

**SEVERITY ASSESSMENT AND PATTERN OF ADVERSE DRUG REACTIONS
WITH ANTI-TUBERCULAR THERAPY.**

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Summary

An open, non-comparative study was carried out in the medicine department of majeedia hospital, jamia hamdard, over a period of 6 months. Potential study subjects were thoroughly interrogated for history in local dialect along with thorough clinical examination for both pulmonary and extra-pulmonary tuberculosis. The patients were followed upon a weekly basis during the period of treatment. Assessment of ADRs was done by formal methods; timing, pattern recognition, background frequency and re-challenge and the same was recorded in ADR reporting and documentation form. A total of 139 patients, satisfying inclusion and exclusion criteria of the study were enrolled. All the categorical data was analysed on 120 patients. 46.7% of patients reported ADRs to anti-tuberculous drugs. The severity of ADR's was graded on 3-point scale (Mild-34.2%, Moderate-9.2%, Severe-3.3%). Close clinical monitoring in all tuberculosis patients for ADRs is important as ADRs remain one of the key factors for non-compliance of treatment, a reason for multi-drug resistance tuberculosis.

Keywords: Adverse Drug Reactions, Pattern of ADR, Pharmacovigilance, Anti-tubercular Therapy

Introduction

Adverse drug reactions (ADRs) are considered as one among the leading causes of morbidity and mortality. Around 6% of hospital admissions are estimated to be due to ADRs and about 6-15% of hospitalized patients experience ADR. (1-3) ADR reporting has become an important component of monitoring and evaluation activities performed in hospitals.(4) Periodic evaluation

of ADRs reported in a hospital helps in characterizing the pattern of ADR and thereby helps in designing steps to improve the safety of drug use in the working setup. Better health care practice could be ensured by applying this knowledge to individual patients. (5) Ultimately data generated contributes in drug safety decision and may serve as a basis for product-labeling revision and design patient education strategies. (6) Though the therapy of tuberculosis is well established with effective regimen for detection and cure of tuberculosis, still noncompliance and discontinuation of antitubercular therapy is one of the major factors contributing to the rise in tuberculosis. Adverse drug reactions not only contribute to noncompliance to therapy but because of their severity also lead to stoppage of treatment occasionally which further causes development of resistant strains requiring second line therapy of drugs with higher cost and more serious adverse drug reactions. (7) Also the nature of adverse drug reaction has changed because of Population Variation - genetic, environmental, dietary factor, disease pattern and drug used. Nutritional Status - 45%-70% population is iron deficient (8), 50% of children malnourished (9) etc. Paucity of Data - very few functioning centers monitoring adverse drug reactions in India and hence adequate information not available even on older drugs. Peculiarities of drug usage in India - many patients tend to use modern drugs along with tradition remedies. All this can lead to adverse drug reactions. Also adverse drug reactions contribute to excessive health care cost through increased patient morbidity and mortality which is of great concern to the general population, the pharmaceutical industry, the regulatory authorities and the medical profession.

Subjects and Methods

The study was carried out in the Medicine Department of Majeedia Hospital, Jamia Hamdard, New Delhi. Total of 139 patients satisfying the inclusion criteria of the study were enrolled into the study. Potential study subjects were thoroughly interrogated for history in local dialect and questioned for detailed information pertaining to the disease. A thorough clinical examination was done for both Pulmonary and Extra-pulmonary tuberculosis by Medical Specialist. After provisional diagnosis, the subjects had to undergo following laboratory investigation for confirmation of diagnosis as inclusion criteria for study.

- X-ray chest (P/A view).
- Sputum for AFB smears (3 samples).
- Sputum for AFB culture and sensitivity test (in selected subjects).
- Blood for T.L.C, D.L.C and E.S.R.
- Montoux test.
- FNAC/ Biopsy (in selected subjects).

All subjects received standard antibiotic for a week during investigation phase to minimize the chance of diagnostic error before confirming for tuberculosis. The patients were followed upon a weekly basis during the period of treatment.

Inclusion criteria

- Patients diagnosed with Pulmonary and Extra pulmonary tuberculosis were based on the various clinical features and laboratory investigations.
- Patients admitted to the wards or visiting Medicine O.P.D of Majeedia Hospital atleast once a week.
- Patients more than 12 years.
- Patients of either sex.
- Oral informed consent.

Exclusion criteria

- Patients less than 12 years.
- Patients unable to respond to verbal questions.
- Pregnant / lactating females.
- Patients with liver and kidney dysfunction.

After enrolment into study, follow up was done at weekly intervals during the treatment. At each follow up patients were asked for any new complaints, and general examination was recorded. Adverse effects if any were recorded in detail at each visit with follow up on the same.

Assessment of adverse drug reaction

The diagnosis for assessment of adverse drug reaction was done by formal methods (10, 11).

- Timing: The time relation between the use of the drug and the occurrence of the reaction was assessed.
- Pattern recognition: The pattern of the adverse effect may fit with the known pharmacology or allergy pattern of one of the suspected medicine or of chemically/pharmacologically related compounds.
- Background frequency: Background frequency of the event and how often it was associated with the drugs.
- Rechallenge: Rechallenge with the same drug.

Further, severity of adverse effects was graded on a 3-point scale:

Mild (awareness of sign and symptoms but easily tolerated).

Moderate (discomfort sufficient to reduce or affect normal daily activity).

