

FREQUENCY OF ADVERSE EFFECTS OF FIXED DOSE COMBINATIONS, IN TUBERCULOSIS AND THERE EFFECTS ON TREATMENT OUTCOME

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ABSTRACT

Introduction: This study was designed to assess the frequency, types and impact of adverse drug reactions (ADR) to category 1 anti-tubercular therapy using fixed drug combinations (FDC). Patients with tuberculosis started on anti TB treatment from 01st of July 2011 to 30th of June 2012 were recruited

Methodology: Patients were followed up for development of ADR. Frequency of ADR, number of patients who required prolongation of therapy, who had alternate regimes, and there treatment outcome were recorded.

Results: Out of 280 patients with tuberculosis 67 (24%), 37 (55.2%) males, 30 (44.8%) females ADR. Thirty three out of 74 (44%) of total population above the age of 60 had ADR, while only 34 out of 206 (16.5%) of patients below the age of 60 had ADR (Chi= 23, p <0.0001). Incidence of ADR were - Dyspeptic symptoms 31(11.1%), itching 20 (7.1%), hepatitis 9 (3.2%), arthralgia 1 (0.4%), vertigo 1 (0.4%), peripheral neuropathy 1 (0.4%), visual impairment 1 (0.4%), rash 1 (0.4%).

Out of 27 patients who had prolongation of therapy 22 (81.4%) were due to ADR (Chi = 54, p <0.0001). Nine (3.2%) were given alternate regimes (Fishers exact p = 0.000017) [6 hepatitis, 1 rash, 1 vertigo, 1 visual impairment]. None of the patients with ADR had relapses or treatment failures.

Conclusion: Adverse reactions were commoner among the elderly, and were associated with prolongation and modification of anti tuberculosis therapy but over all treatment outcomes were not adversely affected.

Key words: Tuberculosis, Fixed Drug Combinations, Adverse Reactions, Alternative Regimes

INTRODUCTION

Tuberculosis is still a major cause of death and one of the most challenging public health problems worldwide. Two billion individuals, about one-third of the total human population, are infected with the causative agent of tuberculosis, *Mycobacterium tuberculosis*.¹ According to the World Health Organization's 2014 global report on Tuberculosis (TB), there were 9 million estimated cases of TB 2013, with a loss of 1.5 million human lives.

Once diagnosed, patients with tuberculosis must undergo immediate treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months and

subsequently, patients with newly detected pulmonary tuberculosis should receive isoniazid and rifampicin for another four months. For an optimal outcome, the treatment should be according to Directly Observed Treatment Short course (DOTS).³

Many adverse effects are associated with anti tubercular treatment (ATT). As TB requires long-term treatment, many adverse effects and patient non adherence remains the most important reason for treatment failure.⁴

In the management of TB patients, fixed-dose combination (FDC) anti-TB drugs are recommended over individual drugs.² Sri Lanka has introduced FDCs for TB treatment since 2005. There are several advantages as well as disadvantages of using fixed dose combination tablets over individual drugs in the treatment of tuberculosis.⁵ Our national policy is to use FDC 4 tablets (INAH – 75mg, Rifampicin 150mg, ethambutol 275mg and pyrazinamide 400mg) for

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intensive phase and FDC 2 (INAH – 75mg, Rifampicin 150mg) for continuation phase, according to weight bands in the category 1 regime.

Since FDC are in wide use now, it is important to have a better understanding of the adverse reactions in order to detect them in time and to study their impact on the treatment outcome. The objectives of our study were to assess the frequency and types of adverse reactions to FDC and to find out the impact of adverse reactions on the treatment regimen. We also aimed to assess the impact of occurrence of adverse reactions and the subsequent changes in the treatment regimens on the treatment outcome in patients with tuberculosis.

METHODOLOGY

This prospective descriptive study was carried out on patients whose anti TB treatment was started from 01st of July 2011 to 30th of June 2012 at Respiratory unit 01, Chest Clinic-Kandy. Ethical approval for this study was granted by the Ethical Committee of Teaching Hospital Kandy. Written informed consent was obtained from all participants of the study.

All patients who were confirmed to have Tuberculosis and were initiated on FDC [FDC4 (HRZE) x 2 months and, FDC2 (HR) x 4 months] with a plan to be treated for six months during the study period of one year were recruited. This population included pulmonary and extra pulmonary TB, but excluding TB meningitis, CNS TB, bone TB and military TB. Both bacterially positive as well as negative patients were included. Only the new cases were included. Case definition given by the national guideline was used to diagnose tuberculosis in this study. They were managed according to daily DOTS strategy.

Patients who met the following exclusion criteria were excluded from the study. Exclusion criteria were: patients on regimes other than the standard (CAT 1) regime, patients who were on individual drugs, patients on long term steroids and anti-histamines, patients with active skin diseases prior to drug treatment, patients with HIV, and patients with TB meningitis, CNS TB, bone TB and military TB who would any way receive ATT for more than 6 months due to the site of infection.

