

## Hepatic Failure in a Patient Taking Rosiglitazone

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**Background:** Rosiglitazone maleate is the second approved oral hypoglycemic agent of the thiazolidinedione class. The first, troglitazone, has been associated with liver failure, occasionally resulting in liver transplantation or death. There have been no reports to date of rosiglitazone-associated elevations in the alanine aminotransferase level or hepatotoxicity.

**Objective:** To report the clinical characteristics of liver failure developing in a patient receiving rosiglitazone.

**Design:** Case report.

**Setting:** University hospital.

**Patient:** 69-year-old man taking rosiglitazone, 4 mg/d.

**Intervention:** Discontinuation of rosiglitazone therapy and treatment with lactulose, vitamin K, fresh frozen plasma, ventilatory assistance, and intensive care unit support.

**Measurements:** Blood test monitoring, including toxicology screening, liver function tests, coagulation studies, serum chemistries, and complete blood counts.

**Results:** After 21 days of rosiglitazone therapy, hepatic failure developed. Other causes of hepatic failure, such as viruses and toxins, were excluded, although it is possible that congestive heart failure was also a causative factor. The patient recovered fully with supportive care.

**Conclusion:** Rosiglitazone may be associated with hepatic failure.

Rosiglitazone maleate (Avandia, SmithKline Beecham, Philadelphia, Pennsylvania) is a thiazolidinedione, a relatively new class of oral anti-diabetic agents that enhance sensitivity to insulin in skeletal muscle, adipose tissue, and liver (1). Troglitazone, its predecessor, has been associated with idiosyncratic hepatotoxicity (2–6). Cases of liver failure, liver transplantation, and death have been reported, and troglitazone was voluntarily withdrawn from the United Kingdom market in late 1997 (7). In premarketing trials, clinically significant elevations in liver enzyme levels were more frequent with troglitazone than with placebo (8, 9). Whether this hepatotoxicity is a class effect of thiazolidinediones remains to be established. Rosiglitazone is structurally very similar to troglitazone. No severe hepatotoxic adverse effects have been previously noted in patients treated with rosiglitazone (10, 11). We report a case of hepatic failure that may have been associated with rosiglitazone administration.

### Case Report

A 69-year-old man presented with shortness of breath and abdominal pain. His medical history included atrial fibrillation, hypertension, coronary artery disease, and New York Heart Association class II congestive heart failure. A baseline left ventricular ejection fraction was not available, but the patient's left ventricular ejection fraction was measured at 35% to 45% on two occasions during his hospitalization. The patient had had coronary artery bypass surgery 10 years before admission. Type 2 diabetes mellitus had been diagnosed approximately 1 month before admission, and the patient was prescribed rosiglitazone, 4 mg/d. The patient's hepatic biochemical markers were normal before rosiglitazone therapy began, except for a total bilirubin level of 29  $\mu\text{mol/L}$  (1.7 mg/dL). The patient's other medications included pravastatin, 20 mg/d; verapamil, 240 mg/d; betaxolol, 5 mg every other day; digoxin, 0.125 mg/d; and warfarin; 3.75 mg/d. He had re-

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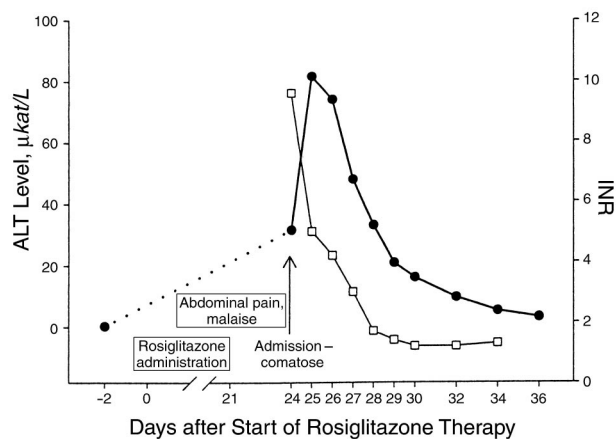
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ceived each of these medications for more than 1 year. The patient reported no history of exposure to hepatotoxins. He admitted to drinking two cans of beer daily. Within 1 week of starting rosiglitazone therapy, the patient experienced nausea, anorexia, fatigue, and abdominal pain. His symptoms progressed, and 5 days before admission, rosiglitazone therapy was discontinued. Therapy with metformin, 500 mg/d, was substituted, but the patient took only two doses, 5 and 6 days before admission. One day before admission, the patient experienced shortness of breath. At presentation, he was tachypneic, with a blood pressure of 104/48 mm Hg, and his abdomen was diffusely tender. Ascites and hepatomegaly were not present on physical examination. Laboratory values at presentation were as follows: total bilirubin, 65  $\mu\text{mol/L}$  (3.8 mg/dL); direct bilirubin, 41  $\mu\text{mol/L}$  (2.4 mg/dL); alanine aminotransferase (ALT), 31.57  $\mu\text{kat/L}$ ; aspartate aminotransferase, 46.68  $\mu\text{kat/L}$ ; alkaline phosphatase, 3.4  $\mu\text{kat/L}$ ; prothrombin time, 92.7 seconds (international normalized ratio, 9.59); amylase, 1.82  $\mu\text{kat/L}$ ; lipase, 3.1  $\mu\text{kat/L}$ ; albumin, 36 g/L; and creatinine, 300  $\mu\text{mol/L}$  (3.4 mg/dL). Arterial blood gas values were as follows: pH, 7.15;  $\text{PCO}_2$ , 14 mm Hg; bicarbonate, 5 mmol/L; and  $\text{PO}_2$ , 257 mm Hg. Chest radiography revealed small bibasilar pleural effusions and mild pulmonary edema. Abdominal computed tomography revealed minimal ascites.

