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Research Article

A STUDY ON ADVERSE DRUG REACTIONS IN HOSPITALIZED PATIENTS WITH DIABETES MELLITUS IN A MULTI-SPECIALTY TEACHING HOSPITAL

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ABSTRACT

Objectives: Adverse drug reactions (ADRs) are well known to occur with any class of drugs when used in normal doses for the management of diseases. Anti-diabetic agents are no exception to this. The main aim of the study was to detect and analyze ADRs in hospitalized patients with diabetes mellitus in a multi-specialty hospital.

Methods: The prospective observational study was conducted in a 1000 bed multi-disciplinary teaching hospital at Dakshin Kannada district in south India over a period of 2-year between June 2013 and May 2015.

Results: A total of 102 ADRs were reported from 99 patients during the study period with male predominance (60.60%) over females. The average age of the patients in the study was found to be 59.8±13.15 years. The majority of the ADRs occurred in the age group of 40-80 years. The average duration of diabetes mellitus in the study was 10.08±7.69 years. The class of drugs most commonly responsible for causing ADRs was found to be anti-diabetic drugs (67.64%) followed by antimicrobial agents (10.78%). The most commonly occurred ADRs was hypoglycemia (63.72%) followed by gastritis (6.86%). Causality assessment by using Naranjo scale indicated that majority of the ADRs (59.80%) were probable, 37.25% were possible, and 2.94% were definite. The severity assessment using the Hartwig and Siegal scale indicated that the majority of the ADRs were "mild" followed by "moderate" and "severe," respectively. Preventability assessment using modified Schumock and Thornton revealed that 57.84% were definitely preventable, 33.33% were probably preventable, and 8.82% were not preventable.

Conclusion: The study shows that the active involvement of a clinical pharmacist helps in monitoring and detecting ARDs and their management through therapeutic interventions would be beneficial in the better patient outcome.

Keywords: Adverse drug reaction, Diabetes mellitus, Clinical pharmacist.

INTRODUCTION

Prescriber's knowledge about pharmacokinetics and pharmacodynamic aspects of medicines and their interaction with normal aging physiology is critical in the management of diabetes mellitus. The knowledge is needed to minimize and even avoid the potentially adverse effects of hypoglycemia and side effects associated with the anti-diabetic drugs [1]. It is well known and obvious that adverse reactions to drugs can occur with any class of drugs as the patient consumes any drug for the various disease conditions. Adverse drug reactions (ADRs) may occur following a single dose or prolonged administration of a drug or result from the combination of two or more drugs. ADR are a great concern and has been recognized as a major limitation in providing healthcare, and patient safety has become a leading topic at both the national and international level [2]. It was in the late 1950s and early 1960s, the thalidomide tragedy was the seminal event leading to the development of modern drug regulations. Furthermore, in the 20th century, great therapeutic advances were accompanied by a growing awareness of the problem of adverse reaction to medicines among both healthcare professionals and consumers [3].

According to the World Health Organization (WHO), ADRs is defined as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. This definition excludes overdose, drug abuse, and treatment failure and drug administration errors [4]. The female gender, age (very young and very old), multiple medications and the physiological state of renal and liver function, breastfeeding, pregnancy, and alcohol intake are considered as the important risk factors for ADRs [5].

ADRs are considered as one of the most important leading causes of mortality in many countries. ADR not only accounts for significant morbidity and mortality but can also lead to increase in the length of hospital stay and healthcare costs [6]. The overall rate of ADRs is estimated to be 6.5%, and 28% of these ADRs are preventable. One of the meta-analysis found an ADR rate of 6.7% among hospitalized patients [7].

The study of ADRs is the realm of what is known as pharmacovigilance. The WHO defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding, and prevention of ADRs or any other drug-related problems." It can help in providing continuous information on the safety of drug used [8,9]. The increase in the prevalence of anti-diabetic medications highlights the need for the importance of clinical pharmacist for monitoring and reporting any suspected ADRs. To detect and analyze the ADRs in patients with diabetes mellitus with an assessment of causality, severity, and preventability in a multi-specialty teaching hospital, the study has been carried out.

