Original Research Article

Pattern of Adverse Drug Reactions with Anti-tubercular drugs and their impact on Non-compliance to therapy in a District General Hospital, Chittoor

Vinay Kumar Sayeli[1], Madhav P[1], Vijay Kumar Sayeli[2*], Ankireddy palli Kameswar Reddy[3]

[1]Asstistant Professor of Pharmacology, Apollo Institute of Medical Sciences and Research, Chittoor,India
[2]Associate Professor of Pharmacology, Mamata Medical College, Khammam,Telangana,India
[3]MBBS student, Apollo Institute of Medical Sciences and Research, Chittoor,India

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Abstract

Background: Poor compliance to anti-tubercular therapy by patients with tuberculosis leads to drug resistance and decreases the cure rates in patients. This study is aimed at understanding the safety pattern of adverse drug reactions with Cat-1 anti-tubercular drugs in our locality. This study is also aimed to understand the chances of non-compliance to anti-tubercular therapy due to adverse drug reactions of anti-tubercular drugs.
Materials and Methods: This study is a cross-sectional study done on 200 patients who received Cat-1 anti- TB treatment regimen at a RNTCP centre in District Government Hospital, Chittoor. Adverse drug reactions experienced during treatment by the patients were enquired. Prevalence of adverse drug reactions and their contribution to non-compliance of anti-tubercular therapy has been captured using a questionnaire.**Results:** Prevalence of adverse drug reactions was 32% in patients receiving Category-1 anti-tubercular treatment, and prevalence for the chances of non-compliance is 8 % due to these adverse drug reactions. This study also concludes that vertigo, visual disturbances, rashes, yellowish discolouration of the sclera and joint pain are the adverse drug reactions that can significantly contribute to chances of non-compliance.
Keywords: TB treatment, adverse effects of anti-tubercular drugs, non-compliance to anti-tubercular therapy, category- 1 anti-TB drugs

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Introduction

Tuberculosis (TB) is a public health problem in India[1]. According to the Global TB report 2015, it is estimated that the prevalence of TB is 2.5 million cases in India[2].Anti-tubercular drugs are given in combination to treat tuberculosis, to decrease the chances of development of drug resistance with individual medications[3]. As per technical and operational guidelines 2016, all new cases of TB, who don't have any history of anti-tubercular drugs usage for greater than one month, need to be treated with Category-1 treatment, which includes two months treatment with first-line anti-tubercular drugs such as Isoniazid, Rifampicin, Pyrazinamide and Ethambutol during the intensive phase and with Isoniazid (H), Rifampicin (R) and Ethambutol (E) for four months during continuation phase[3].Non-adherence to therapy due to adverse effects & poor compliance are the two important risk factors, which contributes to drug resistance. Patients suffering from drug-resistant tuberculosis should use six to seven second-line anti-tubercular drugs, which are less safe and have limited efficacy than first-line drugs. Treatment for drug-resistant TB is usually given for a prolonged time, generally greater than 24 months[4].Anti-tubercular drugs are associated with notably significant adverse effects like hepatitis, rashes, joint pains, visual disturbances etc. Various studies that were published previously reported different patterns of adverse drug reactions[5,6]. A study published by Topno et al. in Pondicherry reported that adverse reactions are seen in 40% of the population. They mentioned that GI adverse effects were more common. Marra F et al. noted that the frequency of adverse drug reactions was 30% of the west Columbian population with first-line anti-tubercular drugs.

**Correspondence*
Dr. Vijay Kumar Sayeli
Associate Professor of Pharmacology,Mamata Medical College, Khammam, Telangana,India
E-mail: vijaykumarsayeli@gmail.com

There is minimal data about the safety of anti-tubercular drugs in our locality. Understanding the pattern of adverse drug reactions in our locality using Category-1 (Cat-1) anti-tubercular drugs & counselling patients about the negative consequences of non-adherence to therapy is extremely important to decrease the chances of drug resistance.

Aim & Objectives

Aim

To report the pattern of adverse drug reactions (ADR) in our locality using Cat-1 anti-tubercular drugs and their contribution to non-compliance of anti-tubercular therapy

Objectives

1. To evaluate adverse drug reactions that are observed with first-line anti-tubercular drugs in patients receiving Cat-1 treatment regimen &
2. To evaluate the chances of non-compliance due to these adverse drug reactions

Study Methodology

Study site

RNTCP Center of District Government Hospital Chittoor.

Study Design

Cross-sectional study design

Ethical Consideration

This study has been initiated after receiving approval from our Institutional Ethics Committee. Study participants were informed about the objective of the study, and they were also told that there is no interventional procedure/ harm involved. Study participants were enrolled into the study only after taking written informed consent.Study population & their enrolment: A total of 254 patients received Category-1 treatment in the RNTCP Center from District Government Hospital, Chittoor, from the period of 05 January 2017 to 29 March 2018, according to the Nikshay database. All these patients were found to be residents of Chittoor as per the records of

the Nikshay database. After contacting these 254 patients, 200 study participants were enrolled in this study as they were willing to participate and after taking informed consent from them.

