MR. Antimicrobial photodynamic therapy combined with conventional endodontic treatment to eliminate root canal biofilm infection. *Laser Surg Med.* 2007; 39: 59-66.
64. Dougherty TJ, Gomer CJ, Henderson BW, Jori G, Kessel D, Korbek M, et al. Photodynamic therapy. *J Natl Cancer Inst.* 1998; 90: 889-905.

