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Original Research Paper

General Medicine

ADVERSE EVENTS AMONG PATIENTS OF DRUG RESISTANT TUBERCULOSIS IN INTENSIVE PHASE RECEIVING SECOND LINE ANTI TB TREATMENT

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ABSTRACT

Setting- A DR-TB (Drug Resistant-Tuberculosis) Tertiary Care Center At GMC Aurangabad.

Objective: To detect adverse effects of drugs used in drug resistant tuberculosis in intensive phase at the earliest to improve compliance.

Design: A cross sectional prospective study.

Results: Out of 151 DR TB patients 50.33% patients developed adverse drug events of which gastro intestinal (nausea-21.19%, vomiting-18.54% & 14.56%) manifestations were most common followed by arthralgia (13.90), psychiatric manifestations (insomnia-10.59% & depression-1.32%), injection site swelling/pain (8.6%), impaired hearing (1.32%) and rash (0.66%).

Conclusions: Gastrointestinal symptoms are the most common adverse drug events. Taking the pills embedded in banana, pedha or mashed potato along with spacing of drugs and proper guidance helps in reducing gastrointestinal symptoms. Maximum number of adverse events occur in the first 2 months and intensive counseling to patients and caregivers is essential to prevent defaulting.

KEYWORDS : adverse drug events, drug resistant tuberculosis, second line anti TB drugs, RNTCP.

INTRODUCTION

Drug-resistant tuberculosis (MDR-TB and XDR-TB) is an increasing global problem, with most cases arising from a mixture of physician error and patient non-compliance during treatment of susceptible Tb[1].

India has highest burden of both TB and DR TB based on estimates reported in Global TB Report 2016[2]. Having achieved the global targets for cure rates among new smear-positive pulmonary TB cases detected under the programme RNTCP, RNTCP has implemented the programmatic management of multidrug-resistant Tb[3].

Multidrug-resistant tuberculosis (MDR-TB) is defined as resistance to at least isoniazid and rifampicin1. Extensively drug resistance (i.e. XDR-TB) is defined as resistance to at least isoniazid and Rifampicin (i.e. MDR-TB) plus resistance to any of the fluoroquinolones and any one of the second-line injectable drugs (amikacin, kanamycin, or capreomycin)[1].

Today DR-TB spreads unchecked in most of the world. It is fueled by poverty at the individual and family levels, – limiting access to effective treatment – and at the regional and national level, where under- resourced governments lack the capacity to tackle this disease[4].

It should be stressed that DR-TB is a man-made phenomenon – poor treatment, poor drugs and poor adherence lead to the development of DR-TB[5].

Treatment of DR-TB is difficult, complicated, much costlier, challenging and needs experience and skills. Reserve drugs are frequently associated with very high rates of unacceptable adverse drug reactions, needing frequent interruption and change of regimen[4]. 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 (Adverse Drug Reactions) of second-line anti-tubercular drugs in India is scanty. Hence, the aim of this study was to assess the adverse drug reactions of second-line anti-tubercular drugs used to treat DR-TB in India.

PRIMARY OBJECTIVE:

To detect adverse effects of drug used in drug resistant tuberculosis in intensive phase at the earliest.

SECONDARY OBJECTIVE:

To counsel patients about means to decrease adverse effects to improve adherence.

MATERIALS AND METHODS:

Present study was carried out at Drug Resistance Tuberculosis Centre of our institute with prior approval of institutional ethics committee.

Study design: Cross-sectional prospective study.

Inclusion criteria:

All DR-TB patients receiving second line anti TB drugs enrolled at Drug Resistance Tuberculosis Centre, during the period of November 2015 to November 2017 were included in the study.

Exclusion criteria:

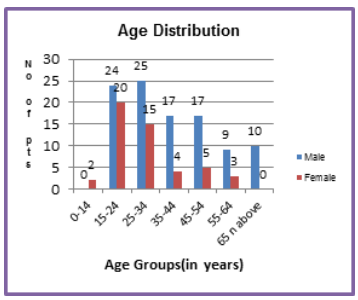
No exclusion criteria except for those patients not willing to give consent for the study.

