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Evaluation of suspected adverse drug reactions of oral anti-diabetic drugs in a tertiary care hospital of Bihar, India: An observational study

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ABSTRACT

Background: Diabetic patients generally require life-long treatment and continuous follow up. In spite of their benefit of achieving glycemic control, there are many safety concerns with antidiabetic drugs such as gastrointestinal side effects, metabolic complications, central nervous system (CNS) symptoms, musculo-skeletal problems, genito-urinary disorders like UTI, development of peripheral oedema, weight gain etc.
Aim: To highlight pattern of Adverse Drug Reactions with use of oral anti-diabetic drugs.
Materials and Methods : All suspected Adverse Drug Reaction Reporting Form having any anti-diabetic drug as suspected cause of ADR were collected. The reported ADRs on the notification forms, after being confirmed by the physician-in-charge, were assessed for causality using WHO-UMC Causality Categories14, preventability using Modified-Schumock and Thornton scale15 and severity using Modified Hartwig and Siegel scale.
Statistical analysis: The data from the forms was presented in tabular form and data will be interpreted by using Microsoft Excel 365 software.
Results: Adverse drug reaction related to gastrointestinal system were most reported ADRs (41.31%). Among GI adverse events, nausea was mostly reported ADR and it was mostly associated with DPP-4 inhibitors. Hypoglycemia was most frequently observed in patients taking sulfonylureas. Causality assessment according to WHO-UMC criteria showed 61.68% ADRs had probable causality while 37.43% had possible causality and only 0.90% had certain causality. Most of the ADRs in our study were non-preventable (57.78%) & were of mild to moderate grade.
Conclusion: Hypoglycemia continues to be major concern in patients taking anti-diabetic medications and sulfonylureas were commonest drugs responsible for it. 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. The physician should report these adverse effects to ADR monitoring centre, so that proper signal could be generated for the welfare of the society.

1. Introduction

Diabetes is a metabolic disorder characterized by hyperglycemia due to defects in either insulin secretion, insulin action or both of them. The chronic complications of diabetes are associated with long-term end organ damage, organ dysfunction, and multi- organ failure cause due to microvascular and macrovascular pathophysiology.[1]

The management principles of diabetes comprise of prevention of risk factors, screening of high-risk population and proper life-style modification for individuals in the pre-diabetic state. Pharmacological treatment is the most important option for these patients.[2] The conventional options for type 2 diabetes mellitus include drugs that have been commonly prescribed for long time such as

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Biguanides, Sulfonylureas, α-glucosidase inhibitors, Meglitinides, Thiazolidinedione (TZD), Dipeptidyl Peptidase 4 (DPP-4) Inhibitors and Sodium Glucose Co-transport 2 (SGLT-2) Inhibitors. Drugs continue to be the most common interventions used to achieve glycemic control but drugs themselves have their adverse effect and can adversely have impact on mental and social health. In spite of their benefit of achieving glycemic control, there are many safety concerns with antidiabetic drugs such as gastrointestinal side effects, metabolic complications, central nervous system (CNS) symptoms, musculo-skeletal problems, genito-urinary disorders like UTI, development of peripheral oedema, weight gain etc.[3,4]

Adverse Drug Reactions (ADRs) has been defined by World Health Organization (WHO) 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 this definition has excluded overdose (from either accidental or intentional), drug abuse, treatment failure and errors in drug administration.[5–7]

Diabetic patients generally require life-long treatment and continuous follow up but due to lack of knowledge and awareness many of them continue or discontinue their medications without regular monitoring of blood sugar level.[8–10] So, they are prone to develop adverse drug reactions and detection of ADR in these patients becomes nearly impossible. Therefore, the medications should be individualized for each patient according to HbA1c level and expected long-term benefit with specific safety concerns, as well as by considering fixed dose combinations including side effects, compliance, expense, concurrent co-morbidities etc.[11,12]

The detection of Adverse Drug Reactions (ADRs) has become important due to introduction of large number of drugs in the last two decades. Adverse drug reactions generally occur daily in hospitals adversely affecting patient's life but are often unreported causing considerable morbidity and mortality. Attention must be given in identifying the development of spurious sign and symptoms in patient with higher risk and concurrent co-morbidities. Drugs most commonly responsible the ADR should be suspected first. Increased supply of drugs in the market, promotion by pharmaceutical representatives and an upward trend in polypharmacy are contributing factors for increases evidence and complexities of ADRs worldwide. Adverse drug reactions can lead to loss of patient's confidence on treatment leading to negative emotions toward their physician and discontinuation on treatment and engagement in self-treatment options, which may consequently precipitate additional ADRs and increase mortality and morbidity in population.[12,13]

This study was planned to highlight pattern of Adverse Drug Reactions with use of oral anti-diabetic drugs.

2. Materials and Methods

This study will be conducted at Department of Pharmacology, IGIMS Patna, after approval by institutional ethics committee of IGIMS, Patna (Bihar).

