Review Article

Diabetes Mellitus – Treatment Using Bi-layer Tablets Containing Fixed-Dose Combination of Antidiabetic Agents

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ABSTRACT

Diabetes mellitus is one of the world's major diseases. It currently affects an estimated 143 million people worldwide and the number is growing rapidly. In 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. Bi-layer tablets can be given to the patients who are taking medication separately for controlling blood sugar level, or whose diabetes cannot be controlled by Metformin HCl alone. The present review summarizes the use of combination of various antidiabetic drugs for the effective treatment of diabetes mellitus and thereby providing superior efficacy and allowing more patients to reach their glycemic targets compared to continuing Metformin HCl monotherapy usually.

Keywords: Diabetes mellitus, Blood glucose, Oral hypoglycemic agents, Metformin HCl.

INTRODUCTION

Diabetes mellitus (DM) is probably one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago. In 1936, the distinction between type 1 and type 2 DM was clearly made. Type 2 DM was first described as a component of metabolic syndrome in 1988. Type 2 Diabetes mellitus (formerly known as non-insulin dependent Diabetes mellitus) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency. Type 2 Diabetes Mellitus results from interaction between genetic, environmental and behavioural risk factors. People living with type 2 DM are more vulnerable to various forms of both short- and long-term complications, which often lead to their premature death. This tendency of increased morbidity and mortality is seen in patients with type 2 DM because of the commonness of this type of DM, its insidious onset and late recognition, especially in resource-poor developing countries like Africa.[1-2]

Lifestyle, Genetics, and Medical Conditions

Type 2 DM is due primarily to lifestyle factors and genetics. A number of lifestyle factors are known to be important to the development of type 2 DM. These are physical inactivity, sedentary lifestyle, cigarette smoking and generous consumption of alcohol. Obesity has been found to contribute to approximately 55% of cases of type 2 DM. The increased rate of childhood obesity between the 1960s and 2000s is believed to have led to the increase in type 2 DM in children and adolescents. Environmental toxins may contribute to the recent increases in the rate of type 2 DM.[3-4] A weak positive correlation has been found between the concentration in the urine of bisphenol A, a constituent of some plastics, and the incidence of type 2 DM. There is a strong inheritable genetic connection in type 2 DM, having relatives (especially first degree) with type 2 DM increases the risks of developing type 2 DM substantially. Concordance among monozygotic twins is close to 100%, and about 25% of those with the disease have a family history of DM. Monogenic forms like Maturity-onset diabetes of the young (MODY), constitutes up to 5% of cases. There are many medical conditions which can potentially give rise to, or exacerbate type 2 DM. These include obesity, hypertension, elevated cholesterol (combined hyperlipidemia), and with the condition often termed metabolic syndrome (it is also known as Syndrome X, Reaven's syndrome). Other causes include acromegaly, Cushing's syndrome, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, cancer, and drugs. Additional factors found to increase the risk of type 2 DM include aging, high-fat diets, and a less active lifestyle.[5]

Pathophysiology[6]

Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure. This leads to a decrease in glucose transport into the liver, muscle cells, and fat cells. There is an increase in the breakdown of fat with hyperglycemia. The involvement of impaired alpha-cell function has recently been recognized in the pathophysiology of type 2 DM. As a result of this dysfunction, glucagon and hepatic glucose levels that rise during fasting are not suppressed with a meal. Given inadequate levels of insulin and increased insulin resistance, hyperglycemia results. The incretins are important gut mediators of insulin release, and in the case of GLP-1, of glucagon suppression. Although GIP activity is impaired in those with type 2 DM, GLP-1 insulinotropic effects are preserved, and thus GLP-1 represents a potentially beneficial therapeutic option. However, like GIP; GLP-1 is rapidly inactivated by DPP-IV *in vivo*.

Two therapeutic approaches to this problem have been developed: GLP-1 analogues with increased half-lives, and DPP-IV inhibitors, which prevent the breakdown of endogenous GLP-1 as well as GIP. Both classes of agents have shown promise, with potential not only to normalize fasting and postprandial glucose levels but also to improve beta-cell functioning and mass. Studies are on going on the role of mitochondrial dysfunction in the development of insulin resistance and etiology of type 2 DM. Also very important is adipose tissue, as endocrine organ hypothesis (secretion of various adipocytokines, i.e., leptin, TNF-alpha, resistin, and adiponectin implicated in insulin resistance and possibly beta-cell dysfunction). A majority of individuals suffering from type 2 DM are obese, with central visceral adiposity. Therefore, the adipose tissue plays a crucial role in the pathogenesis of type 2 DM. Although the predominant theory used to explain this link is the portal/visceral hypothesis giving a key role in elevated non-esterified fatty acid concentrations, two new emerging theories are the ectopic fat storage syndrome. (Deposition of triglycerides in muscle, liver and pancreatic cells) These two hypotheses constitute the framework for the study of the interplay between insulin resistance and beta-cell dysfunction in type 2 DM as well as between our obesogenic environment and DM risk in the next decade.

