Original Research Article

To Study Adverse Drug Reactions in MDR Pulmonary Tuberculosis Patients

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Abstract

Aim: To Study Adverse Drug Reactions In MDR Pulmonary Tuberculosis Patients. **Methods:** The Prospective Observational Study was carried out on patients of MDR/XDR Pulmonary Tuberculosis, registered at DR-TB Centre attended in OPD or admitted in DOTS Plus Site, Medical College, SSG Hospital, Vadodara for any adverse drug reaction, from January-2017 to October-2017. Total 80 MDR/XDR TB patients, who were registered at DR-TB Centre Baroda, were enrolled in the study for duration of 10 months. **Results:** Out of 80 patients most common Adverse drug reactions are gastro-intestinal upset 44/80 (55%), Arthralgia 14/80 (17.25%), Ototoxicity 12/80 (15%) and Psychiatric disturbances 5/80 (6.25%). Neuropathy 4/80 (5%), skin reactions 4/80 (5%), hypothyroidism 3/80 (3.75%) , and hepatotoxicity 3/80 (3.75%) also had been noted. Local toxicity, Visual disturbances, hypokalemia & Renal toxicity noted rarely. Out of 59 male patients most common Adverse drug reactions are gastro-intestinal upset (32 cases), Arthralgia (10 cases), Ototoxicity (10 cases) and Psychiatric disturbances(5 cases). Out of 21 female patients most common Adverse drug reactions are gastro-intestinal upset (12 cases), Arthralgia (4 cases), Ototoxicity (2 cases), Neuropathy (2 cases) and Skin reaction (2 cases). We had stopped the offending drug permanently in 16.3% of the patients. In 22.7% of patients, drug stopped upto recovery from adverse drug events. But in 61% of patients does not required the discontinuation of the offending drug. In some cases dosage of the drug is divided. As per the Preventibility Criteria According To Schumock And Thornton Scale, 62/80 (77.5%) ADRs are Not Preventable, 17/80 (21.25%) ADRs are Probably Preventable, and 1/80 (1.25%) ADRs are Definitely Preventable. Most common presenting symptoms are nausea-vomiting 44/80 (55%), Abdominal pain 18/80 (23%), Joint Pain 14/80 (18%), Hearing loss 12/80 (15%), and Breathlessness 7/80 (8.8%). **Conclusion:** Gastro-intestinal side effects which were commonest can be largely prevented by proper timing and spacing of drugs with food and if necessary, giving antiemetic, antacids and PPIs or H2 receptor blockers. These side effects are a common cause of defaulting and persuasive, sincere counseling is vital to help the patients through this ADR.

Keywords: adverse,OPD,MDR

Introduction

Tuberculosis (TB) is an infectious bacterial disease caused by Mycobacterium tuberculosis, which most commonly affects the lungs. It is transmitted from person to person via droplets from the throat and lungs of people with the active respiratory disease[1].World Health Organization Global TB Report 2016 has reported an estimated 10.4 million incident cases of TB globally in 2015, of which 5.9 million (56%) were among men, 3.5 million (34%) among women and 1.0 million (10%) among children. People living with HIV accounted for 1.2 million (11%) of all new TB cases. In 2015, there were an estimated 480 000 new cases of multidrug-resistant TB (MDR-TB) and an additional 100 000 people with rifampicin-resistant TB (RR-TB) who were also newly eligible for MDR-TB treatment. Out of the estimated global annual incidence of 10.4 million TB cases, 2.84 million have been estimated in India, thus contributing to a fifth of the global burden of TB. Among 580000 MDR-TB cases, 130000 MDR-TB cases from India[2].

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Today, the major problem is the emergence of multi-drug resistant (MDR) and extensively drug-resistant (XDR) TB. Drug resistance surveys, based on state representative community, were carried out in the states of Gujarat, Maharashtra and Andhra Pradesh. The prevalence of MDR-TB was estimated to be 3%, among new TB cases and 12-17%, among previously-treated TB cases[3].

The most effective anti-TB drugs are Isoniazid (INH) and Rifampicin (RIF). Resistant Mycobacteria to at least one of these drugs are the cause of Multidrug-resistant tuberculosis (MDR-TB). This type of resistance is highly problematic due to limited sources of drugs as well as the high toxicity, low efficacy and high cost of second-line tuberculosis drugs[4]. MDR-TB is important as patients with this type of drug resistance respond extremely poorly to standard anti-TB treatment with first-line drugs[5]. Pilot studies have shown that DOTS has been successful in reducing the prevalence of drug-resistant TB on a community level in Mexico, Peru, and India.

