GLITAZONES An Overview

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Introduction:

Diabetes has been known since ages. Once known to be a disease of the affluent society, diabetes has slowly emerged as a global problem in both developed and developing countries over the years. 300 million people are expected to be diabetic by the year 2025. India has already become the diabetic capital of the world. Though known since long, pharmacotherapy of DM is only 75 years old.

Oral antidiabetic agents are classified according to their predominant mode of action(1):

I. Stimulators of Beta cells: e.g Sulphonylureas, repaglinide.
II. Inhibitors of gluconeogenesis : e.g Biguanides
III. Inhibitors of intestinal glucosidases: e.g. Acarbose, Meglitol etc
IV. Drugs which reduce insulin resistance: e.g Glitazones, Biguanides.
V. DPP4 inhibitors which are a new addition to this classification : e.g. Sitagliptin

In type2 DM, the main underlying pathology is not insulin deficiency but insulin resistance at the target tissues viz liver, skeletal muscle and adipose tissue. This leads to hyperinsulinemic condition and when even this fails to maintain blood glucose levels within normal limits, hyperglycaemia and DM ensues. The drugs causing increased insulin release from pancreas, like sulphonylureas can maintain blood glucose levels within normal limits for some time, but eventually result in burn out of b cells ultimately converting NIDDM into IDDM .The most commonly employed oral hypoglycaemic agents (OHAs) are sulphonylureas and biguanides. These drugs have disadvantages such as primary and secondary failure of efficacy as well as potential for induction of severe hypoglycaemia. There is therefore need for new candidate molecules that may effectively reduce insulin resistance or potentiate insulin action in genetically diabetic or obese individuals. Glitazones strike the right cord by reducing insulin resistance.

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Glitazones:

Drugs that reverse insulin resistance without stimulating insulin release from â cells also fulfill a major medical need in the treatment of NIDDM. The search for such drugs with a potential to reduce long term complications of NIDDM is therefore of current interest. Between 1997 and 1999 a new class of drugs known as glitazones was approved by US FDA for the treatment of type 2 DM. These drugs share a common chemical structure, viz. thiazoline-2-4-dione (TZDs).(2)

Various glitazones available in market are rosiglitazone and pioglitazone. Troglitazone which was the first glitazone introduced in the market was withdrawn from the market by US FDA in 2000 owing to serious hepatotoxicity.

Mechanism of action:

As a monotherapy, fasting glucose and glycosylated haemoglobin on average can be reduced by 40 mg/dl and almost 1 % respectively. TZDs reduce insulin resistance not only in type-2 DM but also nondiabetic conditions associated with insulin resistance like obesity and polycystic ovarian disease.

Glitazones bind with peroxisome proliferators activated receptor ã (PPARã). PPAR ã is a transcription factor that regulate expression of specific genes mainly in fat cells but also in other tissues. They have been shown to interfere with expression and release of mediators of insulin resistance originating in adipose tissue like free fatty acids, adipocytokines , such as TNF á, resistin and adiponectin. PPARã activation caused by TZDs also alter transcription of several genes involved in lipid and glucose metabolism including those that code for lipoprotein lipase, fatty acid transporter protein adiposite fatty acid binding protein, fatty acid Co A synthase, malic enzyme, glucokinase and GLUT4 glucose transporter (3). Its direct molecular effect on skeletal muscle cannot be excluded. Interference with transcription entails potential for side-effect risk. In vitro stimulation of adipogenic differentiation may underlie clinical observation of weight gain. Hepatotoxicity seen with troglitazone was not PPARã mediated but was attributed to toxic metabolites. Based on differences in drug metabolism this problem is relatively less with rosiglitazone and pioglitazone (4).

Metabolism:

Metabolized in liver by hydroxylation and oxidation. They are well absorbed from gut and the drug is first measurable in serum within 30 minutes and peak levels are reached in 2 to 3 hours when taken in fasting state. They are metabolized in liver by hydroxylation and oxidation. Excretion of pioglitazone occurs mainly through faeces with only a minor amount excreted in urine. Rosiglitazone is excreted predominantly through urine.

Onset of action :
The action of these drugs commences within 2-3 weeks and may take 8-12 weeks for maximum response. The drug can be safely taken during any time of the day.

Pharmacological Actions:
Given orally glitazones decrease :
1. Insulin resistance and hyperinsulinaemia.
2. Blood glucose and HbA1c
3. Plasma triglycerides.
They increase levels of : HDL and IDL.

Adverse Effects :
Mild to moderate side effects include reductions in hemoglobin, hematocrit and neutrophil count. Other side effects include anorexia, dark coloured urine. Pioglitazone induces hepatic drug metabolizing enzymes and can reduce efficacy of drugs like oral contraceptives. As they are metabolized in liver, they have potential to cause hepatotoxicity.
Recently glitazones are under fire for their cardiac toxicity and bone toxicity which is dose dependant. The serious adverse events following use of glitazones is precipitation of cardiac failure and osteoporosis particularly in postmenopausal women.
Weight gain is another important event associated with glitazones which could be partly due to effect on fat metabolism and partly due to fluid retention. Fluid retention, Cardiac failure and macular oedema associated with glitazones:
Development of oedema is dose related and in most patients it is mild to moderate and responsive to diuretics. Increased vascular endothelial permeability is responsible for oedema. It also leads to fluid retention. Fluid retention may lead to or exacerbate cardiac failure. So the cause of failure appears to be retention rather than left ventricular dysfunction.
Rosiglitazone has dose related effect on pulmonary endothelial permeability. Hence use of glitazones is contraindicated in NYHA Class III and IV heart failure and not recommended in patients with symptomatic heart failure(5). Diabetic macular oedema is shown to worsen with rosiglitazone.

Dosage:
Pioglitazone 15-45 mg/day in single or divided doses. Maximum dose should not exceed 45mg.
Rosiglitazone 4-8mg/day in single or divided doses. No dose adjustment is recommended in renal insufficiency. Data on their safety in pediatric age group is not available.

Other Actions of Glitazones:
Glitazones are being currently studied for use in lipodystrophy syndrome induced by highly active antiretroviral therapy in HIV positive patients with preliminary studies showing conflicting results(6).
Glitazones are able to induce cell differentiation and apoptosis in several cancer cells suggesting possible use of these drugs for treatment of gliomas and other tumors(7). Some studies have implicated PPAR ã in regulation of cancers like thyroid, pancreatic, breast, prostate and testicular cancers. PPAR ã mutations are observed in colonic cancer.

To summarize:
Glitazones reduce HbA1c by 1-1.5% roughly the same as sulphonylureas or metformin in top doses.
Last year's meta-analysis suggested 43% increased risk of MI with rosiglitazone but no significant increase in cardiovascular mortality. Both glitazones increase risk of heart failure. They could be considered as second line therapy but patients need to be carefully monitored for signs of heart failure. As they are known to induce hepatotoxicity, monitoring for liver functions is imperative. Periodic testing for liver enzymes will be helpful in early detection of hepatotoxicity.

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