Methotrexate Hepatotoxicity in Psoriasis - Comparison of Different Dose Regimens

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British Medical Journal, 1972, 1, 654-656

Summary

Liver histological appearances were studied in 44 patients treated for psoriasis with methotrexate. Cirrhosis was found in six and hepatic fibrosis in another 11. Of these 17 patients 12 had received methotrexate by a regimen of frequent small dosage, two had been treated by a regimen of intermittent large dosage, while three had been treated at different times by both methods. The prevalence of cirrhosis and fibrosis was significantly greater in patients treated by frequent small dosage than in those treated by intermittent large dosage, though the dose level (mg/month) was similar in both groups. Hepatic fibrosis, sometimes preceding cirrhosis, seems to develop invariably if treatment with small frequent dosage is sufficiently prolonged. In the few circumstances in which this drug is indicated for psoriasis intermittent large dosage is the treatment regimen of choice.

Introduction

Hepatic fibrosis and cirrhosis have been attributed to treatment with methotrexate in patients with leukaemia (Colsky *et al.*, 1955; Hutter *et al.*, 1960; Taft, 1965) and histiocytosis X (Taft, 1965; Sharp *et al.*, 1969). Less severe abnormalities of liver histology were reported in patients treated for benign ocular disease (Hersh *et al.*, 1966). Methotrexate has been used in the treatment of severe psoriasis for nearly 20 years, but although isolated reports of hepatic fibrosis and cirrhosis have appeared (O'Rourke and Eckert, 1964; Coe and Bull, 1968; Epstein and Croft, 1969; Muller *et al.*, 1969; Dubin and Harrell, 1970) the relationship to methotrexate treatment has been disputed. Recently we have provided clear evidence of the hepatotoxic effects of methotrexate by finding hepatic fibrosis or cirrhosis in 17 (46%) out of 37 psoriatic patients and by showing that the severity of liver damage correlated well with the duration of treatment with methotrexate (Dahl *et al.*, 1971). During the course of that study we formed the impression that hepatotoxicity was less in patients who had received intermittent large doses of the drug compared with those treated with frequent small doses. Evidence for this conclusion is now presented.

Patients and Methods

Forty-four patients (24 males and 20 females) were studied. All had been treated with methotrexate for severe psoriasis. The age range was 17-74 years, with a mean of 53. The duration of treatment with methotrexate was 3 to 74 months.

None of the patients habitually drank spirits, but three regularly drank between 6 and 12 pints (3·4 and 6·8 litres) of beer each week. Patients with a known heavy alcohol consumption and one with evidence of arsenic toxicity were excluded. There was no evidence to suggest liver disease in any of the patients before treatment with methotrexate, although liver biopsy specimens were not obtained at this time. No patient was being treated with systemic corticosteroid drugs at the time of study, although six had been previously treated in this way. One patient had diabetes mellitus controlled with insulin and one had mild non-progressive acromegaly. Apart from one patient studied at necropsy the patients were otherwise in good general health except for their psoriasis and an associated arthritis in some cases.

One patient was studied at necropsy, the presumptive cause of death being septicaemia secondary to a urinary infection. In the other 43 patients percutaneous needle biopsy specimens of liver were obtained (Menghini, 1958). The patients were classified into three groups according to the histological findings: (1) cirrhosis, (2) hepatic fibrosis, and (3) normal and non-specific reactive hepatitis. Most of the patients were included in a previous study and details of the histological findings are as described by Dahl *et al.* (1971).

DOSAGE SCHEDULES

The patients were classified into three groups according to the schedule by which they had been treated with methotrexate.

Group 1. Frequent Small Dosage.—In this group were 22 patients who were treated with tablets on a daily basis. The commonest schedule used was 2·5 mg daily for between two and five days each week with corresponding rest periods. A small number were treated with 2·5 mg every other day or with 2·5 mg daily every other week.

