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A Pharmacovigilance Study Using Tracer Techniques

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Abstract

Objective: To identify adverse drug reactions by using a comprehensive trigger tool method. To categorize the identified adverse drug reactions based upon their Probability, Severity, Harm and Preventability by using different scales.

Methods: A single-center, Cross-sectional, observational study based on medication and laboratory trigger tool methodology was conducted over a period of six months. The World Health Organization definition of adverse drug reactions was adopted. A list of 17 triggers were used to trace the adverse drug reactions which were then analyzed to assess the causality by using Naranjo's scale, severity by Hartwig and Siegel scale, and harm by the National Coordinating Council for Medication Error Reporting and Preventing Index and preventability by Modified Schumock and Thornton scale.

Results: A total of 100 suspected ADRs were collected and analyzed. The drug classes most commonly implicated with ADRs were cephalosporins (25%) followed by anti-diabetic agents (19%). According to Naranjo's scale, the reactions were categorized as probable (80%), possible (10%) and definite (5%). According to the modified Schumock and Thornton preventability scale, 20 cases (20%) were possibly preventable while 80 cases (80%) were not preventable. In 85 cases (85%) the suspected drug was withdrawn while in 10 cases (10%) no change in dose was made and in 5 cases (5%) the dose was altered.

Conclusion: Pharmacovigilance using tracer techniques significantly increases the identification and reporting of ADRs. The tracer technique is relatively simple, sensitive, less expensive and largely effective compared to traditional methods. The Trigger tool provides an additional instrument in improving patient safety. This technique leads to an increase in awareness and reporting of ADRs and provide opportunities for the health care system to review drug selection and prescribing practices affecting patient outcomes.

Keywords: Adverse drug reactions; Tracer techniques; Triggers; Naranjo's scale; Pharmacovigilance

Introduction

The advent of newer medicines has changed the way in which diseases are managed. Despite their benefits, mounting evidence suggests that drug related Adverse Drug Reactions (ADRs) are common, yet often preventable, cause of illness, disability, death and add to the overall healthcare cost [1]. Early detection, evaluation and monitoring of ADRs are essential to reduce harm to patients and thereby improving public health [2].

The detection of ADRs has become increasingly significant because of the introduction of a large number of newer medicines in the last two or three decades. World Health Organization (WHO) has intervened seriously in this regard and established an international ADR monitoring center at Uppsala, Sweden, which is collaborating with National monitoring centers in around 70 countries [3]. Adverse events occur in nearly one in ten hospitalizations with drug-related adverse events accounting for 15% of these [4].

Assessing the actual safety of drug use has been historically difficult, mainly because traditional methods such as chart audits and voluntary reporting of data which have been shown to be expensive, time consuming, insensitive, and largely ineffective for detecting drug related ADRs. Computerized methods for detecting ADRs, employing "tracer drugs or triggers" in a patient's medical record, are effective and relatively inexpensive [5]. A trigger tool is a simple checklist pro-forma containing a selected number of clinical 'triggers' which a reviewer looks to identify while screening electronic medical records. "Triggers or Tracer drugs" are defined as easily identifiable flags, occurrences or prompts in patient records that alert reviewers to potential adverse events which were previously undetected. The trigger tool methodology is a prospective and retrospective review of a random sample of patient records using triggers to identify possible adverse events associated with patient care. Trigger tools provide clues that an ADR has occurred. It focuses on detecting, quantifying and tracking adverse outcomes over time. The methodology is related to actual clinical injury. It can be used in all clinical environments to detect multiple types of Adverse Drug Event (ADE) [6].

Medication-related harm can be detected using a trigger tool methodology towards an adverse drug event. Medication-related triggers include the sudden withdrawal of a medication, a prescription for an antidote, or an abnormal laboratory test value [5]. Detecting

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ADEs using 'triggers' from a patient's medical record was first described in the 1970s, and has been shown to be a practical and less labour-intensive approach for identifying ADEs than the traditional extensive retrospective case note review [7,8].

