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Adverse Effects of Low-Dose Methotrexate in Patients with Rheumatoid Arthritis

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Abstract

Methotrexate is widely used in the management of rheumatoid arthritis patients and is considered a first line drug. This study was conducted on 245 patients suffering from rheumatoid arthritis to study the adverse effects of low-dose methotrexate in adult patients of Kashmir valley fulfilling the revised American College of Rheumatology criteria. Adverse effects of the drug were seen in 96 (32.2%) patients but most of these were mild in nature. GI side effects were the most common adverse effects requiring treatment. Hepatic, haematological and muco-cutaneous effects were also seen. Considering the beneficial effects of the drug and the mild nature of the adverse effects, we recommend methotrexate in all patients of rheumatoid arthritis. Further, we also recommend regular use of folic acid in all patients on methotrexate and a follow-up of all patients to diagnose and manage any adverse effect of the drug.

Key words: Methotrexate, Rheumatoid Arthritis, Adverse effects, Low dose, Enzymes

Introduction

Rheumatoid arthritis is a chronic, progressive multisystemic inflammatory disorder with a prevalence of approximately 0.5-1%[1]. It usually involves middle aged adults with females being affected more than males. The inflammatory process of proliferating synovial membrane is immune mediated leading to destructive articular changes[2]. It is a chronic immuno-inflammatory disorder with symmetric polyarthritis involving small and large joints with repeated attacks of synovial inflammation causing articular cartilage damage with bone erosions.

In rheumatoid arthritis the potential for joint damage is present during the early phases of disease. Thus, the early introduction of effective treatment to maximally inhibit the inflammatory and destructive mechanisms has been recommended in recent times. Methotrexate is the preferred treatment for most of the patients of rheumatoid arthritis.

Methotrexate, synthesized in 1948, was developed primarily as an anti-tumor agent. Although first used to treat arthritis in 1951 by Gubner[3], the drug was not seriously considered as treatment for rheumatoid arthritis until late 1970s when Hoffmeister[4] reported improvement in patients of rheumatoid arthritis treated by intramuscular methotrexate. Methotrexate is a quick acting disease modifying agent and halts the progression of bony erosions, thereby preventing joint deformity and morbidity.

Methotrexate (N-10 methyl aminopterin) is a folate analogue and an ideal agent for rheumatoid arthritis. It is cheap and has a convenient weekly dosage [5,6,7,8,9]. It can be given orally, intramuscularly or by subcutaneous injection, with similar rates of absorption, regardless of the route of administration. Serum levels peak after 1-2 hours. Absorption is delayed by intestinal pathology such as inflammatory bowel disease, shortened bowel or malabsorption syndrome, but not by food. Methotrexate enters the cells where it is polyglutamated and the latter form may be responsible for the therapeutic effects of Methotrexate.

Toxicity is the main reason for discontinuation of the drug[10]. The most common side effects are those involving GIT (nausea, vomiting), hepatic, CNS (headache, dizziness), haematological and rarely respiratory. Most of these can be reduced by supplemented folic acid / folinic acid without interfering with the efficacy of the drug. Methotrexate is teratogenic and thus its use is contraindicated during pregnancy and lactation. Non-Hodgkin's (B-Cell) lymphoma which reversed with discontinuation of methotrexate has also been reported in patients with rheumatoid arthritis[11].

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Materials and Methods

Patients of either sex attending the OPD of the Department of Physical Medicine and Rehabilitation of Sher-e-Kashmir Institute of Medical Sciences, Srinagar were recruited prospectively from June 1997 till October 2004. The main aim of the study was to look for the toxicity of low dose methotrexate in patients of rheumatoid arthritis.

The patients of 18 years and above attending the Physical Medicine and Rehabilitation clinics that fulfilled the revised ACR criteria of rheumatoid arthritis were included. The patients included were both new cases as well as old cases with failure to continue other DMARDs for minimum period of 3 months due to non-effectiveness, non-availability or cost factors.