2.1. Study design

Observational study.

2.2. Study duration

6 Months.

2.3. Source of data

Adverse Drug Reaction Monitoring Centers (AMC), Department of Pharmacology, IGIMS Patna, (Bihar).

2.4. Materials

All suspected Adverse Drug Reaction Reporting Form having any anti-diabetic drug as suspected cause of ADR.

2.5. Inclusion criteria

Suspected Adverse Drug Reaction Reporting Form having any anti-diabetic drug as suspected cause of ADR.

2.6. Exclusion criteria

Adverse drug reaction due to overdosing, CKD patients, intensive care patients and gestational diabetic patients were excluded.

2.7. Study design

All suspected Adverse Drug Reaction Reporting Form having any anti-diabetic drug as suspected cause of ADR were collected. The reported ADRs on the notification forms, after being confirmed by the physician-in-charge, were assessed for causality using WHO-UMC Causality Categories,[14] preventability using Modified-Schumock and Thornton scale[15] and severity using Modified Hartwig and Siegel scale.[16] The data from the forms was presented in tabular form and data will be interpreted by using Microsoft Excel 365 software.

3. Results and Discussion

Adverse drug reaction related to gastrointestinal system were most reported ADRs (41.31%). Among GI adverse events, nausea was mostly reported ADR and it was mostly associated with DPP-4 inhibitors. Singh et al. found that most commonly prescribed observed ADRs in their study were related to endocrine and gastrointestinal system.[17]

There is much controversy regarding mechanisms responsible for gastrointestinal adverse effects in patients

Table 1: Frequency of Different Adverse Drug Reactions (ADRs) among Different Anti-Diabetic Drugs.

Type of ADR	No of ADRs	% of ADRs	Associated Drugs (no of ADRs)
Nausea	99	29.64	Sitagliptin (53), Linagliptin (19), Metformin (11), Glimepiride (4), Canagliflozin (7), Voglibose (5)
Hypoglycemia	51	29.64	Glimepiride (27), Sitagliptin (9), Metformin (6), Canagliflozin (3), Voglibose (2), Linagliptin (4)
Urinary Tract Infection	18	5.39	Canagliflozin (11), Metformin (3), Voglibose (1), Glimepiride (2), Sitagliptin (1)
Fever	21	6.29	Canagliflozin (13), Metformin (4), Linagliptin (2), Voglibose (2)
Respiratory Tract Infection	15	4.49	Sitagliptin (9), Linagliptin (3), Canagliflozin (3)
Weight Gain	33	9.88	Glimepiride (22), Pioglitazone (6), Metformin (5)
Constipation	12	3.59	Metformin (4), Pioglitazone (3), Glimepiride (3), Sitagliptin (2)
Diarrhea	18	5.39	Metformin (5), Voglibose (11), Sitagliptin (2)
Hyperglycemia	9	2.69	Metformin (4), Glimepiride (2), Sitagliptin (2), Linagliptin (1)
Abdominal Pain	9	2.69	Sitagliptin (3), Voglibose (3), Metformin (2), Glimepiride (1)
Cough	6	1.80	Sitagliptin (3), Linagliptin (2), Canagliflozin (1)
Edema	7	2.10	Pioglitazone (4), Metformin (2), Sitagliptin (1)
Dizziness	6	1.80	Glimepiride (3), Sitagliptin (2), Metformin (1)
Insomnia	6	1.80	Metformin (2), Glimepiride (2), Sitagliptin (1), Voglibose (1)
Pruritus	9	2.69	Glimepiride (4), Metformin (3), Voglibose (2)
Arthralgia	9	2.69	Sitagliptin (7), Linagliptin (2)
Back pain	6	1.80	Sitagliptin (5) Linagliptin (1)
Total	334	100	

Table 2: Distribution of Suspected ADRs according to WHO-UMC Causality Categories

Type of ADR	Number of ADR	Certain (%)	Probable/Likely (%)	Possible (%)
Nausea	99	0 (0.00)	62 (62.63)	37 (37.37)
Hypoglycemia	51	2 (3.92)	31 (60.78)	18 (35.29)
Urinary Tract Infection	18	0 (0.00)	12 (66.67)	6 (33.33)
Fever	21	0 (0.00)	13 (61.90)	8 (38.10)
Respiratory Tract Infection	15	0 (0.00)	10 (66.67)	5 (33.33)
Weight Gain	33	1 (3.03)	17 (51.52)	15 (45.45)
Constipation	12	0 (0.00)	7 (58.33)	5 (41.67)
Diarrhea	18	0 (0.00)	13 (72.22)	5 (27.78)
Hyperglycemia	9	0 (0.00)	6 (66.67)	3 (33.33)
Abdominal Pain	9	0 (0.00)	5 (55.56)	4 (44.44)
Cough	6	0 (0.00)	4 (66.67)	2 (33.33)
Edema	7	0 (0.00)	4 (57.14)	3 (42.86)
Dizziness	6	0 (0.00)	3 (50.00)	3 (50.00)
Insomnia	6	0 (0.00)	2 (33.33)	4 (66.67)
Pruritus	9	0 (0.00)	7 (77.78)	2 (22.22)
Arthralgia	9	0 (0.00)	6 (66.67)	3 (33.33)
Back pain	6	0 (0.00)	4 (66.67)	2 (33.33)
Total	334	3 (0.90)	206 (61.68)	125 (37.43)

