Original Article

Assessment of Suspected Adverse Drug Reactions of Anti-Diabetic Drugs in a Tertiary Care Hospital of Eastern India

Dr Deepak Kumar[1], Dr Ram Babu Raman[2]*

1. Dr Deepak Kumar, Tutor, Department of Pharmacology, Government Medical College, Bettiah, Bihar, India.
2. Dr Ram Babu Raman, Tutor, Department of Pharmacology, DMCH, Lakhisarai, Bihar, India.

***Corresponding author's E-mail:** rbraman37@gmail.com

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ABSTRACT

Introduction: Patients with type 1 or type 2 diabetes mellitus need lifelong treatment with insulin or oral anti-diabetic drugs. So, they also have lifelong exposure to various adverse drug reactions (ADRs) associated with these agents. Due to discovery and utilisation of large number of drugs in last two decades, it has become more important to detect and report Adverse Drug Reactions (ADRs). Special attention and knowledge must be applied to identify suspected sign and symptoms in patients who are suffering from many comorbidities and receiving multiple medications.

Aims/ objective: To highlight pattern of ADRs with use of oral anti-diabetic drugs and insulin therapy and to determine the risk factors and association of various drugs with common adverse effects to generate data for clinician for proper modification of pharmacotherapy of diabetes mellitus, thus minimizing incidence of ADRs.

Materials and Method: Patients with any suspected adverse drug reactions (ADRs) to insulin or other anti-diabetic drugs were interviewed at their OPD visit. Information on the adverse event such as start or stop date & time of the ADR; dose, frequency, route and duration of suspected medications; action taken after the reaction; other concomitant medication; relevant laboratory investigation data and relevant past medical history were collected from the patient. Descriptive analysis was done to analyse and compare the results using percentages.

Results: A total of 341 ADRs were reported from 207 patients. Nausea (30.50%) was most common reported ADR in our study followed by hypoglycaemia (17.30%) and weight gain (12.02%). Most of the cases of nausea, respiratory tract infection, abdominal pain, cough, joint pain and back pain were related to DPP-4 inhibitors. Hypoglycaemia and weight gain were mostly related to insulin followed by sulfonylurea. Most of the cases (56.89%) had probable causality relation to suspected drug.

Conclusion: There is significant additional burden of ADRs on patients on type 2 diabetes mellitus who are already at more risk of various metabolic disorders. Proper counselling and measure to improve compliance can decrease the incidence of known adverse effects of anti-diabetic therapy.

Keywords: Diabetes Mellitus, Adverse Drug Reactions, Insulin, Anti-diabetic Drugs.

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INTRODUCTION

In a survey done in 2021, 537 million adults (20-79 years) were living with diabetes which means that every 1 in 10 person is living with diabetes mellitus. It is predicted that this prevalence is going to increase to 643 million by 2030 and 783 million by 2045. In the same survey, it has also been found that nearly 3 out of 4 diabetic patients are from low- and middle-income countries.[1] Thus, diabetes is a much greater worldwide health problem and even more in developing country like India. Diabetes is now greatest risk factor for development macrovascular and microvascular complications such as nephropathy, retinopathy, peripheral neuropathy, atherosclerosis leading to ischemic heart disease (IHD), stroke, and peripheral vascular diseases. With a plethora of these comorbidities associated with diabetes, there is no doubt that diabetes has major impact on the quality of life in elderly population and overall life expectancy. Complications related with diabetes and their progression can only be controlled by early detection, modification of lifestyle, and achieving optimum glycaemic control with best utilization of currently available anti-diabetic medication

Patients with type 1 or type 2 diabetes mellitus need lifelong treatment with insulin or oral anti-diabetic drugs. So, they also have lifelong exposure to various adverse drug reactions (ADRs) associated with these agents. These ADRs leads to additional burden on the physical and mental health of the patient and thus lead to patient's poor compliance and loss of trust in their clinicians. Further, adverse drug reactions (ADRs) are one of the major obstacles in patient's adherence to doctor's advice

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leading to further negative clinical, social and economic outcomes.[2]

World Health Organization (WHO) has defined Adverse Drug Reactions (ADRs) as "any response to a drug which is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function". But drug toxicity due to overdosing and medication error has been excluded from these definitions that can be put under other drug related problems (DRP). [3-5]

Adverse effects of insulin can be classified into ADRs due to action of insulin on body and some related to specific route of administration such as injection site reaction. Hypoglycaemia is the most commonly reported ADR of insulin therapy.[6] The other commonly reported adverse effects of insulin therapy is weight gain. Rare cases of electrolyte disturbances such as hypokalaemia has been reported but were mostly associated with concomitant use of with other drugs causing hypokalaemia. Pain and lipodystrophy at the injection site are other common adverse effects associated with daily subcutaneous injections.[7] There is also some reporting of peripheral hyperinsulinemia and low compliance associated with the subcutaneous route for insulin administration. However, there is requirement of more evidences for the endocrinologists to make better choice of optimum insulin regimen for acceptable benefit-risk ratio and also there is lack of studies that has compared common ADRs between insulin and other anti-diabetic drugs.