The following patients were excluded from the study:

(i) Insufficient kidney function (defined as estimated creatinine clearance of less than 7.5 ml/min).

(ii) Liver disease i.e., clinically significant hepatic impairment, liver enzymes more than twice the upper limit of normal values or dormant serious liver disease (e.g. cirrhosis).

(iii) Uncontrolled diabetes mellitus.

(iv) Severe congestive heart failure; interstitial lung disease; active peptic ulcer; inflammatory bowel disease; malignancies.

(v) Leucopenia (WBC count < 3.5 x 10^9/l); thrombocytopenia (platelet count < 120 x10^9/l).

(vi) Pregnancy; intended pregnancy; breast feeding or inability of adequate contraception[12].

After informed consent, all patients were started with methotrexate 7.5 mg per week given in an intermittent pulse regimen[6,7]. Folate supplementation in the form of folic acid tablets was given in all patients. Baseline investigations performed included haemogram, urine, KFT, LFT, Rh. Factor, CRP, ASO, ANA, X-ray chest and X-ray both hands-AP view[13,14]. Baseline liver biopsy was not done in any patient. In most of the admitted patients, intramuscular methotrexate was initially used for a period of 6-12weeks[15].

The patients were regularly followed up at 2 weeks, 6 wks, 3 months, 6 months and 6 monthly thereafter. At each follow up, a detailed history was elicited and physical examination done, especially with respect to methotrexate toxicity. Laboratory investigations including CBC with platelet count, LFT and KFT were done routinely. ALT and AST was determined every 4-8 weeks along with serum albumin. Special investigations like ultrasonography and pulmonary function tests were done depending upon the symptoms.

Observations

A total of 295 patients attending the Physical Medicine and Rehabilitation clinics between June 1997 and October 2004 were included in the study. Out of these, 27 patients were lost to follow up and hence excluded. 23 patients did not respond to the drug and were also excluded. Of the remaining 245 patients, 186 were female and 59 male with a male to female ratio of 1:3.2. The age of the patients ranged from 24 years to 65 years with the mean age of 43±4 years. Majority of the patients (127 patients) were in the age group 41-60 years.

Table 1: Age and sex distribution

Age (yrs)	*Males*	*Females*
21-30	2	12
31-40	14	34
41-50	31	84
51-60	8	43
>60	4	13
Total	59	186

The duration of the disease ranged from 4 months to 12 years with a mean duration of 6.8 years. Majority of patients (204) were already on NSAIDs, 31 patients on corticosteroids (mostly prednisolone) and 25 patients were on DMARDS other than methotrexate. 8 patients were on sulphasalazine and none of these had shown any improvement. 202 patients were positive for Rh factor and 43 were negative.

All patients were put on methotrexate. Of these, the drug was initially given by intramuscular route in 96 patients as they had NSAID induced GI symptoms. These patients were gradually transferred to oral route in 2-3 months. In the rest, oral drug was used from the beginning. 7.5 mg weekly was the initial dose which was gradually increased to a maximum of 20 mg/week depending on the response to the drug. The patients were gradually tapered off the NSAIDs. Corticosteroids were also gradually tapered off in the patients taking steroids. The average time for tapering off was 8 to 12 weeks – this being the time when methotrexate developed clinical response.

The patients were regularly followed up in the arthritis clinic. The minimum follow up was 6 months and maximum was 7 years. On each follow up, a detailed history, examination and investigations were done to assess the side effects and toxicity of drug. Out of the total 245 patients, 96 patients (39.2%) reported one or

the other adverse effect associated with the use of methotrexate.

