Original Article

Effects of Methotrexate on Prothrombin Time in Rheumatoid Arthritis Patients

Parvin MS[1], Rashid MU[2], Habib MA[3], Ara S[4]

Abstract

The present study was undertaken to evaluate safety and efficacy of methotrexate in Rheumatoid arthritis patients. This study was carried out on ARA criteria fulfilling 35 diagnosed Rheumatoid arthritis patients of either gender, aged 20-60 years, presented in Medicine department of Rajshahi Medical College Hospital, Rajshahi from July 2007 to June 2008. Patients with normal liver function tests and HBsAg and anti-HCV negative cases were given oral methotrexate (10-15 mg/wk) for 6 weeks. Baseline prothrombin time was 12.97±0.34 seconds. After 6 weeks of methotrexate therapy prothrombin time was found 13.47±0.46 seconds. During methotrexate therapy change of prothrombin time was not significant (p>0.05).

Key words: *Methotrexate, Prothrombin time, Rheumatoid arthritis.*

Introduction

Methotrexate was first developed for treatment of leukemia in 1940[1]. Now, it is used widely. It plays important role to halt pathology of various diseases such as rheumatoid arthritis[2]. In Rheumatoid arthritis it acts both by its anti-inflammatory and immunosuppressive effects[3]. Rheumatoid arthritis is not a fully curable disease. However, different types of treatment can be used to alleviate symptoms. Drugs therapy can be divided into DMARDs, analgesics and anti-inflammatory drugs, glucocorticoids, TNF-a blockers and interleukin-1 blocker. As DMARDs methotrexate is most widely used drug and has been found to produce durable remissions and delay or halt disease progression[4]. But methotrexate may affects adversely on various system[5] specially on liver[6] and one of its important marker is Prothrombin time. Department of Medicine, Duke University Medical Center, Durham, Carolina did a study from 1979 to 1988. They showed that the prevalence of methotrexate producing hepatotoxicity was low. Joel M Kremer showed from a continuous review of over 375 journals and other resources (2007) that methotrexate causes hepatotoxicity after a cumulative dose for malignant disease but the incidence was low in rheumatoid arthritis and psoriasis[7]. Rau A and Herborn G (2004) reviewed 216 literatures on the efficacy and toxicity of low dose weekly methotrexate in treatment of rheumatoid arthritis and stated that methotrexate proved to be very effective, had a relatively onset of action and was well tolerated in most cases[2]. Physicians of our country use methotrexate commonly as DMARDs in rheumatoid arthritis. So it is thought worthwhile to evaluate effect of methotrexate on Prothrombin time in rheumatoid arthritis patients.

Objectives

Objectives of present study were to determine safety, adverse effects and efficacy of methotrexate in treatment of rheumatoid arthritis patients.

Materials and methods

This prospective study was carried out in the Department of Pharmacology, Rajshahi Medical College, Rajshahi in collaboration with Medicine Department of Rajshahi Medical College Hospital, Rajshahi from July 2007 to June 2008. Rheumatoid arthritis patients fulfilling criteria of American

1. Mst. Shakila Parvin, Assistant Professor, Department of Pharmacology & Therapeutics, Kushtia Medical College, Kushtia.
2. Mamun Ur Rashid, Professor, Department of Pharmacology & Therapeutics, Islami Bank Medical College, Rajshahi.
3. Md. Anwar Habib, Professor, Department of Pharmacology & Therapeutics, Rajshahi Medical College, Rajshahi.
4. Shahin Ara, Associate Professor, Department of Pharmacology & Therapeutics, Rajshahi Medical College, Rajshahi.

Rheumatism Association (ARA) were selected from Medicine unit of Rajshahi Medical College Hospital. A total number of 35 patients of either gender, aged 20-60 years were selected for the study. Icteric or liver damaged patients, severely debilitated and complicated patients were not included in the study. After taking informed consent, complete history, physical examination were done and recorded in a preformed data sheet. 5ml blood was taken and liver function tests such as SGPT, serum bilirubin and prothrombin time were done. Patients with normal liver function tests and HBsAg and anti-HCV negative cases were given oral methotrexate (dose:10-25mg/wk) for 6 weeks. After 6 weeks patients were assessed to observe clinical improvement and blood samples were taken again and prothrombin time were assessed and compared to control. During this procedure 5 patients were dropped out.

Results

Out of 30 patients 12 were male and 18 were female with a male: female-2:3. Mean age of the study population was 36.70±8.95 years. Occupational distribution reveals most of the patients (40%) were housewife followed by farmer (30%), service holder (20%) and businessmen (10%) (Fig.-1).

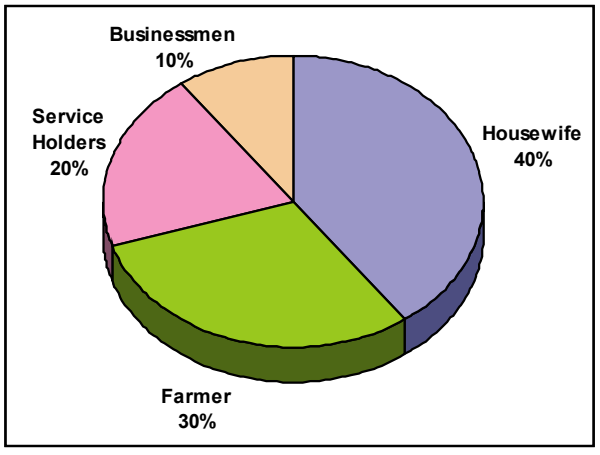

Fig.1: Occupational distribution of patients (n=30)

After getting methotrexate therapy for 6 weeks most of the patients (60%) showed marked improvement of symptoms (Table-1).

