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EVALUATION OF ANTI-TUBERCULOSIS INDUCED ADVERSE REACTIONS IN PATIENTS OF BALOCHISTAN, PAKISTAN

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Abstract:

Objective:

Pakistan is ranked 5th in the world in terms of having immense Tuberculosis (TB) burden. During the course of TB treatment, adverse drug reactions (ADRs) due to anti-TB drugs are a killer problem. Therefore, the present study was conducted on 200 TB patients to explore the incidence of ADRs due to anti-TB drugs.

Methods:

This is a multicenter study conducted at two public healthcare institutes of Quetta city, Pakistan. Data of 200 patients was screened from the official records and evaluated to identify variables of interest. All necessary diagnostic tests were performed before starting the therapy and after every 2 months during the study. Data was collected through a validated information sheet. Descriptive SPSS v.20 was used for data analysis.

Results:

A total of 200 patients were enrolled in the study. In this study, most frequently reported ADR was fever (163, 84.5%) followed by nausea (152, 76%) and epigastric pain (117, 58.5%). Interestingly, the most commonly reported ADR in literature (constipation and weight gain) were least reported in the current study. Thirty nine (19.5%) patients were admitted to hospital during the study because of the observed ADRs. During the study, 46 (23%) patients were given re-challenge to ADRs and were managed by giving additional medicines with TB drug treatment regimen. One hundred and eighty three I(91.5%) patients from both hospitals were given a complete 6 months therapy. However, 5 (2.5%) patients died during the therapy and 12 (6%) patients underwent therapy discontinuation because of unidentified reasons.

Conclusion:

Majority of the patients experienced ADRs and the management of most ARDs was done by therapy modifications. It was also observed during the study that some patients did not report common and clinically mild ADRs, so it is the duty of health practitioners to interrogate and investigate the patients keenly. Health practitioner should also take immediate actions to combat the ADRs and improve the patient's quality of life.

Keywords: *Pulmonary tuberculosis, anti-tuberculosis, adverse drug reactions, Baluchistan, Pakistan*

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INTRODUCTION:

Tuberculosis (TB) is one of the major causes of mortality worldwide, resulting in death of more than 2 million patients annually. The World Health Organization (WHO) has reported that one third population of the world is infected with the disease and 90% of them are from developing countries[1,2]. Hence, TB is a killing disease for less developed and low revenue countries [3]. Within this context, a total of six Asian countries namely Pakistan, China, India, Bangladesh, Philippines and Indonesia were reported with the highest incidence rates of TB [4].

Inline to what is reported, Pakistan is among top 22 underdeveloped countries affected by the disease [5] and is ranked 5th in the world in having the disease burden, with approximately 47% cases of pulmonary TB (PTB) [6] . Additionally, there is increased risk of developing TB among individuals with family history of the disease and the workers of health care settings[7,8]. Other risk factors for the disease are younger age, gender, socioeconomic status (SES), lack of awareness and various other diseases [9 ,10].

During the treatment of TB, the goals are cure without recurrence, prevention of transmission and improved patient survival. Combination treatment for the period of 6-8 months is the current treatment of TB. The treatment is usually completed in two phases: initial phase and continuous phase[11]. The 1st line anti-TB drugs are based on mode of action and are isoniazid (INH), ethambutol (EMB), rifampicin/rifampin (RIF), pyrazinamide (PZA) and rifapentine or rifabutin. For the period of first two months, patients receive 3-4 drugs (RIF, INH, PZA and EMB). During next 4 months they are continued with INH and RIF only. However, Anti-TB drugs can cause frequent and severe ADRs [12]. Different studies have reported that >5% patients on anti-TB drugs develop ADRs. The most common of them are hepatotoxicity and skin reactions [13]. These ADRs can do immense harm to the patients and may need different examination tests and treatments[14]. Such ADRs may lead to prolonged hospitalization and even death of the patient. Detection of such ADRs is a key to monitor drug safety as it motivates the edification of health authorities concerning potential ADRs. Therefore the current study was aimed to explore the incidence of ADRs due to anti-TB drugs attending public hospitals of Quetta, Pakistan.

METHODS:

Research, settings and time frame

The present descriptive questionnaire based observational study was conducted on both hospitalized patients and those attending the outdoor TB clinics of two hospitals i.e. Fatima Jinnah Chest and General (FJGC) Hospital and Bolan Medical Complex (BMC) Hospital, Quetta, Balochistan. The study was carried out for the period of 6 months.

