

NEWER ANTIDIABETIC DRUGS

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INTRODUCTION

The basic defects in Type 2 diabetes consist of (1) Insulin deficiency (2) Insulin resistance and (3) increased hepatic glucose production (HGP) leading to glucotoxicity, beta cell exhaustion and finally beta cell failure. The treatment strategies to overcome these defects are:

- 1) Modified meal Plan
- 2) Exercise
- 3) Blood glucose lowering drugs and
- 4) Insulin

The current oral blood glucose lowering agents and dietary measures only partially correct the multiple metabolic defects in NIDDM with insulin resistance remaining relatively impervious to treatment Hypoglycaemia and secondary failure are common with presently available sulphonylureas and hence the need for newer blood glucose lowering drugs. In case of NIDDM, a successful new drug should correct atleast one of the major underlying metabolic disturbances. i.e. reduce insulin resistance, enhance insulin production and secretion in response to glucose, suppress excessive hepatic glucose production or improve glucose uptake and utilisation in peripheral tissues particularly, skeletal muscle. Within the last few years three new groups of drugs have been identified and they are:

- a) Alpha glucosidase inhibitors, eg. Acarbose
- b) Insulin Sensitizer, eg. Troglitazone.
- c) Insulin secretagogues, eg. Glimepiride and Repaglinide

The following review will discuss each of these groups of drugs in detail.

ALPHA-GLUCOSIDASE INHIBITORS

In human salivary amylase, pancreatic amylase and alpha-glucosidase are the enzymes involved in the digestion of starch. All complex carbohydrates like starch and sucrose have to be converted to simple carbohydrates in the small intestine by an enzyme

alpha-glucosidase before absorption. Drugs which inhibit the action of alpha-glucosidase known as glucosidase inhibitor, preventing the breakdown of complex carbohydrates thereby delay or preventing carbohydrate absorption. Glucosidase inhibitors are three types:

1. Reversible competitive inhibitors of alpha-glucosidase. eg: a. Acarbose; b. Meglital
2. Irreversible glucosidase inhibitor eg: Gasternospermine.
3. Powerful Sucrose inhibitor eg: Veglibose.

Acarbose is freely available for clinical use. Other drugs are under clinical trial.

Acarbose

Acarbose is a pseudotetrasaccharide and is a reversible competitive inhibitor of the brush border alpha glucosidases (mainly glucoamylase, sucrose and maltose) as well as alpha amylase. Acarbose binds to alpha-glucosidase with high affinity.

Mode of Action:

1. Acarbose blocks the digestion of starch, sucrose and maltose. The digestion of carbohydrate is delayed and occurs throughout the small intestine, rather than upper part of jejunum. Absorption of glucose and other monosaccharides is not affected. The net result is a decrease in post prandial rise in blood glucose. Most of the carbohydrate is eventually absorbed and that which is now absorbed is metabolised by the bacteria in the colon to short chain fatty acids which are then absorbed in the colon.
2. Acarbose decreases meal stimulated secretion of gastric inhibitory polypeptide and other gastrointestinal peptide (inhibitors) hormones. There is smaller increase in post prandial blood sugar level that leads to smaller increase in insulin level.
3. Acarbose does not cause weight gain with the therapeutic doses.

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Side Effects:

Abdominal fullness, borborygmi, increased intestinal flatulence and diarrhoea are major side effects of alpha-glucosidase inhibitors. These side effects are due to undigested sugars passing through large bowel where bacterial fermentation occurs, producing both carbondioxide and large quantities of osmotically active glucose load, leading to diarrhoea and flatulence. These symptoms occur in the first few weeks of treatment and abate with continued long term treatment.

Degradation of Acarbose :

Mostly occurs in the intestine. Some of the degradation products and the trivial amount of the parent drug enter systemic circulation and are excreted in urine. When high doses of Acarbose is used, liver enzymes level should be checked.

Concomitant use of antacids, bile acid resins, intestinal absorbents, or digestive enzyme preparations may interfere with the effectiveness of acarbose and should be used with care. Contraindications to Acarbose use are primary therapy for Type 1 diabetes, significant gastrointestinal disorders and pregnancy or lactation.

Acarbose is administered orally three times a day and chewed with the first mouthful of food. Initial dose is 50 mg. Three times a day. Two weeks later the dose is increased to 100 mg, thrice daily and thereafter at 4 weeks interval, the dose is increased upto 200 mg. Thrice daily or until the required glycaemic control is achieved.