Group 2. Intermittent Large Dosage.—This consisted of 14 patients. A single dose of 5-45 mg (usually 10-25 mg) was given either orally or intramuscularly at intervals of one to four weeks.

Group 3. Both Regimens.—This consisted of eight patients who had been treated at different times by both of the above methods.

Comparatively few patients had been treated exclusively by one dose regimen. For this reason patients were assigned to groups 1 and 2 if the drug had been given by the appropriate schedule for at least 80% of the total duration of methotrexate treatment. Otherwise they were placed in group 3. In most patients the dose level was continuously adjusted according to the clinical response. In those cases in which there were breaks in methotrexate treatment, the total duration of treatment is considered as the sum of the periods during which they were receiving the drug.

Results

In the 22 patients in group 1, treated with frequent small doses, cirrhosis was found in three and hepatic fibrosis in nine. In the 14 patients making up group 2, who received intermittent large doses, cirrhosis was not encountered but two had hepatic fibrosis. Among the eight patients in group 3, treated by both regimens, cirrhosis was found in three but the others showed only non-specific hepatitis. The greater prevalence of liver damage in patients treated with frequent small doses of methotrexate is shown in Fig. 1. This figure also indicates that a higher proportion of patients treated with frequent small dosage showed more severe liver damage after shorter periods of treat-

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ment compared with the intermittent large dosage group. In the third group of patients treated at different times by both regimens, the proportion of patients with significant liver damage was intermediate between the other two groups. The numbers in this group are small and since the variation in dosage schedules is so great they have not been analysed further.

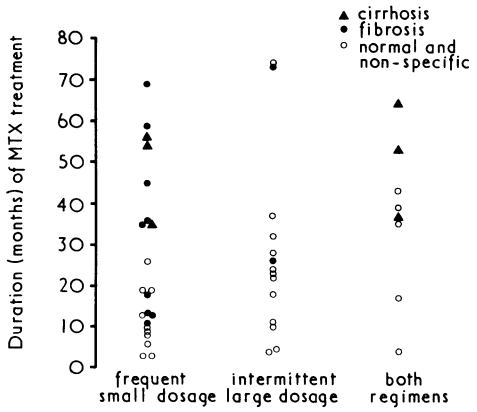

FIG. 1—Liver damage in psoriatic patients treated with two different dose regimens of methotrexate (MTX) in relation to duration of treatment. The increased prevalence of hepatic fibrosis and cirrhosis in the frequent small dose group compared with the intermittent large dose group is just at the level of statistical significance (P = 0·05).

The higher prevalence of cirrhosis and hepatic fibrosis in patients treated with frequent small doses (12 out of 22) compared with those treated with intermittent large doses (2 out of 14) lies just at the level of statistical significance (P = 0·05) using Fisher's Exact Test. This comparison, however, takes no account of the greater severity of liver damage found in the former group, nor of its more rapid onset during treatment. The mean age of the patients was similar in the two groups and they were also comparable as regards mean duration of treatment (24·9 ± 4·2 (S.E.) and 27·6 ± 5·8 months respectively) and mean dose level (41·9 ± 2·6 and 40·6 ± 3·2 mg/month respectively).

In the group of patients treated with frequent small dosage the severity of liver damage was related to the duration of treatment with methotrexate (Fig. 2). The mean duration of treatment (±S.E.) in patients with normal and non-specific liver histology was 11·6 ± 2·4 months, in those with hepatic fibrosis it was 33·3 ± 7·1 months, and in those with cirrhosis it was 48·3 ± 6·7 months. The values for patients with fibrosis and for those with cirrhosis differ significantly from those with normal and non-specific histology (P <0·05 and <0·001 respectively). There was no significant difference in mean dose level between the three histological groups.

