

Dynamic Controversies of Pioglitazone

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Pioglitazone belongs to thiazolidinediones (TZD) class of anti diabetic agents used either as monotherapy or in combination with metformin, sulfonylureas or insulin in treatment of diabetes mellitus. The pioglitazone increase insulin sensitivity by increasing glucose utilization in adipose tissue, muscle, and liver and also by decreasing glucose production.¹ The exact mechanism as to how pioglitazone exerts its effect is not fully understood. It binds to one or more peroxisome proliferator-activated receptors (PPARs), which regulate gene expression.² PPARs are part of the steroid and thyroid super family of nuclear receptors found mostly in adipose tissue, pancreatic beta-cells, vascular endothelium, and macrophages while PPAR-alpha is expressed mostly in liver, heart, skeletal muscle, and vascular walls. Troglitazone and rosiglitazone are purely PPAR-gamma agonists, while pioglitazone also exerts some PPAR-alpha effects. This could explain differential effects of various thiazolidinediones. New thiazolidinediones are being investigated as “dual PPAR agonists,” which could effectively treat both hyperglycemia and hyperlipidemia. There is some evidence that TZD also may improve blood glucose levels by preserving pancreatic beta-cell function.³ Thiazolidinediones have been shown to improve number of cardiovascular risk factors, including dyslipidemia, markers of inflammation, vascular smooth muscle proliferation, vascular reactivity, endothelial function, and progression of atherosclerosis,⁴ but data supporting its role in decreasing cardiovascular events are limited. Rosiglitazone and pioglitazone have a similar effect on the incidence of heart failure, both of them

increase risk, but they demonstrated to have different effects on ischemic outcomes.⁵ Though pioglitazone and rosiglitazone have similar effects on glycemic control, their effects on serum lipid concentrations are different. Pioglitazone produces a more favourable lipid profile.⁶ It has been demonstrated that LDL cholesterol levels typically remained constant when monotherapy or combination therapy with pioglitazone was used, while 8 to 16 percent increases in LDL cholesterol levels were noted in studies of rosiglitazone.¹ HDL cholesterol levels increased by about 10 percent with both drugs. Decrease in triglyceride levels were observed more so with pioglitazone than with rosiglitazone.

ADVERSE REACTIONS AND THEIR MECHANISM

Incidence of adverse reaction with pioglitazone in decreasing order of frequency are: Edema, though it occurs in around 5% of people but in combination with sulfonylureas or insulin, the incidence of edema is about 15%; upper respiratory tract infection (13%); heart failure (6%); headache (9%); fatigue (4%); tooth disorder (5%); anemia (2%); myalgia (5%); sinusitis (6%); pharyngitis (5%). Rare adverse reactions occurring in less than 1% are: bladder cancer, blurred vision, elevation of muscle enzyme like creatinine phosphokinase, dyspnoea, fractures, hepatic failure, hepatitis, macular edema, pulmonary edema and decreased visual acuity.

POSSIBLE MECHANISMS OF SOME OF THE SIDE EFFECTS ARE

1. Weight gain: The weight gain is caused in part by fluid retention.⁷ In a small study, 12 weeks of therapy with pioglitazone 45 mg resulted in 3.1 kg weight gain.⁸ Weight gain may also result from the proliferation of new adipocytes. Upregulation of genes that facilitate adipocyte lipid storage in vivo have been found to responsible.⁹

2. Fluid retention and heart failure: Fluid retention, which is more prominent with concomitant insulin therapy, can

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occur with all the thiazolidinediones, but does not account for all of the weight gain. Peripheral edema occurs in 4 to 6 percent of patients treated with thiazolidinediones and in a higher percentage of patients with a history of heart failure.¹ This fluid retention may lead to the precipitation of heart failure. The thiazolidinediones act by binding to and activating PPAR-gamma.¹ PPAR-gamma is also most abundant in the collecting tubules of nephron, and the fluid retention with thiazolidinediones possibly results from PPAR-gamma stimulation of sodium reabsorption by sodium channels in the luminal membrane of the collecting tubule cells.¹⁰

SKELETAL HEALTH

There are many studies suggesting that thiazolidinediones decrease bone density and increase fracture risk, particularly in women.¹¹ The bone loss was associated with an increase in marrow adipocytes. PPAR-gamma 2 isoform is an important regulator of adipocyte differentiation. Activation of PPAR-gamma 2 results in diversion of bone marrow stromal cells from the osteoblast lineage into the adipocyte lineage, which subsequently leads to a decrease in bone formation rates and increase in adipogenesis.¹² Fractures are seen mainly in the upper and distal lower limbs and are more common in women than in men.

HEPATOTOXICITY

Troglitazone has been removed from the market in the United States and United Kingdom because of reports of severe hepatocellular injury resulting in death or the need for liver transplantation in some patients. Hepatotoxicity with rosiglitazone and pioglitazone is very rare. In data from several double blind trials with rosiglitazone and pioglitazone involving over 5000 patients, fewer than 0.3 percent of patients had alanine aminotransferase levels more than three times the upper limit of normal and no patients had values more than ten times the upper limit of normal.¹³

RECENT CONTROVERSY—BLADDER CANCER

It is not fully clear that pioglitazone use increases the risk of bladder cancer. In preclinical studies, pioglitazone was associated with bladder tumors in male rats. Much available evidence suggests an indirect mechanism of bladder tumorigenesis in male rats treated with drugs

or chemicals that increase formation of urinary solids which may cause mucosal injury and thus regenerative hyperplasia, that ultimately results in tumor formation.¹⁴

In male rats, muraglitazar (dual PPAR agonist) treatment at doses 5 mg/kg was associated with an increased incidence in transitional cell papilloma and carcinoma in the urinary bladder. Bladder tumorigenesis in male rat was potentially due to muraglitazar related alterations in urine composition.¹⁴ In another study, chronic mucosal injury and proliferation due to muraglitazar induced urolithiasis was shown to be the nongenotoxic mechanism for the male rat specific urinary bladder tumorigenesis.¹⁵ The risk of bladder cancer was significantly increased in those with the longest exposure to pioglitazone and to those exposed to the highest cumulative dose.¹⁶

CONTRAINDICATIONS INCLUDE

Hypersensitivity to pioglitazone, NYHA Class III/IV heart failure at initiation of therapy, serious hepatic impairment and pregnancy.

Safety announcement by the U.S. Food and Drug Administration (FDA), regarding use of pioglitazone on (15-6-2011): Use of the diabetes medication pioglitazone, for more than one year may be associated with an increased risk of bladder cancer.¹⁷

LATEST FDA RECOMMENDATION

- Not use pioglitazone in patients with active bladder cancer.
- Use pioglitazone with caution in patients with a prior history of bladder cancer. The benefits of blood sugar control with pioglitazone should be weighed against the unknown risks for cancer recurrence.

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