Suspected Adverse Drug Reactions of Selected Newly Introduced Medicines in Ambulatory Patients

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ABSTRACT

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Each year, drug regulatory authority permits pharmaceutical companies to market hundreds of new medicines. During clinical trials, due to less number of study subjects, only commonly observed adverse drug reactions (ADRs) are reported. However in post marketing phase, more ADRs are observed due to various predisposing factors. Spontaneous reporting method is considered to be easy, economical and more reliable method to detect more number of ADRs. As research studies have corroborated the high incidence rate of ADRs in ambulatory patients, community pharmacists (CPs) can play an important role in monitoring and reporting suspected ADRs. The present prospective study was focussed to study adverse drug reactions (ADRs) of newly introduced medicines in ambulatory patients through community pharmacists. The selected community pharmacists were trained about monitoring and reporting of ADRs to the selected newly introduced medicines. Collected ADRs reports were assessed for causality, severity and preventability. Fourteen trained community pharmacists reported 63 ADRs in 4 months period. Twenty two ADRs were observed with pregabalin (34.92%) followed by voglibose 18 (28.57%), torsemide 09 (14.28%), doxofylline 05 (7.93%), zonisamide 03 (4.76%), moxonidine 02 (3.17%), rupatidine 02 (3.17%), simvastatin 02 (3.17%). The common adverse effects observed were dry mouth, constipation, dizziness and the main organ system affected was gastrointestinal system with 31 ADRs. Most of the reactions were predictable (95.23%) and moderate in their severity level (22.22%). Reporting of ADRs occurred in ambulatory patients to newly introduced medicines in community pharmacies will help to know the safety information about the medicines.

Keywords: Community pharmacists, Adverse Drug Reactions, Newly introduced medicines, Ambulatory patients.

INTRODUCTION

Medicines are being used since ages due to their ability to alter the pathophysiology of the diseases and relieve the signs and symptoms in sufferers. In the process of modifying the disease process, due to various predisposing factors, medicines may leave some unpleasant effects called as adverse drug reactions.[1]

The consequences of adverse drug reactions include morbidity, mortality and huge financial burden. Studies have shown that the cost related due to ADR induced morbidity and mortality accounts about $136 billion annually.[2] In Indian currency, the average cost to treat one ADR was found as Rs. 650 –Rs.3500.[3]

Studies have shown that the average incidence rate of Adverse Drug Reactions in hospitalised patients is 6.7% (range 1.2 to 20.1%) with fatal ADRs of 0.36%.[4, 5] Meta-analysis of the studies suggest that more than 1 million Americans were hospitalized due to adverse drug events, accounting 4.7 per cent of all hospital admission in 1994.[6] A cohort study assessed the ADR incidence rate in ambulatory patients as 25%.[7] In post marketing surveillance studies, signal generation of any suspected ADR is the basic requirement for spontaneous reporting and is the first step in the process of identification and characterization of new ADRs [8]. Drug safety information to health care professionals will enable them to use the medicines prudently in their patients and minimizes medication related health hazards. Many research studies have appreciated the role of community pharmacists in pharmacovigilance activity.[9,10] In Netherlands, community pharmacists contribute highest percentage of reports (40%) to Lareb, the official Pharmacovigilance center of the Netherlands.[11] In a small country like, Cuba, the community pharmacists play significant role in ADR reporting.[12] Considering their professional interaction with the patients, the present study was designed in ambulatory setting to study the types of ADRs for newly introduced medicines involving the community pharmacists.

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MATERIALS AND METHODS

This study was a prospective study conducted in Mysore involving selected trained community pharmacists and institutional ethical committee has approved the study.

A list of newly introduced medicines was prepared considering the medicines approved by Drugs Control

General of India (DCGI) in the last five years. A survey was conducted randomly in selected community pharmacies of Mysore city to assess the frequency of usage of the identified medicines in these selected pharmacies. Based on availability and frequency of sales a final ten medicines were identified.

With the help of regulatory authorities in Mysore, an invitation letter containing the information about the study, role of pharmacist in pharmacovigilance activity and an invitation to participate in the study with informed consent form (ICF) was sent to the owner cum practicing community pharmacists. Upon receipt of the reply, number of community pharmacists was short listed and trained suitably for the purpose of the study. A suitably designed data collection form was used to collect demographic details of the patients with the known history of drug allergies, provisional diagnosis, present medication history, description of the suspected advrse drug reaction, date of onset of the reaction, and the suspected drug. To motivate the trained pharmacists to report ADRs, a thank you note was given when ever a report was submitted and frequent telephone calls were also made to the pharmacists complimented with the personal visits.

