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RESEARCH ARTICLE

Study of Suspected Adverse Drug Reactions of Selected Recently Introduced Medicines in Davangere City

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ABSTRACT

The present prospective study was focused to study the suspected adverse drug reactions of selected recently introduced medicines in Davangere city. Before commencement of the study, ethical committee clearance was obtained from Institutional Ethics Committee. A list of ten recently introduced medicines were selected on the basis of availability and frequency of dispensing, was done by referring the official website of CDSCO. The study was conducted at a tertiary care teaching hospital and randomly selected community pharmacies and obtained the informed consent from patients. After the index visit, the patients were followed and observed for the suspected adverse drug reactions. A total of 36 ADRs were reported from 27 patients. Seven ADRs were observed with Pregabalin (19.44%) followed by Torsamide 6(16.67%), Olmesartan 5(13.89%), Febuxostat 4(11.11%), Voglibose 4(11.11%), Doxofylline 3(8.33%), Moxonidine 3(8.33%), Ivabradine 2(5.56%), Ilaprazole 1(2.78%), Tadalafil 1(2.78%). The most commonly reported ADR was headache 7 (19.44%) and the most common organ system affected was CNS 18(50%). Most of the reactions were 'Predictable' 35(97.22%) and all ADRs were 'Preventable'. Upon causality assessment of reported ADRs using WHO probability scale, majority of ADRs 22(61.11%) were rated as 'Possible'. ADR reporting of recently introduced medicines gives more safety information's about drugs both in-patient and out-patient departments, which enables the health care professionals to handle the medicines rationally.

KEYWORDS

Adverse Drug Reactions, Recently Introduced Medicines, Health Care Professionals

INTRODUCTION

According to World Health Organisation adverse drug reaction is defined as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiologic function".[1]

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Many studies have been carried out in several parts of the world on the incidence in hospitalised patients and of hospital admissions that result from adverse reactions and other drug related problems. It is estimated that adverse reactions cause 2-3% of consultations in general practice, up to 3% of admissions to intensive care units and 0.3% of general hospital admissions.[2] A prospective cohort study conducted by Tejal K.G et al. shown that the adverse drug reactions incidence rate in ambulatory patients is 25%.[3]

These adverse drug reactions are one of the major problems associated during the treatment and resulting in diminished health related quality of life. It is also associated with significant morbidity, mortality, permanent disability and leads to huge economic burden on patients due to prolonged hospitalizations and treatment for these reactions.[4]

In one Indian study conducted by Ramesh M, Pandit J, et al. found that, for to treat one adverse drug reaction 650- 3500 rupees is required.[5]

Now a day, the role of pharmacist is to promote development, maintenance and on-going evaluation of a programme to reduce the risk of adverse drug reactions through detecting, reporting and assessing any suspected adverse drug reaction.[6]

A serious adverse drug reaction leading to withdrawal from the market was detected for 1 of 5 medicines during post marketing surveillance in the past 25 years.[7] During clinical trial phase the drugs are exposed not more than 5,000 human subjects that too having so many inclusion and exclusion criteria's. So, it is very difficult to detect rare adverse drug reactions.[8]

The objectives of the study were:

1. To study the suspected adverse drug reaction of selected recently introduced medicines in Davangere city.
2. To analyse the reported adverse drug reactions for their causality, severity, predictability and preventability.

MATERIAL AND METHODS

The Institutional Ethical Committee of Bapuji Pharmacy College, Davangere has approved the study.

Study Site: This study was conducted at a tertiary care teaching hospital and randomly selected community pharmacies in Davangere city.

Study Design: Prospective, observational study.

Study Duration: The study was conducted for a period of six months.

Study Criteria: The patients were selected and assessed for the development of suspected adverse drug reaction by following the inclusion and exclusion criteria

Inclusion Criteria: Adult patients who had received selected recently introduced medicines in in-patient medicine department of tertiary care teaching hospital and randomly selected community pharmacies, Patients who had given the consent to participate in the study.

Exclusion Criteria: Patients who did not received selected recently introduced medicines, Patients who are admitted in other than the medicine department, Patients who are not co-operated and not willing to give the consent.

All the necessary data was collected by using patient profile form, suspected adverse drug reaction notification form, adverse drug reaction reporting and documentation form, personal interview with patients who received the selected recently introduced medicines from community pharmacy, information collected from community pharmacists.

