ADVERSE DRUG REACTIONS IN INTERMITTENT CHEMOTHERAPY FOR TUBERCULOSIS- A CROSS-SECTIONAL STUDY

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ABSTRACT

BACKGROUND

Tuberculosis is a major public health problem worldwide. Long regimens, multiple drug use, non-availability and accessibility of health care services and drugs, low educational status, low socioeconomic conditions, adverse drug reactions and social stigma of the disease all make the treatment of tuberculosis very difficult in developing countries. About 15% of the patients are likely to develop drug reactions during tuberculosis chemotherapy. These reactions are important as they cause discomfort to the patients and at times life threatening. Older patients, alcoholics and HIV/AIDS patients are more prone for developing drug reactions and deserve more care and monitoring.

The study was done to find out the pattern of drug reactions in intermittent chemotherapy for tuberculosis and to know the various factors related to the development of drug reactions.

MATERIALS AND METHODS

The study is done as a cross-sectional study. The patients who received intermittent chemotherapy for tuberculosis in the wards of Department of Tuberculosis and Respiratory disease, Government Medical College, Thiruvananthapuram were selected and adverse reactions encountered during therapy were recorded. Data entry was done in MS Excel and statistical analysis was done using Epi-Info 6. Descriptive statistics were expressed as proportions. Statistical significance was assessed by doing Chi-square test.

RESULTS

The total number of patients included in the study was 582. Out of this, 92 had drug reactions. Female sex and increasing age are found to be a risk factor for development of drug reactions. The adverse effects encountered are gastrointestinal intolerance, jaundice, cutaneous reactions, peripheral neuropathy, arthralgia, fever, visual disturbances and psychiatric manifestations in the order of decreasing frequency.

CONCLUSION

The National Expert Committee recommends daily treatment for all forms of Tuberculosis based on currently available evidences on TB treatment. Hence, intermittent chemotherapy for tuberculosis will be totally replaced by daily chemotherapy in our country in a few months and this study may be used as a yard stick to compare the adverse reactions in intermittent chemotherapy versus daily therapy for tuberculosis in future.

KEYWORDS

Intermittent Chemotherapy, RNTCP, Daily Therapy, WHO, Adverse Drug Reactions, Hepatotoxicity.

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BACKGROUND

Tuberculosis (TB) remains a world-wide public health problem, despite the fact that the causative organism was discovered more than 100 years ago and highly effective drugs are available making tuberculosis a curable disease. About one-third of the global population is infected with mycobacterium tuberculosis and according to conservative estimates, 2.2 million people develop TB in India every year and 220,000 die from the disease.¹

Technologically advanced countries have achieved spectacular results in the control of tuberculosis,² while the situation in developing countries is different, which account for about 95 percent of tuberculosis cases. Over 95% of TB deaths occur in low and middle income countries. It kills more adults than any other infectious disease.³

Despite an organised national control programme, the burden of illness due to tuberculosis has shown no noticeable decline in India. Long regimens, multiple drug use, non-availability and accessibility of health care services and drugs, low educational status, low socioeconomic conditions, adverse drug reactions and social stigma of the disease all make the treatment of tuberculosis very difficult in developing countries. No other disease has so much sociological, economic and health significance as tuberculosis has. It is a social disease with medical aspects and described as a barometer of social welfare.

The national tuberculosis control programme in India has been in operation since 1962. The treatment completion rate was only less than 30%. Adding to that shortage of drugs,

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multiplicity of drug regimes, etc. made the programme a failure. Hence, the revised National Tuberculosis Control Programme (RNTCP) was introduced in 1993. Intermittent chemotherapy with isoniazid, rifampicin, ethambutol, pyrazinamide for new cases and these four drugs plus streptomycin for re-treatment cases thrice weekly under direct supervision was practiced under RNTCP.

Drug reactions to anti-tuberculosis drugs are one of the causes for non-compliance⁴ and there is a 15% probability of an adverse effect occurring in a patient on a multiple anti-tuberculosis drug regimen.⁵ Our study probably is the first study in India addressing adverse reactions among patients received tuberculosis chemotherapy under Revised National Tuberculosis Control Programme (RNTCP) of India.

