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Causality Assessment of Suspected Adverse Drug Reaction with Anti-Tubercular Therapy by WHO Probability Scale

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ABSTRACT

The objectives of the study is to monitor and causality assessment of suspected ADRs by WHO Probability Scale in patients of tuberculosis undergoing treatment with anti-tuberculous drugs. An Open, Non-Comparative Study was carried out in the Medicine Department of Majeedia Hospital, Jamia Hamdard, over a period of 6 months. A total of 139 patients, satisfying Inclusion and Exclusion Criteria of the Study were enrolled. 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. All the categorical data was analysed by chi-square test on 120 patients. Causality assessment of ADRs was found to be statistically significant by WHO probability scale. 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. ADRs remain one of the key factors for non-compliance of treatment, a reason for multi-drug resistance tuberculosis.

Keywords: Causality Assessment, WHO Probability Scale, Adverse Drug Reactions, Anti-Tuberculous

INTRODUCTION

Tuberculosis has accounted for more human misery, suffering, loss of earnings and failure of economic and social development than any other disease. Despite antituberculous drugs having been available for almost 50 years, Mycobacterium tuberculosis continues to exert an enormous toll in terms of human morbity and mortality (Burgos et al., 2002). Tuberculosis is believed to cause 2 million deaths every year. If more effective preventive procedure are not adopted - nearly 1000 million will be newly infected and 36 million will die of TB between 2002 to 2020. (WHO, 2002). Thus it is appropriate to call it as the world's longest running catastrophe, killing more than 200 people every hour and more than 5000 every day. In India 1 person dies of tuberculosis every minute (Scientific Blueprint, 2001). Thus it remains the leading infectious cause of death in India, killing close to 500000 people a year (Khatri et al., 2002). India has far more cases of tuberculosis than any other country in the world. About 2 million new cases occur each year (Dye et al., 1999), accounting for nearly $1/3^{rd}$ of prevalent cases globally. 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 (Iseman et al., 1989). 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 (Ramesh et al., 1989), 50% of children malnourished (Gupta et al., 1985) 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.

Specific clinical feature;

- Cough (more than three weeks).
- Yellow expectoration / Haemoptysis.
- Evening rise in temperature.
- Night sweats.
- Loss of appetite.
- Loss of weight.
- History of contact with tuberculosis patient.
- Other physical findings.

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.

Study design

This was an open, non-comparative study to monitor adverse reactions in both outpatients and inpatients undergoing treatment with anitubercular therapy at Majeedia Hospital which is a university hospital of Jamia Hamdard.

Study schedule and plan

The patients were enrolled after oral informed consent as per the inclusion and exclusion criteria. Current medical history and diagnosis were noted during the first visit. 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 (Stephens et al., 1987; Lanctot et al., 1994).

- 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.

The patients were grouped into 10 demographic sub groups to evaluate adverse drug reaction with any of them;

- Age
- Sex
- Income
- Addiction
- Smoking
- Dietary Habit
- Concomitant Disease
- Occupation
- Past History of Koch’s

Further, severities of adverse effects were 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 threating). Also causality assessment of suspected adverse drug

Table:1 ADR's on WHO probability scale

GROUP		WHO PROBABILITY Scale							
		No ADR's	Certain	Probable/ Likely	Possible	Unlikely	Conditional/ unclassified	Unassessable/ unclassifiable	Total
NO ADR's	Count	64							64
	% within WHO PROBABILITY Scale	100%							53.3%
ADR's	Count		3	20	16	7	6	4	56
	% within WHO PROBABILITY Scale		100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	46.7%
Total	Count	64	3	20	16	7	6	4	120
	% within WHO PROBABILITY Scale	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Chi-Square Tests	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	85.251(a)	6	0.000

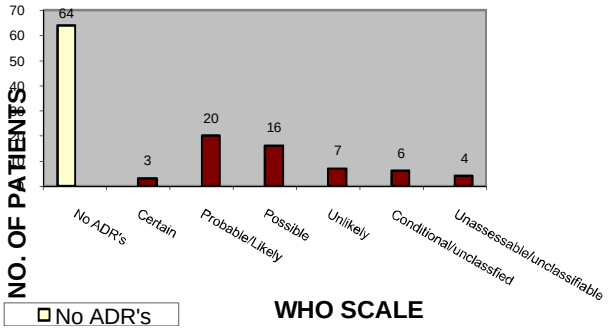
a 8 cells (57.1%) have expected count less than 5. The minimum expected count is .93.

reaction was done by WHO Probability Scale (W.H.O 1991; Stephens et al., 1998).

Causality assessment of suspected adverse drug reactions

1. Certain

- A clinical event, including a laboratory test abnormality, that occurs in a plausible time relation to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals.
- The response to withdrawal of the drug (dechallenge) should be clinically plausible.
- The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.



2. Probable/likely

- A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge).
- Rechallenge information is not required to fulfill this definition.

3. Possible

- A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals.

- Information on drug withdrawal may be lacking or unclear.

4. Unlikely

- A clinical event, including a laboratory test abnormality, with a temporal relation to administration of the drug,
- which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.

5. Conditional/unclassified

- A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are being examined.

6. Unassessable/unclassifiable

- A report suggesting an adverse reaction that cannot be judged, because information is insufficient or contradictory and cannot be supplemented or verified.

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.

Statistical analysis

Categorical data was analysed by chi-square test. Difference for which p-Value remain below 0.05 were labelled as statistical significant.

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