Data Collection

This study is questionnaire-based. The questionnaire has the following questions.

1. Patient. details (Name, Age, Sex, Weight & Address)
2. Medical/ Medication History (Co-existing medical conditions and current treatment for pre-existing conditions)
3. Details about patient's Anti-Tubercular Treatment (All patients received Cat-1 treatment)
4. Is there any discomfort that patient experienced after starting anti-tubercular drugs? (Open-ended question- indicating the prevalence of ADRs)
5. Is there any discomfort that the patient experienced after starting anti-tubercular drugs, which gave them thought of stopping Anti-Tubercular Treatment (Open-ended question- indicating the chances of non-compliance)?
6. Finally, we captured the details about various adverse effects experienced by study participants, which are frequently seen with Category-1 anti-tubercular drugs, by asking Yes/ No questions (eg. Vertigo, Tinnitus, Seizures, Visual disturbances, Paraesthesia, Headache, Confusion, Shortness of breath, Palpitations, Nausea and vomiting, Anorexia, Abdominal pain, Rashes, Pink or red-coloured discharge of Urine/ tears, Yellowish discolouration of the sclera, Fever, Joint pain)

Statistical Analysis

All parametric variables were summarized as mean & SD. All qualitative variables were summarized as proportion. The risk of individual adverse drug reactions and their chances of non-compliance is summarized as odds ratio & 95% confidence intervals. Chi-square test was used as a statistical test to determine the significance between individual adverse drug reactions and their chances to contribute to non-compliance of therapy. For determining significance, a p-value less than 0.05 was considered to be statistically significant. Statistical analysis was done using SPSS software version 16.

Observations and Results

Demographic parameters of study population

The range noted for the age of study participants was 10 to 78 years, and the mean age of study participants in the study is 44.62 years with a standard deviation of 15.393 (Table 1). The range noted for the weight of the study participants was 22 Kgs to 75 Kgs, and the mean body-weight of the study population was 58.62 with a standard deviation of 9.625. Out of the 200 study participants, 142 (71 %) were male, and 58 were female (29%) (Figure 1).

Co-existing co-morbid conditions among the study population: Along with tuberculosis, 60 of the study participants had Diabetes Mellitus (30 %), 56 of them had Hypertension (28 %), 26 of them had Asthma (13%), and 16 of the study participants had co-infection with HIV (8 %) (Figure 2).

Prevalence of adverse drug reactions

Among 200 study participants, the prevalence of adverse drug reactions was found to be 32 % (64 participants) after receiving Cat-1 anti-tubercular drugs in this study and prevalence for chances of non-compliance to therapy was found in 8% (16 participants), as 8% of study participants reported that they felt like stopping anti-tubercular treatment due to the reactions produced by drugs. (Table 2).Out of the various adverse drug reactions reported in this study, the prevalence of red or pink coloured discharge of urine/ tears was found to be high 77% (154 patients), followed by the prevalence of rashes 39% (78 patients) followed by headache 35.5% (71 patients). Prevalence of other adverse drug reactions in descending order is joint pain 30% (60 patients), nausea and vomiting & paraesthesia is 23% (46 patients), visual disturbances 20% (40 patients), anorexia 18% (36 patients), vertigo 13% (26 patients), abdominal pain is 12% (24 patients), shortness of breath is 12% (24 patients), palpitations is 8% (16 patients), fever is 6% (12 patients), confusion is 4% (8 patients), yellowish discolouration of the sclera & tinnitus is 2% (4 patients). Seizures were not at all reported as an adverse effect in study participants. (Figure 3)

Out of the adverse drug reactions reported, adverse reactions like vertigo, visual disturbances, rashes, yellowish discolouration of the sclera and joint pain was found to have a significant odds ratio that can contribute to the chance of non-compliance to treatment (Table 3)

Discussion

Though TB is a curable disease, it is still one of the significant causes of death among infectious diseases[7]. Poor compliance to therapy contributes to the menace of drug-resistant tuberculosis.

Understanding more about the safety information of anti-tubercular drugs and applying such information in counselling patients is really helpful in improving patient compliance to therapy. This study has attempted to get information about the safety information of drugs in our locality.