Clinical Evaluation & Procedures:

Patients for this study were included from all patients diagnosed to have DR-TB (MDR & XDR) diagnosed by DST and admitted in Drug Resistance Tuberculosis Centre of our institute. All study subjects were evaluated after written informed consent. Thorough history was taken regarding the demographic profile, present complaints, past history, history of any addiction, family history of Tuberculosis. Detailed general and systemic examination was done to find out any abnormalities. Pre-treatment investigations done included sputum for acid fast bacilli (AFB) by smear, culture and DST, Chest X-ray, urine for albumin, sugar and pregnancy test for female patients (if 18 to 45 yrs. old), complete haemogram, renal and liver function test, and ELISA for HIV antibodies after counseling, Thyroid function test, psychiatric evaluation and informed consent (as per RNTCP guidelines that every case of TB should be screened for HIV).

RESULTS:

Graph -1 Age Distribution[6,7]



Graph -2 Sex Distribution

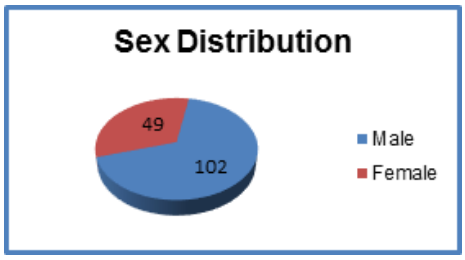
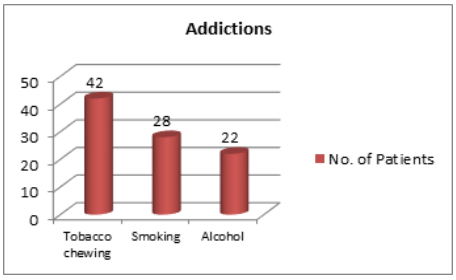


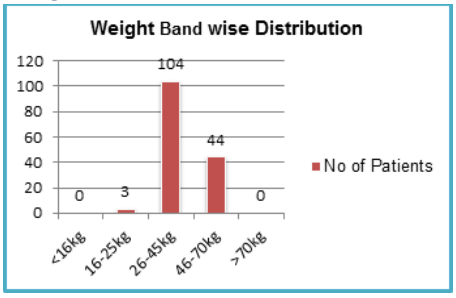
Table -3 Marital Status

Marital Status	No.	%
Married	119	78.80%
Unmarried	32	21.20%
Total	**151**	**100%**

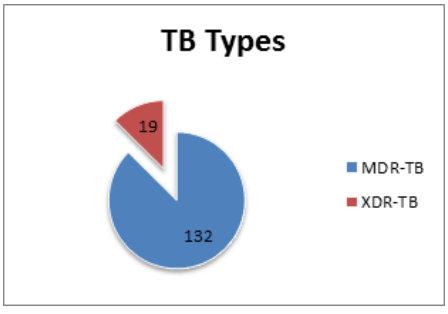
Graph -4 Addictions



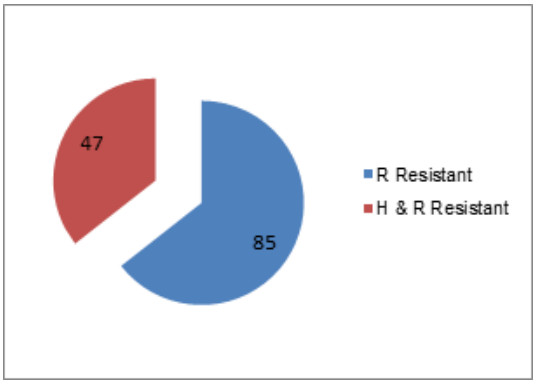
Graph -5 Weight Band Wise Distribution



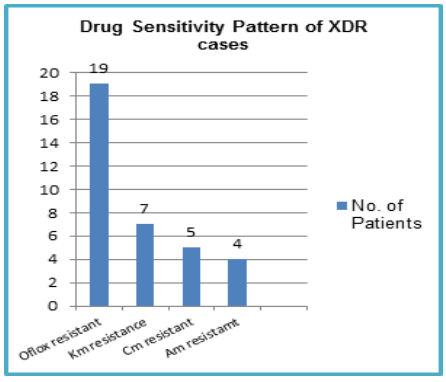
Graph -6 Distribution Of Drug Resistant Cases



