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Original Article

Adverse Drug Reactions of First Line Anti-tuberculosis Drugs used in DOTS Implemented Setting in Lahore

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Abstract

Background: Tuberculosis (TB) is a major health problem in most countries despite the availability of effective chemotherapy. The frequency and nature of anti-TB drugs induced adverse drug reactions (ADRs) have been matter of concern in many countries. In our programme patients take their medicines under the direct observation of a health care provider. It is therefore, important to monitor ADRs and increase awareness of health care providers about ADRs and their management.
Objective: To get an over view of adverse drug reactions caused by first line anti-tuberculosis drugs used in the treatment of TB cases in directly observed therapy short course (DOTS).
Study design, settings and duration: This descriptive observational study was carried out at chest clinic of Sir Ganga Ram Hospital, Lahore for a period of one year.
Patients and Methods: Patient aged ≥15 years of age registered for treatment of tuberculosis in treatment category I at Model Chest Clinic, Sir Ganga Ram Hospital, Lahore were included in the study after obtaining consent. All patients were advised to visit health facility immediately if they had any feeling of drug reaction.
Results: A total of 760 TB patients registered in treatment category I were included in the study. Out of 760 patients, 306 (40.2%) patients showed Adverse Drug Reactions (ADR) with anti TB drugs. Joint pain was the most common ADR, reported by 16.7% patients followed by skin itching in 11.5%, anorexia, nausea, abdominal pain in 7.63% and jaundice in 3.68% patients. Rash and visual impairment was reported by 0.26% each. Within gender, ADRs were mostly reported by females (41.9%) as compared to male patients (37.6%). Age wise majority (36%) of ADRs were reported by patients aged between 15-54 years as compared to those aged 55 years or above (4.2%). Most adverse effects settled themselves or with addition of some anti-allergic drugs for few days and in only 4.2% cases one or more ant TB drugs had to be discontinued.
Conclusion: ADRs were observed in 40.2% TB patients but most reactions were of mild intensity and settled without any intervention. Only 4.2% reaction were severe enough to stop the drug and replace it with another drug.
Key words: Tuberculosis (TB), pulmonary tuberculosis (PTB), adverse drug reactions (ADRs), directly observed therapy short course (DOTS).

Introduction

Tuberculosis is still a major public health problem in most countries despite the availability of effective chemotherapy[1]. Pakistan currently ranks fifth amongst countries with highest burden of tuberculosis alongside the fourth highest burden of drug resistant TB globally. In an estimated population of around 180 million with annual incidence of TB being 231/100,000, Pakistan produces about 420,000 new cases annually[2]. The poor outcome was attributed to poor patient compliance, poly therapy and interruption of treatment due to adverse drug reactions (ADRs)[3].

The most important step to ensure treatment is introduction of directly observed therapy short course (DOTS). DOTS is a methodology for making sure that every patient taking TB medicines gets the best chance of being cured. Patients take their medicines under the direct observation of a health care providers or some other responsible person every day and in fixed dose combination as recommended by world health organization (WHO).

DOTS recommended anti-TB regimens are usually well tolerated. However, some patients may experience problems due to poly therapy. Drugs related adverse reactions may be minor or major. In general, patients who present with minor side effects should be encouraged to continue the treatment with symptomatic

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measures. In patients with major adverse reactions the offending drug, if identified must be stopped or regimen should be modified, so that patient could be protected from worsening of the underlined disease[4].

The frequency and nature of anti-TB drugs induced ADRs have been matter of concern in many countries. There are differences in reported rate of ADRs by these drugs in different studies[5,6]. Adverse reactions of 15% have been reported in a study conducted in Karachi, Pakistan[7]. It is therefore, necessary to study the pattern and rate of anti-TB drugs induced ADRs in our patients. It would be helpful to manage TB patients in a better way.

Patients and Methods

This descriptive observational study was carried out the outpatient department of Model Chest Clinic at Sir Ganga Ram Hospital Lahore. All new TB patients aged 15yrs and above registered for TB treatment in category I during the period Jan to Dec 2012 were included in the study. Patients less than 15 years of age and those registered in treatment category II (treatment after default, failure and relapse) were excluded from the study. Data was collected on a predesigned questionnaire after being interviewed by the researcher.

