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HEPATOTOXICITY OF PHOTOTOXIC DRUGS USED IN SYSTEMIC PHOTOCHEMOTHERAPY

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Abstract — Psoralens are metabolized in the liver and thus can produce liver damage in laboratory animals when given in excessive doses. However, in humans, reports of the effects of psoralens on liver functions during photochemotherapy have been contradictory. We studied 311 patients to observe the effects of various phototoxic drugs: 8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP), 4,5,8-trimethylpsoralen (TMP)-on liver function during photochemotherapy. Of the 311 patients, only seven had transient elevations of transaminases. Incidence of hepatotoxicity of 8-MOP, TMP and 5-MOP showed 0.6%, 6% and 3%, respectively. Although the effects of psoralens on liver functions during photochemotherapy have been contradictory in humans and there have been few cases showing transient elevated values of liver transaminases during photochemotherapy, it is advisable to obtain serial liver function tests before and during photochemotherapy.

INTRODUCTION

In 1974, photochemotherapy (psoralen plus UVA; PUVA) was introduced by Parrish et al.[1] Since then it has been used to treat psoriasis, vitiligo, atopic dermatitis,generalized lichen planus, mycosis fungoides, and prurigo nodularis.[2,3]

Psoralen is metabolized in the liver and primarily excreted in the urine between 12 and 24 hours after ingestion. Psoralen can produce liver damage in laboratory animals when given in excessive doses.[2] However, in humans, reports of the effects of psoralens on liver function during photochemotherapy have been contradictory.[1,4-7] Parrish et al.[1] found that the results of liver function tests showed that it's function was normal before, during, and after the clearing of psoriasis in 21 patients. In a multicenter study, Melski et al.[5] found no clinically significant changes in liver function attributable to PUVA during PUVA therapy given to 1308 patients with psoriasis. However, in 1975 Swanbeck et al.[7] found abnormal levels of serum transaminase in 6 of 40 patients during treatment, although in three there had been some concomitant alcohol intake. Weismann et al.[8] in 1977 found serum alanine transaminase increased to abnormal values in 4 of 31 PUVA-treated psoriasis patients during therapy; in three patients these values returned to normal when alcohol consumption was stopped.

We undertook this study to observe the effects of various phototoxic drugs: 8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP), 4,5,8-trimethylpsoralen (TMP)-on liver function during photochemotherapy.

MATERIALS AND METHODS

Three hundred eleven patients entered this study (171 women, 140 men). Their mean age was 32 years (range 12 to 72 years). The study group included 155 patients with 8-MOP medication and 32 patients with TMP medication, and 124 patients with 5-MOP medication.

The initial dosage of 8-MOP and TMP was 0.5 mg/kg/day and 5-MOP, 1 mg/kg/day. UVA treatment was given two times a week with a starting dose of 1 or 2 joules/cm^2 according to the skin type. Serum transaminase(SGOT and SGPT) levels were determined before and two or more

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† *Abbreviations*
8-MOP : 8-methoxypsoralen
5-MOP : 5-methoxypsoralen
TMP : trimethylpsoralen
SGOT : serum glutamate oxaloacetate transaminase
SGOT : serum glutamate pyruvate transaminase
PUVA : psoralen plus ultraviolet A
anti-HBs : hepatitis B surface antigen antibody
anti-HBc : hepatitis B core antigen antibody
HBsAg : hepatitis B surface antigen

times during photochemotherapy. The liver enzymes were considered to be elevated if their values were above 35 IU/L.

RESULTS AND DISCUSSION

Of the 311 patients, only seven had transient elevations of transaminases. Incidence of hepatotoxicity of 8-MOP, TMP and 5-MOP showed 0.6%, 6% and 3%, respectively (Table 1). In these seven patients, alcohol intake was denied. Six patients were examined for hepatitis markers. Six were free of HBsAg. Five had anti-HBs and anti-HBc, however, they did not have HBsAg. Two patients with vitiligo (cases 1 and 2) were treated with TMP and one patient with psoriasis(case 3) was treated with 8-MOP. Two patients (cases 1 and 3) demonstrated slightly elevated values of SGOT/SGPT to 44/44 and 31/52, respectively. One patient (case 2) treated with TMP demonstrated elevation of SGOT/SGPT to 173/275 4 months after treatment. Four patients (cases 4,5,6 and 7) treated with 5-MOP showed abnormal liver function. Two patients (cases 4 and 7) demonstrated slightly elevated values of SGOT/SGPT, however, two patients (cases 5 and 6) showed markedly elevated values of SGOT/SGPT to 103/235 IU/L and 143/266 IU/L, respectively(Table 2).