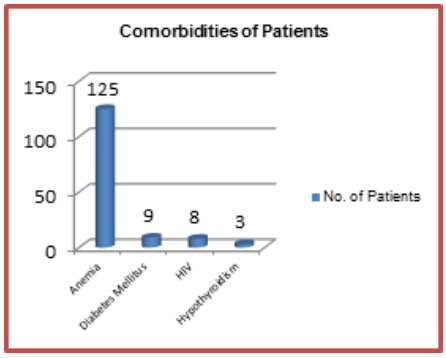
Graph -7 Drug Sensitivity Pattern of MDR cases



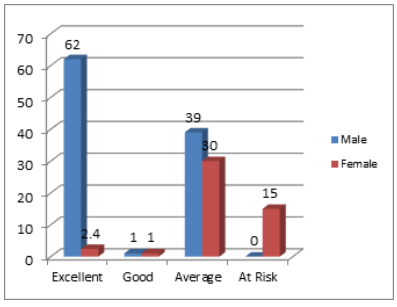
Graph -8 Drug Sensitivity Pattern of XDR cases



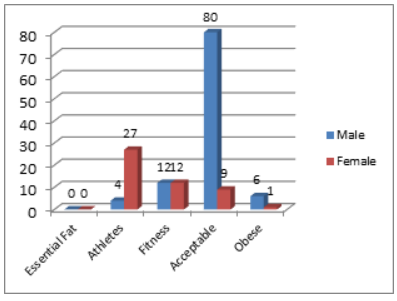
Graph -9 Comorbidities



Graph -11 Distribution according to Waist Hip Ratio



Graph -12 Distribution according to % Body Fat (calculated by Skin Fold Thickness[8])



Graph -13 Anemia Categories

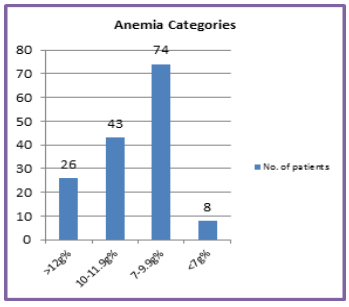
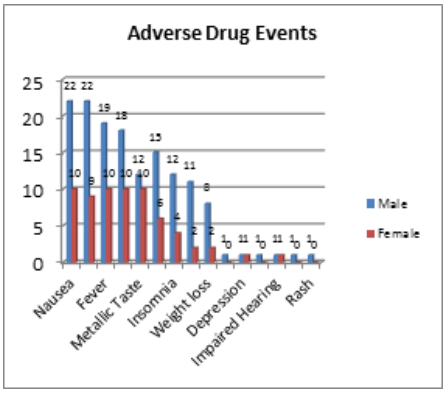


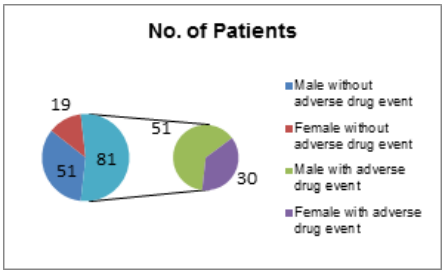
Table -14 Adverse Drug Events

Adverse Drug Events	No. of Patients		Total(%)
	Male	Female	
Nausea	22	10	32(21.19%)
Cough	22	9	31(20.52%)
Fever	19	10	29(19.20%)
Vomiting	18	10	28(18.54%)
Metallic Taste	12	10	22(14.56%)
Arthralgia	15	6	21(13.90%)
Insomnia	12	4	16(10.59%)
Swelling/Pain at	11	2	13(8.60%)
Weight Loss	8	2	10(6.62%)
Impaired Vision	1	0	1(0.66%)
Depression	1	1	2(1.32%)
Water Brash	1	0	1(0.66%)
Impaired Hearing	1	1	2(1.32%)
Glossitis	1	0	1(0.66%)
Rash	1	0	1(0.66%)

