Methoxsalen *(BAN)*

Ammoidin; Amoidina; Methoxalenum; 8-Methoxypsoralen; Metoksaleeni; Metoksalen; Metoxalen; Metoxaleno; Metoxipsoraleno; 8-MOP; Xanthotoxin; Xantotoxina. 9-Methoxyfuro[3,2-*g*]chromen-7-one; 9-Methoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one.

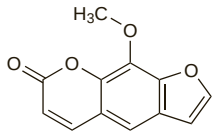
Метоксален

$C_{12}H_8O_4$ = 216.2.

CAS — 298-81-7.

ATC — D05AD02; D05BA02.

ATC Vet — QD05AD02; QD05BA02.



Pharmacopoeias. In *Jpn* and *US*.

USP 31 (Methoxsalen). White to cream-coloured, odourless, fluffy, needle-like crystals. Practically insoluble in water; sparingly soluble in boiling water and in ether; soluble in boiling alcohol, in acetone, in acetic acid, in propylene glycol, and in benzene; freely soluble in chloroform. Protect from light.

Adverse Effects

Methoxsalen given orally commonly causes nausea and less frequently mental effects including insomnia, nervousness, and depression.

Photochemotherapy or PUVA (see under Uses and Administration, below) may cause pruritus and mild transient erythema. Other effects include oedema, dizziness, headache, vesiculation, bulla formation, acneform eruption, and severe skin pain. Overexposure to sunlight or UVA radiation may produce severe burns in patients being treated with psoralens. Hypertrichosis, pigmentation alterations of skin or nails, and onycholysis, have also been reported. PUVA can produce premature ageing of the skin, and may be associated with an increased risk of malignant cutaneous neoplasms.

Carcinogenicity. See under Effects on the Skin, below.

There has been concern about a possible increased risk of noncutaneous malignancies associated with PUVA. However, a long-term study of 1380 patients followed for 20 years reported no overall increase in solid malignancies, lymphoma, or leukaemia.[1]

1. Stern RS, Väkevä LH. PUVA Follow-up Study. Noncutaneous malignant tumors in the PUVA follow-up study: 1975–1996. *J Invest Dermatol* 1997; **108:** 897–900.

Effects on the eyes. Free methoxsalen has been detected in the lens of the eye for at least 12 hours after oral doses.[1] It may become integrated into the structure of the lens if there is exposure to UV light, promoting cataract formation in patients who fail to wear suitable eye protection for 12 to 24 hours after methoxsalen ingestion.[2] However, provided that eye protection is used there appears to be no significant dose-dependent increase in the risk of cataract formation,[3] although a higher risk of developing nuclear sclerosis and posterior subcapsular opacities has been noted in patients who have received more than 100 treatments.[4] Other ocular effects include dose-related transient visual-field defects reported in 3 patients receiving PUVA therapy.[5] Psoralens may also increase the sensitivity of the retina to visible light.[6]

1. Lerman S, *et al.* Potential ocular complications from PUVA therapy and their prevention. *J Invest Dermatol* 1980; **74:** 197–9.
2. Woo TY, *et al.* Lenticular psoralen photoproducts and cataracts of a PUVA-treated psoriatic patient. *Arch Dermatol* 1985; **121:** 1307–8.
3. See J-A, Weller P. Ocular complications of PUVA therapy. *Australas J Dermatol* 1993; **34:** 1–4.
4. Stern RS, *et al.* Ocular findings in patients treated with PUVA. *J Invest Dermatol* 1985; **85:** 269–73.
5. Fenton DA, Wilkinson JD. Dose-related visual-field defects in patients receiving PUVA therapy. *Lancet* 1983; **i:** 1106.
6. Souêtre E, *et al.* 5-Methoxypsoralen increases the sensitivity of the retina to light in humans. *Eur J Clin Pharmacol* 1989; **36:** 59–61.

Effects on the hair. Hypertrichosis was noticed in 15 of 23 female patients receiving PUVA therapy compared with 2 of 14 patients treated with UVA alone.[1]

1. Rampen FHJ. Hypertrichosis in PUVA-treated patients. *Br J Dermatol* 1983; **109:** 657–60.

Effects on the immune system. PUVA therapy appears to have immunosuppressive effects and inhibits lymphocytes, polymorphonuclear leucocytes, and Langerhans' cells.[1-3] It is capable of inducing antinuclear antibody formation and a syndrome similar to systemic lupus syndrome has developed during treatment.[4,5] An immunological basis has also been suspected for the development of nephrotic syndrome in one patient who received PUVA therapy.[6]

See also Hypersensitivity, below.

1. Farber EM, *et al.* Long-term risks of psoralen and UV-A therapy for psoriasis. *Arch Dermatol* 1983; **119:** 426–31.
2. Morison WL, *et al.* Abnormal lymphocyte function following long-term PUVA therapy for psoriasis. *Br J Dermatol* 1983; **108:** 445–50.
3. Chang A, *et al.* PUVA and UVB inhibit the intra-epidermal accumulation of polymorphonuclear leukocytes. *Br J Dermatol* 1988; **119:** 281–7.
4. Bruze M, *et al.* Fatal connective tissue disease with antinuclear antibodies following PUVA therapy. *Acta Derm Venereol (Stockh)* 1984; **64:** 157–60.
5. Bruze M, Ljunggren B. Antinuclear antibodies appearing during PUVA therapy. *Acta Derm Venereol (Stockh)* 1985; **65:** 31–6.
6. Lam Thuon Mine LTK, *et al.* Nephrotic syndrome after treatment with psoralens and ultraviolet A. *BMJ* 1983; **287:** 94–5.

