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Thiazolidinediones

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Continuing Education Activity

Thiazolidinediones are medications used to manage and treat type 2 diabetes mellitus. These medications may be acting as a nuclear transcription regulator and an insulin sensitizer. This activity illustrates the indications, mechanism of action, and contraindications for thiazolidinediones as valuable agents for managing type 2 diabetes.

Objectives:

- Identify the mechanism of action of thiazolidinediones.
- Describe the potential adverse effects of thiazolidinediones.
- Outline appropriate monitoring for the toxicity of thiazolidinediones.
- Review the importance of collaboration and coordination among the interprofessional team and how it can enhance patient care with thiazolidinedione therapy to improve patient outcomes for patients who have diabetes.

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Indications

The use of thiazolidinediones, also called "glitazones," in managing type 2 diabetes can help with glycemic control and insulin resistance. There are two thiazolidinediones, rosiglitazone, and pioglitazone, currently approved by the FDA as monotherapy or combined with metformin or sulfonylureas to manage type 2 diabetes mellitus. These medications should be in conjunction with lifestyle modifications such as diet, exercise, and weight reduction. Thiazolidinediones may also be used to treat polycystic ovarian syndrome, as these may lead to improved endothelial function, improved ovulation, and reduction of insulin resistance.[1] Pioglitazone specifically reduces hepatic fat and may improve liver fibrosis in patients with nonalcoholic steatohepatitis (NASH); however, additional variables and risks require assessment in NASH patients.[2][3] The most significant advantage of TZDs is that they do not cause hypoglycemia as monotherapy and are not contraindicated in patients with renal disease.

Mechanism of Action

Thiazolidinediones (TZDs) are insulin sensitizers that act on intracellular metabolic pathways to enhance insulin action and increase insulin sensitivity in critical tissues.[4] TZDs also increase adiponectin levels, decrease hepatic gluconeogenesis, and increase insulin-dependent glucose uptake in muscle and fat. Adiponectin, a cytokine secreted by fat tissue, increases insulin sensitivity and fatty acid oxidation increases with TZD therapy.[1][5][6][7]

TZDs function by regulating gene expression through binding to peroxisome proliferator-activated receptor-gamma (PPAR-gamma), a nuclear transcription regulator.[6] Peroxisome proliferator-activated receptors (PPARs) are a family of ligand-activated transcription factors of nuclear hormone receptors that regulate energy homeostasis. The genes activated by the PPAR-gamma subtype are present in muscle, fat, and liver, regulating glucose metabolism, fatty acid storage, and adipocyte differentiation.[8] The binding of TZD will induce a conformational change to alter gene expression of numerous pathways involved in metabolism regulation, including lipoprotein lipase, glucokinase, fatty acyl-CoA synthase, and others.[9] PPAR-gamma agonists improve insulin resistance by increasing adiponectin, GLUT4 expression, and opposing the effect of TNF-alpha in adipocytes. Increased GLUT 4 expression will increase glucose uptake in adipocytes and skeletal muscle cells in response to insulin.[8]

In addition to their function in glycemic control and improvement of insulin resistance, TZDs potentially have anti-inflammatory and anti-cancer properties. There is evidence that TZDs may slow the progression of medial intimal thickening and decrease coronary intimal hyperplasia. Research has shown additional beneficial effects on endothelial function, atherogenesis, fibrinolysis, and ovarian steroidogenesis. Some studies demonstrated that activation of PPAR-gamma receptors could induce cancer cell apoptosis. However, these mechanisms are still under investigation due to conflicting studies and possible confounders.[1]

Administration

Thiazolidinediones (TZDs) are taken orally once daily, with or without food. Before initiating treatment and periodically during therapy, LFTs and HbA1C levels require monitoring. Maximal glucose-lowering effects of TZDs are not seen for six weeks to 6 months due to a delayed onset of action via modification of gene expression. For type 2 diabetes management, TZDs should be used in combination with lifestyle modifications and can be used in conjunction with biguanides, sulfonylureas, and insulin injectables.[4][10]

Dosing for treatment of T2DM:

- Pioglitazone: Initial 15 to 30 mg PO with a meal once a day; may increase the dose by 15 mg with careful monitoring to 45 mg once a day. The maximum dose is 45 mg.
- Rosiglitazone: Initial 4 mg PO once a day. If inadequate response after 8 to 12 weeks, may increase the dose to 8 mg PO once a day or 4 mg twice a day.

