ADVERSE DRUG REACTIONS DUE TO ANTITUBERCULAR DRUGS DURING THE INITIAL PHASE OF THERAPY IN HOSPITALISED PATIENTS FOR TUBERCULOSIS IN SRI KRISHNA MEDICAL COLLEGE, MUZAFFARPUR, BIHAR

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ABSTRACT

BACKGROUND

To improve patient care and safety in relation to the use of medicines and providing early warnings regarding ADR and the risk groups associated with its development, which might affect the success of the programme. It will thus support the safe and more effective use of medicine.

MATERIALS AND METHODS

A prospective study done from Indoor Patient Department (IPD) Medicine and IPD Tuberculosis and Chest (including DOTS and DOTS Plus Centre) in Sri Krishna Medical College and Hospital (SKMCH), Muzaffarpur, Bihar, from April 2015 to June 2016. Total of 500 patients included in the study and reviewed for at least first 2 months of initiation of treatment. Naranjo adverse drug reaction probability scale and Hartwig's severity assessment scale were utilised for determination of probability and severity of ADR, respectively.

RESULTS

500 patients included in study were analysed. ADR was found in 60 patients (incidence of ADR12%), mostly presented within first 30 days of initiation of treatment and mostly it is due to multidrug treatment and the most common drugs responsible were isoniazid, then rifampicin and pyrazinamide, which were more common in female patients (36) as compared to male patients (24), most cases were mild and had probable relationship. Most cases recovered spontaneously while some required symptomatic and very few required specific treatment. The most common ADR noted was hepatobiliary (increased in liver enzyme (54.69%)).95% of cases showing ADR were between 31.2 to 56.8 years of age and between 26.47 to 76.87 kg weight.

CONCLUSION

In our study, incidences of ADR of antitubercular drug was around 12% and hepatobiliary manifestations in the form of raised liver enzymes is the most common manifestation. The most common drug responsible is isoniazid. ADRs are more common in females and in rural population with mean age 44 years and mean weight of 51.67 kg and mostly noticed within 30 days of initiation of treatment. Most of the ADRs are minor in severity and resolve spontaneously.

KEYWORDS

ADR-Adverse Drug Reaction, DOTS-Directly Observed Treatment, Short Course, IPD-Indoor Patient Department, SKMCH-SriKrishna Medical College and Hospital, TB-Tuberculosis.

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BACKGROUND

Tuberculosis is an infectious disease caused by mycobacterium tuberculosis, which has now become the second leading infectious cause of death in the world after HIV-AIDS. Incidence of active pulmonary tuberculosis is estimated to be as high as 8 million new cases per year worldwide as well as approximately 2 million deaths per year. More than one-third of the world's population is infected with mycobacterium tuberculosis. In addition, developed countries are experiencing a resurgence of

tuberculosis, whereas tuberculosis has been a major challenge for healthcare providers in developing countries for a long time. There are several chemotherapeutic agents that exist to treat mycobacterial infections. However, the necessity of utilisation of multidrug regimens has been associated with increased incidence of side effects. These side effects maybe mild as well as fatal. A severe side effect against one of the primary antitubercular (anti-TB) drugs, which leads to the discontinuation of that drug has several complications including an increased morbidity and mortality. At the same time, use of alternative agents may result in greater problems of toxicity and compliance. As a result, the risk of treatment failure and relapses are higher.[1-4] Therefore, pharmacovigilance programmes for antitubercular drugs are required to minimise the cost of therapy as well as for patients' compliance to drugs.

In our work, main emphasis is to deal with adverse drug reactions of antitubercular drugs because its knowledge is essential for patients as well as drug providers for better outcome and to prevent serious drug-related problems.

An Adverse Drug Reaction (ADR) is an injury caused by taking a medicine.[5] ADR may occur following a single dose or prolonged administration of a drug or it can result from the combination of two or more drugs. The meaning of this expression differs from the meaning of "side effect", as this last expression might also imply that the effects can be beneficial.[6]

The WHO defines an ADR as "any response to a drug, which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function."[5]

WHO defined pharmacovigilance as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems"[7]

Aim of the Study

1. To study the ADR (adverse drug reaction) occurring due to first line antitubercular drugs and its severity.
2. To study the risk factors for developing ADR.

