treated patients should wear dark glasses for protection for 12–24 hours after treatment, since they have demonstrated free 8-MOP in the human lens for at least 12 hours after oral ingestion. These findings are contrary to the findings of Marqversen et al. (8), who could not demonstrate any accumulation of 8-MOP in human lenses up to 72 hours after oral ingestion. There seems to be some confusion about how rigorous a recommended sunglass regimen should be after ingestion of 8-MOP.

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Methotrexate in Psoriasis with and without Leucovorin: Effect of Different Dosage Schedules on Acute Liver Toxicity

Hugh Zachariae and Peter Bjerring

Department of Dermatology, Marselisborg Hospital, University of Aarhus, Denmark

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Abstract. Studies on thirty-six psoriatics revealed no differences in acute liver toxicity of four different intermittent dosage schedules of methotrexate with or without addition of leucovorin, as judged by daily determinations of SGOT for one week. Three patients with psoriatic erythroderma receiving high-dosage methotrexate (100 mg i.v.) with leucovorin rescue responded extremely well to treatment and did not distinguish themselves from the other patients with regard to acute liver toxicity.

Key words: Methotrexate; Leucovorin rescue; Psoriasis; Liver toxicity

Methotrexate is one of the most useful drugs for controlling severe psoriasis, but the fact that the drug may inflict liver damage that will lead to fibrosis and cirrhosis in some patients has caused great concern (1, 5, 8). Data from an international cooperative study indicated clearly that daily oral therapy was associated with the greatest degree of hepatotoxicity (7), but which of various other dosage schedules is the less damaging to the liver is still under debate. We have tried to evaluate acute liver toxicity in various dosage schedules with and without leucovorin by determining GO-transaminases (SGOT) daily for 8 days following methotrexate administration.

Leucovorin, known also as citrovorum factor or folinic acid, is a useful antidote to methotrexate, but is also in current use as an active principal to improve the therapeutic index of methotrexate. It is this quality which allows the physician to increase methotrexate dosage without any significant increase in toxicity, which is named leucovorin rescue. Leucovorin, although commonly used in methotrexate cancer therapy (6), has received little attention in psoriasis (2, 3, 4).

MATERIAL AND METHODS

Thirty-six psoriatics with a disease severity that indicated use of methotrexate were treated with one of the following dosage schedules: I) a divided oral dose of 5 mg methotrexate three times at 12-hour intervals; II) a single oral dose of 25 mg methotrexate; III) a single intramuscular dose of 25 mg methotrexate; and IV) a divided oral dose of 5 mg methotrexate three times with 12-hour intervals followed by leucovorin 9 mg i.m. 36 hours later. 3 patients with psoriatic erythroderma received 100 mg methotrexate i.v. followed by leucovorin 9 mg i.m. 36 hours later. All patients had normal leukocyte- and thrombocyte counts, normal values of SGOT and alkaline phosphatases as well as a normal serum creatinine clearance prior to treatment. None of the patients were chronic abusers of alcohol. SGOT values were monitored daily for a week; the clinical response was evaluated after one week.

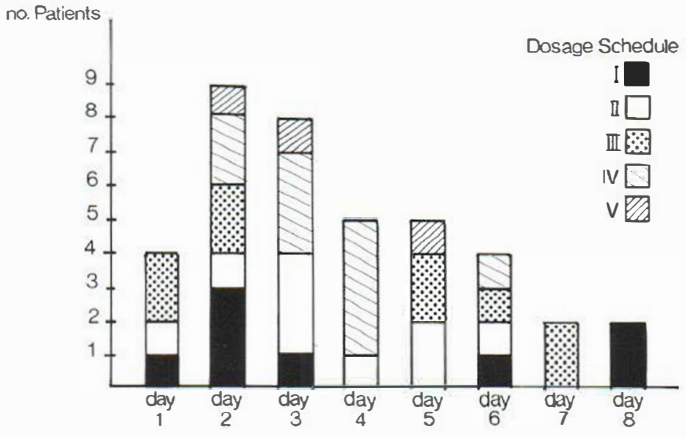

Fig. 1. Time sequence for maximum increase in SGOT. Dosage schedules are: I) 5 mg × 3/12 hours interval, orally. II) 25 mg single dose, orally. III) 25 mg single dose intramuscularly. IV) 5 mg × 3/12 hours interval, orally + "leucovorin rescue". V) 100 mg intravenously + "leucovorin rescue".

RESULTS

An average increase was found in SGOT in all patients but 4. Most patients showed the maximum SGOT increase on day 2. Fig. 1 shows the time for maximum increase in SGOT in relation to the different dosage schedules.

