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Acute Pulmonary Edema Due to Rosiglitazone Use in a Patient With Diabetes Mellitus

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Rosiglitazone is a peroxisome proliferator active receptor γ agonist, which increases insulin sensitivity in adipose tissue, muscle, and liver. Rosiglitazone is a member of the thiazolidinedione group, and because of its significantly positive effect on glycemic control, it is especially preferred in type 2 diabetic patients with a high cardiovascular disease risk. This drug, because of its decreasing effect on insulin resistance, is used alone or combined with type 2 diabetic drugs. A 73-year-old female patient was admitted to the emergency department with dyspnea, pink frothing phlegm, cyanosis, and tiredness. She was lethargic, uncooperative, and had no orientation. In arterial blood gases, hypoxemia and hypercapnia were found. She was taken to the general intensive care unit, and oxygen was applied via mask. The patient had a history of 10 years of diabetes mellitus, hypertension, and atherosclerotic cardiac disease, and she was using rosiglitazone for the past 6 weeks. Her chest x-ray was taken, and acute pulmonary edema was diagnosed. In her last echocardiography, which was performed 1 year before, no signs indicating cardiac failure and pleural effusion could be found. Therefore, it was concluded that pulmonary edema occurred as a complication of rosiglitazone use. After stabilizing the patient's vital signs, blood glucose levels, and lactate levels, medical treatment of diabetes mellitus was rearranged, and she was discharged on the seventh day after her admittance. In a patient with diabetes mellitus who has been admitted to the intensive care unit because of acute pulmonary edema, for differential diagnosis, use of rosiglitazone should be kept in mind during the determination of treatment. Therefore, the authors aim to discuss the effect of rosiglitazone on creating acute pulmonary edema with a case report presentation.

Key words: *rosiglitazone, acute pulmonary edema, type 2 diabetes mellitus, intensive care unit*

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Rosiglitazone is a peroxisome proliferator active receptor γ (PPAR- γ) agonist. It increases insulin sensitivity in adipose tissue, muscle, and liver. Rosiglitazone is a member of the thiazolidinedione (TZD) group, and its use in the treatment of type 2 diabetes mellitus (DM) has recently been increased [1,2]. In addition, it is also used in preventing DM and in polycystic ovarian syndrome and nonalcoholic fatty liver disease, which are due to insulin resistance [3].

However, studies suggest that edema is a side effect of each of the TZD drugs to a similar degree, either when used as monotherapy or when combined with other oral diabetes agents. Edema is more common when the TZD is used in combination therapy, and the symptoms may vary from rigorous peripheral edema to serious pulmonary edema [4-8]. Therefore, these agents should be used cautiously in patients with heart failure symptoms [2].

Specifically, use of TZDs is associated with a triad of fluid retention, edema, and weight gain. Fluid retention generally is considered mild and reversible and may result from a reduction in renal excretion of sodium and an increase in sodium and free-water retention. TZDs may interact synergistically with insulin to cause arterial vasodilatation, leading to sodium reabsorption with a subsequent increase in extracellular volume, thereby resulting in pedal edema. Increased sympathetic nervous system activity, altered interstitial ion transport, alterations in endothelial permeability, and peroxisome proliferator-activated receptor-mediated expression of vascular permeability growth factor represent other possible mechanisms for edema with these agents [2,5,7-9].

For a patient who has been admitted to the intensive care unit because of acute pulmonary edema, the determination of the etiology of this urgent situation is important for the follow-up of the treatment. We aim to discuss the effect of rosiglitazone on creating acute pulmonary edema with a case report presentation.

Table 1. Patient's Daily Arterial Blood Gas Values

	At Admittance	Day 2	Day 3	Day 4	After Intensive Care Unit
Oxygenation, L/min	6 via mask	4 via mask	4 via mask	2 via mask	Room air
pH	7.23	7.42	7.43	7.46	7.45
pO ₂ , mm Hg	49	57	55	75	85
pCO ₂ , mm Hg	55	45	41	34	35
SO ₂ , %	80	89.6	90.5	92.7	94.2
Na ⁺ , mmol/L	124	131	133	139	141
K ⁺ , mmol/L	5.5	3.9	3.3	3.6	3.6
Glucose	191	142	118	126	125
Lactate, mg/dL	9	9	4	3	2
HCO ₃ ⁻ , mmol/L	20.8	28.2	27.3	26.1	25.5
Bex, mmol/L	-6.1	4.1	3.1	1.9	1.1
Hb, d/dL	12	10.9	9.4	12.5	11
Hct, %	36	33.5	29.1	37.5	33

Na⁺ = sodium; K⁺ = potassium; HCO₃⁻ = bicarbonate; Bex = base excess; Hb = hemoglobin; Hct = hematocrit.