METHODS

The prospective observational study was conducted in a 1000 bed multi-disciplinary teaching hospital at Dakshin Kannada district in south India over a period of 3-year between August 2012 and July 2015. The ethical committee clearance was obtained from the institutional ethical committee. All the patients with diabetes mellitus admitted under general medicine department who were exposed to any ADR in the hospital and those who were admitted for the treatment of ADR (i.e. the reason for admission was ADRs) were included in the study.

Patients admitted with incidental and accidental poisoning (overdose) and patients with drug abuse problems were excluded from the study.

All the patients with diabetes mellitus admitted under the general medicine department were enrolled into the study. The patient's case details including the laboratory data and treatment chart were reviewed by the pharmacist and assessed for any ADRs on a daily basis from the date of admission until the date of discharge. When suspected ADRs were detected, they were brought to the notice of the concerned physician for confirmation on drug-induced reactions. The suspected drug reactions were recorded in the ADR documentation form designed as per need of the study for evaluation. All the identified ADRs were assessed by using causality, severity, and preventability scales. The causality assessment of the reported ADRs was carried out using the 'Naranjo causality assessment scale' or ADR probability scale which is a questionnaire based scoring system ranging from 0 to 9. This was used to evaluate the causality relationship between a likely ADR and a drug. The total score calculated from this questionnaire defines the category as possible (1-4), probable (5-8), and definite (≥9). The severity assessment of the reported ADRs as mild, moderate, and severe was determined according to ' Hartwig severity scale.' According to this scale, ADRs were assessed as mild (level 1,2), moderate (level 3,4,5), and severe (level 6,7). The preventability of an ADR was determined by "modified Schumock and Thornton preventability Scale." This scale assesses and categorizes ADRs into definitely preventable, probably preventable, or not preventable. The results were analyzed using descriptive statistics. Age group, gender, drugs involved, type of drug reactions, management of ADRs, causality, severity, and preventability were presented in proportions.

RESULTS

A total of 503 patient case sheets were reviewed, 102 ADRs were reported from 99 patients during the study period. Incidence of ADRs occurrence was higher in male patients ([60] 60.60%) than female patients ([39] 39.39%). The average age of the patients in the study was found to be 59.8±13.15 (mean±standard deviation [SD]) years. The majority of the ADRs occurred in the age group of 40-80 years. The average duration of diabetes mellitus in the study was 10.08±7.69 (mean±SD) years. The average the number of drugs received per patient was 12.03±4.82 (range: 2-27). Most of the patients (34.34%) in our study received 11-15 drugs during their hospital stay. The class of drugs most commonly responsible for causing ADRs was found to be anti-diabetic drugs (67.64%) followed by antimicrobial agents (10.78%), antihypertensive agents (8.82%), and diuretics (5.88%). The most commonly occurred ADRs was hypoglycemia (63.72%) followed by gastritis (6.86%). Hypersensitivity reactions have been identified in 5 cases (4.90%). Diarrhea (3.92%), bradycardia (2.94%), pedal edema (2.94%), and hyperkalemia (2.94%) are the other ADRs reported during the study. A single case of warfarin-induced bleeding, amiodarone-induced hepatitis, and amikacin-induced renal failure has also been identified during the study. The suspected ADRs were assessed for their causality using the Naranjo algorithm probability scale. It was revealed that 59.80% were probable, 37.25% were possible, and 2.94% were definite. The ADRs were assessed for their severity using a modified Hartwig severity scale, which is a standard scale for severity assessment. It was observed that 49% were mild, 46.07% were moderate, and 4.90% were severe.