Effects on the skin. ***MALIGNANT NEOPLASMS.*** Squamous cell carcinoma, basal cell carcinoma, keratoacanthoma, actinic keratosis, Bowen's disease, and malignant melanoma have all been reported during or after cessation of PUVA.[1-3] There have been several large long-term follow-up studies to assess the risk of **non-melanoma** skin cancer in patients receiving PUVA therapy. Early studies from Europe found no clear evidence that PUVA was independently carcinogenic but did find that previous treatment with arsenic, methotrexate, or ionising radiation increased the incidence of skin tumours.[4] Studies from the USA have found an increase in the incidence of basal cell carcinoma and squamous cell carcinoma independent of other treatment,[5] which was dose-related in some studies.[6] Male genitalia appeared to be particularly susceptible.[7] It has been suggested that the differences between the findings might be due to the fact that in Europe higher and fewer doses are used and the median total dose employed may be only 29% of that used in the USA.[8] However, further studies from northern Europe also found a dose-related increase in the risk of developing squamous cell carcinomas.[9-11] One small series suggested that about 50% of the recipients of high-dose PUVA went on to develop squamous cell carcinomas or premalignant lesions.[12] While some European workers have findings that confirm the increased susceptibility of the male genitalia[13] others have failed to find any such evidence.[14,15] Ongoing surveillance of patients is encouraged as US data[16,17] show the risk of skin cancers and genital tumours to persist long-term after stopping PUVA therapy. A few patients have gone on to develop metastatic disease.[18,19]

There are anecdotal reports of **malignant melanomas** occurring in patients who had received PUVA. A prospective study[20] in 1380 patients with psoriasis who were first treated with PUVA in 1975 or 1976 found that the risk of melanoma increases about 15 years after the first treatment with PUVA and that the risk was increased especially in patients who had received 250 treatments or more. The authors suggested that long-term PUVA should therefore be used with caution, especially in younger patients. Further follow-up of this group[21] found the incidence of melanoma to increase over time. However, a similar follow-up study[11] of 4799 patients treated with PUVA found no increase in the risk for malignant melanoma. Comparing their findings with the earlier study, the authors suggested that the results might differ because one-fifth of their cohort had received bath PUVA in which lower UVA doses are used. The comment has also been made[22] that patients receiving long-term therapy should be followed up carefully and that such therapy should not be used in patients at risk for melanoma.

A study[23] of follow-up data on patients who had received trioxysalen bath PUVA did not find an increase in risk of developing either squamous cell carcinoma or malignant melanoma, but the authors suggested that further study is needed to determine the carcinogenicity of trioxysalen PUVA.

1. Reshad H, *et al.* Cutaneous carcinoma in psoriatic patients treated with PUVA. *Br J Dermatol* 1984; **110:** 299–305.
2. Kemmett D, *et al.* Nodular malignant melanoma and multiple squamous cell carcinomas in a patient treated by photochemotherapy for psoriasis. *BMJ* 1984; **289:** 1498.
3. Suurmond D, *et al.* Skin cancer and PUVA maintenance therapy for psoriasis. *Br J Dermatol* 1985; **113:** 485–6.
4. Henseler T, *et al.* Skin tumors in the European PUVA study. *J Am Acad Dermatol* 1987; **16:** 108–16.
5. Forman AB, *et al.* Long-term follow-up of skin cancer in the PUVA-48 cooperative study. *Arch Dermatol* 1989; **125:** 515–19.
6. Stern RS, *et al.* Non-melanoma skin cancer occurring in patients treated with PUVA five to ten years after first treatment. *J Invest Dermatol* 1988; **91:** 120–4.
7. Stern RS, *et al.* Genital tumors among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. *N Engl J Med* 1990; **322:** 1093–7.
8. Moseley H, Ferguson J. Photochemotherapy: a reappraisal of its use in dermatology. *Drugs* 1989; **38:** 822–37.
9. Bruynzeel I, *et al.* 'High single-dose' European PUVA regimen also causes an excess of non-melanoma skin cancer. *Br J Dermatol* 1991; **124:** 49–55.
10. Lindelöf B, *et al.* PUVA and cancer: a large-scale epidemiological study. *Lancet* 1991; **338:** 91–3.
11. Lindelöf B, *et al.* PUVA and cancer risk: the Swedish follow-up study. *Br J Dermatol* 1999; **141:** 108–12.
12. Lever LR, Farr PM. Skin cancers or premalignant lesions occur in half of high-dose PUVA patients. *Br J Dermatol* 1994; **131:** 215–19.
13. Perkins W, *et al.* Cutaneous malignancy in males treated with photochemotherapy. *Lancet* 1990; **336:** 1248.
14. Wolff K, Hönigsmann H. Genital carcinomas in psoriasis patients treated with photochemotherapy. *Lancet* 1991; **337:** 439.
15. Aubin F, *et al.* Genital squamous cell carcinoma in men treated by photochemotherapy: a cancer registry-based study from 1978 to 1998. *Br J Dermatol* 2001; **144:** 1204–6.
16. Stern RS, *et al.* The persistent risk of genital tumors among men treated with psoralen plus ultraviolet A (PUVA) for psoriasis. *J Am Acad Dermatol* 2002; **47:** 33–9.
17. Nijsten TEC, Stern RS. The increased risk of skin cancer is persistent after discontinuation of psoralen+ultraviolet A: a cohort study. *J Invest Dermatol* 2003; **121:** 252–8.
18. Lewis FM, *et al.* Metastatic squamous-cell carcinoma in patient receiving PUVA. *Lancet* 1994; **344:** 1157.
19. Stern RS. Metastatic squamous cell cancer after psoralen photochemotherapy. *Lancet* 1994; **344:** 1644–5.
20. Stern RS, *et al.* Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). *N Engl J Med* 1997; **336:** 1041–5.
21. Stern RS. The PUVA Follow Up Study. The risk of melanoma in association with long-term exposure to PUVA. *J Am Acad Dermatol* 2001; **44:** 755–61.
22. Wolff K. Should PUVA be abandoned? *N Engl J Med* 1997; **336:** 1090–1.
23. Hannuksela-Svahn A, *et al.* Trioxsalen bath PUVA did not increase the risk of squamous cell skin carcinoma and cutaneous malignant melanoma in a joint analysis of 944 Swedish and Finnish patients with psoriasis. *Br J Dermatol* 1999; **141:** 497–501.

