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A PHARMACOVIGILANCE STUDY IN THE DEPARTMENT OF CHEST & TUBERCULOSIS ON ANTI TUBERCULAR THERAPY IN A TERTIARY CARE TEACHING HOSPITAL OF SOUTH INDIA

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Abstract

Tuberculosis has been one of the common diseases in human communities during the past 40 years. It has been reported by World Health Organization (WHO) that one third of the world's population is infected with Mycobacterium tuberculosis resulting in 8.4 million new tuberculosis cases in 1999, this high incidence of infection has caused a large number of morbidity and mortality which is partly due to serious adverse reactions induced by Anti-TB drugs. The current prospective observational study of six months duration was designed to assess the rate of adverse drug reactions (ADRs) induced by anti tubercular drugs in patients admitted in the department of Chest & Tuberculosis from whom a proper consent obtained. The results of the study showed that the incidence of all major adverse effects was 1.48 per 100 person's month of exposure. The occurrence of any major side effect in the study was associated with female sex and increase in age. In our study the major cause of admission was adverse drug reactions in 15.9% of patients. In our study Hepatitis was observed in 25 (25.77%) patients, leading to the death of 2 patients. In conclusion, Anti-TB drugs could cause significant adverse effects both in quantity and severity. These reactions may lead to hospitalization, prolonged hospital stay and even death. These results suggest that the protocol may need some revision to prevent fatalities. To confirm this hypothesis many more studies with large population is needed.

Keywords: Adverse drug reactions, Anti-TB drugs, Pharmacovigilance, Prospective observational study, Tertiary care hospital, Tuberculosis.

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Introduction

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis. The disease spreads by droplet infection. Every untreated sputum positive patient spreads the disease to 10 to 15 persons per year. Every year approx. 18 lakhs people develop TB and 4 lakhs die from it.[1] India is the highest TB burden country accounting more than one fifth of the global incidence. Global annual incidence = 9.23 million, India annual incidence = 1.96 million.[1] Tuberculosis has been one of the common diseases in human communities during the past 40 years. It has been reported by World Health Organization (WHO) that one third of world population is infected with Mycobacterium tuberculosis resulting in 8.4 million new tuberculosis cases in 1999.[2] This high

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incidence of infection has caused a large number of morbidity and mortality which is partly due to serious adverse reactions induced by Anti TB drugs. The detection of adverse drug reactions (ADRs) has become increasingly significant because of introduction of a large number of potent toxic chemicals as drugs in the last two or three decades. WHO has intervened seriously in the matter and established an international adverse drug reactions monitoring centre at Uppsala, Sweden which is collaborating with national monitoring centres in around 70 countries.[3] In India there are very few active ADRs monitoring centres and a lot effort is required in order to collect ADR data which may generate from safety surveillance of billions of therapeutically active substances either alone or in combinations.

Pharmacovigilance is an arm of patient care and surveillance. It aims at getting the best outcome from treatment with medicines. Adverse drug reactions (ADRs) are common causes of morbidity and mortality in both hospital and community settings. Adverse drug reactions (ADRs) are global problems of major concern. They affect both children and adults with varying magnitudes; causing morbidity and mortality.[4-7] ADRs are responsible for about 5% to 20% of hospital admissions.[4, 5]

Good pharmacovigilance will identify the risks within the shortest possible time after the medicine has been marketed and will help to establish or identify risk factors. When communicated effectively, this information allows for intelligent, evidence-based prescribing with the potential for preventing many ADRs. Such information will ultimately help each patient to receive optimum therapy at a lower cost to the health system.[8]

World Health Organization (WHO) defines *Pharmacovigilance* "as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem".[9] Adverse drug reaction (ADR), Definitions of ADRs exist, including those of the World Health Organization (WHO).[9] Karch and Lasagna and the Food and Drug Administration (FDA).[10]

World Health Organization (WHO) – *Adverse Drug Reaction is defined 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 the modification of physiological function".

Karch and Lasagna – *defines Adverse Drug Reaction as* "Any response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose".

Food and Drug Administration (FDA): For reporting purposes, FDA categorizes a serious adverse event (events relating to drugs or devices) as one in which "the patient outcome is death, life-threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage.

Lazarous et al[4] estimated that ADRs were the fourth to sixth cause of death in United States. There are few recent reports on epidemiology of ADRs,[11] In United Kingdom most of the studies were performed in the previous two decades and were restricted to specific areas such as monitoring of ADRs in geriatric patients,[12-13] The largest UK study based on retrospective review of case reports and gave poor documentation.[14]

The goal of current study is to decrease mortality and morbidity due to TB and cut transmission of infection until TB ceases to be a major public health problem in India and the study focuses in assessing the rate of adverse drug reactions (ADRs) induced by anti tubercular drugs and to detect serious and preventable recognized ADRs as the primary objectives.