Table 2: Side effects

Side effect	*No*	*%age*
GIT	51	21
Haematological	29	11.8
Hepatic		
Raised enzymes(< 2 times)	74	30
> 2 times	3	1.2
Skin	3	1.2
Mouth ulcer	5	2.0
Nodulosis	7	2.9
Respiratory	0	0

Gastrointestinal manifestations were the most common adverse effects of methotrexate use requiring treatment, seen in 51 patients (21%). These included a range of side effects like vomiting, diarrhea, nausea, and dyspepsia. Of these, nausea was most prevalent, occurring in 38 (15.5%) patients. Vomiting occurred in 13 patients 13(5.3%), dyspepsia in 19(7.7%) and diarrhea in 6(2.45%). Most of these responded to folate supplementation, H2 blockers and antacids. In 5 patients (2%) oral drug was replaced by intramuscular methotrexate for a period ranging from 4-6 wks. Temporary discontinuation of the drug was needed in nine patients, only to be restarted after 4-6 weeks at a lower dose. Two patients needed complete stoppage of the drug due to severe gastrointestinal side-effects and replacement by other DMARD'S.

Table 3: GIT manifestation

	Female	*Male*
Nausea	29	9
Vomiting	8	5
Diarrhea	4	2
Dyspepsia	13	6

Hematological side effects were seen in 29 patients (11.8%). The most frequent was mild to moderate leucopenia seen in 26 patients. Mild bone marrow depression (pancytopenia) was observed in two patients. This was a transient phenomenon and recovered following temporary withdrawal of drug for a period of 2-3 weeks. Megaloblastic anemia was seen in one patient. The patient likely had a baseline folate storage deficiency and improved with folate supplementation. Drug withdrawal was not needed in any patient. No case of severe bone marrow depression was seen.

Table 4: Hematological

	Female	*Male*
Leucopenia	21	5
Pancytopenia	2	0
Megaloblastic anemia	1	0
Thrombocytopenia	0	0

Hepatic abnormalities following prolonged Methotrexate use were also studied. 74 patients (30%) had elevation of liver enzymes. However, this elevation was mild in most of the patients. In 58 patients (78.3%) increase in liver enzymes was less than 15% above normal. Temporary withdrawal of the drug was required in four patients. Only in 3 patients enzymes increased more than twice the normal and in these cases the drug was discontinued to be replaced by other DMARDs.

Three patients (1.2%) developed recurrent skin rashes. The drug had to be discontinued in these patients. Oral ulcer was seen in five patients. Four patients had appearance similar to aphthous ulcer and one patient had vesicular lesion. Ulcers were single in all patients, except one, who had three ulcers. Two patients each had ulcers in floor of mouth and tongue and one patient had ulcer in buccal mucosa. Temporary discontinuation of the drug was required in these patients and they again started the drug after resolution of symptoms. No case of alopecia, hyperpigmentation and porphyria cutanea tarda was seen in the study.

Accelerated nodulosis was seen in six patients. The nodules were found mostly on the fingers and feet. Nodulosis was managed by decreasing the dose of methotrexate and addition of hydroxychloroquine. All the patients responded favourably. Mild elevation of serum creatinine was seen in 22 patients. However, the patients were clinically normal and the rest of investigations were normal. No case of gynaecomastia or erectile dysfunction was seen.

We did not come across any patient having respiratory system involvement in our study.

Discussion

Methotrexate as an anti-rheumatic agent came into prominence only in late 1970s. Since then, it has become the most widely used DMARD and an important drug in the armamentarium of rheumatologists. The main worry in the use of the drug was its toxicity, especially due to the fact that it is a known anti-neoplastic drug. However, the low dosage of the drug used in rheumatoid arthritis, coupled with a number of studies showing its low toxicity profile, have made it a popular drug now.

