Review Article

Antidiabetic Drugs: An Overview

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ABSTRACT

Diabetes mellitus is one of the world's major diseases. It currently affects an estimated143 million people worldwide and the number is growing rapidly. In the India, about 1-5% population suffer from diabetes or related complication. So there is need to cure this disease. Anti-diabetic drugs treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide, and pramlintide, all are administered orally and are thus also called oral hypoglycemic agents or oral antihyperglycemic agents. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors. Diabetes mellitus type 1 is a disease caused by the lack of insulin. Insulin must be used in Type 1, which must be injected or inhaled. Diabetes mellitus type 2 is a disease of insulin resistance by cells. Treatments include agents which increase the amount of insulin secreted by the pancreas, agents which increase the sensitivity of target organs to insulin, and agents which decrease the rate at which glucose is absorbed from the gastrointestinal tract. Researchers around the world mainly focused on insulin, insulin analogues, oral hypoglycemic agents and various other complementary and alternate medicines to control the blood glucose levels in diabetes. The present review summarizes the various antidiabetic drugs for the treatment of diabetes mellitus.

Keywords: Diabetes mellitus, Blood glucose, antidiabetic drugs.

INTRODUCTION

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long–term damage, dysfunction and failure of various organs. Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non–ketotic hyperosmolar state may develop and lead to stupor, comaand, in absence of effective treatment, death[1,2]. Often symptoms are not severe, or may be absent, and consequently hyperglycaemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made. The long–term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease[3].

CLASSIFICATION OF DIABETES MELLITUS

Earlier classifications

The first widely accepted classification of diabetes mellitus was published by WHO in 1980 (1) and, in modified form, in1985 (3). The 1980 and 1985 classifications of diabetes mellitus and allied categories of glucose intolerance included clinical classes and two statistical risk classes. The 1980Expert Committee proposed two major classes of diabetes mellitus and named them, IDDM or Type 1, and NIDDM or Type 2. In the 1985 Study Group Report the terms Type 1and Type 2 were omitted, but the classes IDDM and NIDDM were retained, and a class of

Malnutrition–related Diabetes Mellitus (MRDM) was introduced. In both the 1980 and 1985 reports other classes of diabetes included Other Types and Impaired Glucose Tolerance (IGT) as well as Gestational Diabetes Mellitus (GDM). These were reflected in the subsequent International Nomenclature of Diseases (IND) in1991, and the tenth revision of the International Classification of Diseases (ICD–10) in 1992. The 1985 classification was widely accepted and is used internationally. It represented acompromise between clinical and aetiological classification and allowed classification of individual subjects and patients in a clinically useful manner even when the specific cause oraetiology was unknown. The recommended classification includes both staging of diabetes mellitus based on clinical descriptive criteria and a complementary aetiological classification.

Revised classification

The classification encompasses both *clinical stages* and *aetiological types* of diabetes mellitus and other categories of hyperglycaemia, as suggested by Kuzuya and Matsuda.The clinical staging reflects that diabetes, regardless of its aetiology, progresses through several clinical stages during its natural history. Moreover, individual subjects may move from stage to stage in either direction. Persons who have, or who are developing, diabetes mellitus can be categorized by stage according to the clinical characteristics, even in the absence of information concerning the underlying aetiology. The classification by aetiological type results from improved understanding of the causes of diabetes mellitus.

Antidiabetic drugs are used to lower the concentration of glucose in the blood of people with diabetes mellitus. By keeping the blood sugar at or close to the normal range, these medicines reduce some of the risks associated with diabetes. Antidiabetic drugs exert their useful effects through: (1) increasing insulin levels in the body or (2) increasing the body's sensitivity (or decreasing its resistance) to insulin, or (3) decreasing glucose absorption in the intestines[4,5].

