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# PATTERN OF ADVERSE DRUG REACTION IN PATIENT ON ANTI-TUBERCULAR THERAPY REPORTED TO ADRS MONITORING CENTRE IN KUMAON REGION.

**Pharmacology**

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## ABSTRACT

**Aim / Objective:-** To evaluate Adverse Drug Reactions (ADRs) due to Anti-tubercular Therapy (ATT) in a tertiary care hospital in Kumaon Region.

**Introduction:-** Tuberculosis is affecting one out of three people worldwide. ADRs due to ATT is one of the major cause of non-compliance, hospitalization, drug withdrawal and financial burden to patient during treatment.

**Material and Methods:-** It was a retrospective study conducted at tertiary care centre at Dr. Sushila Tiwari Government Medical College Hospital from September 2016 to August 2017.

**Results:-** Total 235 ADRs were reported from 117 forms out of which 54.70% were males and 45.30% were females. Most common ADR reported was related to GIT (62.12%) followed by dermatological (13.65%) and Central Nervous System (7.59%). WHO causality scale assessed that 75.31% of reaction falls under possible and 20.62% under probable. Most common drug causing ADRs was Pyrazinamide (28.43%) followed by Rifampicin (26.56%) and Isoniazid (19.68%)

Conclusion:- ADRs leads to patient suffering and financial burden. Antitubercular therapy have a high risk of ADR therefore adapting preventive measures and using the therapy rationally and judiciously can decrease the burden of ADRs to society and will benefit the manking.

## KEYWORDS

Adverse Drug Reaction, PvPI, Tuberculosis, WHO

**Introduction-**

Tuberculosis (TB) is one of the common disease in the world during the past 40 years. It has been public health problem affecting our nation for very long. Great attention is being payed by physicians, public health workers researches and government in devising new efficient cost effective, pragmatic ways to deal with this huge burden to public health.

As per Global TB report 2017 there are 10.4 million active TB cases globally to which India is the highest contributor with 2.7 million cases accouting for about a quarter of world's TB cases. According to report MDR-TB is 6.19% among all TB patients with 2.84% among new and 11.60% among previously treated TB patients[1]. As per India TB Report 2018, in 2017, highest notification of TB cases was from Maharashtra i.e 19,2458 cases followed by Madhya Pradesh and Gujarat but the notification rate of TB was highest of Chandigarh i.e 523/lac/year[2].

In Uttarakhand, total 16,760 cases were reported. Highest number of cases were reported from Haridwar district (4506) followed by Dehradun district (4211).Nainital district accounted for 1786 cases. Notification rate was highest for Dehradun district i.e 228/lac /year followed Haridwar district -213/lac/year. Notification rate of Nainital district was 170/lac/year. It said that India initiated the programmatic management of drug resistant TB (PMDT) in 2007 to address the emerging problem of drug resistant-TB (DR-TB), and the national PMDT scale-up was achieved by March 2013.[3]

The treatment success rate among MDR-TB patients in India is consistently about 46 percent and the death rate is around 20 percent as against the global level of treatment success rate of 52 percent and death rate of 17 percent. "High rates of treatment failure and deaths are associated with fluoroquinolone resistance in the Indian cohort of MDR-TB patients," it said.[3]

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The Government of India has declared TB to be a notifiable disease, that any doctor who treats TB patient, has to notify it to government In order to intensify the efforts to control TB. The Government of India gradually replaced NTP (National Tuberculosis Programme) by DOTS (Directly observed treatment shortcourse) strategy or programme in 1993 now known as Revised National Tuberculosis Programme (RNTCP).

As per new regimen , for new cases- 6 months regimen is followed that includes isoniazid(H), rifampicin(R), pyrazinamide(Z), and ethambutol(E) daily for first 2 months followed by rifampicin(R) and isoniazid(Z) for 4 months. For previously treated casesHRZE is given daily for 2 months followed by HRZES for next 1 month followed by HRE for 5 months.For MDR-TB , kanamycin (km), levofloxacin(Lfx), ethambutol(E), pyrazinamide(Z), ethionamide (Eto) and cycloserine(Cs) are given for 6-9 months followed by levofloxacin ethambutol, ethionamide and cycloserine for next 18 months.

Antitubercular drugs like any other drug also has many and serious adverse drug reactions (ADR) as the treatment of TB almost always involves combination of drugs taken for prolonged period , the occurrence of ADR is quite likely Moreover, the adverse effect of one drug may be enchanced by the concomitant drugs so it becomes difficult to treat and identify the causative drug causing ADRs. The major adverse reactions to antitubercular drugs caused significant morbidity,mortality and compromised treatment regimes. Many of the ADR can be prevented or minimized by due diligence. So ADR monitoring becomes a important tool to detect uncommon and sometimes serious ADR ensuring patients safety.Hence we conducted this study to assess the ADRs due to tuberculosis in the tertiary care hospital in Kumaon Region.