Pharmacotherapy with insulin and other anti-diabetic drugs is the major option for management of diabetes mellitus.[8] The conventional options for pharmacotherapy of type 2 diabetes mellitus are the drugs that have been commonly utilized for long time such as biguanides, sulfonylureas, α-glucosidase inhibitors, meglitinides and thiazolidinedione (TZD). Some newer classes of drugs such as GLP-1 agonists, dipeptidyl peptidase 4 (DPP-4) Inhibitors and sodium glucose co-transport 2 (SGLT-2) Inhibitors are recently introduced with low risk of hypoglycaemia and wight gain. These anti-diabetic drugs help in achieving proper glycaemic control but they have many safety concerns also such as commonly reported ADRs related to gastrointestinal side effects such as nausea, metabolic complications such as wight gain, musculoskeletal problems, genitourinary disorders like UTI, development of peripheral oedema, risk of bladder cancer, osteoporosis etc. [9,10]

Due to discovery and utilisation of large number of drugs in last two decades, it has become more important to detect and report Adverse Drug Reactions (ADRs). Special attention and knowledge must be applied to identify suspected sign and symptoms in patients who are suffering from many comorbidities and receiving multiple medications.

The present study was planned to highlight pattern of ADRs with use of oral anti-diabetic drugs and insulin therapy. The objective was to determine the risk factors and association of various drugs with common adverse effects to generate data for clinician for proper modification of pharmacotherapy of diabetes mellitus, thus minimizing incidence of ADRs.

MATERIALS AND METHODS

This was an observational, cross-sectional, single arm study conducted in department of pharmacology in collaboration with out-patient department of endocrinology of tertiary care hospital of eastern India. The study was conducted from February 2022 to August 2022 after taking permission from institutional ethics committee and after taking informed consent from study participant.

Inclusion Criteria

We have included all patients with either type 1 or type 2 diabetes mellitus from any age and gender who have at least one suspected adverse drug reaction to insulin or other anti-diabetic drugs.

Exclusion criteria

Patients of gestational diabetes mellitus or patients in ICU care were excluded from our study. Patients in ICU are generally on multiple medications and are exposed to adverse effects of other drugs and also drug-drug interaction.

Patients with any suspected adverse drug reactions (ADRs) to insulin or other anti-diabetic drugs were interviewed at their OPD visit. Information on the adverse event such as start or stop date & time of the ADR; dose, frequency, route and duration of suspected medications; action taken after the reaction; other concomitant medication; relevant laboratory investigation data and relevant past medical history were collected from the patient and recorded in suspected adverse drug reaction reporting form issued by Indian pharmacopoeia commission. [11]

The reported ADRs were analysed for causality with suspected drugs using WHO-UMC Causality Categories. Preventability of ADRs was analysed by Modified-Schumock and Thornton scale and severity was analysed using Modified Hartwig and Siegel scale.[12, 13, 14]

Statistical Analysis

Data collected using suspected ADR forms were recorded in tabular form using Microsoft excel 365. Descriptive analysis was done to analyse and compare the results using percentages.

RESULTS

A total of 341 ADRs were reported from 207 patients. Most of the patients (91.79%) have diagnosis of type 2 diabetes mellitus and most of them (69.08%) were of age group 41-60 years. There was male predominance (58.45%) in our study.

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Table 1: Demographic and Clinical Characteristics of Patients

Parameters	Number of Patients	% of Patients (n=207)
Age (in Years)		
0-20	1	0.48
21-40	21	10.14
41-60	143	69.08
>60	42	20.29
Sex		
Male	121	58.45
Female	86	41.55
Type of Diabetes		
Type 1 Diabetes Mellitus	17	8.21
Type 2 Diabetes Mellitus	190	91.79

Nausea (30.50%) was most common reported ADR in our study followed by hypoglycaemia (17.30%) and weight gain (12.02%). Most of the cases of nausea, respiratory tract infection, abdominal pain, cough, joint pain and back pain were related to DPP-4 inhibitors. Hypoglycaemia and weight gain were mostly related to insulin followed by sulfonylurea. Metformin was only related to some of gastrointestinal adverse effects. Diarrhoea was mostly related to α-Glucosidase Inhibitors whereas urinary tract infection was major limiting factor with use of SGLT-2 inhibitors.