The emergence of multidrug resistant TB (MDR-TB), i.e. which is resistant to at least Isoniazid (INH) and Rifampicin(RIF), is of great concern, because it requires the use of second- line drugs that are difficult to procure and are much more toxic and expensive than FLDs[6]. Laboratory monitoring is required for patients receiving a regimen with second-line anti-TB drugs. Adverse effects can be occult (not obviously noted by taking the history of the patient or by

physical examination). The important aspects of laboratory monitoring for adverse effects such as renal toxicity monitoring, electrolyte monitoring, monitoring for hypothyroidism, monitoring liver toxicity, pregnancy testing and audiometry[7].

RNTCP reached a landmark achievement with the launching of RNTCP DOTS-Plus service for the management of MDR-TB patients in the states of Gujarat and Maharashtra in 2007. RNTCP aims to establish a network of accredited, quality assured culture and drug susceptibility testing laboratory across the country. In Gujarat state DOTS Plus site first implemented in Medical College, Ahmedabad in Jan- 2007 and then in Medical College, Vadodara in Feb-2010.Then another two DRTB centers Medical College, Jamnagar and Medical College, Surat functioning as a DOTS Plus site on Jan-2012 & GMERS Patan since March 2014.

The treatment of MDR-TB is of longer duration for about two years. Therefore, it is imperative to monitor and treat adverse drug reactions developed by the patients. This approach ensures better compliance of patients and good treatment outcome. At the same time, data regarding ADRs of second-line anti-tubercular drugs in Central India are scanty. Hence, the aim of this study was to assess the adverse drug reactions of second-line anti-tubercular drugs used to treat MDR-TB in central India on the basis of causality, severity and avoidability scales.

Material and methods

The Prospective Observational Study was carried out on patients of MDR/XDR Pulmonary Tuberculosis, registered at DR-TB Centre attended in OPD or admitted in DOTS Plus Site, Medical College, SSG Hospital, Vadodara for any adverse drug reaction, from January-2017 to October-2017, after taking the approval of the protocol review committee and institutional ethics committee.Total 80 MDR/XDR TB patients who were registered at DR-TB Centre Baroda, were enrolled in the study for duration of 10 months. DOTS Plus Site, Vadodara receive inflow of patients from the Vadodara (Rural , Urban ,Tribal), Narmada , Bharuch , Panchmahal , Dahod , Anand, Mahisagar & Chhotaudaipur districts .

Inclusion Criteria

- All Patients of XDR TB of DR TB center at Medical college & S.S.G. Hospital, vadodara who have complain of any adverse events.
- All Patients of MDR TB of DR TB center at Medical college & S.S.G. Hospital, Vadodara, who have complain of any adverse events.

Exclusion Criteria

Patient with abnormal laboratory value at Pre-treatment evaluation for MDR/XDR TB, were excluded for that particular adverse effect.

Sample collection

Any patient with any adverse event following MDR/XDR drugs presented in OPD & adverse drug reactions defined by laboratory value, at least one documented abnormal value was considered will be taken. For those not defined by laboratory value, event was considered by clinical status (complaints, general condition, respiratory system examination etc.) documented the reaction in the patient case file according to her/his clinical criteria. The study was carried with adverse drug reactions like: Ototoxicity, Hepatic Dysfunction, Nephrotoxicity, Thyroid Dysfunction, Vertigo Depression, G.I. Upset, Peripheral neuropathy, Skin Rash, Artralgia, Qt Prolongation , Thromboembolism. Reporting and Management of these adverse reactions symptomatically with/without modification of MDR/XDR-TB regimen was noted if documented in the case file/treatment card

Results

Total 80 patients of Drug resistant pulmonary tuberculosis with adverse drug reactions were enrolled in the study. From those 80 patients distribution of MDR & XDR TB Patients is as follows:

Table 1: Distribution of MDR/XDR TB patients

Total	Total MDR Patients	Total XDR Patients
80	68	12
	85%	15%

Out of 80 patients, 68 (85%) patients had MDR TB and 12 (15%) patients had XDR TB. From the 80 cases, 59 patients were male & 21 were Female. Among total 80 Cases, middle aged patients of 21-50 years of age were most commonly involved in study group. Of which 26/80 (32.5%) patients are of 21-30 years, 22/80 (27.5%) are of 31-40 years, and 15/80 (18.75%) are of 41-50 years age group.