Graph -14 Adverse Drug Events



Graph -15 Sex wise distribution of patients developing adverse drug events



Graph -16 No. of Adverse drug events per patient

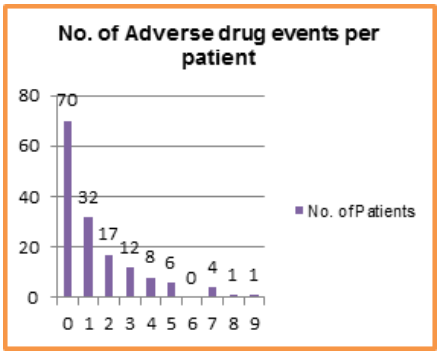
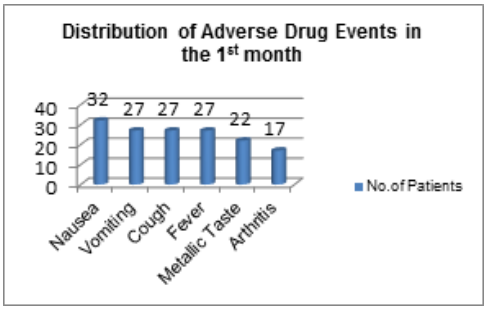


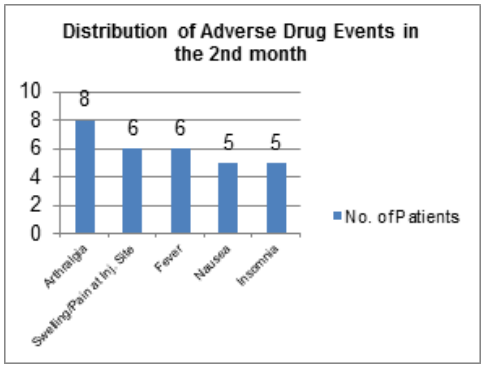
Table -17 Month wise distribution of adverse drug events

Month of Treatment	No. of Adverse events	%
1st	185	65.37%
2nd	50	17.66%
3rd	18	6.36%
4th	17	6%
5th	6	2.12%
6th	7	2.47%
Total	283	100%

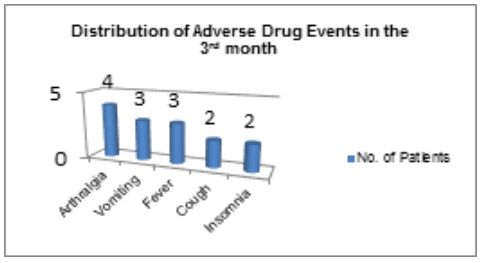
Graph -18 Distribution of Adverse Drug Events in the 1st month



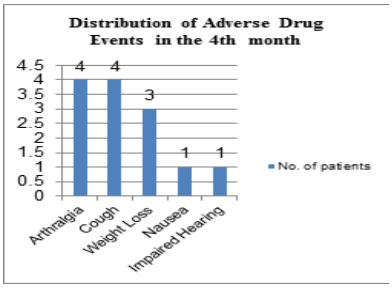
Graph -19 Distribution of Adverse Drug Events in the 2nd month



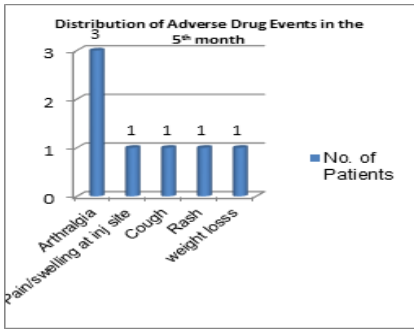
Graph -20 Distribution of Adverse Drug Events in the 3rd month



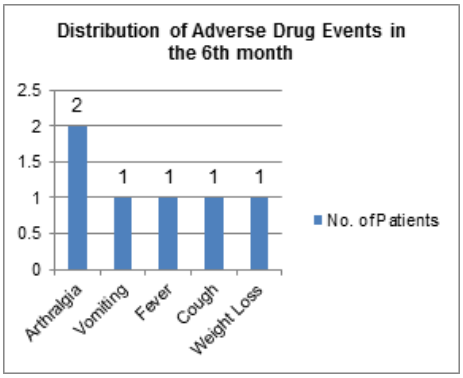
Graph -21 Distribution of Adverse Drug Events in the 4th month



