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Adverse Drug Reactions in Patients on Second Line Anti-Tubercular Drugs for Drug Resistant Tuberculosis in Rural Tertiary Care Hospital in North India

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Abstract

Introduction: The adverse drug events (ADEs) to second-line anti-TB drugs are one of the major reasons for the patients default on treatment. A general awareness of various adverse drug events (ADE) and their management is essential for the effective management of tuberculosis. Identification of adverse drug reaction profile of patients can be useful for the early detection, management and prevention of adverse drug events. **Material and methods:** It was a prospective observational study conducted after approved Institutional Ethics Committee. A total of 104 drug resistant tuberculosis patients registered from 1st November 2012 to 31st October 2013 started with second line anti-tubercular drugs under PMDT-RNCP after taking written informed consent. Adverse drug reaction during treatment recorded and assessed by Hart wig and WHO scale. **Results:** 87% patients experienced adverse drug reactions. Total 346 ADR were reported. Most common were gastritis (65%) and arthralgia (60.6%), others were nausea (35.6%), vomiting (32.7%), hyperuricemia (30.8%), giddiness (27%), anorexia (17.3), generalized weakness (15.4), insomnia (10.6%), psychosis (8.6%), hearing impairment (6.7%), hypersensitivity reaction (5.8%), peripheral neuropathy (4.8%), visual disturbance (3.8%), nephrotoxicity (2.9%), forgetfulness (2.9%), gynaecomastia (1.9%), hypothyroidism (1%), seizure (1%), and thrombocytopenia (1%). **Conclusion:** Majority of patients experienced wide range adverse drug reactions. Most of patients faced the problem within 2 - 3 months of initiation of treatment and managed by symptomatic. Early identification, prompt man-

agement and standardized reporting adverse drug reactions at all the level of healthcare are needed.

Keywords

Drug Resistant Tuberculosis, ADR: Second line Anti-Tubercular Drugs

1. Introduction

Emergence of resistance to anti-tuberculosis drugs and particularly multi-drug-resistant tuberculosis (MDR-TB) has become a significant public health problem in number of countries and an obstacle to effective TB control.

The adverse drug events (ADEs) to second-line anti-TB drugs are one of the major reasons for the patients default on treatment [1]. All second-line anti tubercular drugs may be associated with adverse drug events (ADEs) involving almost all systems in the body, including the gastrointestinal tract, liver, kidney, thyroid, skin, nervous system, vestibulo-auditory apparatus and the eyes [2]. Poor management of adverse effects increases the risk of default or poor adherence to treatment and may result in death or permanent morbidity [3]. A general awareness of various adverse drug events (ADEs) and their management is essential for the effective management of tuberculosis. Considering all these factors the present study was designed to study adverse drug reactions in patients' on second line therapy under PMDT-RNTCP at Dr. RPGMC, Kangra at Tanda.

2. Material and Methods

It was a prospective observational study conducted after approved by Scientific Advisory cum Protocol Review Committee and Institutional Ethics Committee. A total of 104 drug resistant tuberculosis patients were registered from 1st November 2012 to 31st October 2013 and started with second line anti-tubercular drug under PMDT-RNCP after taking written informed consent.

1) Inclusion Criteria

All drug resistant tuberculosis patients registered under PMDT-RNTCP.

2) Exclusion criteria

Patients not willing to participate in the study.

3) Pre-treatment analysis

Patients with drug resistant tuberculosis were admitted at DOT-Plus site for pre-treatment evaluation as per PMDT-RNTCP guidelines [2]. They were explained about the study protocol in their local language and those who gave written informed consent were included in study. Pre-treatment investigations were performed &included complete hemogram, blood sugar, liver function tests, renal function tests, thyroid function tests, pure tone audiometry (PTA) & serology testing for HIV after informed consent.

4) Patient management and treatment logistics

After pre-treatment evaluation, patient was registered for by DR-TB Centre committee as per PMDT guidelines and counseling and health education to the patient and their family members about the disease and about the necessity of taking regular and adequate treatment was provided. After proper counseling second line anti-tubercular drug comprising of six drugs kanamycin, levofloxacin, ethionamide, pyrazinamide, ethambutol and cycloserine were given in intensive phase as per PMDT guidelines with the help of RNTCP established staff.[2] Drugs were given in a single daily dosage schedule under direct observation for 6 days of the week. On the 7th day (Sunday) the oral drugs were administered unsupervised, whereas injection kanamycin was omitted. Pyridoxine was administered to all patients. Drug dosages were decided according to dosage and weight band recommendation of RNTCP-PMDT guidelines [2].

