METHOXSALEN-UV-A THERAPY OF PSORIASIS

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Some drugs have pharmacologic effects when they interact with light. Certain low-molecular-weight, fluorescing chemicals of tricyclic structure absorb ultraviolet or visible light, providing energy for photochemical reactions. Nuclear, cytoplasmic, and cell membrane alterations can be induced in living cells; increasing doses of drug or light can cause death of bacteria, viruses, one-celled organisms, and tissue culture cells. Systemic or topical administration of these chemicals and subsequent exposure to the proper waveband of light can lead to erythema of normal human skin.

Photochemotherapy defines the combination of light and drug to bring about a beneficial effect. Usually, in the doses used, neither the drug alone nor the light alone has any significant biologic activity; it is only the combination of drug and light which is therapeutic. PUVA (psoralen and UV-A) is a term used to describe oral administration of psoralen and subsequent exposure to UV-A (long-wave ultraviolet light, 320–400 nm).

Certain furanocoumarins, called psoralens, are tricyclic structures which may be considered derivatives of coumarin (Fig. 1). Although psoralens can be synthesized by adding a furan ring on a suitably substituted coumarin derivative, the most photoactive psoralens are found in nature in plants and microorganisms. Although the major absorption spectrum for psoralen lies between 210 and 330 nm, the action spectrum for photosensitization and photochemical changes is within wavelengths longer than 320 nm. In the presence of long-wave ultraviolet radiation (320–400 nm, UV-A) these substances induce a reversible cutaneous photosensitivity manifested by what appears as an augmented sunburn reaction and subsequent hyperpigmentation [1]. The two psoralens commercially available in the United States, methoxsalen (8-methoxypsoralen, 8-MOP) and trimethylpsoralen (4,5',8-trimethylpsoralen, TMP) are very potent photoactive drugs causing redness of normal human skin in $\mu g/cm^2$ quantities applied topically if the skin is subsequently exposed to UV-A. When given orally, 8-MOP is much more erythemogenic and melanogenic than TMP for equivalent amounts of drug and UV-A.

It has been shown that 8-MOP and subsequent UV-A exposure leads to inhibition of DNA synthesis [2–4]. Photoexcited psoralen molecules transfer the absorbed ultraviolet energy to DNA. Psoralen covalently binds to DNA forming monofunctional photoadducts with thymine bases and bifunctional interstrand cross-links between opposite pyrimidine base pairs [5–7]. Topical psoralens and UV-A exposure leads to regression of psoriatic plaques [8–10].

This report summarizes the cutaneous effects of oral administration of 0.6 mg/kg of 8-MOP and subsequent exposure to UV-A. This drug–light combination causes erythema and pigmentation of normal skin and has beneficial effects on psoriasis.

The PUVA erythema reaction can be severe and is the limiting factor during treatment. While psoriasis treatment courses may require 10 to 20 PUVA treatments, redness and pigmentation occur after a single PUVA exposure if doses of drug and light are adequate. The occurrence and degree of redness, however, is related to dose of both drug and light and is predictable. The erythema which results from PUVA differs from sunburn in its time course. PUVA redness may be absent or just beginning at 12 to 24 hr after ultraviolet exposure (when UV-B or sunburn erythema is normally at its peak), and may peak at 48 to 72 hr or later. Since skin diseases can be treated at drug-light exposure doses which are less than the doses causing severe redness, careful dosimetry permits relatively safe PUVA treatments.

The pigmentation which results from PUVA appears histologically and morphologically to be similar to normal melanogenesis (delayed tanning). Pigmentation maximizes about 5 to 7 days after PUVA exposure and lasts weeks to months. A patient’s genetic ability to tan (facultative tanning) dictates the degree and limits of delayed pigmentation. Baseline melanization (constitutive tanning) along with sunburn history, number of previous sun or PUVA exposures, and thickness of skin influence the amount of UV-A energy needed to penetrate into the skin to cause photobiologic reactions. In general, one or two erythemogenic PUVA exposures can stimulate melanogenesis to the same degree as can multiple UV-B or sun exposures.

Redness, pigmentation, and therapeutic responses to PUVA depend on (1) the dose of drug,
(2) the time interval between ingestion and irradiation (preirradiation period), and (3) the dose of light. Drug dose of 8-MOP is usually 0.6 mg/kg. Doses significantly higher than this may cause nausea and light-headedness in some patients. The preirradiation period is 2 hr because the drug is maximally susceptible to photoactivation at that time (Fig. 2). It is important to note that the skin remains photosensitive to UV-A for 6 to 8 hr after ingestion. If prolonged sun exposure occurs, persons are at risk of exaggerated erythema from solar UV-A during the 6- to 8-hr period after ingestion.