Graph -22 Distribution of Adverse Drug Events in the 5th month



Graph - 23 Distribution of Adverse Drug Events in the 6th m



DISCUSSION:

The present study has evaluated a DOTS-Plus programme, with special reference to adverse events related to drugs in which standard treatment of drug resistant tuberculosis cases as per RNTCP guidelines has been started in our DR-TB Centre.

Age distribution –

In the present study of 151 patients, the youngest patient was 12 and the oldest was 75 years old. Most of the patients belonged to the age group 15-24(29.13%) years followed by 25-34years (26.49%). Majority (84.08%) patients were in the age group of 15-54years which was comparable to the demographic profile of MDR-TB patients in the study performed by Sachin S Dole et al where the majority of patients belonged to the age group 18-50years. It was also similar to other series with a majority of patients in the economically productive age group 25-54 years[6,9].

Sex distribution –

In the present study, majority of the patients were males (67.54%). In the study performed by Sachin S Dole et al also majority (65.06%) patients were males[6]. This finding was similar to other studies where majority patients were males[9,10]. We also found that, 119 (78.80%) were married and the rest 32(21.20%) were unmarried as most of the latter group 14(9.27%) were below the legal age for marriage. Only 1(0.66%) unmarried male patient was of the age of 70 years. In other studies, marital status was not discussed.

Comorbidies-

In our study, Diabetes mellitus was found in 5.96%, which is less compared to 31.58% diabetics in the study conducted by Joseph et.al[3].

In our study, 92.05% patients had past history of tuberculosis and 7.95% patients were those who never had tuberculosis in the past but developed drug resistance tuberculosis directly first time in life. This observation was in accordance with other studies as R. Singla et al[11], R.Singh et al[12] where 100% patients had previous history of tuberculosis. R. Singla et al[11] observed history of contact with MDR TB patient in 4% patients as opposed to 4.63% patients in the present study.

We also found that all the addicts were males 92/102 (90.19%) and the most common addiction was tobacco chewing 42/151 (27.81%) followed by smoking (18.54%) and alcoholism (14.56%).

Weightband-

In the present study, maximum patients were in the weight band of 26 to 45 kg(68.87%) followed by 46 to 70 kg (29.13%) while in the study by Joseph et.al.[3] majority patients were above 45 Kg (47.36%). The mean age in the preset study was 41.9 kg as opposed to the mean age calculated by Wing Wai Yew et al[10] which was 51.4 kg. In our study, 62.91% patients were underweight with BMI <18.5 Kg/m^2, with median BMI of 17.99 kg/m^2, similar to the study conducted by Cox.H.S et al[13] where median BMI was 17.4 kg/m^2. In both the studies, majority of the drug resistance tuberculosis patients were underweight before the start of treatment.

Skin fold thickness-

In the present study, we have calculated skin fold thickness by Harpenden skinfold calipers and % body fat by Durnin- Womersley Body Fat Formula[8] but the data showed that only 4.63% patients were found to have increased risk of development of metabolic complications, which is very unlikely in patients with drug resistant tuberculosis. We were not able to find any study published related to skin fold thickness in tuberculosis and so we consider that this measurement was not of any use in our study.

Waist hip ratio-

In our study, the waist hip ratio analysis of all cases showed that 9.93% patients were at increased risk of developing metabolic complications which is not comparable with the study conducted by Raghuraman et al[14] where 26/217 (11.98%) patients were found to have obesity by waist hip ratio method as it was conducted in drug sensitive tuberculosis with diabetes and there was no study related to such analysis in patients having drug resistant tuberculosis.

Anemia –

49% patients in our study presented with moderate anemia (hemoglobin 7-10 gm %). 77.47% patients were had hemoglobin between 7-12 gm%. In other studies anemia was not discussed.

