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Adverse Drug Reactions Experienced During Intensive Phase of Standardized Ambulatory Regimen of MDR-TB, A Cross Sectional Study

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Abstract: Aim of our study was to determine the adverse drug reactions experienced by the patients during intensive phase of standardized category IV regimen of multi drug resistant tuberculosis (MDR-TB). All eligible patients with MDR pulmonary -TB were followed up till the end of intensive phase to determine adverse drug reactions encountered during this period by personal interview in questionnaire format and review of medical records. Total 120 patients constituted the final study population. There were 94 (78.3%) male and 26 (21.6%) females. Mean age of cohort was 38.7 years. Total 117(97.5%) patients experienced one or more adverse drug reaction during intensive phase. 85(72.6%) patients experienced gastro-intestinal adverse effects followed by joint pain (n=66, 56.4%). Eleven (9.4%) patients experienced single adverse drug reaction, while majority of patients (n=61, 52.1%) experienced ≥4 adverse drug reaction. Thirty six (30.7%) patients pointed out a particular drug for observed side effects. Ethionamide was most common offending drug in 19 (52.7%) patients; the most common reaction was gastrointestinal side effects. Regimen was modified during intensive phase due to drug toxicity in 11 (9.1%) patients. In 4 (36.3%) patients, Kanamycin was stopped and replaced by PAS while in rest (n=7, 63.6%) drugs other than Kanamycin were stopped and replaced by PAS. In conclusion, adverse drug reactions are extremely common during intensive phase. However; in majority of patients, treatment can be continued without modification in regimen.

Keywords: Multi drug resistant tuberculosis, Intensive phase, adverse drug reactions

INTRODUCTION

Multi-drug resistant tuberculosis (MDR –TB) is a type of tuberculosis caused by infection with M. tuberculosis that is resistant to isoniazid and rifampicin with or without associated resistance to other drugs [1].A review of series of 63 surveys of drug resistant tuberculosis carried out between 1985 and 1994 led to the conclusion that the problem of drug resistance is worldwide [2]. Globally, in 2015, 480 000 people estimated to develop MDR-TB [3]. India, China and Russian Federation together contribute around half of global burden of MDR-TB cases [3].

Like other drugs, the anti TB drugs are associated with risk of side effects and these risk increase with more toxic second line anti TB drugs. The management of drug resistant tuberculosis is more complex than that of drug sensitive tuberculosis that is in part due to fact that baseline resistance to aminoglycosides or fluoroquinolone can affect the efficacy of the MDR TB regimen and poor tolerance to second line drugs more commonly leads to discontinuation of regimen as compared to first line TB drugs [1].

Patient counseling regarding adverse drug reactions should be initiated at very first of MDR-TB treatment as minor adverse reactions are commonly encountered during treatment [1]. The chances of default and poor adherence to treatment rises up if these adverse effects are not managed properly thereby affecting treatment outcomes [1]. Under RNTCP (Revised National Tuberculosis Control Programme) of India, timely identification and management of adverse drug reactions are essential part of its services [1].

This study was planned to determine the adverse drug reactions, experienced by the patients during intensive phase (IP) of standardized ambulatory category IV regimen at our DR-TB (Drug Resistant Tuberculosis) Centre. In addition, we also assessed specific drugs pointed out by patients for specific/reported adverse drug reaction and drugs which

lead to change in regimen due to intolerable side effects.

METHODOLOGY

This was a hospital based cross sectional observational study after due approval by the institutional ethical committee. Study was performed at DR-TB Centre of our institution. Informed written consent of the patients was obtained. All confirmed multidrug resistant pulmonary tuberculosis patients under RNTCP criteria [1] admitted for pre-treatment evaluation to our DR-TB Centre from January 2012 to December 2012 were included and followed up subsequently. Those patients who were unwilling to come for follow up, not traceable, lost during follow up or died during IP were excluded from data analysis. Patients with prior history of allergy to any drug, central nervous system disorders, peripheral neuropathy, psychiatric disorders, dermatological diseases, HIV sero-positive status, hepatitis B and C sero-positive status and with abnormal baseline pre-evaluation investigations were also excluded from study.

