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Folinic Acid Rescue Used Routinely in Psoriatic Patients with Known Methotrexate "Sensitivity"

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Many combinations of methotrexate and folic or folinic acid have been used to limit the side effects of methotrexate therapy in psoriasis or psoriatic arthropathy. Methotrexate inhibits the enzyme dihydrofolate reductase and prevents the formation of DNA and RNA. Folinic acid, the 5-formyl derivative of tetrahydrofolic acid, is the active form of folic acid. We have confirmed in 5 patients that continuous administration of folinic acid with weekly oral methotrexate prevents improvement of psoriasis. When folinic acid was ceased on the day of methotrexate in these patients their psoriasis improved. Five other patients with previous sensitivity to methotrexate, forcing cessation of therapy, were given weekly oral methotrexate and folinic acid every day except the day of methotrexate. Marked improvement of psoriasis or arthropathy occurred in each case without side effects. This method precisely limits the exposure to methotrexate, allowing a therapeutic effect without complication even in those patients who exhibit methotrexate sensitivity.

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Methotrexate is a useful drug in the treatment of severe psoriasis and psoriatic arthropathy. Unfortunately, short and long term side effects often preclude its use. Previously, various combinations of methotrexate (1) and folic or folinic acid have been used to limit these side effects with varying results (2–5). Hanno et al. (6, 7) believe that the use of folinic acid with methotrexate is only of theoretical interest, as they did not experience any side effects on weekly doses of up to 25 mg methotrexate. It is our experience that at least 20% of all patients suffer some form of side effect on doses varying between 2.5 mg and 25 mg per week. Occasionally there are no other treatment options so we have attempted to minimize the therapeutic window, limiting the time of action of methotrexate to 24 h, i.e. 1 or 2 cell cycles.

MATERIALS AND METHOD

Group one

Five patients with severe psoriasis were studied. They were all treated previously with methotrexate without complication. Baseline investigations included a full history and examination, full blood count, liver function tests, urea and electrolytes, and urinalysis. Patients were reviewed and blood count and liver function tests were repeated weekly while on treatment, 6 days after each methotrexate dose (8). The dose of methotrexate used was equivalent to the previous therapeutic dose in each case (range 10–25 mg weekly). Oral methotrexate was administered weekly, while folinic acid was given every day, including the day of methotrexate at a dose of 15 mg. The severity of psoriasis was assessed after 5 weeks; then the methotrexate, folinic acid regime was changed to that of Group two, while maintaining the same methotrexate dose.

Group two

Five patients with severe psoriasis (some also with psoriatic arthropathy) were included in the study. They had all been treated with methotrexate previously but suffered from side effects severe enough to stop treatment. In no case had there been any known precipitant involved in their initial adverse event. Baseline investigations included a full history and examination, full blood count, liver function tests, urea and electrolytes, and urinalysis. Patients were reviewed and blood count and liver function tests were repeated weekly while on treatment, 6 days after each methotrexate dose. Starting doses of methotrexate ranged from 2.5 mg to 10 mg depending on previous toxic effects.

Oral methotrexate was administered weekly, while folinic acid was given orally every day except the day of methotrexate, at a dose of 15 mg. Methotrexate dosage was adjusted according to the therapeutic response. Treatment was maintained until the psoriasis and arthropathy largely cleared.

CASE REPORTS

Group one

One illustrative case history is given below.

A 39-year-old male patient developed psoriasis in 1975. Topical treatment was slow to help and he always relapsed quickly. In 1985, he had grenz rays to the perineum, scrotum and elbows; a total of 1200 rads on 5 occasions. PUVA was started in July 1986 but was ceased due to travel problems. Methotrexate was commenced in March 1989 and ceased in May 1989 as he cleared. His psoriasis recurred in March 1990 but gradually worsened despite topical treatment. He was commenced on methotrexate 15 mg weekly and folinic acid 15 mg daily on 10.1.91. Full blood count and liver function tests remained stable but his psoriasis did not improve. Folinic acid was ceased on the day of methotrexate on 14.2.91. His psoriasis had cleared by 9.5.91 with full blood count and liver function tests still normal. Methotrexate and folinic acid were ceased and he remains clear to date.

Group two

A 70-year-old male developed psoriasis at the age of 20. He developed worsening flexural, trunk and limb psoriasis and was unresponsive to topicals. He had an old dense left hemiplegia and non-insulin dependent diabetes. He was commenced on methotrexate 15 mg weekly in April 1986 and was given intermittent courses of methotrexate to a maximum of 25 mg weekly with minimal side effects and stable full blood count and liver function tests. In June 1990, a course of methotrexate (15 mg weekly) was started; 6 days after the second dose he developed erosions and skin necrosis of the trunk and flanks. Folinic acid rescue was administered i.v. and then orally. He recovered fully with no impairment of blood count or liver function. He was recommenced on methotrexate and folinic acid 15 mg, 6 days a week in November 1990 and to date has had no further adverse reactions.

A 38-year-old male patient developed psoriasis at the age of 16. Since 1985 he had suffered from arthropathy of the fingers and toes. Methotrexate was commenced in September 1990. ALT 72 (5–40) on 8.10.90. Methotrexate was ceased and recommenced 2 weeks later as

ALT had reverted back to normal. The white cell count dropped from 9.8×10^9/L when methotrexate was commenced to 4.9×10^9/L on 29.11.90, so folinic acid 15 mg daily except on the day of methotrexate was added (methotrexate 10 mg weekly). To date the white cell count has increased to 7.9×10^9/L, liver function tests are normal and both the psoriasis and arthropathy are improving.

