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Incidence of Serious Side Effects of First-Line Anti-tuberculosis Drugs amongst Patients treated for Active Pulmonary Tuberculosis in a tertiary care hospital in Goa over a period of 2 years.

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I. Introduction

Tuberculosis is one of the leading causes of morbidity caused by curable infectious diseases worldwide, and India contributes a significant burden of cases.

Tuberculosis is one among the top 10 causes of death across the world, even above HIV-AIDS. In 2017, TB caused an estimated 1.3 million deaths (range 1.2–1.4 million) among HIV-negative people, and there were an additional 300 000 deaths from TB (range 266,000–335,000) among HIV-positive people. There were an estimated 10.0 million new cases of TB (range 9.0–11.1 million), equivalent to 133 cases (range 120–148) per 100,000 population.[1]

First line therapy of TB consists of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol. Although these agents are highly effective for the treatment of TB, they are also associated with minor as well as major side effects.

A major adverse reaction to one of the first-line anti-tuberculosis drugs is one which results in discontinuation of that drug. It has several implications. There may be considerable morbidity, even mortality, particularly with drug-induced hepatitis.[2]

These events may incur substantial additional costs because of added outpatient visits, tests, and in more serious instances, hospitalizations.[3]

Major adverse reactions to anti-tuberculosis drugs can cause significant morbidity, and compromise treatment regimens for tuberculosis.

Among patients treated for active pulmonary TB, we estimated the incidence of major as well as minor side effects due to first-line ATT drugs (isoniazid, rifampicin, ethambutol and pyrazinamide).

Side effects were attributed to drugs on the basis of resolution after withdrawal, and/or recurrence with re-challenge of the drug.

In our study, we estimated the side effect profile of first line Anti-Tubercular Therapy (ATT) in newly diagnosed patients (new cases) of sputum positive pulmonary tuberculosis in a tertiary care center over a period of two years.

II. Materials And Methods

This was a retrospective observational study carried out from September 2016 to August 2018 in a tertiary care hospital in Goa.

Patients' information was retrieved from medical and nursing records.

Only newly diagnosed sputum positive patients aged 13 years and above, suffering from pulmonary tuberculosis and on ATT, were included in the study.

The patients' records were examined to detect cases who had been admitted in the hospital for management of major side effects of ATT like hepatitis, gastritis, Sweet syndrome, Steven-Johnson syndrome, skin rash and any other.

A major side effect was defined as any adverse reaction that resulted in discontinuation of one or more drugs, and/or directly resulted in hospitalization.

Hepatitis was defined as raised levels of liver transaminases more than three times higher than the upper limit of normal in the presence of symptoms such as anorexia, nausea, vomiting, or abdominal pain; or raised transaminases more than five times the upper limit of normal without symptoms; with or without raised serum bilirubin. Episodes of hepatitis were considered drug induced if transaminases were normal before therapy, increased during therapy, and returned to normal after discontinuation of the responsible drug.[2]

Minor side effects of ATT were detected on the basis of side effects registers maintained in the hospital.

A drug was defined as responsible for the side effect if symptoms and signs resolved after withdrawal, and recurred after re-challenge with that drug. Attribution was also made if a major side effect resolved with discontinuation of the drug, even without re-challenge

Exclusion Criteria:

1. Patients aged <13 completed years
2. Extra-pulmonary TB
3. Relapsed/Recurrent cases of Pulmonary Tuberculosis
4. Patients with known seizure disorder, or patients with known ophthalmological disease such as optic neuritis, color blindness etc; or patients with known/proven major renal or hepatic disease prior to initiation of treatment; or any such known health condition prior to starting treatment which would call for modification of the drug regimen at initiation itself.
5. Side effects attributable to a cause other than the drugs (e.g. seizures due to neurological TB or electrolyte imbalance, itching and rash due to scabies etc.)

The incidence of side effects, overall, and by drug were obtained and presented in the forms of pie-charts and graphs.