Case Presentation

A 73-year-old, obese female patient was admitted to the emergency department with tiredness, pink frothing phlegm, cyanosis, and dyspnea. She was lethargic and showed no cooperation and orientation. Hypoxemia and hypercapnia were seen in arterial blood gases (pH = 7.23, pO₂ = 49 mm Hg, pCO₂ = 55 mm Hg, SO₂ = 79%, HCO₃⁻ = 18.2 mmol/L, base excess [Bex] = -7.2 mmol/L). She was immediately transferred to the general intensive care unit, and O₂ ventilation was applied via mask. History taken from her family revealed that the patient had a history of type 2 DM, hypertension, and congestive heart disease for almost 10 years and was using by mouth the following drugs: isosorbide-5-mononitrate, a coronary vasodilator (Monodur R/60 mg 1 × 1); combined losartan potassium, a selective antagonist for angiotensin receptor subtype-1 plus hydrochlorothiazide, a diuretic (Hyzaar R, 50 mg 1 × 1); acarbose, an alpha-glucosidase inhibitor (Glucobay R, 100 mg 3 × 1); rosiglitazone, a PPAR agonist (Avandia R, 4 mg 1 × 1); and gliclazide, a hypoglycemic agent of the sulfanylurea group (Diamicon MR R, 30 mg 1 × 1).

No sign indicating heart failure or pleural effusion was seen on her last echocardiography examination performed 1 year before. Since then, her exercise capacity was normal, and she had no effort-related dyspnea. However, after initiation of rosiglitazone almost 4 weeks before admission to the emergency department, she had complained of fatigue and edema in her legs for 2 weeks. At admission to the intensive care unit, the patient's blood pressure was 200/90 mm Hg, heart rate was 180 beats/min, and respiration rate was 30/min. Her first arterial blood gas measurements were as

follows while 6 L/min O₂ was given by mask: pH = 7.23, pO₂ = 49 mm Hg, pCO₂ = 53 mm Hg, SO₂ = 82%, HCO₃⁻ = 19.8 mmol/L, Bex = -6.1 mmol/L. Daily arterial blood gas and lactate results in the intensive care unit are shown in Table 1. Her cardiovascular system examination revealed that her heart rate was rhythmic but tachycardic. On auscultation, no murmur was heard. There was increased jugular venous distention. In her respiratory system examination, respiration sounds had decreased bilaterally with widespread crepitant rales in both but more in the right basal lung field. Her body weight was measured daily (Figure 1). There was pretibial edema (4+) on the lower extremities bilaterally. Other systemic examinations showed no pathology. In her complete blood counts, her leukocyte count was 11 000 u/L, hemoglobin level was 13 g/dL, and platelet count was 293 000 u/L. In her biochemical tests, her blood glucose level was 191 mg/dL, lactate level was 9 mg/dL, Na⁺ level was 124 mmol/L, K⁺ level was 5.5 mmol, blood urea nitrogen level was 20 mg/dL, creatinine level was 0.8 mg/dL, and liver function tests and complete urine test were in reference range. HbA1c was found to be 5.7% (range, 4.3%-6.0%). Blood cortisol and thyroid-stimulating hormone levels were also normal. On posterior-anterior chest x-ray, the cardiothoracic ratio was increased (>50%), aortic arch was elongated and calcified, and right hemithorax ventilation had significantly decreased due to minimal right pleural effusion seen on chest x-ray at the time of admission. Right-heart catheterization revealed a right atrial pressure of 16 mm Hg. Electrocardiogram and serum creatine kinase (CK), CK-MB, and troponin-T levels were normal, and there was no sign of cardiac ischemia. Bilateral lower extremity venous duplex ultrasonography

and D-dimer, fibrinogen, antithrombin, prothrombin time, international normalized ratio, and activated partial thromboplastin time were normal. There was no sign of deep vein thrombosis or pulmonary embolus. In the echocardiography examination, ejection fraction was 72%, left ventricle functions were normal, and next to the left ventricular posterior wall, 8 mm of pericardial effusion was seen in diastole. There was no aortic, mitral, or tricuspid failure. Systolic and diastolic functions were normal. On bacterial culture from the nasopharyngeal area, no proliferation was indicated. With these clinical and laboratory findings, we diagnosed acute pulmonary edema probably due to rosiglitazone use. Therefore, we stopped the use of it. For the treatment regimen, 5% dextrose 500 mL + 10 U regular insulin; furosemide, a diuretic (20 mg, 2 × 2 intravenously [IV]); salbutamol sulfate, an antiasthmatic and bronchodilator (inhaled 4 × 1); sodium nitroglycerin infusion, a vasodilator (0.5-1.5 µg/kg/min); and theophylline infusion, a bronchodilator (2 × 200 mg IV) were administered. A posterior-anterior chest x-ray taken on the sixth day deemed that the cardiothoracic ratio was decreased. The ventilation of lungs and bronchovascular structures were normal. There were no pleural effusion or infiltrative lesions at the time of discharge from the intensive care unit. Echocardiography on the sixth day showed ejection fraction of 65%. Left ventricular wall and diameters were normal. There was no pericardial effusion. After the patient's vital signs, blood glucose levels, and lactate levels were stabilized and pulmonary edema was improved, metformin HCL, a biguanide (glucophage) 850 mg 3 × 1, was begun orally. The patient was discharged on her seventh day after admittance. Two months later, there were no signs of cardiac failure or pleural effusion on her control physical examination and echocardiography.