Screening and Diagnosis

Tests for screening and diagnosis of Diabetes mellitus are readily available. The test recommended for screening is the same as that for making diagnosis, with the result that a positive screen is equivalent to a diagnosis of pre-diabetes or Diabetes mellitus. Although about 25% of patients with Diabetes Mellitus already have microvascular complications at the time of diagnosis suggesting that they have had the disease for more than 5 years at the time of diagnosis. It is still based on the American Diabetic Association (ADA) guidelines of 1997 or World Health Organization (WHO) National diabetic group criteria of 2006, which is for a single raised glucose reading with symptoms (polyuria, polydipsia, polyphagia and weight loss), otherwise raised values on two occasions, of either fasting plasma glucose (FPG) 37.0 mmol/L (126 mg/dL) or with an oral glucose tolerance test (OGTT), two hours after the oral dose a plasma glucose³ 11.1 mmol/L (200 mg/dL).

The 1997 ADA recommendations for diagnosis of DM focus on the FPG, while WHO focuses on the OGTT. The glycated hemoglobin (HbA1c) and fructosamine is also still useful for determining blood sugar control over time. However, practicing physicians frequently employ other measures in addition to those recommended. In July 2009, the International Expert Committee (IEC) recommended the additional diagnostic criteria of an HbA1c result³ 6.5% for DM.

This committee suggested that the use of the term pre-diabetes may be phased out but identified the range of HbA1c levels³ 6.0% and <6.5% to identify those at high risk of developing DM.

As with the glucose-based tests, there is no definite threshold of HbA1c at which normality ends and DM begins. The IEC has elected to recommend a cut-off point for DM diagnosis that emphasizes specificity, commenting that this balanced the stigma and cost of mistakenly identifying individuals as diabetic against the minimal clinical consequences of delaying the diagnosis in a patient with an HbA1c level <6.5%.

Classification[3]

Insulin and Insulin Analogue

Mechanism of action

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

Short-Acting Preparations

Regular insulin (animal), Regular Human Insulin, Buffered regular insulin, Insulinlispro, Insulinaspart, Insulinglargine.

Intermediate-Acting Preparations

NPH insulin (animal), NPH humaninsulin, Lenteinsulin (animal), Lentehuman insulin

Long-Acting Preparations

Ultralente human insulin, Insulin glargine, Insulin detemir

Insulinotropic Agents (Sulfonylureas)

Mechanism of action: Lowers blood glucose level by stimulating insulin release from β cells of pancreatic islets.

First-Generation Sulfonylurea

Tolbutamide, Tolazamide, Acetohexamide, Chloropropamide

Second-Generation Sulfonylurea

Glyburide, Glipizide, Glimepride, Gliquidone

Glinides (Meglitinides)

Repaglinide, Nateglinide

Insulin Sensitizing Agents

Biguanides

Mechanism of action

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. E.g. Metformin, Buformin

Thiazolidinediones

Mechanism of action

Increase insulin sensitivity by affecting the peroxisome proliferator activated receptorγ (PPAR γ) acting as agonist to these receptors, they decreases insulin resistance in adipose tissue, skeletal muscle and the liver. E.g. Rosiglitazone, Pioglitazone, Troglitazone

Alpha-Glucoside Inhibitors

Mechanism of action

They usually reduce absorption of complex carbohydrate from GI tract. Alpha-glucosidase inhibitors belong to the class a-glucosidase inhibitors act mainly to delay and decrease the absorption of complex carbohydrates from the gastrointestinal tract. Under normal conditions, the enzyme a-glucosidase generates glucose in the gastrointestinal tract by hydrolyzing the dietary oligosaccharides such as starch, dextrin, and maltose. E.g. Acarbose, Miglitol

Di-Peptidyl Peptidase-4 Inhibitors

Mechanism of action

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. E.g. Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Anagliptin, Teneligliptin, Alogliptin

Drug Therapy using Individual Antidiabetic Agent

Table 3 and table 4 indicate various antidiabetic agents most commonly used for a Monotherapy for treatment of diabetes mellitus.

