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Review Article

A Review of Nateglinide in the Management of Type 2 Diabetes

Mistry Ripal*, Haresh T. Mulani
Department of Pharmaceutics
Indubhai Patel College of Pharmacy and Research Centre,
Dharmaj, Gujarat, India
*rx.ripalmistry@gmail.com

ABSTRACT

Diabetes mellitus, or simply diabetes, is a chronic disease that occurs when the pancreas is no longer able to make insulin, or when the body cannot make good use of the insulin it produces. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. The success of oral hypoglycemic drug therapy is usually based on are storation of normal blood glucose levels. Traditionally, the term oral hypoglycemic was used interchangeably with sulfonylureas, but more recently the development of several new drugs has broadened this designation to include all oral medications for diabetes. Nateglinide, a D-phenylalanine derivative, is a novel insulinotropic drug which has recently been launched as a therapeutic agent for Type II diabetes. Clinical studies have shown that nateglinide induces a rapid onset of insulin release synergistic with meal administration which effectively restores the early phase of insulin secretion. Since the loss of early insulin secretion is thought to play an important role in the development of glucose in tolerance the ability of nateglinide to promote early insulin release is potentially of considerable therapeutic benefit.

Keywords: Nateglinide, diabetes mellitus, Glucose Homeostasis

INTRODUCTION

Vast amounts of literature have been written about the current and growing epidemic of diabetes mellitus (DM) and its associated complications. The cost of diabetes to the United States healthcare system is staggering, amounting to $100billion in direct and indirect expenditures annually. Currently 15 million Americans have diabetes, one third of whom have yet to be diagnosed.[1] Now worldwide 375 million people are suffer from diabetes mellitus (DM)and India has the second highest number of people with diabetes in the world which is expected to increase to 101.2 million by the year 2030. Type 2 diabetes accounts for approximately 85 to 90 percent of all the diabetics in the country. [2] The recent rise in obesity in the United States accounts for much of the observed and anticipated rise in cases of diabetes mellitus in this country. Although insulin treatment has greatly increased the life expectancy of the diabetic patient, diabetes remains the third leading cause of death by disease, the second leading cause of blindness, and the second leading cause of renal failure. Diabetes mellitus is a heterogeneous group of disorders characterized by abnormalities in carbohydrate, protein, and lipid metabolism. The central disturbance in diabetes mellitus is an abnormality in insulin production or action or both, although other factors can be involved. Hyperglycemia is a common end point for all

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types of diabetes mellitus and is the parameter that ismeasured to evaluate and manage the efficacy of diabetestherapy. [3,4]

Disease Profile:

Type 2 diabetes mellitus is a progressive disease with an insidious onset. [5] The high incidence and prevalence of this condition, the chronic nature and the high costs associated with the disease and its complications make type 2 diabetes mellitus an ideal candidate for disease management.

According to the American Diabetes Association (ADA) the criteria for the diagnosis of diabetes mellitus are:

- the presence of the classic symptoms of the disease (polyuria, polydypsia and unexplained weight loss) plus a plasma glucose level of ≥11.1 mmol/L (sampled at any time of the day without regard to time since the last meal), or
- a fasting (no caloric intake for ≥8 hours) plasma glucose (FPG)level of ≥7 mmol/L, or
- a 2-hour postload plasma glucose level of ≥11.1 mmol/L[corresponds to a glycosylated hemoglobin (HbA1c) of ≈6.9%]during an oral glucose tolerance test.

The World Health Organization recommends that both FPG level and 2-hour post load plasma glucose level are taken, with the tests confirmed on different days. [1] In many cases, type 2 diabetes mellitus begins as a symptomless disease. Acute symptoms are only manifest when the plasma glucose level is well above its normal range; however, as it progresses, the disease is characterized by the appearance of microvascular and macrovascular complications. Indeed, macrovascular complications can start even before type 2 diabetes mellitus is diagnosed.

Anatomy of Pancrease : [7]

The pancreas is located deep in the abdomen, 12-15 cm long, sandwiched between the stomach and the spine. It lies partially behind the stomach. The other part is nestled in the curve of the duodenum (small intestine). The pancreas is formed of a broad, right extremity, the head, a main part, the body, and a narrow, left extremity, the tail. The ductal system consists of 20 to 30 small lobular ducts, which coalesce to form the main pancreatic duct.