The dose of UV-A is given in joules/cm², a joule being 10⁷ ergs. When speaking of energy dose one should also specify the unit of area and specify which wavelengths, frequency, or photon energy are being used. An example of a dose used to begin therapy in a Caucasian is 3.5 joules/cm² of UV-A (320-400 nm). Initial UV-A exposure doses in Caucasians actually vary from 1.0 to 5.0 joules/cm², depending on melanization and sunburn history. Exposure doses must be increased as tanning occurs.

The ideal light source is one which has high-intensity UV-A and emits most or all of wavelengths below 320 nm. High-intensity UV-A is needed to make treatment times shorter and more practical for the patient. Omission of the shorter, more eryhemogenic wavelengths avoids the discomfort and confusion of superimposing a sunburn reaction on the PUVA erythema reaction. Wavelengths shorter than 320 nm are as much as 1000 times more efficient at causing erythema of normal Caucasian skin than is UV-A. Orally administered psoralens, in the dosage used for methoxsalen photochemotherapy, reduce this difference in eryhemogenic potential to about 100-fold. The shorter wavelengths remain much more eryhemogenic despite large doses of psoralens.

To insure patient comfort, excessive amounts of visible light and infrared radiation must also be omitted. Ideal light systems must also be large enough to radiate all exposed skin surfaces at once. The intensity should be uniform at varying distance from the light source so that all exposed skin surfaces receive the same dose of ultraviolet light. Accurate and reliable means of metering and delivering doses of light should be built into the treatment system.

In initial studies performed in Boston [11] and in Vienna [12] and in subsequent treatment of over 300 additional patients (unpublished data), repeated PUVA exposures (8 to 24) caused complete clearing of psoriasis in over 90% of patients. Another 8% of patients were more than 95% improved, and 2% of patients were not significantly improved. In 54 bilateral comparison studies, PUVA was seen to be superior to conventional UV-B phototherapy. Maintenance therapy kept 85% of patients free of psoriasis for up to 400 days [12].

Severe pruritus and marked redness in localized areas were seen often during the early phases of oral psoralen photochemotherapy but became less severe and less frequent as more experience was gained and dosimetry became more exact. In treatment of the last 100 patients, therapy has not been interrupted because of itching or redness, although in 2% of patients both were a problem. No abnormalities in alkaline phosphatase, serum glutamic oxaloacetic transaminase, complete blood count, urinalysis, bilirubin, or blood urea nitrogen which could be attributed to photochemotherapy were noted in any patient.

Because the effects are limited to the skin irradiated by UV-A, PUVA combines the ease of administration of oral medication with the safety of topical medication. However, scalp and body folds do not respond if light does not reach those areas. The scalp of bald patients or persons with short haircuts responds well. Patients do not have to be hospitalized for therapy. Infrequent treatments are required (2 to 3 times per week) and it appears that weekly maintenance keeps most patients free of psoriasis for months. While the acute limiting factor of the PUVA reaction is erythema, this can be avoided by careful dosimetry.

Large doses of 8-MOP and long exposures to high-intensity UV-A causes skin cancer and cata­racts in laboratory animals. These effects have not been seen in man in over 20 years of use of methoxsalen and UV-A for treatment of vitiligo. These side effects may not be produced in humans in the dose of drug and light used or they may be so infrequent that they have not come to the atten-

Fig. 1. Psoralen.

Fig. 2. Relative UV-A photosensitivity after ingestion of 8-MOP. This relative photosensitivity is determined by delivering a fixed amount of UV-A at various times after ingestion of 8-MOP and comparing the degree of erythema seen at 48 hr after radiation.
tion of the clinician. Careful observation and prospective studies are needed. It may also be that repeated phototoxic reactions over many years may lead to actinic changes in the skin, especially skin which pigments poorly or not at all. On the other hand, patients who tan well may actually be protected by PUVA; the striking melanogenesis, by acting as a sunscreen, may permit less cumulative solar-induced changes over many decades. The physician must weigh the theoretical risks and the psychological stress of psoriasis against the benefits of effective photochemotherapy.

REFERENCES
