Original Article

The Glitch with the Web of Anti Tubercular Drugs — A Prospective Study on Adverse Drug Reactions

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Adverse drug reactions to antituberculous drugs in DOTS are common and can cause significant morbidity and mortality. Gastrointestinal intolerance, hepatitis and cutaneous side-effects are commonly encountered. Early recognition and treatment will prevent the problem of drug non-adherence.

Background : As to the contour of adverse drug reactions (ADRs) due to directly observed treatment, short course, there is very little compiled data of patients receiving anti-tuberculosis (anti-TB) chemotherapy in Bhagalpur, Bihar, India. One of the main reasons for non-adherence, modification or discontinuation of anti-TB therapy (ATT) is ADRs, even under DOTS.

Aims : This study intended to conclude the frequency of ADRs due to DOTS therapy with a TB population of Bhagalpur, India.

Design : A prospective cohort study, and performed during July 2017-December 2018.

Materials and Methods : The study incorporated 108 diagnosed TB patients on anti-TB treatment under DOTS. Every patient was followed-up for the extent he/she received the treatment. Statistical Analysis: Frequency of different ADRs was assessed and p value was determined.

Results : Incidence of TB was more among males than female (73% against 27%). 65% showed one or more ADR. Incidence of ADRs based on affected organ was: Gastrointestinal (GI) disorders in 40 patients (57%), generalized weakness in 12 patients (17%), liver dysfunction in 11 patients (15%), allergic skin reactions in 5 patients (7%), neurological system disorders in 1 patient (1%), and fever in 4 patients (5%). However, 35% did not experience any ADRs.

Conclusion : Frequency of ADRs due to DOTS therapy was 65%. Majority of cases suffered from GI symptoms. This decorated the significance of mounting strategies to improve ADRs both to improve the quality of patient care and to control TB safely.

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Key words **: Revised National Tuberculosis Control Program (RNTCP), Directly Observe Treatment Short Course (DOTs), Anti Tuberculous Drugs (ATT), Adverse Drug Reactions (ADRs).**

Neolithic Old Disease :

Tuberculosis has afflicted the whole human race since time immemorial; this presumption has been confirmed by the fact that tuberculosis lesions have been found in mummies of Neolithic man dating back to 3700 BC[1]. M tuberculosis is transferred from a person harboring it via aerosolized unit of infection, better known as 'droplet nuclei'. The purpose of breaking the nuclei into tiny aerosols is performed by coughing, speaking, singing, sneezing or any other respiratory maneuvers. The size of the infecting speck has got clinical significance because the smaller particulates are competent of sneaking into the alveolar surface whereas the larger ones are caught red handed and cleared by the mucociliary shipping. It has been demonstrated in the smaller mammals that most of the bacilli inhaled as a solitary unit reaches the alveolus and form a tubercle, on the other hand it is highly unlikely that more than a single organism, gets deposited at any one site[2,3]. The problem with the droplet nuclei, which are often 5 μm in diameter, is that once they are dispersed they seldom settle soon and they remain viable for an extended time interval[4].

Editor's Comment :

- **Frequency of ADRs due to anti-tuberculous drugs in DOTs therapy was 65% in this study.**
- **Majority of the patients suffered from GI symptoms, Hepatic dysfunction, Fever and allergic reactions.**
- **Most of ADRs are mild in nature but some may warrant hospitalization.**
- **Early recognition and mounting strategies to improved ADRs will improve not only the quality of patients care but also help in National Tuberculosis Elimination Program (NTEP).**

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Contrary to the popular belief, these nuclei traverse the simple masks. Even covering the mouth and nose during cough doesn't avert it from dispersal.

Modern Weapons :

Directly observed treatment, short course (DOTS) was brought against the face of Tuberculosis in India in 1993 as part of Revised National Tuberculosis Control Programme (RNTCP), subsequent to an appraisal of India's NTP a year earlier[5]. The key components of DOTs comprise of directly observed treatment of TB by thrice weekly doses of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E), and/or Streptomycin (SM) for a duration of 6-9 months[6].