Convenience sampling method was used. Patients fulfilling the inclusion criteria were enrolled after obtaining consent. These patients received treatment as recommended by the national tuberculosis control program for a period of 6 months. Patient first received primary anti-TB drugs including a combination of four drugs isoniazid, rifampicin, pyrazinamide, ethambutol for an initial phase of 2 months, followed by isoniazid and rifampicin for 4 months.

Patients were observed regularly during their whole treatment period which comprised of fortnightly review during the initial 2 months and thereafter, every month. They were informed to visit the doctor immediately if they experience any adverse drug reactions.

The data was statistically analyzed using SPSS version 9 and chi-square test was used to determine the association between the ADRs and the different population parameters.

World Health Organization (WHO) defines drug reaction as" a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis and treatment of disease or for the modification of physiological functions". A major side effect was defined as any adverse reaction that led to the discontinuation of one or more drugs included in the standard therapy like jaundice, skin rash and itching, visual impairment, shock and purpura.

Peripheral neuropathy was diagnosed clinically on the basis of symptoms (tingling, numbness, burning sensation in feet and hand etc.). Retro bulbar neuritis causing loss of visual acuity and red-green colour discrimination was related to ethambutol toxicity. Cutaneous reactions like itching were treated symptomatically with anti-histaminic drugs without holding the anti-tuberculosis drug. Arthralgia as a cause for stopping drug was only when the patient was severely handicapped. Only severe cutaneous reactions with rash led to the discontinuation of the drug and same was true for jaundice, where treatment was replaced with a new drug.

Results

During 2012, a total of 760 new adult patients were registered in the TB clinic and offered treatment in category I for TB. Out of these, 306 (40.26%) cases of reported ADR`s with anti-TB drugs.

Adverse effects included, joint pain in 16.7% cases, skin itching in 11.5%, anorexia, nausea, abdominal pain in 7.63% and jaundice in 3.68% patients, Pruritus with rash, and visual impairment were seen in 0.2% each and burning sensation in feet & hands in 0.1% cases (Table).

Table: Percentage of adverse drug reaction in registered tuberculosis patients.

Adverse drug reactions	*N (%)*	*N (%)*	*Total*
Joint pains	127 (16.71)	633 (83.55)	760
Skin itching	88 (11.57)	672 (88.42)	760
Anorexia, nausea, Abdominal pain	58 (7.63)	702 (92.36)	760
Jaundice	28 (3.68)	732 (96.31)	760
Rash	02 (0.26)	758 (99.73)	760
Visual impairment	02 (0.26)	758 (99.73)	760
Burning sensation in feet and hands	01 (0.13)	759 (99.86)	760
Shock and purpura	0	760 (100)	760
Total	306 (40.26)	506(66.57)	760

Adverse drug reactions were categorised as major (severe enough to stop treatment and change of drug) in 32 (4.21%) patients. Among these, 28 patients had jaundice, 2 had itching with skin rash and 2 visual impairment. Of the major adverse effects, Jaundice occurred in 28 (3.6%) patients. In 21 patients, the first line anti-TB drugs were reintroduced successfully while in 7 patients offending drug, Pyrazinamide was removed and the regimen continued with 3 drugs. Visual impairment was observed in only 2 patients in whom the offending drug ethambutol was withdrawn from the treatment regimen. Rash with itching was observed in 2 patients, pyrazinamide in one and ethambutol in other patient was identified as offending drugs. These drugs were removed from treatment regimen and patients completed their treatment with three drugs regimen.

For all minor ADRs, drug was continued with reassurance and some supporting drugs like anti allergic, antacids, NSAIDs etc.

Within gender, adverse drug reactions were observed in 197 (41.9%) females and 109 (37.6%) males with no significant difference between genders.

Patients were divided into 2 groups of 15-54 years and 55 years and above. Out of 760 patients, 697 (91.71%) were between 15-54 years of age and 63(8.28%) were 55 years and above. In 15-54 years age group, 274 (36.05%) patients developed ADRs, while in 55 years and above, 32 (4.21%) patients developed ADRs but these were not significant.