Patients who were started on ATT were educated on the following symptoms at the commencement of ATT for adverse reactions.

Major reactions

Nausea, vomiting, yellow discoloration of eyes and urine, skin rashes, oliguria, dizziness, confusion, visual impairment and features of shock.³

Minor reactions

Epigastric discomfort and pain, itching of skin, numbness of feet, joint pain and swelling, flue like symptoms and orange colored urine.³

Patients with major reactions were advised to stop treatment and report to the local treatment facility immediately and those who had minor reactions were advised to report to local treatment facility but continue treatment.

All were screened for diabetes, and all patients underwent full blood count (FBC) liver biochemistry, and renal functions before the start of ATT.

Patients were followed up weekly or earlier if they develop adverse reactions.

They were screened for the development of adverse reactions using an interviewer administered questionnaire which evaluated itching, rash, gastritis, hepatitis, visual impairment, arthralgia, vertigo, peripheral neuropathy and acute renal failure.

WHO definition for the diagnosis of ATT induced hepatitis was used in this study to diagnose drug induced hepatitis. FDC induced hepatitis was defined as elevation of serum transaminases more than 2 folds of the normal and elevated serum bilirubin level in symptomatic patients (i.e. patients with nausea, vomiting with or without icterus or hepatomegaly) after clinical exclusion of other causes of hepatitis.⁴

Patients with visual symptoms underwent ophthalmic assessment by an ophthalmologist for diagnosis/exclusion of optic neuritis. Patients with features of peripheral neuropathy underwent nerve conduction studies.

Patients who developed adverse reactions were managed according to WHO guideline for treatment of tuberculosis 2009.³

All patients were followed up for a year since the commencement of treatment and patients with adverse reactions were followed up with sputum cultures for Mycobacterium tuberculosis at 6 months and 12 months to confirm that cultures are negative. WHO treatment outcome definitions were used to categorize the treatment outcomes in our study.³

Data was entered in excel spread sheets and descriptive analysis was done using percentages. Chi square statistics was used to asses if adverse reactions act as a risk factor for prolonged or altered therapy.

DISCUSSION

Adverse reactions to anti tuberculosis medications have been the subject to many researches. According to a study done by WHO anti-tuberculosis drugs are known to be associated with number of adverse effects and that can lead to drug discontinuation in up to 23% of patients.⁴

Studies done on individual drugs were found but, fixed dose combination (FDC) therapy related data were not available in Sri Lanka. Since FDC therapy is being widely used in Sri Lanka since 2005, data related to it would be essential in the program for TB control. Since adverse reactions can lead to significant morbidity and loss of compliance it's vital for a national TB control program to have an assessment of the problem.

Hepatotoxicity is the most common major adverse reaction found in our study (3.2%). This is a significant proportion given the seriousness of the condition and the time taken to desensitize such patients. Overall incidence of hepatotoxicity was 3% in a study done by Daphne Yee et al. Incidence of ATT induced hepatitis is comparable in our study compared to the study done by Daphne.

However the study done by Senarathna et al in pre FDC era in Sri Lanka show an incidence of drug induced hepatitis of 9.5%.⁷ The same study showed that 6 out of 74 patients who had drug induced hepatitis died, but none of the patients in our study died during the study period. One of the most important finding in our study is that the incidence of drug induced hepatitis is less compared to pre FDC era. There are no previous studies done on FDC to find out the adverse reactions in Sri Lanka. Whether incidence of drug induced hepatitis is less with FDC compared to individual drugs is an important finding which should be assessed further. One good reason for this could be the lower doses of isoniazid and pyrazinamide against the standard doses of rifampicin included in FDC used in Sri Lanka.

Efficacy of FDC in treatment of tuberculosis has been comparable to individual drugs as shown in a study done by Christian Lienhardt et al.⁸ This study confirms non inferiority of FDC to individual drugs. The same

study shows that incidence of severe adverse reactions were similar between individual drugs. Therefore it's interesting to know if a low dose of INAH (225 mg) in FDC is enough to treat tuberculosis compared to 300 mg. Similarly proportion of pyrazinamide is lesser in FDC (1200mg instead of 1500mg). Whether this lowered dose is responsible for lower incidence of ADR is a possibility. A further study is suggested to investigate this interesting finding.

The overall incidence of dermatological reactions has been estimated at 5.4%.³ Incidence of skin reactions was higher in our study (7.5%). However most of the patients were having pruritus (7.1%) which did not warrant alternate regimes or discontinuation of treatment. Their treatment regime was continued under antihistamine cover. The only patient who had a rash was secondary to pyrazinamide and the drug was discontinued.