Uses :

In non-diabetics and in Type 2 diabetics acarbose produces a dose related decrease in post-prandial hyperglycaemia. Acarbose therapy causes a corresponding reduction in post prandial plasma insulin response. Long term treatment either as monotherapy or in combination with S.U, acarbose improves basal blood sugar concentration as well. Thus insulin resistance decreases and sensitivity improves consequent to reduction in hyperglycaemia.

1. Primary Therapy:

When FBS is less than 11.1 mmol, acarbose is said to decrease FBS by 1 mmol, PPBS by 3 mmol and HbA_{1c} by 1% Acarbose

does not cause hypoglycaemia when used as primary therapy.

2. As an adjuvant to:

Sulphonylurea, b. Metformin and c. Insulin in Type 2 DM. A reduction in the dosage of these drugs occur when Acarbose is used as an adjuvant.

3. Acarbose decrease serum TGL in patients with hypertriglyceridemia by decreasing VLDL synthesis.

4. Acarbose in impaired glucose tolerance: Acarbose has been tried in persons with IGT for prevention and postponment of onset of Type 2 Diabetes.

5. In IDDM:

Long term treatment with acarbose reduces both post prandial and basal hyperglycaemia and reduces insulin requirement by 10 to 30 % interestingly, episodes of hypoglycaemia between meals may be less frequent and less severe in IDDM.

In treatment of hypoglycemia in patients taking acarbose, only oral or IV (glucose) should be given. Sucrose and other complex carbohydrates should not be used.

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INSULIN SENSITIZERS

Insulin deficiency, insulin resistance and increased hepatic glucose output are the hallmark of pathogenesis of Type 2 diabetes. Sulphonylureas increase insulin secretion and may improve insulin sensitivity while the biguanide metformin improves insulin action. One of the exciting areas in the management of Type 2 diabetes is the development of pathogenetically targeted drugs to overcome insulin resistance, namely the thiazolidinediones. They work mainly by reducing peripheral insulin resistance in adipocytes, skeletal muscles and to a lesser extent by decreasing hepatic glucose production. These drugs facilitate insulin action in liver, muscles and adipose tissue. They do not stimulate insulin secretion. Pioglitazone, englitazone and troglitazone are the thiazolidine derivatives. Only Troglitazone is in clinical use. Troglitazone was developed in 1980 and was synthesized later with an alpha-tocopherol substitution and has antioxidant properties in addition to improving insulin sensitivity.

Mechanism of Action of Troglitazone:

In Adipose Tissue :

1. Thiazolidinediones increase glucose oxidation, lipogenesis and increase the expression of GLUT-4, the glucose transporters in adipose tissues.
2. Recently these drugs are found to interact or bind with the PPAR- γ (Peroxisome Proliferator Activated receptor γ) nuclear receptor of adipocytes. PPAR γ is the binding site for troglitazone and this leads to differentiation of insulin resistant large size adipocytes, into insulin sensitive small adipocytes, without increasing adipocyte mass and thereby reducing insulin resistance and improving insulin sensitivity. Other suggested mechanism of actions are:
 - a. by reducing white adipose tissue mass and increasing brown adipose tissue mass.
 - b. by decreased production of TNF α , leptin, and FFA levels in adipose tissue, all of which cause insulin resistance.

3. In Muscle:

Troglitazone [1] increases GLUT-4 and increases the activity of glycogen synthase. There is increased glycogenesis and glycolysis.

4. In Liver:

Thiazolidinediones reduce hepatic glucose production by suppressing neoglucogenesis. This is by restoring the ability of insulin to suppress the expression in the liver of PEPK (phosphoenolpyruvate carboxykinase) the rate limiting enzymes of gluconeogenesis.

5. Thiazolidinediones have been suggested to decrease hyperglycaemia in activating protein kinase which reduces kinase activity of insulin receptor.
6. Troglitazone reduces triglyceride level and NEFA. It also decreases cholesterol, increases HDL and to a lesser extent increases LDL level.
7. Troglitazone has no effect on body weight.

Safety data and Adverse Events:

Were reported from 30 clinical trials and 74000 weekly patient exposure to Troglitazone.