The standards for TB care in India 2014 laid down by Ministry of Health and Family Welfare of Government of India and World Health Organisation (WHO) state that all patients with tuberculosis should be given daily regimen based on available evidences and WHO treatment of TB guidelines 2010. The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide and ethambutol. The continuation phase should consist of isoniazid, rifampicin and ethambutol for at least four months. Considering this the National Expert Committee has recommended RNTCP to move towards daily regimen for all tuberculosis. Hence, the intermittent chemotherapy for Tuberculosis will be totally replaced in our country by daily chemotherapy using Fixed Drug Combinations (FDC) in a few months. The data on adverse reactions to anti-tuberculosis drugs in intermittent chemotherapy could be used as a yard stick to compare daily chemotherapy in terms of drug toxicity in future studies.

Objectives

1. To study the pattern of drug reactions in intermittent chemotherapy for tuberculosis.
2. To study the various factors related to the development of drug reactions in tuberculosis chemotherapy.

MATERIALS AND METHODS

The study was done as a cross-sectional study. The patients who received intermittent chemotherapy for tuberculosis in the wards of Department of Tuberculosis and Respiratory disease, Government Medical College, Thiruvananthapuram from May 1999 to April 2001 were the study population.

Inclusion Criteria

Patients who received intermittent chemotherapy for tuberculosis were included in the study.

Exclusion Criteria

Patients on daily therapy, patients on second line drugs for drug resistant tuberculosis and patients with history of degenerative joint disease were excluded from the study.

Methodology

Patients who were started on intermittent chemotherapy for tuberculosis were selected and adverse reactions encountered during therapy were recorded. A proforma which includes information about name, age, sex, address, vital statistics, socio-economic status, sputum smear status for Acid Fast Bacilli (AFB), co-morbidities, extent of radiographic lesion, type of drug reaction and investigation

details including liver function tests was prepared. The pattern of drug reactions and the various factors related to it are studied. Data entry was done in MS Excel and statistical analysis was done using Epi-Info 6. Descriptive statistics were expressed as proportions. Statistical significance was assessed by doing Chi-square test and P value less than 0.05 was taken as significant.

RESULTS

Total Number of Patients	: 582
Number of males	: 426
Number of females	: 156
Maximum age was	: 83
Minimum age was	: 09

Total Number of Reactions	: 92
Number of males	: 62
Number of females	: 30
Maximum age was	: 79
Minimum age was	: 17

Age (Years)	Reactions		Total
	Present N (%)	Absent N (%)	
< 30	19 (14.72)	110 (85.28)	129
30 – 60	48 (13.75)	301 (86.25)	349
> 60	25 (24.03)	79 (75.97)	104
Total	92 (15.80)	490 (84.20)	582

Table 1. Age Distribution of Drug Reactions

χ^2 (df 2) Yates corrected: 6.51

P value = 0.0385

	Jaundice		Total
	Present N (%)	Absent N (%)	
Alcoholics	14 (6.06)	217 (93.94)	231
Non-Alcoholics	03 (1.53)	192 (98.47)	195
Total	17 (3.99)	409 (96.01)	426

Table 2. Alcoholism and Hepatotoxicity of Drugs

None of the females in the study population were alcoholic

Total number of males : 426

Number of alcoholics : 231

The chi-square statistic is 5.64. The p-value is 0.017. The result is significant at $p < .05$

Symptoms	Number (N)	Percentage (%)
Gastrointestinal	54	9.27
Jaundice	31	5.32
Cutaneous	24	4.12
Vestibular	07	1.20
Peripheral Neuropathy	06	1.03
Arthralgia	12	2.06
Fever	05	0.85
Visual	05	0.85
Psychiatric	03	0.51

Table 3. Frequency and Type of Drug Reactions

Symptoms	Period of Treatment (Months)					
	1			2	3 - 4	> 4
	1 - 2 Weeks	2 - 4 Weeks	Total			
Gastro-Intestinal	30	12	42	12	-	-
Jaundice	08	11	19	10	-	02
Cutaneous	06	11	17	07	-	-
Vestibular	01	04	05	02	-	-
Visual	02	02	04	01	-	-
Fever	03	02	05	-	-	-
Peripheral Neuropathy	-	02	02	04	-	-
Arthralgia	-	03	03	09	-	-
Psychiatric	01	02	03	-	-	-

