Section: Pharmacology

Original Research Article

A PROSPECTIVE STUDY OF DRUG RELATED PROBLEMS IN TUBERCULOSIS PATIENTS UNDERGOING TREATMENT IN A TERTIARY CARE HOSPITAL

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Abstract:

Background: Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis. It is the most rambling communicable infectious disease on earth and remains out of control in many developing countries. It is the single most common cause of death in individuals aged 15-49 years. India features among the 22 high TB burden countries and has accounted for an estimated one-quarter (26%) of all TB cases worldwide. Pulmonary tuberculosis is the most common presentation among all. Good bacteriological diagnosis and compliance with treatment are the two core stakes of successful treatment of pulmonary tuberculosis. **Materials and Methods:** A prospective study was carried out from January 2020 - December 2020 during which the data was collected from a total of 200 case sheets of the inpatients of all departments (except OBG) of a tertiary care hospital. All the case sheets were checked for DRPs by using Micromedex, Drugs.com database and various standard textbooks along with interview from patients and evaluated as per PCNE classification. **Results:** The data was collected from 200 in-patients using a specially designed data collection form. Out of 200 patients, 90 patients with hepatic impairment, 60 with diabetes, 34 with lower respiratory tract infection, 10 with hypertension & 6 with chronic obstructive pulmonary disease were found. In this study, a total of 1170 drug related problems have been identified in 200 patients by using 6 categories of "Pharmaceutical Care Network Europe" (PCNE) "Drug Related Problems" (DRPs) classification. Drug interactions (50.26%) were the most common drug related problems found, which was clinically significant in tuberculosis patients with comorbidities. Drug choice problem (40.68%) was the second most common drug related problem found, which consists of inappropriate use of drugs (74.37%) like antibiotics and acid suppressant drugs. Hepatic impairment was common ADR found in most of the tuberculosis patients on anti-tubercular drugs. But in future we need to pay more attention to the management of tuberculosis in patients suffering from diabetes, hypertension and other comorbidities and associated drug related problems. **Conclusion:** A substantial proportion of hospitalized patients experience medication-related harm that is preventable. Medication errors have been estimated to account for over a quarter of the causes of adverse drug events. Strategies to prevent such problems are being developed. One such strategy is that the complete clinical status of each patient is considered while identifying drug related problems & the structured review of patient medication by clinicians is done to identify patients with medication errors that may otherwise lead to harm.

INTRODUCTION

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis. It is the most rambling communicable infectious disease on earth and remains out of control in many developing countries.[1] It is the single most common cause of death in individuals aged 15-49 years. India features

among the 22 high TB burden countries and has accounted for an estimated one-quarter (26%) of all TB cases worldwide. Pulmonary tuberculosis is the most common presentation among all. Good bacteriological diagnosis and compliance with treatment are the two core stakes of successful treatment of pulmonary tuberculosis.[2]

To strengthen the efforts to control TB, the Government of India introduced the Revised National Tuberculosis Control Program (RNTCP) in 1997, which implemented DOTS. One of the key components of DOTS therapy is the standard anti-TB short course chemotherapy regimen, which requires continually taking drug combinations for 6-9 months. Despite all these initiatives and positive therapeutic effects, studies have shown that the utilization of multidrug regimens can cause undesirable Adverse Drug Reactions (ADRs) of varying degrees of severity, such as hepatotoxicity, Gastrointestinal (GI) disorders, etc. [3]

Medication adherence is one of the most important factors that determines therapeutic outcome, especially in patients suffering from chronic illness. Medication adherence is defined as "the extent to which a patient's medication-taking behavior coincides with the intention of the health advice he or she has been given." Adherence is also defined by World Health Organization as "the degree to which the person's behavior corresponds with the agreed recommendations from a health care provider." [4]

To improve the rational use of drugs, the clinician has an important role in identifying and solving the problems which have correlation with the use of drugs and causing potential or actual Drug Related Problems (DRPs). Drug Related Problem (DRP) is defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes." DRPs are one kind of problems which appear with the usage of drugs in therapy; which can potentially influence the outcome of therapy, increasing the cost of therapy and also can block the attainment of the therapy purposed.[5] The DRPs are usually caused due to an increase in the number of drugs consumed by the patient (polypharmacy) to overcome the other comorbid diseases that the patient was suffering from.

