Thiazolidinediones

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Uses

- Oral insulin sensitizing agents for the treatment of type 2 DM. Their use in recent years has declined due to concern for increased risk of new or worsening heart failure. Furthermore, questions have been raised about a possible association between TZD use and decreased bone mineral density and bladder cancer.

Perioperative Risks

- Hypoglycemia: Although these agents act primarily to sensitize peripheral tissues to insulin, TZDs carry a mild to moderate risk of hypoglycemia when combined with sulfonylureas or insulin.
- Hepatotoxicity: The first marketed TZD, troglitazone, was removed from the market in USA and UK due to potentially severe liver dysfunction. Currently available TZDs have not shown this same effect on liver function, but liver function tests are still recommended before initiation and as clinically indicated.
- CV risk: Associated with fluid retention and an increased risk of CHF. TZD administration has not been found to be an independent risk factor for myocardial infarction.

Worry About

- Precipitation of heart failure due to volume expansion and sodium retention.
- Hypoglycemia when TZDs are used in conjunction with insulin and sulfonylureas.
- Hyperglycemia, especially when TZDs are stopped in severe insulin resistance.

Overview/Pharmacology

- Orally administered and well absorbed; pioglitazone peaks in 2 h and rosiglitazone peaks in 1 h.
- Distribution: Drug and metabolites are extensively protein bound.
- Excretion and clearance: The two available drugs, pioglitazone and rosiglitazone, are metabolized by different cytochrome P450 isoenzymes, which may make them associated with drug–drug interactions. Primarily excreted in bile and eliminated in feces.
  - Pioglitazone metabolized by hydroxylation and oxidation.
  - Rosiglitazone metabolized by hydroxylation and *N*-demethylation.

Drug Class/Mechanism of Action/Usual Dose

- Peroxisome proliferator activated receptor agonists.
- Sensitizes peripheral tissue to the action of insulin and also preserves pancreatic β cells.
- The mechanism for efficacy is not fully understood. TZDs bind and antagonize one or more peroxisome proliferator-activated receptors (PPAR) subunits, regulating gene expression.
- PPARs control the genetic regulation of complex processes involved in adipogenesis, lipid metabolism, inflammation, and maintenance of metabolic homeostasis.
- PPAR activation in adipose tissue (primary site of action) results in changes to insulin signaling pathways, ultimately resulting in increased insulin sensitivity.
- Animal models have demonstrated that PPAR agonists improved insulin release as a result of the preservation of pancreatic β-cell. They do not, however, directly stimulate insulin secretion.
- Dose of pioglitazone is 15–45 mg/d (as once-daily preparation).
- Dose of rosiglitazone is 2–8 mg/d (as once-daily preparation).

Assessment Points

System	Effect	Assessment by Hx	PE	Test
GENERAL	Increased body weight (average of 3–5 kg)	Pre-drug body weight	Increased SQ fat and decreased visceral fat	Improved waist-hip ratio
CV	Increased fluid retention Vasodilatation Worsening heart failure, esp. in NYHA III & IV	Increased ankle swelling	Edema	
HEME	Increased anemia (dilutional)	Easily fatigued	Pallor	Decreased Hgb by up to 4 g/dL
MS	Increased risk of fractures	Spontaneous fractures; low impact fractures		X-ray
HEENT	Sinusitis, pharyngitis, URI	Coryza, headache, rhinorrhea		
GI	Hepatotoxicity (1:100,000)	Loss of appetite, abdominal pain	Jaundice, dark urine	LFTs
ENDO	Hypoglycemia (in combination with insulin and sulfonylureas)	Sweating, tremors, blurring of vision, palpitation	Tachycardia, altered consciousness	Glucose
OPHTH	Increased macular edema (rare)	Blurring of vision	Decreased visual acuity	Fundus exam
OB	Increased ovulation (increased chances of pregnancy in PCOS women)			

Key References: Della-Morte D, Palmirotta R, Rehni AK, et al.: Pharmacogenomics and pharmacogenetics of thiazolidinediones: role in diabetes and cardiovascular risk factors, *Pharmacogenomics* 15(16):2063–2082, 2014; Vann MA: Management of diabetes medications for patients undergoing ambulatory surgery, *Anesthesiol Clin* 32(2):329–339, 2014.

Perioperative Implications

Preoperative Concerns

- Recommend holding morning dose on the day of surgery.
- Due to the dynamic nature of diabetes, carefully question the pt about their individual signs and symptoms of hypoglycemia.
- Close monitoring of glucose levels due to the risk of hypoglycemia or hyperglycemia.
- Measurement of liver function tests only if clinically indicated.
- Due to the increased risk of fluid retention and heart failure (and disputably MI) associated with TZDs, careful attention should be directed toward obtaining a thorough CV history, physical, and review of symptoms.

Induction/Maintenance

- Intraop administration of insulin may be necessary. Glucose may be necessary to treat hypoglycemia.
- Closely monitor glucose levels because of the risk of hypoglycemia and hyperglycemia.

Postoperative Period

- Closely monitor glucose levels because of the risk of hypoglycemia and hyperglycemia.
- Resume drug therapy if no problem with fluid retention or CV event once the pt is able to eat and drink normally.

Anticipated Problems/Concerns

- Drug-drug interactions have been reported with fluoroquinolones (variable effects on blood glucose), beta-blockers (mask symptoms of hypoglycemia), ACE inhibitors (increased risk of hypoglycemia), and insulin (increased risk of hypoglycemia, fluid retention, and heart failure).
- If in doubt, stop or delay the resumption of TZDs.

Latest Developments

- Rosiglitazone has been pulled from the market in Europe and New Zealand over CV and bone fracture concerns.
- Further investigation has revealed that rosiglitazone primarily affects PPAR-gamma receptors, while pioglitazone exerts effects on both the gamma and alpha receptors. Pharmacogenomic studies have revealed that human genetic variability influences the effectiveness of treatment and perhaps more importantly, the side effect profile of TZDs.

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