Drug resistance –

In our study, out of 132 MDR patients, 85 (64.39%) patients had only Rifampicin resistance whereas 47 (35.6%) had both Isoniazid (H) as well as Rifampicin (R) resistance. Initially, when our DR TB center started, only solid cultures were available in the program due to which both rifampicin and isoniazid resistance was reported together. As line probe assay became available, rifampicin mono resistance cases started getting picked up. But during earlier days when line probe assay was not available all (100%) patients were resistant to both Isoniazid and Rifampicin as seen in studies by Goble et al[9] and Helen S. Cox et al[15]. Amongst the 19 Extensively Drug Resistant (XDR) tuberculosis cases, 7(36.84%) had Kanamycin (Km) resistance, 5(26.31%) had Capreomycin (Cm) resistance and 4(21.05%) of them had Amikacin resistance; while all 19(100%) of them were Ofloxacin (Oflox) resistant. In the study conducted by Pauline Joseph et al, it was found that 5/38 (13.15%) patients had ofloxacin resistance and 1/38 (2.63%) patients had Kanamycin resistance[3]. This discrepancy was probably due lesser sample size in the latter study.

ADVERSE DRUG EVENTS

- In our study adverse drug events were observed in 53.64% patients which was less as compared to Singla et. al.[11] (58%) and Joseph et. al.3 (58%). As we enquired adverse drug events telephonically in patients after discharge in those who could not follow up personally due to long distance stay from DR-TB centre, this may have lead to recall bias. Some patients were not traceable telephonically. This may be reason for decreased prevalence of adverse drug events observed in our study.
- Gastro intestinal symptoms (Nausea, vomiting, metallic taste) were most common adverse reaction observed in our study similar to other studies3,[11,16–18]. Hire R. et. al.[19],Dutta et. al.[20] and Kapadia et. al.[18] observed gastrointestinal adverse drug events in 30%, 36% and 22.22% patients respectively. Joseph et.al.3, Singla et.al.[11] and Sing R. et.al.[12], Furin et. al.[16] observed gastrointestinal adverse drug events in 42%, 60% and 100% patients respectively.
- They were mild but required immediate treatment. These gastrointestinal symptoms occurred mostly within a week of starting treatment. Taking the pill embedded in pedha, shira, a small piece of banana, mashed potato along with spacing of tablets and proper counseling helped in reducing this adverse event. No patient required alteration in DOTS-Plus treatment due to gastrointestinal adverse drug events.

- Fever and cough were the next common symptoms that we observed in our study after the treatment was started; but whether they developed as a part of the disease or as adverse drug events was doubtful. They subsided with tablet paracetamol and cough syrup and did not require withdrawal of any drug.
- Arthralgia 13.90% was the next common adverse drug event observed in our study, more than that found in K. Rathod et. al.[21], Hire R. et. al.[19] and Kapadia V. et. al.[18] who observed arthralgia in 4.15%, 4.5 % and 7.94 % respectively. Jain k. et. al.[22] and Joseph et. al.[3] observed arthralgia in 31% and 23.68% patients. Though it occurred right from the 2nd month to 6th month, it did not require withdrawal of any drug. It responded to paracetamol and other NSAIDs and local application of warmth.
- Psychiatric manifestations are the next common manifestations in our study which included insomnia (10.59%) and depression (1.32%). Psychiatric adverse drug events were less common in our study as compared to Singla et. al[11] (15.9%),Singh R. et. al.[12](15%) and Bloss E. et. al.[23](13.2%) but more than study conducted by K. Rathod et al[21] (5.28%). None of the patients required withdrawal of any drug and these adverse events responded to benzodiazepines and antidepressants along with good counseling.
- The next common adverse drug event observed in our study was injection site swelling/pain 8.6% more than Jain et. al.[22] who observed injection site swelling/pain in 2% patients and K. Rathod et al[21] who observed it in 4.90% patients. Joseph et. al.[3] observed injection site swelling/pain in 21.05% patients. None of the patients required withdrawal of injection Kanamycin.
- Ototoxicity was found in 1.32% patients in our study which was in the form of reduced hearing demonstrated by audiometry. This observation in our study was lower than the findings of Kapadia V. et. al.[18] who observed ototoxicity in 4.75% patients. Jain k. et. al.[22] and Singh R. et. al.[12] observed ototoxicity in 15% and 13% of patients. Kanamycin was withdrawn in these patients and substituted with PAS (p- aminosalicylic acid).
- Cutaneous reaction (0.66%) was the least common adverse drug event which was in the form of rash with itching which subsided on its own within 5 days with application of calamine lotion. Frequency of cutaneous reaction found in our study is similar to Kapadia V. et. al.[18](1.58%), Singla R. et. al.[11](4%) and Törün T. et. al.[24](4.5%). Furin et. al.[16] observed cutaneous reactions in 43.3% patients.
- None of our patients developed jaundice, impotence, convulsions or suicidal tendencies.
- Though it was found that the adverse drug events were more in males than females, the result was not statistically significant i. e. there was no correlation between the sex of the patient and the occurrence of adverse drug events.
- Maximum number of adverse drug events in a patient was 9. Most patients -61(40.38%) had developed 1-3 adverse drug events.
- Month wise analysis showed that maximum adverse events occurred in the first two months (83.03%) and had significantly decreased during the later months.
- Detailed monthly analysis of the 1st month of treatment showed that the predominating adverse event was mainly gastrointestinal which included nausea and vomiting.
- Arthralgia was the predominating adverse drug event in the later (2-6) months of intensive phase as per our study.