Discussion

Among 760 patients, adverse drug reaction by anti TB drugs was seen in 40.2% patients, with only 4.2% having major ADRs. The findings of our study are comparable to previous studies[8,9].

Joint pains were experienced by 127 patients (16.7%) in the present study and this figure is slightly higher than 10.3% reported in an other study[10] the drug responsible for joint pain (arthralgia) could be Pyrazinamide. In the present study, ATT drug was not discontinued however, non-steroidal anti-inflammatory drugs were added to reduce pain for few weeks.

Anorexia, nausea and abdominal pain were observed in 7.6% patients and another local study also reported these ADRs commonly[11]. These side effects resolved spontaneously in most of the patients without treatment. However, in few cases antacid was prescribed by the health care provider. Drugs responsible for these gastrointestinal (GI) side effects included, Pyrazinamide, Rifampicin and Isoniazid. Generally GI side effects are generally mild but in some cases these may be severe enough to modify treatment.

Skin itching without rash was reported by 88 patients (11.5%). Drugs responsible for this side effect, are either Pyrazinamide, Rifampicin or Isoniazid. All patients in the present study continued ATT drugs with addition of antihistamine for some days. Previous studies also reported this side effect commonly[12,13].

Peripheral neuropathy characterized by burning sensation in feet and hands occurred in only 1 patient who was not given pyridoxine supplementation. Isonicotinic acid hydrazide (INH) is usually the suspected drug for this side effect. This patient continued the first line anti-TB drugs comprising of four drug regimen with addition of pyridoxine. Peripheral neuropathy is rare with recommended doses of INH used in DOTS strategy regimen[14], therefore addition of pyridoxine in the standard DOTS regimens in Pakistan is unnecessary. The finding of our study was in contrast to other studies which showed higher rates of peripheral neuropathy[8,12].

Jaundice was observed in 28 patients. In 21 patients, the first line anti-TB drugs were reintroduced successfully while in 7 patients the offending drug was removed and the regimen continued without Pyrazinamide. Comparable rates of hepatotoxicity reported in other studies varies i.e. 2.4%, 4.25%, 9.52% respectively[7,15,16], while other studies have reported higher rates 14.38%, 12.84%, 87.4% [17,18,19]. The wide variation in these reports could be attributed to many host and environmental factors[20].

Most minor ADRs did not require change in treatment as the side effects resolved spontaneously without treatment or with addition of some supportive drug by the health care provider. The major adverse effects leading to the discontinuation of one or more drugs included jaundice, skin rash and itching, visual impairment, which all accounted for 4.21% cases. This figure is in agreement with other studies[7,8] but is in contrast to study conducted in Germany where offending drug was terminated in 23% cases[21].

Generally females due to various factors are considered more at risk of adverse drug reaction[22]. In our study though females experienced adverse reactions more than males (40.9%vs. 37.6%) but the difference was not significant. Similar findings were reported by other workers[8,23]. The findings of our study are not supported by one study[24].

In this study frequency of adverse drug reactions did not show any association with age and similar findings were reported by others[15]. Few other studies showed old age as a risk factor for more adverse drug reactions[18,25].

Conflict of interest: None declared.

References

1. Grange JM. Drug resistance and tuberculosis elimination. Bull Int Union Tuberc Lung Dis 1990;65:57-9.
2. Khan JA, Malik A. Tuberculosis in Pakistan: Are we losing the battle? J Pak Med Associ.2003;53(8):320.
3. American Thoracic Society. Treatment of tuberculosis and tuberculosis infection in adults and children. Am J Respir Crit Care Med 1994;149:1359-74.
4. Banu Eris-Gulbay OUG, OznurAkkocaYildiz, Zeynep Pinar Onen, FerdaOnerErkekol, SayseBaccioglu, TuranAcican. Side effects due to primary anti-tuberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. J Resp Med 2006;100:1834-42.
5. Rehman M, Mishuk A, Halder S, Kabir AKL. Comparative analysis of adverse reactions in directly observed treatment short course(DOTS) in TB patients. GJMR 2013;13(6):7-10.
6. Kurniawati F, Sulaiman SAS, Gillant SW. Adverse drug reaction of primary anti-tuberculosis drugs among tuberculosis patients treated in chest clinic. Int J of pharmacy & life sciences 2012;3(1):1331-38.

