Original Article

Fenofibrate Reversibly Increases Serum Creatinine Level in Chronic Kidney Disease Patients by Reducing Glomerular Filtration Rate

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Abstract

BACKGROUND. Fenofibrate is a potent lipid-lowering agent that was found to increase serum creatinine, but the underlying mechanism remains controversial.

METHODS. Thirteen hypertriglyceridemic patients, composed of 9 males and 4 females with a mean age of 62 (51-76) presenting with an acute rise of serum creatinine 2 weeks to 6 months after starting fenofibrate (200 mg daily) treatment, were recruited. Other possible causes of acute renal failure were excluded based on clinical judgment. The serum creatinine level, BUN, creatinine clearance calculated using a 24-h urine collection, and estimation of glomerular filtration rate using the Cockroft-Gault formula were obtained on fenofibrate treatment. The same tests were repeated 2 weeks after discontinuing the treatment.

RESULTS. The data showed serum creatinine rose from 1.8 (1.3-4.9) mg/dL before the treatment to 3.0 (1.8-5.0) mg/dL ($P < 0.05$) and BUN from 27 (18-40) to 38 (27-58) mg/dL ($P < 0.05$) 2 weeks to 6 months after the treatment. After discontinuing fenofibrate, serum creatinine declined from 3.0 (2.0-4.5) to 2.1 (1.7-4.1) mg/dL ($P < 0.05$), BUN from 34 (52-26) to 24 (19-39) mg/dL ($P < 0.05$), Cockroft-Gault estimated GFR increased from 32 (23-49) to 47 (31-65) mL/min ($P < 0.05$) and creatinine clearance increased from 37 (25-49) to 54 (39-67) mL/min ($P < 0.05$). However, daily urine creatinine excretion did not significantly change, from 18.1 (15.1-24.5) to 19.3 (13.2-22.7) mg/kg/day.

CONCLUSION. Our study shows fenofibrate reversibly increased the serum creatinine level with simultaneous BUN changes, but there was no change in creatinine production. The results suggest a reduction of glomerular filtration rate is responsible for an elevation of serum creatinine. (Acta Nephrologica 2011; 25: 1-4)

KEY WORDS: fenofibrate, serum creatinine, glomerular filtration rate

Introduction

Lipid metabolism abnormality is common in chronic kidney disease (CKD) patients that are at greater risk of developing accelerated atherosclerosis and cardiovascular events (1, 2). Fenofibrate is a lipid-modifying agent that is mainly used to reduce low-density lipoprotein cholesterol and triglyceride levels, and to increase high-density lipoprotein cholesterol levels (3). Fibrate exerts its therapeutic effects through activating the peroxisome proliferator-activated receptor α (PPARα), nuclear receptors. These nuclear receptors, once bound by fibrates, down-regulate the expression of the inducible cyclooxygenase-2 (COX-

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Table 1. Demographic data of thirteen patients with fenofibrate-associated hypercreatininemia

Patient number	13
Age (years)	62 (51–76)
Sex (male/female)	9/4
Height (cm)	165 (157–172)
Weight (kg)	68 (49–88)
Serum creatine phosphokinase (IU/L)	134 (110–203)
Serum creatinine (mg/dL)	
before treatment	1.8 (1.3–4.9)
during treatment	3.0 (1.8–5.0)
Blood urea nitrogen (mg/dL)	
before treatment	27 (18–40)
during treatment	38 (27–58)
Underlying disease	
Normal	3
Chronic interstitial nephritis	4
Nephroslerosis	2
Chronic glomerulonephritis	2
Diabetes nephropathy	1
Right nephrectomy	1

2) enzyme, which may be critical for the maintenance of vasodilatory prostaglandins within the kidneys (4-6). Fenofibrate treatment is generally well tolerated and adverse effects include myalgia, rhabdomyolysis, liver enzymes elevation, and gastrointestinal upset (7). In combination with statins, rhabdomyolysis-associated acute renal failure has been reported in some patients (8). However, there are few reports addressing the influence of renal function in patients without rhabdomyolysis. In our clinical observation, many patients on fenofibrate for treating hypertriglyceridemia developed a reversible elevation of their serum creatinine levels. This study examined the changes of renal function parameters in this clinical setting.

