Thiazolidinediones

Diabetes mellitus is a disease that affects more than 16 million Americans nationwide. Approximately 95% of all diabetic patients have non-insulin-dependent diabetes mellitus (NIDDM), also known as Type 2 diabetes. Insulin resistance, an increase in hepatic glucose output, and hepatostriatal glucose uptake, characterizes Type 2 diabetes mellitus (DM). Unfortunately, insulin resistance is present in essentially all patients with Type 2 DM. Therefore, it seems practical to incorporate a medication into a patient's regimen that will normalize this fundamental abnormality.

The thiazolidinediones (TZD) are a novel class of oral antidiabetic agents used in the management of Type 2 DM. The first agent of this class, Rosulin (rosiglitazone), received FDA approval in January 1997. The two most recent agents to join this class, Actos (pioglitazone) and Avandia (rosiglitazone), were marketed in May and July of the current year. However, rosiglitazone was removed from the market on March 21, 2000 due to the severe hepatocellular damage and liver failure associated with this agent.

The TZD's are indicated as an adjunct to diet and exercise to improve glycemic control. They can be used as monotherapy or for use in combination with sulfonylurea, metformin, or insulin when pioglitazone or rosiglitazone as a single agent fail to produce adequate glycemic control.

CLINICAL PHARMACOLOGY

The TZD's depend on the presence of insulin for their mechanism of action. They decrease insulin resistance in the periphery and liver, resulting in an increase in insulin-dependent glucose disposal and decreased hepatic glucose output. They are not chemically or functionally related to the sulfonylureas, biguanides, or α-glucosidase inhibitors, they do not promote the secretion of insulin from the pancreatic β cells. They are highly selective agonists for peroxisome proliferator-activated receptor gamma (PPARγ). PPARγ receptors are found in tissues important for insulin action, such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors regulate the transcription of a number of insulin-responsive genes involved in the control of glucose and lipid metabolism.

CLINICAL PHARMACOKINETICS

The TZD's are well absorbed with an oral bioavailability of 40-50%. Peak plasma concentrations occur approximately 2-3 hours postdose. These agents are greater than 99% protein bound in the serum. The main volume of distribution is 15.4L/kg for pioglitazone and 17.6L/kg for rosiglitazone. Both of these agents are metabolized via N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronide acid. The CYP450 isozymes, 3A4 and 2C8, are partially responsible for the metabolism of pioglitazone. Conversely, rosiglitazone is predominately metabolized via the isoenzyme CYP2C8 with CYP2C9 and CYP1A1 as minor pathways. The half-life of pioglitazone ranges from 3-7 hours and 3.15-3.59 hours for rosiglitazone.

The recommended dose for pioglitazone is 45mg orally every day, except when used in combination with insulin, when the dose is 30mg every day. As for rosiglitazone, the recommended dose is 4mg orally twice a day, or 4mg once a day when used with insulin. The TZD's are typically used in combination with insulin or metformin.

Preclinical studies in mice, discovered that the TZD's were found to cause plasma volume expansion and preload induced cardiac hypertrophy. Fortunately, results from two 3-year echocardiography studies in humans, designed to detect a change in left ventricular mass of 10% or more, showed no deleterious alteration in cardiac structure or function. However, patients with a predisposition for congestive heart failure should not receive a TZD.

The TZD's are classified as category C antidiabetic agents. They should not be used during pregnancy unless the benefit justifies the potential risk to the fetus. Insulin monotherapy is the preferred drug during pregnancy to maintain blood glucose levels as close to normal as possible. These agents are also likely to be secreted in breast milk, and should not be administered to nursing mothers.

