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Original Article

Thiazolidinedione-Associated Congestive Heart Failure and Pulmonary Edema

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Abstract

- ***Objective*: To evaluate the effect of thiazolidinediones on the development of cardiac failure and pulmonary edema during treatment of type 2 diabetes mellitus.**
- ***Patients and Methods*: We retrospectively reviewed the medical records of 6 men (aged 66 to 78 years) treated at our institution between August 1, 2001, and May 21, 2002, who had type 2 diabetes and developed signs and symptoms of congestive heart failure and pulmonary edema after 1 to 16 months of therapy with pioglitazone or rosiglitazone.**
- ***Results*: Four patients had chronic renal insufficiency; only 1 had ischemic cardiomyopathy. Symptoms resolved promptly in all 6 patients after administration of diuretics and discontinuation of the thiazolidinedione.**
- ***Conclusion*: We conclude that thiazolidinediones can cause or exacerbate heart failure and pulmonary edema and should be avoided in patients with left ventricular dysfunction or chronic renal insufficiency.**
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LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VEGF = vascular endothelial growth factor

Thiazolidinediones are oral hypoglycemic drugs that are increasingly being used to treat type 2 diabetes mellitus. These agents improve insulin sensitivity through activation of peroxisome proliferator–activated receptor γ.[1] Although thiazolidinediones are well known to cause idiosyncratic hepatotoxicity and fluid retention, [2-5]

only a few patients have been reported to have developed congestive heart failure and pulmonary edema.[2,3] We describe 6 patients with type 2 diabetes mellitus who developed congestive heart failure and pulmonary edema during thiazolidinedione treatment. None of these patients had acute myocardial infarction, pronounced arrhythmia, or other conditions to explain deterioration of cardiac status. The study was approved by the Institutional Review Board of the Department of Veterans Affairs Medical Center in Dallas, Tex.

PATIENTS AND METHODS

Between August 1, 2001, and May 21, 2002, 6 male patients at the Dallas Veterans Affairs Medical Center, Dallas, Tex, were identified with new-onset congestive heart failure and pulmonary edema, which occurred shortly after the initiation or a dose increase of pioglitazone or rosiglitazone (Table 1). Two patients (cases 1 and 2) were admitted to one of the author's inpatient service (A.K.); subsequent patients were identified during clinic visits, hospitalizations, and retrospective chart reviews. The mean age of the patients was 69 years, with a range of 66 to 78 years. The duration of thiazolidinedione therapy ranged from 1 month to 16 months, but dose increases typically occurred 3 weeks to 3 months before the onset of congestive heart failure. In all patients, thiazolidinedione agents were discontinued, and diuretic agents were administered with resolution of congestive heart failure. Follow-up since treatment of congestive heart failure ranged from 1 month to 24 months.

- **For editorial comment, see page 1076.**

REPORT OF CASES

Case 1

A 67-year-old man with ischemic cardiomyopathy and a history of congestive heart failure, New York Heart Association (NYHA) functional class II, presented with orthopnea and paroxysmal nocturnal dyspnea of 1 week's duration. Transthoracic echocardiography conducted 2 months before admission revealed a left ventricular ejection fraction (LVEF) of 15%. Pioglitazone, 30 mg/d, had been initiated 3 months previously and increased to 45 mg/d 3 weeks before admission. Physical examination revealed respiratory distress and severe edema up to the sacrum. Chest radiography showed cardiomegaly and right pleural effusion. The serum creatinine level was 1.0 mg/dL, slightly reduced compared to baseline values of 1.3 to 1.9 mg/dL. Pioglitazone was discontinued, and furosemide was given intravenously and then orally. The patient was asymptomatic 6 days later. Three months later, the pleural effusion had resolved.

TABLE 1. CLINICAL CHARACTERISTICS OF 6 PATIENTS WITH NEW-ONSET CONGESTIVE HEART FAILURE AND PULMONARY EDEMA

	Patients					
Variable	1	2	3	4	5	6
Age (y)	67	70	78	68	66	67
Ethnicity	Hispanic	African American	Caucasian	African American	Caucasian	Caucasian
Preexisting congestive heart failure	Yes*	No	No	No	No	No
Duration of diabetes (y)	20	4	7	12	21	15
Thiazolidinedione						
Agent	Pioglitazone	Rosiglitazone	Rosiglitazone	Rosiglitazone	Rosiglitazone	Rosiglitazone
Dosage (mg/d)	45	4	8	8	8	8