Table 4. Time of Occurrence of Reactions

Symptoms (N)	Number of Patients Required Modification of Treatment	% (of Toxicity)
Gastro-intestinal (54)	NIL	-
Jaundice (31)	15	48.38
Cutaneous (24)	07	29.16
Visual (05)	05	100
Vestibular (07)	05	71.42
Arthralgia (12)	03	25
Psychiatric (03)	02	66.6

Table 5. Number of Patients required Modification of Chemotherapy

DISCUSSION

The study was done to find out the pattern of drug reactions in intermittent chemotherapy for tuberculosis and to know the various factors related to the development of drug reactions. The total number of patients included in the study was 582. Out of this, 92 had drug reactions. Majority of the study population were males (73.2%). Among males 14.55% had drug reactions, while 19.23% of females had drug reactions. But this difference was found to be statistically non-significant (P value = 0.214). Several studies have shown that the hepatotoxicity of isoniazid is higher in women when compared to general population.^{6,7}

Increasing age was found to be a risk factor for development of drug reactions.⁸ In our study, most of the patients come under the age group of 30 - 60 years. The study shows that there is a definite increase in the incidence of drug reactions as the age advances and our results were found to be statistically significant (χ^2 (df 2) Yates corrected: 6.51, P value = 0.0385). The results are shown in Table 1.

The most common adverse effect encountered in the study was gastrointestinal intolerance. A total of 54 patients (9.27%) had symptoms related to this system. Tripathy et al, reported a 12% incidence of gastrointestinal upset in rifampicin based regimens.⁹

About 5.23% of patients had clinical jaundice during the treatment period. Three major drugs used in tuberculosis, i.e. isoniazid, rifampicin and pyrazinamide are hepatotoxic drugs. Our study shows that alcoholics are more prone for developing hepatotoxicity, while on anti-tuberculosis drugs.

None of the females in the study population were alcoholic. Among males, 231 were alcoholics (54.2%). About 6.06% male alcoholics developed clinical jaundice, while only 1.53% of male non-alcoholic developed jaundice. This difference in toxicity was found to be statistically significant (the chi-square statistic is 5.64. The p -value is 0.017. The result is significant at $p < .05$). The initial status of liver function in alcoholics was found to be a useful predictor for the development of hepatotoxicity during the treatment period. Elevated liver enzymes were found in 124 alcoholics and it was normal in 107 alcoholics. Eleven had jaundice in the former group and 3 had jaundice in the latter group. This is also found to be significant [Odds ratio 3.37 (95%, CI 0.84 - 15.71)].

Sivaraman et al reported a 7% incidence of jaundice in those received isoniazid, rifampicin, pyrazinamide and ethambutol in combination.¹⁰ Several other authors reported an incidence ranging from 4 - 22% with various regimens.^{11,12,13} Kamat et al reported a higher incidence of hepatotoxicity to anti-tuberculosis drugs in alcoholics and out of 28 patients under his study who developed jaundice eight (20%) had a history of alcoholism, while in those without jaundice twenty (16%) were alcoholics.¹² Christine M. S et al¹⁴ and others also described the higher incidence of hepatotoxicity in alcoholics. The results of our study correlate well with the existing literature and is shown in Table 2.

Among females the incidence of jaundice was found to be higher (8.97%), despite the fact that none of them were alcoholics, not on oral contraceptives or other hepatotoxic drugs and not having any pre-existing liver disease. Most of the patients developed jaundice were in the reproductive age group. The increased incidence of hepatotoxicity to anti-tuberculosis drugs in women is well described in literature, though its mechanism is not fully known.⁵

An attempt was made to find out the relationship if any between body weight and hepatotoxicity. But the study does not reveal any significant statistical relationship between the two factors ($\chi^2 = 3.55$, P value = 0.16). Mehrotra et al also fail to establish any relation between body weight and hepatotoxicity. One probable explanation is that the dose of rifampicin used in RNTCP is only 450 mg in those weigh less than 60 kg and 600 mg in those weigh 60 kg or more.

