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A REVIEW OF NATEGLINIDE IN THE MANAGEMENT OF TYPE 2 DIABETES

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ABSTRACT

Nateglinide is oral hypoglycemic agent approved for alone use or in combination with metformin for the treatment of type 2 diabetes mellitus. Nateglinide is amino acid derivative of D- phenylalanine, binds to the ATP potassium channels in pancreatic beta cells and stimulates the secretion of insulin. Approximately one month therapy is required for decrease in fasting blood glucose level. It lowers postprandial blood glucose level and also reduces HbA1c level. Nateglinide is effective at lowering postprandial blood glucose than metformin, sulfonylureas and thiazolidinediones. It is rapidly and completely absorbed in small intestine and has high bioavailability. It is extensively metabolized in liver and excreted in urine and feces.

KEYWORDS: Hypoglycemic agent, diabetes mellitus, nateglinide, metformin, postprandial, HbA1c level.

INTRODUCTION

It is oral hypoglycemic agent used for treatment of non insulin dependent diabetes mellitus. Nateglinide is amino acid derivative of D- phenylalanine, binds to the ATP potassium channels in pancreatic beta cells and stimulates the secretion of insulin. It should only be taken with meals. It lowers postprandial blood glucose level and also reduces HbA1c level which is reflective of the last 8-10 weeks of glucose control. It is more effective than metformin, sulfonylureas and thiazolidinediones. It is extensively metabolized in the liver and excreted in urine and feces.

Name	Dosage	Strength
Nateglinide	Tablet	60mg/1
Nateglinide	Tablet, coated	60mg/1 120 mg/1
Nateglinide	Tablet , film coated	60mg/1

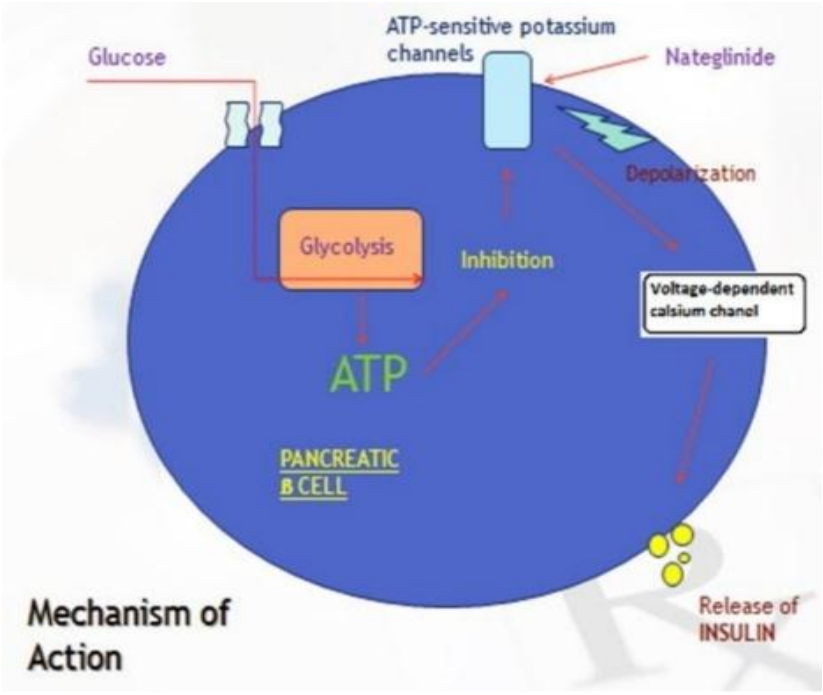
Structure

IUPAC NAME: 3- phenyl-2-[(4-propan-2-ylcyclohexanecarbonyl)amino]propanoic acid.

Mechanism of action

Cellular membrane potential controls the insulin secretion from pancreatic β-cells. It is regulated through relationship between ATP-sensitive potassium channels and extracellular glucose level. Extracellular glucose enters the cell via GLUT2 transporter. Glucose is metabolized in the cell to produce ATP. High concentration of ATP inhibits ATP-sensitive potassium channels causing membrane depolarization.