This study evaluated the pattern of adverse drug reactions, only in patients receiving Category-1 treatment regimen. Patients on Category-1 anti-tubercular treatment regimen needed to be treated with first line anti-tubercular drugs like Isoniazid, Rifampicin, Pyrazinamide and Ethambutol. Streptomycin is the supplemental first-line anti-tubercular drug that was used in the Category-2 treatment regimen. Patients with a history of anti-tubercular medications usage for greater than one month were used to receive this treatment regimen, if their TB is sensitive to first-line anti-tubercular drugs. Streptomycin can produce notably different types of adverse effects like nephrotoxicity and ototoxicity. WHO has recommended performing drug sensitivity testing for all patients who have received prior anti-tubercular treatment and recommended using appropriate drug-resistant regimens instead of category-2 anti-tubercular treatment regimen. Several studies reported that the category-2 regimen had a 60- 80% success rate and it is associated with worse outcomes[8]. In this study, it was found that prevalence of adverse drug reactions was found to be 32% and 8% of patients had prevalence for the chance of non-compliance to therapy due to the adverse drug reactions seen with category- 1 anti-tubercular drugs. Previous studies reported that the prevalence of adverse drug reactions to anti-tubercular drugs was found to be 30-40 % [5,6]. The prevalence of adverse drug reactions found in this study is similar with the previous studies that were published[5,6]. In this study, the prevalence of seizures is found to be zero. Usually this particular adverse effect is common if the patient is receiving high doses of INH (>10 mg/Kg)[9], as patients under Cat-1 treatment regimen under RNTCP program of India are receiving relatively low doses (5 mg/kg/ day approximately)[2]. This might be the reason for absence of seizures in our study population. Pink or red coloured discharge of urine/ tears is the scariest effect due to a first line anti-tubercular drug Rifampicin, but it is not a harmful effect[9]. The prevalence of this effect was found to 76.5% but we found that is not contributing to the chances of non-compliance significantly. Participants in the study population informed us that they were properly counselled before initiation of the treatment that this is not a harmful effect. "Patient general information" given by National Tuberculosis Elimination Program (NTEP) can be used to give counselling and to educate patients about adverse effects of drugs.Vertigo, visual disturbances, rashes, yellowish discolouration of the sclera and joint pain are the adverse drug reactions that were found to significantly contribute to the chance of non-compliance due to adverse drug reactions in this study[10].

Conclusion

This study concludes that prevalence for adverse drug reactions is 32% in patients receiving Category-1 treatment, and prevalence for the chance of non-compliance is 8 % due to these adverse drug reactions.

Vertigo, visual disturbances, rashes, yellowish discolouration of the sclera and joint pain are the adverse drug reactions that can significantly contribute to the potential for non-compliance.

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Table 1: Age Distribution and Weight distribution in the study population

Age Distribution of study population		
Range (In Years)	**Mean**	**Standard Deviation**
10-78	44.62	15.393
Weight Distribution		
Range (In Kilograms)	**Mean**	**Standard Deviation**
22-75	58.62	9.625

Table 2: Prevalence

	Number	**Percentage**
Prevalence of ADRs	64	32
Prevalence for chances of non-compliance	16	8

Table 3:Adverse effects and their odds ratio indicating the potential for non-compliance to category I drug therapy

Adverse effects	**Odd's Ratio (95% OF CI)**	**p VALUE (significance)**
Vertigo	4.92(1.616-14.981)	0.002 (significant)
Tinnitus	1.089 (1.044-1.135)	0.551 (insignificant)
Visual disturbances	8.556 (2.891-25.321)	0.0001 (significant)
Paraesthesia	2.16(0.74- 6.304)	0.151 (insignificant)
Headache	2.53 (0.9- 7.115)	0.71 (insignificant)
Confusion	4.238(0.78-22.974)	0.07 (insignificant)
Shortness of breath	1.1(1.05- 1.153)	0.124 (insignificant)
Palpitations	1.735(0.358-8.41)	0.489 (insignificant)
Nausea & Vomiting	2.16 (0.74- 6.304)	0.151 (insignificant)
Anorexia	1.583(0.48-5.226)	0.447 (insignificant)
Abdominal pain	1.052(0.224-4.942)	0.949 (insignificant)
Rashes	13.125(2.893-59.552)	0.0001 (significant)
Pink coloured discharge ofUrine/ tears	5(0.643- 38.9)	0.09 (insignificant)
Yellowish discoloration of sclera	13.00 (1.701—99.375)	0.002 (significant)
Fever	1.093 (1.046-1.142)	0.292 (insignificant)
Joint pain	4.467 (1.543- 12.931)	0.003 (significant)