**Material and Methods-**

Study Area:- The study was conducted at the tertiary care centre at Dr. Sushila tiwari Government Medical College Hospital & TB Chest Institute Haldwani Nainital. Approval of the Institutional Ethical Committee was Obtained for the study.

Study Period and Study Population:- The data was obtained from suspected ADRs reporting forms, between September 2016 to August 2017, from the TB Chest department to the ADRs monitoring centre attached to department of Pharmacology under the Pharmacovigilance Programme of India (PvPI).

**Study Design:-** It was a retrospective study conducted from ADR reporting form, reported from TB chest department, who were treated with anti-tubercular drugs during study period. The demographic

details of the patients were recorded. Details of medication given were also noted. Chief Complaint, past history, drug history were also recorded. Details about the occurrence and nature of ADRs, severity, de challenge and rechallenge were recorded. Concomitant medications administered were also obtained. Relevant laboratory investigations was also noted.

Patients of both sexes and all ages diagnosed with tuberculosis and treated with chemotherapy for the same, developing at least one ADR during or after the treatment period were included in the study.

Study Tool:- ADR reporting form designed by centre for drug standard control organization (CDSCO) was used to collect data. The reported ADRs were assessed for causality using WHO causality assessment scale[4]. The severity was assessed using Hartwig and Siegel scale[5]. The WHO causality assessment scale determines the causal relationship of a suspected drug to the ADR in question and categorize into " Certain", "probable", "possible", "unlikely", "conditional", / "unclassified" and "unassesseable" / "unclassifiable".

| PARAMETERS | NUMBER (n =117) | PERCENTAGE (%) |
|---|---|---|
| GENDER | | |
| Male | 64 | 54.70 |
| Female | 53 | 45.30 |
| AGE IN YEARS | | |
| 0 -10 | 0 | 0 |
| 11-20 | 13 | 11.11 |
| 21-30 | 34 | 29.05 |
| 31-40 | 21 | 17.94 |
| 41-50 | 18 | 15.38 |
| 51-60 | 11 | 9.40 |
| 61-70 | 15 | 12.82 |
| 70 and above | 05 | 4.2 |

The data collected, analyzed using Microsoft excel and frequency and percentage were determined for each variable[6].

**Results:-**

A total of 117 patients were included in our study of which 64 males (54.70 %) and 53 females (45.30 %) reported ADRs. Most common age group experiencing ADRs was 21 to 30 years ( Table 1, Fig. 1).

**Table 1. Demographic details and its association with ADRs.**

| | | |
|---|---|---|
| 31-40 | 21 | 17.94 |
| 41-50 | 18 | 15.38 |
| 51-60 | 11 | 9.40 |
| 61-70 | 15 | 12.82 |
| 70 and above | 05 | 4.2 |

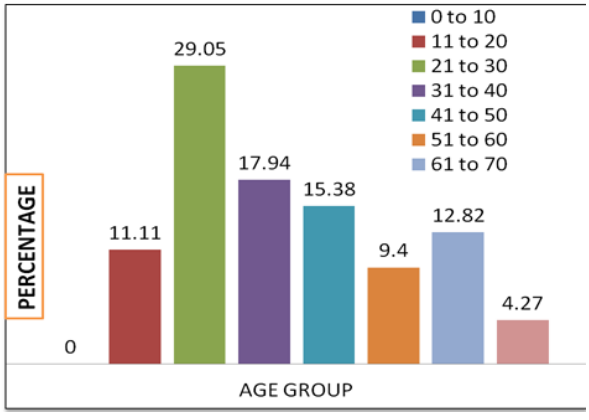



**Figure-1 Age Distribution**

Most common tuberculosis was found to be pulmonary tuberculosis (77.11%) including 20 cases of multidrug resistance tuberculosis and 4 cases of extensively drug resistance tuberculosis followed by extra-pulmonary tuberculosis (22.03%) which involves lymph node, gastrointestinal, nervous system .(Table 2).

**Table 2. Type of Tuberculosis.**

| Type of Tuberculosis | | Number (n=117) | Total Percentage % |
|---|---|---|---|
| Pulmonary | Non-resistance | 67 | 77.78 % |
| | Multi-drug resistance(MDR) | 20 | |
| | Extensively drug resistance (XDR) | 04 | |
| Extapulmonary | Lymph node | 14 | 22.22% |
| | Gastrointestinal | 07 | |
| | Nervous system | 05 | |

The most common system affected was gastrointestinal tract 62.12% followed by Dermatological involvement 13.61% followed by Nervous system melabotic, otovestilular, hematological ( Table 3, Fig. 2).