The patient was admitted and rapidly became comatose. Two hours after admission, he became bradycardic and hypotensive, and he was given atropine, normal saline, epinephrine, and sodium bicarbonate. He had not received sodium bicarbonate therapy up to that point. His systolic blood pressure increased to 117 mm Hg and remained above 90 mm Hg during the remainder of his hospital course. During his hospital course, results of serologic testing were negative for hepatitis A, B, and C; Epstein-Barr virus; and cytomegalovirus. Toxicology screening was negative for acetaminophen, alcohol, and other known hepatotoxins. The patient was negative for antinuclear antibody (titer, 1:80). The patient's aspartate aminotransferase level peaked at 184.94  $\mu\text{kat/L}$ , and his albumin level decreased to 29 g/L. The patient was not considered a candidate for liver transplantation because of his age and cardiac history. A liver biopsy was not performed. The patient was managed with intensive medical care, including ventilatory assistance, lactulose, vitamin K, and fresh frozen plasma. He received no cardiovascular support during his hospital admission other than renal-dose dopamine.

The patient gradually improved over the subsequent 2 weeks, and his mental status and prothrombin time returned to normal. At discharge, his albumin level was 39 g/L, his creatinine concentration



**Figure.** The patient's clinical course. Changes in the patient's alanine aminotransferase (ALT) level (circles) and international normalized ratio (INR) (squares) after rosiglitazone therapy are shown. The dotted line represents the time from the start of rosiglitazone therapy to the patient's hospital admission.

was 106  $\mu\text{mol/L}$  (1.2 mg/dL), and his ALT level was 3.28  $\mu\text{kat/L}$  (Figure).

## Discussion

Thiazolidinediones, agents that contain a thiazolidine-2,4-dione structure, were first synthesized in 1982. Differences in side chains influence their pharmacologic actions and potential adverse effects (1). They are selective agonists for the peroxisome proliferator-activated receptor- $\gamma$ , but their mechanism of action is not well understood (12). Activation of the peroxisome proliferator-activated receptor- $\gamma$  regulates the transcription of several genes involved in insulin-mediated glucose uptake in peripheral tissues and in preadipocyte differentiation (13).

Rosiglitazone maleate is the second thiazolidinedione to be approved in the United States. Unlike troglitazone, rosiglitazone does not have a lipophilic  $\alpha$ -tocopherol moiety (1). It has a higher affinity for the peroxisome proliferator-activated receptor- $\gamma$  than does troglitazone. Rosiglitazone is 99% bioavailable, reaching peak plasma concentrations 1 hour after administration. It is 99.8% bound to plasma proteins, primarily albumin. Rosiglitazone is extensively metabolized in the liver, mainly by *N*-demethylation and hydroxylation, followed by conjugation with glucuronic acid and sulfate. In vitro data indicate that rosiglitazone is predominantly metabolized by cytochrome P4502C8 and, to a lesser extent, CYP2C9. In contrast to troglitazone, rosiglitazone does not appear to induce CYP3A4 metabolism. It does not inhibit any of the major P450 enzymes at clinically relevant concentrations. Mild to moderate renal failure, age, ethnicity, and

tobacco and ethanol intake do not change the pharmacokinetics of rosiglitazone (10, 11).

Rosiglitazone has not been previously considered to be hepatotoxic. In particular, premarketing trials found no evidence of rosiglitazone-induced elevation of aminotransferase levels or other signs of hepatotoxicity (14). Of 3455 patients who received rosiglitazone and had frequent liver function tests, the proportion of patients with ALT levels more than three times the upper limit of normal (0.17% [6 of 3455]) was similar to that in patients receiving placebo (0.18% [1 of 561]) or metformin or sulfonylureas (0.48% [4 of 828]). Patients who developed ALT levels more than three times the upper limit of normal during rosiglitazone treatment eventually had normalized, improved, or unchanged ALT levels during continued therapy (14). Moreover, in a study involving rat hepatocytes, rosiglitazone showed no cytotoxicity at concentrations of 100  $\mu\text{mol/L}$  or more, unlike troglitazone, which was toxic to these cells at the much lower concentration of 20  $\mu\text{mol/L}$  (15).