Methods

Thirteen hypertriglyceridemic patients presenting with an acute rise of serum creatinine 2 weeks to 6 months after beginning fenofibrate at a dose of 200 mg daily were recruited. The patients were referred to nephrology outpatient clinics for assessing an acute rise in serum creatinine of unknown cause. Medical records and medication history were carefully studied. None of these patients had a history of myositis, concurrent use of nephrotoxic agents such as aminoglycoside, or other lipid-lowering agents such as statins. All patients had a normal serum creatinine phosphokinase level. Other possible causes of acute renal failure were excluded based on clinical judgment. Their baseline median serum creatinine was 1.8 (1.3-4.9) mg/dL and BUN 27 (18-40) mg/dL. All the patients had received fenofibrate treatment, 200 mg per day, from 2 weeks to 6 months for hypertriglyceridemia before recruitment. Their serum creatinine level, serum creatine phosphokinase level, BUN, creatinine clearance calculated using a 24-h urine collection, and estimation of glomerular filtration rate using the Cockroft-Gault formula were obtained during fenofibrate treatment and two weeks after cessation of treatment. The biochemistry data were measured using an Express Plus Chemistry Analyzer (Chiron Corp, Boston, MA, USA). The Human Research Review Committee of Kaohsiung Veterans General Hospital approved the protocol and informed written consent was obtained from each patient.

Statistics

Data are expressed as medians (range). Non-parametric paired *t*-tests were used for comparisons during use and after discontinuing fenofibrate. A P value < 0.05 was set as the criterion for significance in all comparisons.

Results

Table 1 shows the demographic data of the thirteen hypertriglyceridemia patients. The median age is 62 (51-76) years old, with 9 males and 4 females. Their baseline median serum creatinine of 1.8 (1.3-4.9) mg/dL and BUN 27 (18-40) mg/dL rose to 3.0 (1.8-5.0) mg/dL and 38 (27-58) mg/dL, respectively ($P < 0.05$). All the patients had received fenofibrate treatment,

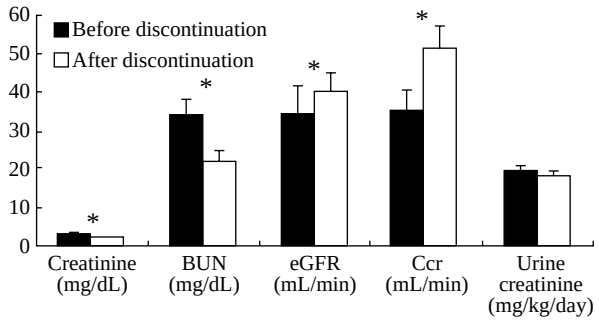

Fig. 1. Parameters before and 2 weeks after discontinuation of fenofibrate treatment. *$P < 0.05$.

200 mg per day, from 2 weeks to 6 months for hypertriglyceridemia on recruitment. The serum levels of creatine phosphokinase remained normal in all patients with a mean value of 134 (110-203) IU/L during fenofibrate treatment. Except for three patients with normal renal function, there were four cases of chronic interstitial nephritis, two of nephrosclerosis, two of diabetes nephropathy, one of chronic glomerulonephritis, and one of right nephrectomy.

Fig. 1 shows the values of serum creatinine, BUN, estimated GFR, 24-h urine creatinine clearance, and daily urine creatinine excretion before and 2 weeks after discontinuing fenofibrate treatment. Except for the daily urine creatinine excretion, those values changed significantly after discontinuing the treatment before *vs*. 2 weeks after discontinuation: serum creatinine, 3.0 (2.0-4.5) *vs*. 2.1 (1.7-4.1) mg/dL; BUN, 34 (52-26) *vs*. 24 (19-39) mg/dL; estimated GFR, 32 (23-49) *vs*. 47 (31-65) mL/min; 24-h urine creatinine clearance, 37 (25-49) *vs*. 54 (39-67) mL/min; daily urine creatinine excretion, 18.1 (15.1-24.5) *vs*. 19.3 (13.2-22.7) mg/kg/day.

