JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

ADVERSE DRUG REACTIONS OF ANTI-DIABETIC MEDICATIONS

[1] M.RangaPriya*, [2] R.Manivannan, M.Elamparuthi, C.Elavarasan
[1] Professor, Department of Pharmacy Practice, Excel College of Pharmacy
[2] Principal, Excel College of Pharmacy

***Corresponding Author**
Dr.M.RangaPriya, M.Pharm., Ph.D.,
Professor & Head,
Department of Pharmacy Practice,
Excel College of Pharmacy, Komarapalayam,
Namakkal, Tamilnadu – 638 183

Abstract

Adverse drug reactions (ADRs) continue to be a problem in modern medicine, especially in light of the complexity of therapies, the ageing of the population, and the rise in multimorbidity. Due to an increase in the number of new drug classes, studies have also revealed that admitted patients have a higher frequency of ADR. ADRs accounted for 6.2% of hospitalisations and 3.2% of ADRs during hospitalisation, per an Indian study. Sulphonylureas, thiazolidinediones, alpha-glucosidase inhibitors, and biguanides are diabetes medications that have significant ADR. Compared to patients receiving monotherapy, ADRs are manifested more frequently in patients receiving combo medication. Though there are no absolute contraindications to insulin therapy, the dose of insulin needs to be adjusted and monitored in numerous settings. The most common adverse drug reactions of metformin were lactic acidosis followed by hypoglycemia, hypersensitivity reactions, nausea, decreased appetite, vomiting, weakness, and diarrhoea. Thiazolidinediones have a few negative side effects, especially with prolonged use. Even while some ADRs are unanticipated, like anaphylaxis in a patient after a single uneventful exposure to a penicillin-containing drug, many may be avoided with enough planning and monitoring. However, reducing the likelihood of an ADR happening can be a significant method to lessen the risk of patient damage. Therefore, raising public awareness of the negative effects of anti-diabetic medications is necessary in the modern period. The Pharmacists play a vital role in monitoring ADR, educating the health care team and designing the medication chart. Thus, it is highly significant to frame a systematic protocol in ADR monitoring and managing them.

***Index Terms*:** Adverse drug reactions, anti-diabetic medications, hypersensitivity, absolute contraindications, uneventful exposure, ADR monitoring

INTRODUCTION

The term "side effects" also applies to negative medication reactions. Adverse drug responses (ADRs) are harmful, unplanned, and unwelcome side effects that might develop during pharmacological therapy. These reactions are brought either by self-medication or by using unprescribed medications in excess. Adverse drug reactions might result from the prescription medications' ability to create side effects in addition to their intended impact, majority of negative medication reactions can be avoided.

Adverse drug reactions (ADRs) continue to be a problem in modern medicine, especially in light of the complexity of therapies, the ageing of the population, and the rise in multimorbidity. This page discusses the prevention, diagnosis, reporting, and management of ADRs in current clinical practise, as well as some of the most important information about ADRs.

While research indicates that between 5% and 10% of patients may experience an ADR at admission, during hospitalisation, or at discharge, despite numerous prevention measures, the incidence of ADRs has remained largely stable over time. The approach employed to identify such events is invariably correlated with the event frequency, and the majority of ADRs do not result in significant systemic signs. Nevertheless, given the related morbidity and mortality, the potential financial burden, and the potential impact on the prescriber-patient relationship, it is important to carefully examine the frequency of potential damage.

Antiplatelet, anticoagulant, cytotoxic, immunosuppressant, diuretic, antidiabetic, and antibiotic medications have all been specifically linked to ADR-related hospital admissions. When fatal ADRs do occur, haemorrhage is frequently blamed on them, with an antithrombotic/anticoagulant co-administered with an NSAID being the most frequently suspected culprit.

Due to an increase in the number of new drug classes, studies have also revealed that admitted patients have a higher frequency of ADR. ADRs accounted for 6.2% of hospitalisations and 3.2% of ADRs during hospitalisation, per an Indian study.