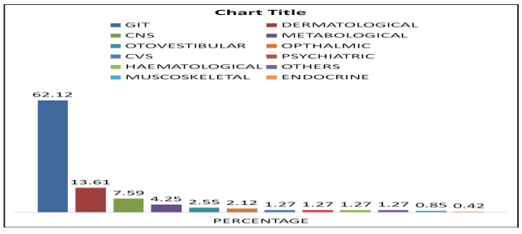



**Fig.2 Systemic distribution of ADRs**

**Table 3. Incidence of ADR in different system.**

| System affected | Type of ADRs | Frequency (n =237) | Total Percentage % |
|---|---|---|---|
| Gastrointestinal | Hepatotoxicity | 40 | 62.12 |
| | Vomiting | 37 | |
| | Anorexia | 27 | |
| | Nausea | 21 | |
| | Gastritis | 13 | |
| | Abdominal pain | 07 | |
| | Constipation | 01 | |
| Dermatological | Rash | 5 | 13.61 |
| | Acne like rash | 3 | |
| | Papular rash | 3 | |
| | Macular rash | 2 | |
| | Maculopapular rash | 1 | |
| | Itching | 14 | |
| | Urticaria | 2 | |
| | Discoloration of skin | 1 | |
| Nervous system | Dizziness | 4 | 7.59 |
| | Sedation | 2 | |
| | Drowsiness | 2 | |
| | Headache | 1 | |
| | Seizures | 1 | |
| | Slurring of speech | 1 | |
| | Anxiety | 1 | |
| | Peripheral neuropathy | 6 | |
| Metabolic | Hyperuricaemia | 10 | 4.25 |
| Otovestibular | Decreased hearing | 3 | 2.55 |
| | Loss of hearing | 2 | |
| | Tinnitus | 1 | |
| Ophthalmic | Decreased vision | 4 | 2.12 |
| | Loss of vision | 1 | |
| Haematological | Anaemia | 2 | 1.27 |
| | Decreased leukocyte count | 1 | |
| Cardiovascular | Multiple ectopics | 2 | 1.27 |
| | T-Wave inversion | 1 | |
| Others | Flu like syndrome | 1 | 1.27 |
| | weakness | 1 | |
| | Oedema face | 1 | |
| Muscoskeletal | Generalised body ache | 02 | 0.85 |

| | | | |
|---|---|---|---|
| Psychiatric | Emotional quietening | 1 | 0.84 |
| | Aggressiveness | 1 | |
| Endocrine | Hypothyroidism | 1 | 0.42 |

Most common drug causing ADR was Pyrazinamide 28.43% followed by Rifampicin 26.53% and Isoniazid 19.68% ( Table 4).

**Table 4 Causality distribution of ADRs.**

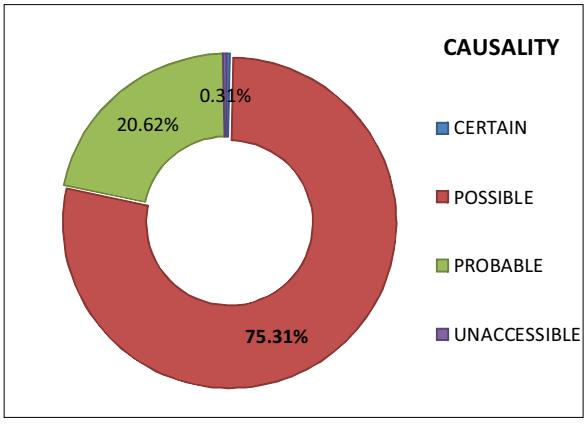
| Suspected Drug | Type | Number (n=325) | Total Percentage % |
|---|---|---|---|
| Isoniazid | Probable | 17 | 19.68 |
| | Possible | 46 | |
| Rifampicin | Probable | 23 | 26.56 |
| | Possible | 61 | |
| | Unaccessible | 1 | |
| Pyrazinamide | Certain | 1 | 28.43 |
| | Probable | 22 | |
| | Possible | 68 | |
| Ethambutol | Probable | 10 | 11.87 |
| | Possible | 37 | |
| Kanamycin | Possible | 03 | 3.43 |
| | Probable | 08 | |
| Streptomycin | Possible | 1 | 0.62 |
| | Probable | 1 | |
| Ethionamide | Possible | 03 | 3.43 |
| Cycloserine | Possible | 05 | 1.56 |
| Levofloxacin | Possible | 10 | 3.12 |
| Moxifloxacin | Possible | 02 | 0.62 |
| Clofazimine | Possible | 02 | 0.62 |
| Paraaminosalicylic acid | Possible | 02 | 0.62 |
| Linezolid | Possible | 1 | 0.31 |
| Amoxyclav | Possible | 1 | 0.31 |

Most of the ADRs were possible 74.46% followed by 24.92% as probable. Only one case each of certain and unaccessible was there ( Table 5, Fig. 3).