Only 5 cases of hypoglycaemia, 2 cases of weight gain, 3 cases of urinary tract infection, and 1 case each of hypokalaemia, joint pain and acute pancreatitis had probable causality relation to the suspected drug. Most of the cases of nausea, diarrhoea, abdominal pain, edema, and back pain had probable causality relation to the suspected drug whereas most of the cases of respiratory tract infections, constipation, cough and insomnia had possible causality relation with the suspected drug. Overall, most of the cases (56.89%) had probable causality relation to suspected drug.

Table 2: Frequency of Different ADRs and Their Distribution among Different Drug Groups

Type of ADRs	Number of ADRs (%)	Insulin	Biguanides (Metformin)	Sulfonylureas	DPP-4 inhibitors	α Glucosidase Inhibitors	SGLT-2 Inhibitors	Thiazolidinediones
Nausea	104 (30.50)	0	15	7	**74**	8	0	0
Hypoglycaemia	59 (17.30)	**28**	3	19	1	2	6	0
Weight Gain	41 (12.02)	**21**	0	13	0	0	0	7
Diarrhoea	25 (7.33)	0	8	0	3	**14**	0	0
Urinary Tract Infection	19 (5.57)	0	1	1	0	2	**15**	0
Respiratory Tract Infections	16 (4.69)	0	0	0	**14**	0	2	0
Constipation	14 (4.11)	0	**5**	3	2	0	0	4
Abdominal Pain	13 (3.81)	1	3	1	**4**	**4**	0	0
Cough	10 (2.93)	0	0	1	**7**	0	1	0
Edema	9 (2.64)	2	1	0	0	0	0	**6**
Hypokalaemia	8 (2.35)	**6**	0	2	0	0	0	0
Joint Pain	8 (2.35)	0	0	0	**7**	0	1	0
Dizziness	6 (1.76)	**3**	1	2	0	0	0	0
Insomnia	5 (1.47)	0	3	1	0	2	0	0
Back Pain	3 (0.88)	0	0	0	**3**	0	0	0
Acute Pancreatitis	1 (0.29)	0	0	0	**1**	0	0	0
Total	**341 (100)**	**61**	**40**	**50**	**116**	**32**	**25**	**17**

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Table 3: Distribution of ADRs into Various WHO-UMC Causality Categories

Type of ADRs	Number of ADRs (%)	Certain (%)	Probable/Likely (%)	Possible (%)
Nausea	104 (30.50)	0 (0)	66 (63.46)	38 (36.54)
Hypoglycaemia	59 (17.30)	5 (8.47)	32 (54.24)	22 (37.29)
Weight Gain	41 (12.02)	2 (4.88)	20 (48.78)	19 (46.34)
Diarrhoea	25 (7.33)	0 (0)	18 (72)	7 (28)
Urinary Tract Infection	19 (5.57)	3 (15.79)	11 (57.89)	5 (26.32)
Respiratory Tract Infections	16 (4.69)	0 (0)	7 (43.75)	9 (56.25)
Constipation	14 (4.11)	0 (0)	6 (42.86)	8 (57.14)
Abdominal Pain	13 (3.81)	0 (0)	9 (69.23)	4 (30.77)
Cough	10 (2.93)	0 (0)	3 (30)	7 (70)
Edema	9 (2.64)	0 (0)	6 (66.67)	3 (33.33)
Hypokalaemia	8 (2.35)	1 (12.5)	4 (50)	3 (37.5)
Joint Pain	8 (2.35)	1 (12.5)	5 (62.5)	2 (25)
Dizziness	6 (1.76)	0 (0)	3 (50)	3 (50)
Insomnia	5 (1.47)	0 (0)	2 (40)	3 (60)
Back Pain	3 (0.88)	0 (0)	2 (66.67)	1 (33.33)
Acute Pancreatitis	1 (0.29)	1 (100)	0 (0)	0 (0)
Total	**341**	**13 (3.81)**	**194 (56.89)**	**134 (39.3)**

Table 4: Preventability of ADRs using Modified-Schumock and Thornton scale

Categories	Number of ADRs (n=341)	% of ADRs
Definitely Preventable ADRs	102	29.91
Probably Preventable ADRs	52	15.25
Non-Preventable ADRs	187	54.84

Table 5: Severity of ADRs using Modified Hartwig and Siegel scale

Categories	Number of ADRs (n=341)	% of ADRs
Mild	131	38.42
Moderate	201	58.94
Severe	9	2.64