MATERIALS AND METHODS

A prospective study was carried out from January 2020 - December 2020 during which the data was collected from a total of 200 case sheets of the inpatients of all departments (except OBG) of a tertiary care hospital.

Inclusion criteria:

TB patients with comorbidities

Patients of all age groups

Exclusion criteria:

Patients with only TB

Pregnant and lactating women

Data analysis: All the case sheets were checked for DRPs by using Micromedex, Drugs.com database and various standard textbooks along with interview from patients and evaluated as per PCNE classification.

Statistical methods: The present study was analyzed by using descriptive statistics. Data was collected in predesigned Microsoft Excel and Word 2010. For descriptive statistics, results were expressed in terms of percentages and presented using tables and bar diagrams according to the types of tools used.

RESULTS

The data was collected from 200 in-patients using a specially designed data collection form. Out of 200 patients; 90 patients with hepatic impairment, 60 with diabetes, 34 with lower respiratory tract infection, 10 with hypertension and 6 with chronic obstructive pulmonary disease were found. In this study, a total of 1170 drug related problems have been identified in 200 patients by using 6 categories of "Pharmaceutical Care Network Europe" (PCNE) "Drug Related Problems" (DRPs) classification. Drug interactions (50.26%) were the most common drug related problems found, which was clinically significant in tuberculosis patients with comorbidities. Drug choice problem (40.68%) was the second most common drug related problems found, which consists of inappropriate use of drugs (74.37%) like antibiotics and acid suppressant drugs. Hepatic impairment was common ADR found in most of the tuberculosis patients on anti-tubercular drugs. But in future we need to pay more attention to the management of tuberculosis in patients suffering from diabetes, hypertension and other comorbidities and associated drug related problems.

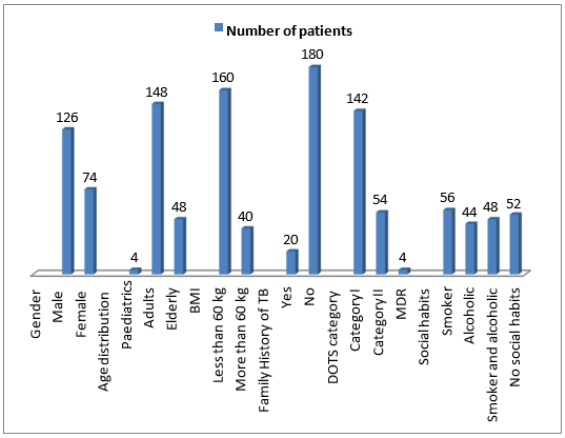

Figure 1: Patient demographics

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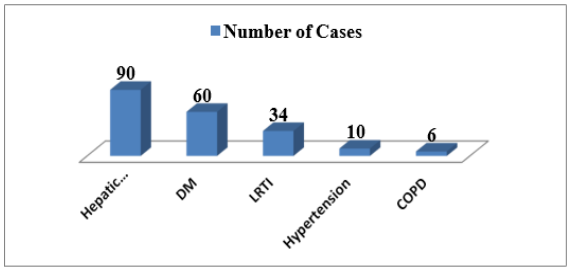