Discussion

Hypertriglyceridemia is one of the most important risk factors of cardiovascular morbidity and mortality. Fenofibrate is a potent triglyceride-lowering agent that might cause rhabdomyolysis with or without acute renal failure. In this study, there was no laboratory evidence of rhabdomyolysis in our patients. Patients on fenofibrate treatment without rhabdomyolysis have previously been reported as showing a reversible increase in serum creatinine levels in some previous studies in normal healthy subjects and chronic kidney disease patients (9-11). The mechanism underlying the rise of serum creatinine remains controversial. Possible causes of an increased serum creatinine include over-production of creatinine from damaged muscles (8, 9), laboratory interference of serum creatinine levels, inhibition of tubular secretion of creatinine (10), and a decreased glomerular filtration rate.

There is a previous report suggesting fenofibrate might induce elevation of serum creatinine without influencing the glomerular filtration rate, but with increased daily urine creatinine excretion. It has been proposed increased creatinine production is responsible for the creatinine rise (9). Ansquer *et al*. demonstrated a decline of creatinine clearance, unchanged urine creatinine excretion, and a constant glomerular filtration rate based on inulin clearance calculation, suggesting an inhibition of creatinine secretion (10). In our study, the daily urine creatinine excretion before and after discontinuing fenofibrate did not change significantly, suggesting an increased production of creatinine did not occur in our patients. Further, the simultaneous rise of BUN and serum creatinine level also made both laboratory interference and inhibition of creatinine secretion less likely causes. Our data suggest a glomerular filtration rate reduction is the major cause of the elevation of serum creatinine in patients for fenofibrate treatment.

A possible mechanism is fibrate lowers the glomerular filtration rate to bind the peroxisome proliferator-activated receptors and downregulate the expression of the inducible COX-2 enzyme. The enzyme is critical for maintaining vasodilatory prostaglandin action in kidneys (4, 5). Activation of peroxisome proliferator-activated receptors (PPARs) might also attenuate angiotensin II-mediated vascular remodeling (12).

Some previous reports have demonstrated fenofibrate has a long-term beneficial effect in slowing renal progression through a presumed lipid modifying mechanism. Among them, two previous animal studies demonstrated a beneficial effect of fenofibrate on reducing albuminuria and renal injury in diabetes rats without significant changes in plasma creatinine, but with an increased BUN (13, 14). Further, in a study to assess the effect of fenofibrate on cardiovascular disease events in 9795 diabetes patients, the results showed plasma creatinine remained at an average of 0.11-0.14 mg/dL higher in the fenofibrate group compared to the placebo group (15). Some patients in the investigation were restudied 8 weeks after ceasing medications at the end of the trial. The plasma creatinine declined from a median of 1.04 to 0.87 mg/dL in the fenofibrate group. In the latter study, it also showed more patients in the fenofibrate group had less progression of albuminuria. Therefore, the short-term reversible effect on plasma creatinine and BUN observed in those studies is similar to the four findings.

There are some major limitations to our study. First, the small sample size and retrospective design may not have enough power to detect the underlying mechanisms of the elevation of serum creatinine. Second, the duration of treatment varied among the

patients, so other causes of kidney injury might have confounded the investigation results. Third, the reliability of glomerular filtration rate assessment used in our study is not as accurate as inulin clearance.

In conclusion, fenofibrate is a potent lipid-lowering agent, widely used in patients with renal impairment. Physicians taking care of CKD patients should consider its effects on the serum creatinine level. Our study suggests fenofibrate reversibly increased serum creatinine levels in CKD patients by reducing the glomerular filtration rate. However, different mechanisms were reported. Further clarification of the underlying mechanisms requires studies with a large sample size and measurements of creatinine dynamics and accurate renal function tests such as inulin clearance.

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