NON-MALIGNANT SKIN DISORDERS. Toxic pustuloderma, marked by erythema and superficial pustular lesions, has been reported in a patient given PUVA therapy for mycosis fungoides.[1] There have been a number of reports of bullous pemphigoid occurring, or recurring, in patients treated with PUVA, usually for psoriasis.[2] A case of lichen planus pemphigoides has also been described in a woman treated with topical PUVA.[3] Another effect sometimes associated with PUVA is severe skin pain;[4,5] the pain may respond to treatment with topical capsaicin.[5] Long-term PUVA treatment accelerates ageing of the skin.[6]

1. Yip J, *et al.* Toxic pustuloderma due to PUVA treatment. *Br J Dermatol* 1991; **125:** 401–2.
2. Barnadas MA, *et al.* Bullous pemphigoid in a patient with psoriasis during the course of PUVA therapy: study by ELISA test. *Int J Dermatol* 2006; **45:** 1089–92.
3. Kuramoto N, *et al.* PUVA-induced lichen planus pemphigoides. *Br J Dermatol* 2000; **142:** 509–12.
4. Burrows NP, *et al.* PUVA-induced skin pain. *Br J Dermatol* 1993; **129:** 504.
5. Burrows NP, Norris PG. Treatment of PUVA-induced skin pain with capsaicin. *Br J Dermatol* 1994; **131:** 584–5.
6. Sator P-G, *et al.* Objective assessment of photoageing effects using high-frequency ultrasound in PUVA-treated psoriasis patients. *Br J Dermatol* 2002; **147:** 291–8.

Hypersensitivity. Hypersensitivity reactions to methoxsalen and PUVA therapy occur rarely but there have been reports of drug-induced fever,[1] bronchoconstriction,[2] and contact dermatitis.[3] Cases of anaphylaxis have also been attributed to methoxsalen[4] and 5-methoxypsoralen.[5]

1. Tóth Kása I, Dobozy A. Drug fever caused by PUVA treatment. *Acta Derm Venereol (Stockh)* 1985; **65:** 557–8.
2. Ramsay B, Marks JM. Bronchoconstriction due to 8-methoxypsoralen. *Br J Dermatol* 1988; **119:** 83–6.
3. Takashima A, *et al.* Allergic contact and photocontact dermatitis due to psoralens in patients with psoriasis treated with topical PUVA. *Br J Dermatol* 1991; **124:** 37–42.
4. Park JY, *et al.* Anaphylaxis to 8-methoxypsoralen during photochemotherapy. *Photodermatol Photoimmunol Photomed* 2003; **19:** 37–8.
5. Legat FJ, *et al.* Anaphylaxis to 5-methoxypsoralen during photochemotherapy. *Br J Dermatol* 2001; **145:** 821–2.

Precautions

Methoxsalen should not generally be given to patients with diseases associated with light sensitivity such as porphyria, although it may be used with care in some photosensitivity disorders to decrease sensitivity to sunlight. Other contra-indications include aphakia, melanoma or a history of melanoma, and invasive squamous cell carcinoma. It is generally recommended that PUVA therapy should not be used in children. Methoxsalen should be used with caution in patients with hepatic impairment.