MATERIALS AND METHODS

The cases were selected from the patients admitted in IPD (Indoor Patient Department) Medicine and IPD TB and Chest in SKMCH, Muzaffarpur, Bihar, India, and who were already detected as a case of tuberculosis from April 2015 to June 2016.

Study Design

The study conducted was on 500 tuberculosis patients (250 males, 250 females) as a prospective spontaneous reporting study involving active method (by actively looking for suspected ADR) and passive methods (by stimulating prescribers to report suspected ADR) in all age groups of patients and of either sex in the Medicine IPD and IPD of TB and Chest Department from April 2015 to April 2016 and review of patients done till June 2016.

Confidentiality of the information obtained was assured throughout the study.

Drug Used for Studying ADR

Isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin.

Study Groups

1. Patients on antitubercular drugs who developed ADR after prospective study.
2. Patients on antitubercular drugs who had developed adverse drug reactions (ADR) which have been already reported earlier or collected from review of books.

Operational Procedure

The diagnosis of tuberculosis was made by physicians on the basis of sputum smear examination and x-ray report of patients.

Treatment of tuberculosis done by physician as recommended by our National Tuberculosis Program; (RNTCP) total treatment period was 6 to 9 months as per case. Patients first received primary anti-TB drugs including a combination of 4 or 5 drugs (isoniazid (H), rifampin (R), pyrazinamide (Z), ethambutol (E) or streptomycin (S)) during an initial phase of 2 months, followed by a continuation phase of 4 to 7 months as per case consisting of H and R.[8] Treatment was given as per DOTS regimen and at least the initial phase administered during hospitalisation. Improvement of clinical status of patients treated by antitubercular drugs by their physicians were also noted. Drug dosages are presented in Table 1.

Previous history of diabetes mellitus, COPD, cor pulmonale, renal failure, hepatitis, HBsAg (+), epilepsy, alcohol consumption, presence of malignant tumour, presence of extensive disease, presence of HIV (AIDS) were noted. Their demographic features, gender and age also noted.

If any ADR arise during antitubercular treatment, it was noted in patients file before starting treatment following investigations were done CBC (complete blood count), Liver Function Test (LFT), Renal Function Test (RFT) and x-ray chest. Regular laboratory monitoring of LFT, RFT and CBC were done during treatment with anti-TB drugs, which was twice weekly in first two weeks, then weekly for two weeks, then twice a month in second month and then monthly.

All ADRs were observed during the hospital stay of the patients in the initial two months of the anti-TB chemotherapy and if any patient discharged before two months of treatment advised to meet in hospital if any such events occur. While receiving anti-TB treatment, an increase in SGPT and/or SGOT of more than three times the upper normal limit in the presence of symptoms such as anorexia, nausea, vomiting or abdominal pain or in SGPT or SGOT of more than 5 times the upper normal

limits without symptoms and/or in total bilirubin to ≥2 mg/dL was accepted as "hepatotoxicity." Definitive termination of 1 of 3 first line anti-TB drugs was considered as "severe hepatotoxicity."

During anti-TB treatment, an increase in uric acid levels of more than 7mg/dL was accepted as "hyperuricaemia," which is a well-known side effect of pyrazinamide. Patients with hyperuricaemia and/or arthralgia related to therapy were analysed for renal disease, concomitant use of other drugs causing renal failure as NSAIDS (nonsteroidal anti-inflammatory drugs). Persistent hyperuricaemia and/or arthralgia in spite of symptomatic treatment were accepted as valid causes for quitting administration of pyrazinamide.

Well-known side effects of streptomycin as ototoxicity (auditory (e.g., tinnitus and high-frequency hearing loss), vestibular (e.g., vertigo, ataxia and loss of balance)) and of ethambutol as retrobulbar neuritis causing loss of visual activity and red-green colour discrimination, flu-like syndrome noted. Also, other drugs causing such symptoms and other risk factors for it noted.