Study Procedure

Procedure for the Selection of Recently Introduced Medicines

- Selection of recently introduced medicines list was done by referring the official website of central drug authority for discharging functions assigned to the Central Government under the Drugs and Cosmetics Act, Director General of health services, Ministry of Health and Family welfare, Government of India's Central Drugs Standard Organization (CDSCO) of (http://www.cdsco.nic.in/writereaddata/list_of_drugs_approved)[9] newly approved drugs from the year 2003 to 2013.
- Based on the availability and frequency of dispensing in the hospital and community pharmacies selected ten recently introduced medicines.

Procedure for Data Collection and its Analysis

- The pharmacist's attended the ward rounds on daily basis in the medicine department and

followed all the patients who had been prescribed with selected recently introduced medicines. And explained about the study, later received their consent for participation in project.

- Collected all the necessary information from patients who have received selected recently introduced medicines from randomly selected community pharmacy.
- Assessed and analysed the collected data of the patients who has been developed suspected adverse drug reactions after receiving selected recently introduced medicines.
- The collected data was documented in the patient profile form, suspected adverse drug reaction notification form and adverse drug reaction reporting and documentation form for future reference. The computerised database was created by using Microsoft Excel Sheet and all the details of the patient profile and adverse drug reaction documentation form was entered in that.

RESULTS

Details of Selected Recently Introduced Medicines

Based on the available data source of Central Drug Standard Control Organization official website recently introduced drugs in the last 10 years was selected. From that list based on the availability and frequency of dispensing 10 drugs were selected. The drugs selected for the study are enlisted in table 1.

Table 1: List of recently introduced medicines selected for the study

Sr. No.	Selected newly introduced medicines	Year of approval	Indication(s)
1	Tadalafil	2003	Erectile dysfunction
2	Torsamide	2003	Hypertension
3	Olmesartan	2005	Hypertension
4	Pregabalin	2005	Neuropathic Pain
5	Voglibose	2005	Diabetes Mellitus
6	Doxofylline	2006	Bronchial Asthma and COPD
7	Moxonidine	2007	Hypertension
8	Ivabradine	2008	Chronic Stable Angina Pectoris
9	Febuxostat	2009	Chronic Hyperuricemia
10	Ilaprazole	2011	Duodenal Ulcer

A total of 54 patients were enrolled in our study. Out of which, 27(50%) were in-patients and 27(50%) were out patients. 27 patients developed ADRs from 10 inpatients and 17 out patients.

Table 2: Details of total patients developed ADRs

Total patients developed ADRs	Out patients	In patients
27	17(62.96%)	10(37.04%)

Demographic Characteristics of the Patients Experienced ADRs

Gender

A total of 36 ADRs were reported from 27 patients. Male predominance [16 (59.26%)] was observed over female patients [11 (40.74%)].

Table 3: Details of gender of patients developed ADRs (n=27)

Gender	Number of the patients	Percentage
Male	16	59.26%
Female	11	40.74%

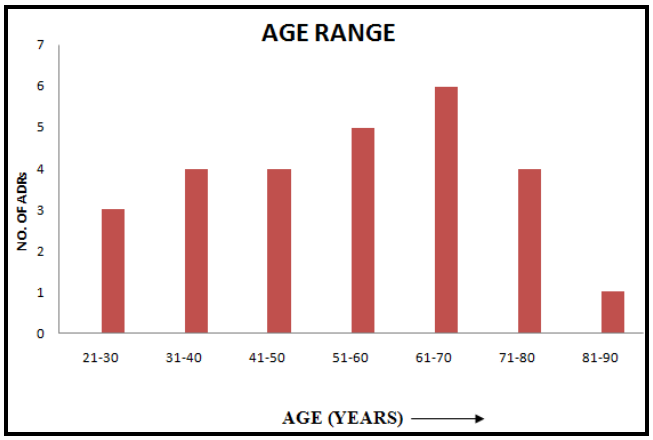

Figure 1: Age wise distribution of ADRs

Number of ADRs Reported for Individual Drugs

During the study period, more number (7 ADRs 19.44%) of ADRs were observed with Pregabalin followed by torsamide [6 (16.67%)], olmesartan [5(13.89%)], febuxostat [4(11.11%)], Voglibose [4(11.11%)], doxofylline [3(8.33%)], moxonidine [3(8.33%)], ivabradine [2(5.56%)], ilaprazole [1(2.78%)] and tadalafil [1(22.78%)].