Patients should not sunbathe for 24 hours before and 48 hours after PUVA treatment. They should avoid exposure to sunlight, even through glass or cloud cover for at least 8 hours after methoxsalen ingestion and should wear wrap-around UVA absorbing glasses for 24 hours after ingestion. Photosensitivity is more prolonged after topical application and treated skin should be protected from exposure to sunlight for at least 12 to 48 hours, and possibly for up to a week. Unless specific treatment is required male genitalia should be shielded during PUVA therapy. It has been recommended that patients undergo an ophthalmic examination before starting therapy and at regular intervals thereafter, especially those at increased risk of cataracts. Patients should also receive regular examinations for signs of premalignant or malignant skin lesions. Anti-nuclear

antibody titre may be tested before starting therapy, particularly if there is a suggestion of connective tissue disease; frequent evaluation during treatment is probably not necessary for patients with uncomplicated psoriasis, an initial negative test, and no symptoms of connective tissue disease.

Porphyria. Methoxsalen should not be given to patients with porphyria.

Interactions

Methoxsalen should be used with caution with other drugs also known to cause photosensitivity. It inhibits the action of cytochrome P450 isoenzyme CYP2A6, and may increase plasma concentrations of drugs metabolised via this enzyme.

Antiepileptics. Failure of PUVA treatment due to abnormally low serum concentrations of methoxsalen in a patient with epilepsy was probably a result of induction of hepatic enzymes by *phenytoin*.[1]

1. Staberg B, Hueg B. Interaction between 8-methoxypsoralen and phenytoin. *Acta Derm Venereol (Stockh)* 1985; **65:** 553–5.

Emollients. Some emollient preparations may have a photoprotective effect, and if applied immediately before UVA irradiation could interfere with the efficacy of PUVA therapy.[1,2]

1. Hudson-Peacock MJ, *et al.* Photoprotective action of emollients in ultraviolet therapy of psoriasis. *Br J Dermatol* 1994; **130:** 361–5.
2. Otman SGH, *et al.* Modulation of ultraviolet (UV) transmission by emollients: relevance to narrowband UVB phototherapy and psoralen plus UVA photochemotherapy. *Br J Dermatol* 2006; **154:** 963–8.

Food. Some foods, for example, celery, parsnip, and parsley, contain psoralens and eating large quantities may increase the risk of phototoxicity with methoxsalen. A patient[1] who ate a large quantity of celery soup the evening before and 2 hours before undergoing PUVA therapy for atopic eczema developed severe phototoxicity after treatment, which was attributed to the additive effects of methoxsalen and psoralens contained in the celery.

1. Boffa MJ, *et al.* Celery soup causing severe phototoxicity during PUVA therapy. *Br J Dermatol* 1996; **135:** 334.

Xanthines. For mention of the effect of systemic methoxsalen on the metabolism of theophylline, see Methoxsalen, under Interactions of Theophylline, p.1145.

Pharmacokinetics

When taken orally methoxsalen is well but variably absorbed from the gastrointestinal tract and there is considerable interindividual variation in peak serum concentrations. Depending on the oral formulation used increased photosensitivity is present 1 hour after a dose, reaches a peak at about 1 to 4 hours, and disappears after about 8 hours. Methoxsalen is highly protein bound. It appears to be preferentially taken up by epidermal cells. It also diffuses into the lens of the eye. Methoxsalen is almost completely metabolised. About 95% of a dose is excreted in the urine within 24 hours. The photosensitising action of methoxsalen may persist for several days after topical application. The erythema induced by oral or topical PUVA is usually delayed and peaks after 2 to 3 days.

◊ References.

1. de Wolff FA, Thomas TV. Clinical pharmacokinetics of methoxsalen and other psoralens. *Clin Pharmacokinet* 1986; **11:** 62–75.

Uses and Administration

Methoxsalen, a psoralen, is a constituent of the seeds of *Ammi majus* and the roots of *Heracleum candicans*. It is a photosensitiser that markedly increases skin reactivity to long-wavelength ultraviolet radiation (320 to 400 nm), an effect used in photochemotherapy or PUVA [psoralen (P) and high-intensity long-wavelength UVA irradiation]. In the presence of UVA methoxsalen bonds with DNA, inhibiting DNA synthesis and cell division, and can lead to cell injury. Recovery from the cell injury may be followed by increased melanisation of the epidermis and thickening of the stratum corneum. Methoxsalen may also increase pigmentation by an action on melanocytes.

PUVA is used to treat idiopathic vitiligo and severe, recalcitrant, disabling psoriasis not adequately responsive to conventional topical therapy. It may also be useful in selected cases of atopic eczema and polymorphic light eruptions and may be used in T-cell lymphomas such as mycosis fungoides.

Methoxsalen is given orally or applied topically in PUVA regimens. *Differing oral dosage forms of methoxsalen may exhibit significantly varying bioavailabilities and times to onset of photosensitisation.* The UVA exposure dose should generally be based on prior measurement of the minimal phototoxic dose although it can be calculated with regard to the skin type of the patient if phototoxic dose testing cannot be carried out.