**Table 5 Causality distribution according to WHO Causality scale.**

| Causality | Number n=325 | Percentage |
|---|---|---|
| Certain | 1 | 0.31 |
| Possible | 242 | 74.46 |
| Probable | 81 | 24.92 |
| Unaccessible | 1 | 0.31 |

**Fig. 3 Causality distribution**

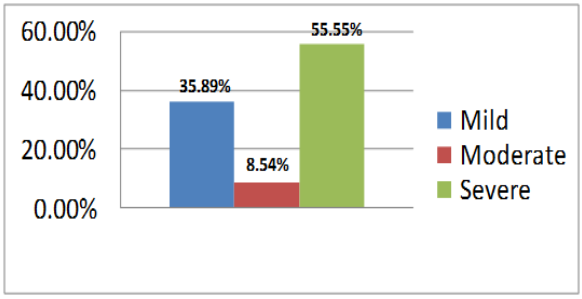



There were 40.17% cases of ADRs which were mild and 32.48% were severe (Table 6, Fig 4).

**Table 6 Severity assessment according to Hartwig and Siegel scale.**

| Severity | Number( n= 117) | Percentage % |
|---|---|---|
| Mild | 47 | 40.17 |
| Moderate | 32 | 27.35 |
| Severe 1 | 38 | 32.48 |

**Fig. 4 Severity Assessment using Modified Hartwig Siegel scale**




**Discussion:-** Identifying adverse drug reactions, treating and thereby improving compliance is very important aspect in the treatment of tuberculosis. This has proven to be an effective way in signal generation. Tremendous effect is being made by the PvPI in this regard.

In our study , total 235 ADRs were reported from 117 forms 54.70% were males and 45.30% were female. Males are more vulnerable to ADRs because of higher incidence of smoking, alcoholism, drug addiction and poorer health condition. This was in the agreement with the study done by which showed 66% of the ADRs were in males[7] contrary with the another study which showed female preponderance[8,9]. Most common age group expensing ADRs was 21-30 yrs (29.05%) followed by 31-40 yrs (17.94%). This result is in contrast to the another study done where age over 60 yrs were associated with increased incidence[10].

The most common system affected was GIT (62.12%) followed by dermatological (13.65%). This is in as per the study done by in which 53% of the patients develop ADRs[8]. Among GIT the most common ADR being hepatotoxicity and vomiting, this was in accordance to the ADR reported by other workers[8,11]. Several other studies have documented the hepatotoxic effect of ATT drugs[12]. The risk factors of hepatotoxicity are old age, alcoholism, malnutrition, hepatitis B and C HIV[13]. This drug related hepatotoxicity is usually seen within the initial few months of intensive phase of antitubercular chemotherapy. It is always good to have liver function test done before starting therapy[14]. Health care professions have the responsibility to counsel the patients regarding signs and symptoms of hepatotoxicity.

Most common drug causing ADR was Pyrazinamide (28.43%) closely followed by Rifampicin (26.56%) and Isoniazid (19.68%) similar finding was noted by[8] some researchers whereas Russian reported streptomycin as the most common drug causing ADR[15]. There can be difference in the drug causing these ADRs depending on the genetic make up, regime followed , dose of the drug and compliance to therapy.

Assessment of the WHO causality scale indicated 74.46 % of the reactions were possible 24.92 % were probable. There was one certain reaction one and unaccessible. We found majority of the ADRs as possible relationship to the suspected drug which was in accordance to study done by[8].

In order to take appropriate action toward managing these ADRs caused by ATT drug it is necessary to use Hart wing scale to study the severity of ADR ( Hartwig et al 1992). In our study majority of the ADR were mild 40.17 % cases followed by severe 32.48 % which required either hospitalization or prolonged stay or some intervention or caused disability. This is in agreement with the some other study done[8,9]. Most of these recovered over time.

**Conclusion:-**

The antitubercular drugs cause significant adverse effects so there is a need for prompt detection to decrease morbidity and mortality. Pharmacovigilance should be encouraged and a holistic approach should be adopted by health care professional, drug regulations, drug manufacturers policy makers and the government. Judicious use and rational prescribing reduce the burden of ADRs in the society and benefit the mankind.

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