Classen et al. described the use of electronic ADE monitoring using computer database developed in hospital information systems in the early 1990s. While this methodology highlighted a faster method of screening for ADEs in a way that could be used to prevent patient harm rather than voluntary reporting of medical records review, it was deemed to require expensive investment and expertise in such technology [9,10]. The Institute of Healthcare Improvement (IHI) simplified the manual medical record review process and developed the Global Trigger Tool (GTT) consisting of 19 triggers in order to monitor adverse events rates in a way that was easy to replicate in hospitals, with or without computerized records [11]. The methodology cannot capture every adverse event, as it uses the periodic review of small, randomly selected samples of case notes and therefore is more of a surveillance tool. This regular review of notes is meant to take place alongside focused safety and quality improvement activities, with serial measurements of adverse event rates as a guide to their effectiveness.

The objectives of the study include to utilize the tracer methodologies in identifying the ADRs and to categorize the detected ADRs based on probability, severity, Harm and Preventability by using different scales.

There are quite a few studies conducted in India regarding the incidence, monitoring and reporting of ADRs in different departments and settings. But there are no published data regarding the use of triggers to identify ADRs. This is a first of its kind at our institution and will help us to provide insight into the prevalence of ADRs.This will also highlight the tool which could be used by the pharmacists to improve the identification of ADRs and thus their reporting.

Methods

A single-center, cross-sectional and observational drug safety study was conducted for a period of six months between March to August 2013 at a 630 bed tertiary care hospital. The study was initiated after the approval of the study protocol by the Institutional Ethics Committee (IEC) (Protocol No: SVCP/05/2013).

The study involved an active surveillance medication and laboratory module trigger tool methodology adapted from the IHI Global trigger tools and tools used by Rozich et al. [5]. A list of 17 triggers (Appendix-A), were used to trace the ADRs. Some triggers were removed from IHI list as they were either not used or available in our setting. Four new lab triggers were added in our study, which were identified as a potentially valuable trigger.

Data were collected in a questionnaire designed to include all relevant data for the study. Data on patient demographics, medical history, suspected drugs, ADRs, laboratory data were collected from the medical charts, nursing notes and medical records department. Inpatients of both sexes and all age groups who developed an ADR were included in the study; and patients treated on an outpatient basis or cancer patients or who developed an ADR to due to poisoning or administration of fresh blood/blood products were excluded from the study.

During the six month period, all the patient medical charts were reviewed for the presence of triggers. About 300 patient records were found to have the required triggers out of which 200 cases had to be excluded because no ADRs observed in those cases and the triggers were used for various other indications. If a suspected ADR was reported and met the inclusion and exclusion criteria, data on that particular suspected drug and reaction was collected and documented.

All the investigators were trained to detect ADRs using the trigger tool methodology. The charts were reviewed daily. Each suspected ADR was assessed by all the investigators and approved by the Clinical Pharmacologist. The severity of the ADEs was evaluated using Hartwig and Siegel's scale. Harm was assessed by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Index, which categorizes harm into E-I that correlates with the actual occurrence of harm to patients. The investigators also determined if hospital acquired ADEs could be preventable or not preventable using Modified Schumock and Thornton preventability scale.

Data was made anonymous and extracted into Excel® for analysis. Descriptive statistics were used to report the results. The Positive Predictive Value (PPV) for each trigger was calculated as the no. of ADRs identified with the Trigger/no. of Triggers found was generated.

Results

In this study, 100 triggers were identified and were found to be associated with ADRs. A total of 15,500 patients were admitted to the hospital during the study period. So the prevalence of ADRs in the institution over a period of six months is 0.64%. About 66% of the patients affected with ADRs were males and 54% were adults. The majority of the patients who developed an ADR were receiving anywhere between 6-10 medications. The demographic characteristics of patients are summarized in the Table 1.

