Pioglitazone

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Introduction

Pioglitazone is the only freely available member of the thiazolidinedione (TZD) or glitazone group of oral anti-diabetic drugs (OADs). Other drugs in the class: troglitazone, englitazone and darglitazone have been withdrawn from the market, or discontinued from clinical development Rosiglitazone, which was banned in many countries due to cardiovascular safety concerns, has recently been removed from the risk evaluation and mitigation strategy (REMS) list by the United States Food and Drugs Administration (FDA).

Pioglitazone is a safe, potent, well tolerated, and versatile insulin sensitizer, which does not cause hypoglycaemia, needs minimal dose titration, requires no specific meal-related timing of administration, and can be combined with virtually every other anti-diabetic drug. These properties make it an attractive drug for use in settings where frequent patient follow up or investigations are not possible. This review discusses a pragmatic approach to the rational use of pioglitazone in clinical practice.

Basic Pharmacology

The primary targets for TZDs are the insulin-sensitive tissues-namely, adipose tissue, skeletal muscles, and the liver. It acts upon the nuclear peroxisome proliferator-activated receptor- gamma (PPARγ), and modulates the activity of multiple genes and protein synthesis. Pioglitazone increases adipogenesis and allows increased lipid deposition in adipocytes. Parking of lipid in adipocytes implies a reduced availability of non-esterified fatty acids and triglycerides as an energy source, and favours greater utilization of glucose. This leads to correction of hyperglycaemia. Reduced intramyocellular FFA content and decreased liver fat content also results in improved insulin sensitivity and better utilization of glucose.

Pioglitazone has other mechanisms of action as well. It increases transcription of glucose transporter-4 (GLUT 4), improves adiponectin levels, reduce adipocyte tumour necrosis factor-alpha (TNFα), concentrations, and inhibits resistin production. The drug also has beneficial effects on lipid metabolism, exerts a potent anti- inflammatory effect, and slows vascular proliferation as well as atherogenesis.[1]

Administered as a single daily oral dose, pioglitazone reaches peak concentration in 2 hours and attains steady state in 4-7 days. Bound to serum albumin, it is metabolized in the liver by CYP2C8 and CYP3A4 pathway. Most of the drug is excreted into the bile and eliminated through faeces, while 15-30% is recovered in urine. The half life of pioglitazone is 5-6 hours, while the half life of its active metabolites is 16-23 hours.[1]

Efficacy

The efficacy of pioglitazone is well documented as monotherapy and in combination with both OADs and insulin.[2,3]

Pioglitazone exerts its effect on both fasting and post prandial glycaemia, thus lowering HbA1c by 1.3 to 1.6%. The drug is equipotent to metformin and sulfonylureas. Hence it can be used as monotherapy in persons in whom metformin is either contraindicated or not tolerated. Pioglitazone is a versatile molecule and can be used as part of dual oral therapy (with meformin or with oral therapy) or triple oral therapy (with metformin and sulfonylurea). Fixed dose combinations are available to facilitate this use. Pioglitazone can be added to persons who are poorly controlled on insulin, with or without other OADs, It displays an insulin sparing effect, reducing the dose of insulin in a significant number of people, and obviates the need for injectable therapy in many.[2]

Cardiovascular Health

Pioglitazone has been reported to have a cardioprotective effect. Subgroup analysis of the PROActive Trial has revealed reductions in myocardial infarction and stroke, in persons who had experienced these events previously.[4] Similar beneficial effects have been reported upon meta-analysis of trials using clinical end points.[5]

Surrogate end points or laboratory end points can also be used to assess cardiovascular safety and benefit. Pioglitazone has demonstrated to slow progression of carotid intima media thickness (CIMT), reduce rates of restenosis and target vessel revascularization in patients

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who have had percutaneous coronary intervention, reduce incidence of in-stent restenosis, have no negative effects on left ventricular remodeling diminish triglyceride levels, and correct microalbuminuria.[6]

All this evidence supports the use of pioglitazone as part of combination therapy in persons not well controlled on metformin monotherapy. It also supports the use of this molecule in preference to sulfonylureas. In clinical practice in South Asia, however low dose combinations of metformin+ sulfonylurea offer an effective, economical and easier way of achieving safe glycaemic control.

Prevention of Diabetes

Pioglitazone has been studied in persons with impaired glucose tolerance in various studies.[7] Though not approved for the same, it is able to prevent conversion of impaired glucose tolerance (IGT) to diabetes. In one study, it has been found to be more efficacious than metformin in this regard.

Extra-Glycaemic Effects

Pioglitazone has multiple pleiotropic effects which allow its use in conditions other than type 2 diabetes.[8] The molecule has been tried in the management of non alcoholic fatty liver disease (NAFLD), in delaying the onset of mild cognitive impairment due to Alzheimer's disease, and in polycystic ovary syndrome (PCOS).