Figure 2: Comorbidities

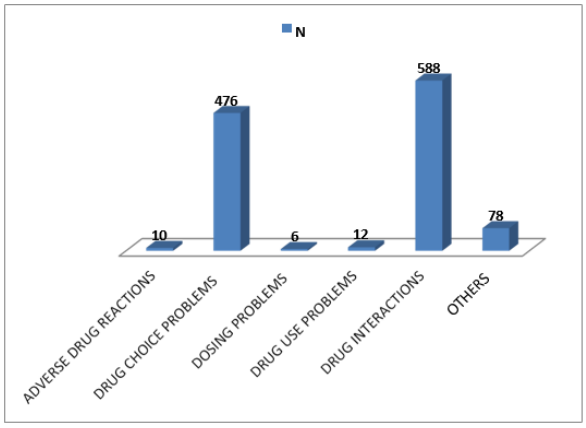

Figure 3: Drug Related Problems (DRPs)

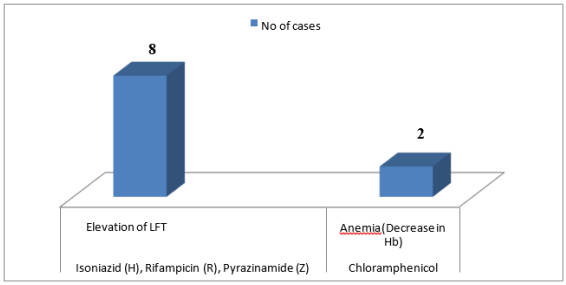

Figure 4: Adverse Drug Reactions

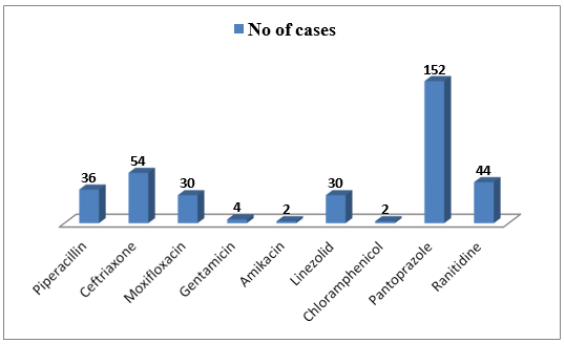

Figure 5: Inappropriate drug

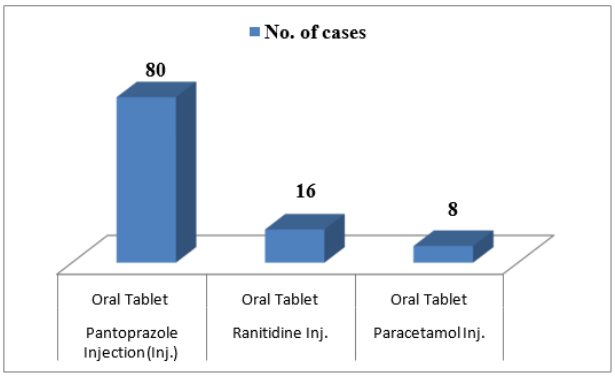

Figure 6: Inappropriate Drug Form

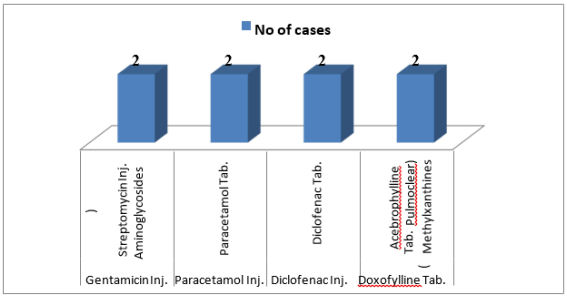

Figure 7: Inappropriate Duplication of Therapeutic group / Active drug

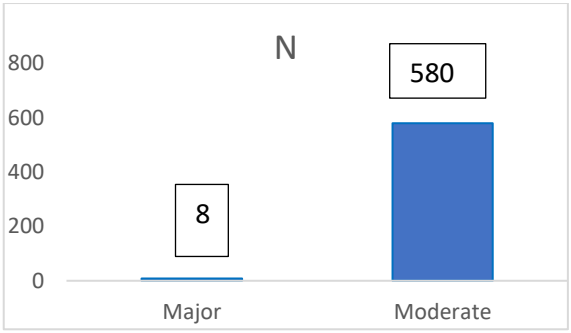

Figure 8: Drug Interactions

Table 1: Patient demographics

Characteristics	Number of patients (%)
Gender	
Male	126 (63)
Female	74 (37)
Age distribution	
Pediatrics	4 (2)
Adults	148 (74)
Elderly	48 (24)
BMI	
Less than 60 kg	160 (80%)
More than 60 kg	40 (20%)
Family History of TB	