Photochemotherapy with per oral psoralen followed by exposure to high-intensity, long-wave ultraviolet light was introduced in 1974.[1] Since then, linear psoralens such as 8-MOP, TMP and 5-MOP have been used for various diseases such as psoriasis, vitiligo, atopic dermatitis, generalized lichen planus, mycosis fungoides, and prurigo nodularis. The most commonly recommended treatment for vitiligo or psoriasis involves the ingestion of either 8-MOP or TMP followed by exposure to solar radiation (PUVASOL) or to UVA radiation(PUVA) from an artificial light source.

Table 1. Incidence of hepatotoxicity of phototoxic drugs

Phototoxic drug	8-MOP (n=155)[a]	TMP (n=32)	5-MOP (n=124)
No. of hepatotoxicity	1[b](0.6%)[c]	2(6%)	4(3%)

[a] Number of studied. [b] Number of patients with hepatotoxicity. [c] Percentage of patients with hepatotoxicity.

Recently, 5-MOP has been found to provide considerable advantages over 8-MOP in the treatment of psoriasis and vitiligo because of its therapeutic effectiveness combined with pharmacologic and photobiologic properties which has a lower phototoxic potential and complete lack of drug intolerance, such as nausea, vomiting and pruritus.[9-11]

Side effects of PUVA are related to intolerance to the drug or to an overdosage of UVA. In therapeutic doses, psoralens are well-tolerated by most individuals. However, pruritus, epigastic discomfort, nausea, insomnia, nervousness, fatigue and drowsiness may be observed in some patients. Phototoxic reactions like erythema are the most frequent side effects due to overexposure. Phototoxic reactions occur mostly with 8-MOP PUVA and are rarely observed in patients

Table 2. Seven patients with transient elevation of liver transaminases during photochemotherapy

	Case 1	Case 2	Case 3	Case 4	Case 5	Case6	Case 7
Sex/Age(yrs)	M/34	F/49	M/27	M/37	F/46	F/15	F/18
Clinical diagnosis	Vitiligo	Vitiligo	Psoriasis	Psoriasis	Psoriasis	Vitiligo	Vitiligo
Duration of treatment (months)	30	4	4	5	3.5	20	14
Phototoxic drug	TMP	TMP	8-MOP	5-MOP	5-MOP	5-MOP	5-MOP
Total times of PUVA	128	29	24	31	37	66	111
Total cumulative dose of photoxic drugs(mg)	3840	1160	720	1460	1960	2640	4440
Total amount of UVA (joules/cm^2)	415	150	293	368	541	684	729.5
SGOT/SGPT(IU/L)							
before treatment	10/13	16/14	13/21	18/30	13/10	12/9	11/7
during treatment	44/44	173/175	31/52	33/59	103/235	143/266	42/59
after stop treatment	22/27	20/20	15/20	16/25	16/16	25/21	11/9
Hepatitis markers							
HBs Ag	not done	negative	negative	negative	negative	negative	negative
anti-HBs	not done	positive	negative	positive	positive	positive	positive
anti-HBc	not done	positive	not done	positive	not don	not done	positive

receiving oral TMP[12]. It may appear in extremely photosensitive patients receiving 5-MOP[13].

Psoralens are metabolized in the liver and thus can produce liver damage in laboratory animals when given in excessive doses. However, in humans, reports of the effects of psoralens on liver functions during photochemotherapy have been contradictory. Parrish et al[1]. and Melski et al[5]. in a multicenter study found no clinically significant changes in liver function attributable to PUVA. In 1986, Nyfors et al[14] who had performed liver biopsies before and after 1 year of PUVA therapy in 12 patients who had received a mean number of 79 treatments, found no histologic evidence of hepatotoxicity. However, Swanbeck et al[17]. and Weismann et al[8]., found abnormal levels of serum transaminases during PUVA therapy for psoriasis, although in some patients there had been some concomitant alcohol intake. Hann et al[15]., in 1992, found transient elevation of serum transaminases during photochemotherapy in 3 of 162 patients with vitiligo or psoriasis. Rare reports of liver injury associated with elevation to abnormal values of liver enzymes may represent an allergic or idiosyncratic reaction[4,16].

