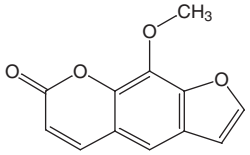
Methoxsalen with Ultraviolet A Therapy (PUVA)*

Known to be a human carcinogen
First Listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

Methoxsalen (8-methoxypsoralen) with ultraviolet A (UVA) long-wave therapy (PUVA) is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans. A cohort study of 1,380 psoriasis patients treated with PUVA reported that the risk of squamous-cell cancer increased with increasing exposure to PUVA; exposure to high doses of PUVA increased the risk of cancer by more than 50 fold. The risk was independent of any possible confounding from treatment with ionizing radiation or coal tar. An association between basal-cell cancer and PUVA exposure also was observed, although the risk estimate at high exposure was lower (four fold) than that observed for squamous-cell cancer. Increased risks of skin cancer were not reported in two smaller cohort studies; however, one study may not have had power to observe an effect because of the low dose used, and there were only 94 patients in the second study. A case-control study also reported an increased risk of skin cancer among psoriasis patients treated with PUVA. Supporting the association between skin cancer and PUVA exposure are several case reports of basal-cell cancer, squamous-cell cancer, and malignant melanoma in patients treated with PUVA for psoriasis or mycosis fungoides (a form of lymphoma primarily affecting the skin). Methoxsalen alone did not affect the incidence of skin cancer over two years in two small randomized clinical trials evaluating whether methoxsalen would protect against sunlight-induced skin cancer (by increasing pigmentation and cornification of the skin) (IARC 1980, 1982, 1987).

There is sufficient evidence of carcinogenicity of PUVA in experimental animals. Methoxsalen administered in the diet, by intraperitoneal injection, or by skin application in combination with ultraviolet light induced epidermal and dermal skin tumors in mice. These included epidermal papillomas and carcinomas, squamous-cell carcinomas, fibrosarcomas, lymphosarcomas, basal-cell carcinomas, and hemangiomas. Some squamous-cell and basal-cell carcinomas metastasized. Tumors of the eye (epidermal fibrosarcomas and squamous carcinomas) and ear regions (epidermal fibrosarcomas, squamous carcinomas) were observed following intraperitoneal administration of methoxsalen to female mice (IARC 1980, 1987).

Properties

Methoxsalen is a derivative of psoralen and belongs to the furocoumarin class of compounds. It has a molecular weight of 216.2 and occurs as a white to cream-colored odorless solid that forms needle-like crystals. Its melting point is 148°C. Methoxsalen is practically insoluble in cold water but is soluble in acetone, acetic acid, propylene glycol, and benzene, and sparingly soluble in boiling water and ether. It is sensitive to air and light and is easily hydrolyzed (IARC 1980, HSDB 2003).

Methoxsalen readily absorbs ultraviolet light, particularly UVA wavelengths (320 to 400 nanometers). It is a photosensitizing agent that can produce phototoxic erythema (a reaction similar to sunburn) when applied to the skin followed by excess exposure to UVA radiation (see separate profile "Ultraviolet Radiation Related Exposures" for properties of ultraviolet radiation). Chronic reactions may result in hyperpigmentation and skin thickening. The UVA radiation causes a photochemical reaction that results in DNA adducts forming between methoxsalen and pyrimidine bases (Rice and Cohen 1996).

Due to interindividual differences in phototoxic response, determination of the initial UVA dose is very important. There are two predominate methods to determine the initial UVA dose. Under one protocol, the initial UVA dose is determined by assessing an individual's minimal phototoxic dose (MPD). MPD is the dose of UVA radiation that, when given with the appropriate dose of methoxsalen, produces an erythema on the UVA-exposed skin. In practice, MPD is determined by exposing small areas of the thigh region to increasing UVA doses of 0.5 to 9 J/cm^2. The other method relies solely on the patient's skin type to determine initial UVA dose, with fairer skin types that easily burn receiving lower doses than darker skin types that are less prone to burn. Following the initial dose, therapy is usually repeated two to four times per week with a 0.5 to 2.0 J/cm^2 increase in UVA radiation dose per treatment. Generally, the dose of methoxsalen does not increase for an individual during treatment (Kostović *et al.* 2002).

Use

The first known uses of psoralen-containing plant extracts in photochemotherapy to treat vitiligo date back to 1500 B.C. in Egypt and India. The acronym "PUVA" was first coined in 1974 following successful treatment of severe psoriasis using psoralen (P) (specifically 8-methoxypsoralen) and UVA. Methoxsalen is now used in combination with UVA in the treatment of vitiligo, severe psoriasis, atopic dermatitis, alopecia areata, lichen planus, urticaria pigmentosa, mycosis fungoides, cutaneous T-cell lymphoma, and some forms of photosensitivity (Wyatt *et al.* 2001, MEDLINEplus 2004).

There are topical, bath, oral, and extracorporeal (outside the body) treatments available by prescription only. The topical solution may be used to treat vitiligo. It is applied to the affected area and allowed to dry for several minutes before a second application. The treated area is exposed to UVA about 2 hours later. For treatment to small areas (e.g., hands and feet) a bathwater PUVA may be used; the area to be treated is soaked in a dilute solution of methoxsalen for 30 minutes and then immediately exposed to UVA. Oral preparations include both hard and soft gelatin capsules that may be used to treat mycosis fungoides, psoriasis, and vitiligo. The oral preparations may be given two to three times per week with at least 48 hours between doses. Methoxsalen also is used along with UVA to treat white blood cells to control skin problems caused by cutaneous T-cell lymphoma, a cancer of the lymph system. The white blood cells are removed from the blood and treated in a process called photopheresis. After treatment the blood cells are returned to the body (MEDLINEplus 2004).

Production

Methoxsalen is produced naturally by several plants (e.g., limes, celery, figs, parsnips, and others) found in both temperate and tropical regions (Drugge and Dunn 2003). It was first marketed in the United States in 1955, and in 1980, one U.S. company reportedly produced the chemical, but no production data were available (IARC 1980). There are no longer any U.S. producers, but there were at least 11 domestic suppliers in 2003 (ChemSources 2003, SRI 2003). Two U.S. pharmaceutical companies with four drug products approved by the U.S. Food and Drug Administration (FDA) containing methoxsalen as the active ingredient were identified in 2003 (FDA 2003).

Exposure

The primary routes of potential human exposure to methoxsalen are dermal contact and ingestion. Individuals with skin diseases (e.g., vitiligo and severe psoriasis) may be exposed to PUVA during treatment. Methoxsalen rapidly penetrates the epidermis and dermis upon contact with the skin. For medicinal effectiveness, both oral and topical administration requires subsequent exposure to ultraviolet light.

Methoxsalen formulations are available in 10 mg capsules (hard and soft), 1% topical solutions, and 0.02 mg/mL injectable solutions (FDA 2003). Oral dosage (adults and children 12 years of age or older) is 0.4 to 0.6 mg/kg body weight three times per week and is given 1.5 to 4 hours before UVA exposure (the action spectrum for PUVA is 320 to 400 nanometers) (Wyatt *et al.* 2001, MEDLINEplus 2004). No information was found regarding the number of people treated with PUVA therapy.

Potential occupational exposure to methoxsalen may occur during preparation, formulation, administration, or application of the pharmaceutical formulations. Occupational exposure to ultraviolet light also may occur during therapy or subsequent exposure to sunlight.

Regulations

CPSC

Any orally-administered, prescription drug for human use requires child-resistant packaging

FDA

Regulated as a prescription drug/therapy

*No separate CAS registry number is assigned to methoxsalen (methoxypsoralen) with ultraviolet A (PUVA).

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