Pattern of Adverse Drug Reactions and Performed Monitoring Laboratory-Tests in Patients Receiving Anti Tuberculosis Treatment in an Endemic Region, Zabol

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Abstract

Background: Efficient anti TB treatment considered crucial globally. Anti TB drugs can cause various adverse drug reactions (ADRs). Clinical and laboratory monitoring will decrease rate of these ADRs, improve patient safety as well as drug adherence and treatment outcome.

Methods: In this cross-sectional study total of 136 newly diagnosed TB patients were included. All patients received standard anti-TB 4 drug regimen. Predesigned data collection forms were used to gather patient's lab data as well as clinical symptoms they experienced during treatment course. Monthly follow up visits or phone calls were also performed by investigators and all health issues were recorded.

Results: The majority of our patients aged over 70-year-old. About 54% of them were female. We recorded at least one ADR in 80.8% of patients, and hepatic-gastrointestinal (GI) ADRs ranked first (64.7%). Although ADRs were more common in women and patients over 70-year-old, but there was no statistically significant relationship between sex or age and rate of ADRs ($P > 0.05$). We also observed that recommended baseline laboratory tests for monitoring anti TB treatment was not performed in any of our patients, except complete blood count (CBC) that was performed in 11 cases. This led to diagnoses of anemia and thrombocytopenia in one case.

Conclusion: The majority of our patients experienced ADR. Recommended drug monitoring tests that could guarantee safe and effective treatment were not performed routinely in our TB management centres. These facts highlighted the importance of improving surveillance system for TB management based on national standards.

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Keywords: Tuberculosis; Adverse Drug Reactions; Anti TB Treatment

Introduction

Tuberculosis (TB) is an ancient disease which has global impact on public health. It is caused by Mycobacterium Tuberculosis; a virulent bacterium that mostly attacks lungs. According to the World Health Organization (WHO), in 2022, 10.6 million individuals became ill with TB and 1.3 million died (1). Anti TB drugs opened new horizons in treatment of TB, by reducing disease burden and promoting patients' quality of life. But they can be accompanied with different adverse drug reactions (ADRs) like hepatotoxicity, neurotoxicity and……. Fortunately, most of ADRs' are minor and can be managed without discontinuation of treatment. Some of these adverse drug reactions can be serious or life-threatening, leading to hospitalization, disability, or even death. These adverse effects may also increase treatment costs and decrease patients' compliance which may lead to treatment failure (2). Therefore, it is really important to monitor patients taking anti TB treatment, not only for treatment outcome and patient compliance but also for adverse drug reactions. There are established recommended tests for monitoring, each anti TB drug such as Isoniazid, Rifampin and …. These recommendations are emphasized to be followed carefully. These tests should be performed at baseline (treatment initiation) and reassessed during regular follow up visits (e.g. monthly

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intervals). Patients also should be educated about signs and symptoms of adverse drug reactions with anti TB drugs. This would help to discover and manage suspected patients as soon as possible (3,4).

The incidence of TB is higher in Sistan and Baluchestan province as well as the city of Zabol compare to other parts of Iran, that makes it an endemic disease. Therefore, it is important to evaluate the current situation to improve patient care and safety in our TB treatment centers.

Methods

All patients diagnosed with TB in different TB management sites across the city of Zabol during one-year period, were included in this descriptive prospective cross-sectional study. Sputum smear and culture ordered for all suspected patients. Diagnoses of TB was made by doctors, considering patient's clinical symptoms, radiological findings and positive sputum smear result. Patients who were registered as TB patients in each TB management site, were then interviewed by investigator to record all required information. They were then followed weekly by investigator, making phone calls, during their 6 months' treatment course. Patients also had monthly follow up visits by their treatment team in each TB management site and information about each follow up visit were kept in their files there. Predesigned forms were used for data collection by investigator. These forms included data about patient's demographics, co-morbidities (cardiovascular (CVS) diseases, diabetes mellitus (D.M), pulmonary diseases (asthma and chronic obstructive pulmonary disease (COPD)) and other diseases like gastrointestinal, rheumatoid and …), family history of TB, therapeutic drug regimen, different potential adverse effects (described as any new symptom experienced by patient after starting anti TB treatment), how those adverse effects were managed (either by doctors or by themselves) , sputum smear and culture results as well as any laboratory results ordered for patients like CBC and LFT. ADRs were diagnosed and managed using TB national treatment guide in all TB management sites by their treatment team (4).

The study was approved by The Scientific and Ethical Committee of Zabol University of medical sciences. Our study did not interfere with patients' treatment. All patients signed consent forms and no one withdrew from the study. Data entry and analysis were conducted using SPSS, version 19. Descriptive statistics were used in the form of mean, median, and standard deviation (SD). Differences between ADRs regarding different demographic variables were tested using Chi-square test. The statistical significance was determined by a P-value < 0.05.

Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 25.0, Armonk, NY: IBM Corp.) was used for analysis of data. Descriptive statistics such as frequencies, percentages, mean and standard deviation were calculated. Differences regarding various parameters and ADRs were tested using. The statistical significance was determined by a P-value < 0.05.

Results

Total number of 136 patients who aged between 4 months to 116 years, were included in this cross-sectional study. Number of patients aged 70 years and over were more than other age groups (34.6%). About 30 % of our study population suffered from at least one comorbid disease and CVS diseases (hypertension, dyslipidemia, coronary artery disease, heart failure and…) were the most common comorbidity. Patients were diagnosed with either pulmonary or extra-pulmonary TB, 103 (75.73%) and 33 (24.27%) cases, respectively. Pulmonary TB was significantly more prevalent in patients aged over 70-year-old (42.7% vs 9%, P=0.00) while the majority of extra-pulmonary tuberculosis cases (9 cases) aged between 20-30 years (P value= 0.00). There was no significant relation between sex and type of TB infection (P value > 0.05). First sputum smear sample was positive for mycobacterium tuberculosis in 85(62.5%) patients. Total number of 51(37.5%) patients were smear negative from which 33 patients (24%) were finally diagnosed with extrapulmonary TB. Diagnosis was confirmed with positive culture results (sputum, ascetic fluids and gastric lavages) in 131 cases (96.3%). In smear and culture negative pulmonary TB (5) patients, diagnoses were made based on clinical symptoms, Chest X ray result and clinician judgement. Demographic data are presented in table 1.

Anti TB treatment started with 4 drug fixed-dose combination (FDC) tablets in 132 (97.04%) patients for 2 months as initial phase (considering patient's body weight). Treatment carried on with 2 drugs FDC for continuation phase (4 months). The treatment discontinued in 8 patients because of some sort of ADR (one case of pancytopenia and 7 cases of drug induced hepatitis). Anti TB treatment re-started in these patients after ADR resolved with single-drug formulation, considering national guideline for management of ADR (4) FDC tablets were not used in 4 patients because they weighed less than 30 kilograms.

During the treatment course, 110 patients (80.8%) reported at least one ADR; 45 patients (33%) one ADR, 43 patients (31.6%) 2 ADRs and 22 patients (16.2%) 3 ADRs at the same time. Gastrointestinal/hepatic ADRS

ranked first (64.7%) between different adverse drug reactions. All reported ADRs and their frequencies are described in table 2. Although rate of ADR was higher in some subgroups of patients (patients aged more than 70 years and female gender) but there was not any statistically significant relationship between different demographic factors like sex, age, substance abuse, comorbidity and rate of ADR in our study population (P value > 0.05).

Table1. Demographic characteristics of participants.

Characteristics		
Weight, Mean (SD), Kg		51±14.3
Sex, Number (%)	Male	62 (45.6)
	Female	74 (54.4)
Past history of TB, Number (%)		6 (4.4)
Family history of TB, Number (%)		36 (26.4)
Age, Number (%), Y	<20	12 (9.6)
	20-30	17 (12.5)
	30-40	16 (11.8)
	40-50	5 (3.7)
	50-60	14 (10.3)
	60-70	24 (17.6)
	>70	48 (34.6)
Ethnicity, Number (%)	Persian	133 (97.8)
	Afghani	3(2.2)
Substance abuse, Number (%)	Cigarette smoker	6 (4.4)
	Opium abuser	31 (22.8)
	Cigarette smoker and opium abuser	5 (3.7)
Comorbidity	Diabetes	6 (12.2)
	Cardiovascular diseases	20 (40.7)
	Pulmonary diseases	3 (6.2)
	Diabetes and Cardiovascular diseases	11 (22.5)
	Others	9 (18.4)

Table2. Reported ADRs in study population

Organ involved	Type of involvement	Number (%)
Gastrointestinal/ hepatic	Jaundice	7(5)
	Fatigue	24(17.6)
	Anorexia	68 (50)
	Nausea and vomiting	55(40.5)
	Abdominal pain	24(17.6)
	Heartburn	5(3.7)
	hepatitis	7(5)
Central and peripheral nervous system	Fever	8(5.9)
	Head ache	13(9.6)
	Dizziness	18(13.2)
Cardiovascular	Palpitation	1(0.7)
Skin	Pruritus	43(31.6)
	Rash	14(10.3)
Blood	Anemia/ thrombocytopenia	1(0.7)
Endocrine	Rise of blood glucose	2(1.5)
Musculoskeletal	Muscular pain	34(25)
	Articular pain	36(26.5)
	Numbness	13(9.6)
Visual	Blurred vision	4(2.9)

Regarding base line monitoring lab tests, only complete blood count (CBC) was performed in 11 (8%) patients that was repeated 2 months later, indicating anemia and thrombocytopenia in one case. None of other recommended baseline tests; blood urea nitrogen, hepatic enzymes (serum aminotransferases), bilirubin, and serum uric acid as well as visual examination were performed in our study population. Chest x-rays were ordered only in 60 patients (44.1%) at the beginning and end of treatment course. Liver function tests (LFT) were checked in 23 patients who reported GI symptoms during treatment. Drug induced hepatitis were confirmed in 7 cases that led to discontinuation of drug therapy. Sputum culture was performed in all patients at baseline and then 3 months after commencing treatment. The follow up cultures were reported negative in all patients. Sputum smears were also re-performed at the end of initial phase as well as 2 months after starting continuation phase and were reported negative in all cases.