p-value less than 0.05 indicate statistical significance

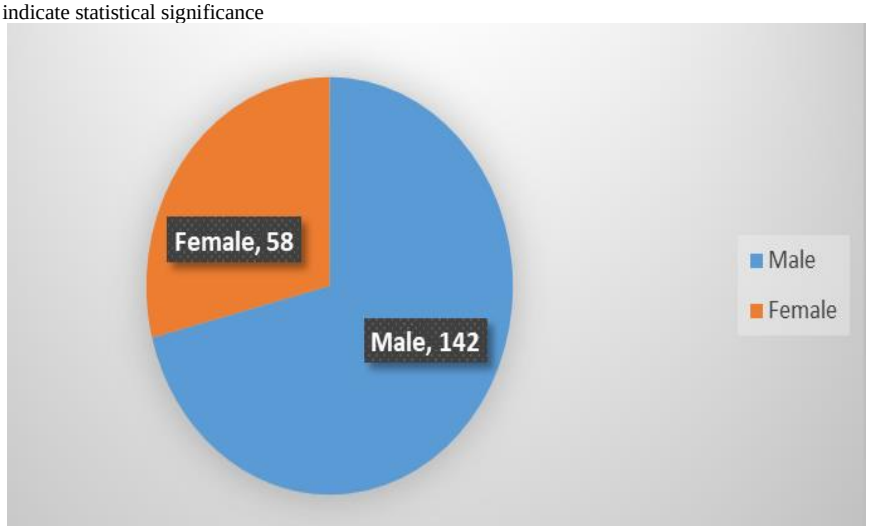

Fig 1:Sex distribution

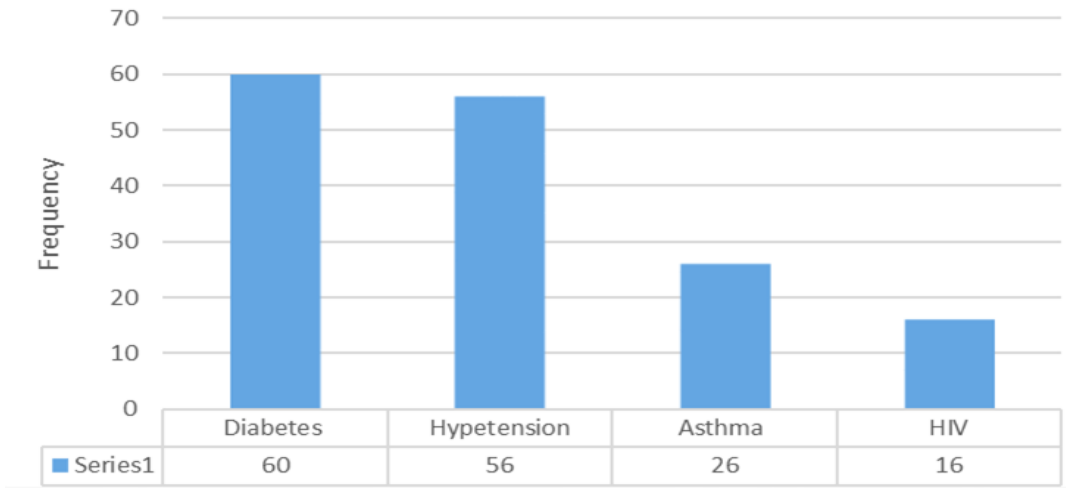

Fig 2:Co-morbid conditions

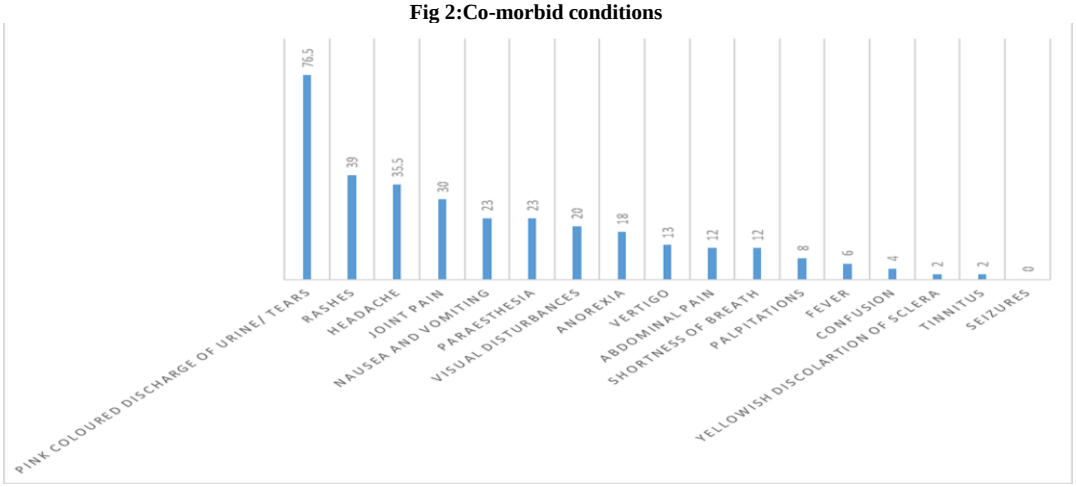

Fig 3:Prevalence of adverse drug reactions in percentage

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