A comparative study of active and passive adverse drug reaction reporting systems in terms of false reporting rate

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Abstract:

Background: World Health Organisation Uppsala Monitoring Centre (WHO-UMC) was set up in 1968 to collect Adverse Drug Reactions (ADRs) periodically for all drugs across the globe. It identifies two main approaches to pharmacovigilance: active (intensive) and passive (spontaneous). However, very few studies are available to compare these two methods of adverse drug reaction reporting. **Methods:** A prospective observational study was done on 303 newly diagnosed patients with tuberculosis receiving directly observed therapy short-course (DOTS) in the Sawai Man Singh (SMS) Hospital, Jaipur between 1 January 2019 and 31 December 2019. They were randomly divided into groups A (150 patients) and B (153 patients). Group A patients were followed actively at fixed intervals of time for ADRs till next six months through electronic conversation or personal interview. Group B patients were required to report spontaneously for any ADRs to pharmacovigilance centre. After data collection causality assessment was done using the WHO-UMC scale to identify false reporting and finally results were analysed statistically by means of the t-test using Minitab 14 software Pennsylvania, USA. **Results:** 153 ADRs were reported in active and 39 in passive group. Hence the yield of ADR was four times more in active method. After causality assessment, 31 in group A and 12 in group B were found to be falsely related (unlikely) to antitubercular drugs. Two sample t-test revealed active method reported more false ADR (p = 0.005). **Conclusion:** Although active method of surveillance identifies more ADRs than passive method, it is also more prone to false reporting. Hence its benefits should be weighed against its cost before adopting it for countries with limited resources.

Keywords: Adverse drug reaction; Adverse drug reaction reporting systems; Tuberculosis; Pharmacovigilance

INTRODUCTION

Adverse Drug Reactions (ADRs) are inevitable part of drug administration. They account for 5% of all hospital admissions, occur in 10-20% of hospitalised patients and are the fourth leading cause of death [1]. To collect and analyse the ADRs of all drugs across the world, a pharmacovigilance programme (also known as drug safety monitoring abbreviated as DSM or drug surveillance) was started in 1968 [2]. Pharmacovigilance is defined by the World Health Organisation (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" [3].

WHO identifies two main approaches to pharmacovigilance: passive (spontaneous) surveillance and active (intensive) surveillance [4]. Most of the countries including India usually follow the passive (spontaneous) method of reporting ADR, though, some developed nations like Australia, The Netherlands, Cambodia have well organised active system for drug safety monitoring also using the claims, electronic health records, pharmacy benefits manager, registry, medical records, practitioner-generated data and questionnaire based e-tools [5][6][7]. In spontaneous method, ADR reporting is done by health care workers or patients themselves to the pharmacovigilance centre (also known as ADR Monitoring Centre). This method covers a larger population and is useful for hypothesis generation, signal detection and for rare diseases but is often targeted for its under-reporting, the Weber effect (maximum

ADRs are reported in first two years of launch of a medicine and then keeps on decreasing) [8][9][10].

On the other hand, in active surveillance method, investigator does not wait for the patients or healthcare facility itself to report ADRs. Rather, they themselves take the initiative to find them in a pre-organised manner. Active surveillance is promoted for early detection of ADRs and signals [11][12]. Government of India has also initiated active DSM in 2015 for second line and newer drugs used in multi drug resistant (MDR) and extremely drug resistant (XDR) cases of tuberculosis (TB) but there are still negligible data regarding comparison of these two methods of ADR surveillance in terms of actual yield and false reporting [13].

The objective of the present research was to compare active and passive ADR reporting methods with special focus on false reporting rate in category I tubercular patients. TB was selected owing to high incidence of ADRs due to antituberculosis treatment (ATT) and importance of the disease to the country.

METHODS

It was a prospective, observational type of study conducted at Directly Observed Therapy Shortcourse (DOTS) centre and ADR Monitoring centre (AMC), also known as pharmacovigilance centre, attached to the Sawai Man Singh (SMS) Hospital, Jaipur from 1 January 2019 to 31 December 2019.

A total of 303 category I TB patients who were visiting DOTS centre for the first time for treatment of TB were enrolled into the study after their informed consent. Category I TB comprises newly diagnosed case of TB susceptible to first line antitubercular drugs, ie isoniazid, rifampicin, pyrazinamide, ethambutol. Category II TB patients, those on immunosuppressants, pregnant and lactating women were not included in the study. A total of 303 enrolled patients were randomly divided into two groups A (150) and B (153). If anyone proved to be resistant to any of the above four drugs during the study later on, he/she was excluded and a fresh recruitment was done untill the sample size of 150 in each group was achieved.

Group A (active surveillance) patients were monitored actively for adverse drug reactions. For it, they were interviewed personally through face-to-face meetings or by phone at predecided intervals of time (on days 3, 7, 15, 30, 90, 180) using a pre-validated structured questionnaire. WHO-endorsed ADR forms were then filled up using the collected ADR information.