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Yes	20 (10)
No	180 (90)
DOTS category	
Category I	142 (71)
Category II	54 (27)
MDR	4 (2)
Social habits	
Smoker	56 (28)
Alcoholic	44 (22)
Smoker and alcoholic	48 (24)
No social habits	52 (26)

Table 2: Comorbidities

S. No	Comorbidities	Number of Cases (%)
1	Hepatic impairment	90 (45)
2	DM	60 (30)
3	LRTI	34 (17)
4	Hypertension	10 (5)
5	COPD	6 (3)

Table 3: Drug Related Problems (DRPs)

Problem	N (%)
ADVERSE DRUG REACTIONS	**10 (0.85)**
Side effects (non-allergic)	10 (0.85)
DRUG CHOICE PROBLEMS	**476 (40.68)**
Inappropriate drug	354 (74.37)
Inappropriate drug form	104 (21.85)
Inappropriate duplication of therapeutic group / active ingredient	8 (1.68)
Contraindication for drug	2 (0.42)
No clear indication for drug use	8 (1.68)
DOSING PROBLEMS	**6 (0.51)**
Drug dose too high / dosage regimen too frequent	6 (0.51)
DRUG USE PROBLEMS	**12 (0.68)**
Wrong drug taken/administered	12 (0.68)
DRUG INTERACTIONS	**588 (50.26)**
Potential Interaction	588 (50.26)
OTHERS	**78 (6.67)**
Insufficient awareness of health and diseases	78 (6.67)

Table 4: Adverse Drug Reactions

S. No	Drug	ADR	No of cases
1	Isoniazid (H), Rifampicin (R), Pyrazinamide (Z)	Elevation of LFT	8
2	Chloramphenicol	Anemia (Decrease in Hb)	2

Table 5: Inappropriate drug

S. No	Drugs	No of cases
	Beta-lactams	
1	Piperacillin	36
2	Ceftriaxone	54
	Fluroquinolones	
3	Moxifloxacin	30
	Aminoglycosides	
4	Gentamicin	4
5	Amikacin	2
	Others	
6	Linezolid	30
7	Chloramphenicol	2
	Proton Pump Inhibitors	
8	Pantoprazole	152
	H_2 Receptor Antagonists	
9	Ranitidine	44

Table 6: Inappropriate Drug Form

S. No	Drug dosage form	Appropriate dosage form	No. of cases
1	Pantoprazole Injection (Inj.)	Oral Tablet	80
2	Ranitidine Inj.	Oral Tablet	16
3	Paracetamol Inj.	Oral Tablet	8

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Table 7: Inappropriate Duplication of Therapeutic group / Active drug

S. No	Drug	Therapeutic group	No of cases
1	Gentamicin Inj.	Streptomycin Inj. (Aminoglycosides)	2
2	Paracetamol Inj.	Paracetamol Tab.	2
3	Diclofenac Inj.	Diclofenac Tab.	2
4	Doxofylline Tab.	Acebrophylline (Tab. Pulmoclear) Methylxanthines	2

Table 8: Contraindication of Drug

S. No	Drug	Reason	No. of cases
1	Chloramphenicol	Bone marrow suppressant (Anemia)	2

Table 9: No Clear Indication of Drug Use

S. No	Drugs	No. of cases
	Antimalarials	
1	Lumefantrine + Artemether	8

Table 10: Drug Dose is too high / Dosage Regimen is too frequent

S. No	Drug	Reason	No of cases
1	Isoniazid/Rifampicin/Pyrazinamide	Dose should be adjusted for patient with alcoholic induced hepatic impairment based on liver function tests	6