- To repigment **vitiliginous** areas, methoxsalen is given in a dose of 20 mg or up to 600 micrograms/kg *orally* 2 to 4 hours before measured periods of exposure to UVA, depending on the preparation. Treatment is usually given twice a week or on alternate days, but always at least 48 hours apart.
- Methoxsalen may also be applied *topically* to repigment small, well-defined vitiliginous lesions. Preparations containing up to 1% have been used but dilution to 0.1 or 0.01% may be necessary to avoid adverse cutaneous effects. The surrounding skin should be protected by an opaque sunscreen. Some suggest that the treated area should be exposed to UVA soon after application while others recommend waiting up to 2 hours. After exposure the lesions should be washed and protected from light; protection may be necessary for up to 48 hours or longer. Treatment is repeated usually once weekly. Significant repigmentation may not appear until after 6 to 9 months of treatment.
- For the treatment of **psoriasis** a dose of up to about 600 micrograms/kg *orally* is given 1.5 to 3 hours before UVA, depending on the preparation. Treatment is usually given twice a week although increased frequencies, but with at least 48-hour intervals between doses, have been suggested. If there is no response or only minimal response after the fifteenth PUVA treatment some suggest that the dosage may be increased by 10 mg and that this higher dose be used for the remainder of the course of treatment.
- Methoxsalen may also be used *topically* with UVA exposure for the treatment of psoriasis. For direct application to affected areas of skin a preparation containing approximately 0.15% (or diluted to 0.015% if necessary to avoid adverse cutaneous effects) is applied 15 minutes before UVA exposure. Alternatively the patient may take a whole body bath for 15 minutes in a methoxsalen solution, followed immediately by UVA exposure. UK guidelines (see also Skin Disorders, below) suggest a typical concentration of methoxsalen 2.6 mg/litre for such solutions although higher concentrations (up to about 3.7 mg/litre) have been used. Hand and foot soaks may be used to treat only those affected areas; a solution containing methoxsalen 3 mg/litre may be used with the affected areas immersed for 15 minutes followed by a delay of 30 minutes before UVA exposure. Baths or soaks are generally given twice a week.

Psoralen itself has also been used.

Administration. The dose of methoxsalen is usually calculated on the basis of body-weight. This method of dose calculation produces a considerable difference between the doses received by heavy and light patients. A study in 41 patients with psoriasis[1] suggested that using methoxsalen 25 mg/m^2 gave more consistent plasma concentrations and may reduce the potential for burning in heavy patients and prevent underdosing in light patients undergoing PUVA therapy.

1. Sakuntabhai A, *et al.* Calculation of 8-methoxypsoralen dose according to body surface area in PUVA treatment. *Br J Dermatol* 1995; **133:** 919–23.

PUVA. PUVA combines psoralens with UVA irradiation. The psoralens may be given directly to the patient, either orally or topically, and the patient is then exposed to UVA. In extracorporeal PUVA (extracorporeal photochemotherapy; photopheresis), an oral dose of a psoralen is given, after which the patient's leucocytes are isolated, exposed to UVA extracorporeally, and then reinfused. In another method of extracorporeal photopheresis methoxsalen is added directly to leucocytes that have already been removed from the patient. The mixture is then treated with UVA after which it is returned to the patient; the total dose of methoxsalen used by this method is lower than that used orally. PUVA has been used in a wide range of disorders including skin disorders, mycosis fungoides, and organ and tissue transplant rejection (below).

MYCOSIS FUNGOIDES. PUVA therapy is used in the treatment of the manifestations of cutaneous mycosis fungoides and Sèzary syndrome, two forms of cutaneous T-cell lymphoma (see p.657). Extracorporeal PUVA therapy (photopheresis; see above) has also been used,[1-6] particularly for disease with erythrodermic features. The Photopheresis Expert Group[7] (from the UK and Scandinavia) suggests a usual treatment cycle of 2 consecutive days, which is repeated every 2 to 4 weeks. More frequent treatment may be given to symptomatic patients and those with a high peripheral blood tumour burden. Response is assessed every 3 months and then, when complete or maximal response has occurred, treatment is tapered to every 6 to 12 weeks before stopping. Relapse may be treated with the same schedule. After the first 3 months of therapy, treatment should generally be continued for a further 3 months in patients with stable disease (no response). However, consideration should be given to stopping treatment, or using combination therapy (photopheresis with interferon alfa and/or bexarotene), if there is disease progression. At 6 months and beyond, treatment should be stopped, or combination therapy considered, in patients with stable or progressive disease, but for those already receiving combination therapy, photopheresis should be stopped.

1. Duvic M, *et al.* Photopheresis therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1996; **35:** 573–9.
2. Zic JA, *et al.* Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. *J Am Acad Dermatol* 1996; **35:** 935–45.
3. Zic JA, *et al.* The North American experience with photopheresis. *Ther Apher* 1999; **3:** 50–62.
4. Rubegni P, *et al.* Extracorporeal photochemotherapy in long-term treatment of early stage cutaneous T-cell lymphoma. *Br J Dermatol* 2000; **143:** 894–6.
5. Zic JA. The treatment of cutaneous T-cell lymphoma with photopheresis. *Dermatol Ther* 2003; **16:** 337–46.
6. McKenna KE, *et al.* Evidence-based practice of photopheresis 1987-2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin Lymphoma Group. *Br J Dermatol* 2006; **154:** 7–20.
7. Scarisbrick JJ, *et al.* Photopheresis Expert Group. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. *Br J Dermatol* 2008; **158:** 659–78.