When extracellular concentration of glucose is low, ATP- sensitive potassium channel opens causing membrane repolarization. High glucose concentration cause ATP-sensitive potassium channel to close resulting in membrane depolarization and opening of L-type calcium channels. The influx of calcium ions stimulates calcium dependent exocytosis of insulin granules. Nateglinide increases insulin release by inhibiting ATP sensitive potassium channel in a glucose dependent manner.



Pharmacodynamics

Activity of nateglinide is dependent on the presence of pancreatic β-cells and glucose. 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. Nateglinide is more effective at reducing postprandial blood glucose levels than fasting blood glucose levels and requires a longer duration of therapy. 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 concentration (greater than 15mmol/L). Nateglinide affects only on pancreatic β-cells and does not affect skeletal or cardiac muscle or thyroid tissue.

Parameter	**Effect**
Administration	Oral
Absorption	Rapidly absorbed prior to meal
Bioavailability	73%
Peak Plasma Concentration	Within 1 hour of oral administration
Onset Of Action	<20 minutes
Duration Of Action	Approximately 4 hours.
Volume Of Distribution	10 liters in healthy subject
Protein Binding	98% to serum protein and to lesser extent to α1 acid glycoprotein
Metabolism	Hepatic via cytochrome p450 isoenzymes CYP2C9 and CYP3A4. Metabolized by hydroxylation followed by glucuronidation.

Route Of Elimination	Urine (83%) and feces (10%)
Half Life	1.5 hours
Hba1c Level**.**	0.5% – 1%
Clearance	Not available
Toxicity	Over dose results in hypoglycemic symptoms.
Food Interaction	Take 30 minutes before meal.

Contraindication

Diabetic ketoacidosis, IDDM, lactation.

Precautions

Geriatric patient, debilitated and malnourished patients; adrenal and pituitary insufficiency, moderate to severe hepatic impairment; severe renal impairment. Monitor glycemia levels during periods of stress, pregnancy.

Adverse reactions

Dizziness, back pain, arthropathy, upper respiratory tract infection, flu like symptoms, bronchitis, cough, hypoglycemia, accidental trauma, diarrhea.

Drug interaction

Increased levels with enzyme inhibitors (e.g. fluconazole). Increased hypoglycemic effects with salicylates, MAOIs, non-selective α-blockers, alcohol, NSAIDs. Decreased effect with enzyme inducer (e.g. rifampicin). Decreased hypoglycemic effect with thiazide diuretics, corticosteroids, thyroid products and sympathomimetic agents.

Modes to select anti diabetic drug treatment

The therapy of choice is frequently based on the early combination therapy and the major determinants are body weight, the risk of hypoglycemia, and renal as well as cardiopulmonary function including heart failure. The stage of diabetes with its metabolic phenotype may influence the decision on the choice of therapy.

Anti diabetic regimens targeting mealtime hyperglycemia are a valuable monotherapy for early stage of glucose intolerance, or a constructive add-in treatment for later stages, delaying or even preventing the deterioration of β-cell function in the first instance and achieving optimum glycemic control. Enhancer of early phase insulin secretion, short acting insulinotropic agents, α- glycosidase inhibitors and rapid acting insulin are already in use for the control of postprandial glycemia.

Current recommendation suggests that starting combination therapy early, to maximize efficacy and minimize side effects. Additionally a medium dose of any ant diabetic agent will typically provide 70% to 80% of the maximum blood glucose lowering effect. It is preferable to look for synergistic combination therapy instead of medium dose monotherapy.

Current treatment approaches to T2DM management

Loss of endogenous insulin secretion has been substantiated to cause the progression of T2DM and the reaching of a near normal glycemic target is the golden goal, irrespective of the mode of therapy. The recent consensus statement by the American Diabetes Association and the European Association for the study of Diabetes suggests initiation of metformin together with lifestyle changes as initial therapeutic approach to patient with T2DM. However, addition of either insulin secretagogues or glitazones or insulin is suggested when the HbA1c goal is above 7%. The greatest advance in the treatment of T2DM in recent years is the advent of polypharmacy, initially suggested by the UKPDS. This synergy has been strengthened of late with the development of early phase insulin secretion agents.

CONCLUSION

Nateglinide when given to subjects with T2DM just 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 nateglinide therapy. This sulfonylureas 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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