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Comparison of Outcomes of Two Anti tubercular Regimens in Pulmonary Tuberculosis at Tertiary Care Hospital

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ABSTRACT

Objective: To study the outcomes of two anti tubercular regimens in pulmonary tuberculosis under direct observation therapy short course (DOTS).

Materials and Methods: Ninety patients of pulmonary tuberculosis of age above 14 years were enrolled. Patients were allocated to two groups i.e. GI and GII receiving two antitubercular drug regimens. GI received the drugs under daily dose regimen protocol. However, GII were treated under intermittent (thrice weekly) dose regimen protocol according to the treating physician. Both the regimens consisted of 4 first line drugs viz Isoniazid, Rifampicin, Ethambutol and Pyrazinamide and their doses used were according to WHO recommendation. All the patients were treated under DOTS. The percentage of adverse drug reactions (ADRs) of both predictable and unpredictable and their severity were assessed in each patient and compared at week 1, 4 and 8. In addition, the biochemical parameters in each patient were also assessed and compared at respective weeks. The ANOVA (one way classification) was applied for analysis of biochemical parameters and results were expressed as Mean± SD. A probability value of less than 0.05 ($p < 0.05$) was considered to be statistically significant. However, the results of adverse drug reactions assessed in both the treatment groups were expressed as percentage.

Results: A significant difference was noted in incidence of ADRs in both the treatment groups. The total symptom wise and system wise incidence of ADRs in group I and II were 61.76% & 50% respectively. Comparatively there were less percentage of ADRs with no severity in patients who received intermittent dosage regimen during initial two months period of the treatment protocol. Moreover, a significant ($p<0.05$) difference in mean biochemical parameters was recorded in both the treatment regimes. Small fluctuation in mean biochemical parameters was noted in intermittent dosage regime group. However, a significant fluctuation in biochemical parameters were recorded in daily dose regime group though the parameters were in normal acceptable range.

Conclusion: This study reveals that the antitubercular drug regimen given on intermittent dosage schedule i.e. thrice in a week produced less number of ADRs and small fluctuation in biochemical parameters in initial two months period of the treatment protocol.

Keywords : Adverse Drug Reaction, Isoniazid, Pyrazinamide, Rifampicin, Pulmonary Tuberculosis

INTRODUCTION

Tuberculosis (TB) is a bacterial infection caused by organisms belonging to the Mycobacterium tuberculosis complex [1]. The World Health Organization (WHO) declared TB as a global health emergency in 1996 [2]. It is a major public health problem in India. India accounts for one-fifth of the global TB incident cases and topping the list among high burden countries [3]. Each year nearly two million people in India develop TB, of which around 0.87 million are infectious cases. It is estimated that annually around 330,000 Indians die due to TB [4]. Though several initiatives have been taken to combat TB globally but the most important step to ensure effectiveness of the treatment is the patient's adherence to treatment protocol [5, 6]. Hence, introduction of DOTS and use of fixed dose combination, were recommended by WHO [7, 8]. DOTS is a methodology for making sure that every patient starting TB treatment gets the best chance of being cured [9]. The patients take their medicines under the direct observation of a healthcare worker or some other responsible person. RNTCP is implementing the WHO recommended "Stop TB Strategy", which in addition to DOTS, addresses all the newer issues and challenges in TB control [10].

Despite the availability of affective chemotherapy, TB is still a major health problem in most of the countries [11]. The poor outcome was attributed to poor patient compliance, primary multidrug resistance and interruption partly due to adverse drug reaction [12]. Adverse reactions to medicines, is a common problem though preventable, are a major cause of illness, disability and even death [13]. Individual patients may exhibit particular and unpredictable sensitivities to certain medicines. In addition, if more than one medicine is prescribed, there is always a risk of negative interactions [14]. In view of the high prevalence of TB and widespread use of antitubercular drugs, it has become the need of the hour to monitor for ADRs and increase awareness of ADRs among consumers. Data regarding ADRs related to anti tubercular therapy are scant in local population.

This prompted the present study to assess the incidence of ADRs and outcomes of two antitubercular drug regimens as recommended by RNTCP under DOTS in pulmonary TB patients.