DIABETES MELLITUS

The prevalence of diabetes mellitus is a significant global health issue. Hyperglycemia, a chronic metabolic disease brought on by impaired insulin secretion, resistance to insulin action, or a combination of the two, characterises diabetes mellitus. Type I and type II diabetes mellitus have different classifications. Any harmful, unanticipated, or undesirable medication effect that develops at levels administered to humans for prevention, diagnosis, or treatment is known as an ADR. This does not include drug misuse, intentional and unintentional poisoning, or failed therapies. Types A, B, C, D, E, F, and U adverse medication reactions are all possible. Sulphonylureas, thiazolidinediones, alpha-glucosidase inhibitors, and biguanides are diabetes medications that have significant ADR. CHF, hypoglycaemia associated with human insulin analogue, hypersensitivity associated with sulphonylurea, and renal function impairment associated with biguanides are all seen in thiazolidinediones[1].

The first-line therapy for the treatment of Type II diabetes is oral hypoglycemic medication. These medications, either as monotherapy or in combination with insulin, are widely used to treat Type II Diabetes because they are both cost-effective and safe[2]. Oral antidiabetic drugs have demonstrated a variety of adverse drug reactions (ADRs) in the various racial populations, in addition to their capacity to lower plasma levels,[3]Biguanides, Sulfonylureas, Meglitinide, Thiazolidinediones, and SGLT2 Inhibitors are commonly prescribed medications for Type II Diabetes Mellitus patients who are taking oral anti-diabetic medications. These patients frequently experience hypoglycemia, gastrointestinal distress, dizziness, bloating, and diarrhoea [4]. Compared to patients receiving monotherapy, ADRs are manifested more frequently in patients receiving combo medication [5].

ANTI-DIABETIC MEDICATIONS

TYPE I DIABETES

Insulin

The beta cells of the pancreatic islets of Langerhans release insulin, a peptide hormone that controls blood glucose levels, into the body [6]. When the body's need for insulin increases or production is insufficient, medical treatment with insulin is necessary.

Adverse Effects

Insulin side effects can be divided into two categories: those brought on by the medication itself and those brought on by a particular delivery method. By far, the most frequent side effect of insulin therapy is hypoglycemia[7]. Weight gain and, less frequently, electrolyte changes like hypokalemia are the other side effects of insulin therapy, especially when combined with other medications that also cause hypokalemia.

There are negative effects from administering via the subcutaneous approach as well. The most frequent side effects of daily subcutaneous injections include pain and lipodystrophy at the injection site. The population that uses the subcutaneous method for insulin delivery also experiences other negative consequences such peripheral hyperinsulinemia and poor compliance.

Those who take insulin before bed may experience the Somogyi effect, where they awaken with high blood sugar levels. This effect happens when insulin induces a hypoglycemic state in the body, which triggers the antihyperglycemic hormones like cortisol and adrenaline, resulting in rebound hyperglycemia. This effect can be treated by lowering the dose of bedtime insulin or switching the time of insulin dosing.

The dawn phenomenon is when the body has high blood sugar levels in the early morning hours because of insufficient insulin production. To reverse this occurrence, the dose of bedtime insulin must be increased to maintain stable blood glucose levels during the night and into the early morning [8].

Contraindications

Though there are no absolute contraindications to insulin therapy, the dose of insulin needs to be adjusted and monitored in numerous settings.

- As insulin is metabolised in the liver and discharged in the urine, insulin dosage needs to be adjusted in individuals with renal impairment and liver failure.
- In patients with a history of hypoglycemic episodes, the dosage of insulin and blood glucose levels should be closely monitored.
- Medications like diuretics that also cause hypokalemia shouldn't be taken with insulin.
- Clinicians and patients should use caution when delivering insulin because it also produces hypokalemia. Vomiting and diarrhoea cause a hypokalemic state in the body.
- Since insulin preparations contain cresol, they should not be used by people who are sensitive to it.

TYPE II DIABETES

Metformin

Metformin is a dimethyl biguanide and first-line agent for the treatment of type 2 diabetes. The most common adverse drug reactions were lactic acidosis followed by hypoglycemia, hypersensitivity reactions, nausea, decreased appetite, vomiting, weakness, and diarrhoea.

Adverse Effects

Gastrointestinal intolerance (widespread)

Gastrointestinal side effects include diarrhoea, nausea, meteorism, and constipation and affect approximately 20% of the patients [9, 10].

