Methoxsalen with Ultraviolet A Therapy

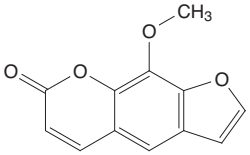
CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Methoxsalen is also known as 8-methoxypsoralen (CAS No. 298-81-7)

Methoxsalen with ultraviolet A therapy is also known as PUVA



Carcinogenicity

Methoxsalen (psoralen) with ultraviolet A (UVA) long-wave therapy (PUVA) is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

A cohort study of 1,380 psoriasis patients treated with PUVA found that the risk of skin cancer (squamous-cell carcinoma) 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 by treatment with ionizing radiation or coal tar. An association between basal-cell carcinoma and PUVA exposure also was observed; however, the estimated risk at high exposure was fourfold lower than that observed for squamous-cell carcinoma. Increased risks of skin cancer were not reported in two smaller cohort studies; one study included only 94 patients, and the other used a low dose and may not have had sufficient statistical power to detect an effect. 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 skin cancer (basal-cell and squamous-cell carcinoma and malignant melanoma) in patients treated with PUVA for psoriasis or mycosis fungoides. In two small randomized clinical trials evaluating whether methoxsalen would protect against sunlight-induced skin cancer (by increasing pigmentation and cornification of the skin), methoxsalen administered alone for over two years did not affect the incidence of skin cancer (IARC 1980, 1982, 1987).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of PUVA from studies in experimental animals. Methoxsalen administered in the diet, by intraperitoneal injection, or by dermal application in combination with ultraviolet light caused benign and malignant epidermal and dermal skin tumors in mice. These included epidermal papilloma and carcinoma, squamous-cell carcinoma, fibrosarcoma, lymphosarcoma, basal-cell carcinoma, and hemangioma. Some squamous-cell and basal-cell carcinomas metastasized. Malignant tumors of the ears and the eye region (epidermal fibrosarcoma and squamous-cell carcinoma) were observed in female mice following intraperitoneal administration of methoxsalen and exposure to ultraviolet light (IARC 1980, 1987).

Studies on Mechanisms of Carcinogenesis

Methoxsalen readily absorbs ultraviolet light, particularly UVA wavelengths (320 to 400 nm). As a photosensitizing agent, it can produce phototoxic erythema (a reaction similar to sunburn) when skin to which it has been applied receives excess exposure to UVA. Chronic reactions may result in hyperpigmentation and skin thickening. UVA causes a photochemical reaction that results in formation of adducts between methoxsalen and the pyrimidine bases of DNA (Rice and Cohen 1996).

Properties

Methoxsalen belongs to a group of drugs known as psoralen derivatives and exists as white to cream-colored fluffy crystals at room temperature (NTP 1989). It is practically insoluble in water, sparingly soluble in ether and liquid petrolatum, soluble in boiling alcohol, acetone, benzene, acetic acid, fixed vegetable oils, and propylene glycol, and freely soluble in chloroform. Methoxsalen is easily hydrolyzed and is unstable in the presence of air and light (Akron 2009). Physical and chemical properties of methoxsalen are listed in the following table. (For properties of ultraviolet radiation, see the profile for Ultraviolet Radiation Related Exposures.)

Property	Information
Molecular weight	216.2[a]
Density	1.539 g/cm^3[b]
Melting point	148°C[a]
Boiling point	415°C[b]
Log K_{ow}	2.14[c]
Water solubility	0.0476 g/L at 30°C[c]
Vapor pressure	4×10^{-7} mm Hg at 25°C[b]

Sources: [a]HSDB 2009, [b]Akron 2009, [c]ChemIDplus 2009.

Use

Psoralen-containing plant extracts were first used in photochemotherapy to treat vitiligo in Egypt and India as far back as 1500 B.C. The acronym PUVA was coined in 1974 following successful treatment of severe psoriasis with 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, cutaneous T-cell lymphoma, and some forms of photosensitivity (Wyatt *et al.* 2001).

Topical, bath, oral, and extracorporeal (outside the body) treatments are available by prescription only. To treat vitiligo, the topical solution is applied to the affected area and allowed to dry for several minutes before a second application, and the treated area is exposed to UVA about 2 hours later. For bath treatment of small areas (e.g., hands and feet), 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 hard and soft gelatin capsules for treatment of mycosis fungoides, psoriasis, and vitiligo; they may be given two or 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 lymphatic system. The white blood cells are removed from the blood, treated in a process called "photopheresis," and returned to the body (LLS 2006).

Production

Methoxsalen is produced naturally by several plants (e.g., limes, celery, figs, and parsnips) found in both temperate and tropical regions (Drugge and Dunn 2003). It was first marketed in the United States in 1955. In 1980, one U.S. company reportedly produced the chemical, but no production data were available (IARC 1980). In 2009, no U.S. producers of methoxsalen were identified (SRI 2009), but it was available from 14 U.S. suppliers (ChemSources 2009), and four drug products approved by the U.S. Food and Drug Administration

containing methoxsalen as the active ingredient were produced by two U.S. pharmaceutical companies (FDA 2009).

Exposure

The primary routes of human exposure to methoxsalen are dermal contact and ingestion. Individuals with skin diseases 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 require subsequent exposure to UVA (at 320 to 400 nm). Methoxsalen formulations are available in 10-mg capsules (hard and soft), 1% topical solutions, and 0.02 mg/mL injectable solutions (FDA 2009). The oral dosage (for adults and children aged 12 years or older) is 0.4 to 0.6 mg/kg of body weight, given 1.5 to 4 hours before UVA exposure (Wyatt *et al.* 2001). Because of differences in phototoxic response, the initial UVA dose must be determined for each individual. Under one protocol, the initial UVA dose is based on an individual's minimal phototoxic dose (the dose that when given with the appropriate dose of methoxsalen produces erythema), which is determined by exposing small areas of the thigh to UVA doses increasing from 0.5 to 9 J/cm^2. Alternatively, the initial UVA dose is based on the patient's skin type; patients with fairer skin that burns easily receive lower doses than those with darker skin that is less prone to burn. Following the initial dose, therapy usually is repeated two to four times per week, and the UVA dose is increased by 0.5 to 2.0 J/cm^2 per treatment. Generally, the dose of methoxsalen is not increased during treatment (Kostović *et al.* 2002). No information was found regarding the number of people treated with PUVA therapy.

Occupational exposure to methoxsalen may occur during preparation, formulation, administration, or application of the pharmaceutical products. Individuals occupationally exposed to methoxsalen may also be exposed to ultraviolet light during therapy or during subsequent exposure to sunlight.

Regulations

Consumer Product Safety Commission (CPSC)

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

Food and Drug Administration (FDA, an HHS agency)

PUVA is regulated as a prescription drug or therapy.

Guidelines

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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