WHO Probability scale and Naranjo's Probability scale were applied to assess the causality, Modified Hartwig and Siegel ADR Severity Assessment Scale was used to assess the reaction severity and Modified Shumock and Thronton scale was used to assess the preventability of the suspected adverse drug reaction. The assessed ADR data of suspected reaction was entered in to the ADR documentation form for future reference. A computerized data base was created using Microsoft Access software, to record all the information in the patient profile form, ADR notification form and ADR documentation form.

RESULTS:

Based on the available data sources of DCGI new drugs introduced in the last five years 10 new drugs were short listed. The drugs selected for the study are presented in table 1.

Demographic characteristics of Patients experienced the ADRs

A total of 63 ADRs were reported by the pharmacists from 34 patients. Male predominance [20 (58.82%)] was observed over female patients [14 (41.17%)]. The demographic details of the patients are summarized in table 2.

Predisposing factors for reported ADRs

Predisposing factors for reported adverse drug reactions were analyzed. Intercurrent diseases [31 (49.20%)] multiple drug therapy [12 (42.85%)], and age [05 (7.93%)] are major predisposing factors responsible for ADRs. The predisposing factors contributing ADRs are summarized in figure 1.

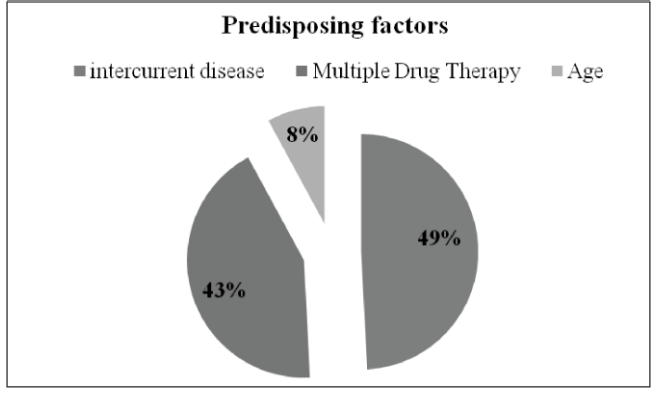
Table 1: List of Newly Introduced Medicines Selected for the study

Sl No.	Selected Newly Introduced Medicines	Source
1	Voglibose	DCGI
2	Pregabalin	DCGI
3	Doxofylline	DCGI
4	Zonisamide	DCGI
5	Simvastatin	DCGI
6	Eplerenone	DCGI,
7	Rupatidine	DCGI
8	Moxonidine	DCGI
9	Olmesartan	DCGI
10	Torsemide	DCGI

Table 2: The demographic details of the patients experienced ADRs.

Demographic characteristics	Number of the Patients (N=34)	Percentage.
Sex		
Male	20	58.82
Female	14	41.17
Age		
21-30	02	5.88
31-40	03	8.82
41-50	07	20.58
51-60	04	11.76
61-70	14	41.17
71-80	02	5.88
81-90	02	5.88

Fig.1: Predisposing factors for ADRs



Systems associated with reported ADRs

The systems most commonly affected by ADRs was the gastrointestinal system [31 ADRs (49.20%)], central nervous system [16 ADRs (25.39%)], musculoskeletal system [5 ADRs (7.93%)], respiratory system [2 (ADRs 3.17%)] and others [9 ADRs (14.28%)].

Number of ADRs reported for individual drugs

During the study period, more number (22 ADRs) of ADRs were observed with pregabalin followed by voglibose, (18 ADRs (28.57%)), Torsemide (09 ADRs (14.28%)), doxofylline (05 ADRs (7.93%)), Zonisamide (03 ADRs (4.76%)), Moxonidine (02 ADRs (3.17%)), Rupatidine (02 ADRs (3.17%)), and Simvastatin (02 ADRs (3.17%)).

Commonly reported adverse drug reactions with the selected medicines

The commonly reported ADR in our study was dry mouth (12.69%), constipation (9.52%), dizziness (6.34%), flatulence (6.34%) and the details of other ADRs are presented in table 3

Causality assessment of the reported ADRs

Causality assessment of the reported ADRs as per WHO Probability scale, majority of the ADRs were found as 'possible' [35 (55.55%)] followed by 'probable' [23 (36.50%)] and Unassessable/ unclassifiable [5 (7.93%)].

As per Naranjo's scale, majority ADRs were found 'probable' [33 (52.38%)] followed by 'possible' [30 (47.61%)]. Causality assessment details of the reported ADRs are given in table 4.

Severity of reported ADRs

Severity level of the reported ADRs was analyzed. Out of 63 ADR reports, 49 reports (77.77%) were found 'moderate' in their severity and 14 (22.22%) reports were found mild in nature. The severity of the reported ADRs is presented in figure 2.

Predictability of the reported ADRs

Of the total 63 ADRs, 60 (95.23%) reactions were predictable and 03 ADRs (4.76%) were not predictable. The predictability of reported ADRs is presented in figure 3.