ORGAN AND TISSUE TRANSPLANTATION. PUVA[1,2] and extracorporeal PUVA therapy[3-6] (photopheresis; see above) have been tried in both acute and chronic graft-versus-host disease (GVHD) that is unresponsive to usual treatment (see Haematopoietic Stem Cell Transplantation, p.1811). As well as improvements in GVHD, particularly cutaneous manifestations, PUVA therapies have enabled the doses of corticosteroids and other immunosuppressants to be reduced. The Photopheresis Expert Group[7] (from the UK and Scandinavia) suggests, for chronic GVHD, a usual treatment cycle of 2 consecutive days, repeated every 2 weeks. Response is assessed after 3 months and treatment reduced to once every 4 weeks if there has been a complete or partial response. Treatment is then reassessed every 3 months and tapered or stopped when a complete or maximal response has occurred. It should be stopped if there is no response or disease progression.

Photopheresis has also been tried in treating rejection of solid organ transplants,[3,6,8] particularly after heart transplantation (p.1812). It has also shown promise in a study[9] of the prevention of heart transplant rejection.

1. Bonanomi S, *et al.* Bath PUVA therapy in pediatric patients with drug-resistant cutaneous graft-versus-host disease. *Bone Marrow Transplant* 2001; **28:** 631–2.
2. Furlong T, *et al.* Psoralen and ultraviolet A irradiation (PUVA) as therapy for steroid-resistant cutaneous acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2002; **8:** 206–12.
3. Zic JA, *et al.* The North American experience with photopheresis. *Ther Apher* 1999; **3:** 50–62.
4. Foss FM, *et al.* Extracorporeal photopheresis in chronic graft-versus-host disease. *Bone Marrow Transplant* 2002; **29:** 719–25.
5. Kanold J, *et al.* Extracorporeal photochemotherapy for graft versus host disease in pediatric patients. *Transfus Apheresis Sci* 2003; **28:** 71–80.
6. McKenna KE, *et al.* Evidence-based practice of photopheresis 1987-2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin Lymphoma Group. *Br J Dermatol* 2006; **154:** 7–20.
7. Scarisbrick JJ, *et al.* Photopheresis Expert Group. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. *Br J Dermatol* 2008; **158:** 659–78.
8. Dall'Amico R, Murer L. Extracorporeal photochemotherapy: a new therapeutic approach for allograft rejection. *Transfus Apheresis Sci* 2002; **26:** 197–204.
9. Barr ML, *et al.* Photopheresis for the prevention of rejection in cardiac transplantation. *N Engl J Med* 1998; **339:** 1744–51.

SKIN DISORDERS. PUVA has been used in a wide range of skin disorders and guidelines have been published by the British Photodermatology Group,[1,2] which are summarised as follows:

- Indications for PUVA in chronic plaque **psoriasis** include severe extensive psoriasis unresponsive to conventional topical therapies, relapse within 3 to 6 months of successful topical treatment, or patient refusal of topical treatment if UVB phototherapy has failed (see p.1583 for a discussion of the various treatments of psoriasis). Initial UVA exposure should preferably be determined on the basis of prior measurement of the minimal phototoxic dose rather than on the skin type. Increases in UVA irradiation are then calculated as a percentage of previous doses.

  Methoxsalen in an oral dose of 600 micrograms/kg given 2 hours before UVA exposure is the widely accepted standard regimen. Alternatively, 5-methoxypsoralen 1.2 mg/kg, again 2 hours before UVA exposure, can be given and appears to be almost free of the adverse reactions such as nausea, pruritus, and erythema induced by methoxsalen. However, until the clinical efficacy of 5-methoxypsoralen has been clearly shown, methoxsalen should remain the psoralen of choice for most clinical situations.

  Alternatives to oral PUVA are baths or soaks using methoxsalen or trioxysalen. For whole body bathing a concentration of methoxsalen 2.6 mg/litre is typically utilised with the patient bathing for 15 minutes followed by immediate exposure to UVA. For hand and foot soaks a concentration of methoxsalen 3 mg/litre is used with the affected area immersed for 15 minutes followed by a delay of 30 minutes before UVA exposure. For trioxysalen a concentration of about 330 micrograms/litre is used for a 15-minute whole body bath or hand and foot soak followed by immediate UVA exposure for whole body therapy, or a 30 minute delay before hand and foot UVA exposure. Whole body baths or hand and foot soaks are given twice each week.

  Methoxsalen may also be applied topically to the affected areas. A concentration of about 0.15% (or 0.015% if erythema occurs) is used in an emulsion, or 0.005% in an aqueous gel, and applied 15 minutes before UVA exposure.