The main pancreatic duct enters the duodenal wall with the biliary duct at the papilla of Vater in the majority of humans (90%), the rest having the accessory duct and the papilla as the main routes for pancreatic secretion.

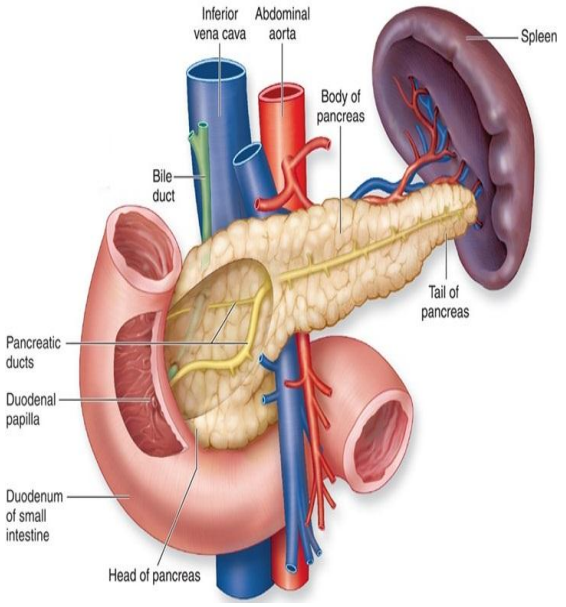

Figure 1: Anatomy of Pancrease

Glucose Homeostasis : [8]

Carbohydrates, particularly glucose, are an important source of fuel for living organisms. Glucose is a major energy source for all cells, and some tissues (e.g., brain) need a continuous delivery of glucose. Maintenance of serum glucose concentrations within a normal physiological range, critical to the maintenance of normal fuel use, is primarily accomplished by two pancreatic hormones, insulin and glucagon. Derangements of glucagon or insulin regulation can result in hyperglycemia or hypoglycemia, respectively.

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Glucose penetrates most tissues slowly unless insulin is present to facilitate its uptake; however, central nervous system (CNS) cells, capillary endothelial cells, gastrointestinal epithelial cells, pancreatic cells, and renal medullary cells are freely permeable to glucose. The endocrine portion of the pancreas, called the islets of Langerhans, consists of cordlike groups of cells arranged along pancreatic capillary channels. Two major types of secretory cells exist within the islets: α-cells, which produce glucagon; and β-cells, which produce insulin. Other cell types are also present in the islets, including the δ-cells, which secrete somatostatin, and PP cells, which produce pancreatic polypeptide. These pancreatic cells monitor changes in the availability of small calorigenic molecules, namely glucose, and to a lesser extent amino acids, ketone bodies, and fatty acids. Pancreaticβ-cells appropriately alter their rates of insulin secretion in response to fluctuations in the levels of these calorigenic molecules, with glucose playing the dominant role in regulation of insulin secretion. Pancreatic α-cells secrete glucagon in response to increases in amino acid and fatty acid levels; however, glucose inhibits glucagon secretion. If blood glucose levels fall (e.g., during hypoglycemia or fasting), glucagon secretion is augmented, providing a counter regulatory hormonal response that stimulates gluconeogenesis in the liver and other tissues to avoid hypoglycemia.

Blood glucose concentrations are strictly maintained within homeostatic limits by a variety of biochemical and physiological control mechanisms. Circulating glucose levels are determined by the balance among absorption, storage, production, and use (metabolic rate). Glucagon and insulin are the two most important hormones that maintain glucose homeostasis when blood concentrations are perturbed.

Type of Diabetes mellitus : [8,9,10]

Diabetes mellitus has been traditionally classified into insulin-dependent diabetes mellitus (IDDM), also known as type I (formerly called juvenile-onset diabetes mellitus), and non–insulin-dependent diabetes mellitus (NIDDM), also known as type II (formerly referred to as adult-onset diabetes mellitus).