MATERIALS AND METHODS

A prospective longitudinal non-randomized case study was conducted from May 2012 to December 2012 in the Department of Respiratory Medicine, Mahatma Gandhi Medical College & Hospital, Jaipur, India. Ninety patients of pulmonary TB of age above 14 years were enrolled. Newly diagnosed or previously untreated cases of smear positive pulmonary tuberculosis cases admitted to the wards or visiting pulmonary medicine O.P.D at routine basis were included. While the patients with history of renal or hepatic impairment and the cases of extrapulmonary tuberculosis were excluded from the study. A thorough clinical examination was done for pulmonary tuberculosis to exclude other associated illnesses. After provisional diagnosis, the subjects had to undergo some laboratory investigations like x-ray chest and sputum smear examination etc. for confirmation of diagnosis. The patients were allocated to two groups (GI and GII). GI received the drug treatment on daily dose pattern while as GII were treated under intermittent (thrice weekly) dose pattern under DOTS. Each treatment regimen consisted of 4 first line drugs viz Isoniazid, Rifampicin, Ethambutol and Pyrazinamide. The patients in each group were assessed for percentage and severity of adverse drug reactions and compared between groups at first, fourth and eighth week. In addition, the biochemical parameters i.e alkaline phosphatase (ALP), aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) were also assessed and recorded for monitoring the hepatic status, as majority of antitubercular drugs are hepatotoxic [15-18]. The severity of the ADRs were graded on 3 point scale- mild, moderate and severe. Written informed consent of all the patients and the approval of the Institutional Ethics Committee (IEC) were obtained before the start of the study.

STATISTICAL ANALYSIS

The ANOVA (one way classification) was applied for analysis of biochemical parameters and results were expressed as Mean± SD. A probability value of less than 0.05 ($p<0.05$) was considered to be statistically significant. The results of ADRs were expressed as percentage.

RESULTS

Out of 90 a total of 68 patients completed the study. All the patients had more or less similar demographic characteristics. The patients were allocated to Group I and Group II consisted of 34 patients each. Each treatment regimen consisted of four first line drugs viz Isoniazid, Rifampicin, Ethambutol and Pyrazinamide. The percentage of ADRs associated to particular treatment regimen were assessed and compared. In addition, the biochemical parameters were also assessed at week 1, 4 and 8, respectively.

The total symptom wise and system wise incidence of ADRs in group I and II were 61.76% & 50% respectively. While comparing the symptom wise percentage of ADRs recorded in treatment group I and II (Table-1), no occurrence of tinnitus and ataxia was recorded in group II and no occurrence of edema of feet and dim vision was recorded in group I. Only 5.88% dermatological manifestations were recorded in group II as compared to 20.58% in group I. Interestingly only 11.76% of the patient population in group II had back pain/ muscle pain. On the contrary the back pain/muscle pain was recorded in 23.53% of the patients in the group I. A similar percentage of occurrence of headache, fever, cough, burning sensation in eyes and nocturnal leg cramps were recorded in both treatment groups. Moreover, the total percentage of adverse effects occurred in group II were comparatively less than the ADRs in group I.

Symptom wise ADRs	Group I, n=34	Group II, n= 34
Joint pain	8(23.53)	6(17.64)
Back pain / muscle pain / Body ache	8(23,53)	4(11.76)
Epigastric pain / Epigastric burning	7(20.58)	5(14.70)
Tingling and burning sensation in hands and feet	7(20.58)	4(11.76)
Anorexia / Nausea /Vomiting	6(17.64)	4(11.76)
Dermatological manifestations (Generalized itching / itchy rashes)	7(20.58)	2(5.88)
Headache	3(8.82)	3(8.82)
Vertigo/ Dizziness	3(8.82)	4(11.76)
Diarrhea	3(8.82)	1(2.94)
Weakness	3(8.82)	2(5.88)
Fever	2(5.88)	2(5.88)
Tinnitus	2(5.88)	0(0)
Shortness of breath on mild exertion	2(5.88)	1(2.94)
Constipation	1(2.94)	2(5.88)
Agitation	2(5.88)	1(2.94)
Cough	1(2.94)	1(2.94)
Edema of feet	0(0)	2(5.88)
Ataxia	2(5.88)	0(0)
Burning sensation in eyes	1(2.94)	1(2.94)
Dim vision	0(0)	2(5.88)
Nocturnal leg cramps	1(2.94)	1(2.94)
Miscellaneous	6(17.64)	3(8.82)

Table: 1. Symptom wise comparison of percentage of ADRs recorded between group I & II

When comparing the percentage of ADRs on systems involved basis there were less percentage of skin, endocrine and ocular system related ADRs in treatment group II while CNS related ADRs are more frequent with treatment group II (Table 2). The total occurrence of percentage of system wise ADRs were comparatively less in group II as compared to group I. The majority of ADR's disappeared on continuation of therapy with or without symptomatic treatment. Only 2.66% of the patients suffered from severe adverse effect which required discontinuation of therapy till recovery and only associated with treatment Group I.