Antidiabetic Drugs

Insulin

The hormone insulin s endogenously release from the β cells of pancreas. Patients with type 1 diabetes mellitus have an absolute deficiency of insulin and patients with type-2 diabetes mellitus may also have decreased production of endogenous insulin. Insulin is required for all type-1 diabetic patients as a lifelong treatment. Insulin is commonly used in type-2 diabetic patients as either adjunct therapy to oral antidiabetic agents or as monotherapy as a disease progress. Various substitutions on insulin molecule and other modification led to multiple types of insulin. These characterized and administered based on their pharmacodynamic and pharmacokinetic characteristics such as onset, peak, duration of action. Most significantly they are classified as rapid-acting, short- acting , intermediate-acting or long-acting types of insulin.

Mechanism of action for drug class

Insulin lowers blood glucose by peripheral glucose uptake, especially in skeletal muscle fat and by inhibiting hepatic glucose production.

Usage for the drug class

Type -1 diabetes mellitus, Type -2 diabetes mellitus, hyperkalemia, DKA/diabetic coma.

Dosing for drug class

Initial dose: 0.5-1 unit/kg per day sub-Q.

Maintenance dose

Adjust doses to achieve premeal and bed time glucose level of 80-140 mg/dl **Renal dosage adjustment:** CrCl 10-50 ml/min: administer 75% of normal dose CrCl< 10 ml/min: administer 25-50% of normal dose.

Adverse reaction

Most Common Hypoglycemia, weight gain.

Adverse reaction
Rare/sever/Important
Severe hypoglycemia, edema, lipoatrophy or lipohypertrophy at site of injection. **Major drug interaction for the drug class-Drug Affecting Insulin (Decrease Hypoglycemic Effect):** Acetazolamide, Diuretic, Oral contraceptives, Albuterol, Epinephrine, Phenothiazine, Asparginase, Tolbutaline, Corticosteroids, HIV antiviral, Diltiazem, Lithium, Thyroid hormones. **Drug Affecting Insulin (Increase Hypoglycemic Effect):** Alcohol, Fluoxitine, Sulphonamides, Anabolic steroids, β blocker, Clonidine. **Cntraindications for the drug class:** Use during severe hypoglycemia. Allergy or sensitivity to any ingredient of the product.

Types of Insulin
Insulin Glulisine
Brand Name
Apidra**. Generic Name:** Insulin Glulisine (rapid acting insulin) **Dosage Forms:** Injection 100 units/ml **Dosing:** Administer Sub-Q 15 min before or immediately after starting a meal.

Insulin Lispro
Brand Name
Humalog
Generic Name
Insulin lispro (rapid acting insulin)
Dosage Forms
Injection 100 units/ml. **Dosing:** Administer Sub-Q 15 min before or immediately after starting a meal.

- **Insulin NPH**

Brand Name
HumulineN, Novolin N
Generic Name
Insulin NPH (intermediate acting insulin)
Dosage Forms
Injection, Suspensions 100 units/ml.
Dosing
PH should mix only with regular insulin. Draw regular insulin into the syringe first; then add NPH insulin into the syringe.
Insulin regular
Brand Name
Humuline R, Novolin R
Generic Name
Insulin regular (short acting insulin)
Dosage Forms
Injection 100 units/ml.
Dosing
Administer Sub-Q 30 min before a meal.

Insulin Glargine
Brand Name
Lantus
Generic Name
Insulin Glargine
Dosage Forms
Injection 100 units/ml.
Dosing
When changing to Insulin Glargine from once- daily NPH, the initial dose of insulin glargine should be the same. When changing to Insulin Glargine from twice-daily NPH, the initial dose of insulin glargine should be reduced by 20% 7 adjusted according to patient response.

- Administer once daily
- Starting dose in type 2 diabetic patient is 10 units at bed time and titrate according to patient response.

- **Insulin Detemir**

Brand Name
Levemir
Generic Name
Insulin Detemir (long acting insulin)

Dosage Forms
Injection 100 units/ml.

Dosing
- Indicated for once or twice daily dosing
- Once daily is dosed Sub-Q with the evening meal or bed time.
- Twice daily dosed every 12 hours.