Neuropsychiatric manifestations such as inability to concentrate, psychosis, obsessive-compulsive neurosis, dysphoria and memory loss were noted with isoniazid. The risk factors for psychiatric problems such as family environment, diabetes, old age, alcohol consumption, hepatic or renal insufficiency were also analysed in these patients. Cutaneous reactions such as pruritus with or without rash and transient morbilliform rash were recorded during the therapy.[1]

Drugs	Daily Therapy		Thrice Weekly	
	Dose	Maximum	Dose	Maximum
Isoniazid	5 mg/kg per day	300 mg/day	10-15 mg/kg	900 mg
Rifampicin	10 mg/kg per day	600 mg/day	10 mg/kg	600 mg
Pyrazinamide	25 mg/kg per day	2 g/day	35 mg/kg	
Ethambutol	15 mg/kg per day	1500 mg/day	30 mg/kg	
Streptomycin	15 mg/kg per day	1 g/day	15 mg/kg	1000 mg

Table 1. Doses of the Drugs Used to Treat Active Tuberculosis, which are Taken for Study

Category	Intensive Phase	Continuation Phase	Total Duration in Months
I	2 (HRZE) thrice a week	4 (HR) thrice a week	6
II	2 (HEZES) thrice a week+1 (HRZE) thrice a week	5 (HRE) thrice a week	8

Table 2. Treatment Strategy Adopted

Further data has been analysed to find out age and sex of the patients affected with ADR, incidence rate, drugs and body systems/organs involved, time of occurrence of adverse drug reactions.

Various types of ADR noted during study and its incidence rate is compared with already documented ADR in different books and journals.

RESULT AND ANALYSIS

ADR Reported From Drugs

Parameter		Number	Percentages
Sex	Male	24	40%
	Female	36	60%
Age in Years	11-20	8	13.33%
	21-30	12	20%
	31-40	9	15%
	41-50	8	13.33%
	51-60	8	13.33%
	61-70	7	11.67%
	71-80	6	10%
	81-90	2	3.33%
Body Wt. in Kg	36-45	24	40%
	46-55	20	33.33%
	56-65	6	10%
	66-75	6	10%
	76-85	3	5%
	86-95	1	1.67%
Ethnic Group	Rural	36	60%
	Urban	24	40%

Table 3. Demography Distribution of the Patients on ATT Affected with ADR (n=60)

Age Group and Weight Analysis of Adverse Drug Reactions

Age Group Analysis

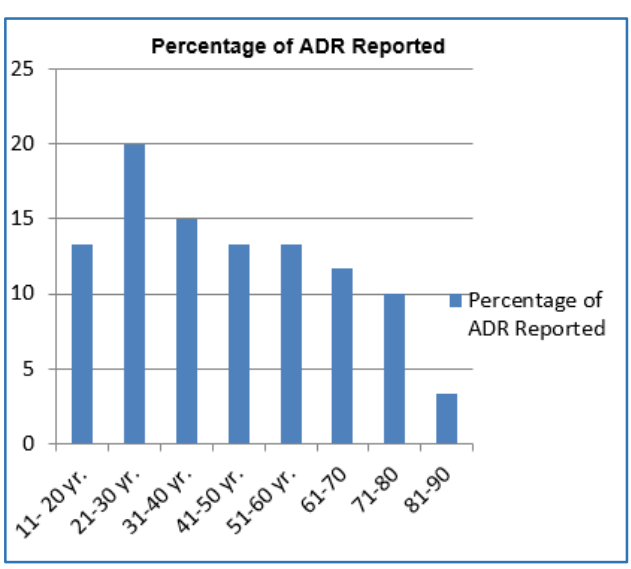
Mean=44 years.

Median=41.75 years.

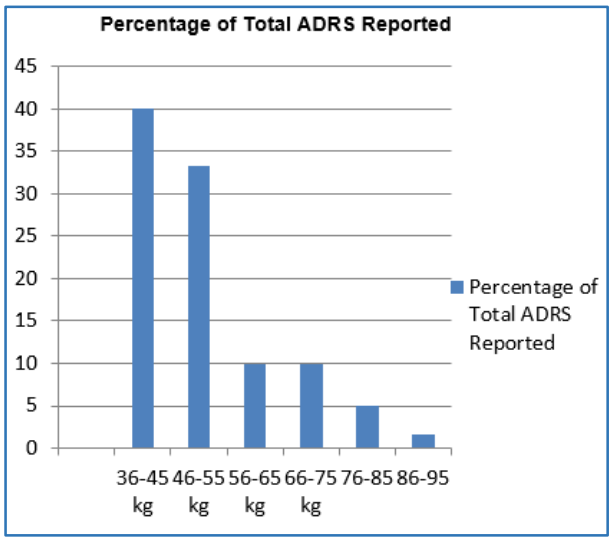
Mean deviation about median=17.625 years.