Type 1 diabetes (Insulin-Dependent Diabetes Mellitus)

This form of diabetes, which accounts for only 5–10% of those with diabetes, called by the terms Insulin Dependent Diabetes or Juvenile-onset diabetes, results from a autoimmune destruction of the cells of the pancreas. The factor or factors that trigger this autoimmune response are unknown. The progression of the autoimmune response is characterized by lymphocytic infiltration and destruction of the pancreatic cells resulting in insulin deficiency. In this form of diabetes, the rate of b-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Some patients, particularly children and adolescents, may present with ketoacidosis as the first manifestation of the disease.

Type II diabetes (Non-Insulin-Dependent Diabetes Mellitus)

This form of diabetes, which accounts for ;90–95% of those with diabetes, called as Non–Insulin-Dependent Diabetes, type 2 diabetes, or adult onset diabetes, encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency. In contrast, type II is not an autoimmune process and may or may not be insulin dependent; that is, a diabetic state that is most effectively managed by insulin therapy. In this type of DM pancreas doesn't produce enough insulin or defective responsiveness of body tissues to insulin is believed to involve. Most patients with this form of diabetes are

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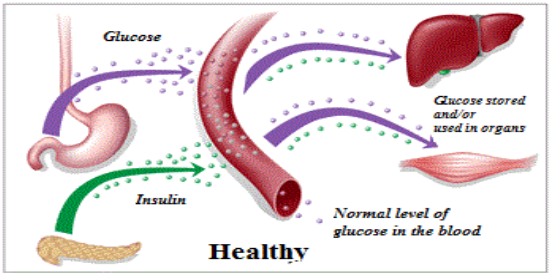
obese, and obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region.

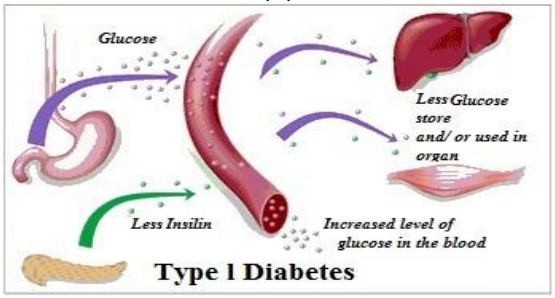
Table 1: Features Of Type I And Type II Diabetes Mellitus

Characteristic	Type I	Type II
Onset (age)	Usually ≤ 30	Usually ≥ 40
Type of onset	Abrupt	Gradual
Nutritional status	Often thin	Often obese
Clinical symptoms	Polydipsia,polyuria, polyphagia	Often asymptomatic
Ketosis	Present	Usually absent
Endogenous insulin	Absent	Variable
Insulin therapy	Required	Sometimes

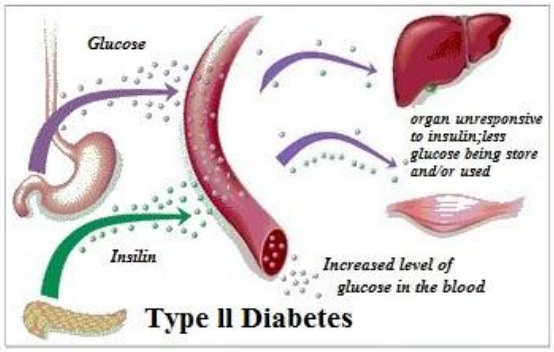
Because the incidence of diabetes is high in families of persons with NIDDM, a strong genetic predisposition is suspected. However, NIDDM is most likely a polygenic disease, involving multiple genetic predispositions to the development of the diabetic state. The three major metabolic abnormalities that contribute to hyperglycemia in NIDDM are defective glucose-induced insulin secretion, increased hepatic glucose output, and inability of insulin to stimulate glucose uptake in peripheral target tissues.



(1)



(2)



(3)

Figure 2 : 1) Glucose uptake in Healthy person. 2) In DM 1 less Insulin release and more glucose in blood stream. 3) In DM 2 the organ unresponsive to the released Insulin

Current Management Strategies :

The success of oral hypoglycemic drug therapy is usually based on a restoration of normal blood glucose levels. Traditionally, the term oral hypoglycemic was used interchangeably with sulfonylureas, but more recently the development of several new drugs has broadened this designation to include all oral medications for diabetes.