PAS (Para amino salicylic acid) was reserved for patients who developed adverse drug reaction or who could not be given kanamycin.

5) Reporting of adverse drug events

During the stay in the hospital each patient was checked twice a day (morning and evening) till he/she is discharged for any adverse drug event. After discharge patient was contacted every weak telephonically to inquire about any untoward event till the patient was excluded from the study. Patient was encouraged to come for follow up in the department of Pulmonary Medicine as frequently as possible. The symptom based approach for monitoring of adverse drug events was followed. Patients who reported any adverse drug event or any symptom were called in the department of pulmonary medicine and managed either on OPD basis or were admitted and managed with appropriate investigations and treatment. Patients who did not want to come were managed in their respective DOTS and microscopy centre and senior treatment supervisor (STS), senior TB laboratory supervisor (STLS) and DOT providers were requested to provide details of the events and blood test report to the investigator.

3. Results

Adverse drug reactions experienced by patients:

Of 104 patients, 87% experienced adverse drug reactions and 13% patients did not complain of any adverse drug events (ADE) (**Figure 1**).

Total 346 ADR were reported. Most common symptoms were gastritis and arthralgia, others were nausea, vomiting, hyperuricemia, giddiness, anorexia, generalized weakness, insomnia, psychosis, hearing impairment, cutaneous reaction (rashes & itching), peripheral neuropathy, visual disturbance, nephrotoxicity, forgetfulness, gynaecomastia, hypothyroidism, seizure and thrombocytopenia (**Table 1**).

4. Discussion

The adverse drug events (ADEs) to second-line anti-TB drugs are one of the major reasons for the patients default on treatment. Identification of adverse

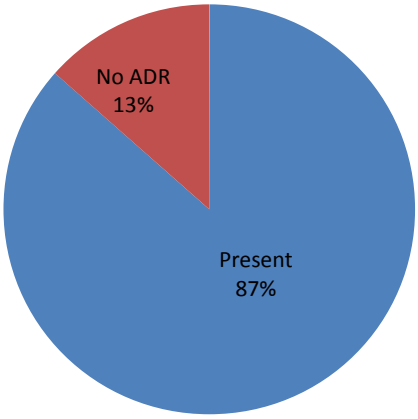

Figure 1. Adverse dug reaction of patients (N = 104).

Table 1. 346 Adverse drug reactions in patients on treatment for drug resistant tuberculosis (N = 104).

Adverse Drug Event	Frequency	(%)
Gastritis	65	62.5
Nausea	37	35.6
Vomiting	34	32.7
Anorexia	18	17.3
Hepatotoxicity	0	
Arthralgia	63	60.6
Hyperuricemia	32	30.8
Insomnia	11	10.6
Psychosis	9.0	8.6
Peripheral Neuropathy	5.0	4.8
Forgetfulness	3.0	2.9
Seizure	1.0	1.0
Weakness	16	15.4
Hearing impairment	7.0	6.7
Giddiness	28	26.9
Visual disturbance	4.0	3.8
Hypersensitivity reaction	6.0	5.8
Nephrotoxicity	3.0	2.9
Gynaecomastia	2.0	1.9
Hypothyroidism	1.0	1.0
Thrombocytopenia	1.0	1.0

drug reactions profile of patients can be useful for the early detection, management of adverse drug events and prevent the default or poor adherence.

87% patients (N = 104) had adverse drug reactions of varying severity. This is

on higher side of the range of ADRs documented by other similar studies that is 58% - 90% [4]-[9].

A total of 346 (**Table 1**) incidences of adverse drug reactions were reported. Majority of patients faced the problem within 2 - 3 months of initiation of treatment and most of them managed by symptomatic treatment. Most common were gastritis and arthralgia. In other studies also, most common adverse drug reaction was gastritis that ranged from 42% - 88.3% [5] [10].

Nausea and vomiting in present study was comparable to other study conducted on drug resistant patients reported nausea and vomiting was present in 32.8% patients [11] (**Table 2**).

Arthralgia in current study was higher than that reported in other studies where it was ranged in 13.7% to 31% patients [7] [9] [10] [11] [12] [13].

Hyperuricemia in present study was 30.7%. Other study conducted on multi-drug resistant patients hyperuricemia was reported in 84.5% patients [14].