System wise ADRs	Group I	Group II
Gastro intestinal system	30.67%	29.90%
Musculo-skeletal system	25.33%	23.52%
CNS	18.67%	27.44%
Skin	9.33%	3.92%
Respiratory system	4.00%	3.92%
Endocrine system	4.00%	1.96%
Vestibular system	4.00%	3.92%
Ocular system	2.67%	1.96%
CVS	1.33%	3.92%

Table 2: Systemic comparison of percentage of ADRs recorded between group I & II

Assessing the biochemical parameters, an elevation in mean ALP, SGOT and SGPT was noted in treatment group I i.e. daily dose regimen though the mean value of biochemical parameters in both the groups were within normal range at week 1, 4 and 8 (table 3). Interestingly no elevation in mean biochemical parameters indicates the comparative safety of antitubercular regime when taken on intermittent dosage schedule (thrice weekly).

Tests of daily dose treatment regimen during initial two month of treatment (Mean ± SD)			
Biochemical tests	1st week	4th week	8th week
Serum Alkaline phosphatase	66.14 ± 17.40	75.38 ± 23.56	77 ± 23.91
Serum AST (SGOT)	30.79 ± 8.48	34.94 ± 9.26	35.70 ± 9.55

Serum ALT (SGPT)	30.35 ± 8.22	34.5 ± 8.53	35.38 ± 9.10
Tests of Intermittent treatment regimen during initial two month of treatment (Mean + SD)			
Biochemical tests	1st week	4th week	8th week
Serum Alkaline phosphatase	65.91 ± 16.62	68.32 ± 15.23	73.47 ± 15.79
Serum AST (SGOT)	29.58 ± 7.44	33.17 ± 7.55	33.26 ± 6.63
Serum ALT (SGPT)	29.17 ± 6.84	32.94 ± 7.24	33.05 ± 6.29

Table.3: Comparison of mean biochemical parameters in treatment group I and II.

DISCUSSION

Tuberculosis (TB) is a major public health problem across the globe and particularly in India. Compliance with anti-TB medication is essential to effective management. ADRs are the major cause of poor compliance and sometimes warrant the discontinuation of therapy [19]. The frequency of drug dosage in every clinical situation has an important role on compliance of effective management. Two strategies to ensure compliance are DOTS and fixed dose combination in the management of TB [20]. Two RNTCP recommended antitubercular drug regimes allocated to two patient groups were assessed for incidence of ADRs and changes in biochemical parameters (APL, SGOT and SGPT). The treatment protocol of the patients groups followed in this study was DOTS strategy.

A significant difference in incidence of ADRs was noted in both the treatment groups. Generally antitubercular drugs are well tolerated [21], may be associated with unwanted effects of different origin [22]. The percentage of system wise ADRs noted in daily dose regimen were gastro intestinal system 30.67%, musculo-skeletal system (25.33%), central nervous system (18.67%), skin (9.33%), respiratory system (4%), endocrine system (4%), vestibular system (4%), ocular system (2.67%) and cardiovascular system (1.33%). On the contrary, the percentage of system wise ADRs recorded in intermittent dosage regime were gastro intestinal system 29.90%, musculoskeletal system (23.52%), central nervous system (27.44%), skin (3.92%),respiratory system (3.92%), endocrine system (1.96%), vestibular system (3.92%), ocular system (1.96%) and cardiovascular system (3.92%) (Table: 2). As per results of this study the symptom wise as well as the system wise percentage of ADRs were comparatively low in patients who received the intermittent dosage regime i.e. thrice in a week. This low incidence in total ADRs as compared to patients who received the daily dosage regime could be due to better compliance and less dosage frequency. As far as the severity of ADRs recorded in this study is concerned only 2.66% exhibited serious adverse effects e.g. dermatological and menstrual disturbance by patients who were treated with daily dose regime. These results are in support of a study reporting almost the same percentage of severity of ADRs [21]. As against this another study reported higher percentage of severity of ADRs [23].

As majority of the antitubercular drugs cause hepatotoxicity. Hence, it was found worthwhile to monitor the biochemical parameters in each patient at different weeks of the treatment protocol for a period of initial two months therapy. A significant difference ($P<0.05$) was noted in all the mean biochemical parameters i.e. ALP, SGOT and SGPT at week 1, 4 and 8 respectively. There were significant fluctuations in the biochemical parameters in patients who were treated by daily dose regime though the levels were within normal range. However, there was small fluctuation in biochemical parameter in patients who were treated by intermittent dose regime. Interestingly, this indicates the intermittent dosing schedule may reduce the risk of toxicity and thereby improve the safety profile of drug regime known to cause side effects.

The results of this study reveals that the intermittent antitubercular drug regime consisted of 4 first line drugs viz Isoniazid, Rifampicin, Ethambutol and Pyrazinamide, has comparatively noted less incidence of ADRs and small fluctuation in biochemical parameters in intial two months (intensive phase) of the treatment period. More studies in this direction are required to further explore the results of this study before a comment on preference on use of intermittent antitubercular dose regime in pulmonary TB is made.

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