Photochemotherapy (PUVA): An Overview

1Fakir Mohan Debta, 2Anil Ghom, 3Priyanka Debta, 4Abhijeet Deoghare

1Reader, Department of Oral Medicine and Radiology, Chhattisgarh Dental College and Research Institute, Sundra, Rajnandgaon, Chhattisgarh, India
2Professor, Department of Oral Medicine and Radiology, Chhattisgarh Dental College and Research Institute, Sundra, Rajnandgaon, Chhattisgarh, India
3Lecturer, Department of Oral Pathology and Microbiology, Chhattisgarh Dental College and Research Institute, Sundra, Rajnandgaon, Chhattisgarh, India
4Lecturer, Department of Oral Medicine and Radiology, Chhattisgarh Dental College and Research Institute, Sundra, Rajnandgaon, Chhattisgarh, India

Correspondence: Fakir Mohan Debta, Reader, Department of Oral Medicine and Radiology, Chhattisgarh Dental College and Research Institute, Staff Quarter No. 8/16, College Campus, PB No. 25, Sundra, Rajnandgaon, Chhattisgarh-491441, India e-mail: fm_debta@rediffmail.com

ABSTRACT

Photochemotherapy (PUVA) has become a useful alternative in dermatologic therapy. Start from historical date up to modern era the safe and useful modes of PUVA has been documented in many immunological disorder. Despite side effect and potential long-term hazards photochemotherapy shown in clinical routine as an effective alternative to conventional immunosuppressive therapy. A wide range of diverse field for its possible utility provides an alternative armamentarium in many immunological disorder for dermatologist and also for oral diagnostician.

Keywords: Psoralens, UVA, PUVA.

INTRODUCTION

Photochemotherapy is the treatment method in which radiation of appropriate wavelength is used to induced a therapeutic response in the presence of a photosensitizing drug. The radiation must be absorbed by a target molecule—a chromophor, which is an exogenous drug in photochemotherapy. Ultraviolet and visible radiation are used therapeutically in dermatology; UVC—100 to 290 nm is absorbed by the ozone layer, UVB—292 to 320 nm for phototherapy, UVA—320 to 400 nm for photochemotherapy (PUVA, psoralens plus UVA) and visible light—400 to 800 nm for photodynamic therapy.1,2

History of Photochemotherapy (PUVA)

Photochemotherapy using plant extracts and subsequent exposure to sunlight as a form of treatment in vitiligo has been used since ancient times, as early as 1500 BC in India and Egypt. However the first scientific use of phototherapy dates back to 1948 AD, when Fahmy et al in the University of Cairo, isolated three chemical compounds from the fruit of a plant Ammi majus. They named these three compounds as Ammoidin (8-methoxypsoralen), Ammidin and Majudlin (5-methoxypsoralen).3 Lerner in 1953 further documented the role of psoralens photochemotherapy in patients with vitiligo.4 The first synthetic psoralens and trimethylpsoralen (TMP) was introduced in 1964 and used for treatment of vitiligo.5 Parrish et al reported successful treatment of severe psoriasis with 8-methoxypsoralen (p) with UVA and coined by acronym PUVA.1,2 The modern form of photochemotherapy using high intensity UV-A sources was introduced at the Harvard – Massachusetts General Hospital Dermatology Laboratories.5

Chemistry

Psoralens belongs to the furocoumarin class of compounds, which are derived from fusion of furan with a coumarin found naturally in certain plant species or synthesized in vitro. It occur naturally in many plant including many limes, lemons and parsnips. Among the three psoralens, the trimethyl derivative only synthesized in vitro, 8-methoxypsoralens (methoxysalens), 5-methoxypsoralens (Bergapten) and 4, 5, 8 trimethylpsoralens (trioxsalen); the trimethyl derivative is not found naturally and is synthesized in vitro.5

Pharmacokinetic

The psoralens are absorbed rapidly after oral administration. Absorption of psoralens is dependent upon many factors namely the formulation of drug, coexistent food intake, first pass effect in liver and individual differences in absorption of drug but this accounts partly for the rare cases, which not gives respond expectedly to PUVA therapy in the usual dose.7,8 After absorption psoralens get distributed to all tissues and are excreted in the urine with in an average of 12 hours. Peak levels of psoralens in the blood after oral intake are seen 1 to 8 hours with a mean of 2 hours. This forms the basis for giving UV radiation after 2 hours of oral intake in PUVA therapy.8 Photosensitivity on average is maximal 1 to 2 hours after ingestion of methoxysalen. Liquid formulation are superior to the previously used crystalline preparation and produce more rapid, higher and more reproducible peak serum level. Methoxysalen has a serum half life approximately 1 hour but the skin remains sensitive to light to 8 to 12 hours. Despite widespread distribution of drug throughout the body, it is activated on the skin, where the UVA penetrates. When psoralens are applied topically they rapidly penetrate the skin and can be detected in the urine after about 4 hours.9
Mechanism

The action spectrum for oral PUVA is between 320 to 400 nm. Two type of reaction are involved in causing photosensitivity after photochemotherapy. One, an anoxic reaction that affects cellular DNA with formation of photo adducts that may inhibit the proliferation of epidermal cells and induce apoptosis, and the other an oxygen dependent reaction that give rise to free radicals and reactive oxygen that may damage membrane by lipid per oxidation. PUVA promotes melanogenesis in normal skin, increased pigmentation results from the transfer of melanosomes from melanocytes to epidermal cells, however there is no change in the size of melanosomes or in their distribution.10-14 In vitiligo, a stimulatory effect on melanocytes secondary to action on c-AMP pathway is postulated. There is an effect on DNA synthesis, proliferation of cells, immunological alternation and on the biosynthesis of prostaglandin in the skin. Psoralen act much more on cells that are actively dividing than on resting cells. This explain why they are effective only in the active stage of sclerosis and not in the fibrotic stage. Action on actively dividing or activated immune cells especially on T cell, explain their action in immune mediated disease like psoriasis, lichen planus, graft versus host disease.10,15-18