Table 2. Adverse Drugs Events in different studies.

	Shin, S.S. [7] (%)	**Safwat, T.M.** [10] (%)	**Napthanson, E.** [11] (%)	**Akshata, S.** [13] (%)	**Present Study** (%)
Type of study	Retrospective	Retrospective	Retrospective	Retrospective	Prospective
Gastritis		88.3	8.6	-	62.5
Nausea	75.4	-	32.8	71.1	35.6
Vomiting		-			32.7
Anorexia	-	-	9.2	-	17.3
Hepatotoxicity	16.8	8.3	2.2	1.2	0
Arthralgia	3.7	14.4	16.4	14	60.6
Hyperuricemia	-	-	-	-	30.8
Insomnia	-	-	-	-	10.6
Psychosis	11.9	-	3.4	1.6	8.6
Peripheral neuropathy	9.8	76.7	7.9	5.8	4.8
Forgetfulness	-	-	-	-	2.9
Seizure	11.5	-	4	2.5	1.0
Weakness	-	-		-	15.4
Hearing impairment	5.6	13.3	12	3.0	6.7
Giddiness	-	-	14.3	-	26.9
Visual disturbance	-	-	4.4	0.2	3.8
Hypersensitivity reaction	-	-	5.1	4.3	5.8
Nephrotoxicity	4.1	-	1.2	5.8	2.9
Gynaecomastia	-	5.0	-	-	1.9
Hypothyroidism	17.2	44.4	3.5	-	1.0
Thrombocytopenia	-	-	-	-	1.0

Psychosis was experienced by 8.7% patients. Other studies document an incidence of 1.6% - 11.9% of psychosis in patients on Cat-IV regime [7] [11] [13] (**Table 2**).

Hearing impairment in our study was 6.7%. Other studies conducted on drug resistant patient's report so to toxicity in 3% to 18.75% patients [7] [11] [13] [15] [16] [17].

Hypersensitivity reactions were present in 5.8% patients. The incidence of hypersensitivity reactions reported in other studies is 4.3% to 5.1% patients [11] [13] (**Table 2**).

Peripheral neuropathy was present in 4.8% patients. One study conducted on drug resistant tuberculosis patient's reports peripheral neuropathy in huge 76.7% patients [10]. In other studies peripheral neuropathy was present in 5.8% - 9.8% [7] [11] [13] (**Table 2**).

Diminished vision in current study is similar to other study conducted on drug resistant patients' reports ocular toxicity in 4.4% patients [11] (**Table 2**).

Nephrotoxicity was present in 2.9% patients. Other studies conducted on drug resistant patients reported renal toxicity in 1.2% to 5.8% patients [6] [7] [11] [13] [15].

Gynaecomastia was present in 1.9% patients. In a study conducted on drug resistant patients gynaecomastia was reported in 5% patients [10] (**Table 2**).

Hypothyroidism was present in only one patient. Other studies conducted on drug resistant patients report the incidence of hypothyroidism 3.5 to 44.4% in patients treated with this regime [7] [10] [11] (**Table 2**).

Giddiness in present study higher than other study conducted on drug resistant patients reported giddiness 13% - 14.3% patient [8] [11].

2.9% patients complained of forgetfulness but could not be assessed further. It presented 5 month after start of treatment in all of them.

This pattern of Adverse Drug Reactions suggests a variable incidence of ADRs from study to study and so it could be associated with local ethnic, dietary, environmental factors, different experience with variety of patients, variation in health care worker ability to detect ADR. Timely detection & prompt action of ADR and their management is essential for effective treatment of tuberculosis and further comparative studies are required to study this variability in detail

Our study had few limitations, this was an observational study. Since CAT-IV is a combination therapy and discontinuation of any drug for the purpose of the study would have been unethical it is very difficult to find a causal relationship between individual drug and adverse drug reactions (ADRs).

5. Conclusion

Majority of patients experienced adverse drug reactions with most common symptoms being gastritis and arthralgia and managed by symptomatic treatment. In the light of increasing incidence of drug resistance tuberculosis DOT provider, health worker, patients and relative should be sensitized for ADR de-

tection and directly observed therapy should be very strict to eliminate the default or not adherence of therapy. Effort should be made for voluntary ADR monitoring, therapeutic drug monitoring and further needs to develop new anti-tuberculosis drugs to shorten duration of treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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