Insulin Aspart
Brand Name
Novolog
Generic Name
Insulin aspart (rapid acting insulin)
Dosage Forms
Injection 100 units/ml.
Dosing
Administer Sub-Q 15 min before or immediately after starting a meal.

70% NPH and 30% Rgular Insulin Mixture
Brand Name
Humuline 70/30, Novolin 70/30
Generic Name
70% NPH and 30% Rgular Insulin Mixture
Dosage Forms
Injection, Suspensions 100 units/ml.
50% NPH and 50% Rgular Insulin Mixture
Brand Name
Humuline 50/50
Generic Name
50% NPH and 50% Rgular Insulin Mixture
Dosage Forms
Injection, Suspensions 100 units/ml.
75% Intermediate acting Lispro Suspension and 25% Rapid acting Lispro Solution
Brand Name
Humalog Mix 75/25
Generic Name
75% Intermediate acting Lispro Suspension and 25% Rapid acting Lispro Solution
Dosage Forms
Injection 100 units /ml.
70% Intermediate Acting Insulin Aspart Suspension and 30% Rapid Acting Aspart Solution
Brand Name:
Novolog Mix 70/30
Generic Name
70% Intermediate Acting Insulin Aspart Suspension and 30% Rapid Acting Aspart Solution
Dosage Forms
Injection 100 units/ml.

Oral hypoglycemic agents
Biguanides
The Biguanides metformin is the drug of choice as initial therapy for a newly diagnosed patient with type 2 diabets as an adjunct to diet and exercise.Metformin is contraindicated in certain patient to prevent lactic acidosis, as rare but serious side effect.It is offen used in combination with other antidiabetic agents and/or insulin patients who do not reach glycemic goal on these therapies HbAlc reduction with metformin generally between 1.5% to 2%.

Mechanism of action for drug class
Improves glucose tolerance by lowering both basal and postprandial plasma glucose.Decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Metformin
Brand Names
Fortamet, Glucophage, Glucophage XR, Glumetza, Riomet. **Generic Names**
Metformin, Metformin extended release.
Dosage Forms
Tablets, Extended release tablets, oral solution.
Usage
Type 2 diabetes mellitus, PCOS, antipsychotic–induced weight gain.
Dosing
Initial dose
500 mg twice daily with morning and evening meals,850 mg once daily with meal,500 mg extended release once daily with meal.
Maintenance dose
2000-2550 mg daily in divided doses or 2000 mg extended release once daily.
Renal dosage adjustment Not recommended in patients with renal dysfunction (see contraindication below)
Adverse reaction
Most Common Diarrhea, vomiting. dyspepsia, flatulence, metallic taste, weight loss. **Adverse reaction: Rare/Sever/Important** Lactic acidosis, megaloblastic anemia.
Major Drug Interactions
Drugs Affecting Metformin**,** Alcohol potentiates lactate metabolism**,** Iodinated contrast media can lead to acute renal failure and metformin toxicity.

Contraindications
Renal disease, heart failure requiring pharmacologic therapy,acute or chronic metabolic acidosis, active liver disease.

DI- PEPTIDYL PEPTIDASE-4 INHIBITOR
Sitagliptin is the first Di peptidyl peptidase-4 (DPP-4) inhibitor available.It inhibits the breakdown of active GLP-1through the inhibition of the enzyme DPP-4. Active

GLP-1 is release from α cells of pancreas in response to food intack.GLP-1plays role in regulating blood glucose by increasing secretion of insulin from the pancreas in glucose dependent manner.GLP-1 also help in regulate glucagon secretion and decreases hepatic glucose production. Sitagliptin is also used as monotherapy as an adjunct to diet and exercise or in combination with other oral antidiabetic agents in patients who do not reach glycemic goals. Average HbAlc reductions are between 0.7% and 1%.

Mechanism of action for drug class
Inhibition of DPP-4 enhances the activity of active GLP-1,thus increasing glucose-dependent insulin secretion and decreasing level of circulating glucagon and hepatic glucose production[6].