Group B (passive surveillance) patients registered for receiving ATT were asked to report any adverse reactions either by themselves or through healthcare workers (HCW) to pharmacovigilance centre of the institute. For self-reporting a tollfree phone number was shared with them and a drop box was placed in DOTS centre.

The recruitment period was six months and data were collected for the next six months after ATT had been started in each patient, as ATT is given for six months in category I TB patients as per National Guidelines. The information collected was then analysed statistically by Chi-squared test and two sample t-test using the software Minitab 14 Pennsylvania, USA.

Institutional Ethical clearance was obtained via letter No 4123/MC/EC/2018 dated 9 October 2018.

Causality assessment and identification of false reporting

With the advancement in technology and growing sources of ADR reporting (even social media like Twitter, Facebook), a number of methods and algorithms for filtering entities to optimise ADR identification have been developed [14]. But as this study was constrained to single institute with limited ADRs, so WHO-UMC scale for causality assessment was followed for false reporting also. According to Varallo et al also, it is the most consistent way for use in hospitals, since it allows evaluating the quality of the report [15].

WHO-UMC system is basically a combined assessment taking into account the clinico-pharmacological aspects of the case, history and the quality of the documentation of the ADR. There are six WHO-UMC causality categories – certain, probable/likely, possible, unlikely, conditional/unclassified and unassessable/unclassifiable. Since by far the most frequent categories in case reports are 'possible' and 'probable', the usual approach is to choose one of these categories (depending on the impression of the assessor) and to test if the various criteria fit with the content of the case report for ADR. To see if that category is the right one or if it does again not seem to fit, the next adjacent term is tried. Those that fell into the category 'unlikely' were considered as falsely attributed to drug(s) being used [16].

RESULTS

Characteristics of the patients included in active and passive study groups are shown in Table 1.

Table 1. *Characteristics of the patients in active and passive study groups*

Characteristics	Active (150)	Passive (153)
Mean age (years)	29	31
Male	96	91
Female	54	62
Pulmonary TB	126	128
Extrapulmonary TB	24	25
Education – high level and above	113	101
Associated comorbidities		
HIV	3	3
Diabetes mellitus	10	10
Addiction – smoking/alcoholism	16	16

Chi-squared test applied for the characteristics between two groups gave p value of 0.990 showing no significant difference between the study groups.

A total of 192 ADRs were reported from 303 patients in this study. When the ADRs collected by active and passive surveillance method separately were compared, it revealed that the ratio of ADR detection was 4:1 in active verses passive ADR surveillance group. By active method, a total of 153 ADRs were reported and 39 ADRs were collected by passive reporting. On causality assessment of the reports, it was seen that out of them 31 and 12 were falsely attributed to ATT by active and passive methods, respectively (Table 2).

These falsely reported ADRs were either not in timeline with intake of drug or other diseases/drugs provided plausible explanations.

Table 2. *Distribution of false positive ADRs in active and passive methods*

ADR	Active	Passive
Nausea, vomiting	2	2
GI upset	4	2
Abdominal pain	2	1
Jaundice	1	0
Skin rash	3	1
Pruritus	4	1
Flushing	2	1
Paraesthesia	2	0
Numbness	0	0
Visual toxicity	2	0
Mental disturbances	3	2
Loss of Diabetes control	1	-
Arthritis	1	0
Decrease urine	0	0
Others – fever, shock, acne, vertigo, dyspnoea	4	2

Statistical analysis and interpretation

Initially normality of the data distribution was checked by probability plots before applying the t-test. As almost all the points lied within the 95% confidence interval, it was inferred that the study population in both the groups was following the normal distribution (Figure 1).