  PUVA treatment should be stopped as soon as disease clearance is achieved; maintenance PUVA should be avoided to minimise cumulative UVA exposure, but may be considered if there is rapid relapse. A combination of PUVA with acitretin (300 to 700 micrograms/kg orally) or etretinate (0.5 to 1 mg/kg orally) may be considered in patients who have reached 50 treatment sessions or relapsed within 6 months of PUVA. PUVA and methotrexate are also effective for severe psoriasis but should be reserved for such cases because of the possible increased risk of skin cancer
- Oral PUVA twice weekly with methoxsalen 600 micrograms/kg or 5-methoxypsoralen 1.2 mg/kg has been effective in many patients with **vitiligo** (see Pigmentation Disorders, p.1582). If patches are well demarcated topical application of methoxsalen 0.15% may be preferable
- In **mycosis fungoides** PUVA is an effective symptomatic treatment for early disease and a useful adjunct for late-stage disease but optimal regimens have not been established (see above)
- PUVA is effective for atopic **eczema** (p.1579) but clearance is less certain than for psoriasis, twice the number of treatments may be needed, and relapse is more frequent. It should therefore be reserved for severe disease unresponsive to conventional treatments. Optimal regimens have not been established
- In **polymorphic light eruptions** (see Photosensitivity Disorders, p.1581) PUVA is effective in up to 90% of patients but is only indicated in those who are frequently or severely affected despite the regular use of high-protection broad-spectrum sunscreens. Several arbitrary regimens are in use
- Variable results have also been reported in a variety of other disorders but data has been insufficient to establish precise guidelines. Such disorders include actinic prurigo, alopecia areata, aquagenic pruritus, chronic actinic dermatitis, granuloma annulare, lichen planus, nodular prurigo, pityriasis lichenoides, localised scleroderma, solar urticaria, and urticaria pigmentosa. In most cases relapse occurs in the absence of maintenance therapy and PUVA should usually only be tried as a last resort.

Extracorporeal PUVA has been tried in patients with severe epidermolysis bullosa acquisita,[3,4] lichen planus,[5] and scleroderma.[6,7]

1. British Photodermatology Group. British Photodermatology Group guidelines for PUVA. *Br J Dermatol* 1994; **130:** 246–55.
2. Halpern SM, *et al.* Guidelines for topical PUVA: a report of a workshop of the British Photodermatology Group. *Br J Dermatol* 2000; **142:** 22–31. Also available at: http://www.bad.org.uk/healthcare/guidelines/Topical_PUVA_Therapy.pdf (accessed 27/09/07)
3. Miller JL, *et al.* Remission of severe epidermolysis bullosa acquisita induced by extracorporeal photochemotherapy. *Br J Dermatol* 1995; **133:** 467–71.
4. Gordon KB, *et al.* Treatment of refractory epidermolysis bullosa acquisita with extracorporeal photochemotherapy. *Br J Dermatol* 1997; **136:** 415–20.
5. Guyot AD, *et al.* Treatment of refractory erosive oral lichen planus with extracorporeal photochemotherapy: 12 cases. *Br J Dermatol* 2007; **156:** 553–6.
6. Zic JA, *et al.* The North American experience with photopheresis. *Ther Apher* 1999; **3:** 50–62.
7. Knobler RM, *et al.* A randomized, double-blind, placebo-controlled trial of photopheresis in systemic sclerosis. *J Am Acad Dermatol* 2006; **54:** 793–9.

Preparations

USP 31: Methoxsalen Capsules; Methoxsalen Topical Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Oxsoralen Ultra; ***Austral.:*** Oxsoralen; ***Austria:*** Oxsoralen; ***Belg.:*** Mopsoralen; ***Braz.:*** Oxsoralen; ***Canad.:*** Oxsoralen; Ultramop; ***Chile:*** Oxsoralen; ***Cz.:*** Oxsoralen; Uvadex; ***Denm.:*** Geroxalen†; ***Fr.:*** Meladinine; Uvadex; ***Ger.:*** Meladinine; ***Gr.:*** Melaoline; ***Hong Kong:*** Oxsoralen; ***Hung.:*** Geroxalen†; Oxsoralen; ***India:*** Macsoralen†; Manaderm; Melanocyl; ***Indon.:*** Delsoralen; Oxsoralen; ***Irl.:*** Deltasoralen; ***Ital.:*** Oxsoralen†; ***Jpn:*** Oxsoralen; ***Malaysia:*** Meladinine†; Oxsoralen; ***Mex.:*** Dermox; Meladinina; Oxsoralen; ***Neth.:*** Geroxalen; Meladinine; Oxsoralen†; ***Norw.:*** Geroxalen†; ***NZ:*** Oxsoralen; ***Pol.:*** Geralen; Oxsoralen; ***Rus.:*** Oxsoralen (Оксорален); ***S.Afr.:*** Oxsoralen; ***Singapore:*** Oxsoralen; ***Spain:*** Oxsoralen; ***Switz.:*** Meladinine; ***Thai.:*** Meladinine†; ***Turk.:*** Geroxalen; Vitspo; ***UK:*** Puvasoralen; ***USA:*** Oxsoralen; Uvadex.

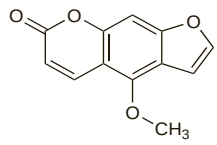
Multi-ingredient: ***India:*** Melanocyl.