- a. No hypoglycaemia occurs with Troglitazone when used alone.
- b. 2 to 3 % reduction in haemoglobin level with 5 to 7% elevation in plasma volume have been reported. Hb% level did not fall outside the normal range.
- c. **Liver Enzyme Activity** increased to more than 3 fold of normal in some patients on Troglitazone treatment. Varying degrees of liver damage have been received by US, FDA. This includes irreversible damage and death in one. This is probably an idiosyncratic reaction.

Prescribing Information

Troglitazone is metabolised by the liver and excreted into the bile. The presence of renal insufficiency does not affect the serum level or metabolism of the drug.

1. In Type 2 diabetics, this is accompanied by concomitant reduction in both fasting and post prandial insulin levels. There will be significant reduction in triglyceride level and an increase in HDL cholesterol level. Dosage is 200-600 mg/day average dosage is 400 mg/day. Dosage is once per day with breakfast and titration is not necessary. Troglitazone may be started either as monotherapy or in combination with

sulphonylureas, acarbose, metformin and with insulin.

2. In poorly controlled Type 2 diabetics on insulin therapy, the insulin dosage reduction is not recommended at the outset. Along with insulin, troglitazone therapy is started. Once fasting blood sugar falls to 120-140 mg a reduction of 10 to 20% of insulin dose is recommended in order to avoid hypoglycaemia. Some studies have reported (i) a reduction of insulin dosage up to 58%, (ii) reduction of insulin injection from three to one per day in 40% of diabetics treated with Troglitazone and (iii) discontinuation of insulin in 10% of diabetics.
3. Troglitazone is the ideal drug for syndrome X and other insulin resistant states.

4. In IGT :

In patients with IGT, Troglitazone decreases insulin resistance and improves insulin sensitivity. It reduces insulin level and normalises blood glucose level and prevents or postpones onset of Type 2 DM.

5. In Women with Polycystic Ovary Syndrome with IGT :

Troglitazone improves glucose tolerance, insulin sensitivity and causes a fall in androgen level Plasminogen activator inhibitor – 1 (PAI-1) level also falls (a prothrombotic factor).

Advantages of Troglitazone :

1. Once a day dosage
2. No dosage titration
3. No hypoglycaemia when used alone
4. No weight gain
5. Can be used along with sulphonylurea, Metformin and Insulin.

Hidden Benefits of Troglitazone:

1. Decrease in systolic, diastolic and mean blood pressure.
2. Decrease in triglyceride level. This means (1+2) indirectly a reduction in anti-hypertensive and triglyceride lowering drugs.

3. Decreases PAI-1 level, a prothrombotic factor.
4. May prevent or delay beta cell exhaustion.

Recommendations:

Whatever be the benefits, while on Troglitazone, patients liver enzymes are to be checked periodically once a month initially and once in three months subsequently. If the enzymes values are more than three times of the normal value, the drug should be discontinued at once.

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INSULIN SECRETAGOGUES

Beta Cell Secretory defect, namely the insulin deficiency is an important factor in the pathogenesis of Type 2 diabetes, particularly during later stages of the disease. As the disease progresses, there is:

1. Loss of sensitivity of insulin secretion to a rise in blood glucose concentration and
2. Impaired processing of pro-insulin.

Insulin secretagogues provide useful therapeutic approaches if used early in the natural history of the disease. An ideal insulin secretagogue would restore beta cell sensitivity to glucose and at the same time ensure adequate biosynthesis, processing and secretion of insulin to other nutrients, hormones and neural factors. Insulin secretagogues can be divided into (i) Initiators of Insulin secretion eg. Glimepiride and Repaglinide; (ii) Potentiators of insulin secretion eg. GIP and GLP –1 (Gastric Inhibitory polypeptide, Glucagon Like Peptide).

GLIMEPIRIDE

Glimepiride is a newer, novel second generation sulphonylurea. It increases insulin secretion by stimulating beta cells and also has significant extrapancreatic activity.

1. Beta Cell Action:

Glimepiride binds to a specific receptor site 65 KDs region in the beta cell while glibenclamide binds to 140 KDs region. Glimepiride binds to its receptor 2.5 to 3 times faster and dissociates from it binding site 8 to 9 times greater than glibenclamide.

The mechanism of insulin secretion and release is similar to glibenclamide i.e. via the closure of ATP dependent potassium channel and opening up of voltage dependent calcium channel and increase of intracellular calcium concentration leading to exocytosis of insulin.