Preventability of reported ADRs

The Modified Shumock and Thornton scale was used to assess the preventability of ADRs. Among the reported ADRs, 62 ADRs (98.42%) was not preventable and only 1 (1.58%) ADR was found preventable.

Table 3: List of commonly reported adverse drug reactions of selected new medicines

Description of reactions	Number of reactions (N=63)
Dry Mouth	08 (12.69%)
Constipation	06 (9.52%)
Dizziness	04 (6.34%
Flatulence	04 (6.34%
Drowsiness	03 (4.76%)
Headache	03 (4.76%)
Peripheral edema	03 (4.76%)
Weakness	03 (4.76%)
Abdominal Pain	02 (3.17%)
Blurring of vision	02 (3.17%)
Diarrhea	02 (3/17%)
Fatigue	02 (3.17%)
Gastric irritation	02 (3.17%)
Increased frequency of cough	02 (3.17%)
Nausea	02 (3.17%)
Tremors	02 (3.17%)
Abdominal Bloating	01 (1.58%)
Abdominal disturbances	01 (1.58%)
abdominal fullness	01 (1.58%)
Abdominal pain with gastritis	01 (1.58%)
Ataxia	01 (1.58%)
Co-Ordination Problem	01 (1.58%)
Irritability	01 (1.58%)
Memory loss	01 (1.58%)
Slurred Speech	01 (1.58%)
Somnolence	01 (1.58%)
Speech disorder	01 (1.58%)
Stomach upset	01 (1.58%)
Taste sense altered	01 (1.58%)

Fig. 2: Level of severity of reported ADRs

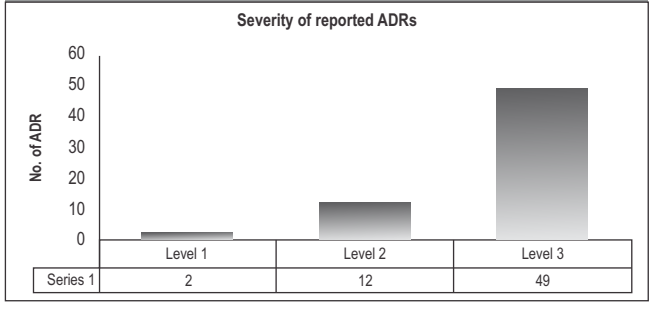


Fig. 3: Predictability of reported ADRs

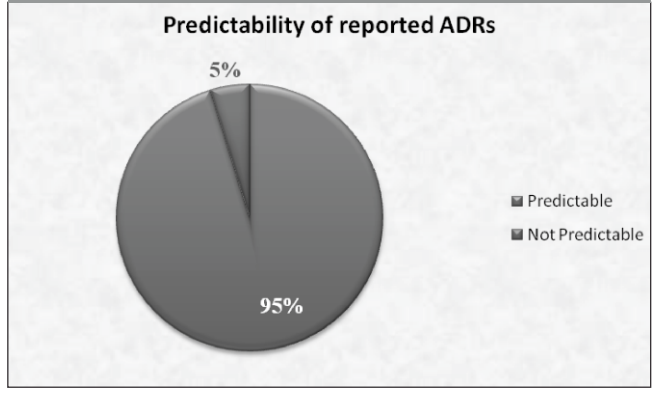


Table 4: Causality assessment of reported ADRs

Causality assessment Scale	Certain/ Definite	Probable	Possible	Unassessable/ Unclassifiable	Unlikely	Conditional/ Unclassified
WHO Probability Scale	00 (00)	23 (36.50%)	35(55.55%)	05 (7.93%)	00 (00)	00(00)
Naranjo's algorithm	00(00)	33 (52.38%)	30 (47.61%)	00(00)	00(00)	00(00)

DISCUSSION

Present study was focused on assessing the ADRs for selected newly introduced medicines, which got approval from DCGI in the last five years. During clinical trials, around 5000 study subjects may get exposed to the test medicine. During the post marketing, patients with co-morbidities and poly pharmacy are exposed to the newly introduced medicine. Various predisposing factors may influence the incidence rate of ADRs for new medicine. Charecterisation of ADRs such as causality, severity and preventability may help in identifying the patient population vulnerable and strategies to prevent the ADRs. Due to poor reporting systems of ADRs both in hospital and primary care setting, majority adverse drug reactions go undetected. Since the research studies have revealed that, high incidence rate of ADRs in ambulatory patients, the present study was carried out in primary care setting. Patients in ambulatory care generally receive medicnes form local community pharmacies. If the community pharmacists are trained to monitor and report the suspected ADRs for the new the medicines in their patients, the data will be highly useful for regulatory authorities for continuation of the approval and health care professionals for rational prescribing.