Under RNTCP of India [1], patient with MDR-TB are hospitalized for pre-treatment evaluation and treatment initiation. The pretreatment evaluation consist of detailed clinical evaluation, weight and height measurement, complete blood counts, blood sugars, renal function tests, liver function tests, TSH levels, urine examination, chest X- ray and pregnancy test (for women in child bearing age group) including voluntary HIV testing.

Under RNTCP of India [1], the MDR TB regimen consist of initial six drugs during IP namely, Kanamycin, Levofloxacin, Ethionamide, Pyrazinamide, Ethambutol and Cycloserine and 4 drugs (Levofloxacin, Cycloserine, Ethambutol, Ethionamide) during the continuation phase. The available reserve drugs used in case of modification of regimen are p-aminosalicylic acid (PAS), Moxifloxacin, and Capreomycin. Drugs are provided on basis of weight bands. Once discharged and initiated on treatment, patients are seen for clinical evaluation at monthly interval during IP. Follow-up chest radiographs are taken at the end of IP, end of treatment and when clinically required. Similarly, serum creatinine is repeated every month for the initial 3 months and afterwards, every three months till patient is on Kanamycin. Thyroid function tests are done whenever indicated. Drugs are given under direct observation as single daily dosage by a DOT (directly observed treatment) provider. Drugs are supervised on six days of week but on Sunday, the oral drugs are administered without supervision and the injection kanamycin is omitted [1].

Baseline information including medical disorders, history of previous anti tuberculosis treatment, pattern of drug resistance, extent of disease, socio-economic status, addiction history and baseline hematological, biochemical investigations as per RNTCP guidelines [1] were noted from records maintained at DR-TB Centre.

Study participants were followed up at the end of IP for development of adverse drug reactions during this period if any. The information was obtained by interviewing study subjects using pre-designed questionnaire. The medical records maintained at DR-TB Centre were also reviewed during IP to determine any documented adverse drug reactions. Any symptoms that can mimic drug reaction if present well before treatment initiation as per medical records or patient self-reports were excluded from final analysis. Relevant biochemical investigations done during IP were also obtained from medical records at DR-TB Centre.

At the end of IP, patients were asked about any development of adverse drug reactions like nausea, vomiting, heartburn, indigestion, diarrhea, depression, anxiety, psychosis, seizures, tingling sensation, tinnitus, hearing loss, musculoskeletal pain, rashes, itching, bronchospasm, facial puffiness, thyroid swelling, weakness, fatigue, drowsiness, vision disturbances, etc. during course and at end of intensive phase treatment using pre designed questionnaire. Patients were also asked for any drug specific intolerance or adverse effect. In addition to clinical assessment, certain laboratory investigations like serum uric acid, serum creatinine, thyroid function test, audiometry, liver function test were also done whenever required and indicated to detect occult adverse effects and to confirm or exclude manifested adverse drug effects. Every patient was reviewed by psychiatrist from Department of Psychiatry for evaluation of development of depression, suicidal tendencies, anxiety and other psychiatric complications.

During IP, regimen of certain patients modified by DR-TB Centre committee in the event of intolerance and or significant adverse drug reactions was also analyzed. Under RNTCP of India, Capreomycin (or PAS in case if injectable drugs not tolerable) was the reserved drug in case of Kanamycin related intolerance. PAS was the substitute drug in case of termination of other oral drugs [1].

STATISTICAL ANALYSIS

Data were entered into Microsoft excel 2010 worksheet in the form of master chart. Continuous variables were expressed as mean+SD whereas categorical variables were expressed in absolute numbers or percentages. The statistical analysis was done using MaxStat Lite Version (Version 3.60).

RESULTS

A total of 120 patients constituted final study population. There were 94 (78.3%) male and 26 (21.6%) females. Mean age of cohort was 38.7 years (with C.I. (95%) of mean ± 2.38). Mean BMI of cohort was 15.87 (C.I. (95%) of mean was ± 0.42). Total 117(97.5%) patients experienced one or more adverse drug reaction during IP while only 3(2.5%) patients did not experienced any type of adverse drug reaction.