Standard deviation=6.4096.

P-value=0.016126.



Graph 1. Showing Age Group of Patients on X-Axis and Percentages of Total ADR Reported

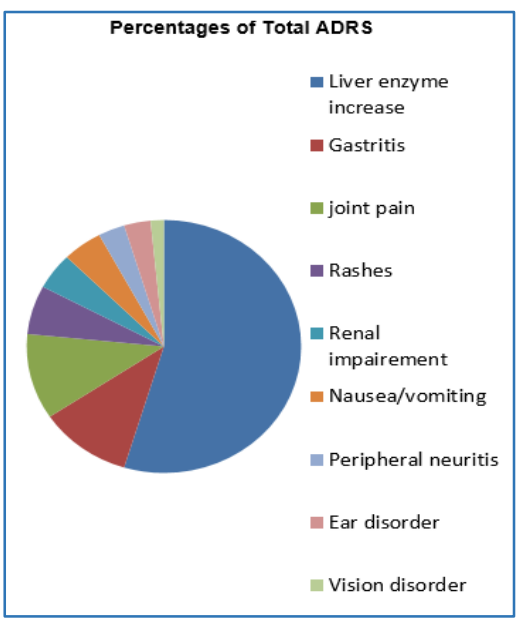


Graph 2. Showing Wt. of Patient on X-Axis with Respect to Percentages of Total ADR Reported on Y-Axis

Mean=51.67 kg.
Median=48.5 kg.
Mean deviation about median=9.56667 kg.
Standard deviation=12.6.
P-value=0.007778.

For Weight Analysis

Various Types of ADR Reported With Respect to Total ADR (64)



Type of the ADR	Number of Reports	Percentage of Total ADR (n=64) Reported
Elevated hepatic enzymes/hepatitis	35	54.69%
Gastritis	7	10.94%
Joint pains	7	10.94%
Erythematous/Macular rash	4	6.25%
Interstitial nephritis/Renal failure	3	4.68%
Nausea/Vomiting	3	4.68%
Peripheral neuritis	2	3.13%
Vestibular neuritis/Ear disorder	2	3.13%
Defective vision	1	1.56%

Table 4. Various Types of ADR Reported With Respect to Total ADR (64)

DISCUSSION

In our study, the incidence of ADR was 12%. Studies from Russia reported an incidence of 72.8% (Chukanov et al, 2004),[9] 60.2% (Tashpulatova, 2003)[10] and 16.9% (Mishin et al, 2003).[11] Study from Nepal reported an incidence of 12.27% (Kishore PV et al, 2008)[12] while from United Kingdom 5.1% (Ormerod and Horsfield, 1996).[13]

In our study, females had higher incidence of ADR. In general, females are at higher risk of developing ADR (Puavilai and Timpatanapong, 1989).[14] It might be because they pass through life stages like pregnancy, menarche, etc., which modify the drug response (Wilson, 1984).[15] Studies from the UK and Canada also reported females to have a significantly higher incidence of ADR due to ATT drugs (Ormerod and Horsfield, 1996; Yee et al, 2003).[13] So, there is need of special attention while prescribing ATT drugs to females.

Old age group persons are more susceptible to gastrointestinal adverse effects due to the fact that elderly individuals have a slower metabolism, which is due to reduced enzymatic activity, reduced hepatic clearance and reduced availability of essential endogenous factors.

The most common system affected by the ADR in our study was hepatobiliary. In a study in India on ADRs due to ATT drugs majority of the patients (53%) had gastrointestinal reactions, the commonest presenting complaint being nausea and vomiting (Dhingra et al, 2004).[16] Several studies have documented the hepatotoxic effect of ATT drugs (Rossouw and Saunders, 1975).[17] A study from Nepal reported an incidence of 8% hepatotoxicity to ATT drugs (Shakya and Rao, 2004).[18]