Based on the safety data collected during post marketing surveillance studies, many approved molecules such as terfinadine, astemiozole, and rofecoxib were withdrawn from the market. FDA had approved Rofecoxib in 1999 for the management of acute pain, menstrual symptoms and osteoarthritis. However, due to incidents of increased deaths due to cardiovascular accidents in individuals using Rofecoxib, Merck & Co withdrawn the drug from the US and world market in 2004. [13,14]

In the present study, the trained community pharmacists have submitted 63 suspected ADR reports for selected newly introduced medicines from 34 patients. Out of 34 patients 20 were males and 14 were females. Several studies have shown that geriatric populations develop more ADRs when compared to adults.[4,5] In our study we observed that the age group between 61-70 developed more ADRs due to decreased physiological function and the metabolism of the drug.

Various literatures suggest that multiple drug therapy, intercurrent disease, age and sex are the predisposing factors for developing ADRs.[1] In our study, we observed that the intercurrent diseases [31 (49.20%)] is the major factor responsible for ADRs followed by multiple drug therapy [12 (42.85%)] and age [05 (7.93%)].

Among the reported ADRs, more number of ADR reports were due to Pregabalin [22 (34.92%)], followed by Voglibose [18 (28.57%)], Torsemide [09 (14.28%)], Doxofylline [05 (7.93%)], Zonisamide [03 (4.76%)], Moxonidine [02 (3.17%)], Rupatidine [02 (3.17%)] and Simvastatin [02 (3.17%)].

The descriptions of the reported adverse reactions are dry mouth, constipation, dizziness, flatulence, drowsiness, headache, peripheral edema, weakness, abdominal pain, blurring of vision, diarrhea, fatigue, gastric irritation, increased frequency of cough, nausea, tremors, abdominal bloating, abdominal disturbances, abdominal fullness, abdominal pain with gastritis, ataxia (unable to walk), co-ordination problem, irritability, memory loss, slurred speech, somnolence, speech disorder, stomach.

Causality assessment of ADR by WHO Probability scales and Naranjo's algorithm did not show much significant discrepancy. According to WHO Probability scale, most of the reactions belonged to the category 'possible' [35 (55.55%)] followed by probable [23 (36.50%)], Unassessable/ Unclassifiable [05 (7.93%)]. According to Naranjo's algorithm most of the reactions belong to the category 'probable' [33 (52.38%)], possible [30 (47.61%)].

The severity of the reported ADRs was analyzed by using Modified Hartwig Siegel ADR severity assessment scale. Out of 63 ADR reports, 49 reports were 'moderate' in their severity and 14 reports were minor in their severity.

The predictability of ADRs was done by using 'criteria for determining predictability of an ADR'. Among the reported 63 ADRs, 60 (95.23%) adverse drug reactions were predictable and 03 (4.76%) reactions were not predictable.

In our study, we used 'Modified Shumock and Thornton scale' to assess the preventability of ADRs. The majority of the ADRs [62 (98.42%)] were not preventable and only 1 (1.58%) ADR was found to be probably preventable. In a prospective cohort study conducted by Tejal K. Gandhi et al in Boston (involving two hospital and two community pharmacies) 25% of the ambulatory patients experienced ADEs and 13 % of ADRs were serious and 11% were preventable.[15]

Among the reported ADRs, one patient had experienced memory loss after using the Pregabalin. The literature review suggests that, Pregabalin can cause weight gain, dizziness, sleepiness, dry mouth, blurred vision, swelling of hands and feet, constipation however memory loss observed in this patient is new and not reported in Indian population and considered as a rare reaction.[16]

To monitor and report the suspected ADRs in ambulatory patients for the newly introduced medicines, patients were given counseling regarding their medication use and motivated them to report back to the pharmacist in case of any unpleasant effect experienced. This activity motivated the patients for self reporting of ADRs to community pharmacists. Pharmacists' attitudes also play vital role in collection of more reports. In studies conducted in Mysore and Nepal regarding adverse drug reaction reporting attitudes of the pharmacists, the intensive training and motivation plays vital in collection of ADRs.[17,18] The same phenomenon was also manifested in the present study.

CONCLUSION

In this present study, selected and trained community pharmacists has showed positive attitude towards reporting of adverse drug reactions to selected newly introduced medicines in ambulatory patients. Continuous motivation, through personal visits, phone calls and thank you notes have increased the ADR reporting. More number of ADRs were collected for pregabalin 22 (34.92%) including a rare ADR with pregabalin followed by voglibose 18 (28.57%), torsemide 09 (14.28%), doxofylline 05 (7.93%). During the study period good number of ADRs reports for newly introduced medicines was collected. The reporting of ADR to newly introduced medicines in community pharmacies will help to increase the safety information of medicines in ambulatory patients.

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