Gastrointestinal symptoms such as loss of appetite, nausea, mild abdominal pain, vomiting and diarrhea have been reported with rifampicin and which may lead to modification of the regimen in up to 9% of patients.⁹ Dyspepsia was the commonest adverse reaction (11.1%) shown in our study.

It is estimated that rifampicin associated acute renal failure occurred in 0.05% of patients treated for TB, but in our series we didn't find any patient with this ADR.

Twenty three percent of patients in our study had adverse reactions which is comparable to the study done by Schaberg T et al.¹⁰ Therefore nearly one fourth of the patients commenced on ATT develop ADR which is quite a significant proportion. Although data on overall incidence of adverse reactions to ATT in Sri Lanka is lacking, one of the previous preliminary study done by same authors has shown that incidence of major adverse reactions is 15%.¹¹ Same study showed that among the patients who needed hospital admission 48% had drug induced hepatitis.

Male female ratio was similar to studies done in Sri Lanka previously.¹² Proportion of females in the adverse reaction group was higher but this difference was not statistically significant.

Patients who had ADR were slightly older compared to patients who didn't have ADR. A significant proportion of patients (44%) above the age of 60 had adverse reactions. This finding is comparable with past studies which identifies age as a risk factor for adverse

reactions. This emphasizes the importance of closely following up elderly patients for adverse reactions.

A significant finding in this study is that patients with ADR were more prone to have a prolonged therapy for >6 months. That means having an ADR considerably increases morbidity. Although there were many studies looking into adverse reactions this knowledge is new and highlights the importance of monitoring patients closely for development of ADR. However having adverse reactions did not adversely affect the overall treatment outcome. In fact the failures were zero among ADR group this could be due the better supervision and more interaction with the health care workers in patients who had ADR. All patients with ADR underwent sputum cultures for mycobacterium tuberculosis which was negative at 6 and 12 months which confirms that the alternative regimes were safe and effective. This study provides valuable new information regarding adverse reactions to anti tubercular treatment in Sri Lanka as there are only few studies done on this field despite the number of patients with tuberculosis.

RESULTS

A total of 280 patients were on study 168 (60%) males and 112 (40%) females. The mean age of the total 280 patients was 48 years (SD 18.7), 67 (24%) had adverse reactions out of which 12 (4.3%) were major reactions and 55 (19.6%) were minor reactions.

Mean age of patients with adverse reactions was 51.3 years (SD 16.54; range 18 to 91) while mean age of patients without ADR was 45y (SD 18).Thirty seven males (21.8%) and 30 females (27%) had adverse reactions (Chi = 0.68) (p= 0.51).

Thirty three out of 74 (44%) of total population above the age of 60 had adverse reactions in our study, while only 34 out of 206 (16.5%) of patients below the age of 60 had adverse reactions (Chi= 23) (p <0.0001).

Frequency of adverse reactions is shown in table 1.

ADR (Major)	n	%	incidence
Hepatitis	9	13.4	3.2
Vertigo	1	1.5	0.4
Vision	1	1.5	0.4
Rash	1	1.5	0.4
ARF	0	0.0	0.0
ADR (Minor)			

Dyspeptic	31	46.3	11.1
Itching	20	29.9	7.1
Arthralgia	3	4.5	1.1
Peripheral	1	1.5	0.4

Twenty seven patients had prolonged treatment of >6 months out of which 22 (81.4%) were due to adverse reactions (chi = 54, p<0.0001).

Treatment outcome and ADR is shown in table 2

Outcome	With ADR	%	Without ADR	%
Treatment successful	67	100	190	89.2
treatment interrupted	0	0	4	1.9
failures	0	0	6	2.8
not analyzed	0	0	13	6.1
Total	67	100	213	100.0

Nine patients (13.4%) out of 67 who had ADR had to be given alternative regime while none of the patients out of 213 who did not have adverse reactions were put on alternative regimes [Fishers exact p = 0.000017].

Out of 22 who had prolonged therapy 9 (40.9%) received alternate regimes while rest of the 13 (51.1 %) were successfully desensitized or the same regime was continued. For majority of patients with pruritus same regime was continued with antihistamines.

Table 3 shows the frequency of patients who required alternate regimes due to ADR.

ADR	n
Itching (with skin eruption)	1
Hepatitis	6
vertigo	1
visual impairment	1

Three patients with hepatitis were successfully desensitized. None of the patients died due to ADR.

CONCLUSIONS

Adverse reactions were associated with prolongation of anti tuberculosis therapy and altered regimes, but overall outcome was not adversely affected. Adverse reactions are commoner among the elderly.

Acknowledgement

We acknowledge all the staff members of the respiratory unit, of Teaching Hospital Kandy, Chest Clinic Kandy and staff at DOTS centers who helped us to make this research a success.

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