Preventability of the reported ADRs was assessed using the "modified Schumock and Thornton preventability scale." Using this scale, results revealed that 59 (57.84%) were definitely preventable while 34 (33.33%) were probably preventable and 9 (8.82%) were not preventable. Considering the management of the reported ADRs, the majority of the ADRs (27.45%) were managed by withdrawing the suspected drug followed by specific treatment in 23.52% and in 20.58% of the cases the dose has been altered of the suspected drug.

DISCUSSION

Occurrences of ADRs to medicines are common; bur is often under-recognized. Anti-diabetic drugs are medications used to improve blood glucose control in patients with diabetes mellitus. However, untoward adverse reactions to medicines, in general, have been associated with non-compliance leading to therapeutic failure. It can also lead to prolonged hospital stay and increased healthcare cost [10]. Anti-diabetic drugs are no exception to this. Understanding the nature and severity and early identification of these ADRs allow for appropriate management.

In our study, a predominance of male gender (60.60%) for ADRs was noted over females (39.39%). Studies carried out by Rao *et al*. [11] and Dilip *et al.* [12] also found similar results. Patients in the age group of 40-80 years experienced maximum ADRs (86 [86.8%]) followed by 7 (7.1%) in the age group between 20 and 39 years (Table 1). Various studies carried out by Rajesh *et al*. [13] and Pirmohamed *et al*. [14] have reported that the percentage of ADRs found was higher in adults and the geriatric population. The present study revealed adult and geriatric predominance over other age groups. This might be due to the fact that most adult and geriatric patients with diabetes mellitus presented with associated comorbidities such as hypertension, renal failure, myocardial infarction, heart failure, and dyslipidemia, which forces them to receive multiple drug therapy. It is known that multiple drug therapy and co-morbidities predispose patients to ADRs.

The class of drugs most commonly responsible for causing ADRs was found to be anti-diabetic drugs (67.64%) followed by antimicrobial agents (10.78%), antihypertensive agents (8.82%), and diuretics (5.88%) (Table 2). Our results were similar to the finding observed by the Zaman Huri and Fun Wee [15]; anti-diabetic drugs were associated with about one-third of all the cases. The study carried out by Vijayakumar and Dhanaraju [16] and Patidar *et al*. [17] showed more ADRs with antibiotics in their study. This is in contrast to our study where anti-diabetic agents are the class of drugs involved in the drug reaction. This could be because of differences in the underlying disease and the study population as our study involved patients with diabetes mellitus as compared to the general population.

The most commonly identified ADRs were hypoglycemia in 65 (63.72%) cases followed by gastritis in 7 (6.86%) patients and hypersensitivity reactions in 5 (4.90%) patients (Fig. 1). It is well known that anti-diabetic agents cause hypoglycemia and various studies reported incidences of hypoglycemia related to insulin and

Table 1: Socio-demographic characteristics of study populations (n=99)

Characteristics	Value (%)
Gender	
Male	60 (60.60)
Female	39 (39.39)
Age (years)	
20-39	7 (7.0)
40-59	43 (43.4)
60-79	43 (43.4)
≥80	6 (6.0)
Duration of diabetes mellitus	
<5	41 (10.21)
6-10	25 (25.25)
11-15	14 (14.14)
16-20	8 (8.1)
21-25	4 (4.0)
≥26	7 (7.1)
No of drugs received per patient	
1-5	7 (7.07)
6-10	32 (32.32)
11-15	34 (34.34)
≥16	26 (26.26)

sulfonylureas and considered hypoglycemia as one of the important cause for hospital related admissions in patients with diabetes mellitus [15,18,19]. A Danish study by Hallas *et al.* [20] reported 14 out of 157 admissions due to hypoglycemia related to insulin use. Two Hong Kong studies [21,22] where diabetes mellitus is common reported higher rates of hypoglycemia with sulfonylurea. The prospective cohort pharmacovigilance study in Sicily [23] reported 11% of the total number of patients with diabetes mellitus developed ADRs. The most common ADRs reported was hypoglycemia, especially with insulins and gastrointestinal events for biguanides and meglitinides.