III. Results

A total of 572 patients were started on Anti-tubercular treatment during the study period.
The incidence of major side effects and the causative drug were as follows:

- Hepatitis: 28
- Gastritis (requiring hospitilisation): 13
- Deranged renal function tests: 3
- Rash: 9 (3 due to Pyrizinamide,2 each due to Isoniazid, Ethambutol and Rifampicin)
- Seizures: 2 (Isoniazid)
- Sweet Syndrome: 1 (Rifampicin)
- Complete blindness: 1 (Ethambutol)
- Steven Johnson Syndrome: 1 (Pyrazinamide)
- Color blindness: 1(Ethambutol)

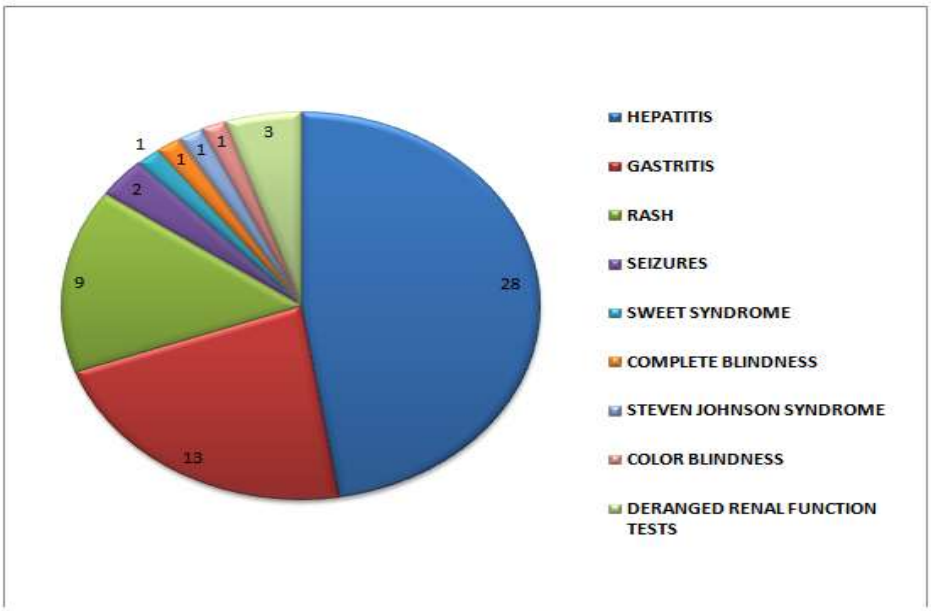

Fig 1: Incidence of major side effects

The incidence of minor side effects was as follows:

- Nausea, epigastric discomfort: 58
- Weakness, malaise: 14
- Hyperuricemia: 5
- Itching: 4