Adverse Effects

There are several undesirable side effects to thiazolidinediones, particularly with long-term use. The risks versus benefits require discussion with patients, and alternative first-line agents attempted before using TZDs.

Edema and Congestive Heart Failure

TZDs have been shown to cause dose-related fluid retention in up to 20% of patients. Methods of fluid retention include PPAR-gamma receptors in the distal nephron and insulin-activated epithelial sodium channels in the collecting tubules. PPAR-gamma activation stimulates sodium reabsorption, acting at the same site as aldosterone. Patients with preexisting edema or concomitant insulin therapy are at higher risk of edema and should start on the lowest available

spironolactone if the edema is mild or loop diuretics for severe cases. Furthermore, lower doses of 15 and 30 mg a day decreases the risk of edema and weight gain.

There are reports of an increase in intravascular volume to the point of congestive heart failure. Thus TZDs should be used with caution in patients with diastolic dysfunction or a history of CHF. The risk of heart failure and death is higher in rosiglitazone than pioglitazone.[12]

Weight Gain

Adipocytes have the highest concentration of PPAR-gamma receptors in the body. The mechanism behind the weight gain is due to a combination of factors. TZDs upregulate PPAR-gamma receptors in the central nervous system, leading to increased feeding. TZD agents expand adipose tissue mass via the maturation of preadipocytes into mature adipocytes and increase fat storage by increasing free fatty acid movement into cells. Additionally, fluid retention can increase weight.[4][13] Fat gain occurs primarily in the subcutaneous tissues, sparing the visceral area. As with edema and CHF, weight gain becomes exacerbated by concomitant insulin use, but the risk decreases when using metformin and lower doses of TZDs.

Fractures

Several studies have demonstrated an increased fracture risk and decreased bone density in patients taking TZDs compared to those taking insulin or other oral agents such as sulfonylureas. Proposed mechanisms for this include PPAR-gamma activation and insulin-like growth factor down-regulation, which diverts the differentiation of osteoblasts into adipocytes and leads to bone loss.[1][14] These fractures appear to be more likely in the distal extremities (forearm, wrist, ankle, foot, tibia) than the axial skeleton (hip, pelvis, femur). The fracture risk is further increased by additional risk factors, such as postmenopausal females or patients concurrently taking glucocorticoids or proton pump inhibitors (PPIs).[15][16][17]

Bladder Cancer

Pioglitazone has, in some studies, shown correlations with an increased risk of bladder cancer. This effect varies in a duration-dependent and dose-dependent fashion. Also, most recent analyses do not support an increased risk. In contrast, rosiglitazone was not associated with an increased risk of bladder cancer in any analysis, suggesting the risk is drug-specific and not a class effect.[18]

Hepatotoxicity

Troglitazone, the original PPAR-gamma activator, was removed from the market primarily due to hepatotoxicity. However, the other agents, rosiglitazone and pioglitazone, have rarely been linked to acute liver injury.[5][10] Baseline and routine monitoring of alanine aminotransferase levels and monitoring for clinical symptoms of liver injury are recommended.[19][20][21]

Diabetic Macular Edema

Combination TZD and insulin therapy have correlated with an increased incidence of diabetic macular edema at 1-year and 10-year follow-up. However, more studies are underway to evaluate confounding factors and define the frequency of this adverse event.[22][23]

Increased Ovulation and Teratogenic Effects

Patients with polycystic ovarian syndrome have shown an increased ovulation rate when using

anovulatory women, leading to improved rates of spontaneous pregnancy. However, TZDs have also been shown to have some teratogenic potential by decreasing fetal maturation. Premenopausal women should use contraception if they are not trying to conceive and switch to another insulin sensitizer, such as metformin, after conception.[24]

Contraindications

When considering management for T2DM, primary interventions should be lifestyle changes such as diet, exercise, and weight reduction. First-line monotherapy should be metformin or sulfonylureas due to their favorable side effect profiles. However, TZDs may be used as monotherapy or as combination therapy when first-line medications are contraindicated. TZDs may be necessary for high-risk hypoglycemic patients; however, the contraindications require evaluation before starting treatment.