Our study was done to study the toxicity of low dose methotrexate in Rheumatoid arthritis patients attending

our out-patients' clinic. In this study 245 patients with a mean duration of disease of 6.8 years were evaluated and the adverse effects of the drug studied using clinical & laboratory parameters. Gastrointestinal side effects were the most prominent, occurring in 21% of the patients. These included anorexia, nausea, vomiting dyspepsia and diarrhea. Most of the studies have reported a similar percentage[16,17,18,19]. Bologna et al reported adverse effects involving GIT in 19.7% of cases. These effects are usually mild and managed with drugs (H2 blockers, antacids, folate supplementation). Haematological effects are also seen with long term Methotrexate use. In our study, 11.8% of patients had haematological side effects. Different studies have given different results, ranging from 4.5% (Bologna et al) to 25% (Gispan et al). These effects are generally mild leucopenia and mostly occur in elderly patients with diminished folate stores. Folate supplementation is sufficient for most of patients. Elevation of Mean Corpuscular Volume (MCV) usually precedes the occurrence of hematological toxicity[20]. Mild bone marrow suppression responds to temporary withdrawal of the drug for 2 weeks. Severe pancytopenia in a patient with renal insufficiency and hypoalbuminemia receiving salicylates and probenecid has been reported[21]. Pancytopenia most likely represents severe folate deficiency in a patient with baseline abnormal folate storage. Pancytopenia has also been seen after accidental methotrexate overdose in patients with hypoalbuminemia. Moderate to severe bone marrow suppression usually needs folinic acid.

Hepatic involvement with long-term methotrexate use is mostly mild increase in liver enzymes. We observed elevation of hepatic enzymes in 30% of patients which in most of cases was a mild increase not needing drug withdrawal. One case of clinically significant liver disease has been seen per 1000 patients treated for 5 years[22]. Predisposing factors include age of patient (or age at methotrexate initiation) & duration of treatment (or cumulative dose). Methotrexate probably induces liver toxicity by intracellular accumulation of methotrexate-polyglutamates. Routine liver biopsy is not recommended. Pulmonary involvement is a rare event with methotrexate treatment occurring in 0.5-1% patients (Beyder et al)[23]. However, Hilliquin did report pulmonary involvement in 12 patients with hypersensitivity pneumonitis (HSP) occurring in 4 patients and non-HSP lung disease in rest. The former occurred at 1-5 months of treatment. Most of their patients improved with symptomatic treatment. In our study, we did not observe any case of Methotrexate associated lung disease. New or accelerated nodulosis was first reported in 1986[24,25]. The prevalence ranges from 8-11% but we observed new or accelerated nodulosis in only 2.8% of cases. Methotrexate-induced nodulosis is more common in RF-negative patients. Adenosine-A1 receptors have been implicated in the development of the nodulosis.

Mucocutaneous involvement was seen in only 6 patients (2.4%) compared to 4.5% as seen by Carpenter et al[26]. The low incidence of stomatitis was probably low in our study as all patients received folic acid supplementation from the start of therapy with methotrexate. In the present study no case of hyperpigmentation, alopecia, porphyria cutanea tarda, gynaecomastia, interstitial pulmonary pneumonitis, osteopathy or teratogenesis was seen.

The overall incidence of adverse effects with the use of methotrexate in our study compare well those reported in most of the studies (Hilliquin et al, Beyeler et al, Besler et al, Buhroo et al)[27,28]. Most of the side effects were mild and usually responded to symptomatic treatment, folate supplementation and dose changes or temporary withdrawal. Only 8 patients had to stop the drug permanently. The low incidence of side effects can be attributed to regular evaluation of patients and the use of folic acid in all patients. The beneficial effects of folic acid have been reported by a number of authors. Folic acid has been noted to cause disappearance or decrease in adverse effects in 86% of patients[6].

Conclusions

Methotrexate is widely used for treatment of rheumatoid arthritis at early stage with minor side effects which are mostly reversed with folic acid/folinic acid. GIT, hematological and hepatic adverse effects are usually reversed with folic acid supplementation and other drugs.

In our study on 245 patients in different stages and of different age groups we found minimal side effects of the drug considering the duration for which the drug was used. Besides, most of the adverse effects responded to treatment. Hence, we recommend methotrexate to be considered in all cases of rheumatoid arthritis at any stage of disease so as to give maximum benefit to the patient. We also advocate routine supplementation with folic acid.

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