Studies have shown that anti-tuberculous may cause many uninvited side effects like hepatic dysfunction, GI side effects, rashes, neuropathy and many ADRs[7-11]. Studies propose that 1 out of 20 patients on anti-tubercular drugs (ATT) develop ADRs[12,13]. Not even a single anti-TB drugs is devoid of unfavorable reactions, although only seldom are the adverse reactions grave. ADRs can be a impending factor leading ill fitting compliance[14]. ADRs substantiates patient anguish and invite considerable burden to the patients and some may need hospital admission. The aim of this study is to make a review of ADRs caused by Anti-tuberculous Therapy.

Materials and Method

Study Design and Sample Selection :

This observational prospective study was undertaken in the Department of Respiratory Medicine, Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar from July 2017 to December 2018. We obtained the proper approval from the Institutional Ethical Committee. The study included 108 successively diagnosed patients of pulmonary or extra-pulmonary Tuberculosis attending our outpatient facility. The patients were chosen without the constraints of age, sex, and race. Those patients who were simultaneously being treated for some other ailments were barred from being part of our study. Those who were transferred, or those who deserted the treatment regimen, and those whose diagnosis was changed during the course of the treatment, and succumbed due to other illness during the monitoring were also disqualified.

Investigation and Follow-up :

Before starting the ATT, participants selected accomplished the baseline feedback form. The laboratory investigation included Complete Blood Count (CBC), Routine urine test, liver and renal function test, base line ECG and serum electrolyte. During the follow-up laboratory investigations were repeated 2 months after commencement of DOTs Therapy. The patients were asked to use a diary to self-record any unpleasant reactions and to report to the Medical College Outpatient Clinic. Once an alleged adverse reaction was reported it was recorded by treating physicians and follow-up was done till the completion of the course. ADR patients had their therapy tailored according to their side effect profile. Follow-up was done every fortnight to all patients during the full duration of DOTs.

Unwanted Reactons :

ADRs are considerably damaging or obnoxious reaction, consequential to an intervention connected to a drug, which predicts vulnerability from future use needing prevention, dose change or withdrawal of the product. ADRs and the timing of their appearance during treatment, as well as subsequent modifications in the treatment regimen, were noted[15].

Sternness of the ADRs was classified according to Hartwig *et al*[16], as: mild, moderate and severe.

(i) Mild ADRs were self-limiting and resolved without any treatment.

(ii) Moderate ADRs were reactions which required treatment resolving within a day. and

(iii) Severe ADRs were those that were life-threatening illness needing urgent hospitalization or intensive care management or even death of patients.

Results

73% Patients in our study were males, whereas 27% were females. 65% of those getting the anti-tubercular therapy were associated with some side effects.

Incidence of ADRs by DOTs therapy has been exhibited below in Table 1.

The unwarranted drug reactions occurred more amongst the younger population group with a maximum incidence amongst ≤25 years old and those above 50 years of age were least affected. This variance in ADRs amongst the dissimilar age groups was significant statistically (P 0.001). Although females comprised of only 27% of our study population, the preponderance

Table 1 — *Showing ADR based on Body Systems*

ADR based on Body Systems	No of Patients	% age of ADR
Gastrointestinal (GI) Symptoms	40	57%
Generalized Weakness	12	17%
Hepatitis	11	15%
Cutaneous Drug Rashes	5	7%
Neuropathy	1	1%
Pyrexia	4	5%
No ADRs	35	0%

of adverse reactions was more in the female TB patients as compared with the males (86% against 63%) and this difference was again statistically significant (P 0.001).

Discussion

The most primitive recorded human case of tuberculosis dates back to almost 9000 years. Early treatment modalities, such as bloodletting, were replaced by infirmary regimens in the late nineteenth century. The unearthing of Streptomycin in mid 19th century launched the epoch of antibiotic treatment for TB. Over ensuing decades, the discovery of supplementary agents and the use of multiple- drug regimens permitted progressive curbing of the treatment course from years to as little as 6 months for drug-susceptible TB. Latent TB infection and active TB disease are diagnosed by history, physical examination, radiographic imaging, tuberculin skin test, interferon γ release assays, acid-fast staining, mycobacterial cultures, and/or new molecular diagnostics.