Table 3: Distribution of ADRs based on Preventability using Modified-Schumock and Thornton scale

Categories	Number of ADRs (n=334)	% of ADRs
Definitely preventable ADRs	103	30.84
Probably preventable ADRs	38	11.38
Non-preventable ADRs	193	57.78

Table 4: Distribution of ADRs based on Severity using Modified Hartwig and Siegel scale

Categories	Number of ADRs (n=334)	% of ADRs
Mild	132	39.52
Moderate	197	58.98
Severe	5	1.50

of diabetes mellitus taking oral anti-diabetic drugs. Gastrointestinal symptoms are commonly reported adverse events in patients taking oral hypoglycemic drugs.[18] However, gastrointestinal symptoms are also very common in the world and many persons who are not taking medication also suffer from these, so a causal relationship is very difficult to prove in these ADRs. Furthermore, there is conflicting observations among previous studies done regarding possible risk factors for gastrointestinal side effects in diabetes patients;[19–21] and the most of the studies were lacking proper methodology.

In our study, metformin was frequently associated with diarrhoea. This association between use of metformin and diarrhoea is not a new finding. A questionnaire-based survey was done on 285 diabetic patients in which it was found that metformin was the most common cause of chronic diarrhoea and faecal incontinence, 20% of the patients taking metformin reported these adverse effects.[22] Recently, Lysy et al.[23] also found that the commonest cause of severe diarrhoea in their survey of 861 patients taking anti-diabetic medications. However, these studies haven't investigated on other possible risk factors, like complications related to diabetes mellitus, adequate glycaemic control, sex, age distribution, or use of other concurrent medications, so authenticity of the findings can't be confirmed. The mechanisms of pathogenesis of diarrhoea by taking metformin is not clear. Dandona et al. has hypothesized that increase in intestinal motility caused by metformin can be the reason.[22]

Hypoglycaemia was most frequently observed in patients taking sulfonylureas. Hypoglycaemia is a major limiting factor for use of sulfonylureas. In various studies, there is significant variations in prevalence and severity of hypoglycaemia caused by sulfonylureas.[24–26] In a recently conducted observational study,[27] the yearly risk for development of hypoglycaemia caused by use of sulfonylurea was 1.8% (180 per 10,000 person-years). higher hypoglycaemia risk was associated with long-acting formulations of the drug, chronic kidney disease, old age group and infrequent use of sulfonylureas.

In a recent systematic review,[25] the risks of development of hypoglycaemia with the use metformin was reported to be between 0 and 21%. Since metformin has no direct action on insulin release, risk of hypoglycaemia is generally low.

Arthralgia and back pain were reported from the patients taking DPP-4 inhibitors. Studies conducted among patients with inflammatory disorders have found that decrease in DPP-4 levels are was related with more severity.[28] Furthermore, Busso et al. found in their study that increased level of technetium was found the synovial exudative fluid of mice who were genetically deficient with DPP-4 enzyme.[29] In some other studies, it has been found that levels several inflammatory mediators (including SDF-1 a\b) are decreased by DPP-4. SDF-1 a\b plays a vital role in the pathogenesis of inflammatory disorders and SDF-1 is also confirmed as a pro-inflammatory marker.[30]

Causality assessment according to WHO-UMC criteria showed 61.68% ADRs had probable causality while 37.43% had possible causality and only 0.90% had certain causality. Shanthi et al. found that 64% of the ADRs caused by anti-diabetic drugs in their study were probable.[31] In another study conducted in a tertiary care hospital it was found that 73.33% of ADR were possible.[32]

Most of the ADRs in our study were non-preventable (57.78%) & were of mild to moderate grade. Shanthi et al. found that most of the ADRs in their study were not preventable (63%) as per modified Schumock and Thornton preventability scale and no severe ADR was reported in their study.[31]

4. Conclusion

Gastrointestinal adverse effects were mostly related to DPP-4 inhibitors whereas diarrhoea was frequently reported by patients taking metformin. Hypoglycaemia continues to be major concern in patients taking anti-diabetic medications and sulfonylureas were commonest drugs responsible for it. There were some reports of back pain and arthralgia with the use of DPP-4 inhibitors and some other studies also reports evidences of hyperalgesia caused by DPP-4 inhibitors. The adverse effects should be taken into account while prescribing to patients with related co-morbid conditions. 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. The physician should report these adverse effects to ADR monitoring centre, so that proper signal could be generated for the welfare of the society.

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6. Conflict of Interest

No conflict of interest.

7. Source of Funding

None.

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