Although the effects of psoralens on liver functions during photochemotherapy have been contradictory in humans and there have been few cases showing transient elevated values of liver transaminases during photochemotherapy, it is advisable to obtain serial liver function tests before and during photochemotherapy.

REFERENCES

1. Parrish, J. A., T. B. Fitzpatrick, L. Tanenbaum and M. A. Pathak (1974) Photochemotherapy of psoriasis with oral methoxsalen and longwave ultraviolet light. *N Engl. J. Med.* **291**, 1207-1211.
2. Hönigsmann, H., T. B. Fitzpatrick, M. A. Pathak and K. Wolff (1993) Oral Photochemotherapy withpsoralens and UVA(PUVA): Principles and practice. In T. B. Fitzpatrick, A. Z. Eisen, K. Wolff, et al.(eds): Dermatology in general medicine. 4th ed., pp. 1728-1754, McGraw-Hill, New York.
3. Hann, S. K., M. Y. Cho and Y. K. Park (1990) UV treatment of generalized prurigo nodularis. *Int. J. Dermatol.* **29**, 436-437.
4. Bjellerop, M., M. Bruze, A. Hansson, G. Krok and B. Ljunggren (1979) Liver injury following administration of 8-methoxypsoralen during PUVA therapy. *Acta Derm. Venereol.* (Stockh) **59**, 371-372.
5. Melski, J. W., L. Tanenbaum, J. A. Parrish, T. B. Fitzpatrick, H. L. Bleich and 28 Participating investigators (1977) Oral methoxsalen photochemotherpy for the treatment of psoriasis: A cooperative clinical trial. *J. Invest. Dermatol.* **68**, 328-335.
6. Tucker, H. A. (1959) Clinical and laboratory tolerance studies in volunteers given oral methoxalen. *J. Invest. Dermatol.* **32**, 277-280.
7. Swanbeck, G., M. Thyresson-Hök, A. Bredberg and B. Lambert (1975) Treatment of psoriasis with oral psoralens and longwave ultraviolet light. *Acta Derm. Venereol.* (Stockh) **55**, 367-376.
8. Weismann, K., J. Howitz and A. Bro-Joergensen (1977) Treatment of resistant psoriasis with 8-methoxypsoralen and longwave ultraviolet light(PUVA): A treatment schedule and a follow-up study. *Acta Derm. Venereol.* (stockh) **57**, 73-76.
9. Hönigsmann, H., E. Jaschke, F. Gschnait, W. Brenner, P. Fritsch and K. Wolff (1979) 5-Methoxypsoralen (Bergapten) in photochemotherapy of psoriasis. *Br. J. Dermatol.* **101**, 369-378.
10. Tanew, A., B. Ortel, K. Rappersberger and H. Hönigsmann (1991) 5-Methoxysoralen (Bergapten) for photochemotherapy. *J. Am. Acad. Dermatol.* **18**, 333-338.
11. Hann, S. K., M. Y. Cho, S. Im and Y. K. Park (1991) Treatment of Vitiligo with oral 5-methoxypsoralen. *J. Dermatol.* **18**, 324-329.
12. Ortonne, J. P. (1989) Psoralen therapy in vitiligo. *Clinics in Dermatology.* **7**, 120-135.
13. Hönigsmann, H. (1986) Psoralen photochemotherapy : Mechanisms, drugs, toxicity. *Curr. Probl. Dermatol.* **15**, 52-66.
14. Nyfors, A., B. Dahl-Nyfors and D. Hopwood (1986) Liver biopsies from patients with psoriasis related to photochemotherapy(PUVA): Findings before and after 1 year of therapy in twelve patients. *J. Am. Acad. Dermatol.* **14**, 43-48.
15. Hann, S. K., Y. K. Park, S. Im, S. W. Koo and I. B. Haam (1992) The effect on liver transaminases of phototoxic drugs used in systemic photochemotherapy. *J. Am. Acad. Dermatol.* **26**, 646-648.
16. Pariser, D. M. and R. J. Wyles (1980) Toxic hepatits from oral methoxsalen photochemotherapy (PUVA). *J. Am. Acad. Dermatol.* **13**, 248-250.