Out of the 17 selected trigger tools, only 7 were identified during our study. The rest were not traced and hence no ADRs reported. The system most commonly affected by an ADR was the dermatology (56%) followed by the endocrine (19%). The PPV of the 7 triggers ranged from 0.17 to 0.65. Three triggers had PPVs at 0.33 or higher (Antihistamines, C difficile positive stool and INR>6). The trigger, PPV, suspected reactions and the systems involved are shown in the Table 2.

The drug class most commonly implicated with ADRs was antibiotics (56%) followed by insulin's (19%). The drug class least implicated were analgesics (1%).

The drugs most commonly implicated with ADRs were cephalosporins (25%) followed by insulins (19%) and penicillins (15%). The results of the drugs implicating ADRs were summarized in Table 3.

The majority of the reactions were type A (80%) followed by type B (10%). The results are summarized in the Figure 1.

Based upon the Naranjo's causality assessment scale, the ADRs were categorized as probable (85%), possible (10%) and definite (5%). According to the modified Hartwig and Siegel's severity assessment scale, the majority of the reactions were moderate (95%) followed

Demographics	No. Of Cases n=100
1. Age	
Paediatrics (<18 years)	6
Adults (18-60 years)	54
Geriatrics (>60 years)	40
2. Sex	
Male	66
Female	34

Table 1: Demographic characteristics.

Trigger Tools	Suspected reaction	Organ systems affected	No. of Triggers found on charts	No. of ADRs (n=100)	PPV
Antihistamines	Drug rashes	Dermatology	86	56	0.65
25% dextrose	Hypoglycemia	Endocrine	108	19	0.17
Calcium Gluconate, Insulin+ 25% dextrose Sodium polystyrene	Hyperkalemia	Systemic	47	12	0.25
Steroids	Hypersensitivity	Immune system	30	6	0.2
Vitamin K INR>6	Warfarin overdose, bleeding	Haematology	20 3	4 1	0.2 0.33
Clostridium difficile positive stool	Antibiotic induced diarrhea	Gastrointestinal	6	2	0.33

PPV=No. of ADRs identified with the Trigger/No. of Trigger found

Table 2: Trigger tools.

Drug class	Medicines	No. of ADR Reports n=100, (%)
1. Antibiotics: Cephalosporins	Cefoperazone Cefuroxime Ceftriaxone Cefotaxime	**25 (25%)**
Penicillins	Amoxicillin Ampicillin Piperacillin Ticarcillin	15 (15%)
Fluoro-quinolones	Ciprofloxacin Levofloxacin Ofloxacin	9 (9%)
Amino-glycosides	Amikacin	4 (4%)
Anti-Fungal	Ketoconazole Fluconazole	4 (4%)
Tetracyclines	Doxycycline	3 (3%)
Carbapenems	Meropenem Ertapenem	2 (2%)
Miscellaneous Antibiotics	Vancomycin	2 (2%)
Sulfonamides	Co-trimaxozole	1 (1%)
Anti-Amoebic	Metronidazole	1 (1%)
2. Insulins		19 (19%)
3. Anticoagulants	Warfarin Acenocoumarin	5 (5%)
4. Anti-Hypertensives	Telmisartan Lisinopril Losartan	3 (3%)
5. Skeletal Muscle Relaxants	Succinylcholine	3 (3%)
6. Immuno-suppressants	Cyclosporine Tacrolimus	2 (2%)
7. Analgesics	Diclofenac + Paracetamol	1 (1%)
8. Hormones and Contraceptives	Medoxyprogestrone	1 (1%)

Table 3: Medications Implicated in ADRs.

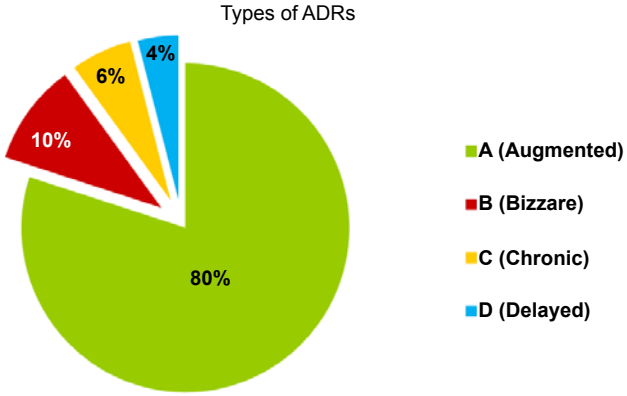

Figure 1: Classification of ADRs.