Table 1: Diagnostic criterion for Diabetes Mellitus[7]

Types of Diabetes	Diagnostic criteria	
	Fasting plasma glucose mg/dL (mmol/L)	2 hrs. plasma glucose mg/dL (mmol/L)
Normal	<100 (5.6)	< 140 (7.8)
Impaired fasting glucose	100-125 (5.6-6.9)	----
Impaired glucose tolerance	----	140-199 (7.8-11.0)
Diabetes mellitus	≤126 (7.0)	or ≤200 (11.1)

Table 2: Insulin to Treat Type 2 Diabetes[7]

Name of Drug	Brand Name	Generic Name	Dosage Form	Dosing
Insulin Glulisine	Apidra	Insulin Glulisine (rapid acting insulin)	Injection 100 units/ml	Administer Subcutaneous 15 min before or immediately after starting a meal.
Insulin Lispro	Humalog	Insulin lispro (rapid acting insulin)	Injection 100 units/ml	Administer Subcutaneous 15 min before or immediately after starting a meal.
Insulin NPH	Humuline N, Novolin N	Insulin NPH (intermediate acting insulin)	Injection, Suspensions 100 units/ml.	NPH should be mixed only with regular insulin.
Insulin regular	Humuline R, Novolin R	Insulin regular (short acting insulin)	Injection 100 units/ml.	Administer Subcutaneous 30 min before a meal.
Insulin Glargine	Lantus	Insulin Glargine	Injection 100 units/ml.	Once daily at any time during the day. It should be administered at the same time every day.
Insulin Detemir	Levemir	Insulin Detemir (long acting insulin)	Injection 100 units/ml.	Once or twice daily subcutaneous with the evening meal or bed time.
Insulin Aspart	Novolog	Insulin aspart (rapid acting insulin)	Injection 100 units/ml.	Administer Sub-Q 15 min before or immediately after starting a meal.

Table 3: Oral Hypoglycaemic agents used to Treat Type 2 Diabetes[7]

Name of Drug	Brand Name	Generic Name	Dosage Form	Dosing
Metformin	Fortamet, Glucophage, Glucophage XR, Glumetza, Riomet.	Metformin, Metformin extended release.	Tablets, Extended release tablets, Oral solution.	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.
Sitagliptin	Januvia	Sitagliptin	Tablets	100 mg daily once with or without food.
Glipizide	Glucotrol, Glucotrol XL	Glipizide, Glipizide extended release.	Tablets, Extended release tablets.	Initial dose - Glucotrol - 2.5-5 mg once daily Glucotrol XL: 5 mg extended release once daily Maintenance dose - Glucotrol: 10-40 mg, Glucotrol XL: 5-20 mg extended release once daily.
Rosiglitazone	Avandia	Rosiglitazone	Tablets	Initial dose - 4 mg once daily, Maintenance dose - 8 mg once a day
Miglitol	Glyset	Miglitol	Tablets	Initial dose - 25 mg orally 3 times a day with each meal. Maintenance dose - 50 mg orally 3 times a day
Acarbose	Precose	Acarbose	Tablets	Initial dose - 25 mg orally 3 times a day. Maintenance dose - 50 to 100 mg orally 3 times a day.

Table 4: Combination of Oral Hypoglycemic Agents[19-20]

Brand Name	Class	Combination of Drugs	Primary Action	Typical Dosage (mg)
Glucovance™	Sulfonylureas and Biguanide	Glyburide and Metformin	Decreases hepatic glucose production and increases insulin secretion.	Initial Dose - 1.25/250 once or twice a day, Second line - 2.5-5/500 to maximum of 7.5/1500 twice a day
Metaglip™	Sulfonylureas and Biguanide	Glipizide and Metformin	Decreases hepatic glucose production and increases insulin secretion.	Initial - 2.5/250 once or twice a day Second line - 2.5–5/500 twice a day
Avandamet™ Actoplus Met™	Thiazolidinedione and Biguanide	Rosiglitazone and Metformin, Pioglitazone and Metformin	Decreases hepatic glucose production, increases glucose uptake and Insulin.	15 mg/500 mg to 15 mg/850 mg
Avandaryl™	Sulfonylurea and Thiazolidinedione	Glimepiride and Rosiglitazone	Decreases insulin resistance and increases insulin	4 mg/8 mg once daily
Janumet	Biguanide and DPP-IV inhibitor	Metformin and Sitagliptin	Decreases hepatic glucose production, and enhances pancreatic islet cell responsiveness to glucose	500 mg/50 mg to 1000 mg/50 mg
Janumet XR	Biguanide and DPP-IV inhibitor	Metformin ER and Sitagliptin		500 mg ER/50 mg, 1000 mg ER/50 mg and 1000 mg ER/100 mg
GALVUMET®	Biguanide and DPP-IV inhibitor	Metformin and Vildagliptin		500 mg/50 mg, 850 mg/50 mg to 1000 mg/50 mg

Disadvantages of Individual Therapy

Therapy using individual antidiabetic agent is often associated with the risk of hypoglycemia, weight gain and alteration of common cardiovascular risk factors (hypertension and lipid profile). Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems.