Table 2: Sex distribution

Sex	No. of Cases	Percentage (%)
Male	59	73.75
Female	21	26.25
Total	80	100

Table 3: Different adverse drug reactions reported

Adverse Drug Reactions	Cases	%
Gastro-Intestinal upset	44	55
Ototoxicity	12	15
Hepatotoxicity	3	3.75
Renal toxicity	1	1.25
Arthralgia	14	17.5
Psychiatric disturbance	5	6.25
Neuropathy	4	5
Skin reactions	4	5
Local toxicity	2	2.5
Visual disturbances	2	2.5
Hypothyroidism	3	3.75
Hypokalemia	1	1.25

Table 4: Different presenting symptoms in the adverse drug reactions

Symptoms	Total no. of patients	%
Nausea/vomiting	44	55
Hearing loss	12	15
Decreased Urination	1	1.3
Joint pain	14	18
Psychosis	5	6.3
Jaundice	3	3.8
Abdominal pain	18	23
Burning in sole/ Tingling numbness	4	5
Skin lesion/ Rashes	4	5
Breathlessness	7	8.8
Chest Pain	1	1.3
Local Site Pain	2	2.5
Decrease vision	2	2.5

Table 5: Categorization of ADRS by using who standardised case-causality assessment scale[8]

No.of ADRs	Categorization By Causality Scale					
	Certain	Probable/ Likely	Possible	Unlikely	Conditional/ Unclassified	Unassessable/ Unclassifiable
80	2	21	57	0	0	0
%	2.5	26.25	71.25	0	0	0

As per the WHO standardised Case-Causality assessment scale, 57/80 (71.25%) ADRs are possible, 21/80 (26.25%) ADRs are probable and 2/80 (2.5%) ADRs are certain.

Table 6: Adverse drug reactions reported in various studies

Adverse drug reactions	J.S.Akshata et al[11] %	Tomsk, Russia[13]%	Dots plus pilot project[14] %	Lima, peru[15]%	Present study %
Gastro-Intestinal upset	71.1	75.4	61.2	100	55
Ototoxicity	3	15.6	12	6.7	15
Hepatotoxicity	1.2	16.8	2.2	1.7	3.75
Renal toxicity	0.5	9.8	1.2	3.3	1.25
Arthralgia	14	47.1	16.4	6.7	17.5
Psychiatric disturbance	1.6	11.9	3.4	10	6.25
Neuropathy	5.8	4.1	7.9	20	5
Skin reactions	4.3	16	4.6	43.3	5
Local toxicity	-	-	-	-	2.5
Visual disturbances	0.2	-	4.4	-	2.5
Hypothyroidism	3.1	17.2	3.5	10	3.75
Hypokalemia	-	-	-	-	1.25

Out of 80 patients most common Adverse drug reactions are gastro-intestinal upset 44/80 (55%), Arthralgia 14/80 (17.25%), Ototoxicity 12/80 (15%) and Psychiatric disturbances 5/80 (6.25%). Neuropathy 4/80 (5%), skin reactions 4/80 (5%), hypothyroidism 3/80 (3.75%), and hepatotoxicity 3/80 (3.75%) also had been noted.Local toxicity, Visual disturbances, hypokalemia & Renal toxicity noted rarely. Out of 59 male patients most common Adverse drug reactions are gastro-intestinal upset (32 cases), Arthralgia (10 cases), Ototoxicity (10 cases) and Psychiatric disturbances(5 cases). Out of 21 female patients most common Adverse drug reactions are gastro-intestinal upset (12 cases), Arthralgia (4 cases), Ototoxicity (2 cases), Neuropathy (2 cases) and Skin reaction (2 cases).Suspected Drugs of MDR/XDR TB regimen that causing adverse drug reactions in this study shows that Ethionamide 38/80 (47.5%) is more common drug that causing adverse drug reactions. After that Cycloserine 24/80 (30%), Pyrazinamide 15/80 (18.75%), Kanamycin 13/80 (16.25%), Moxifloxacin 8/80 (10%) & Linezolide 5/80 (6.25%) are the drugs that are associated with the adverse drug reactions.

In the present study, standard regimen used. Here we had stopped the offending drug permanently in 16.3% of the patients. In 22.7% of patients, drug stopped upto recovery from adverse drug events. But in 61% of patients does not required the discontinuation of the offending drug. In some cases dosage of the drug is divided.

Most common presenting symptoms are nausea-vomiting 44/80 (55%), Abdominal pain 18/80 (23%), Joint Pain 14/80 (18%), Hearing loss 12/80 (15%), and Breathlessness 7/80 (8.8%).

Mild adverse drug reactions noted in most patients in which no need to change the regimen, only symptomatic treatment cure the ADRs.

But in some patients Moderate ADRs also occur in which cases we have to modify the regimen as per guideline, whether to modify the dose of the causative drug or hold the drug for the ADRs resolved then restart the drug. In Severe ADRs we had stopped the causative drug and replaced by the substitute drug as per the guideline.

