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Original Article

Early Hepatotoxicity of Methotrexate in Rheumatoid Arthritis

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Abstract

The present study was undertaken to evaluate methotrexate induced early hepatotoxicity 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 (10-25mg/week) for 3 months. Baseline level of SGPT, serum bilirubin and prothrombin time was 10.07±0.32u/l, 0.59±0.03mg/dl and 12.97±0.34 seconds respectively. After 3 months of methotrexate therapy, level of SGPT, serum bilirubin and prothrombin time was found to be 12.60±1.16 u/l, 0.70±0.06mg/dl and 13.87±0.45 seconds respectively. During methotrexate therapy SGPT level changed significantly ($p<0.05$). Change of serum bilirubin and prothrombin time was not significant.

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Introduction

Rheumatoid Arthritis is a chronic multi system disease, seen throughout the world and affects all races[1]. The characteristic feature of rheumatoid arthritis is persistent inflammatory synovitis, usually involving the peripheral joints in a symmetric distribution[2]. Rheumatoid Arthritis is a common inflammatory articular disease[3]. It affects nearly 1% of the adult population worldwide[4]. It can lead to long-term joint damage resulting in pain, loss of function and disability.

Rheumatoid Arthritis is not a fully curable disease. However, many different types of treatment can be used to alleviate symptoms. Pharmacological therapy of rheumatoid arthritis can be divided into DMARDs, analgesics and anti-inflammatory drugs, glucocorticoids, TNF-α blockers and interleukin-1 blocker. DMARDs treatment should be introduced as early as possible in the course of the disease to suppress disease activity and thereby provide the possibility of avoiding joint damage and disability. Among DMARDs methotrexate are most widely used worldwide[5].

Methotrexate as DMARDs has been found to produce durable remissions and delay or halt disease progression[6]. They have both anti-inflammatory and immunosuppressive action[7]. They interrupt inflammation of joints by the cells of immune system that signal to one another and are thought to set up self-perpetuating chronic inflammation. They also depress cytokine production and cellular immunity. Analgesic and anti-inflammatory drugs improve pain and

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stiffness but do not prevent joint damage or slow the disease progression that methotrexate does[8].

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[9]. Rau R and Herborn G (2004) reviewed 216 literatures on the efficacy and toxicity of low dose weekly methotrexate treatment in rheumatoid arthritis and stated that methotrexate proved to be very effective, had a relatively rapid onset of action and was well tolerated in most cases[5].

Among DMARDs physicians in our country commonly use methotrexate. But so far I know, study on methotrexate induced hepatotoxicity has not yet been studied in our country context. So it is thought worthwhile to evaluate methotrexate induced hepatotoxicity 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 in collaboration with Medicine Department of Rajshahi Medical College Hospital, Rajshahi from July 2007 to June 2008. Rheumatoid arthritis patients fulfilling the criteria of American Rheumatism Association (ARA) were selected from medicine department 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. 5 ml blood was taken and liver function tests such as SGPT, serum bilirubin and prothrombin time was done. Patients with normal liver function tests and HBsAg and anti-HCV negative cases were given oral methotrexate (dose –10-25mg/week) for 3 months. After 3 months patients were assessed to observe clinical improvement and blood samples were taken again and same liver function tests were done 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 (Fig. 1). Mean age of the study population was 36.70±8.95 years (Table-I). Occupational distribution reveals most of the patients (40%) were housewife followed by farmer (30%), service holder (20%) and businessmen (10%) (Fig. 2).

After getting methotrexate therapy for 3 months, most of the patients (80%) showed marked improvement in symptoms (Fig. 3). Results of liver function tests were analyzed and it revealed significant change was observed in level of SGPT after three months of methotrexate therapy but no significant changes observed in serum bilirubin and prothrombin time (Table-II, Fig. 4).

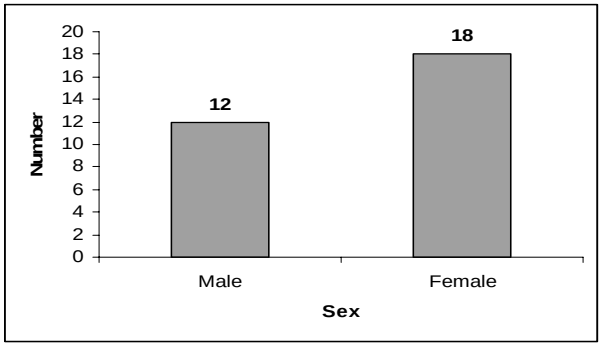

Fig. 1: Sex distribution of the patients (n=30).