CLINICAL TOXICOLOGY

There are only a minimal number of drug-drug interactions associated with the TZD's. The pharmacokinetics of digoxin, warfarin, metformin, nifedipine, ethanold, acarbose, and sulfonamides were not altered when administered concomitantly with TZD's. However, there is a major interaction between oral contraceptives and pioglitazone. Administration of pioglitazone, but not rosiglitazone, with oral contraceptives containing ethinyl estradiol andnorethindrone reduces the plasma concentration of both hormones by 30%. Consequently, loss of contraception could occur leading to pregnancy. Unfortunately, there has not been a specific formal pharmacokinetic interaction study with other drugs, such as erythromycin, calcium channel blockers, cyclogor, or corticosteroids, which are metabolized by the CYP3A4 pathway. However, patients receiving drugs that are inhibitors of the CYP3A4 pathway, such as ketocanazole and itraconazole, should be evaluated more frequently with respect to glycemic control.

The TZD's are generally well tolerated when given as the usual daily dose. Commonly experienced adverse effects associated with the TZD's are headache, upper respiratory tract infection, back pain, edema, hypoglycemia, fatigue, weight gain, diarrhea, sinusitis, myalgias, and pharyngitis. Toxicity occurs when doses of greater than 45mg for pioglitazone and greater than 8mg for rosiglitazone are taken.

A TZD overdose is not considered to be fatal. The most severe adverse effects from a TZD overdose are hypoglycemia, hepatic abnormalities, pulmonary edema, and anemia. The degree of hypoglycemia is categorized as mild, moderate, or severe. Symptoms related with mild hypoglycemia (Blood Glucose 55-70mg/dl) include irritability, diaphoresis, nervousness, pallor, palpitations, shakiness, and tachycardia. In moderate hypoglycemia (BG 40-55mg/dl) patients will have evidence of neuroglycopenia. These symptoms consist of blurred vision, changes in mood, extreme fatigue, mental confusion, slowed reaction time, and somnolence. Coma, convulsions or seizures, or unconsciousness characterizes the last stage, severe hypoglycemia (BG <40mg/dl).

Although there have not been any reported cases of idiosyncratic drug reactions leading to hepatic failure associated with pioglitazone or rosiglitazone, they are structurally related to troglitazone. As a result, patients receiving these agents may have increases in their liver function tests. Elevations in alanine aminotransferase (ALT) greater than three times the upper limit of normal was revealed in patients who overdosed. Also,
patients presented with jaundice, sepsis, severe nausea, vomiting, abdominal pain, anorexia, dark urine, and fatigue.1 Pulmonary edema presents as a persistent cough, tachypnea, dyspnea, rales on auscultation, and decreased lung compliance (stiff lungs).14

In an acute overdose with a TZD patients become anemic.5 Even though this effect is transient, treatment is required to bring one's hemoglobin and hematocrit levels within the normal range. Symptoms of anemia include weakness, fatigue, tachycardia, vertigo, headache, faintness, pallor, loss of skin color, and sensitivity to cold.6

LABORATORY ASSESSMENT

Determination of the TZD's and their metabolites in the blood and urine is possible via high-performance liquid chromatography (HPLC).17 Results from the HPLC method are valid and reliable, therefore, it is an appropriate method to use. Distinguishing if a patient is hypoglycemic does not entail a comprehensive exam. If a patient is found unconscious, a single fingerstick test, to measure the blood sugar, using a glucose machine is all that is needed. If the level is less than 70 mg/dl treatment is required. As for the hepatic abnormalities that could occur, physicians should measure the patient's serum liver enzymes, especially the ALT. A CT scan of the liver may also be helpful to determine if any physical damage has occurred in the liver. To diagnose a patient as anemic, a complete blood count is required along with blood cell indices, a reticulocyte index, examination of the peripheral blood smear, mean corpuscular volume, hemoglobin, and hematocrit levels.6 A chest x-ray is used to establish if a patient has pulmonary edema. The less invasive method would be to listen to the patient's lungs as they take deep breaths. Hearing crackles or rales would be indicative of pulmonary edema.

