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Rosiglitazone

Updated: June 6, 2018.

OVERVIEW

Introduction

Rosiglitazone is an insulin sensitizing agent and thiazolidinedione that is indicated for the treatment of type 2 diabetes. Rosiglitazone has been linked to rare instances of acute liver injury.

Background

Rosiglitazone (roe" si gli' ta zone) an insulin sensitizing agent that improves glucose control in patients with type 2 diabetes. Like other thiazolidinediones, it is thought to act by engagement of PPAR-γ receptors which induce multiple genes involved in glucose and fatty acid metabolism. In clinical trials, rosiglitazone was found to lower blood glucose and HbA1c levels and had additive effects with the sulfonylureas and metformin. Rosiglitazone was approved for use in the United States in 1999. While the initial thiazolidinedione – troglitazone – had been associated with high rates of serum aminotransferase elevations and multiple reports of severe liver injury and death from acute liver failure, rosiglitazone was associated with a lower rate of ALT elevations and with only rare instances of clinically apparent liver injury. Rosiglitazone is approved as an adjunct to diet and exercise in the glycemic control of patients with type 2 diabetes. Rosiglitazone is available as 2 and 4 mg tablets generically and under the brand name Avandia and the usual recommended dosage is 4 to 8 mg daily in two divided doses. Rosiglitazone is used as monotherapy as well as in combination with metformin, sulfonylureas or insulin. In 2010, the FDA published a drug safety alert concerning the cardiovascular risks of rosiglitazone and the drug has been withdrawn in many countries of the world, because of these potential long term adverse effects. In the United States, it remains available but is recommended only for patients who are unable to achieve glycemic control with other diabetes medications.

Hepatotoxicity

In contrast to troglitazone, rosiglitazone is not associated with an increased frequency of aminotransferase elevations during therapy. In clinical trials, ALT elevations above 3 times the ULN occurred in only 0.25% of patients on rosiglitazone, compared to 0.25% of placebo recipients (and 1.9% of troglitazone recipients in similar studies). In addition, clinically apparent liver injury attributed to rosiglitazone is very rare, fewer than a dozen cases having been described in the literature despite extensive use of this agent. The liver injury usually arises between 1 and 12 weeks after starting therapy (thus, a shorter latency than typically occurs with troglitazone) and all patterns of serum enzyme elevations have been described including hepatocellular, cholestatic and mixed. Allergic phenomena are rare and autoantibodies have not been typically present. Fatal instances have been reported usually in cases with a hepatocellular pattern of injury. In most instances, recovery is complete within 1 to 2 months.

Likelihood score: C (probable rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of liver injury due to rosiglitazone is not known, but the general pattern and course differs somewhat from troglitazone and it is unlikely that the thiazolidinediones share a single mechanism for liver injury.

Outcome and Management

The liver injury from rosiglitazone is usually reversed with stopping the medication. Fatal cases of rosiglitazone associated liver injury have been reported, but most cases were self-limiting. Chronic liver disease and vanishing bile duct syndrome have not been reported with rosiglitazone therapy. There is at least some degree of cross sensitivity to the liver injury caused by the different thiazolidinediones, so that patients with rosiglitazone hepatotoxicity should avoid use of pioglitazone.

References to the safety and hepatotoxicity of rosiglitazone are given together with references to pioglitazone and troglitazone in the Overview section on the Thiazolidinediones (updated June 2018).

Drug Class: Antidiabetic Agents

Other Drugs in the Subclass, Thiazolidinediones: Pioglitazone, Troglitazone

CASE REPORT

Case 1. Acute hepatitis after 8 days of rosiglitazone therapy.

[Modified from: Al-Salman J, Arjomand H, Kemp DG, Mittal M. Hepatocellular injury in a patient receiving rosiglitazone. A case report. Ann Intern Med 2000; 132: 121-4. PubMed Citation]

A 61 year old man with diabetes was started on rosiglitazone and developed symptoms of nausea and abdominal pain within 8 days and jaundice within 2 weeks. The patient had poorly controlled diabetes for which he took sulfonylureas and metformin without adequate control. He was tried on troglitazone therapy, but it was discontinued after 8 days because of nausea and upset stomach. After failure to tolerate repaglinide because of nausea and dizziness, he was started on rosiglitazone. Eight days later he developed anorexia, nausea and abdominal pain and subsequently noted onset of dark urine and fever. His liver test results had been normal before starting rosiglitazone, but 11 days later he had marked elevations in serum aminotransferase levels and jaundice (Table). Rosiglitazone was stopped and he began to improve. Tests for hepatitis A, B and C were negative as were autoantibodies. Ultrasonography showed no evidence of gallstones or biliary tract disease. He also had chronic obstructive pulmonary disease and a remote history of alcoholism. After a week in the hospital, he was discharged. Subsequent testing showed a slow improvement in his liver tests. Serum aminotransferase levels were normal two months later.

Key Points

Medication:	Rosiglitazone (4 mg daily for 11 days)
Pattern:	Hepatocellular (R=12)
Severity:	3+ (jaundice and hospitalization)
Latency:	8 days to nausea and abdominal pain, 11 days to jaundice
Recovery:	2 months

Table continued from previous page.

Other medications:	Bronchodilators, theophylline, prednisone, zafirlukast, acetaminophen (<2 g/day), and remotely repaglinide, metformin, sulfonylureas

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre		40			
11 days	0	1706	331	9.6	Rosiglitazone stopped
15 days	4 days	1349	412	13.8	
18 days	7 days	1251	519	12.8	Discharge
24 days	2 weeks	558	486	12.1	
31 days	3 weeks	133	274	4.9	
9 weeks	7 weeks	41	165	2.3	
11 weeks	10 weeks	38	144	1.8	
Normal Values		**<40**	**<117**	**<1.2**	

Comment

Acute hepatocellular injury without signs of allergy (fever, eosinophilia and rash) developed within 1 to 2 weeks of starting rosiglitazone. While the pattern of liver enzyme elevations and severity of injury resembles that described with troglitazone, the short latency is atypical for the other thiazolidinediones. Interestingly, the patient did not tolerate troglitazone in the past, although no liver tests were performed at the time. Thus, the rapid development of liver injury upon starting rosiglitazone may have been due to cross reactivity of the injury with troglitazone and a form of reexposure. The timing of onset and recovery make rosiglitazone a highly likely cause of this hepatic injury.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Rosiglitazone – Avandia®

DRUG CLASS

Hypoglycemic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Rosiglitazone	122320-73-4	C18-H19-N3-O3-S