85(72.6%) patients experienced gastro-intestinal adverse drug reactions as most common followed by joint pain (n=66, 56.4%) followed by insomnia (n= 38, 32.4 %) and depression (n=31, 26.4%). Suicidal thoughts were also in 18 (15.3%) patients (table 1). Only 11(9.4%) patients experienced single adverse drug reaction, 20(17.0%) patients experienced at least 2 adverse drug reaction, 25 (21.3%) patient experienced at least 3 adverse drug reaction while majority of patients (n=61,52.1%) experienced ≥4 adverse drug reaction (table 2).

36 (30.7%) patients pointed out a particular drug for observed /reported side effects (table 3). Ethionamide was most common offending drug in 19 (52.7%) patients, the most common reasons was gastrointestinal side effects. This was followed by Ethambutol (n=7, 19.4%), Cycloserine (n=6, 16.6%), Levofloxacin (n=4, 11.1%), Pyrazinamide (n=3, 8.3%), Kanamycin (n=3, 8.3%) and PAS (n=1, 2.7%). Cycloserine was found to be associated with both psychological and gastrointestinal adverse drug reactions.

Regimen was modified during IP due to drug toxicity in 11 (9.1%) patient (table 4). In 4 (36.3%) patients, Kanamycin was stopped and replaced by PAS while in rest (n=7, 63.6%) drug other than Kanamycin was stopped and replaced by PAS.

Table−1: Adverse drug reactions experienced by patients

S.No	Adverse drug reaction	No. of Patients (N=117)	Percentage (%)
1	Gastrointestinal*	85	72.6
2	Joint pain	66	56.4
3	Insomnia	38	32.4
4	Depression	31	26.4
5	Weakness/Fatigue	28	23.9
6	Visual disturbances	26	22.2
7	Hearing loss	21	17.9
8	Itching	20	17.0
9	Suicidal thoughts	18	15.3
10	Drowsiness	14	11.9
11	Tinnitus	13	11.1
12	Tingling/Burning sensation	11	9.4
13	Headache	9	7.6
14	Vertigo	8	6.8
15	Rashes	8	6.8
16	Psychosis	4	3.4
17	Facial Puffiness	4	3.4
18	Pain at injection site	3	2.5
19	Anxiety	2	1.7
20	Ataxia	2	1.7
21	Thyroid swelling	2	1.7
22	Any other**	15	12.8

*Gastrointestinal manifestations include nausea, vomiting, heart burn, acid indigestion and diarrhea.
**4 patients having agitation, 3 patients having memory disturbances, 1 patient each having numbness, burning sensations in nose, sneezing, tremors, burning micturition, delirium, slurred speech and heaviness of eyes.

Table−2: Number of adverse drug reactions among patients

Number of Adverse drug reactions	Number of patients (N=117)	Percentage (%)
1	11	9.4
2	20	17.0
3	25	21.3
≥ 4	61	52.1

Table−3: Individual drug and reported adverse drug reactions

S.No	Offending drug mentioned/reported	Number of Patients (n=36)	Adverse drug reaction observed/reported
1	Ethionamide	19	Headache, Nausea, Tinnitus, Heartburn, Vomiting, Insomnia
2	Ethambutol	7	Heart burn, Tingling, Nausea, Heaviness of eyes, Joint pain
3	Cycloserine	6	Nausea, Nasal burning sensation, Abdominal discomfort, Insomnia, psychosis
4	Levofloxacin	4	Double vision, Nausea, Drowsiness
5	Pyrazinamide	3	Heart burn, Joint pain, Nausea, Vertigo
6	Kanamycin	3	Drowsiness, Nausea, Pain at injection site
7	PAS	1	Nausea

Table–4: Modification of regimen during intensive phase.

S.No	Regimen Changed	Number of Patients (n=120)	Percentage
1	A.Yes	11	9.1%
a.	Kanamycin to PAS	4	36.3%
b.	Cycloserine to PAS	4	36.3%
c.	Pyrazinamide to PAS	2	18.1%
d.	Ethionamide to PAS	1	9.0%
2.	B. No	109	90.8%

DISCUSSION

In post marketing settings, adverse drug reaction is ‘‘one that is noxious, is unintended, and occurs at doses normally used in man’’ [4]. Adverse drug reactions can be of two types, the less common idiosyncratic reactions that are unpredictable reactions and more common pharmacological reactions in which the well-known pharmacological drug action is enhanced [5].