Material & methods

Study site:

The study entitled "A Pharmacovigilance Study in the Department of Chest & Tuberculosis on Anti Tubercular Therapy in a Tertiary Care Teaching Hospital of South India" was carried out in a 1200 bedded tertiary care teaching hospital located at Ananthapuramu, Andhrapradesh, India.

Study design: Prospective Observational Study.

Study duration:
06 months (March 2014 to August 2014).

Study sample: 100 patients.

Inclusion criteria:

- All patients of either sex who were getting admitted to the study site during study period with pulmonary TB.

Exclusion criteria:

- Patients with chronic hepatitis illness such as cirrhosis, chronic hepatitis and acute viral hepatitis were excluded.
- The patients who all are unwilling to participate in the study and terminally ill will not included in the study.

Plan of study: Study procedure was categorized to three phases (I, II & III) respectively.

Phase I:

1. Submission of protocol and obtaining consent from hospital authority.
2. Literature survey: The literatures supporting the study were gathered from various sources such as: British Medical Journal, American Medical Journal, Journal of Clinical Pharmacy and Therapeutics, Journal of Pharmacy Practice, The Annals of pharmacotherapy, Journals of antimicrobial chemotherapy, Journal of national medical association, Indian journal on medical microbiology
3. Designing of: Data entry format, Patient information & consent form.

Data entry form for incorporating inpatient details were designed and the format contains provision to enter the details such as name, age, sex, height, weight, IP. No, date of admission, date of discharge, vital signs, reason for admission, past medical history, past medication history, and any predisposing factors. Provision was given in the format for entry of details like Blood sugar levels, Blood counts, Liver function test, Renal function test, Electrolytes, Urine examination, Lipid profile, Diagnosis, Drug chart, ADR monitoring chart and Drug interaction chart and dose and any interventions.

Patient information form has been prepared, to inform the patients or the care givers about the purpose and the necessity of the study by providing the patient information form and assured them that the confidentiality will be strictly maintained and also it will help the betterment of patients' health.

Patient Consent form has also been prepared and written consent was collected from all the patients or from the caregivers by using patient consent form after providing the information format.

Phase II:

1. Data collection through standard data entry format.
2. Literature survey.
3. Data analysis
   - To assess the rate of adverse drug reactions (ADRs) induced by anti tubercular drugs in the department of Chest & Tuberculosis.
   - To detect serious and preventable recognized ADRs.

Phase III:

1. Literature survey.
2. Data analysis
   - The obtained data will be thoroughly analyzed to evaluate the appropriateness of anti tubercular drug use.
3. Preparation and submission of reports.

Sources:
Causality and severity of reactions, determined using Naranjo Algorithm and Hartwig questionnaire as standard.

Results

During the 06 months study period 100 patients were diagnosed with positive TB. These patients were put on routine treatment protocol. Of these patients, 53 (53%) developed at least one adverse drug reaction. Total number of 97 adverse drug reactions detected in this study. The 53 patients with ADR consisted of 13 females and 40 males.

Occurrence of adverse reactions led to prolongation in hospital stay for 31 (59%) patients. The rate of adverse reactions was various in different age groups. It does appear that with Anti-TB drugs used in this study the rate of ADRs increases with increased age reported in Table I (Anti-TB induced adverse drug reactions in different age groups).

Table No. 01: Anti-TB induced adverse drug reactions in different age groups

S.No	Age groups	Patients	Patients with ADR
01	0 – 10 years	0	0
02	11 – 20 years	05	03
03	21 – 30 years	18	09
04	31 – 40 years	16	10
05	41 – 50 years	21	10
06	51 – 60 years	27	12
07	>60 years	13	09
Total		100	53

The most frequent system – organ classes affected by ADRs reported in Table II.

Table No. 02: Frequency of organ system involved in ADRs induced by Anti – TB drugs

S.No	Site of reactions	Frequency	%
01	Liver and biliary system disorders	35	36.08
02	Gastrointestinal system disorders	20	20.62
03	Central & peripheral system disorders	14	14.43
04	Metabolic & nutritional disorders	08	8.24
05	Skin & appendage disorders	05	5.15
06	Urinary system disorders	05	5.15
07	Musculo-skeletal system disorders	04	4.12
08	Platelet, bleeding & clotting disorders	03	3.09
09	Vision disorders	03	3.09
	Total	97	100

The most serious adverse reaction induced by Anti-TB therapy was reported in Table III, in which hepatitis was (25.77%), leading to death in two patients.