We describe a patient with severe hepatotoxicity that seemed to be associated with rosiglitazone therapy after only 21 days of exposure to the drug. The patient developed nonspecific symptoms during rosiglitazone treatment that in retrospect probably reflected acute liver injury within 1 week of the start of rosiglitazone therapy. Although the patient took metformin, his initial metabolic acidosis is more likely attributable to hepatic failure itself than to metformin therapy; he took only two doses of metformin more than 5 days before presentation. This patient was also taking verapamil and pravastatin, both of which can cause hepatitis, but the patient had been receiving these drugs for more than 1 year. Results of tests for viral or toxic causes of hepatic failure were negative.

It is possible that ischemic hepatitis ("shock liver") played a superimposed role in this patient's hepatic dysfunction, but ischemia alone is unlikely to explain the patient's initial clinical picture. He did not have a documented episode of prolonged hypotension or hypoxemia before presentation, and he had only mild congestive heart failure according to physical examination and chest radiography on admission. He did have a bradycardic/hypotensive episode 2 hours after admission, but his liver function test results and prothrombin time were already documented to be markedly abnormal before this event occurred. The profound acidosis that accompanied the patient's liver failure may have led to the hypotensive episode, given his history of cardiac disease. Furthermore, the hypotensive episode and potential ischemia cannot explain the weeks of hepatitis-related symptoms that preceded this patient's admission. Of note, a decrease in the serum albumin level was associated with this patient's illness, a

phenomenon not typically associated with shock liver (16, 17).

Therefore, this case may represent an idiosyncratic reaction to rosiglitazone, the basis of which is not apparent. The patient's liver disease may also represent an adverse reaction to the concomitant administration of rosiglitazone with verapamil, pravastatin, or both. Additional investigations of the metabolism of rosiglitazone are necessary to help elucidate the mechanisms underlying this hepatotoxicity. We suggest that liver enzyme levels be monitored frequently in patients taking rosiglitazone, particularly soon after initiation of therapy. It is important to emphasize the need for patients to report adverse symptoms promptly. If anorexia, fatigue, abdominal pain, nausea, or jaundice occur, it is wise to stop therapy with this agent and monitor for hepatic dysfunction.

The manufacturer of rosiglitazone and the U.S. Food and Drug Administration were notified of this case.

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## References

1. Henry RR. Thiazolidinediones. *Endocrinol Metab Clin North Am.* 1997;26:553-73.
2. Gitlin N, Julie NL, Spurr CL, Lim KN, Juarbe HM. Two cases of severe clinical and histologic hepatotoxicity associated with troglitazone. *Ann Intern Med.* 1998;129:36-8.
3. Neuschwander-Tetri BA, Isley WL, Oki JC, Ramrakhiani S, Quiason SG, Phillips NJ, et al. Troglitazone-induced hepatic failure leading to liver transplantation. A case report. *Ann Intern Med.* 1998;129:38-41.
4. Shibuya A, Watanabe M, Fujita Y, Saigenji K, Kuwao S, Takahashi H,

- et al.** An autopsy case of troglitazone-induced fulminant hepatitis. *Diabetes Care*. 1998;12:2140-3.
5. **Vella A, deGroen PC, Dinneen SF.** Fatal hepatotoxicity associated with troglitazone [Letter]. *Ann Intern Med*. 1998;129:1080.
  6. **Herrine SK, Choudhary SC.** Severe hepatotoxicity associated with troglitazone [Letter]. *Ann Intern Med*. 1999;130:163-4.
  7. **Plosker GL, Faulds D.** Troglitazone: a review of its use in the management of type 2 diabetes mellitus. *Drugs*. 1999;57:409-38.
  8. **Watkins PB, Whitcomb RW.** Hepatic dysfunction associated with troglitazone [Letter]. *N Engl J Med*. 1998;338:916-7.
  9. **Spencer CM, Markham A.** Troglitazone. *Drugs*. 1997;54:89-101.
  10. **Balfour JA, Plosker GL.** Rosiglitazone. *Drugs*. 1999;57:921-30.
  11. Prescribing information contained in the manufacturer's insert for Avandia. Philadelphia: SmithKline Beecham; May 1999.
  12. **Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Klierer SA.** An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem*. 1995;270:12953-6.
  13. **Saltiel AR, Olefsky JM.** Thiazolidinediones in the treatment of insulin resistance and type II diabetes. *Diabetes*. 1996;45:1661-9.
  14. **Salzman A, Patel J.** Rosiglitazone is not associated with hepatotoxicity [Abstract]. *Diabetes*. 1999;48:A63.
  15. **Elcock FJ, Lyon JJ, Hitchcock J, Morgan DG, Bertram TA, Bugelski PJ.** Toxicity of troglitazone in cultured rat hepatocytes [Abstract]. *Diabetes*. 1999;48:A95.
  16. **Gibson PR, Dudley FJ.** Ischemic hepatitis: clinical features, diagnosis and prognosis. *Aust N Z J Med*. 1984;14:822-5.
  17. **Fuchs S, Bogomolski-Yaholom V, Paltiel O, Ackerman Z.** Ischemic hepatitis. *J Clin Gastroenterol*. 1998;26:183-6.
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