Table 4: Drugs implicated to cause ADRs

SL No.	Drugs	Number of ADRs (N=36)	Percentage (N=36)
1	Pregabalin	7	19.44%
2	Torsamide	6	16.67%
3	Olmesartan	5	13.89%
4	Febuxostat	4	11.11%
5	Voglibose	4	11.11%
6	Doxofylline	3	8.33%
7	Moxonidine	3	8.33%
8	Ivabradine	2	5.56%
9	Ilaprazole	1	2.78%
10	Tadalafil	1	2.78%

Predisposing Factors of ADRs

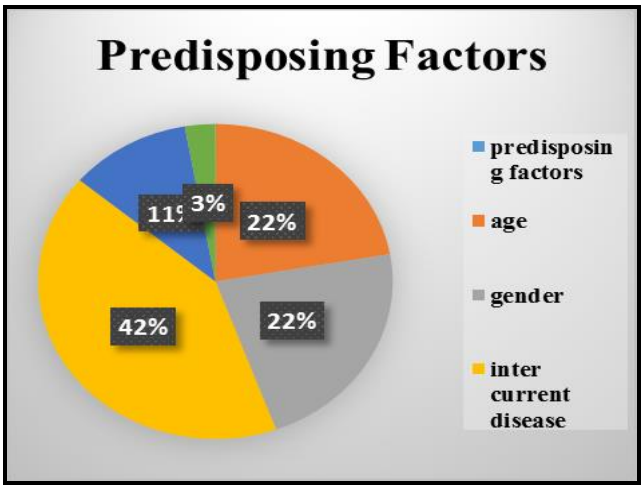

Figure 2: Predisposing factors involved in the development of ADRs

Systems Associated With ADRs

The system most commonly affected by ADRs was the central nervous system [18(50%)], gastro intestinal tract [9(25%)], musculo skeletal system [4(11.11%)], respiratory system [2(5.56%)], cardio vascular system [1(2.78%)] and others [2(5.56%)].

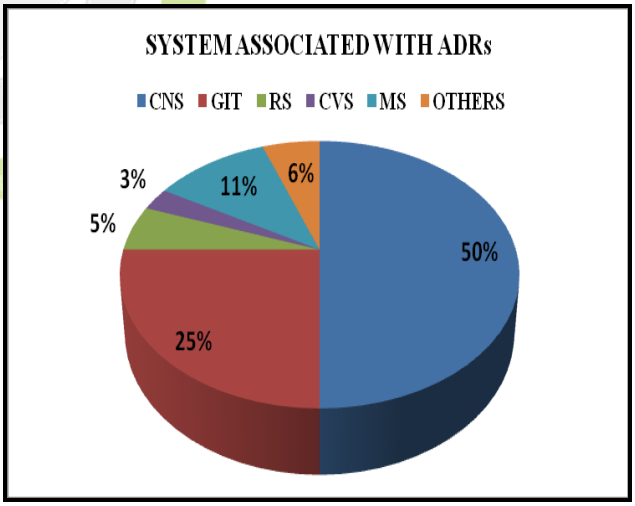

Figure 3: System affected by ADRs

Commonly Reported Adverse Drug Reactions with the Selected Medicines

Headache [7(19.44%)] was commonly reported ADR in our study followed by dizziness [5(13.89%)], dry mouth [4(11.11%)], arthralgia [2(5.56%)], cough [2(5.56%)], oedema [1(2.78%)] and others.

Table 5: List of commonly reported ADRs of selected recently introduced medicines

Description of reactions	Number of reactions (N=36)	Percentage (%) (N=36)
Headache	7	19.44%
Dizziness	5	13.89%
Dry mouth	4	11.11%
Arthralgia	2	5.56%
Cough	2	5.56%
Oedema	1	2.78%
Insomnia	1	2.78%
Gastric burning	1	2.78%
Flatulence	1	2.78%
Fatigue	1	2.78%
Tremor	1	2.78%
Bradyarrythmia	1	2.78%
Nausea	1	2.78%
Back pain	1	2.78%
Abdominal fullness	1	2.78%
Bloating	1	2.78%
Increased thirst	1	2.78%
Constipation	1	2.78%
Muscle spasm	1	2.78%
Irritability and disorientation	1	2.78%
Weakness	1	2.78%

Dechallenge of the Suspected Drug

Out of 36 ADRs, drugs were dechallanged in 16 cases (44.44%). No drug was rechallenged during our study.