Ethical approval, data collection & variables of the study

Institutional Review Committee of Faculty of Pharmacy & Health Sciences, University of Balochistan approved the study. In addition, permissions for the study were obtained from the concerned medical superintendents and an informed consent was signed by the patients before the beginning of the study. The patients were informed about the purpose of the study and were counseled regarding the disease, treatment and possible adverse effects. Re-counseling was performed when necessary. A structured data collection sheet was used for data collection.

Before starting anti TB therapy the recruited participants completed a questionnaire and received different laboratory examinations, including routine blood and urine tests, serological tests for hepatitis B surface antigen (HBsAg) and anti-hepatitis C antibody (anti-HCV), liver function test (LFT) and renal function test (RFT). During the follow up period, all examinations were measured after every 2 months during the treatment. The participants were also instructed to self-record any ADR by using a diary and to report them to the researcher/doctor. Once a suspected ADR was identified, it was followed up until resolution or completion of therapy. The participants of study visited the doctor/researcher once weekly and presented their data to doctor/researcher until the completion of therapy. Detection and monitoring was done by interviewing patients and reviewing laboratory tests.

Sampling

The study was conducted on 200 patients (n=200) suffering from pulmonary TB (PTB) after fulfilling inclusion and exclusion criteria irrespective of age, sex, and race.

Inclusion criteria

The patients of any age and gender, suffering from PTB, not enrolled in any TB support or educational program were targeted for the study. Patients with hyper-vitaminosis, not able to visit the hospital regularly, receiving other treatment regimens, compromised or having MDR (Multi Drug Resistance) TB were excluded from the study. Both hospitalized patients and the patients from outdoor TB clinics of the hospitals were enrolled in the study after fulfilling the inclusion and exclusion criteria.

Statistical analysis

Statistical analysis was performed with statistical package for social sciences (SPSS) software version 20.0. Descriptive statistics were used to describe demographic and disease characteristics of the patients. Percentages and frequencies were used for the categorical variables, while means and standard deviations were calculated for the continuous variables. The characteristics of the whole sample were presented.

RESULTS:

Two hundred patients attended the survey. One hundred and forty two (71%) were ranked as out-patients while the rest were admitted to the hospital. The cohort was dominated by males (123, 61.5%) and majority was in

the age range of 20-29 years (62, 31.0%). One hundred and forty one were married (141, 70.5%) and belonging to the middle class (111, 55.5%) as shown in Table 1.

Table 1: Demographic characteristics of the patients

Characteristics	Frequency	Percentage
Age (years)	7	3.5
<10	30	15.0
10-19	54	27.0
20-29	62	31.0
30-39	25	12.5
40-49	11	5.5
50-59	7	3.5
60-69	4	2.0
> 70	7	3.5
Gender		
Male	123	61.5
Female	77	38.5
Status		
Single	34	17.0
Married	141	70.5
Divorced	18	9.0
Widowed	7	3.5
Body Mass Index		
Underweight	17	8.5
Normal weight	85	42.5
Overweight	91	45.5
Obesity	7	3.5
Socio-economic status		
Lower (< 10,000 Pk. Rs per month)	89	44.5
Middle (10,000-30,000 Pk. Rs per month)	111	55.5
Educational status		
Not going to school	11	5.5
Illiterate	119	59.5
Primary	37	18.5
Middle	16	8.0
Matric	16	8.0
Bachelor	1	0.5

Table 2 provides the data on the incidence of ADR among the patients. In this study, most frequently reported ADR was fever (163, 84.5%) followed by nausea (152, 76%) and epigastric pain (117, 58.5%). Interestingly, the most commonly reported ADR in literature (constipation and weight gain) were least reported in the current study. An important observation of the study was that the incidence of ADR was almost equal to both hospitals.

In FJGC hearing loss was observed in 24, vertiligo in 33, new-onset tinnitus in 18, itching in 28, hives in 8, fever in 77, petechial rash in 4, anorexia in 42, nausea in 80, vomiting in 56, epigastric pain in 59, diarrhoea in 31, constipation in 3, yellow coloration of eyes (jaundice) in 32, hepatitis in 3, fatigue in 75, weight gain in 2, sluggish reflexes in 6, depression in 42, gout-like manifestations in 5, joint pain in 46, headaches in 60, agitation in 37, suicidal ideation in 15, numbness or paresthesias of feet or hands in 17, urine discoloration in 16, hematuria in 5, azotemia in 5, vision loss in 7, colour blindness in 6, uveitis in 4, rashes with itching in 55, rashes without itching in 25, urticaria in 18, angioedema in 6 and skin eruption in 9 patients.