Table-I: Percentages of Clinical improvement of the patients (n=30)

Category of improvement	Number of Patients	Percentages of Improvement
Excellent	3	10
Good	15	50
Fair	9	30
Variable	3	10

Prothrombin time was analyzed and it revealed changes of prothrombin time was not significant after 6 weeks of methotrexate therapy (Table-II, Fig.-2).

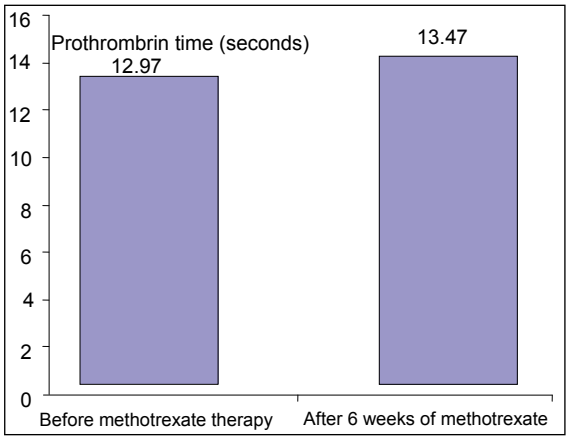

Figure 2: Mean level of Prothrombin time before and after 6 weeks of methotrexate therapy.

Before methotrexate therapy prothrombin time	After methotrexate therapy prothrombin time	P value
12.97±0.34 seconds	13.47 ±0.46 seconds	p > 0.05

Table-II: Estimated prothrombin time before and after methotrexate therapy

Discussion

Marked (>40% joint symptoms improvements) improvement of joint symptoms occurred in 60% patients. Some researchers observed the beneficial effects of methotrexate. Weinblatt ME et al[8], (1998) showed marked improvemet occurred more than 50% patients. Improvement of 69% patients occurred in another study[9]. Our study is in well agreement with those studies.

In this study female are affected more than male. Several studies showed female were more affected than male[10,11] which is also in agreement with our study. The peak incidence of rheumatoid arthritis is in third and fifth decades of life[10]. In the present study mean age of the patients was 36.7 years which was in well

agreement with above study. In present study, only occupational distribution of patients was revealed but difference of methotrexate effects was not studied. In present study no significant changes observed in prothrombin time during methotrexate therapy. We did not exclude exposure to coumarin drugs and vitamin k deficiency that may increase prothrombin time[12]. From observations from this study we can assume that methotrexate does not alter the synthetic function of liver.

Conclusion

From the results it can be concluded that methotrexate therapy in rheumatoid arthritis could not alter Prothrombin time. Hence methotrexate can be useful as DMARDs in treatment of rheumatoid arthritis with close monitoring. Further study on large population may clarify therapeutic exploration.

References

1. Carol & Richard Eustic. In the 70's it was experimental. Now it's the standard treatment for RA. Available: http://arthritis.about. com/cs/mtx/ a/mtx. Accessed on 02/11/08.
2. Rau R and Herborn G. Benefit and risk of methotrexate treatment in Rheumatoid Arthritis. Clin exp Rheumatol.2004; 22:83-94.
3. Van Ede AE, Laan RFJM, Blom HJ, De Abreu RAD, van de Putte LBA. Methotrexate in rheumatoid arthritis: an update with focus on mechanisms involved in toxicity. Semin Arthritis Rheum.1998; 27:277-92.
4. Prabha Ranganathan and Howard L. McLeod. Methotrexate Pharmacogenetics; The First Step toward Individualized Therapy in Rheumatoid Arthritis. 2006; 54 (5):1366-1377.
5. Rau R.Toxicity of methotrexate in rheumatoid arthritis. In Weinblatt ME (Ed.): A Comprehensive Guide to New Therapeutic Approaches of Methotrexate in Rheumatoid Arthritis Chicago, Pharma Libri.1997: 63-77.
6. West SG.Methotrexate hepatotoxicity.Rheum Dis Clin North Am 1997;23:883-915.
7. Kremer JM, 2007. Hepatotoxicity associated with chronic oral Methotrexate for nonmalignant disease. Google search engine-UP to date website [online] <http:// www.patients.uptodate.com. Accessed on 12/11/ 2009.
8. Weinblatt ME, Trentham DE, Fraser PA. Long-term prospective trial of low-dose methotrexate in rheumatoid arthritis. Arthritis Rheum.1988; 31:167-75.
9. Rau R.Toxicity of methotrexate in rheumatoid arthritis. In Weinblatt ME (Ed.): A Comprehensive Guide to New Therapeutic Approaches of Methotrexate in Rheumatoid Arthritis Chicago, Pharma Libri.1997; 63-77.
10. Gibson T and Hammed K, 1993. The prevalence of rheumatoid arthritis in two urbanized Pakistan; population. Scientific Abstracts, 57th meeting of the American College of Rheumatology. Atlanta: American College of Rheumatology. P.17.
11. Lipsky PE, 2005. Rheumatoid Arthritis. In: Harison, 17th edition. Principles of internal medicine. united states of America: McGraw Hill Companies; 2083-92.
12. Bauer JD, 1982.Clinical laboratory methods.United states in America:The C.V.Mobsy Company,pp.581-582.