7. Aziz S, Agha F, Hassan R, Hassan K, Fairoz H. Hepatotoxicity to different anti-tuberculosis drugs combinations. J Pak Med Asso 1990;40(12):290-4
8. Chhetri AK, Saha A, Verma SC, Palaian S, Mishra P, Shankar PR. A study of adverse drug reactions caused by first line anti-tubercular drugs used in directly observed treatment, short course (DOTS) therapy in Western Nepal, Pokhara. J Pak Med Asso 2008;58:531-36.
9. Gholami K, Kamali E, Hajiabdolbagh MI, Shaiviri G. Evaluation of anti-tuberculosis induced adverse reaction in hospitalized patients. Pharmacy Practice 2006;4(3):134-38.
10. Damasceno GS, Guaraldo L, Engstrom EM, Theme Filha MM, Souza-Santos R, Vasconcelos AG, et al. Adverse reactions to ant tuberculosis drugs in Manguinhos. Rio de Janeiro Brazil. Clinics 2013;68(3): 329-37.
11. Shinde KM, Pore SM, Bapat TR. Adverse reaction to first-line anti-tuberculosis agents in hospitalized patients: pattern, causality, severity and risk factors. Ind J Med Specialities 2013;4(1):16-21.
12. Koju D, Rao BS, Shresha B, Shakya R, Makaju R. Occurrence of side effects from anti-tuberculosis drugs in urban Nepaleae population under DOTS treatment. Kathmandu University. J Sci Eng Tech 2005:1(1):15-8.
13. Sinha K, Marak ITR, Singh WA. Adverse drug reactions in tuberculosis patients due to directly observed treatment strategy therapy: Experience at an outpatient clinic of teaching hospital in the city of Imphal, Manipue, India. The J of Asso of Chest Physici 2013;1(2):50-3.
14. NehaulLK. Tuberculosis. In: Walker R, Edwards C, eds. Clinical Pharmacy and Therapeutics. 3rd ed. Edinburgh: Churchill Livingston, 2003, pp 583-95.
15. Gulbay BE, Gurkan OU, Yildize OA, Onenn ZP, Erkekol FO, Baccioglu A, et al. Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. Respir Med 2006; 100:1834-42.
16. Tak DK, Acharya LD , Gowrinath K, Rao Padma GM, Subish P. Safety evaluation of anti-tubercular therapy under Revised National Tuberculosis Control Programme in India. J Clinicl & Diagnost Res 2009; 3:1395-401.
17. Zaman R. Prevalence and risk factors of antitubercular drug – induced hepatitis in urban population of Bahwalpur district, Punjab. Pakistan. JAPP Pharma 2011;2(03):221-33.
18. Abbasi MA, Ahmad N, Suleman A, zaman H, Tariq S, Anwar SA, et al..Common risk factors for the development of antituberculosis treatment induced hepatotoxicity. J Ayub Med Coll 2014; 26(3):384-8
19. Rahman N, Ali S, Khan MY, Umar M, Iqbal Z, Basit A, et al. of risk factors for hepatotoxicity in patients with antituberculosis drug induced hepatitis. Pak J Chest Med 2015;21(1):4-9.
20. Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during anti tuberculosis treatment. Am J Respir Crit Care Med 2002; 166:916-.
21. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. Eur Respir J 1996;9:2026-30.
22. Wilson K. Sex-related difference in drug disposition in man. Clin Pharmacokinet 1984;9:89-202.
23. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line anti tuberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med 2003; 167:1472-7.
24. Javadi MR, Shalviri G, Gholami K, Salamzadeh J, Maghooli G, Mirsaeedi SM. Adverse reactions of anti-tuberculosis drugs in hospitalized patients: incidence, severity and risk factors. Pharmacoepidemiol Drug Saf. 2007; 16(10):1104-10.
25. Khoharo HK, Ansari S, Sddiqui AK, Qureshi F. Standard antituberculosis drug induced hepatotoxicity. Do the risk factors matter? J LUMHS 2010;9(2):84-7.