Among the 120, only 3 (2.5%) patient did not experienced any type of adverse drug reaction while majority of them experienced one or more adverse drug reactions during the treatment. A study performed at Gujarat [6] found rate of adverse drug reactions as high as 93.8% (n=76) in their study. Their observations were similar to our rates of adverse drug reactions of 97.5%. In another study [7], 33 (86.8%) patients experienced side effects to drugs during treatment. A study [8] conducted in South Africa reported 98% (n=119) of patients reported at least one adverse drug reaction during IP and insomnia (67%) being the most common side effect. The most common side effect observed in our study are gastrointestinal (n=85, 72.6%) followed by joint pains (n=66, 56.4%)) and insomnia (n=38, 32.4 %). Various studies [6, 7, 9-13] also found gastrointestinal side effects as most common while in study conducted at Tanzania [14], arthralgia was reported as most common side effect. Eleven (9.4%) patients experienced single adverse drug reaction at some point of time, while majority of patients (n=61, 52.1%) experienced ≥4 adverse drug reaction in our study. The average number of adverse drug reaction reported per patient during IP was 8.6 in one study [8]. In another study conducted at Vietnam [15], under programme conditions, most patient (n=25, 31.6%) reported single adverse drug reaction during treatment.

In our study, 117 (97.5%) patients suffered from adverse drug reactions with the gastrointestinal manifestation being most common. Such frequent adverse reactions may lead to drug interruptions. As depression (n=31, 26.4%) and suicidal thoughts (n=18, 15.3%) were found to be important morbid side effects, evaluation by psychiatrist should be an important follow-up strategy while patient receiving three important drugs having psychological adverse effects namely Cycloserine, Ethionamide and Levofloxacin.

We also studied any drug specific adverse reactions, observed or reported by the patient. Thirty six (30.7%) patients reported individual drug causing adverse drug reactions, among these, Ethionamide (n=19), Ethambutol (n= 7) and Cycloserine (n=6) were the common culprit drugs. In a South African study [12], Aminoglycoside and Ethionamide were the common drugs that patient refused. The Ethionamide in our study was mostly reported for gastritis. Probable causal relationship with gastrointestinal upset was also reported for Ethionamide and Quinolones in an Indian study [13].

In 11 (9.1%) patient, drug toxicity was severe enough to lead to discontinuation of drug and replacement with substitute drug during IP in our study. Most common drugs stopped were Kanamycin and

Cycloserine due to related ototoxicity and psychiatric complications respectively. The rate of treatment modification due to major adverse drug reactions has been reported as 12% (n=9), 15.1% (n=10), 18% (n=22) in some studies [6, 9, 16] and Cycloserine and Kanamycin were found to be the most common offending drugs, in view of psychotic and ototoxic reactions in these studies. An Indian study pointed out that, one of the predictor of successful treatment outcome is no change in regimen during treatment [17]. Aminoglycosides are important bactericidal drug and regimen without these drugs can have poorer outcomes. The Cycloserine related psychotic reactions were morbid and frequently leads to drug discontinuation. Since both PAS and Cycloserine are bacteriostatic drugs [1], in view of high psychological side effects associated with Cycloserine, PAS may be considered a suitable alternative at treatment initiation.

CONCLUSION

Adverse drug reactions are extremely common during IP. However; in majority of patients, treatment can be continued without modification in regimen.

Limitations

There were few limitations in our study. Since there is very limited literature available for adverse drug reactions during IP, we have to compare our data with studies with final treatment outcome. Another limitation was recall bias. There always remains a risk of both over and under reporting in studies which rely on self-reporting [18]. Despite these limitations, there is paucity of data with specific concern on adverse drug reactions during IP and we believe that our results will add to existing knowledge of adverse reactions associated with second line anti TB drugs in standardized ambulatory regimen during IP.

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