Table 11: Wrong Drug Administered

S. No	Drug	Reason	No of cases
1	Montelukast	It is only indicated in chronic asthma / Exercise induced asthma and Seasonal Allergic Rhinitis	12

Table 12: Drug Interactions

Type of Interaction	No. of interactions
Major	8
Moderate	580

DISCUSSION

A substantial proportion of hospitalized patients experience medication-related harm that is preventable. Medication errors have been estimated to account for over a quarter of the causes of adverse drug events. Strategies to prevent such problems are being developed. One such strategy is that the complete clinical status of each patient is considered while identifying drug related problems & the structured review of patient medication by clinicians is done to identify patients with medication errors that may otherwise lead to harm.[6]

The gender distribution of study population showed that among 200 patients, 126 (63%) were males and 74 (37%) were females [as shown in Figure 1 & Table 1]. This data showed that males are at more risk to get infection than females because of hormonal differences owned by male and female. Hormone testosterone, which is owned by male, may increase the effects of immunosuppression so that the ability of the body to fight with the bacteria has decreased. Meanwhile, the hormone estrogen works vice versa so that it can trigger an immune response. Other researchers also reported that the risk of infection in postmenopausal females were almost equal to males. This corresponds to a decrease in estrogens, and it was found that the 5-reductase enzyme converts dehydroepiandrosterone hormone into dihydrotestosterone, which lowers the body's immune system.[7]

In this study, 148 patients were adults (74%), 48 patients were elderly (24%) and 4 patients were children (2%) [as shown in Figure 1 & Table 1]. This might be because adults are usually more exposed to the risk factors/infections compared to elderly and children age group.[8]

In this study, 160 patients weighed less than 60kg (80%) and 40 patients weighed more than 60kg (20%) [as shown in Figure 1 & Table 1].

Out of 200 patients, the majority of patients 180 (90%) do not have any family history of TB [as shown in Figure 1 & Table 1].

Out of 200 patients, the majority of patients, 142 (71%) came under Category I TB and 54 patients (27%) under category II TB and 4 patients (2%) under MDR TB [as shown in Figure 1 & Table 1].

Out of 200 patients, 90 patients were diagnosed with hepatic impairment (45%), 60 with DM (30%), 34 with LRTI (17%), 10 with hypertension (5%) & 6 with COPD (3%) [as shown in Figure 2 & Table 2].

A total of 1170 DRPs have been identified in 200 patients by using 6 categories of PCNE DRPs classification [as shown in Figure 3 & Table 3].

Elevation of LFT was observed in 8 patients (with Isoniazid (H), Rifampicin (R), Pyrazinamide (Z)), 2 anaemia cases were observed due to chloramphenicol. [as shown in Figure 4 & Table 4].

The present study shows that a greater number of DRPs occurred in TB patients with comorbidities compared to TB alone, as the chronic comorbid conditions require regular medication that will contribute more potential drug-drug interactions.[9]

Ceftriaxone is currently listed in the antibiotic policy for the following conditions - epiglottitis, brain abscess, bacterial meningitis, pyelonephritis in children, empiric therapy of septicaemia in children, in ascites for the treatment of sub-acute bacterial

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peritonitis, skin and soft tissue infections managed via out-patients IV antibiotic programme, acute septic mono-arthritis if patient is allergic to penicillin, spontaneous bacterial peritonitis.[10]

Here, a few patients have received a combination of anti-TB antibiotics along with other antibiotics like ceftriaxone, which was not effective against tuberculous bacteria, while the culture and sensitivity test results showed only the presence of mycobacteria. In this study, the use of other antibiotics was not needed because there was no specific indication in those patients. Result of one study showed that inappropriate use of ceftriaxone is high which currently paves a way for the emergence of bacterial strains that are resistant to the available antimicrobial agents, which in turn leads to increase in cost of therapy and treatment failure.