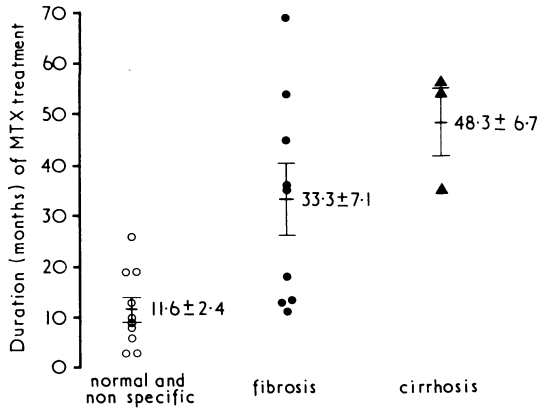

FIG. 2—Severity of liver damage in relation to duration of methotrexate treatment in 22 patients treated by a frequent small dose regimen of methotrexate. The values for the fibrosis group and for the cirrhosis group differ significantly from the normal and non-specific group (P < 0·01 and < 0·001 respectively).

Discussion

The findings in our patients treated with frequent small dosage confirm our previous conclusions that the prevalence and severity of liver damage is related to the duration of treatment with methotrexate (Dahl *et al.*, 1971). It is also clear that hepatic fibrosis regularly occurs if the drug is given for sufficient time by this schedule. Our own unpublished data suggest that the speed of onset of hepatic fibrosis may also be dose dependent and thus concur with the view of Hersh *et al.* (1966) that this effect on the liver is due to direct toxicity. Clearly long-term treatment with frequent small doses of methotrexate should be avoided if possible.

Weinstein *et al.* (1970) reported liver biopsy findings in 21 patients with psoriasis who had been treated with intermittent large doses (up to 50 mg/weekly) of methotrexate. Eight of these had received treatment continuously for two years or more and although minor abnormalities, particularly fatty change, were found in six of these only one had cirrhosis. These observations are comparable to our own findings in seven patients similarly treated by a large intermittent dose schedule for two years or more, of whom two were found to have hepatic fibrosis. This contrasts strikingly with our data from nine patients treated with frequent small dosage for two years or more. Of these, three had cirrhosis and five showed hepatic fibrosis.

It is not yet clear what proportion of patients treated by large intermittent dosage will eventually develop significant liver damage if treatment is prolonged for many years. The case of one patient has been reported whose liver biopsy specimen showed only moderate fatty change after 10 years of treatment by this regimen (Weinstein *et al.*, 1970). Zachariae and Schiødt (1971) found hepatic fibrosis in only one out of 35 patients who had received intermittent large doses of methotrexate for up to 72 months. This suggests that it may be possible in some patients at least to find a therapeutically effective dose which if given long-term by an intermittent schedule would be below that producing significant hepatotoxicity.

The frequent histological combination of fatty change and fibrosis has been suggestive of alcoholic liver disease. However, certain features of alcoholism, such as Mallory's hyaline, neutrophil infiltration, and centrizonal fibrosis, have not been present. Abnormal liver function tests have invariably returned to normal levels after cessation of methotrexate, and there has been a reduction in ascites and hepatic or splenic enlargement in a few patients with abnormal physical signs. Moreover alcoholics were so far as possible excluded from the study. Although Almeyda *et al.* (1971) suggested that alcohol and methotrexate may act synergistically to produce cirrhosis our data indicate that methotrexate alone, at least in frequent small dosage, can by itself lead ultimately to cirrhosis. Indeed the difference in prevalence and severity in the two dosage groups is further evidence that the pathological state is due to methotrexate alone since the two groups were similar in all other respects. This argument does not, of course, conflict with the idea that alcohol may potentiate the hepatotoxic effect of methotrexate.

It has been suggested that oral as opposed to parenteral methotrexate might prove more hepatotoxic because of high concentrations reaching the liver via the portal circulation during absorption. Although our data can neither confirm nor refute this suggestion, it is noteworthy that both patients in the large intermittent dosage group who had hepatic fibrosis had been treated exclusively by intramuscular injection.