Table-I: Age distribution of the patients (n = 30)

Age Range/Interval	Number of Patients	Age (Mean±SD) in years)
20-30	6	36.70±8.95
31-40	17	
41-50	5	
51-60	2	

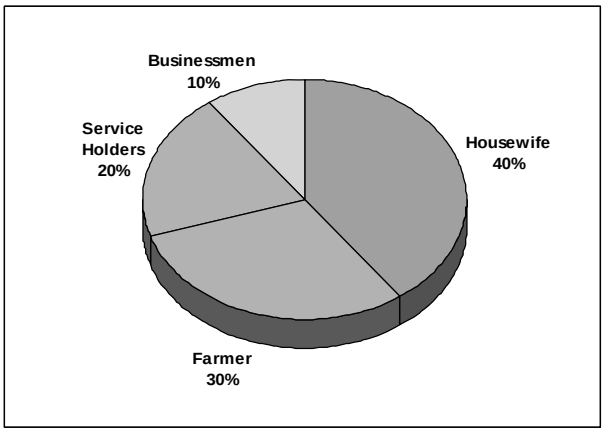

Fig. 2: Occupational distribution of the patients (n=30).

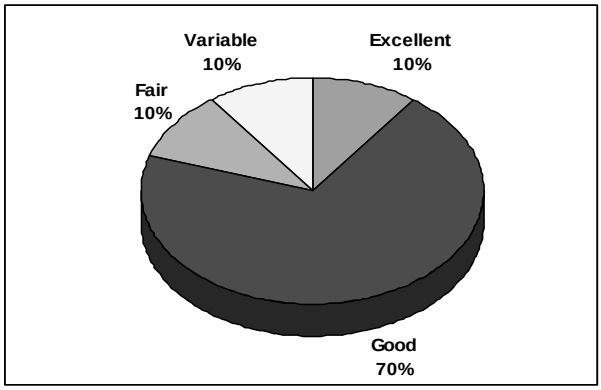

Fig 3. Percentage of clinical improvement of the patients (n=30).

Table- II: Result of Liver Function Tests

Liver function tests (N=30)	Before Methotrexate Therapy Mean ±SEM	After Methotrexate therapy Mean ± SEM	t value	P value
SGPT	10.07±0.32U/L	12.60±1.16 U/L	2.25	*< 0.05
Serum Bilirubin	0.59 ±0.03mg/dl	0.70±0.06 mg/dl	1.85	> 0.05
Prothrombin time	12.97±0.34 sec	13.87±0.45 Sec	1.7	> 0.05

* Indicates significant

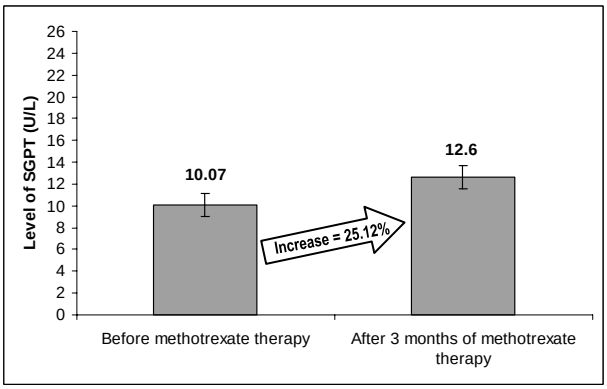

Fig. 4: Mean level of SGPT before and after 3 months of methotrexate therapy and percentage of increases after therapy.

Discussion

Marked (>50% joint symptoms improvements) improvement of joint symptoms occurred in 80% patients. Some researchers observed the beneficial effects of methotrexate. Weinblatt ME *et al*., (1998) showed marked improvement occurred more than 50% patients[10]. Improvement of 69% patients occurred in another study[11]. Our study is in well agreement with those studies.

Several studies showed female were more affected than male[12],[1].In this study female are also affected more than male which is also in agreement with the studies mentioned above. The peak incidence of rheumatoid arthritis is in third and fifth decades of life[12]. 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.

Significant change was observed in level of SGPT after three months of methotrexate therapy. Similar observations on SGPT were made by number of researchers. Taqween MA (2005) demonstrated SGPT was elevated during follow up. Among SGPT elevated patients all patients remained stable with methotrexate treatment[13]. Weinblatt ME (1985) showed slight elevations in liver enzyme in 48% of patients[14]. Transient slight elevations in liver enzymes up to 53% patients were found in a more recent study[15]. In present study elevations in liver enzymes up to 50% patients were found which is also in agreement with the studies mentioned above. The slight

differences may be due to differences in patient dosing and concurrent use of other drugs.

