

## ORIGINAL CONTRIBUTION

### METHOTREXATE : SIDE EFFECTS AND THE ROLE OF FOLIC ACID SUPPLEMENTATION IN PSORIASIS - A STUDY

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In 50 patients of psoriasis, side effects observed with methotrexate pulse were studied. Folic acid ameliorated majority of the side effects without compromising with the therapeutic efficacy of methotrexate.

**Key words : Psoriasis, Methotrexate, Folic acid**

Psoriasis is one of the commonest skin disorder. Methotrexate is a time tested, well proven drug for severe forms of psoriasis. Its use even with low dose, once weekly schedule in psoriasis is often associated with unpleasant side effects; particularly significant, are gastrointestinal side effects seen in upto 30 percent of patients.<sup>1</sup> The mechanism by which low dose methotrexate therapy induces these symptoms has not been fully elucidated. The treatment of choice for these adverse effects also remains unclear. Prompted by study of Duhra et al,<sup>2</sup> we decided to examine the nature and frequency of various side effects seen with methotrexate therapy, its possible mechanism of action, and effects of folic acid supplementation.

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#### Materials and Methods

The study was carried out in 50 patients of psoriasis attending skin out-patient department, 37 of these were males and 13 females; mean age being 40 years. Forty-four patients had generalized plaque form psoriasis, 4 erythrodermic, 6 pustular and 7 arthropathic psoriasis. All these patients were given fixed 15 mg. weekly methotrexate pulse (5mg 12 hourly 3 doses a week)<sup>6</sup> for a weeks periods. Twenty four out of fifty already had some past experience with methotrexate for their psoriasis, and almost 50 percent of them were unwilling to restart methotrexate owing to its unpleasant side effects. All necessary investigations and precautions were carried out before instituting methotrexate therapy.

All side effects, gastrointestinal as well as non-gastrointestinal were recorded. The following points were clarified, in relation to the side effects. Onset of symptoms in relation to methotrexate ingestion, duration

and severity of symptoms and action taken to avoid these side effects. Folic acid 10 mg was supplemented from day one of symptoms till the end of study period. For those patients who already had experience with methotrexate therapy, folic acid was supplemented from the very beginning of therapy period. The effect of folic acid supplementation was determined by direct questioning.

### Results

Twenty-three out of 50 (46%) patients experienced some kind of side effects with methotrexate therapy. In 15 (30%) of them, side effects were gastrointestinal in nature (Table I), 4 (8%) had non-gastrointestinal side effects and 4 (8%) had side effects of both GI and non-GI nature. There was no significant difference in side effects between

smoker and nonsmoker and alcoholic and non alcoholic patients. Non-gastrointestinal side effect included burning in lesion in 4 (8%) giddiness following methotrexate pulse in 2 (4%) while 1 patient each had coarse tremors, flu-like syndrome and altered mentation. A significant number of these side effects were drug limiting (Table I) i.e. patients preferred not to take next methotrexate pulse rather than suffer from side effects with each pulse. Majority of these symptoms appeared with the first or at most second pulse of methotrexate. Onset of symptoms was reported within 12 hours of taking methotrexate and continued for upto 1-3 days. Majority of these patients had taken conventional antiemetics and H2 blockers for methotrexate related G I symptoms in past with little or no benefit. Once folic acid was

Table I : Side effects of methotrexate

Side effects	Total side effects		Drug limiting side effects	
	No. of patients	Percentage (%)	No. of patients	Percentage (%)
Nausea / vomiting	9	18	6	12
Heart burn	5	10	5	10
Anorexia	12	24	8	16
Oral ulcer / glossitis	2	4	-	-
Burning in lesions	4	8	-	-
Fissuring	1	2	1	2
Altered mentation	1	2	-	-
Giddiness	2	4	2	4
Flu-like syndrome	1	2	1	2
Tremors	1	2	-	-

**Table II : Result of folic acid supplementation**

Symptoms	No. of Patients improved	Percentage improved
Nausea / vomiting	8	88.8
Heart burn	4	80.0
Anorexia	12	100.0
Oral ulcer / glossitis	2	100.0
Burning in lesions	4	100.0
Fissuring	1	100.0
Altered mentation	0	0.0
Giddiness	1	50.0
Flu-like syndrome	1	100.0
Tremors	0	0.0

supplemented, the side effects reported with methotrexate pulse were reduced to minimum (Table II) and patients were able to accept therapy much better. Addition of folic acid also did not interfere with therapeutic efficacy of methotrexate.

### Discussion

Majority of side effects seen in this study find mention in standard text books of dermatology. A few of the side effects such as flu-like syndrome and tremors however, have not yet been reported. One should also be aware of these side effects while using methotrexate. We chose fixed 15 mg oral methotrexate schedule to treat our patients. It is possible that incidence of side effects may be less with lower dosage or with parenteral route as reported in some studies.<sup>1</sup> However dosage lower than 15 mg/week may not achieve the desired control of psoriasis. Intracellular accumulation of methotrexate and its metabolites result in depletion of folate store.<sup>3,4</sup> Reduced folate is involved in normal synthesis and metabolism

of neurotransmitters in central nervous system.<sup>5</sup> Therefore, the centrally mediated gastrointestinal effects of methotrexate may be produced via intracellular folate depletion. Thus, it should be possible to abolish these adverse effects by reducing intracellular methotrexate to folate ratio by folic acid supplementation. In this study it was possible to abolish or reduce severity of gastrointestinal symptoms induced by methotrexate by supplementation with folic acid. Similar results were experienced by Duhra et al.<sup>2</sup> They were able to use methotrexate in even higher dosage without associated gastrointestinal symptoms. How folic acid supplementation could take care of non-gastrointestinal side effects as well is difficult to explain. A dose of 10mg folic acid daily did not compromise therapeutic efficacy of methotrexate. This finding is in accordance with results of other controlled studies.<sup>6</sup> This supports the view that methotrexate may exert a beneficial effect in psoriasis by mechanism other than inhibition of dihydrofolate reductase. Methotrexate inhibits neutrophil chemotaxis,<sup>7</sup> and has an effect on production or activity of leucotriene B<sub>4</sub>, interleukin 1 and 2, natural killer cells and T8 - positive cells.<sup>8</sup> However, the contribution of methotrexate on controlling these effects individually in psoriasis is not yet very clear. In spite of having number of therapeutic modalities for psoriasis (retinoids, PUVA, cyclosporin) methotrexate still remains one of the cornerstone of therapy in psoriasis. Addition of folic

acid to methotrexate therapy should allow dermatologists to use methotrexate in a much better way and enhance patient compliance. Encouraged by our results, we are now routinely supplementing folic acid in the dose of 5-10 mg daily in every psoriatic patient on methotrexate therapy.

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