MANAGEMENT

Decontamination is the mainstay of therapy when a patient first arrives in the emergency department. Activated charcoal is indicated for hospital management of acute drug overdose. Activated charcoal is most effective if administered within one hour of ingestion. It enhances elimination of the offending agent, thereby, preventing further absorption.18 Gastric lavage is also useful if performed within one hour post-ingestion. However, this procedure is least efficacious. The reason being that it is the most labor intensive, associated with more complications, and is least favored by the recipient.9

A patient that overdosed on an antidiabetic agent who presents as hypoglycemic must receive prompt attention. Treatment is dependent upon the stage of hypoglycemia that the person is experiencing. In a conscious patient (mild hypoglycemia), the immediate administration of a sugar containing food is warranted.11,12,21 The patient should be directed to consume 15 grams of carbohydrate, wait 15 minutes, then have their blood glucose level tested. If the glucose level is not greater than 80mg/dl, repeat the aforementioned process. Examples of carbohydrate containing foods consists of a 1/2 cup fruit juice (orange or apple), eight lifescapers, 4-6 ounces of a sugar containing soft drink, 1/4 cup raisins, 1 cup skim milk, or 2-3 glucose tablets. The patient's symptoms should resolve within 10-20 minutes.11,12,21

In the unconscious patient (moderate hypoglycemia), the situation is more urgent. A 1-mg dose of glucagon given subcutaneously should be administered as soon as possible. For children, the dose of glucagon is 0.25-1mg/kg/dose, not to exceed 1mg/dose. This pediatric dose can be repeated in 20 minutes if needed. Patients will regain consciousness in 10-15 minutes, and then should be instructed to consume 20-40 grams of carbohydrate due to the fact that glucagon has a duration of action that only lasts 1-1.5 hours.11,12,21

Severe hypoglycemia is definitely a medical emergency since patients may be comatose.11,21,22 In this situation patients are hospitalized, and given 50mL of D5W followed by 10% dextrose solution IV until persistent or slight hyperglycemia occurs. The pediatric dose of D5W is 0.5-1gm/kg. If the blood glucose is not sustained, the infusion can be continued along with 100mg of hydrocortisone sodium succinate or sodium phosphate and 1mg glucagon added per liter of 10% dextrose. Once the blood glucose becomes stable the infusion can be reduced to 5% dextrose and the above agents can be discontinued. Fortunately, symptoms respond quickly to a dextrose infusion and the patient does not suffer from any severe brain damage.11,12,21

When a patient comes in to the emergency room with a TZD overdose and there are signs of hepatic problems, as mentioned before, treatment is usually supportive.4 Liver function tests (LFTs) must be monitored very closely. If rhabdomyolysis or myoglobinuria are part of the patient's daily diabetic medications, stopping the drug for 1-3 days may be necessary. When the LFTs begin to return to the normal level, the drug may be restarted.4

Anemic patients are treated based on the specific type of anemia they have. For instance, a patient who presents with iron deficiency anemia would take ferrous sulfate 325mg orally three times a day.14 Hemoglobin and hematocrit levels start to rise in three weeks. Once stable, the ferrous sulfate is stopped and the patient is recommended to eat a diet high in iron, such as dark green leafy vegetables and red meat.14

Furosemide is the mainstay of therapy in patients with acute pulmonary edema. The dose is 40mg IV over 1-2 minutes, if this is not sufficient the dose may be increased to 80mg IV.4

CONCLUSION

Thiazolidinediones generally are not life threatening when used as a single agent. However, when used in combination with sulfonylurea or insulin, there is the increased risk of an exacerbated hypoglycemic attack. Currently, the exact number of patients who overdose on these agents is unknown. This may be because they are brand new agents and have not been prescribed as much. As time progresses and these agents become more popular, the rates of overdose may increase. Physicians, as well as other healthcare professionals, need to be aware of the symptoms of a toxic overdose of a thiazolidinedione so they can effectively treat the patient. As for the remainder of the population, a major way to prevent most hospitalizations for overdoses is to educate all diabetic patients on the importance of properly taking their medication.

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REFERENCES

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