Other antibiotics contributing to DRPs are 36 prescriptions of Piperacillin, 30 prescriptions of moxifloxacin, 30 prescriptions of Linezolid, 2 prescriptions of chloramphenicol and 6 prescriptions of aminoglycosides - gentamicin (4) and amikacin (2) [as shown in Figure 5 & Table 5]. Piperacillin-Tazobactum were currently listed in the antibiotic policy for the following conditions - pneumonia or septicaemia in neutropenic patients, (as a single agent or in combination with gentamicin) for the treatment of sepsis which has not responded to first line treatment or if it is not appropriate for gentamicin to be added to first-line therapy.

The following criteria has been proposed to protect the linezolid from overuse, which comes under reserve antimicrobials indicated specially for severe sepsis, as defined by more than one organ failure of new onset and/or elevated serum lactate, clinical failure of other classes of antibiotics over 48 hours in terms of worsening inflammatory markers, unresolving fever and new/worsening hemodynamic instability, underlying severe immuno-suppression, neutropenia, immuno-suppressive therapy, diabetic ketoacidosis and the organism is susceptible to only linezolid, as per culture report. In the present study, inappropriate drug form (104) of prescriptions included pantoprazole injection (80) and ranitidine injection (16), instead of oral tablets, with no clear indication [as shown in Figure 6 & Table 6].

Paracetamol injection was found to be inappropriate in 8 prescriptions instead of oral tablets where the patients were having low grade fever [as shown in Figure 6 & Table 6].

Therapeutic duplication of drugs/class is found to be less in this study, a total of 8 are identified [as shown in Figure 7 & Table 7]. Aminoglycosides like gentamicin with streptomycin injection were administered together even though both the drugs fall under the same class of antibiotics. NSAIDs like paracetamol and diclofenac were given in injection form as well as tablet form. Oral methylxanthines like doxofylline with acebrophylline were given concomitantly while both drugs fall under the same class of bronchodilators.

In this study, 2 anaemic patients were prescribed chloramphenicol which is contraindicated in anaemic patients and the patient showed further lowered haemoglobin level after administration of chloramphenicol, as it is known to cause bone marrow depression [as shown in Table 8].

In the current study, 8 patients were prescribed with antimalarial drugs like lumefantrine and artemether [as shown in Table 9]. Over-prescription of Artesunate Combination Therapy (ACT) without any clear indication may result in substantial unnecessary use of this class of drugs and the risk of developing drug resistance. In addition to it, blind treatment of malaria without parasitological confirmation of the parasite deviates from best practices.

In this study, a total of 6 dosing problems were found. Drug dose was too high in 6 (0.35%) alcoholic patients with abnormal LFT [as shown in Table 10]. Alcoholism is one of the main risk factors which aggravates the anti-TB induced hepatotoxicity. For all types of liver diseases caused by alcohol, the main treatment is to stop consumption of alcohol completely.

In the present study, a total of 12 COPD patients were administered with the wrong drug montelukast, (Leukotriene modifier) [as shown in Table 11]. Leukotriene modifiers target the inflammatory pathway in asthma. Montelukast is used as an option for controller therapy, particularly in children. It is only indicated in patients with chronic asthma/ exercise induced asthma and seasonal allergic rhinitis.

In this study, a total of 588 potential drug interactions were found - major 8 and moderate 580 [as shown in Figure 8 & Table 12]. Drug-drug interactions showed significant impact on TB patients with co-morbid diseases like hepatic impairment, DM, hypertension and COPD etc.as the patients were already on regular medications for their chronic illnesses.

CONCLUSION

In this study, nonadherence to prescribed therapy was found to be the DRP causing hospitalization at higher incidence followed by ADR. Most identified risk factors in patients having chronic diseases are lack of knowledge about - the disease, need of adherence to the therapy as prescribed, and outcomes of treatment provided. The severity of DRPs was majorly assessed to be moderate.

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