Discussion

Edema is a complication of TZDs. Edema may develop because of rosiglitazone, and the incidence ranges from 2% to 5%. If combined with insulin, this ratio increases to 14.7% for rosiglitazone [5-7]. The reason for the development of edema is not certain, but it is probably multifactorial [2,5,7-9]. Increased plasma volume, increased renal sodium reabsorption, reflex sympathetic activation, intestinal ion transport exchange and increased vascular endothelial growth factor production are proposed as the probable mechanisms for edema [7,9].



Fig 1. Obese patient with peripheral edema.

Cheng and Fantus recently published 2 case reports [10]. In the first case, after 4 weeks of pioglitazone and insulin combination in a 57-year-old, obese male patient with no prior history of congestive heart failure (CHF) and with a good exercise capacity, CHF and acute pulmonary edema developed. The second report concerned a 50-year-old male patient with no prior cardiac problems and with no reason for cardiogenic shock. Cardiogenic shock was seen after 6 weeks of rosiglitazone use by the patient. In both cases, the cause of CHF development was found to be TZD use [10].

Peripheral edema is seen more frequently in TZD monotherapy and in combination with other antidiabetics compared to placebo. But CHF is not seen with the same frequency, and this ratio is not different from placebo [2,7].

Nevertheless, other clinical studies suggest that CHF due to TZD is not seen often. In rosiglitazone use, combined with other oral antidiabetics or alone, the ratio of CHF is less than 1%. However, if it is combined with insulin, this ratio increases to 2% to 3%. Therefore, it is suggested that this ratio increases with the age of the patient and the duration of diabetes [2,5,7,9,11,12].

In our case, there was no sign of heart failure or pericardial and pleural effusion in the patient's 1-year-old echocardiography examination. Also, according to her history, her exercise capacity was normal until rosiglitazone use and there was no effort dyspnea, but after 6 weeks of rosiglitazone use, acute pulmonary edema developed. We presume that this situation might be due to rosiglitazone use.

It has been reported that being older than 70 years, having atherosclerotic heart disease, having DM for longer than 10 years, being obese, and having hypertension are risk factors for the development of CHF due to rosiglitazone use [2,5,7,9].

These risk factors were present, but other risk factors such as CHF, left ventricle hypertrophy, aortic and mitral valve disease, insulin use, and chronic renal failure (creatinine >2 mg/dL) [2,5] were not present in our patient. Still, we think that no serious consideration had been given before rosiglitazone use, and acute pulmonary edema developed under these risk factors, which may have triggered the probable mechanisms for edema.

Kermani and Garg, in their recently published article, discussed 6 patients with CHF and acute pulmonary edema, which developed because of the use of TZDs [7]. In their risk evaluation, all of the patients were older than 65 years, 4 patients had chronic renal failure, 1 patient had ischemic cardiomyopathy, and 1 patient had no predisposing factor. All of these patients showed good response to the stopping of the drug and intensive diuretic treatment [7]. Singh also reported recently that in 1 case of CHF due to rosiglitazone use, treatment by stopping use of the drug, followed by a diuretic, was effective in relieving CHF [13]. But Wang et al suggested that peripheral edema and water retention due to glitazone use may be resistant to diuretics but can be sensitive to stopping use of the drug [14]. In our patient, omitting the drug followed by furosemide treatment was effective, and the patient's clinical situation improved swiftly. Our opinion is that in CHF seen after the use of TZDs, stopping use of the drug followed by intensive diuretic therapy is the best approach.

Kermani and Garg proposed that TZDs should not be used in patients with CHF ranging from New York Heart Association (NYHA) class I to class IV [7]. In our patient, no NYHA class III or IV cardiac functional situation was present, and after rosiglitazone use, acute pulmonary edema developed. Our patient was suitable for TZD use according to the American Heart Association and American Diabetes Association's 2003 consensus decision. Despite these criteria, the development of a mortal side effect made us think that Kermani and Garg's proposal is more valid. In addition, we suggest that in risk evaluation, not only is CHF a contraindication, but the other probable risk factors, such as old age, atherosclerotic heart disease, DM longer than 10 years, obesity, and hypertension are risk factors for the development of acute pulmonary edema and should also be considered during rosiglitazone use.

Conclusion

In conclusion, because of their effect on decreasing insulin resistance, TZDs can be used in patients with type 2 diabetes as a monotherapy or in combined therapies. Nevertheless, if the patient selection is not done carefully, mortal side effects can be seen. In most diabetic patients, asymptomatic cardiac dysfunction may be present. For patients with DM who have been admitted to the intensive care unit with symptoms of acute pulmonary edema, for differential diagnosis, use of rosiglitazone should be kept in mind during the determination of treatment, especially in type 2 diabetes patients with old age, hypertension, atherosclerotic heart disease, and obesity.

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