Rees *et al.* (1967) considered that frequent small dosage of methotrexate was both more effective and less toxic than large intermittent dosage. The opposite view was put forward by McDonald and Bertino (1968), who considered that the thera-

peutic effects of both regimens were comparable. They argued both from an analysis of published deaths attributed to methotrexate and also from experimental pharmacological data that toxicity was less with large intermittent dosage though the data did not specifically relate to hepatotoxicity. Nevertheless, Baker (1970) reported major side effects in 5 out of 18 patients treated in this way.

Although the toxicity of methotrexate makes it a far from ideal treatment for psoriasis it remains of great value in very severe forms of this disease. Our findings indicate that a regimen of intermittent large dosage is safer in these circumstances if treatment is prolonged.

We thank the dermatologists of the Royal Victoria Infirmary, Newcastle upon Tyne, St. John's Hospital for Diseases of the Skin, the London Hospital, and the Royal Free Hospital for allowing us to study patients under their care. We are also grateful for help from the departments of pathology in these hospitals. Professor Sam Shuster has provided much helpful criticism and advice.

M.G.C.D. is in receipt of a Medical Research Council Junior Research Fellowship.

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Diabetic Amyotrophy: A Follow-up Study

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British Medical Journal, 1972, 1, 656-659

Summary

A clinical follow-up study of 12 patients with diabetic amyotrophy is reported. Re-examination after an interval indicated that improvement had occurred in all but one instance, and had been maintained over an average follow-up period of four and a half years. Improvement in the neurological syndrome appeared to follow improvement in diabetic control or institution of treatment in those whose diabetes had not previously been diagnosed.

Seven patients made a good functional recovery, three no longer having any muscular weakness. Five showed significant residual disability.

Introduction

The commonest form of diabetic neuropathy is a symmetrical sensory disturbance in the lower limbs with depression or loss of tendon reflexes (Goodman, Frankel, Baumoel, Marcus, and Wassermann, 1953; Fry, Hardwick, and Scott, 1962).

Garland and Taverner (1953) described an asymmetrical motor syndrome occurring in elderly subjects in which wasting and weakness principally affected proximal muscles in the legs. Sullivan (1958) described cases of both types, and contrasted the two clinical syndromes. Garland (1955, 1960) noted that the motor syndrome, which he called diabetic amyotrophy, tended to recover if good diabetic control was established, and this has been the general experience (Fry *et al.*, 1962; Redwood, 1962; Gilliatt, 1965; Hamilton, Dobson, and Marshall, 1968). Few reports, however, have dealt particularly with the natural history of diabetic amyotrophy. We thought a long-term clinical follow-up study of a group of patients with diabetic amyotrophy would be of interest.

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Methods

Fourteen patients had been diagnosed in the neurological department of the Middlesex Hospital or at the National Hospital, Queen Square, between 1958 and 1968 as suffering from diabetic amyotrophy as described by Garland. One died of carcinomatosis and one moved abroad. The remaining 12 were traced and studied. Information was sought from the hospital records about the duration and severity of the diabetes mellitus before the development of the neurological syndrome, and about the presenting symptoms and degree of functional disability.

All the patients were re-examined by one or both of us. We asked them about the control of their diabetes and their neurological symptoms, and compared our findings on clinical examination with those recorded at the time of diagnosis. Diabetic clinic notes gave additional information on the degree of diabetic control. This was considered "poor" if glycosuria or random blood sugar levels of over 200 mg/100 ml had occurred frequently, "fair" if glycosuria occurred only occasionally, and "good" if glycosuria was rare and no random blood sugar levels had been over 200 mg/100 ml.

The follow-up period ranged from 10 months to 12 years. The results are presented in summarized form and illustrative case histories are given. Three of the cases have been reported before. Cases 1 and 10 were briefly described by Gilliatt (1965) and Case 9 by Gilliatt and Willison (1962, Case 7).

Clinical Data

The 12 patients (nine men and three women) were aged 51 to 72 (mean 63) years at the time of the diagnosis of diabetic