Safety

Pioglitazone is a safe drug, and rarely causes hypoglycaemia. Common adverse effects include weight gain, oedema, and precipitation of heart failure. In various meta-analysis and retrospective data based studies, pioglitazone has been associated with reduced risk of mortality, myocardial infarction stroke, and hospitalization.[4,5]

Pioglitazone may lead to reduction in natriuresis, with a concomitant increase in plasma rennin and aldosterone.[8]

An increase in the incidence of diabetic macular oedema (DME), and fractures has also been reported. TZDs may shift osteoblast precursor cells to fat precursor cells in the bone marrow, or decrease osteoblast production by reducing insulin and amylin levels (both of these are osteogenic hormones).

Pioglitazone increases weight, increases subcutaneous adipose tissue, decreases visceral adipose tissue, increases lean body mass, and may reduce liver fat content. Weight gain is more prominent if pioglitazone is combined with insulin or sulfonylureas, and if pioglitazone is used in high doses.

There is controversy regarding the effect of pioglitazone on bladder cancer. According to the FDA, the cumulative exposure to pioglitazone is associated with a higher risk of cancer, a long term follow up of the PRO active trial, however, revealed no such link.[9]

Prescription of pioglitazone must be accompanied by a detailed medication counseling, which should include information to contact the prescriber in case of excessive weight gain, swelling feet, breathlessness, or passing of bloody urine.[10]

Place in Guidelines and Recommendations

Pioglitazone figures as an acceptable OAD in all international guidelines and recommendations. In fact, it is included in the National list of Essential Medicines of Bhutan and Thailand. The American Diabetes Association (ADA) and European Association for Study of Diabetes (EASD) the International Diabetes Federation (IDF), and the American Association of Clinical Endocrinologists (AACE) all recommend use of pioglitazone. Japan recommends a starting dose of 30mg once daily in all male adults, and 15 mg in women and elderly.

The US FDA recommends that pioglitazone should not be used in patients of bladder cancer, or prior history of bladder cancer. Appropriate patient selection will help reduce the risk associated with pioglitazone therapy and maximize benefit: risk ratio.

Pioglitazone is a safe drug to use during Ramadan, and needs no dose adjustment before or during fasting.[11] It has been recommended for this purpose by the South Asian Guidelines on Management of Ramadan.

Terminology

Conventionally, the terms 'maximal dose' and 'half-maximal dose' have been used for metformin and sulfonylureas. For pioglitazone, the terms 'low dose' (7.5-15mg/day) and standard dose (15-45mg/day) are preferred. Low dose pioglitazone has been found to be effective, safe and well-tolerated, without any risk of fluid retention or oedema.[12]

Recommendations

Pioglitazone as a first line option is justified only if metformin is contraindicated or not tolerated. These include situations such as renal impairment, malnutrition (metformin is a calorie restriction mimetic and may act as a mitochondrial toxin), and gastrointestinal intolerance.

Pioglitazone is a suitable second line drug to add to metformin when glycaemic control cannot be achieved with the latter drug alone. Sulfonylureas are commonly used for this purpose in South Asia, because of their economy and rapid onset of action. Gliptins are also

recommended in such cases because of their sustainable, beta cell sparing action. Pioglitazone should be preferred if the person being treated is at risk of hypoglycaemia, or does not have care givers to manage an episode of hypoglycaemia. This will include elderly persons, those with mild renal impairment, autonomic neuropathy, and history of frequent hypoglycaemic episodes. Pioglitazone will also be preferred over other second line options if the other drugs are contraindicated.

As a third line drug, pioglitazone can be added if glycaemic control is inadequate but insulin is not acceptable or not feasible as a treatment option. Pioglitazone can be added to insulin if there is a clear need for insulin sensitization (high insulin dose requirement). Pioglitazone should be initiated in low doses (7.5-15mg/day), and maintained at lowest required doses. It may be discontinued if metabolic response (0.5% reduction in HbA1c over 6 months) is not achieved.

Pioglitazone should be a preferred agent if clinical symptoms and signs of insulin dose requirement, central obesity, hypertension, dyslipidaemia, acanthosis nigricans, NAFLD and PCOS) are present, or if there is history of excellent response to pioglitazone or other TZDs in the past. A therapeutic trial may be considered if there is a history of poor response, or lack of tolerance, to other OAD classes.

Conclusion

Pioglitazone is a safe, and effective, OAD which has great potential in the management of type 2 diabetes. Pragmatic usage of this molecule will allow its benefits to reach the maximal number of people. At the same time, appropriate patient education must be ensured, and pharmacovigilance maintained, while using this molecule.

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