A 30-year-old male developed psoriasis in 1985. He had only maintained brief periods plaque-free on topical treatment, and PUVA aggravated his psoriasis. Methotrexate was commenced in September 1988, which cleared his psoriasis, and was ceased in December 1988. Methotrexate was recommenced in June 1989 and ceased in August 1989 as his skin was clear. Methotrexate was recommenced in October 1989 though in February 1990 ALT and total bilirubin became elevated and methotrexate was ceased. It was recommenced in April 1990 and ceased in May 1990 as the patient was apprehensive about the possibility of an eventual liver biopsy. In June 1990, tigason 25 mg 3 times a day was commenced but was ceased after 6 weeks due to hair loss and lack of response. Methotrexate was recommenced in August 1990. On 22.11.90 total bilirubin 23 (< 17), conjugated bilirubin 7 (< 5), ALT 67 (5–40), so folinic acid 15 mg daily except on the day of methotrexate was added. Liver function tests reverted to normal within 2 weeks. Methotrexate was ceased 12.12.90 as his psoriasis cleared. On the 28.3.91 methotrexate 15 mg weekly and folinic acid 15 mg daily six days per week was recommenced, and liver function tests and full blood count remain normal to date.

A 38-year-old female had had psoriasis since 1970. Previous systemic treatments include PUVA for 81/2 years and hydroxyurea for a number of years which was ceased in January 1989. She was commenced on methotrexate 10 mg per week and the psoriasis cleared, so the methotrexate was decreased to 5 mg weekly. In July 1990 her white cell count dropped from 9×10^9/L to 2.3×10^9/L. Methotrexate was stopped and folic acid was given with reversion to normal within 2 weeks. By September she had developed a severe destructive arthropathy of the toes with relapse of the psoriasis. Methotrexate to a maximum of 15 mg weekly and folinic acid 15 mg daily except on the day of methotrexate was commenced. By December 1990 the psoriasis had cleared, the arthropathy was well controlled and her white cell count was stable at 9.2×10^9/L. Methotrexate was ceased and she has had no relapse of her arthropathy or psoriasis to date.

A 74-year-old female with psoriasis since 1988 was difficult to control with topical treatment. She was commenced on methotrexate in January 1989. A maintenance dose of 10 mg weekly caused her white cell count to drop from 6.1×10^9/L to 3.1×10^9/L with associated nausea and malaise. Liver function tests were stable. Her white cell count recovered to 4.5×10^9/L on cessation of methotrexate, which was reintroduced 2 weeks later at a dose of 5 mg weekly. Her blood count was stable but she still had marked nausea and malaise. Methotrexate was ceased and hydroxyurea started 100 mg b.d., which caused a decrease in platelet count from 159×10^9/L to 99×10^9/L. Her platelet count recovered after stopping hydroxyurea, and the patient was inadequately managed on a lower dose of hydroxyurea so this was ceased. Methotrexate with folinic acid 15 mg daily except on the day of methotrexate was commenced on 14.2.91 and a maximum dose of methotrexate 15 mg weekly was needed. The patient initially felt some malaise which was shortlived. The white cell count was no lower than 4.4×10^9/L and liver function tests are stable. The psoriasis cleared by 23.5.91 and remains so to date.

DISCUSSION

A myriad of combinations of methotrexate and folinic acid and folic acid have been used previously; including intravenous, oral and intramuscular methotrexate and oral or intramuscular folinic acid (2–5). The timing of folinic acid with respect to methotrexate dosage is considered to be of importance. Methotrexate comprehensively inhibits the enzyme dihydrofolate reductase and prevents the formation of tetrahydrofolate, which is essential for the production of DNA and RNA. Folinic acid, the 5-formyl derivative of tetrahydrofolic acid, is the active form of folic acid. Therefore with continuous folinic acid and methotrexate one would expect no improvement in psoriasis, which has been confirmed with 5 patients in Group one.

During the 5-week period none of the patients experienced any improvement of their psoriasis, nor did they suffer any side effects from methotrexate. They all noted marked improvement when they passed into the Group two regime, still without side effects.

All the patients in Group two had suffered side effects to methotrexate sufficiently severe to warrant cessation of therapy. Giving folinic acid on the 6 methotrexate-free days means that in theory we have limited the activity of methotrexate to a mere 24 h. This is important when considering gastrointestinal and bone marrow side effects particularly. Olsen (9) states that there is a specific dose-time threshold for each particular organ's toxicity, this being 2×10^{-8} mol/L and approximately 42 h respectively for the most vulnerable organs, i.e. bone marrow and gastrointestinal epithelium.

Methotrexate is converted intracellularly to polyglutamyl metabolites, which are potent inhibitors of dihydrofolate reductase (10). These polyglutamates are retained within the cell in preference to methotrexate, and those of longer chain length dissociate more slowly from dihydrofolate reductase. The situation in humans is unclear but in rat epidermis over 90% of the polyglutamates are of longer chain length. This may explain the prolonged skin/plasma ratio of antifolate activity seen after methotrexate administration and also the prolongation of side effects well beyond its known half life. Folic acid itself will not act as a brake on the activity of methotrexate and will only counteract damage after the antimetabolic activity has ended.

We acknowledge that the two groups of psoriatic patients studied are not entirely comparable. Group one consists of patients who have never had any problems with methotrexate previously, while Group two consists of patients who have suffered side effects to methotrexate severe enough to warrant cessation of therapy. While we cannot show that this regime limits side effects in Group one patients, the Group two results suggest that side effects are limited with this combination of methotrexate and folinic acid. Our technique is superior in that it sets precise limits on the patients' exposure to methotrexate and has enabled us to show that therapeutic benefits can be achieved without complication even in those patients who have shown themselves to be sensitive to the effects of this most useful drug.

A more extensive controlled study on the routine use of folinic acid rescue in all psoriatic patients needing methotrexate is now required. This is under way but in this small department it will take years to collect the 120 patients required for statistical analysis.

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