Most of the metformin hydrochloride salt's absorption occurs in the small intestine when it is typically taken orally. The organic cation transporter 1 (OCT1) is responsible for drug transport, and the quantity inside the enterocyte can be up to 300 times higher than the level in the circulation [11]. Metformin also enhances the generation of lactate inside the enterocyte and the consumption of glucose in the anaerobic cycle. Adverse responses may be linked to localised increased lactate production [12].

Altered Taste(frequent)

The accumulation and secretion of metformin in saliva can result in a side effect known as taste disturbance, and the salivary glands' high levels of the organic cation transporter OCT3—which carries metformin and may be involved in this side effect's mechanism—can also contribute to this effect [13].

Sulfonylureas

Sulfonylureas are the oldest class of oral antidiabetic medication dating back to the 1950s. All sulfonylureas contain a phenyl-sulfonyl-urea structure, which exerts the hypoglycemic effect. Patients with type 2 diabetes mellitus use sulfonylureas as monotherapy or in combination with other oral or injectable medications [14].

Adverse Effects

Regardless of the levels of serum glucose, sulfonylureas promote the release of insulin. As a result, the most frequent adverse effect of sulfonylureas and a significant cause for concern is hypoglycemia. When blood glucose levels fall below 70 mg/dL, hypoglycemia sets in [15]. Patients may experience tachycardia, shakiness, irritation, disorientation, perspiration, and a sense of hunger. Particularly after skipping a meal, working out, or taking large doses of sulfonylureas, hypoglycemia may be severe.

Sulfonylureas have a high propensity for binding to plasma proteins, therefore when certain drugs displace sulfonylureas from their plasma protein binding sites, the risk of hypoglycemia rises. Sulfonamides, gemfibrozil, and warfarin are a few examples [16].

Thiazolidinediones

Thiazolidinediones, often known as "glitazones" can help with glycemic control and insulin resistance when used to treat type 2 diabetes. The FDA has currently approved the use of two thiazolidinediones, rosiglitazone and pioglitazone, either alone or in combination with metformin or sulfonylureas, to treat type 2 diabetes mellitus. In addition to lifestyle changes like diet, exercise, and weight loss, these drugs should be taken. Thiazolidinediones may also be used to treat polycystic ovarian syndrome due to their potential to enhance ovulation, lower insulin resistance, and enhance endothelial function. In individuals with nonalcoholicsteatohepatitis (NASH), pioglitazone selectively lowers hepatic fat and may improve liver fibrosis; however, other factors and dangers need to be assessed in NASH patients. The main benefit of TZDs is that they are safe to use in people with renal impairment and do not cause hypoglycemia when used alone [17].

Adverse Effects

Thiazolidinediones have a few negative side effects, especially with prolonged use. Before using TZDs, patients should be informed about the risks and benefits and try several other first-line medications.

Edema and Congestive Heart Failure

Up to 20% of individuals who take TZDs have been observed to experience dose-related fluid retention. PPAR-gamma receptors in the distal nephron and insulin-activated epithelial sodium channels in the collecting tubules are two mechanisms for fluid retention. Acting at the same location as aldosterone, PPAR-gamma activation promotes salt reabsorption. Patients who already have edoema or are taking insulin concurrently are more likely to develop edoema, thus they should begin treatment with the lowest dose possible [18,19]. Diuretics such thiazides or spironolactone if the edoema is minor, or loop diuretics for severe cases, will typically work to reduce fluid retention in patients. Additionally, edoema and weight gain are reduced at lower doses of 15 and 30 mg per day.

Congestive heart failure has been reported because of an increase in intravascular volume. As a result, individuals who have diastolic dysfunction or a history of CHF should utilise TZDs with caution. Rosiglitazone has a higher risk of death and heart failure than pioglitazone [20].

Weight Gain

Most PPAR-gamma receptors in the body are found in adipocytes. There are several contributing variables that make up the process for the weight increase. The central nervous system's PPAR-gamma receptors are up regulated by TZDs, which increases appetite. TZD medications increase the bulk of adipose tissue by maturing preadipocytes into mature adipocytes and by promoting the uptake of free fatty acids into cells [11,12]. Retention of fluids might also make you weigh more. The visceral region is largely spared while fat accumulation takes place in the subcutaneous tissues. Like edoema and CHF, concurrent insulin administration makes weight gain worse, but the risk is reduced when metformin and lower doses of TZDs are used.

