Liver Injury Following Administration of 8-Methoxypsoralen During PUVA Therapy

Mats Bjellerup, Magnus Bruze, Arne Hansson,[1] Gösta Krook and Bo Ljunggren

Departments of Dermatology and Clinical Chemistry ([1]Section of Toxicology), University of Lund, General Hospital, S-214 01 Malmö, Sweden

Received January 8, 1979

Abstract. A case of liver injury caused by 8-methoxypsoralen given orally during PUVA therapy is presented. The reaction, manifested by elevated serum alanine-aminotransferase and serum aspartate-aminotransferase, was provoked on three consecutive occasions, on the last one with 8-MOP only. The liver injury seems to be of the hepatocellular and nonpredictable type.

Key words: Liver injury, 8-methoxypsoralen, PUVA treatment.

CASE REPORT

The patient is a 57-year-old woman. During childhood she developed psoriasis vulgaris which has been treated with a variety of topical medications, including corticosteroids, over the years. She has also shown signs of psoriasis arthritis since 1977. She was referred to our department in June 1977 for treatment of her psoriasis. Until April 1978 she was treated without success for periods with various topical preparations including tar, dithranol and betamethasone valerate.

Photochemotherapy with 8-methoxypsoralen (8-MOP) (AB Draco, Lund, Sweden) and long-wave ultraviolet light (PUVA) was started in April 1978 according to the principles of the European Cooperative Clinical Trial (ECCT) described by Wolff et al. (7). Treatment was given 4 days a week. The patient was irradiated 2 h after receiving an oral dose of 40 mg 8-MOP. Source of the long-wave radiation was a PUVA 4000 apparatus (Waldmann AG, Schwenningen, GFR). The starting dose of UVA was 2.0 J/cm^2. The dose at the end of the initial treatment course was 7.0 J/cm^2. The laboratory tests were carried out before, immediately after and 3 months after initial treatment, and included liver enzymes, serum creatinine, haematologic screening and antinuclear antibodies.

Treatment was interrupted after 7 weeks because of symptoms of common cold. During the last week of treatment she noticed itching in her fingers. Liver enzymes immediately after treatment showed elevated serum alanine-aminotransferase (ALAT) to 6.13 μkat/l (normal <0.67) and serum aspartate-aminotransferase (ASAT) to 3.43 μkat/l (normal <0.67) (Fig. 1). Serum glutamyltransferase (GT) was only slightly elevated, to 0.80 μkat/l (normal <0.60). Before treatment these values had been normal. Serum alkaline phosphatase and serum bilirubin were normal. Serum proteins showed signs of a slight inflammatory reaction. Hepatitis B (Au-) antigen and antinuclear antibodies could not be detected. Serum creatinine was normal. There was no abdominal pain and a thorough clinical examination revealed nothing but swollen fingers. ASAT, ALAT and GT returned to normal values within 7 weeks (Fig. 1).

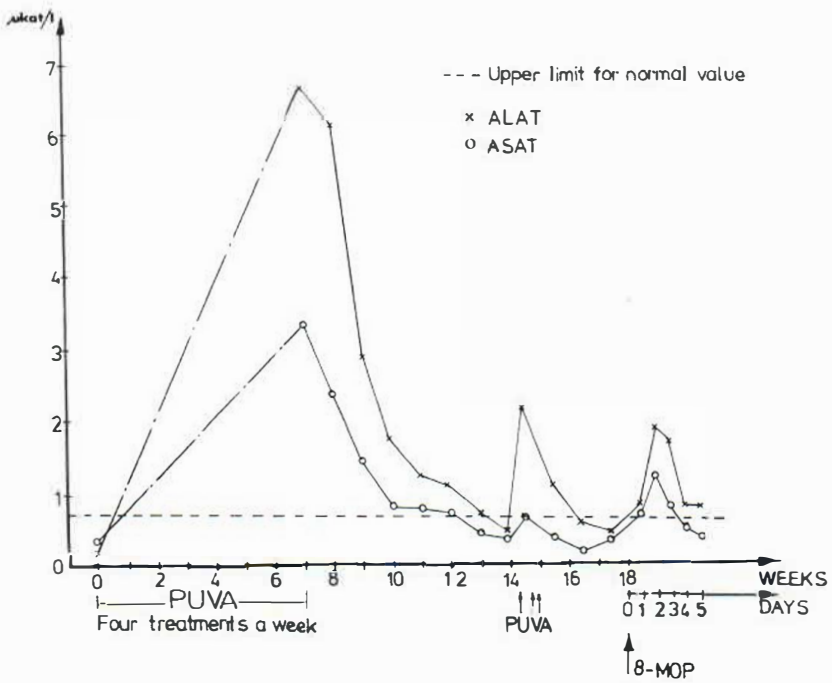

Fig. 1. ALAT och ASAT during two periods of PUVA treatment followed by a single dose of 8-MOP without UVA.