Duration (mo)	7	1	5.5	16	6	8
Other hypoglycemic drugs						
Agent	Insulin	None	Insulin	Glipizide	Insulin	Glyburide
Dosage	140 U/d	…	740 U/d	20 mg/d	82 U/d	2.5 mg/d
Recent weight gain (kg)	8	6	1	5.4	8.6	11.6
Baseline serum creatinine (mg/dL)	1.3-1.9	2.7	1.1	1.8-2.9	2.1-3.1	1.4-2.2
Hospitalization	Yes	Yes	No	Yes	Yes	No
Other medications at baseline	Captopril, carvediol, Furosemide, aspirin, isosorbide, simvastatin, spironolactone	Losartan, metoprolol, verapamil, digoxin, minoxidil, furosemide, simvastatin, aspirin	Ranitidine, diethylstilbestrol, aspirin	furosemide, lisinopril	Clonidine, felodipine, fosinopril, furosemide, gemfibrozil, levothyroxine, simvastatin, metoprolol	Simvastatin, aspirin, isosorbide, metoprolol, furosemide, lisinopril, felodipine, terazosin
*New York Heart Association class II.						

Case 2

A 70-year-old man with hypertension and chronic renal insufficiency presented with dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Metformin had been replaced with rosiglitazone, 4 mg/d, 1 month previously. The patient had no history of congestive heart failure. Physical examination revealed tachypnea and bilateral lower extremity edema. Chest radiography showed cardiomegaly with bilateral basilar infiltrates. Transthoracic echocardiography revealed left ventricular hypertrophy and diastolic dysfunction but normal LVEF. The serum digoxin level was slightly increased at 2.3 ng/mL. Serum creatinine values did not change. Rosiglitazone was discontinued, and intravenous furosemide was administered. Metoprolol, digoxin, minoxidil, and verapamil were replaced with losartan and felodipine. After 3 days, the patient was asymptomatic.

Case 3

A 78-year-old man who had undergone coronary artery bypass grafting, had no history of congestive heart failure, and had stable metastatic prostate cancer presented with dyspnea and orthopnea of 2 days' duration. Rosiglitazone, 8 mg/d, had been initiated 5 months previously. Physical examination revealed new onset of bilateral rales and pedal edema. Serum creatinine values were not different from baseline. Furosemide was administered intravenously, followed by daily oral administration. Transthoracic echocardiography revealed an LVEF of 35% and dilatation of the left atrium and ventricle. Three weeks later, the patient still had bilateral basilar rales and pedal edema and continued to be symptomatic. Rosiglitazone was discontinued. His symptoms resolved after 3 days.

Case 4

A 68-year-old morbidly obese man with hypertension and chronic renal insufficiency presented with acute dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Rosiglitazone, 8 mg/d, had been initiated 3 months previously. Physical examination revealed pulmonary rales and bilateral lower extremity edema. Serum creatinine values ranged from 1.5 to 1.7 mg/dL, compared to baseline values of 1.8 to 2.9 mg/dL. Chest

radiography disclosed small bilateral pleural effusions and infiltrates. Transthoracic echocardiography revealed normal LVEF. The patient had no history of congestive heart failure and had preserved left ventricular systolic function on previously performed transthoracic echocardiography. Furosemide was administered intravenously, and then orally. Thirteen months later, similar problems recurred. Repeated transthoracic echocardiography revealed no reduction in LVEF. Furosemide was given intravenously, and its oral dose was increased. Rosiglitazone was discontinued. The patient was asymptomatic 10 weeks later.

Case 5

A 66-year-old man with coronary heart disease, nephrotic syndrome, chronic renal insufficiency, and hypertension presented with anasarca, dyspnea, and orthopnea of 2 months' duration. Rosiglitazone, 4 mg/d, had been initiated 6 months before admission and had been increased to 8 mg/d 3 months later. The patient had no history of congestive heart failure. Physical examination revealed bilateral rales and severe edema. Chest radiography showed mild cardiomegaly, bilateral minimal pleural effusions, and vascular prominence. The serum creatinine value was 2.1 mg/dL, similar to baseline values of 2.1 to 3.1 mg/dL. The patient was treated with intravenous furosemide and oral metolazone. Rosiglitazone was discontinued. Four weeks later, he had no breathlessness or edema.

Case 6

A 67-year-old man with coronary artery disease, hypertension, and chronic renal insufficiency presented with progressive weight gain, lower extremity edema, dyspnea, and paroxysmal nocturnal dyspnea of 4 weeks' duration despite an increase in the dose of furosemide 2 weeks previously. Rosiglitazone, 4 mg/d, had been initiated 8 months previously and increased to 8 mg/d 3 months previously. The patient had no history of congestive heart failure. Physical examination revealed bilateral basal rales. Chest radiography showed cardiomegaly. Serum creatinine values did not change. Rosiglitazone was discontinued, and metolazone was initiated. Four days later, the patient was asymptomatic, and the furosemide dose was reduced.