Adherence to medications is significant in achieving a cure with anti- mycobacterial therapy. In addition to directly observed therapy by trained staff, case management interventions such as education/ counseling of patients, field/ home visits, and patient reminders are also recommended to improve treatment adherence. The use of mobile based health technologies including videos, messaging, electronic pillboxes etc, show assurance in promoting adherence to treatment. In susceptible TB, monthly administration of TB medications is also advocated to permit indispensable clinical monitoring for hepatotoxicity due to these.

Monitoring includes at least monthly appraisal for symptoms (queasiness, vomiting, GI discomfort, and inexplicable fatigue) and signs of hepatotoxicity including jaundice. The existence of such symptoms and signs mandates interim discontinuation of potentially hepatotoxic agents; discontinuation at the onset of hepatitis symptoms curtails the risk of progression to life threatening hepatic derangments. Biochemical testing of at least Serum Glutamic Pyruvic Transaminase (SGPT) and total bilirubin levels and segregation of other causes of these abnormalities are also indicated during treatment for those at risk for hepatotoxicity.

Our study was planned to find out the adverse reactions of ATT among the TB patients presenting to our hospital. The males compose the chief population of the study, that is, 73% males against 27% females. Males are the favorites for acquiring the disease pertaining to their higher risk factors like smoking, alcoholism and drug addiction. In addition the male are socially more malleable then the female counterpart[17]. It has been established that tuberculosis was more widespread in the age group of 25- 45 years. Edoh and Adjei also instituted high frequency in the age group of 21-40 years with the highest peak of 29% in the group of 31-40 years[18]. This, in all probability, is for the reason that the people in this age group are involved in TB infectious activities resulting in the deteriorating immunity[19].

The preponderance of TB cases was 59% with the weight of ≤55 kg and 41% in body weight of 55 kg body weight. In the study done by Iyer *et al*, TB patients (80%), weighed underneath standard for Indian reference adult man[20]. These patients often experience severe weight loss, a symptom that is considered immunosuppressive and a major determinant of ruthlessness of the disease[21]. Undernourishment is an imperative risk factor for TB, since cell- mediated immunity is the key host defence against TB.

The most common unwanted drug reaction was those of GI symptoms (57%) mostly caused by rifampicin and pyrazinamide. 15% patients developed hepatic dysfunction. The drugs that are responsible for this side effect may be H, R & Z[22]. 7% patients experienced allergic skin reactions. In the present study, 35% did not experience any ADRs. Most of the reactions were of milder degree not requiring any specific interventions or hospitalizations but a few others warranted the discontinuation or tailoring of the drugs being used for treating the disease. Although GI symptoms were the most common unwanted effects which on most occasions were annoying and discomforting, they seldom encouraged the discontinuation of ATT.

Limitations :

Sample size in our study was small, although its findings show similarity with national data. Large population study will provide better composite picture of ADRs.

Conclusion

Local Story In Global Framework :

Our study population although diverse in composition and cultural values, it showed similarity with the national data in the demographic and epidemiological values. The males were found to be more caught in hand by the M. tuberculosis, females were less adversely affected but the ATT was found to be harsher to them and the younger ones giving them more frequent side effects. The side effect profile being the major determinant in the adherence to the prolonged regimen, our study gave better insight into the side

effect profile of demographic zone of Bhagalpur, Bihar.