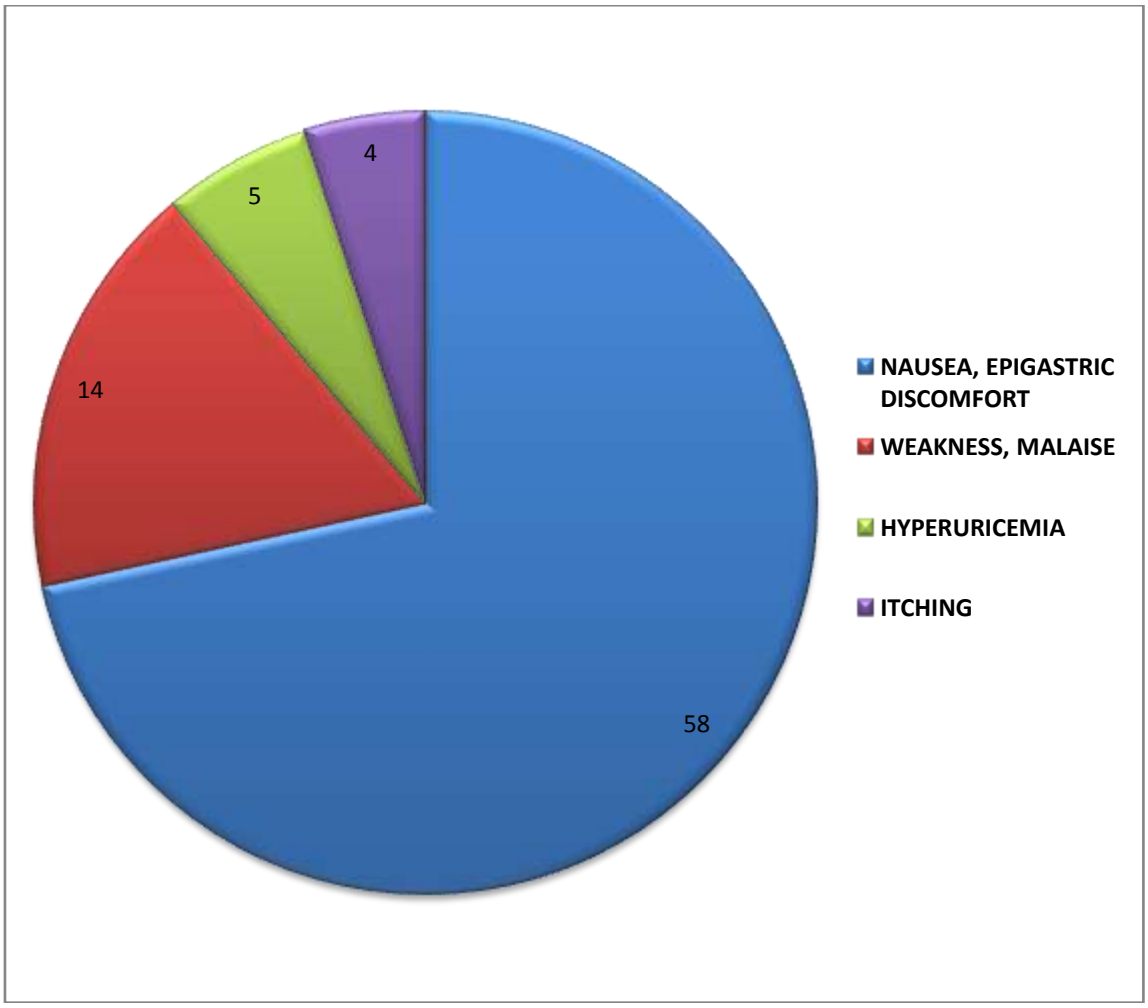

Fig 2: Incidence of minor side effects

IV. Discussion

Adverse drug effects were observed in patients taking anti TB treatment, majority of which were mild, including abdominal symptoms in the maximum number of cases.

A total of 572 patients were started on anti-tuberculosis treatment over the period of 2 years out of which 140 patients developed side effects.

59 patients developed major side effects while 81 patients developed minor side effects not requiring hospitalization.

Pyrazinamide was the most common drug responsible for causing drug rash, while seizures were most commonly due to isoniazid.

Patients who developed gastritis were given injectable proton-pump inhibitors, and their ATT was stopped for a period of 3-5 days till their symptoms improved. Drugs were restarted at lower doses under cover of antacids, and the doses were gradually increased. Patients who could not tolerate full doses were started on alternate regimens.

Patients who developed hepatitis were admitted and ATT drugs were stopped for a period of approximately 5-7 days till their liver function tests became normal. Abdominal ultrasound was done to assess liver status. If cirrhosis was present, alternate regimens were started. Patients who developed icterus and severely deranged liver enzymes with markedly elevated serum bilirubin were started on alternate regimen. Patients liver function tests were monitored weekly after starting ATT[3,4]

In case of the rare side effects like Steven Johnson Syndrome, Sweet syndrome, blindness, etc. the causative drug was stopped and substituted with an alternate drug.

Treatment was successfully restarted in all patients and no patients were kept without ATT.

One short coming of the study is that we have not categorized the side effects according to the type of treatment that the patient was on. During the initial phase of the study the DOTS (alternate day) regimen was being followed, where the patients would receive each drug as separate tablets. For the remainder of the study, the Daily ATT regimen was started as per the latest recommendations of RNTCP, where the patients would receive a fixed dose combination (FDC). However both regimens contained the same drugs. Perhaps more studies would be needed to compare and contrast the side effect profiles in the 2 regimens.

V. Conclusion

Most patients are known to tolerate ATT very well. However, some patients may experience problems, usually due to the bulk of the medicines; a single day's dose consisting of 2-5 tablets. Medicine-related side effects can be minor or major. Therefore, rather than concentrating only on the treatment, the adverse effects of the drugs should also be looked upon for achieving better patient compliance.[5]

Efforts should be made to diagnose and treat the adverse drug reactions on time, and also to provide emotional support to the patients. Perhaps multi-disciplinary involvement (e.g. dermatologist, internal medicine, neurologist etc.) would make the management of these side effects superior.

Conflicts Of Interest

None.

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