Chapter - SEVEN

Summary & Conclusions
The minor adverse events from the anti-tuberculosis drugs (anti-TB) are relatively common and can be managed by reassurance. However, serious adverse reaction during Directly Observed Treatment Short-course (DOTS) therapy with first-line anti-TB drugs, which results in discontinuation of that drug, has several implications. During the course of therapy there may be considerable morbidity, even mortality, particularly with drug-induced hepatitis, which have been reported in past. The static data are important, because alternative agents may have greater problem of drug toxicity and are often less effective, so the treatment must be prolonged, with challenges to ensure compliance. As a result, the risk of treatment failure and relapses are higher. Hence monitoring is crucial, but costly. Awareness of the risk groups may decrease the cost as well as the incidence of serious drug-related adverse effects. The results of the present study indicated that intolerance to DOTS therapy due to adverse effects is still a serious concern.

Seasonal variations in the incidence of tuberculosis have been observed in the present study. Higher incidence of tuberculosis was reported during the month of April to June and the number of patients enrolled was higher among the category-I treatment (i.e. isoniazid, rifampicin, pyrazinamide and ethambutol) while the percentage of adverse events reported was higher among category-II treatment (i.e. isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin).

Incidence of tuberculosis was found to be higher in patients having education up to high school. They also contributed to higher percentage of adverse events. It was also noted that adverse events were higher in low income group patients as compared to high income group patients as well as the incidence of adverse events was reported to be higher in semi skilled workers as compared to skilled workers. According to socio-economic class, adverse events were reported to be more in patients of lower socio-economic class.

Incidence of new cases of tuberculosis was four times higher as compared to retreated cases, which shows low rate of relapse, default or failure. Cure rate and death rate was lower as per Revised National Tuberculosis Control Programme (RNTCP) guidelines.
Failure rate in new pulmonary positive patients was slightly higher, but the overall failure rate was lower than the expected RNTCP guidelines. Default rate in the new positive and extra-pulmonary case was very low but it was slightly higher in the new negative cases.

In the retreated patients, cure rate among failure positive patients was lower, while cure among relapse positive and default positive patients was as per RNTCP guidelines. Death rate among failure positive was slightly higher but death rate among the relapse positive and default positive was as per RNTCP guidelines. Failure rate among failure positive was very high, whereas failure rate in relapse positive and default positive patients were as per RNTCP guidelines.

Incidence of adverse drug reaction with DOTS therapy was very low, but still a serious problem in India because of high TB burden in the country. Therefore monitoring for possible adverse drug reactions, especially in patients at risk, is a part of good clinical practice and should be carried out routinely.

Severe hepatotoxicity in 2.58% patients during anti-TB drugs led to discontinuation of drug(s) was observed in this study. The possible mechanism of hepatotoxicity may be due to defect in uptake by hepatocytes and defect in excretion through sinusoids and canaliculi respectively or due to formation of toxic metabolite of monoacetyl hydrazine, which binds covalently to liver proteins. In some patients an allergic mechanism has also been proposed.

Hyperuricemia was reported in 1.08% patients, which needed discontinuation of one of the anti-tuberculosis drugs. The possible mechanism of hyperuricemia might be due to defective formation of uric acid or decreased excretion of uric acid form kidney.

Peripheral neuropathy occurred in 1.08% patient, which may due to deficiency of pyridoxine and pyridoxal phosphate, which might be due to pharmacological changes in pyridoxine metabolism. The subsequent reduction in pyridoxine and pyridoxal phosphate inhibits the formation of the inhibitory neurotransmitter, gamma aminobutyric acid.
Hypersensitivity reactions occurred in 1.38% of patients and usually characterized by an allergic reaction which may be due to antibody-mediated immune reactions. It is dose independent reaction and may occur at any time during therapy.

Ototoxicity was the most important adverse drug reaction which needs attention and was observed in 0.49% patients, which might be primarily due to lesion in the vestibular sensory epithelium, rather than the organ of corti and that changes in vestibular nerves and central vestibular nuclei are secondary to this event, resulting from an ascending atrophy.

Psychological illness occurred in 0.18% of patients and might be due to deficiency of vitamin B6 due to excessive excretion of the vitamin, which in turn leads to a disturbance of normal tryptophan metabolism. Isoniazid also inhibits the activity of brain pyridoxal-5-phosphate, which leads to a decrease in brain gamma-aminobutyric acid and other synaptic transmitters, resulting in neurologic ill effect.

The adverse events observed in this study were assessed with Naranjo's probability scale. The adverse events were classified as definite, probable, possible and doubtful. Majority of the adverse events reported in this study were possible. Hartwig preventability scale was used to measure the preventable and non-preventable nature of adverse event. Most of the adverse drug reactions were found to be preventable in nature. Severity of drug related adverse events was measured according to Hartwig severity scales. Most of the adverse drug events reported in the present study was mild to moderate and few reactions were found to be severe.

Plasma isoniazid concentration among the tuberculosis patients receiving standard DOTS therapy was determined by HPLC. The standard curve was found linear and coefficient of correlation was found to be greater than 0.998 throughout the experiment. After three injections the coefficient of variation (% CV) for area was found to be 0.8%. The method was accurate and precise for analyzing plasma samples as within – day variation ranges from 0.86% to 4.13% and day to day variation ranges from 1.38% to 6.04%.
Plasma isoniazid concentration among the tuberculosis patients receiving standard DOTS therapy shows distinct acetylation pattern. The histogram is bimodal with an antimode at 2-2.5 μg/mL. Patients whose plasma isoniazid concentration greater than antimode were assigned as slow acetylator (55.56%) and those with plasma concentration less than antimode were assigned as fast acetylators (44.44%). Most patients in the defined area of LRS Institute of Tuberculosis and Respiratory Diseases were slow acetylators. The rate of inactivation of isoniazid has been shown to be determined genetically. Marked racial differences in the incidence of rapid and slow inactivators of isoniazid are due to genetic polymorphism which has been reported by various investigators. In the present study there was very slight difference between the distribution of slow and fast acetylator among the patients, so dose of INH should be modified on individual basis according to the patient's acetylator phenotype and/or plasma isoniazid concentration to increase the efficacy and optimize the adverse events.

In conclusion it can be stated that all the components of the DOT was associated with a low incidence of adverse events. This suggests that DOT is effective and safe as compared to daily treatment regimens, but increased incidence of tuberculosis, presented more number of patient at risk of these adverse events. Most of the adverse events reported in this study were preventable in nature. Patients receiving DOT therapy needed close monitoring for adverse events. Therefore, a pharmacovigilance program should be added at National level to accesses the incidences of these adverse events. The rate of inactivation of isoniazid is genetically determined and shows marked racial differences. Therefore, dose of isoniazid should be modified on individual basis according to the patient acetylator phenotype and/or plasma isoniazid concentration to increase the efficacy and optimize the adverse events. However the sample size in the present study was small and further studies are required to support these finding.