Bathon JM *et al.* (2001) showed methotrexate increases serum aminotransferases up to 32 percent[16]. Several studies showed these elevated levels returned to normal after dose reduction, a change in the concurrent NSAID therapy, folic acid supplementation or even the unchanged continuation of treatment[17],[11]. In our study methotrexate increases level of SGPT up to 25 percent that is in agreement with Bathon JM *et al.* study.

No significant changes observed in serum bilirubin in this study. Taqween MA (2005) showed serum bilirubin remained unaltered during methotrexate therapy[13]. Observations of present study about serum bilirubin are in well agreement with this study.

In present study no significant changes observed in prothrombin time during methtrexate therapy. We did not exclude exposure to coumarin drugs and vitamin k deficiency that may increase prothombin time[19]. 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 could produce mild hepatocellular damage but not an alarming severe hepatotoxicity. Hence methotrexate can be useful as DMARDs in treatment of rheumatoid arthritis with close monitoring especially periodic determination of SGPT that becomes normal after stoppage of therapy. Further study on large population in this aspect may clarify therapeutic exploration.

References

1. Lipsky PE. Rheumatoid Arthritis.In: Harrison, 17th edition. Principles of internal medicine.united states of America: McGraw Hill Companies. 2005; 2083-92.
2. Pincus T. Long term outcomes in rheumatoid arthritis, Br. J Rheu .1995; 34;59-73.
3. Ali ML, Alam MN, Haq SA, Das KK, Baral PK. Efficacy of Methotrexate in Rheumatoid Arthritis. Bangladesh Med Res Counc Bull. 1997; 23(3); 2-6. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/9621475 [accessed on 12/12/2008].
4. Extrapolations of prevalence and incidence statistics for Rheumatoid Arthritis, 2007 [Online]. [Accessed 2nd December 2008] Available: http://www.current research.com/r/Rheumatoid arthritis/stats-contry.htm.
5. Rau R and Herborn G. Benefit and risk of methotrexate treatment in Rheumatoid Arthritis. Clin exp Rheumatol 200422 :83-94.
6. Prabha Ranganathan and Howard L. McLeod. Methotrexate Pharmacogenetics; The First Step Toward Individualized Therapy in Rheumatoid Arthritis. 2006; 54 (5): 1366-1377.
7. 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.
8. Carol & Richard Eustic, 2006.In the 70's it was experimental. Now it's the standard treatment for RA. Also available: http://arthritis.about.com/cs/ mtx/a/mtx. Accessed on 2nd November 2008.
9. 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 12th January, 2009.
10. Weinblatt ME, Trentham DE, Fraser PA. Long-term prospective trial of low-dose methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998; 31: 167-75.
11. 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.
12. Gibson T and Hammed K. The prevalence of rheumatoid arthritis in two urbanized Pakistan; population. Scientific Abstracts, 57th meeting of the Americal College of Rheumatology. Atlanta; American College of Rheumatology. 1993; 17.
13. Taqween MA,Zafar A, Amera T, Masudur Rahman. Methotrexate induced hepatotoxicity in patients of rheumatoid arthritis. J postgard Med Inst.2005; 19(4):387-91.
14. Weinblatt ME. Toxicity of low dose Methotrexate in rheumatoid arthritis. J Rheumatol .1985;12:35-39.

15. Van Ede AE, Laan RF, Rood MMJ et al.Effect of folic or folinic acid supplementation on the toxicity and efficacy of Methotrexate in rheumatoid arthritis: a forty-eight week, multi-center, randomized, double blind, placebo-controlled study. Arthritis Rheum . 2001; 44: 1515-24.

16. Bathon JM, Martin RW, M.D, Roy M.A Comparison of Etanercept and Methotrexate in Patients with Early Rheumatoid Arthritis. The New Eng Jour Med. 2001; 343(22): 1586-93.

17. Kremer JM. Liver biopsies in patients with rheumatoid arthritis receiving methotrexate: Where are we going? J Rheumatol .1992; 9:9-91.

11. 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; 3-77.

13. Taqween MA,Zafar A, Amera T, Masudur Rahman. Methotrexate induced hepatotoxicity in patients of rheumatoid arthritis. J Post Grad Med Inst. 2005; 19(4); 387-91.

19. Bauer JD. Clinical laboratory methods. United states in America:The C.V.Mobsy Company. 1982; 581-82.

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