Discussion

Our results show that the majority of study population experienced side effects with anti-tuberculosis treatment. However, most of these complications were not recorded in patient's files or managed by their treatment team. Minor ADRs were ignored even by patients and they referred to hospitals or doctors only in severe cases. Furthermore, we found that baseline and follow-up laboratory tests, that are recommended by national and international treatment guidelines, were not performed in most cases. This can interfere with the process of detection and management of ADRs.

In our study pulmonary TB was most prevalent in patients aged over 70 years. This finding is similar to other studies performed in Brazil and Damghan (5,6) as well as our national TB prevalence report (7). Higher prevalence of TB in elderly, might be related to progressive decline in function of immune system by aging process. So, this group of patients should be considered as high-risk patients for TB infection. The disease should be suspected in older patients with chronic cough, un- explained weight loss or … and they should be screened for tuberculosis more carefully (8,9). On the other hand, extra pulmonary tuberculosis was more common in younger patients that is similar to the results of other study in Zahedan (10). Other study in Norway showed higher rate of extrapulmonary TB in adolescence which may be related to less developed immune system in this age group (11). This type of TB is often less suspected, more difficult to diagnoses and requires invasive procedures to obtain desired sample.

Globally, the prevalence of infection with Mycobacterium tuberculosis is similar in males and females until adolescence, after which it is higher in males (12). But we observed that TB was slightly more prevalent in females. This might be the result of lower overall health condition as well as lower immune function in women who leave in this area or underreporting of TB by men. Nowadays it is questioned that weather higher prevalence of TB in men describes the epidemic, or whether this is only an artifact of reporting bias or confounding factors like smoking, and HIV infection which are more prevalent among men. Sputum smear was routinely performed for all patients. Most of our patients had positive sputum smears. Pulmonary TB was much more common than extrapulmonary TB in our study population. These findings are also confirmed by national prevalence report about tuberculosis and other studies (7,13, 14)

Like other studies, the majority of our patients experienced ADR with anti TB treatment (15,16,17). In this study, the most common ADRs were gastrointestinal complications. While in some other studies drug induced hepatitis was reported as the most common side effect (18,19). LFT was not evaluated at baseline almost in all cases and patients were not monitored carefully during treatment in some centres. These may interfere with diagnoses drug induced hepatitis in our patients. ADRs were reported more common in females and older patients. These findings are similar to what has been reported in other studies conducted in other parts of Iran or other countries (3, 19,). Although some risk factors are drug class specific, but female gender and older age are recognised as established risk factors for ADR across multiple therapeutic classes of drugs (20).

Regarding other tests, we observed that chest X-ray was requested only in about half of cases. Baseline and follow up laboratory tests, that are recommended for drug monitoring, were not ordered in our study population. The only test that was performed in a small group of patients was CBC. Without baseline levels, sometimes it would be difficult to differentiate weather the problem is induced by drug therapy. Besides, in case of drug induced hepatitis for example, there is a significant and linear association between the degree of liver function abnormality during anti TB treatment and the presence of abnormal baseline LFT tests. Routine performing recommended lab tests would allow early detection of patients experiencing ADR especially in those without significant clinical symptoms. Therefore, we would be able to cease the drug therapy before it causes dramatic consequences (21).

Most ADRs happens in first 2 months, initial phase, of treatment in our study population. In other studies, in Brazil, also most ADRs happens in first month after starting anti TB treatment (22,23). This fact indicate that patients need to be monitored for ADR more carefully in initial phase of treatment of TB.

Our study had some limitations. One of the major limitations was the fact that minor ADRs were not reported by patients. Besides ADRs were not documented carefully in patient's files in some centers. Some patients were not cooperative and did not answer carefully to follow up phone calls by investigator. Monitoring lab tests were not performed based on national guideline and this interferes with diagnoses and monitoring ADRs.

In conclusion, rate of ADRs was high in patients who were treating for TB. Unfortunately, recommended monitoring lab tests were not performed carefully in these patients. This can interfere with the process of detecting and managing ADR. Therefore, it is crucial to encourage and discipline doctors and nurses who work in TB management centers to practice based on approved guidelines.

Conflict of interest: No potential conflict of interest was reported by the authors.

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