Patients with diabetes mellitus are at increased risk of developing cardiovascular events and infectious diseases leading to increased incidence of cardiovascular drugs and antibiotics related ADRs. Antihypertensive agents that caused ADRs were calcium channel blockers, diuretics, and ARBs. It has been reported that amlodipine caused bilateral leg swelling; electrolyte disturbances were reported as ADRs with losartan and hydrochlorothiazide. Diarrhea and hypersensitivity reactions including rashes and urticaria were the most common adverse reactions reported with the antibiotic usage in our study. One case report of insulin-induced hypersensitivity reactions, amiodarone-induced hepatitis, bleeding secondary to warfarin and amikacin-induced renal failure were also reported during our study period. This further emphasizes the importance of monitoring ADRs, especially in the elderly patients with diabetes mellitus and other co-morbid ailments.

Table 2: ADRs distribution according to drug class

Drug classes	Number of ADRs (n=102)	ADRs (%)
Anti-diabetics	69	67.64
Antihypertensive	9	8.82
Diuretics	6	5.88
Antiplatelets	1	0.98
Antianginal	2	1.96
Antiarrhythmic	1	0.98
Antiepilepsy	2	1.96
Antibiotics	11	10.78
Anticoagulants	1	0.98

ADRs: Adverse drug reactions

Table 3: Management of ADRs

Treatment	Number of ADRs (n=102)	ADRs (%)
Drug changed	15	14.70
Drug withdrawn	28	27.45
Symptomatic treatment	3	2.94
No change	11	10.78
Dose altered	21	20.58
Specific treatment	24	23.52

ADRs: Adverse drug reactions

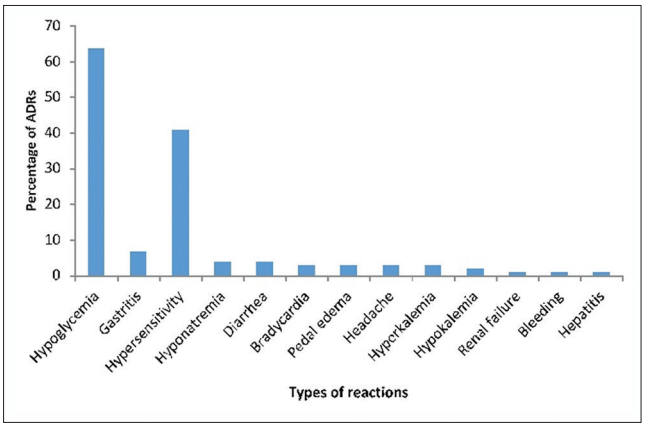

Fig. 1: Classification of observed reactions from reported adverse drug reactions (n=102)

In our study, the offending drug was withdrawn in 28(27.45%) cases, and dose was altered in 21 (20.58%) patients (Table 3). Specific treatment was provided in 24 (23.52%) cases; specific treatment was given to 3 (2.94%) patients and no change in the treatment in 11 (10.78%) patients.

To strengthen and further emphasize the validity of the study, causality assessment was done using Naranjo's scale. The assessment showed that out of 102 ADRs, 61 (59.80%) were probable, 38 (37.25%) were possible, and 3(2.94%) were definite to the study (Fig. 2). These findings are similar to the study carried out by Palaniswamy *et al.* [3] and Patidar *et al*. [17] which stated that most of the ADRs belong to category probable. On the evaluation of the severity of ADRs by the Hartwig and Siegel severity assessment scale, it was evident that most of the ADRs reported in the study were moderate (50 [49.01%]) in nature followed by 47 (46.07%) were mild and 5 (4.90%) were severe. No lethal outcomes were observed or produced during the study period (Fig. 3). This is a contrast to the study by Rajesh *et al.* [13] which showed that majority of the ADRs were mild (54%) followed by moderate (35%) and severe (10.81%). Assessment of the preventability of the ADRs using modified Schumock and Thornton scale, it was evident that 57.84% were definitely preventable followed by 33.33% were probably preventable, and 8.82% were not preventable (Fig. 4). The high incidence rate of definitely preventable calls for the urgent need to reinforce the monitoring of ADR to drugs, public education against self-medication and the role of self-care in disease management. By implementing such programs could lead to a reduction in the incidence of ADRs.