Fractures

In comparison to people on insulin or other oral medications like sulfonylureas, research has shown that patients receiving TZDs have a higher risk of fracture and lower bone density. The diverted differentiation of osteoblasts into adipocytes, which results in bone loss, is thought to be caused by PPAR-gamma activation and insulin-like growth factor down-regulation [21]. Forearm, wrist, ankle, foot, and tibia

fractures appear to be more common in the distal extremities than in the axial skeleton (hip, pelvis, and femur). Additional risk factors, such as postmenopausal women or individuals using proton pump inhibitors (PPIs) or glucocorticoids concurrently, raise the risk of fracture even more [22].

Bladder Cancer

Pioglitazone has been linked in some studies to an increased risk of bladder cancer. The variation in this impact is time- and dose-dependent. Moreover, most recent investigations do not suggest an elevated risk. In contrast, rosiglitazone was never linked to a higher risk of bladder cancer, demonstrating that the risk is medication-specific and not a class effect [23].

Hepatotoxicity

The primary reason that troglitazone, the original PPAR-gamma activator, was taken off the market was hepatotoxicity. The two medications, rosiglitazone and pioglitazone, have, on the other hand, infrequently been connected to acute liver damage. It is advised to monitor alanine aminotransferase levels at baseline and on a regular basis, as well as any clinical signs of liver damage [23, 24].

Diabetic Macular Edema

At 1-year and 10-year follow-up, TZD and insulin therapy have been associated with an increased incidence of diabetic macular edoema. However, more research is being done to determine the frequency of this adverse event and to assess confounding variables [25].

Increased Ovulation and Teratogenic Effects

When taking TZD and other insulin sensitizers, patients with polycystic ovarian syndrome have demonstrated an enhanced ovulation rate. Some an ovulatory premenopausal women may ovulate because of this impact, increasing the likelihood of spontaneous pregnancies. By reducing foetal maturation, TZDs have also been demonstrated to have some teratogenic potential. Premenopausal women should utilise contraception if they are not seeking to get pregnant and switch to another insulin sensitizer, like metformin, after pregnancy [25,26].

PREVENTING ADVERSE DRUG REACTIONS

Even while some ADRs are unanticipated, like anaphylaxis in a patient after a single uneventful exposure to a penicillin-containing drug, many may be avoided with enough planning and monitoring. Preventability (or avoid ability) typically refers to the extent to which the drug treatment plan is at odds with the most recent evidence-based guidelines or is impractical in light of the available information[25]. Despite the fact that preventability is much easier to identify in retrospect, epidemiological studies often indicate that between a third and a half of ADRs are (at least possibly) preventable. However, reducing the likelihood of an ADR happening can be a significant method to lessen the risk of patient damage.

There are two basic steps that can be followed to prevent an ADR occurring:

- Determine the subset of patients who are most likely to experience the negative effect and adjust your treatment plan accordingly.
- Ensure that any potential negative effects are minimized in the treatment strategy.

IDENTIFYING SUSCEPTIBILITY

Knowing the patient's susceptibilities will help you make better prescription choices and lower the possibility of an adverse drug reaction. Any prior ADRs will be noted in a patient's medication history, preventing further exposure to the medication. Other times, risk variables for developing an ADR, like age, gender, pregnancy status, and ethnicity, can aid in predicting the likelihood that it will occur. Angiotensin-II receptor blockers, rather than ACE inhibitors, should be prescribed to patients of African or Caribbean descent with hypertension, according to National Institute for Health and Care Excellence guidance, given the possibility of ACE inhibitor-induced angioedema.

ANTIDIABETIC DRUGS AND ADVERSE DRUG REACTIONS

Adverse reactions of anti-diabetic medication include hypoglycemia, hypersensitivity, hypoglycemic coma, hepatotoxicity, drug-induced erythema multiforme, photodermatitis, and others. Therefore, raising public awareness of the negative effects of anti-diabetic medications is necessary in the modern period [26,27].