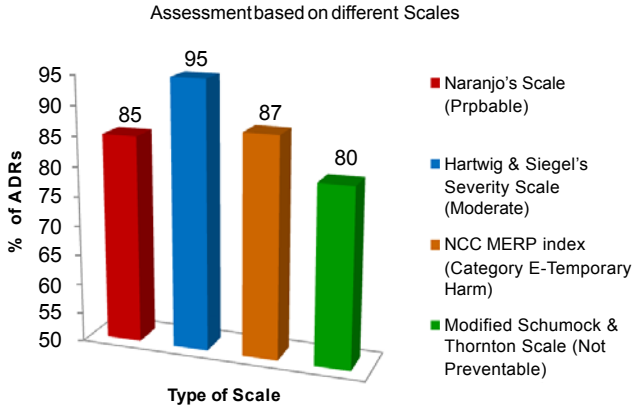

Figure 2: Assessment of ADRs based on different scales.

by severe (5%). Although some of the reactions were mild, patients received antidotes for the reactions as a routine practice in the hospital. According to the National Coordinating Council for Medication Error Reporting and Preventing (NCC MERP) index harm, 87% of the reactions fall under E category i.e., only temporary harm occurred to the patient and required intervention. According to the modified Schumock and Thornton preventability scale, 80% of the ADRs were not preventable. The management of the reported ADRs varied greatly. This study showed that most of the offending antibiotic class of drugs was withdrawn. As an outcome of the management, all the patients are recovered. The results are summarized in the Table 4.

While comparing with different ADR scales, we found that Naranjo's probability scale showing 85% of the reactions were probable, Hartwig and Siegel severity scale showing 95% of the ADRs were moderate, NCC MERP index harm category showing 87% of the reactions as a category E (temporary harm which requires intervention), and Modified Schumock andThornton preventability scale showing 80% of the ADRs were not preventable. The results are summarized in Figure 2.

Discussion

Numerous studies reported that approximately 5% to 15% of all hospital admissions are caused by ADRs and as many as 28% of the hospitalized patients experienced an ADR during their hospital stay. Under-reporting by doctors is a well known fact, even in countries with well established ADR reporting and monitoring programs. In India, the

Causality		
Score	**Naranjo's scale**	**No. of ADR Reports n=100, (%)**
≥ 9	Definite	5 (5%)
5-8	Probable	85 (85%)
1-4	Possible	10 (10%)
<1	Doubtful	0 (0%)
Severity		
Level	**Hartwig and Siegel's scale**	**No. of ADR Reports n=100, (%)**
1, 2	Mild	0 (0%)
3, 4, 5	Moderate	95 (95%)
6, 7	Severe	5 (5%)
NCC MERP Index		
Harm	**Category**	**No. of ADR Reports n=100, (%)**
E	Temporary harm and requires intervention	87 (87%)
F	Temporary harm and requires hospitalization	13 (13%)
G	Permanent harm	0 (0%)
H	Intervention required to sustain life	0 (0%)
I	Patient death	0 (0%)
Preventability		
Modified Schumock and Thornton Scale		**No. of Cases n=100, (%)**
Definitely Preventable		0 (0%)
Probably Preventable		20 (20%)
Not Preventable		80 (80%)
Management		
Management of ADR		**No. of cases n=100, (%)**
Drug withdrawn		85 (85%)
No change in dose		10 (10%)
Dose altered		5 (5%)
Outcomes		
Category		**No. of ADR Reports n=100, (%)**
Fatal		0 (0%)
Continuing		0 (0%)
Recovering		0 (0%)
Recovered		100 (100%)
Unknown		0 (0%)

Table 4: Assessment of ADRs.

major problem is a lack of a proper system of Pharmacovigilance which has led to a lack of decreased awareness of ADRs and their importance in early detection and prevention.