Sulphonylureas act at the level of potassium – ATP channel. However current sulphonylureas may not stimulate beta cells in a controlled fashion or in proportion to the blood glucose level, because of their fixed blocking of potassium-ATP channel. Agents that accomplish this in a more flexible fashion may lead to less secondary failure. Glimepiride which binds to a different portion of sulphonylurea receptor, leading to less fixed blockage of potassium-ATP channel may have less secondary failure.

The amount of insulin secretion is more or equivalent to that of glibenclamide but the secretion with glimepiride is very quick and lasts for a short time than glibenclamide and hence there will be no hyperinsulinism and reduced likelihood of in-between meal hypoglycaemia.

2. Insulin-independent blood glucose decreasing activity of Glimepiride: (Extra-pancreatic):

Glimepiride exhibits a more pronounced insulin independent blood glucose decreasing activity compared to glibenclamide. This can be explained by stimulation of glucose transport and non-oxidative glucose metabolism and adipose tissue and muscle cells. The increased glucose transporter activity is brought out by increased translocation of GLUT-4 isoform from inside the cell to surface of adipocytes and muscle. It increases insulin sensitivity and decreases insulin resistance. If hyperinsulinemia is a concern in therapy of Type 2 diabetes, the higher insulin-independent blood glucose decreasing activity of glimepiride might be of therapeutic relevance.

Thus the more pronounced blood glucose decreasing activity of glimepiride is brought out by its quick insulin release in conjunction with an insulin-independent glucose decreasing activity at the periphery.

The extra pancreatic effects of glimepiride may explain the lesser degree of insulin stimulation for a given fall in blood glucose, in both short term and longer clinical studies compared with other sulphonylureas. In vitro, glimepiride stimulates glycogen formation, glucose transport and other insulin like effect. It decreases hepatic gluconeogenesis.

There is not much difference in absorption whether glimepiride is given just before or along with food.

The peak concentration of the drug is attained in one hour. The half life of the drug is 9 hours. The drug is 100% bioavailable. It has dual mode of excretion 40% through liver and 60% through kidney. The metabolites are not much active.

The quick insulin release, increased peripheral tissue glucose disposal and the peak action at one hour are responsible for smooth control of post-prandial hyperglycaemia. The prolonged half life suggests that once daily dosing of glimepiride is enough to maintain blood glucose control for 24 hours.

Efficacy wise glimepiride is equivalent to that of glibenclamide. It decreases both fasting and post prandial hyperglycaemia. The HbA_{1c} decreases 1 to 2% within three months with 1 to 2 mg dose. The fall in HbA_{1c} is upto 3.5% when the drug is initiated in diabetics with HbA_{1c} more than 10.5%. There is no increase in fasting C – peptide and insulin levels even upto one year of treatment.

The hypoglycaemic episodes are very few in number, lesser in intensity and are of shorter duration. The hypoglycaemic episodes vary from 0.9 to 1.7% when compared to glipizide and glibenclamide, both of which cause more severe hypoglycaemic episodes.

Glimepiride safeguards the physiological suppression of endogenous insulin release during active physical exercise, implying that post exercise induced hypoglycaemia may not occur with the drug.

It has been observed in animal studies that platelet inhibitory effect of glimepiride is much more pronounced than gliclazide and hence it may have a preventive effect in the development of microvascular complications.

Dosage and Administration:

Glimepiride is indicated in Type 2 diabetics when diet and exercise fails. Dosage is individualised for each patient so as to achieve and maintain satisfactory blood glucose level at a minimum effective dose. The fasting blood glucose and HbA1c measurements should be performed periodically.

The usual starting dose of glimepiride is 1 mg. Maximum initial dose 2 mg once daily taken just before breakfast or with the first main meal of the day. Further increments can be made at 1 or 2 week intervals in increments of 2 mg. The patient's blood glucose response should guide dosage titration. The usual maintenance dose is 1 to 4 mg once daily. Maximum recommended dose is 8 mg once daily. There is no need to split the dosage to twice daily. Once daily dosage will improve patient's compliance.

Combination Therapy with Insulin :

For patients with secondary failure to other sulphonylureas when glimepiride and insulin therapy is indicated, the recommended dosage of glimepiride is 8mg once daily, Insulin is then titrated from a low dosage upward with approximately once-weekly dose increase guided by fasting blood sugar measurements. Glimepiride lowers daily insulin dosage requirements.