Members of drug class
Sitagliptin
Brand Name
Januvia
Generic Name
Sitagliptin
Dosage Forms
Tablets
Usage
Type 2 diabetes mellitus
Dosing
100 mg daily once with or without food.
Renal dosage adjustment
50 mg once daily: CrCl>=30 to <50 ml/minute. 25 mg once daily: CrCl<30 ml/minute.
Adverse reaction
Most Common Nasopharyngitis, Nausea, diarrhea, vomiting, hypoglycemia, weight loss.
Adverse reaction
Rare/sever/Important Acute pancreatitis, rash (Steven- Johnson Syndrome). **Major Drug Interactions** Sitagliptin effects on other drugs. Digoxin: Increased levels
Sulfonylureas
The sulfonylureas are used as adjuctants to diet and exercise in patient with type-2 diabetis mellitus. Although periodically used as monotherapy, sulfonylureas are more commonly used in combination with other oral antidiabetic agents in patient who do not reach glycemic goals, sometimes in the same formulation. General dosing guidelines are to start with low dose and titrate according to patient response while monitoring singh and symptoms of hypoglycemia, which is common adverse effect. Use caution in patient with renal and hepatic impairment. HbAlc reductions between 1% and 2%.

Mechanism of action for drug class
Lowers blood glucose level by stimulating insulin release from β cells of pancreatic islets.
Glimepiride
Dosage Form
Tablets **Dosing**
Initial dose
1 -2 mg once daily at breakfast.
Maintenance dose
1 -8 mg once daily.
Glipizide
Brand Name
Glucotrol, Glucotrol XL
Generic Name
Glipizide, Glipizide extended –release.
Dosage Form
Tablets, extended – release tablets.
Dosing
Initial dose
Glucotrol: 2.5-5 mg once daily 30 minutes before breakfast. Glucotrol XL: 5 mg extended- release once daily with breakfast.
Maintenance dose
Glucotrol: 10-40 mg(>15 mg/day should be divided). Glucotrol XL: 5-20 mg extended- release once daily.

Thiazodinediones
The thiazodinediones, pioglitazone and rosiglitazone decrease insulin resistance by enhancing insulin -receptor sensitivity. They are used as adjuncts to diet or exercise in patients with type-2 diabetes mellitus.Although periodically used as monotherapy, thiazodinediones are more frequently used in combination with other oral antidiabetic agents and/or insulin in patients who do not reach glycemic goals. Recent clinical data suggest that patients taking thiazodinediones may be at increased risk of myocardial infarction and death, and so they should be used with caution in patients with history of previous

cardiac disease. They are not recommended in patients with NYHA class III and IV heart failure. A structurally similar thiazodinedione, troglitazone, was removed from the market due to liver failure and death. It is recommended to avoid used in patients with hepatic dysfunction. HbAlc reduction is between 1 % - 1.5%.

Mechanism of action for drug class

Increase insulin sensitivity by affecting the peroxisome proliferator activated receptor γ (PPAR γ) acting as agonist to these receptors, they decreases insulin resistance in adipose tissue, skeletal muscle and the liver[4,5,6].

Usage for the drug class

Type -2 diabetes mellitus.

Adverse reaction

Most Common

Weight gain. Edema, hypoglycemia (when used with insulin or other oral antidiabetic drugs that may cause hypoglycemia)

Adverse reaction: Rare/sever/Important

Hepatic failure, heart failure, anemia, ovulation in anovulatory, premenopausal woman, bone loss.

Members of the drug class

In this section: Pioglitazone, rosiglitazone

CONCLUSION

Diabetes is a life-long disease marked by elevated levels of sugar in the blood. It is the second leading cause of blindness and renal disease worldwide. Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by ineffectiveness of the insulin produced. It is a silent killer disease and affects millions of peoples in the world. This article focuses on the causes, types, factors affecting DM, incidences, preventive measures and treatment of the acute and chronic complications of diabetes with summarizes the accounts of antidiabetic drugs. The emphasis has been laid in particular on the new potential biological targets and the possible treatment as well as the current ongoing research status on new generation hypoglycemic agents.

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