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' [22(61.11%)] followed by 'probable' [13(36.11%)] and unlikely [1(2.78%)].

As per Naranjo's scale, majority of ADRs were found 'possible' [23(63.89%)] followed by 'probable' [13(36.11%)].

Table 6: Causality assessment of ADRs – WHO probability scale

Probability Scale	Number of ADRs (N=36)	Percentage (%) (N=36)
Certain	00	00.00
Probable	13	36.11%
Possible	22	61.11%
Unlikely	1	2.78%
Conditional	00	00.00
Unassessable	00	00.00

Table 7: Causality assessment of ADRs- Naranjo Algorithm

Scale	Number of ADRs (N=36)	Percentage (%) (N=36)
Definite	00	00.00
Probable	13	36.11%
Possible	23	63.89%
Doubtful	00	00.00

Severity of Reported ADRs

Severity of the reported ADRs was analysed by using Modified Hartwig and Siegel scale. Out 36 ADR reports, 18(50%) were found moderate in their severity and 18 reports (50%) were found mild in nature.

Table 8: Severity of ADRs*

Severity	Number of ADRs (N=6)	Percentage (%) (N=36)
Mild		
Level 1	6	16.67%
Level 2	12	33.33%
Moderate		
Level 3	14	38.89%
Level 4a	0	00.00
Level 4b	4	11.11%
Serious		
Level 5	00	00.00
Level 6	00	00.00
Level 7	00	00.00

*As per Modified Hartwig & Siegel severity scale

Predictability of the Reported ADRs

Of the total 36 ADRs, 35(97.22%) reactions were predictable and 01ADRs (2.78%) were not predictable.

Preventability of Reported ADRs

Preventability of reported ADRs was assessed using Modified Schumock and Thronton criteria. All the reported ADR was found to be 'definitely preventable'36 (100%).

Table 9: Preventability of ADRs*

Preventability Criteria	Number of ADRs (N=36)	Percentage (%) (N=36)
Definitely preventable	36	100.00%
Probably preventable	0	00.00
Not preventable	0	00.00

*As per Modified Schumock and Thronton scale

Management of ADRs

Out of 36 ADRs, suspected drug was withdrawn in 14(38.89%) cases, dose was altered in 2(5.56%) cases and there was no change in 20(55.56%) cases.

Symptomatic treatment was given for 13(36.11%) ADRs and no treatment were given in 23(63.89%).

Outcome of ADRs

We observed that majority 18(50%) of the patients who experienced ADRs due to the suspected drugs are still continuing.

Table 10: Outcome of ADRs

Outcome	Number of ADRs	Percentage
Recovered	16	44.44%
Continuing	18	50%
Unknown	2	5.56%

DISCUSSION

Drugs are used for the treatment of disease but sometimes prove to be fatal, as the saying rightly goes: "drugs are double edged weapons." An ADR is any undesirable effect of a drug beyond its anticipated therapeutic effect during treatment course.[10] ADR causes prolonged hospital admission and may result in disability or death.[11] The ADR will pose a huge economic burden to the patients.[12]

In the present study, 10 drugs were selected which are recently introduced in the market based on the availability and frequency of sales of medicines in Davangere city. We had reported 36 suspected ADR reports from 27 patients including both community and hospital set up.

Demographic details of the patients were studied and revealed that, male prevalence 16(59.26%) was noted over female 11(40.74%) in the

development of ADRs. In our study, male prevalence was high because maximum number of people we got in our study was males. The findings were similar to a study conducted by Ravinandan AP et al.[13] But in general, women are at greater risks for developing ADRs.[14,15] As the sample size is too small in our study, hence we can't conclude males are more prone to ADR.

In our study, we observed that the age group 61-70 developed more ADRs 6(22.22%) due to decreased physiological function and the metabolism of the drug. Several studies have shown that geriatric populations develop more ADRs when compared to adults.[16]

The predisposing factors to reported ADRs were analysed. In our study intercurrent disease 15(41.67%) is the major factor responsible for the development of ADRs followed by age, gender 8(22.22%) and poly pharmacy 4(11.11%).In a study conducted by Richard M et al. elderly (24.82%)are more prone to be predisposed to ADRs.[17]