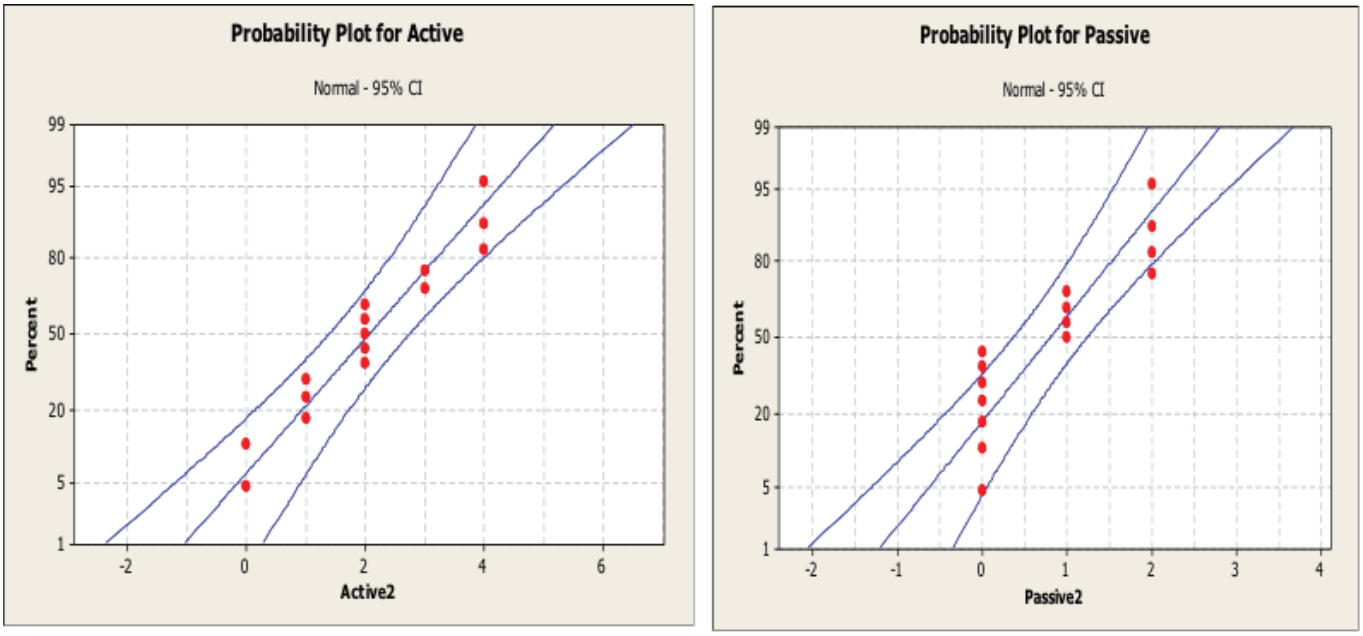

Figure 1.
Normality check of the data distribution for active and passive surveillance

Then the two-sample t-test was applied for statistical comparison of false reporting rate between the active and passive methods (Table 3). To apply the t-test it was assumed that null hypothesis (H_0) was true and hence there was no difference between them.

Table 3. *Two-sample t-test and confidence interval (CI) for false ADRs in active and passive method*

	N	Mean	SD	SE
Active	15	2.07	1.33	0.34
Passive	15	0.80	0.86	0.22

95% CI for difference: (0.41, 2.11); t = 3.09; p = 0.005;
N = number of variables; SD = standard deviation; SE = standard error of means

Since this p value was less than 0.05 (level of significance in the study) so the null hypothesis was rejected and it was concluded that there was a significant difference of false reporting rate between the methods. As the mean, standard deviation, standard error of mean (SE) mean values were higher for active method, it means high incidence of false reporting in active in comparison to passive method.

DISCUSSION

Isoniazid, rifampicin, pyrazinamide, ethambutol are the first line anti-TB drugs given in all category I TB patients and some category II TB patients depending on susceptibility. Anti-TB drugs are documented to have high incidences of ADRs, next to chemotherapy and antiretroviral drugs [17]. The most common ADRs induced by first-line anti-TB drugs are hepatotoxicity, gastrointestinal disorders, allergic reactions, arthralgias, neurological disorders etc. In this study, active surveillance and spontaneous reporting for ADR contributed 80% and 20% of total ADRs, respectively. Similar study by Tandon et al reported 66.13% versus 33.86% of the total ADRs [18]. Many other studies have also shown that that active surveillance pro-

grams detected additional ADRs compared to those of spontaneous reporting programs. They noted not only causative drugs, clinical features also varied in two methods [18][19][20].

In the present study, after causality assessment, 22.3% of ADRs were found to be falsely attributed to ATT with 72.1% and 27.9% from active and passive reporting methods, respectively. Statistical analysis confirmed that active method is prone to false reporting of ADR (p = 0.005). These findings are in concordance to the study by Berry et al that for level of specificity, the decreasing order for the three ADR reporting methods was voluntary reports (passive), pharmacist screening of medication orders and pharmacist screening of laboratory reports (active); with the differences among all three methods being significant [21]. Tandon et al also raised the concern of false reporting if it is made mandatory for HCW and thus compromising the quality of reports [18].

The main purpose of the study presented in this paper was to investigate the potential of a surveillance system for yield and false reporting and not to evaluate the drug reactions reported. Presented findings are akin to those by Lynn et al who also found that although two systems are clearly different, they could complement each other [22]. If an active reporting system is to be used in routine for ADR collection, it will be necessary to improve ADR ascertainment and decrease false reporting.

STRENGTHS OF THE STUDY

This is the first data-based study to compare active and passive methods in terms of yield and false reporting.

LIMITATIONS OF THE STUDY

The study was restricted to a particular disease in a single institution.

CONCLUSION

Active surveillance for ADRs definitely increases the yield in comparison to passive spontaneous reporting but at the same time chances of false reporting are also significantly higher in it.

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Conflict of interest

None.

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