The reason for an increase in the detection of ADRs was due to the use of a trigger tool reporting system.

Literature surveys have shown that ADRs were common in geriatric and paediatric populations. But in our small study population adults were more prone to ADRs compared to other age groups. This may be due to the fact that most patients who were admitted to the hospital were adults. Another possible reason could be within the adult age group, most reported cases were from the patients who were ≥ 45 years old that those who were aged ≤ 44 years. Higher number of ADRs in the adult and geriatric population are due to the risk factors like co-morbid conditions, polypharmacy, drug interactions, impaired renal and hepatic function and altered physiological effect of the drugs have attributed to this variation.

Out of the 17 selected trigger tools, only 7 were identified ADRs in our study and the majority were antihistamines and the least commonly found were INR>6. Among other identified trigger tools were 25% dextrose, sodium polystyrene, steroids, vitamin K. Naessens et al. showed anti-emetic trigger tool has the maximum probability followed by diphenhydramine and vitamin K [12]. Ganachari et al. reported abrupt medication stoppage as the maximum probability followed by hypotension [6]. The difference in above mentioned findings may be due to the variability in trigger tool usage.

The maximum number of suspected reactions was allergic rash due to antibiotics and least were diarrhoea induced by antibiotics. These findings were consistent with the study carried out by Palanisamy et al. which reported skin rash was the most commonly identified ADR followed by nausea and vomiting [13].

Antibiotics were found to be the most common class of drugs for ADRs. Among antibiotics, ADRs were maximum with cephalosporins followed by penicillins, fluoroquinolones and aminoglycosides. Our findings are consistent with the study carried out by Krishna et al. However, they reported fluoroquinolones followed by cephalosporins and aminoglycosides as common offenders [14] .This difference may be due to the higher number of cephalosporin prescriptions compared to fluoroquinolones in our study site.

PPVs of the triggers were highly variable. Many PPVs were in the lower range.

According to the type of reactions occurred, the majority were type A followed by type B. This result is consistent with the study carried out by Mandavi et al. [15]. There are no published reports showing prevalence of type C and D reactions.

Based on the Naranjo's causality assessment scale the ADRs were maximum in the category of probable followed by possible and definite. No ADRs were found in doubtful class.

As per the modified Hartwig and Siegel's scale maximum number of ADRs of moderate category was observed in our study. These findings were consistent with the literature reported by Ganachari et al. and Singh et al. [6,16].

As per the NCC MERP index harm category, the majority of the reactions were under the E category i.e., Temporary harm to the patient and requires intervention followed by F category i.e., Temporary harm to the patient and requires hospitalization. As per the Modified Schumock and Thornton preventability scale, maximum number of ADR were in not preventable category followed by probably preventable.

For better patient outcomes ADRs were managed with appropriate interventions and patients recovered. In our study, we found offending drug was withdrawn in the majority of cases followed by no change in dose and alteration of drug dose.

Limitations

In this study, the prevalence of ADRs was less when compared to other healthcare centers which could be due to its relative short duration and also since the hospital selected for our study is known for its highly developed patient safety programs. Thus, the findings cannot be generalized to other centers. As this was a pilot study evaluation of the performance of the trigger tool was not done. An improvement in the patient outcomes before and after the implementation of the trigger tool was not examined.

Conclusion

Adverse drug reactions are inevitable risk factors associated with the use of medicines. The present work is the maiden Pharmacovigilance study using tracer drugs conducted in the institution. It has provided baseline information about the prevalence of ADRs and their distribution among different age groups, genders, organ systems affected, therapeutic classes of medicines, and usage of trigger tools list. As the reporting of ADRs are very poor in the country and in the institution as well these trigger tools will help the clinical pharmacists to improve the identification and thus reporting the ADRs which will improve patient safety. The present study highlights the role of clinical pharmacists in Pharmacovigilance program.

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