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Table 3.4: Classification of Antidiabetic drug

Classifaction :	
Sulfonylureas:-	
First generation analogs Acetohexamide Acetohexamide Chlorpropamide Tolazamide	Second generation analogs Glibenclamide Glipizide Glicazide
Meglitinides	
Repaglinide Nateglinide	
Biguanides:	
Phenformin Metformin	
α-Glucosidase inhibitors	
Acarbose Miglitol	
Thiazolidinediones	
Ciglitazone Pioglitazone	

The success of oral hypoglycemic drug therapy is usually based on a restoration of normal blood glucose levels. Traditionally, the term oral hypoglycemic was used interchangeably with sulfonylurea's, but more recently the development of several new drugs has broadened this designation to include all oral medications for diabetes.

NATEGLINIDE [11-18]

In the normal individual the pancreatic β-cell responds in a biphasic manner to insulin secretagogues (such as glucose and amino acids). Essentially there is an early burst of insulin release within the initial 10 minutes and a second-phase characterized by a progressive increase in insulin secretion lasting up to several hours. The early burst of insulin secretion is critically important as it plays an important role in priming target tissues of insulin, especially the liver, responsible for normal glucose homeostasis following food uptake. The loss of first-phase insulin secretion in response to glucose occurs relatively early in the development of T2DM and the early impairment of the functional integrity of plasma incretins, ie, glucagon-like peptide 1(GLP-1) and gastric inhibitory peptide (GIP), has a major contribution to the β-cell deterioration and failure to suppress glucagon release post-meal. As a result, an excessive prolonged insulin release from the pancreas will manage to eventually return glucose levels back to normal. Therefore, the patient is obligated to experience a prolonged period of hyperglycemia and hyperinsulinemia.

Nateglinide is an insulinotropic agent that restores the physiological pattern of insulin secretion lost in T2DM in a transient and glucose-sensitive manner and thus can control glucose mealtime excursions. Nateglinide can be used inmonotherapy, in order to control excessive mealtime glucose spikes early in the development of diabetes, or in combination with other agents that have complementary modes of action, such as metformin or

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glitazones, thus providing better overall chronic glycemic control by reducing HbA1c .

Mechanism of Action : [19,20]

Nateglinide activity is dependent on the presence functioning β cells and glucose. In contrast to sulfonylurea insulin secretatogogues, nateglinide has no effect on insulin release in the absence of glucose. Rather, it potentiates the effect of extracellular glucose on ATP-sensitive potassium channel and has little effect on insulin levels between meals and overnight. As such, nateglinide is more effective at reducing postprandial blood glucose levels than fasting blood glucose levels and requires a longer duration of therapy (approximately one month) before decreases in fasting blood glucose are observed. The insulinotropic effects of nateglinide are highest at intermediate glucose levels (3 to 10 mmol/L) and it does not increase insulin release already stimulated by high glucose concentrations (greater than15 mmol/L). Nateglinide appears to be selective for pancreatic β cells and does not appear to affect skeletal or cardiac muscle or thyroid tissue.

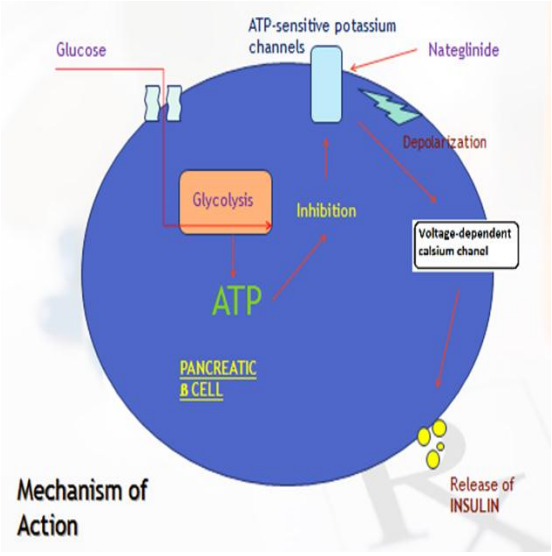

Figure 3: Mechanism of action of nateglinide

Absorption : [19,20]