In BMC hearing loss was observed in 18, vertiligo in 26, new-onset tinnitus in 23, itching in 11, hives in 17, fever in 86, petechial rash in 9, anorexia in 35, nausea in 72, vomiting in 40, epigastric pain in 58, diarrhoea in 28, yellow coloration of eyes (jaundice) in 28, hepatitis in 5, fatigue in 77, weight gain in 1, sluggish reflexes in 18, depression in 32, gout-like manifestations in 10, joint pain in 48, headaches in 34, agitation in 41, suicidal ideation in 15, numbness or paresthesias of feet or hands in 15, urine discoloration in 14, hematuria in 18, azotemia in 16, vision loss in 7, colour blindness in 5, uveitis in 6, rashes with itching in 57, rashes without itching in 29, urticaria in 10, angioedema in 9 and skin eruptionin 8 patients, as represented in Table 2.

Table 2: Incidence of ADR development in two hospitals

ADR	FJGC*	BMC*
Hearing loss	24	18
Vertigo	33	26
New-onset tinnitus	18	23
Itching	28	11
Hives	8	17
Fever	77	86
Petechial rash	4	9
Anorexia	42	35
Nausea	80	72
Vomiting	56	40
Epigastric pain	59	58
Diarrhoea	31	28
Constipation	3	0
Jaundice	32	28
Hepatitis	3	5
Fatigue	75	77
Weight gain	2	1
Sluggish reflexes	6	18
Depression	42	32
Gout like manifestations	5	10
Joint pain	46	48
Headache	60	34
Agitation	37	41
Suicidal ideation	15	15
Numbness or paresthesias of feet or hands	17	15
Urine discoloration	16	14
Hematuria	5	18
Azotemia	5	16
Vision loss	7	7
Color blindness	6	5
Uveitis	4	6
Rashes with itching	55	57
Rashes without itching	25	29
Urticaria	18	10
Angioedema	6	9
Skin eruption	9	8

number of patients

A total of 39 (19.5%) patients were admitted to hospital during the study for the observed ADRs. However, 44 (22 %) patients were already admitted to hospital for TB treatment purpose. A total of 46 (23%) patients were given re-challenge to ADRs and conversely, 154 (77%) patients were managed by giving additional medicines with TB drug treatment regimen (Table 3).

Table 3: Frequency distribution patients admitted to hospital and re-challenged for ADRs

Admitted to Hospital	**Frequency**	**Percent**
Yes	39	19.5
No	117	58.5
Already hospitalized	44	22.0
Re-challenge to patients on ADR		
Yes	46	23.0
No (ADRs managed with additional drugs)	154	77.0

Table 4: Frequency distribution of other diagnosed diseases during TB treatment

Disease	**Frequency**	**Percent**
No disease	176	88.0
Gout	9	4.5
Hepatitis	3	1.5
Hepatitis and Impaired Renal Functions	3	1.5
Hepatitis and Renal Failure	2	1.0
Impaired Renal Functions	5	2.5
Impaired Renal Functions and Impaired Liver Function	1	0.5
Piles (already)	1	0.5

During the study it was observed that 1 (0.5%) patient was already suffering from piles. During the disease treatment (9, 4.5%) developed gout, 3 (1.5%) developed drug induced hepatitis, 3 (1.5%) developed drug induced hepatitis along with impaired renal function, 2 (1%) developed drug induced hepatitis and renal failure, 5 (2.5%) developed impaired renal function and 1 (0.5%) patient developed both impaired renal and impaired liver functions. However, 176 (88%) patients did not develop any other disease as shown in Table 4. In the study, 183 (91.5%) patients from both hospitals were given a complete 6 months therapy. However, 5 (2.5%) patients died during therapy and 12 (6%) patients underwent therapy discontinuation results were shown in table 4.

DISCUSSION & CONCLUSION:

Among 200 patients all experienced ADRs, which was significantly a large number. Management of most ARDs was done by therapy modifications and by adding certain medicines. It was observed during the study that some patients often did not report common and clinically mild ADRs, so it is the duty of health practitioner and researcher to interrogate and investigate the patients keenly. Health practitioner should also take immediate actions to combat the ADRs and improve the patient's quality of life.