Fundamentals of PUVA Therapy

The therapy usually consists of oral administration or topical application of a psoralens followed by exposure to ultraviolet-A light (320-400 nm wavelength) at a time when the concentration of the psoralens in the tissues is adequate. The main aim of PUVA therapy is to bring about a controlled, persistent phototoxic reaction. For this purpose UV-A sources having an action spectrum 320 to 380 nm is given. In case of oral PUVA therapy the drug is given usually on an empty stomach and the patient is exposed to UV light after 1 to 3 hours, the initial UV-A dose determined either by skin typing or by phototoxicity testing. In case of phototoxicity testing the patient’s minimal phototoxic dose (MPD) is first calculated and this usually forms the initial doses of UV-A exposure. MPD is defined as the least possible dose of UV-A that causes a barely perceptible erythema of skin in an individual patient. The UV-A dose is then sequentially increased as per the protocol followed (European, American or any other). The frequency of UV-A exposure is either 3 or 4 times per week and this frequency of treatment is usually continued till the patient goes into remission. After attaining remission, especially in immune mediated diseases like psoriasis, lichen planus, etc. the frequency of exposure is then reduced and the last UV-A does is continued during the maintenance therapy. The duration of this maintenance therapy depends upon the disease being treated and its propensity to relapse. With topical treatment the psoralen rapidly penetrates the epidermis, within approximately 10 minutes in normal skin and presumably faster in psoriatic skin.11 Frequency of treatment remains the same as in oral PUVA, i.e. about 3 to 5 times per week. Several regimens exists for PUVA therapy, the most commonly being administration of 8-MOP 0.6 mg/kg body weight, on alternate days followed 2 hours or later by exposure to UV range.19 A lotion containing 1% Methoxysalen (oxsoralen) also is available for topical application. It can be diluted for bath water delivery, a method that produce low systematic psoralen level. A combination of etretinate and PUVA (RE-PUVA) is popular.20 It causes faster clearing of skin lesions with fewer side effects.6,12 In both American and European multicenter cooperative studies of PUVA for the treatment of psoriasis, initial success rates close to 90% were achieved.12

Indication of PUVA therapy—PUVA finds its use in a number of cutaneous and systematic disease at present. The disorder in which PUVA has been used till date include: (1) Psoriasis specially in cases with greater than 20% body surface area involvement (2) Vitiligo (3) Lichen planus (4) Cutaneous T-cell lymphoma (5) Morphea (6) Chronic graft vs host disease (7) Dermatitis herpetiformis (8) Histocytosis X (9) Prevention of photosensitive disorders like solar urticaria, chronic actinic dermatitis, poly morphic light eruption. Other disorders like systemic sclerosis, scleromyxedema and mixed connective tissue disease. PUVA can induce melanocyte pigmentation in vitiligo, resulting in cosmetic pigmentation.6,12,21

Contraindication

1. Pregnancy and lactation
2. Severe liver disease
3. Renal failure
4. Xeroderma pigментosum
5. SLE or porphyrias
6. Family history of melanoma.6

Toxicity and Monitoring

The major acute side effects of PUVA include nausea, blistering and painful erythema.22 PUVA-induced inflammation is more delayed and reaching a peak of 48 to 72 hours after exposure. Chronic effects occur within the skin like actinic keratosi, photo aging, hypertrichosis, lichenoid eruption and lichen planus, development of multiple keratoacanthoma, bullous pemphigoid, koebhner phenomenon, systemic lupus erythematous may develop during PUVA therapy or existing potential lesion may exacerbated.23-27 Squamous cell carcinomas occur as the most potential hazards of PUVA therapy.6,28

Extracorporeal Photophoresis

Extracorporeal photophoresis (ECP) was introduced in 1987 as a treatment option for cutaneous T cell lymphoma. It is a variant of photochemotherapy in which irradiation of selective blood fractions is done outside the human body in presence of a psoralen. The process combines leukopheresis with either oral administration of 8-MOP or injection of liquid 8-MOP into the leukocyte rich fraction of blood followed by selective irradiation of the leukocyte fraction. In case the psoralen (8-MOP) is administered orally, its level in the blood needs to be measured at the time of the procedure and this level should ideally be more than 50 micrograms per milliliter of blood. ECP has been found to be an effective therapeutic option in a wide range of
cutaneous disorder like atopic dermatitis, cutaneous T-cell lymphoma, bullous pemphigoid, graft versus host disease, epidermolysis bullosa aquisa, morphea, erosive lichen planus, pemphigus vulgaris and foliaceous, psoriasis, scleroderma, and in systemic disorder like SLE, systemic sclerosis, dermatomyositis, rheumatoid arthritis, chronic HCV infection, multiple sclerosis, leukemias and lymphomas.29,30

**CONCLUSION**

The present overviews regarding PUVA provides a sound ideas in over all aspects from historical age to morden era as one of the alternative effective therapy for many immunological disorder and systematic disease. To be on safer side, steps should be taken to lower the dose of PUVA by changing the dose schedule, reducing the unnecessary maintaining dose and by adding a psoralens, or oral retinoides to the regimen. PUVA therapy is best avoided in patients with a history of skin cancer or those, who require a higher maintaining dose.

**REFERENCES**