Following oral administration immediately prior to a meal, nateglinide is rapidly absorbed with mean peak plasm a drug concentrations (Cmax) generally occurring within 1 hour (Tmax) after dosing. When administered to patients with Type 2 diabetes over the dosage range 60 mg to 240 mg three times a day for one week, nateglinide demonstrated linear pharmacokinetics for both AUC (area under the time/plasma concentration curve) and Cmax. Tmax was also found to be independent of dose in this patient population. Absolute bioavailability is estimated to be approximately 73%. When given with or after meals, the extent of nateglinide absorption (AUC) remains unaffected. However, there is a delay in the rate of absorption characterized by a decrease in Cmax and a delay in time to peak plasma concentration (Tmax). Plasma profiles are characterized by multiple plasma concentration peaks when nateglinide is administered under fasting conditions. This effect is diminished when nateglinide is taken prior to a meal.

Distribution :

Based on data following intravenous (IV) administration of nateglinide, the steady-state volume of distribution of nateglinide is estimated to be approximately 10 liters in healthy subjects. Nateglinide is extensively bound (98%) to serum proteins, primarily serum albumin, and to a lesser extent α1 acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1-10 µg/mL.

Metabolism : [19,20]

Hepatic, via cytochrome P450 isoenzymes CYP2C9 (70%) and CYP3A4 (30%). Metabolism is via hydroxylation followed by glucuronidation. The major metabolites have less antidiabetic activity than nateglinide, but the isoprene minor metabolite has antidiabetic activity comparable to that of nateglinide.

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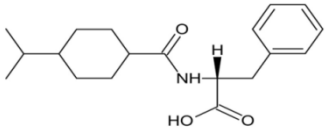
Excretion : [19,20]

Nateglinide and its metabolites are rapidly and completely eliminated following oral administration. Within 6 hours after dosing, approximately 75% of the administered 14C-nateglinide was recovered in the urine. Eighty-three percent of the 14C-nateglinide was excreted in the urine with an additional10% eliminated in the feces. Approximately 16% of the 14C-nateglinide was excreted in the urine as parent compound.

Physicochemical Properties :

CHARACTERISTIC	PROFILE
Name	Nateglinide
Structure	
Formula	$C_{19}H_{27}NO_3$
CAS No.	105816-04-4
IUPAC Name	3-phenyl-2-[(4-propan-2-ylcyclohexanecarbonyl)amino]propanoic acid
Categories	Hypoglycemic Agents; Meglitinides
Bioavailability	73%
Protein binding	98%
BCS class	class II
Route of elimination	Urine (83%) and feces (10%)
water solubility	8.48-03 g/l
logP	4.21±0.43
Plasma Half life	1.5 hr
Peak plasma concentration	1 hour
Duration of action	<4 hours
HbA1c reduction	0.5%–1%

Contraindications : Diabetic ketoacidosis; IDDM. Lactation

Warnings /Precautions :

Geriatric patients, debilitated and malnourished patients; adrenal or pituitary insufficiency, moderate to severe hepatic impairment; severe renal impairment. Monitor glycaemic levels during periods of stress. Pregnancy.

Adverse Reactions :

Dizziness; back pain; arthropathy; upper respiratory tract infection; flu-like symptoms; bronchitis; cough; hypoglycaemia; accidental trauma; diarrhoea.

Drug Interactions :

Increased levels/effects with enzyme inhibitors (e.g. fluconazole). Increased hypoglycaemic effects with salicylates, MAOIs, nonselective â-blockers, alcohol, NSAIDs. Decreased levels/effects with enzyme inducers (e.g. rifampicin). Decreased hypoglycaemic effects with thiazide diuretics, corticosteroids, thyroid products and sympathomimetic agents.

CONCLUSION

Nateglinide when given to subjects with T2DMjust before meals decreases mealtime glucose excursions which improves overall glycemic control with a minimal risk of hypoglycemia. Compared with placebo, HbA1c values are approximately 1% lower after

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nateglinide therapy. This non-sulfonylurea entity seems to be particularly appropriate for the control of postprandial hyperglycemia. It also, allows a more flexible lifestyle and the possibility to skip a meal without the risk of hypoglycemia that would be experienced with glibenclamide therapy. Conversely, an additional meal can be incorporated into the meal plan, preceded by an extra dose without worsening glycemic control.

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