In Special Populations :

In American clinical trials, tight control ie. HbA1c levels of 7.2% or lower was achieved in 68% of obese diabetics and in 78% of diabetics with hypertension.

No marked difference in the safety profile and daily dosage were observed between patients who were young and elderly, obese and non-obese, male and female and among patients of various racial phenotypes.

Glimepiride has less effect on cardiovascular system than do glyburide and glipizide and has decreased binding to cardiovascular ATP dependent potassium channel causing one-third the degree of inhibition seen with glyburide. There is also less alteration of coronary blood flow. Thus interestingly, glimepiride appears to be "Pancreas Specific" in its effect on the potassium-ATP channel and hence it could be used in cardiac patients with mild to moderate hyperglycaemia.

Glimepiride should not be used in pregnancy and in lactating mothers.

No clinically significant drug interactions were observed with commonly used drugs such as calcium channel blockers, ACE inhibitors, H₂ receptors antagonists, fibrates, NSAID, sympathomimetic agents, sulphonamides and thyroid hormones.

Clinical studies indicate that glimepiride offers significant benefits in the management of Type 2 diabetics.

1. It has the greatest (mgm. for mgm.) glucose lowering effect when compared to other sulphonylureas.
2. It achieves tight control in more than two thirds of the patients.
3. It maintains effective control upto 2 1/2 years .
4. It reduces insulin resistance and has a unique beta cell receptor binding capability.
5. Once daily dosage will improve patients compliance.
6. It has insulin sparing activity. Glucose levels are controlled without meaningful increase in fasting insulin and in Type 2 diabetics requiring exogenous insulin, glimepiride lowers daily insulin dosage requirements.

For Further reading :

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REPAGLINIDE---- PRANDIAL GLUCOSE REGULATOR

Repaglinide is a non-sulphonylurea antidiabetic agent and a short acting insulin secretagogue. It is a benzoic acid derivative and is an analog of meglitinide family.

The meglitinide shares the non-sulphonylurea moiety of glibenclamide.

MODE OF ACTION:

Repaglinide has a unique binding site on beta cell, different from that of glibenclamide. It acts via closure of ATP dependent K channel in beta cell. It is 3 to 5 times more potent insulin releaser than glibenclamide but its action is short lived. The half life of the drug is 2.5 hours and peak action is less than one hour. It reduces post-prandial blood sugar by 4 to 6 mmol and HbA_{1c} by 2%. It is metabolised in the liver and secreted in bile.

Repaglinide vs Glibenclamide:

When compared to glibenclamide, Repaglinide has the following characteristic feature:

1. Fast Absorption
2. Short biological half life
3. Short duration of insulinotropic activity
4. Lowest post-prandial Blood glucose
5. No in-between meal hypoglycaemia or hyperinsulinemia.

Uses :

a) Primary Therapy in Type 2 Diabetes

Repaglinide is a prandial glucose regulator. It has a fast onset and short duration of action. The initial dose is 0.5 to 1 mg and gradually increased upto 2 to 4 mg. It should be administered three times a day just, before along with or immediately after a meal and offers greater flexibility in meal times and drug dosing.

b) Useful in patients who eat at irregular times or miss a meal:

Repaglinide increases insulin secretion sufficient to control the post meal surge and not for so long as to produce hypoglycaemia in-between meals and especially when a meal is missed or delayed as is the case with long acting insulinotropic agents. So, there is no in-between meal hypoglycaemia and there is no in-between mean hyperinsulinemia.

The Other Notable Features of Repaglinide Actions and Uses are:

1. The intermittent stimulation of K channel that prevents down-regulation of receptors and consequent refractoriness and secondary failure of therapy.
2. It has no effect on ATP-regulated K channel of cardiocytes or vascular smooth muscle cells (Landry D. L. Oliver, Jan. 1992) and therefore may be preferable to compounds that produce this effect.
3. Rapid non-renal inactivation and elimination results in a shortswift, "Antihyperglycaemia" action. So, it can be administered safely in patients with compromised early renal or hepatic function.

Combination Therapy : Repaglinide and Metformin:

Repaglinide acts only at beta cells leading to insulin release, whereas metformin bypasses beta cell and acts at periphery, liver, muscle and adipose tissue. The actions are complementary to one another, when both the drugs are combined. The fall in HbA_{1c} is significant within three months in most Type 2 diabetics.

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