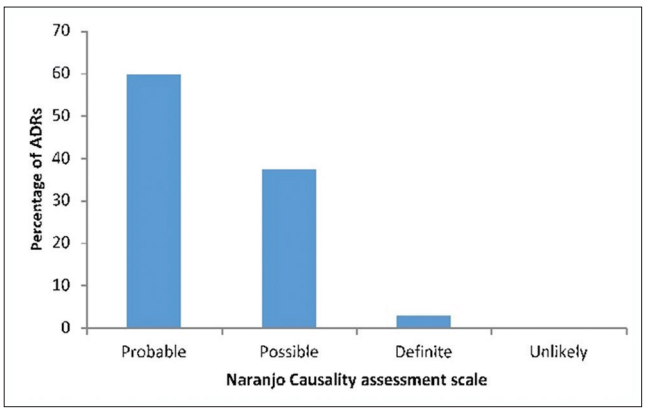

Fig. 2: Naranjo causality assessment of reported adverse drug reactions (n=102)

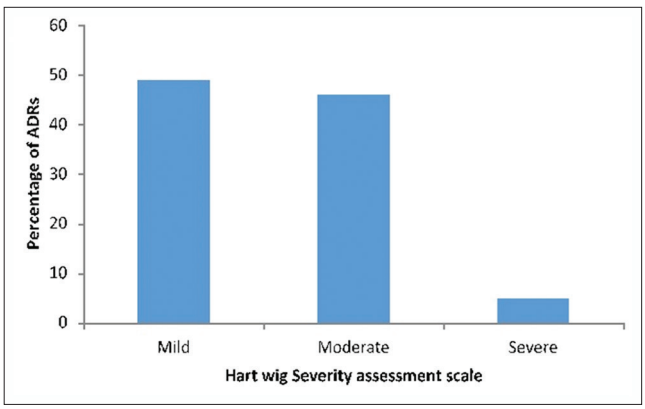

Fig. 3: Hart wig and Siegel severity assessment of reported adverse drug reactions

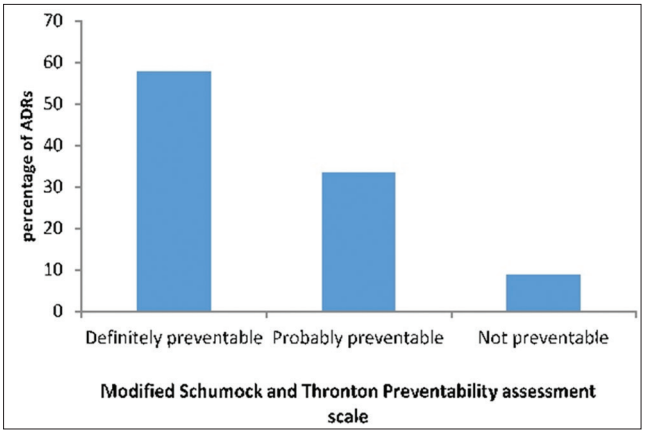

Fig. 4: Modified Schumock and Thornton preventability assessment of report adverse drug reactions

CONCLUSIONS

ADRs are one of the drug related problems being considered as the important cause of hospital-related admissions and are a challenge for drug safety. Monitoring ADRs in patients using anti-diabetic agents is a matter of importance since it is well known to cause hypoglycemia. These study results provide insight to the healthcare providers on the importance of monitoring and reporting of ADRs especially in elderly patients with diabetes mellitus who might suffer significant deleterious effects associated with the drugs. The active involvement of clinical pharmacist for detecting and monitoring ADRs and their management through therapeutic interventions would be beneficial in the better patient outcome.

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