Table 1: Antidiabetic drugs and reported ADR

Class of antidiabetic drug	Example	Dosage form	Reported ADR
Thiazolidinedione antidiabetic	Actos	Tablet	Upper respiratory tract infection, headache, sinusitis, Myalgia, Tooth disorder, pharyngitis
Human insulin analog	Apidra	Subcutaneous injection solution	Nasopharyngitis, Upper respiratory tract infection, headache, influenza, Vomiting, Cough, ear infection, abdominal pain
Sulfonylurea class	Glipizide	Tablet	A headache, dizziness, weakness, numbness, pain, skin sensitivity, tremor, blurred vision, insomnia, diarrhea, nausea, constipation.
Biguanides	Metformin	Tablet	Trouble breathing, dizziness, nausea, vomiting, slow heart rate, diarrhea, stomach pain,
Dipeptidyl peptidase-4 (dpp-4) inhibitor	Sitagliptin	Tablet	skin/subcutaneous tissue disorders, Nasopharyngitis, Constipation, Peripheral edema, Pharyngitis, Osteoarthritis, URI.
Alpha-glucosidase inhibitor	Acarbose		Flatulence, diarrhea, abdominal pain

Table 2 :Summary of Key Benefits and Risks of Medication

	MET	DPP4 inhibitor	GLP-1 Agonist (Incretin mimetic)	SU	Glinide
Risks Hypoglycemia	Neutral	Neutral	Neutral	Moderate	Mild
Gastrointestinal symptoms	Moderate	Neutral	Moderate	Neutral	Neutral
Risk of use with renal insufficiency	Severe	Reduce Dosage	Moderate	Moderate	Neutral

Contraindicated in liver failure or predisposition to lactic acidosis	Severe	Neutral	Neutral	Moderate	Moderate
Heart failure / edema	Use with caution in CHF	Neutral	Neutral	Neutral	Neutral
Weight gain	Benefit	Neutral	Benefit	Mild	Mild
Fractures	Neutral	Neutral	Neutral	Neutral	Neutral
Drug-Drug Interactions	Neutral	Neutral	Neutral	Moderate	Moderate

CARDIOVASCULAR RISK IN ANTI-DIABETIC TREATMENT

The main cause of morbidity and death in diabetic patients is cardiovascular disease; therefore, it is important to choose anti-diabetic medications that do not raise cardiovascular risk but may lower the risk of cardiovascular diseases and other problems. Recent studies on diabetic patients with heart failure revealed a distinct reaction to conventional medicine, with these patients more likely to experience adverse effects than those with the same degree of heart failure but without diabetes. Therefore, a rigorous pharmacological therapy selection strategy is essential to maximizing diabetic treatment with a focus on cardiovascular safety [26].

The creation, evaluation, and prescription of anti-diabetes medicines presents unique issues for researchers, doctors, and regulating authorities considering the results from glycemic control trials and the connections between anti-diabetes drugs and cardiovascular risk. To begin with, it's important to find treatments that can reduce cardiovascular risk while enhancing glycemic control. Given that diabetes mellitus is linked to several cardiovascular risk factors, such as obesity, high blood pressure, high cholesterol, systemic inflammation, and endothelial dysfunction, which are not always improved with treatment of hyperglycemia, the lack of a consistent association between improved glycemic control and improved cardiovascular outcomes is perhaps not surprising. In fact, numerous studies have recently demonstrated that treating diabetes with a multifactorial strategy improves outcomes.

In order to prevent the already existing high cardiovascular risk that people with type 2 diabetes experience, it is important to guarantee that both present and future medications do not increase it. The Food and Drug Administration (FDA) created new criteria for assessing the cardiovascular effects of anti-diabetes drugs in response to concerns regarding the possibility for poor cardiovascular outcomes with anti-diabetes therapy.[27]

CONCLUSION

The study indicates that there is a high risk of ADR generation due to irrational use of anti-diabetic medication. Monitoring of ADR's is very essential to manage the therapy in a proper manner and to bring down non-compliance as well as the ill effects of the medication. The Pharmacists play a vital role in monitoring ADR, educating the health care team and designing the medication chart. Thus, it is highly significant to frame a systematic protocol in ADR monitoring and managing them.

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