ATT-induced hepatotoxicity maybe severe and lead to mortality of patient. The principal clinical risk factors for hepatotoxicity are old age, malnutrition, alcoholism, HIV infection as well as chronic hepatitis B and C infections (Yew and Leung, 2006).[19] Drug-induced hepatic dysfunction usually occurs within the initial few weeks of the intensive phase of antituberculosis chemotherapy (Yew and Leung, 2006).[19] It is also recommended that liver function should be studied every two weeks during ATT to prevent serious hepatotoxicity (Wada, 1998).[20] A few guidelines were also published mentioning the management of hepatotoxicity due to ATT drugs (BTS guidelines, 1998; Harries et al, 1998).[21]

In our study, INH causes more ADR, then rifampicin and pyrazinamide caused almost an equal number of ADR. A study from Russia reported streptomycin as the drug responsible for more ADR (Mishinet al, 2003).[11] There can be differences among the drugs causing higher number of ADR and it depends mainly on the type of regimen used, dose of the drugs, genetic makeup of the population, etc. Onset of the ADR is an important factor helpful in early detection of the ADR. In our study, more than half the ADR occurred within the first 30 days of the initiation of ATT. Also, in a study from India (Dhingraet al, 2004), 67% of the ADR occurred in the first four weeks.[16]

The most common laboratory abnormality observed was deranged hepatic enzymes. Since, hepatotoxicity is the most common ADR, there were morenumber of patients with liver enzymes derangement. The Naranjo algorithm (Naranjo et al, 1981)[22] is used widely in carrying out the causality assessment of ADR.

Scoring

≥9 = Definite ADR; 5-8 = Probable ADR; 1-4 = Possible ADR; 0 = Doubtful ADR.

Question	Yes	No	Do Not Know	Score
1-Are there previous conclusive reports on this reaction?	+1	0	0	
2- Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3- Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4-Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
5- Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6- Did the reaction reappear when a placebo was given?	-1	+1	0	
7- Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8- Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9- Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10- Was the adverse event confirmed by any objective evidence?	+1	0	0	
Naranjo Adverse Drug Reaction Probability Scale[22]				

In order to take appropriate initiatives towards the management of the ADR, it is necessary to study the severity of the ADR. Hartwig scale (Hartwig et al, 1992)[23] is widely used for the purpose.

Level 1	An ADR occurred, but required no change in treatment with the suspected drug.
Level 2	The ADR required that treatment with the suspected drug be held, discontinued or otherwise changed.No antidote or other treatment requirement was required. No increase in Length of Stay (LOS).
Level 3	The ADR required that treatment with the suspected drug be held, discontinued or otherwise changed and/or an antidote or other treatment was required. No increase in Length of Stay (LOS).
Level 4	Any level 3 ADR, which increases length of stay by at least 1 day or the ADR was the reason for the admission.
Level 5	Any level 4 ADR, which requires intensive medical care.
Level 6	The adverse reaction caused permanent harm to the patient.
Level 7	The adverse reaction either directly or indirectly led to the death of the patient.
Hartwig's Severity Assessment Scale[23]	

Scoring

Mild= Level 1 and 2, Moderate= Level 3 and 4, Severe= 5, 6 and 7.

We found majority of the ADR are mild in severity and had a probable relationship with the suspected drug. However, nearly 7.5% of the ADRs had a 'definite' relationship with the suspected drug.

CONCLUSION

The following conclusions come out from our present study-

- Incidence of ADR 12%.
- Hepatobiliary ADRs were the most common type and derangement of liver enzymes was the most common laboratory abnormality.
- Majority of the ADRs were 'minor' and had a 'probable' relationship with the suspected drugs and more in rurals (60%) and in females (60%) and mostly in first 30 days of initiation of treatment.
- 95% of ADR are reported between 31.2 to 56.8 years of age and 26.47 to 76.87 kg weight.
- Most common drug responsible are isoniazid, then rifampicin and pyrazinamide.
- Most of the ADR recovered spontaneously, some require symptomatic treatment and very few require specific treatment and withdrawal of drugs.
- From comparing our study with documented one, it is found that the type of reported ADR are same, but their incidence rates are different.
- Proper counseling of patients about ADR are required to prevent its occurrence and for its detection and management.

Since TB is a common problem in India and 12% incidence of ADR with anti-TB treatment had a substantial impact on TB control in India. Special emphasis is needed to tackle the drug-related complications associated with ATT drugs. So, there should be pharmacovigilance programme to detect newer ADR associated with drugs and also counseling of patients required to minimise it.

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