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References

1 Morse D, Brothwell DR, Ucko PJ — Tuberculosis in ancient Egypt. *Am Rev Respir Dis* 1964; **90:** 524.
2 Ratcliffe HL — Tuberculosis induced by droplet nuclei infection. *Am J Hyg* 1952; **55:** 36.
3 Ratcliffe HL, Palladino VS — Tuberculosis induced by droplet nuclei infection: initial homogeneous reponse of small mammals(rats, mice, guinea pigs and hamsters) to human and to bovine bacilli, and the rate and pattern of tubercle development. *J Exp Med* 1953; **97:** 61.
4 Wells WF — On airborne infection II. Droplets and droplet nuclei. *Am J Hyg* 1934; **20:** 611.
5 Balasubramanian VN, Oommen K, Samuel R — DOT or not? Direct observation of anti-tuberculosis treatment and patient outcomes, Kerala State, India. *Int J Tuberc Lung Dis* 2000; **4:** 409-13
6 World Health Organization — An expanded DOTS framework for effective tuberculosis control. Stop TB Communicable Diseases. Geneva: WHO Press; 2002. p. 1-20.
7 Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D — Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med* 2003; **167:** 1472-7.
8 Vieira DE, Gomes M — Adverse effects of tuberculosis treatment: Experience at an outpatient clinic of a teaching hospital in the city of São Paulo, Brazil. *J Bras Pneumol* 2008; **34:** 1049-55.
9 Zaka-Ur-Rehman Z, Jamshaid M, Chaudhry A — Clinical evaluation and monitoring of adverse effects for fixed multidose combination against single drug therapy in pulmonary tuberculosis patients. *Pak J Pharm Sci* 2008; **21:** 185-94.
10 Marra F, Marra CA, Bruchet N, Richardson K, Moadebi S, Elwood RK, *et al* — Adverse drug reactions associated with first-line anti-tuberculosis drug regimens. *Int J Tuberc Lung Dis* 2007; **11:** 868-75.
11 Chhetri AK, Saha A, Verma SC, Palaian S, Mishra P, Shankar PR — 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 Assoc* 2008; **58:** 531-6.
12 Dhingra VK, Rajpal S, Aggarwal N, Aggarwal JK, Shadab K, Jain SK — Adverse drug reactions observed during DOTS. *J Commun Dis* 2004; **36:** 251-9.
13 Chukanov VI, Kaminskaia GO, Livchane E — Frequency and pattern of adverse reactions due to treatment of patients with pulmonary tuberculosis with antitubercular reserve drugs. *Probl Tuberk Bolezn Legk* 2004; **10:** 6-10.
14 Awofeso N — Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis treatment. *Bull World Health Organ* 2008; **86:** B-D.
15 Edwards IR, Aronson JK — Adverse drug reactions: Definitions, diagnosis, and management. *Lancet* 2000; **356:** 1255-9.
16 Hartwig SC, Siegel J, Schneider PJ — Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm* 1992; **49:** 2229-32.
17 Lönnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C — Alcohol use as a risk factor for tuberculosis - a systematic review. *BMC Public Health* 2008; **8:** 289.
18 Edoh D, Adjei R — Rapid assessment of a National Tuberculosis (TB) Control Programme in Eastern Ghana. *Afr J Health Sci* 2002; **9:** 159-64.
19 Horne N — Tuberculosis and other mycobacterial disease. In: Cook G, editor. Manson2 s tropical diseases. London: W.B. Saunders; 1996. p. 971-1015.
20 Iyer SP, Umakumar K, Mahajan A — Impact of HIV Infection on utcome of abdominal tuberculosis. *Bombay Hospital J* 2008; **50:** 553-9.
21 van Crevel R, Karyadi E, Netea MG, Verhoef H, Nelwan RH, West CE, *et al* — Decreased plasma leptin concentrations in tuberculosis patients are associated with wasting and inflammation. *J Clin Endocrinol Metab* 2002; **87:** 758-63.
22 Steele MA, Burk RF, DesPrez RM — Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest* 1991; **99:** 465-71.

Evaluation of DOTS Therapy and Indian Policy

India is one of the highest TB burden Countries accounting for one fifth of incidence of TB. Directly Observed Treatment, short course (DOTs) started a India in 1993 as a part of Revised National Tuberculosis Control Program.

DOTs involves free diagnosis of TB and free full six months treatment. The patient needs to visit TB clinic thrice a week in first couple of months and then once weekly during continuous phase.

Thus in DOTs patients adheres to complete duration of treatment and reduces the chances of Drug Resistance TB.

Although Government policy is to notify and treat 70% of all TB cases but notification and cure rate is far from satisfactory

High priority is needed to improve the quality and reach of DOTs services in the country.

Patients treated outside the DOTs strategy needs to be minimized to reduce incidence of Resistant TB.

In order to achieve universal access to the program government should engage the private sector to achieve the goal of NTEP (National Tuberculosis Elimination Program).

In start of year 2020, RNTCP was renamed as NTEP which had the aim to achieve the larger goal of elimination of the disease of tuberculosis by 2025.