During our study periods, more number of ADRs were collected for Pregabalin 7(19.44%) followed by torsamide 6(16.67%), olmesartan 5(13.89%), febuxostat 4(11.11%), Voglibose 4(11.11%), doxofylline 3(8.33%), moxonidine 3(8.33%) ivabradine 2(5.56%), tadalafil 1(2.78%) and ilaprazole 1(2.78%). Similar results were obtained from a study conducted by Ravinandan AP et al. 22(34.92%) ADRs were reported for Pregabalin followed by voglibose 18(28.57%).[13]

We found that, most commonly affected system by ADRs was the central nervous system 18(50%) followed by Gastro Intestinal Tract 9(25%), Musculo Skeletal 4(11.11%), Respiratory System 2(5.56%), Cardio Vascular System 1(2.78%) and others like weakness 2(5.56%). Our findings were similar to a study conducted by Padmaja Udaykumar et al. in India, percentage of the ADR developed was associated with CNS was 23.1%.[2] and a study conducted by Arulmani R et al, 56(34.1%) of the ADRs was associated with dermatological system(skin) followed by 31(18.9%) CNS.[18]

The most commonly reported ADRs in our study was headache 7(19.44%), dizziness 5(13.89%), dry mouth 4(11.11%), arthralgia 2(5.56%), cough 2(5.56%), oedema, insomnia, gastric burning, flatulence, fatigue, tremor, bradyarrythmia, nausea, back pain. In one study conducted by Palanisamy et al found that skin rashes (30.0%) were the most commonly identified adverse reaction followed by nausea, vomiting headache etc.[6]

Causality assessment of ADR by WHO probability scales and Naranjo scales shows that majority of the reaction were coming under possible category. According to WHO probability scale, most of the reactions belonged to the category 'possible'22(61.11%) followed by probable 13(36.11%) and unlikely 1(2.78%). Similar results were obtained from a study conducted by Sivanandy P et al. 71.67% were possibly drug related followed by 26.67% probable.[6] Study conducted by Vora MB et al. found that 59.57% was found to be certain and 29.79% was possible.[19]

A study conducted by conducted by Maulik SD et al. 92(60%) were probable followed by possible 59(38%).[20] In this study according to Naranjo's algorithm most of the reactions belong to the category possible 23(63.89%), possible 13(36.11%).

The severity of the reported ADRs was analysed by using Modified Hartwig Siegel sale. Out of 36 ADR reports, 18(50%) reports were moderate in the severity and 18(50%) reactions were minor in severity. In one Indian study conducted by Palanisamy S et al. found that 61.37% reactions were moderate in nature followed by 32.42% ADRs were mild in nature.[21]

Preventability is analysed by using Modified Shumock and Thronton assessment scale. 36(100%) reported ADRs were found to be definitely preventable. Study conducted by Palanisamy et al. found that a majority of ADRs were 'definitely preventable' (40.42%).[21] Similar results were observed in a study conducted by M Shamna et al. most of the ADRs 27 (55.10%) were definitely preventable.[10]

The reported ADRs were assessed for whether the drugs have been dechallenged or rechallenged. In our study no drug was rechallenged. Dechallenge was done for16 (44.44%) ADR cases, 20(55.56%) cases no changes were done.

In majority of the patients, 20(55.56%) the drug was not changed despite the ADR. In 14(38.89%) patients the suspected drug(s) was withdrawn followed by dose alteration 2(5.56%) patients. In a study conducted by M Shamna et al. in 28 (57.14%) cases, suspected drug was withdrawn while no change was made in 17(20.83%).[10]

Thirteen (36.11%) patients received symptomatic treatment and 23(63.89%) patients got no treatment for ADR management. When we are reported majority of the reactions were continuing 18(50%) and 16(44.44%) patients recovered from the reactions and 2(5.56%) still unknown.

In our study thank you note was given to the pharmacist who co- operated in collecting the data from the ambulatory patients. Alert card was given to one patient who took 0.3mg of voglibose which caused severe dizziness. This kind of reaction is not reported in any of the previously published articles or journals according to our knowledge.[23] Our study findings were similar to the study conducted earlier.

CONCLUSION

From the study, the following conclusions was drawn a total of 36 ADRs were reported from 27 patients. Seven ADRs were observed with pregabalin and most commonly reported ADR was headache. Most of the reactions were predictable and preventable.

During our study, we found that voglibose induced severe dizziness, its nature and severity of this reaction was different when compared to available literature sources. From this research work we concluded that ADR reporting of recently introduced medicines gives more safety information's about drugs both in-patient and out-patient departments, which enables the Health Care Professionals to handle the medicines rationally.

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