In this study, increase in plasma uric acid was observed in 4 patients (4.12%) due to pyrazinamide. These reactions occurred in average 26.7 days after the beginning of treatment and followed by arthritis. After discontinuing of Pyrazinamide, the level of uric acid returned to normal range within 10 days (2.1 – 8.5 mg/dl). Isoniazid caused reactions such as constipation (17.53%), and peripheral neuropathy (6.20%), while rifampicin was the major cause of headache (8.25%), rash and pruritus (5.15%) and diarrhoea (4.12%). The only adverse reaction suspected to be induced by Ethambutol was vision abnormality such as blurred vision and burning eyes in two patients (2.06). The main action taken in patients with detected ADR was discontinuation of drug regimen (35.05%). The action mainly was taken when hepatotoxicity was detected. There was no specific treatment for alleviating the adverse reactions, other than headache and constipation. The causality assessment of ADRs revealed that 8 (8.2%) cases were detected as certain, 43 (44.33) as possible and 46 (47.42) as probable reactions reported in Table IV

Table No. 03: Type of detected ADRs induced by Anti-TB drugs

S.No	Reaction	Frequency	%
01	Hepatitis	25	25.77
02	Constipation	17	17.53
03	Increased Liver Transaminases	11	11.34
04	Hyperglycemia	08	8.25
05	Headache	08	8.25
06	Peripheral Neuropathy	06	6.20
07	Dysuria	05	5.15
08	Rash	05	5.15
09	Diarrhoea	04	4.12
10	Increased Uric Acid	04	4.12
11	Vision Abnormality	02	2.06
12	Prolonged PT	02	2.06
	Total	97	100

Table No. 04: Causality of ADRs induced by Anti-TB drugs according to Naranjo algorithm

S.No	Scale	%	Frequency
01	Probable	47.42	46
02	Possible	44.33	43
03	Certain	8.2	08
Total		100	97

Table V reports the evaluation of the severity of ADRs indicated that most of the ADRs detected had severity in level 1 (38.14%) and 4a (35.05%).

Table No. 05: Severity of ADRs induced by Anti-TB drugs

S.No	Severity	Number	%
01	Level 1	37	38.14
02	Level 2	02	2.06
03	Level 3	16	16.49
04	Level 4a	34	35.05
05	Level 4b	05	5.15
06	Level 5	01	1.03
07	Level 6	0	0
08	Level 7	02	2.06

Discussion

Among 100 patients entered the study, 53(53%) patients showed at least one adverse reaction. This relatively high percentage of occurring adverse reactions indicates that there is a need for more evaluation of susceptibility of patients for developing Anti-TB induced ADRs.

Daphne Yee et al [15] conducted a study to estimate the incidence and risk factors of major side effects from first line Anti-TB drugs between. They evaluated 430 patients treated with Anti-TB drugs between 1990-1999. The results of the study showed that the incidence of all major adverse effects was 1.48 per 100 person's month of exposure. The occurrence of any major side effect in the study was associated with female sex. It does appear that with Anti-TB drugs used in this study the rate of ADRs increases with increased age.

In our study the major cause of admission was adverse drug reactions in 15.9% of patients. In similar study conducted in Iranian population hospitalized in general medical ward, ADR has been reported the cause of admission for 8% patients.

In our study Hepatitis was observed in 25 (25.77%) patients, leading to the death of 2 patients. It has been estimated that 10 to 20% of INH receptors developed elevated liver enzymes [16]. However, In case of mild, subclinical hepatic damage, the reaction does not progress to evident hepatitis and recover completely despite of the continuing INH therapy. In contrast, if clinical symptoms occur, severe Hepatocellular toxicity could be happened which is associated with a higher fatality rate than that of patients whose INH was discontinued immediately. Some evidence initially suggested that concurrent use of INH and rifampicin might lead to a greater risk of hepatotoxicity. It is believed that Rifampicin can induce the metabolism of INH to hepatotoxins.

A Meta-analysis conducted by Steele et al, looking at the incidence of hepatitis in all studies between 1966 and 1989 using regimens contained INH without Rifampicin, Rifampicin without INH and regimens containing both drugs, revealed that the incidence of clinical hepatitis was greater in regimen containing both the drugs. The authors suggested that this effect was additive not synergistic, therefore the use of the two drugs together, is not contraindicated.

However, caution should be taken in high risk individuals such as elderly, alcoholics, those taking additional hepatotoxic agents and those with pre-existing liver diseases. Rifampicin usually causes cholestasis, which leads to raise alkaline phosphatase and bilirubin. Liver toxicities can be the major side effect of all three main anti-TB drugs, Isoniazid, Rifampicin and Pyrazinamide.

Generally, in order to decrease the risk of liver damage of these drugs the following points are helpful:

- Recording liver enzymes baseline levels before prescribing the anti-TB drugs.
- Monitoring the transaminases serum levels in patients over 20 years of age. This monitoring should be performed twice in a week in the first two weeks and once a week in the next two months.
- Discontinuing the drug regimen immediately after raising the enzymes 3 times the baseline.
- Avoid concurrent use of anti-TB drugs with CYTP450 inducers.
- Avoid concurrent use of anti-TB drugs with other hepatotoxic drugs.

Conclusion

In conclusion, Anti-TB drugs could cause significant adverse effects both in quantity and severity. These reactions may lead to hospitalization, prolonged hospital stay and even death. Asian people may develop more frequently severe adverse reactions, such as hepatitis, induced by this class of medicines. These results suggest that the protocol may need some revision to prevent fatal hepatotoxicity. To confirm this hypothesis many more studies with large population is needed.

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