5-Methoxypsoralen

Bergapteeni; Bergapten; Bergapteno; Bergaptenum; 5-Metoxipsoraleno; 5-MOP. 4-Methoxy-7*H*-furo[3,2-g]chromen-7-one.

5-Метоксипсорален

$C_{12}H_8O_4$ = 216.2.
CAS — 484-20-8.
ATC — D05BA03.
ATC Vet — QD05BA03.



Profile

5-Methoxypsoralen is a photosensitiser with actions similar to those of methoxsalen (above). It may be given orally in the PUVA therapy (see under Methoxsalen, above) of psoriasis and vitiligo.

5-Methoxypsoralen is included in some cosmetic suntan preparations to enhance tanning but because of its potential phototoxicity this is considered unwise by authorities in Europe and the USA. Photosensitivity caused by 5-methoxypsoralen is sometimes known as Berloque dermatitis.

5-Methoxypsoralen is an ingredient of bergamot oil (p.2265).

◊ References.

1. McNeely W, Goa KL. 5-Methoxypsoralen: a review of its effects in psoriasis and vitiligo. *Drugs* 1998; **56:** 667–90.

Hypersensitivity. For mention of anaphylaxis associated with the use of 5-methoxypsoralen, see Hypersensitivity, under Adverse Effects of Methoxsalen, p.1605.

Preparations

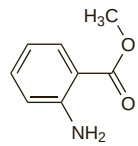
Proprietary Preparations (details are given in Part 3)
Austral.: Pentaderm†; ***Austria:*** Geralen; ***Fr.:*** Psoraderm 5†; ***UK:*** Pentaderm.

Methyl Anthranilate

Metilo, antranilato de; Metylu antranilan. Methyl 2-aminobenzoate.

Метилантранилат

$C_8H_9NO_2$ = 151.2.
CAS — 134-20-3.



NOTE. Do not confuse with menthyl anthranilate (see Meradimate, p.1604).

Profile

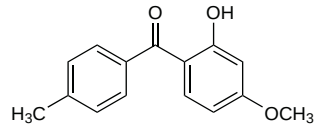
Methyl anthranilate has been used in sunscreen preparations. It is a constituent of several essential oils.

Mexenone *(BAN, pINN)*

Benzofenon-10; Benzophenone-10; Mexenona; Mexénone; Mexenonum. 2-Hydroxy-4-methoxy-4′-methylbenzophenone.

Мексенон

$C_{15}H_{14}O_3$ = 242.3.
CAS — 1641-17-4.



Pharmacopoeias. In *Br.*
BP 2008 (Mexenone). A pale yellow odourless or almost odourless crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone.

Profile

Mexenone, a substituted benzophenone, is a sunscreen (p.1576) with actions similar to those of oxybenzone (p.1608). It is effective against UVB and some UVA light (for definitions, see p.1580)

Preparations

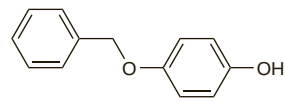
BP 2008: Mexenone Cream.

Monobenzone *(rINN)*

Benoquina; Hydroquinone Monobenzyl Ether; Monobenzona; Monobenzonum. 4-Benzyloxyphenol.

Монобензон

$C_{13}H_{12}O_2$ = 200.2.
CAS — 103-16-2.
ATC — D11AX13.
ATC Vet — QD11AX13.



Pharmacopoeias. In *US.*
USP 31 (Monobenzone). Store at a temperature not exceeding 30° in airtight containers. Protect from light.

Adverse Effects and Precautions

Monobenzone may cause skin irritation and sensitisation. In some patients this is transient and the drug need not be withdrawn. In others, an eczematous sensitisation may occur. Excessive depigmentation may occur even beyond the areas under treatment and may produce unsightly patches.

Monobenzone frequently produces permanent depigmentation and should not be used as a substitute for hydroquinone.

Interactions

Agalsidase. For the recommendation that monobenzone not be used with agalsidase alfa or beta, see p.2252.

Uses and Administration

Monobenzone has actions similar to those of hydroquinone (p.1598) but in some patients it also produces extensive and selective destruction of melanocytes. It is used locally for final, permanent depigmentation of normal skin in extensive vitiligo (see Pigmentation Disorders, p.1582). Monobenzone is not recommended for freckling, chloasma, or hyperpigmentation following skin inflammation or due to photosensitisation after the use of certain perfumes. It has no effect on melanomas or pigmented naevi.

For vitiligo a cream containing monobenzone 20% is applied to the affected areas two or three times daily until a satisfactory response is obtained, and thereafter as necessary, usually about twice weekly. Depigmentation only becomes apparent when the preformed melanin pigments have been lost with the normal sloughing of the stratum corneum and this may take several months. If, however, no improvement is noted after 4 months, treatment should be stopped. Excessive exposure to sunlight should be avoided during treatment. After depigmentation the skin will be sensitive for the rest of the patient's life and a sunscreen must be used during sun exposure.

Preparations

USP 31: Monobenzone Cream.

Proprietary Preparations (details are given in Part 3)
Canad.: Benoquin; ***India:*** Benoquin†; ***USA:*** Benoquin.