No significant difference in SGOT increase could be established between the different dosage schedules (Table 1). It should be noted, however, that 100 mg methotrexate, together with leucovorin rescue, given to 3 patients with psoriatic erythroderma, did not show higher degrees of liver toxicity as judged by SGOT than the more conventional dosages with and without leucovorin given to patients with uncomplicated psoriasis. It was not possible after one week to distinguish between the clinical responses to the different dosage schedules. The results of 100 mg methotrexate and leucovorin rescue were excellent in all 3 patients with psoriatic erythroderma. No clinical signs of over-dosage were found in these patients.

DISCUSSION

The results of our study clearly indicate an acute liver toxicity from methotrexate in all dosage schedules employed. It is not possible, however, to choose on the basis of our data between the various schedules. In long-term studies with serial liver biopsies, 15 mg methotrexate weekly according to the divided intermittent oral dosage schedule seems to give the same frequency of liver cirrhosis (8) as in patients treated with the 25 mg weekly single oral dosage schedule (5). No similar long-term studies exist on intramuscular weekly dosages, and no long-term studies at all have been presented on dosage supply with leucovorin.

The data on leucovorin and methotrexate in psoriatics found in the literature are contradictory (2, 4). The limited data from our study, however, do indicate that higher dosages of methotrexate with leucovorin rescue may be used, at least on a short-term basis. The combination of 100 mg methotrexate i.v. followed by leucovorin was highly effective in our 3 patients suffering from psoriatic erythroderma.

ADDENDUM

Further three patients have been treated with and evaluated after methotrexate 100 mg i.v. with leucovorin 9 mg i.m. thirty-six hours later. None of the patients distinguished themselves from the patients of the study in relation to liver toxicity, but in one patient ulcerations of lesions appeared on day four after methotrexate.

Table 1. *Percentage increase in average SGOT values following methotrexate given according to different dosage schedules with and without 9 mg leucovorin 36 hours later*

Methotrexate dosage schedules	No. of patients	Percentage increase ± SE
5 mg × 3, orally	8	135±54
25 mg, orally	9	110±41
25 mg, i.m.	9	163±135
5 mg × 3, orally + leucovorin	10	187±65
100 mg, i.v. + leucovorin	3	126±45

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Galactose Tolerance Test and Methotrexate-induced Liver Fibrosis and Cirrhosis in Patients with Psoriasis

Poul Lenler-Petersen, Helmer Søgård, Kristian Thestrup-Pedersen and Hugh Zachariae

Department of Dermatology, Marselisborg Hospital and Department of Pathology, Aarhus Kommunehospital, DK-8000 Aarhus C., Denmark

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Abstract. A total of 151 galactose tolerance tests (GTT) and liver biopsies were performed in a consecutive study of 45 psoriatic patients with methotrexate-induced liver fibrosis; of these, 23 had cirrhosis. Most patients with an abnormal liver histology had a normal GTT. We conclude that an oral GTT is not sensitive enough to reveal methotrexate-induced liver fibrosis or cirrhosis. The results indicate that the histological changes in methotrexate-induced liver fibrosis and cirrhosis may be of a rather non-aggressive nature.

Key words: Galactose tolerance test; Liver fibrosis/cirrhosis; Methotrexate; Psoriasis

Table 1. *Correlation of galactose tolerance test and liver histology in 45 psoriatic patients receiving methotrexate therapy*

GTT = galactose tolerance test

		Liver histology		
	In all	Normal	Fibrosis[a]	Cirrhosis
Normal GTT	133	43	90	33
Abnormal GTT	18	3	15	8

[a] Cirrhosis included.

Methotrexate (MTX) is valuable for psoriatic patients, where topical treatment cannot control the disease. MTX is, however, a hepatotoxic drug and also affects the bone marrow. Regular control of leukocytes, thrombocytes, liver function and liver histology is necessary. Liver biopsy is an unpleasant investigation, attended by potential risk of abdominal damage (e.g. bleeding), and the patient must be hospitalized for one day. In order to assess the usefulness of a non-invasive liver function test, we have compared the galactose tolerance test (GTT) with the liver histology in patients who developed fibrosis/cirrhosis during MTX therapy.

PATIENTS AND METHODS

During 1972–81, liver biopsies revealed fibrosis in 45 psoriatic patients treated with MTX; 23 of these had cirrhosis. Cirrhosis usually occurred after a total of 2200 mg had been given (4). All patients were seen in our outpatient clinic for blood test and admitted at approximately one-year intervals for liver biopsy (*ad modum* Menghini) and performance of a GTT. This was done by giving 40 gram of galactose orally to the fasting patient, and then collecting the urine excreted during the ensuing 8-hour period. Normally, the galactose excretion is less than 3 g per litre of urine. The liver biopsies were studied by one of two pathologists (Dr G. Pallesen and Dr H. Søgård, Department of Pathology, Aarhus Kommunehospital).