As per the Preventability Criteria According To Schumock And Thornton Scale, 62/80 (77.5%) ADRs are Not Preventable, 17/80 (21.25%) ADRs are Probably Preventable, and 1/80 (1.25%) ADRs are Definitely Preventable.

Discussion

Median age of ADRs in drug resistant TB in present study is 36 years. It is similar to other studies such as T.Torun et al[9] 37.8 years , and Sagan et al[10] 34.5 years. Male to female ratio in present study was 2.8:1 which is comparable to J.S.Akshata et al[11] 1.96:1, T.Torun et al[9] 3.78:1, Rathod KB et al[12] 2.27:1.

Different adverse drug reactions in present study are comparable with the DOTS Plus pilot project done in 2004. In present study, G I upset noted in 55% of patients, where as in J.S.Akshata at el had reported 71.1%, Tomsk-Russia had 75.4%, dots plus pilot project had 61.2% and Lima-peru had reported 100%. In present study, local toxicity, visual disturbances and hypokalemia is noted. Whereas other studies had not reported such ADRs.

In present study, common ADRs are GI upset, Arthralgia, Ototoxicity And Psychiatric Disturbances. Whereas Other Studies apart from the dots plus pilot project, had noted GI upset, Hepatotoxicity, Renal Toxicity, Ototoxicity, Hypothyroidism, Skin Reactions, Arthralgia And Psychiatric Disturbances more commonly. In the present study, Permanent Discontinuation of The Offending Drugs is 16.3%, which is comparable with the J.S.Akshata et al and Lima-Peru.

In the present study, the commonest ADR is GI Upset.(55%) GI ADRs are presented mostly with nausea or vomiting after taking the drugs. In this study Nausea and vomiting are most common GI upset 44/80 (55%). Abdominal pain is the next GI Upset 18/80 (23%)

Gastrointestinal Upset is noted mostly in first 3 months of treatment. For to manage this ADR, offending drug is given in divided doses. In 29/44 patients, This ADR is resolved or minimised, and in another 15 patients along with dividing the dosage of the drug, symptomatic treatment also offered.Patients with GI Upset also had associated ADRs such as hepatotoxicity in 3 patients, psychiatric illness in 2 patients, skin lesions in 2 patients and ototoxicity and arthralgia in 1-1 patient.

Arthralgia was the second most common ADR, which was observed in 14/80 (17.5%) patients, earliest at 1 month and as late as 12 months. Arthralgia was seen in 3/14 (21.42%) patients as early as at 1 month, in 2/14(14.28%) at 2 months, in 1/14 (7.14%) at 3 months, in 3/14 (21.42%) at 4 months, in 2/14 (14.28%) at 6 months and 3/14 (21.42%) at 12 months.In 5/14 patients pyrazinamide was stopped for 15-30 days and then reintroduced the drug when symptoms were subsided.Ototoxicity was the another common ADR observed in 12/80 (15%) patients due to kanamycin (11/12) or capreomycin (1/12).In 8/12 patients had moderate to severe sensorineural hearing loss evidenced by pure tone audiometry (PTA). While in 4/12 patients had mild hearing loss or otherwise normal audiometry.In cases of moderate to severe hearing loss the inj.Kanamycin or Inj. Capreomycin was withdrawal and replaced with PAS in case of Kanamycin and with Clarithromycin in case of Capreomycin.

Limitation of the study

Our DOTS Plus Site, Vadodara is catering MDR & XDR Pulmonary Tuberculosis patients of NINE districts only, results of study may not

reflect real picture of MDR & XDR Pulmonary TB of State level or National level . So study with larger population size and longer duration is required for implementation of this study interpretation in general population.

Conclusion

Most common Adverse drug reaction is gastro-intestinal upset 44/80 (55%), Arthralgia 14/80 (17.25%), Ototoxicity 12/80 (15%) and Psychiatric disturbances 5/80(6.25%), Male are more commonly affected. Most commonly suspected drugs that causing ADRs are Ethionamide 38/80 (47.5%), Cycloserine 24/80 (30%), Pyrazinamide 15/ 80 (18.75%), Kanamycin 13/80 (16.25%), Moxifloxacin 8/80 (10%) & Linezolide 5/80 (6.25%). Gastro-intestinal side effects which were commonest can be largely prevented by proper timing and spacing of drugs with food and if necessary, giving antiemetic, antacids and PPIs or H2 receptor blockers. These side effects are a common cause of defaulting and persuasive, sincere counseling is vital to help the patients through this ADR.

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