There are several contraindications for using thiazolidinediones, including:

- Heart failure (New York Heart Association class III, IV): The American Heart Association and the American Diabetes Association has stated that patients with New York Heart Association class III, IV symptomatic heart failure should use TZD at the lowest possible dose or not at all due to risk of fluid retention and diastolic heart dysfunction.[12]
- Moderate to severe hepatic impairment: Troglitazone was removed from the market due to hepatoxicity. While rosiglitazone or pioglitazone have not shown the same hepatotoxic effects, the recommendation is still that patients undergo baseline and periodic monitoring of liver function. Patients with AST or ALT greater than or equal to 3 times the upper reference limit should discontinue TZD therapy.[25]
- Bladder cancer: Pioglitazone should not be used in patients with active bladder cancer. In patients with a history of bladder cancer, the risk of recurrence versus the benefits of glycemic control should merit consideration before starting pioglitazone treatment. Rosiglitazone has not shown similar risks of bladder cancer.[18]
- Pregnancy: The FDA labels TZDs as pregnancy class C with teratogenic potential, as PPAR-gamma is necessary for terminal differentiation of the trophoblast and placental vascularization. Pregnant patients should switch to another insulin sensitizer, such as metformin.[24]
- High risk of fractures: Due to increased fracture risk, patients who are at a high risk of fractures, such as those with a history of osteoporosis, postmenopausal women, or patients taking other medications that increase fracture risk (such as glucocorticoids and PPIs), should not start on TZD therapy.[1][14][15][16][17]
- Cytochromes CYP 2C8 and CYP 3A4 are necessary for the metabolism of TZDs; therefore, cytochrome inducers and inhibitors should be used with caution as these medications may affect the drug plasma levels of TZDs.

Monitoring

Before beginning TZD therapy and periodically during treatment, patients should have liver function tests (LFT) evaluated. If LFTs are greater than or equal to 3 times the upper limit, then TZD should not be started or should be discontinued. Additionally, physicians should monitor for

monitor patients' bodyweight to detect possible fluid overload. Signs and symptoms of fluid overload or heart failure, such as rapid weight gain, peripheral edema, dyspnea, S3 heart sounds, or decreased ejection fraction, require close monitoring. HbA1c should be monitored at least twice a year to assess glycemic control and consider dosage adjustments.[13][26]

Enhancing Healthcare Team Outcomes

The use of thiazolidinediones in the management of T2DM requires an interprofessional healthcare team. These agents can help with glycemic control and insulin resistance in patients with functional pancreatic beta-cells. Though they are not first-line agents, they can act synergistically with other oral agents and insulin. They modify gene transcription to increase adiponectin and insulin sensitivity, lower plasma glucose by increasing glucose utilization, decrease plasma fatty acids by increasing fatty acid oxidation, decrease serum triglycerides, and decrease visceral fat. Early use of TZDs in the course of the disease may benefit the pancreas, but there are many long-term dose and duration dependant adverse effects that limit their use. Such effects may include heart failure, weight gain, and bone density loss.

When properly prescribed and carefully monitored, they can effectively reduce fasting plasma glucose and HbA1c levels in some patients by increasing insulin sensitivity. These adverse effects are why a pharmacist consult may be necessary to verify the dosing regimen, check for interactions, and perform medication reconciliation. To receive maximum benefit from TZDs, patient body weight, liver function, plasma glucose, and HbA1c levels need monitoring at follow-up visits; these are functions that a diabetes nurse educator can perform and keep the prescriber informed regarding progress. In addition to being used as adjunctive therapy for diabetes, they have a place in patients with steatohepatitis since they reduce liver fat in clinical trials. With an appropriate interprofessional team approach to thiazolidinedione therapy, patient outcomes for type 2 diabetes can improve with minimal adverse events. [Level 5]

Review Questions

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