When liver enzymes had returned to normal, PUVA was started again because of a relapse of her skin disease. After only one treatment the patient had renewed symptoms of common cold, with fever and an elevation of ALAT and ASAT. After treatment was stopped, ALAT and ASAT returned to normal within 3 weeks (Fig. 1).

The patient was then challenged with a single dose of 40 mg 8-MOP without UVA and reacted only 2 hours later with chills, fever in excess of 39°C, a sensation of heat in her head and hands and a temporary elevation of ALAT and ASAT (Fig. 1).

DISCUSSION

Many reports on PUVA treatment have appeared during recent years. Some of them have described slight and transient elevations of liver enzymes which, however, have been attributed in most cases to pre-existing liver injury such as caused by abuse of alcohol or intake of other drugs (1, 4, 5). Transient elevations of liver enzymes have also been noted in two of our own PUVA patients (unpublished observation). We have been unable to find any reports in the literature documenting psoralens as being the cause of liver injury during PUVA treatment.

In the present case there is a clear correlation between liver injury and intake of 8-MOP as demonstrated by the reappearance of symptoms and laboratory abnormalities after repeated provocations. There was no history of preceding liver disease.

The liver damage seems to be of the hepatocellular and nonpredictable type. However, a liver biopsy was not available. The short delay between intake of the drug and symptoms suggests an allergic mechanism as a possible explanation. There are some similarities between this case and liver injury after halothane anaesthesia. Halothane has been reported to cause liver injury in a small number of patients receiving it. There was a significant relation between the number of exposures to this anaesthetic and the rapidity with which liver injury developed after exposure (2). Evidence has been provided that halothane may be immunogenic (6).

It may be of additional interest that imperatorin, a phototoxic furocoumarin isolated from various plants, such as *Ammi majus*, has been shown to induce cirrhotic changes in the liver of rats and to inhibit respiration and phosphorylation in isolated liver mitochondria (3). The chemical structures of imperatorin and 8-MOP are closely related. Whether this may have any bearing upon the case reported here is not known, however.

REFERENCES

1. Dahl, K. B. & Brodthagen, H.: Treatment of psoriasis vulgaris with carbon-arc light baths and 8-methoxypsoralen. Ugeskr Laeger *138:* 2221, 1976.
2. Inman, W. H. W. & Mushin, W. W.: Jaundice after repeated exposure to halothane: An analysis of reports to the Committee on Safety of Medicines. Br Med J *i:* 5, 1975.
3. Kramar, R. & Kaiser, E.: Effect of imperatorin, a toxic principle from Ammi majus, on energy-transfer in mitochondria. Toxicon *6:* 145, 1968.
4. Swanbeck, G., Thyresson-Hök, M., Bredberg, A. & Lambert, B.: Treatment of psoriasis with oral psoralens and long wave ultraviolet light. Therapeutic results and cytogenetic hazards. Acta Dermatovener (Stockholm) *55:* 367, 1975.
5. Weismann, K., Howitz, J. & Bro-Jørgensen, A.: Treatment of psoriasis with 8-methoxypsoralen and long-wave ultraviolet light. Ugeskr Laeger *138:* 2225, 1976.
6. Williams, B. D., White, N., Amlot, P. L., Slaney, J. & Toseland, P. A.: Circulating immune complexes after repeated halothane anaesthesia. Br Med J *ii:* 159, 1977.
7. Wolff, K., Fitzpatrick, T. B., Parrish, J. A., Gschnait, F., Gilchrest, B., Hönigsmann, H., Pathak, M. A. & Tanenbaum, L.: Photochemotherapy for psoriasis with orally administered methoxsalen. Arch Dermatol *112:* 943, 1976.

Comparison of Clobetasol Propionate and Betamethasone-17,21-Dipropionate with Reference to Adrenal Suppression

Knud Eriksen

Department of Dermatology, Hvidovre Hospital, University of Copenhagen, Denmark

Received November 6, 1978

Abstract. 32 adult hospitalized patients with common skin disorders were controlled in a double-blind comparison study with clobetasol propionate (Dermovat®) and betamethasone-17,21-dipropionate (Diproderm®) with regard to adrenal suppression. The latter, when assessed by plasma cortisol, was significantly greater in the dermovat-treated group after the 1st and 2nd week with daily treatment with both 25 g and 15 g ointment. Daily treatment of skin areas >25% with 25 g Diproderm® also showed clear adrenal suppression, whereas no such effect was obtained with daily treatment with 10 g Diproderm®