SUMMARY:

This study was conducted on the patients of Drug Resistance Tuberculosis (DR-TB) admitted in our Drug Resistance Tuberculosis Centre, during the period of November 2015 to November 2017. The present study has evaluated the Demographic profile of Drug Resistance Tuberculosis patients, types of adverse drug events, time of onset of those adverse drug events, number of adverse drug events per patient and various possible ways to alleviate these drug events.

- Patients from 4 districts were admitted in our DRT Centre.
- During the 25 months study period from November 2015 to November 2017 a total of 151 patients were studied of which 132 (87.41%) were MDR TB and 19 (12.58%) were XDR TB patients.
- The age group ranged from 12 years to 75 years.
- Majority of cases were male –67.54%.
- Co morbidities,
- 9/151 (5.96%) patients had Diabetes Mellitus.
- 8/151 (5.29%) patients had HIV.
- 3/151 (1.98%) patients had hypothyroidism
- Majority (68.87%) of patients were in the weight band of 26 to 45 Kg.
- 49% patients presented with moderate anemia.
- 62.5% were underweight with BMI <18.5 kg/m2, with median BMI of 17.9kg/m2.
- Out of 132 MDR patients, 85 (64.39%) patients had only Rifampicin resistance whereas 47 (35.6%) had both Isoniazid (H) as well as Rifampicin (R) resistance.
- Amongst the 19 Extensively Drug Resistant (XDR) tuberculosis cases, 7(36.84%) had Kanamycin (Km) resistance, 5(26.31%) had Capreomycin (Cm) resistance and 4(21.05%) of them had Amikacin resistance; while all 19(100%) of them were Ofloxacin (Oflox) resistant.
- At the end of this study, out of 151 DR TB patients 50.33% patients developed adverse drug events of which gastro intestinal (nausea-21.19%, vomiting- 18.54% & 14.56%) manifestations were most common followed by arthralgia (13.90), psychiatric manifestations (insomnia-10.59% & depression-1.32%), injection site swelling/pain (8.6%), impaired hearing (1.32%) and rash (0.66%).
- None except injection Kanamycin required withdrawal in few patients.

CONCLUSION:

- Gastrointestinal symptoms are the most common adverse drug events followed by arthralgia in the intensive phase of treatment of drug resistant tuberculosis.
- Taking the pills embedded in banana, pedha or mashed potato along with spacing of drugs and proper guidance helps in reducing gastrointestinal symptoms.
- The reduction in the adverse drug events in half of the patients in our study was the result of meticulous counseling and the use of above strategy.
- Maximum number of adverse events occur in the first 2 months and intensive counseling to patients and caregivers is essential to prevent defaulting.

ACKNOWLEDGEMENT:

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