DISCUSSION

In our study, most of the patients have diagnosis of type 2 diabetes mellitus and most of them were of age group 41-60 years. The epidemic of type 2 diabetes has clear link to rising rates of obesity and metabolic syndrome, but projections estimate from research suggest that even after reduction of incidence rate of diabetes, the prevalence of diabetes mellitus is going to be doubled in the upcoming 20 years with the aging of the population as one of major contributors.[15] There was more prevalence of type 2 diabetes mellitus in the first half of the 19th century but now there is equal prevalence among men and women according to some surveys, with some studies reporting more prevalence in males especially in early middle age. Men seems to be at more risk of the complications of indolence and obesity than women possibly due to different insulin sensitivity and deposition of regional fat. [16]

Most of the ADRs (45.75%) reported in our study was gastrointestinal side effects of the drugs. In a similar study conducted by hameed et al., adverse drug reaction related to gastrointestinal system were mostly reported. [17] There are many controversies on mechanisms and pathophysiology of development of gastrointestinal adverse effects of anti-diabetic drugs in patients of diabetes mellitus. Many studies have reported gastrointestinal symptoms as one of major limiting factors in pharmacotherapy of diabetes mellitus. [18] However, gastrointestinal symptoms are frequently reported in

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patients on other medication and also by many persons who are not taking any medication, so causality with suspected drug is very cumbersome to prove in these ADRs. Furthermore, conflicting observations were reported from earlier studies which were conducted to analyse possible risk factors related with gastrointestinal adverse effects in diabetes patients; and there was lack of optimum methodology in most of the studies. [19–21] Gastrointestinal adverse effects of α-glucosidase inhibitors are generally due to fermentation of unabsorbed carbohydrate in the distal ileum and colon. These events can be reduced by slowly adjusting the dose of the drug. These adverse effects generally subside with continued therapy as α-glucosidase enzymes are induced later in the distal part of small intestine.

The incidence of biochemical hypoglycaemia in patient who are at insulin therapy differ significantly among type 1 and type 2 diabetes mellitus due to difference in awareness about state of hypoglycaemia. These events are relatively less frequent in patients with optimum awareness of hypoglycaemia and this association is strengthened by the results of a large multicentre prospective study in the UK.[22] In view of the more risk of hypoglycaemia in patients with poor awareness of hypoglycaemia, the possible development of hypoglycaemia with insulin should be monitored in patient of both type 1 and type 2 diabetes mellitus. Detection and counselling on suspected symptoms and regular check-up should be done routinely by treating clinician. The method of Gold et al. to analyse awareness of hypoglycaemia is fast and feasible to be implemented in clinical practice and helps in identification of most people with insulin associated hypoglycaemia.[23]

In a recently conducted observational study on hypoglycaemia caused by sulfonylurea, there was higher risk of hypoglycaemia associated with long-acting formulations of the drugs of sulfonylurea group. Old age and infrequent use of sulfonylureas was also identified as common risk factor.[24] Since metformin has negligible direct action on insulin release, there is low risk of hypoglycaemia with metformin.

Incidence of wight gain can be reduced by adding drug causing weight loss such as metformin, GLP-1 agonists, DPP-4 inhibitors and SGLT-2 agonists.

Use of TZDs is associated with peripheral oedema and increases in plasma volume. The mechanism is attributed to increase endothelial cell permeability caused by TZDs.[25] There is more frequent occurrence of peripheral oedema if TZDs are used in concomitantly with insulin therapy. Increase in urinary glucose excretion have a role in incidence of urinary tract infection with SGLT-2 inhibitors and it can be reduced by maintaining proper personal hygiene.

Most of the cases of nausea, respiratory tract infection, abdominal pain, cough, joint pain and back pain were related to DPP-4 inhibitors. Cases of severe hypersensitivity reactions, including anaphylaxis, angioedema, and exfoliative skin reactions were reported with use of DPP-4 inhibitors that can occur after the first dose or after as long as 3 months of therapy.[26] Occurrence of these with use of DPP-4 inhibitors suggest that these drugs can have significant effect on the immune system, as lymphocytes also express DPP-4. In some other studies, it has been reported that levels of many inflammatory mediators like SDF-1 a\b are decreased by DPP-4. SDF-1 a\b plays a significant role in the pathogenesis of many inflammatory disorders and SDF-1 has also been identified as a pro-inflammatory marker. [27]

There were certain limitations in our study. Analysis regarding prescribing pattern of anti-diabetic drug was not done in our study and thus, we couldn't do any analysis on association of ADRs with most and least frequent prescribed drugs.

CONCLUSION

There is significant additional burden of ADRs on patients on type 2 diabetes mellitus who are already at more risk of various metabolic disorders. Proper counselling and measure to improve compliance can decrease the incidence of known adverse effects of anti-diabetic therapy. As anti-diabetic medication is generally taken for lifetime, the risk of development of adverse effects related to concurrent related co-morbidities of patients shouldn't be ignored while prescribing.

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