Pulmonary tuberculosis (PTB) is a complex disease to treat and ADRs to anti-TB drugs are a rising problem worldwide. As the disease treatment involves use of drugs in combination for a lengthened time period, there is high incidence of ADRs. Additionally, the ADR of one drug may possibly be augmented by associated drug, which may be a major cause for the false patient treatment. Demographic factors including gender, age, TB history in family, smoking history, socio-economic status (SES) and education, affect a person's health condition. Javadi et al., (2007)[15] conducted a study on 204 hospitalized patients receiving 1st line anti-TB drugs. The study was aimed to evaluate the frequencies of ADRs. A total of 92 patients were presented with ADRs in the study. The ADRs were more frequently reported by patients with TB history in family. However in our study all 200 (100%) patients reported the ADRs and 117 (58.5%) patients were having TB history in family. Frequency of TB patients with family history of

the disease was more than those without TB history in their families.

Tariq et al. (2010)[16] carried out a study 500 outdoor patients suffering from PTB and extra PTB (EPTB). The study revealed that the disease was more common in early adulthood and adolescence. However the present study was carried out on 200 patients both outdoor and hospitalized. Among them 58 (29%) patients were hospitalized for the disease and 142 (71%) were outdoor TB patients. A total of 39 (19.5%) patients were admitted to hospital during the study for the observed ADRs. Additionally, Tariq et al. (2010) [16] supported our results of age. Similarly, to their study, our investigations also revealed that the disease was common in the age of 20-39 years and even, more common in the age range of 30-39 years.

Khan et al. (2013) [17] carried out a retrospective study to assess the incidence of TB in the hospital of Penang, Malaysia on 1548 patients. In the study, 77.5% TB patients were male and 22.5% patients were female. Concluding, in their study the disease was found more prevalent in males[17]. In our study, a total of 123 (61.5%) males and 77 (38.5%) females fulfilling the inclusion criteria were enrolled. The male TB patients were more in number in our study like the study conducted by Kurniawati et al., (2012) [18] and Khan et al., (2013) [17].

Amin et al., (2014) [19] performed a study to determine the risk factors for TB on 164 patients for the period of 6 months. It revealed that TB was more common in patients with low SES, illiterate or less educated people, males and those with family history of the disease [19]. Gopi et al., 2007 [20] also reported that illiteracy (71%) was exceedingly prevalent among TB patients [20] (Gopi et al., 2007). Similarly, our study was carried out for the period of 6 months revealing that the disease was more common in illiterate people (n = 119, 59.5%), the diseases was found more common in males (n=123, 61.5%) and in patients of middle class (earning 10,000-30,000 Rs per month).

Drug hepatotoxicity, hyperglycemia, headache, peripheral neuropathy, dysuria, increased uric acid, tingling sensation of feet and hands, Joint pain, generalized itching, skin rashes, anorexia, nausea, headache, vomiting, tinnitus [21,22], fever, hyperbilirubinemia, porphyria, constipation, diarrhea, cough, red blood cells (RBC) and white blood cells (WBC) disturbances, thrombocytopenia and dim vision are commonly reported ADRs of anti-TB drugs [14,23,24]. All these ADRs were also reported in our study.

RIF, EMB and INH are the common drugs causing headache. Agitation, blurred vision or decrease in visual, uveitis, depression and suicidal ideation are other ADRs of INH. These ADRs are dose dependent. The symptoms can be improved by administrating other medicines. In our study, headache was reported in 94 (47%) patients, agitation in 78 (39%) patients, vision impairment in 14 (7%), uveitisin only 10 (5%) patients, depression in 74 (37%) patients and suicidal ideation in 30 (15%) patients.

Damasceno et al. (2013) [24] conducted a descriptive study in Manguinhos, Rio de Janeiro, Brazil, by reviewing the record of TB patients from 2004-2008. The study was designed to characterize and evaluate the frequency of ADRs to anti-TB drugs. RBC and WBC disturbances were observed in the study [24]. Similarly, in our study RBC count was below normal in 37 (18.5%) patients and WBC count was below normal in 17 (8.5%) patients. However, it was above normal in 7 (3.5%) patients.

Limitations

The limited sample size is an issue while discussing about the generalizability of the results.

Disclosure

The authors have no conflict of interest to declare. No funding was received for this study.

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