DISCUSSION

At our medical center during the past year, 648 patients with type 2 diabetes mellitus were treated with thiazolidinediones: 181 (28%) with pioglitazone and 467 (72%) with rosiglitazone. Thus, these 6 cases represent 0.9% of patients being treated at our facility with thiazolidinedione therapy. Seventy-one patients (11%) were receiving monotherapy with either pioglitazone or rosiglitazone; 227 patients (35%) were taking a combination of a thiazolidinedione and insulin. The remaining 350 patients (54%) were prescribed a combination of a thiazolidinedione with a sulfonylurea and/or metformin or with metformin alone.

Previously, pulmonary edema has been reported in 5 patients receiving troglitazone or rosiglitazone therapy.[2-4] Of these 5 patients, 2 had chronic renal insufficiency, and 1 had ischemic cardiomyopathy.[3] All responded to intravenous diuretics and discontinuation of thiazolidinediones. Recently, the Canadian Adverse Reaction Monitoring Program[5] received reports of 9 patients with heart failure and pulmonary edema due to rosiglitazone or pioglitazone. However, details of these cases are not available.

Several features of our cases support thiazolidinediones as the cause of congestive heart failure and pulmonary edema. First, none of these patients had any acute cardiac event to explain deterioration of cardiac status. Second, 3 patients became symptomatic shortly after the dose of rosiglitazone or pioglitazone was increased. Third, all the patients experienced improvement within a few days of discontinuation of thiazolidinediones and administration of diuretics. Of note, in case 4, the initial episode of pulmonary edema during rosiglitazone treatment responded to diuretic therapy; however, the second episode occurred during diuretic therapy and resolved only when rosiglitazone was discontinued. Case 3 also remained symptomatic despite oral furosemide therapy, and his symptoms resolved only after rosiglitazone was discontinued.

All our patients were older than 65 years. Four of these patients had chronic renal insufficiency, 1 had ischemic cardiomyopathy, and 1 had no known predisposing factors for congestive heart failure or pulmonary edema. Five of the 6 patients were taking maximum doses of thiazolidinediones. One patient was taking a thiazolidinedione alone. Three of the patients were also taking insulin, and 2 were taking sulfonylureas in addition to a thiazolidinedione. Neither insulin nor sulfonylureas is known to increase risk of congestive heart

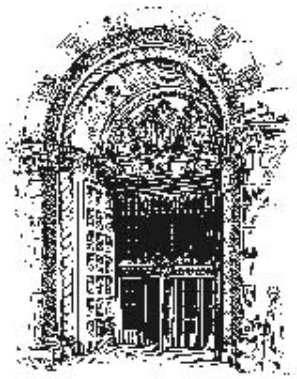
failure and pulmonary edema.

The prescribing information for pioglitazone and rosiglitazone warns against their use in patients with NYHA class III and IV cardiac status, particularly in combination with insulin. In contradistinction to the prescribing information, our data suggest that increased risk of congestive heart failure and pulmonary edema may not be related to concomitant therapy with insulin. Furthermore, our data indicate that patients with NYHA class I or II cardiac status may also be at risk of thiazolidinedione-associated cardiac failure. All but 1 patient in our series had NYHA class I or II functional status and no prior congestive heart failure. However, most of our patients had at least mild chronic renal insufficiency.

The manner in which thiazolidinediones cause pulmonary edema and congestive heart failure is unclear. According to the prescribing information, thiazolidinediones cause an increase in plasma volume, which also results in reduction of hemoglobin concentration. Interestingly, marked elevations in plasma vascular endothelial growth factor (VEGF), a potent vascular permeability factor, were reported in patients treated with troglitazone compared with those treated with insulin, sulfonylureas, and diet.[6] The levels of VEGF normalized 3 months after discontinuation of troglitazone therapy. Thus, it could be speculated that both fluid overload and increased vascular permeability due to high levels of VEGF may contribute to thiazolidinedione-induced pulmonary edema and congestive heart failure.

CONCLUSION

We conclude that thiazolidinediones can cause pulmonary edema or exacerbate heart failure. Further study is needed to identify patient groups at risk of this complication and to determine precise mechanisms of fluid retention. Our data suggest that thiazolidinediones should be used with caution or avoided in patients with left ventricular dysfunction or chronic renal insufficiency.



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