Severe (causes inability to work or adverse drug reactions is associated with hospitalization, permanent disability or is life threatening).

Results

Data was recorded from 139 patients. Out of the 139 patients enrolled at the beginning, 19 patients dropped out and were not included in the analysis. Ultimately a total of 120 patients were included for statistical analysis. 46.7% of patients reported adverse drug reactions. Most of the adverse drug reactions were mild to moderate and majority of the adverse drug reactions disappeared on continuation of the therapy with symptomatic treatment. 3.3% of the patients reported severe adverse drug reactions and hence discontinued the treatment till recovery.

Severity of ADR

It was observed that 46.7% of the cases reported ADR's to antituberculous drugs. Most of the ADR's were observed during the initial intensive phase of antitubercular therapy. The severity of ADR's was graded on 3 point scale. Most of the ADR's were mild to moderate and majority of ADR's disappeared on continuation of therapy with symptomatic treatment. Only 3.3% of the patients suffered from severe adverse effect which required discontinuation of therapy till recovery.

Table. 1 Severity of ADR.

Group	Frequency	Valid Percent	Cumulative Percent
No ADR'S	64	53.3	53.3
MILD	41	34.2	87.5
Moderate	11	9.2	96.7
Severe	4	3.3	100.0
Total	120	100.0	-

Table. 2 Pattern of ADR.

Adverse Drug Reactions		Frequency	Percent
Valid	Ototoxicity.	1	7.7
	Urine Discolouration.	2	1.6
	Hepatic effects.	3	2.5
	Arthralgia.	9	7.5
	Gastro- Intestinal effects.	10	8.3
	Dermatological effects.	8	6.6
	Neurological effects.	2	1.6
	Dermatological & Neurological effects.	3	2.5
	Urine Discolouration, Arthralgia and Gastro- intestinal effects.	1	0.8
	Arthralgia & Gastro- Intestinal effects.	3	2.5
Respiratory & Dermatological effects.	1	0.8	

	Peripheral Neuropathy, Arthralgia, Dermatological & Neurological effects.	1	0.8
	Respiratory & Arthralgia.	1	0.8
	Peripheral Neuropathy & Gastro- Intestinal effects.	1	0.8
	Dermatological effects & Neurological effects.	1	0.8
	Urine Discolouration & Dermatological effects.	1	0.8
	Respiratory, Arthralgia & Gastro- Intestinal effects.	1	0.8
	Respiratory & Hepatic effects.	1	0.8
	Arthralgia & Dermatological effects.	1	0.8
	Total.	51	47.1
Missing	69	69	52.9
Total		120	100.0

Discussion

In the present study we monitored and characterized the pattern of ADR's to antituberculous drugs (first line) in different categories of patients.

Ototoxicity was reported by 7.7% of the patients. It is the most important ADR's caused by streptomycin and includes vestibular and hearing disturbances. An elderly man (≥ 50 years) with pulmonary kochs (category II) reported hearing disturbance during intensive phase of antitubercular therapy which coincides with the literature already reported i.e increased risk of ototoxicity in elderly patient (12).

Gastrointestinal effects were reported by 8.3% of the patients which included anorexia, nausea, vomiting, abdominal pain and diarrhea. Mild anorexia and nausea were more common (12) but were rarely severe enough to necessitate discontinuation of therapy. Vomiting and diarrhea were rare.

Arthralgia was reported by 7.5% of patients. It usually appeared during intensive phase of therapy. This is a well known adverse effect of pyrazinamide but unlike classical gout it affects both large and small joints (13, 14). This effect of pyrazinamide is because of inhibition of renal tubular uric acid secretion leading to hyperuricemia (12). These arthralgias were generally self limiting and respond readily to symptomatic treatment. This rarely requires discontinuation or dosage adjustment of the drug.

Hepatotoxicities were reported by 3 (2.5%) of patients. It was found more commonly during intensive phase and was severe enough to discontinue the antitubercular therapy because of development of jaundice, malaise, anorexia and fever accompanied by altered mental status. Hepatotoxicity was more common when the drug is given in combination with Isoniazid 2.7% (15). Asymptomatic elevations in hepatic enzymes two to three times too was seen during intensive but were not significant enough (16).

Respiratory effects were reported along with other adverse effects by 3.3% of patients and characterized by dyspnea. It was reported to occur within two to three hours after the dosage as earlier reported. (17).

A discolouration of body fluids because of rifampicin (18, 19) was reported by 1.6%. This universal effect of drug was noted during the beginning of therapy. It dose not required any alteration or discontinuation of therapy.

Peripheral neuropathy were reported along with other side effects by 2 (1.6%) of patients characterized by numbness and tingling sensation. The side effect appears to be dose related and were prevented with concomitant pyridoxine therapy. Further it coincides with the literature that it occurs commonly in adults and rarely in children (20, 21).

Neurological effects were reported by 2 (1.6%) of patient which included headache dizziness and mental confusion. These ADRs were not severe enough to necessitate discontinuation of therapy.

Dermatological effects were reported by 6.6% of patients alone and 6.6% along with other adverse effects which includes rashes, dermatitis and acne .Which slowly resolved over a period of one month. This ADR's were not severe enough to discontinue the therapy. Further, ADR's were reported in combinations.

Conclusion

Present study emphasize the need of close clinical monitoring of adverse drug reactions which is one of the key factors for early discontinuation of treatment by the patients, a reason for multi drug resistance (MDR) tuberculosis.

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