About 4.12% of patients had cutaneous drug reactions. Girling DJ et al reported a 5% incidence of cutaneous reactions in those on daily rifampicin.¹⁵ Pruritus in 4% and erythematous rashes in 2.5% were reported by Purohid SD et al.¹⁶

Seven patients had vestibular toxicity in the form of dizziness and ataxia. All those developed this toxicity were on streptomycin. About 9.85% of patients on streptomycin had vestibular toxicity and it is found to be increasing as the age advances. This was found to be statistically significant (χ^2 (df 2) Yates corrected: 6.42, P value = 0.04). None of them had evidence of renal dysfunction. Streptomycin induced vestibular toxicity is well described and increases linearly with the age and dose.¹⁷

Arthralgia was reported in 12 cases (2.06%). This is in contrary to the findings of the study by K. Nataraja Iyer et al in 1978, where 30 patients out of 45 studied had arthralgia affecting one or more joints. This difference may probably be due to the use of intermittent regimen in our study and the

cumulative dose is much less in comparison to the earlier studies with daily pyrazinamide.

Peripheral neuropathy was said to be the most common toxic manifestation of isoniazid. But in our study, only 1.03% of patients had symptoms related to neuropathy.

Visual disturbances in the form of diminished vision were noticed in 5 cases (0.85%). All patients responded well to withdrawal of ethambutol.

There were 5 cases of drug fever and 3 cases of psychiatric manifestations noted in the study period. Three cases of fever were due to isoniazid and one each was due to rifampicin and pyrazinamide. The type and frequency of drug reactions are shown in Table 3.

Most of the reactions were reported during the first month of therapy. Only 2 cases of jaundice were reported after 4 months of the initiation of treatment. Jagota et al, reported that the occurrence of reactions are maximum during the first 2 months of treatment,¹⁸ while Riska N reported isoniazid induced hepatotoxicity is maximum during the first 16 weeks of therapy.⁸ The time of occurrence of drug reactions are shown in Table 4.

The relationship between drug reactions and factors like diabetes, smear Acid Fast Bacilli (AFB) status and radiological extent of lesions were also studied. But none were found significant statistically.

Out of the 11 HIV/AIDS patients who received tuberculosis chemotherapy, 3 had drug reactions; 2 had cutaneous reactions and 1 had jaundice. Ungo JR and Jones D et al reported a 4-fold increase in drug induced hepatotoxicity in HIV positive individuals.¹⁹

Fifteen cases of jaundice required modification of chemotherapy, while seven cases of cutaneous reactions required modification. In all cases with visual impairment ethambutol was withdrawn. Pyrazinamide was withdrawn in 3 cases of arthralgia. Drug modification was done in 2 cases of psychiatric manifestations. After a short period of interruption of treatment, pyridoxine 20 mg/day was added along with anti-tuberculosis drugs and the patients tolerated the original regimen. In two patients, isoniazid could not be restarted. Both were cutaneous reactions.

None of the patients with gastro-intestinal symptoms or fever required modification of the original regimen. They required a few days of stoppage of drugs and symptomatic treatment and the original regimen could be resumed without trouble.

In our study, altogether 6.35% of patients required modification of treatment. In a study conducted by Jagota et al in 1989 reported that six percent of patients required modification of original regimen.²¹ Number of patients required modification of treatment is shown in Table 5.

CONCLUSION

- Out of the 582 cases, 92 had drug reactions (15.80%).
- The most common drug reaction is related to gastrointestinal system (9.27%).
- Next in frequency is jaundice (5.32%).
- Cutaneous reactions account for 4.12% of drug reactions.
- Visual disturbances occurred in 5 cases. All cases were due to ethambutol.
- None of the females in the study population were alcoholics. Among alcoholic males, 6.06% had jaundice,

while only 1.53% of non-alcoholic males had jaundice. About 8.97% of females had jaundice.

- Eleven HIV/AIDS patients had received chemotherapy for tuberculosis, out of which 3 had drug reactions.
- No relation could be found out between drug reactions and factors such as diabetes, smear acid-fast bacilli status and radiological extent of the lesions.
- In all cases, chemotherapy could be continued. Modification of drug regimen was required in 37 cases (40.21% of reactions, 6.35% of cases). Isoniazid could not be restarted in 2 cases.

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