Combination Therapy[8-10]

Combinations of two or more oral agents with different mechanisms of action are often used for the management of hyperglycaemia in type 2 diabetes. While these combinations have customarily been taken as separate tablets, several fixed-dose single tablet combinations are now available. These are based on bioequivalence with the separate tablets, giving similar efficacy to the separate tablets and necessitating the same cautions and contraindications that apply to each active component. Fixed-dose combinations can offer convenience, reduce the pill burden and simplify administration regimens for the patient. They increase patient adherence compared with equivalent combinations of separate tablets, and this is associated with some improvements in glycaemic control. Presently available antidiabetic fixed-dose combinations include Metformin combined with a Sulphonylurea, Thiazolidinedione, Dipeptidylpeptidase- 4 inhibitor or Meglitinide as well as Thiazolidinedione–Sulphonylurea combinations, each at a range of dosage strengths to facilitate titration. Anticipated future expansion of multiple drug regimens for diabetes management is likely to increase the use of fixed-dose single tablet combinations.

Therapy Using Bi-Layer Tablets Containing Fixed-Dose Combination of Antidiabetic Agents

Bilayer tablet provides successful development of controlled release formulation along with various features to make a successful drug delivery system. Bi-layer tablets have improved beneficial technology to overcome the drawbacks of the single layer tablet by ensuring safety and improved efficacy of drug as well as patient compliance. Bilayer tablets have enabled the delivery of Active Pharmaceutical Ingredients (API) with predetermined drug release profile by combining layers with various release patterns or by combining slow release with immediate release layer. The technology is appropriate for combination of two drugs and also for biphasic release where, one layer is an initial dose and other layer is maintenance dose. Furthermore, bi-layer tablet technology can administer incompatible drugs in combination as well as same drug with different release rate. The concept of bi-layer tablet avoids frequent administration of dosage form in diseases like diabetes, hypertension, inflammation, asthma to offer better patients compliance.[11] Fixed-dose single tablet combinations of antidiabetic agents offer several potential advantages over separate tablets, particularly associated with compliance. They also impose the same cautions associated with separate tablet combinations.[12-14]

Bi-layer tablets can be given to the patients who are taking medication separately for controlling blood sugar level, or whose diabetes cannot be controlled by Metformin HCl alone. Various combinations of antidiabetic agents are available in market as depicted in table no 5. Metformin is an oral antidiabetic drug in the bigunide class. It is the first drug of choice for the treatment of type 2 diabetes mellitus, in particular in overweight and obese people and those with normal kidney function. Metformin works by suppressing glucose production by the liver. Metformin is the only antidiabetic drug that has been conclusively shown to prevent the cardiovascular complications of diabetes. It helps reduce LDL cholesterol and triglyceride levels, and is not associated with weight gain. As of 2010, Metformin HCl is one of only two oral antidiabetic in the World Health Organization Model List of Essential Medicines.[15]

DPP-IV inhibitors are novel oral antidiabetic agent that enhances pancreatic islet cell responsiveness to glucose. These produce no weight gain. Main advantages of drugs are they are given orally with very less gastrointestinal side effects like vomiting and nausea.[11] An extensive clinical program involving approximately 22,000 patients and 7000 patient-years of exposure to DPP-IV inhibitor has shown that the agent is well tolerated and efficacious in improving glycemic control in patients with type 2 diabetes mellitus (T2DM). Monotherapy trials have shown that significant HbA1c lowering is accompanied by body weight-neutral and lipid-neutral effects, low risk of edema, and low risk of hypoglycemia. These characteristics make DPP-IV inhibitor an ideal partner for combination therapy. Studies of DPP-IV inhibitor as an add-on to Metformin have shown significant improvements in glycemic control (comparable to that of thiazolidinedione add-on), with the combination being well tolerated and associated with low risks for hypoglycemia and adverse effects on weight or lipid levels.

Disadvantages of combination therapy[16-18]

All forms of combination therapy require special vigilance to comply with the contraindication; precautions and monitoring that apply to both agents. Interactions between the different classes of antidiabetic agents are rare, but a potentially heightened risk of hypoglycaemia must be appreciated, especially when aiming for near-normal levels of glycaemia. Appropriate selection of the combination and the starting dose should take this into account, noting that agents that do not usually precipitate hypoglycaemia as monotherapy may

nevertheless act together to lower glycaemia into the subnormal range.

CONCLUSION

Fixed-dose combinations of oral antidiabetic agents are slowly becoming established as convenient options in the treatment of type 2 diabetes. They can simplify administration and improve compliance, especially for patients taking many different therapies. The combination of two oral anti-diabetic agents with complementary mechanisms of action provides superior efficacy and allows more patients to reach their glycemic targets compared to continuing Metformin HCl monotherapy usually. Fixed-dose combinations provide an expedience for extra medication without extra tablets.

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