Effect of Fenofibrate on Uric Acid Metabolism in Japanese Hyperlipidemic Patients

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Forty Type IIb or IV hyperlipidemic patients (serum triglyceride concentrations were higher than 150 mg/dl) were treated with fenofibrate (300 mg/day) for 12 weeks. Lipid profile and uric acid metabolism were evaluated before and after the treatment; the serum concentrations of total cholesterol and triglyceride respectively decreased from 224 ± 41.9 mg/dl to 199 ± 35.2 mg/dl and from 205 ± 71.7 mg/dl to 134 ± 67.5 mg/dl ($p < 0.001$). The uric acid concentrations in the serum also significantly decreased from 7.0 ± 1.58 mg/dl to 5.2 ± 1.57 mg/dl ($p < 0.001$). Fenofibrate treatment did not cause any change in the serum xanthine and hypoxanthine concentrations. Instead the urinary concentrations of uric acid decreased from 7.0 ± 1.58 mg/dl to 5.2 ± 1.57 mg/dl ($p < 0.01$), while the clearance ratio of uric acid and creatinin increased from 6.1 ± 2.56 to 9.9 ± 3.87 ($p = 0.02$) by the fenofibrate treatment. Fenofibrate decreases uric acid concentrations in the serum not as a result of inhibition of uric acid production but by increasing the urinary excretion of uric acid. *J Atheroscler Thromb*, 2004; 11: 335–340.

Key words: Fenofibrate, Uricosuric action, Metabolic syndrome

Introduction

Hyperuricemia is a common condition in Japan (1). Patients with hyperuricemia have been increasing for several decades in Japan and it is thought that the increase is closely related to the change of life style in Japan (2, 3). Recently hyperuricemia has been considered as one component of multiple-risk factor syndromes, especially the visceral fat and the serum triglyceride concentrations are closely correlated to the serum uric acid concentrations (4–7). Analogous conditions to multiple-risk factor syndromes such as Syndrome X, visceral fat syndrome, and the deadly quartet are now termed “metabolic syndrome” (8). It is not clear whether hyperuricemia is one of the independent risk factors and the reduction of serum uric acid concentrations improves the prognosis of

patients with metabolic syndromes. The serum uric acid level is, however, at a good indicator of severity and prognosis of such patients with metabolic syndromes (9–13). Patients with hyperuricemia caused by metabolic syndrome have a large number of metabolic abnormalities and need several kinds of medicines if they attempt to treat each problem independently. Recently it has been reported that fenofibrate, one of the fibrates, has the effects that are observed in the fibrate class agents and the anti-hyperuricemic effect (14–16). Some authors report that the anti-hyperuricemic effect of fenofibrate comes from its uricosuric action (17). There are several reports on the anti-hyperuricemic effect of fenofibrate as mentioned above, and the reports are focused on the hyperuricemic patients or healthy volunteers. This time, we have evaluated the anti-hyperuricemic effect of fenofibrate on patients with hyperlipidemia in the outpatient situations. Also we have considered the mechanism of the hyperuricemic effect of fenofibrate through the evaluation in the change of metabolism and excretion of uric acid by the treatment.

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Subjects and Methods

Subjects and study design

Forty cases of Type IIb or IV hyperlipidemic patients whose serum triglyceride concentrations were higher than 150 mg/dl were enrolled for this study from outpatients of the Second Department of Chiba University Hospital (all cases). The patients were fasted for 12 h before collecting the samples of blood and urine. Eighteen cases of hyperuricemic patients having uric acid concentrations higher than 7.0 mg/dl out of the forty cases were evaluated separately (hyperuricemic group). Patient profiles are shown in Table 1.

Fenofibrate was given orally, a once daily dose of 300 mg in the morning for 12 weeks after the collection of the initial blood and urine samples before noon. At the 12th week of the repeated administration, the blood and urine samples were collected in the same way. Any drugs that had been given before the evaluation were to be continuously administered until this study finished. The same type and levels of diet and exercise continued until the end of the study. No case dropped out because of any side effects.

Items to be measured in this study were as follows: serum concentrations of total-cholesterol (T-Cho), triglyceride (TG), HDL-cholesterol (HDL-C), uric acid (UA), xanthine, and hypoxanthine, urinary concentrations of creatinin and UA. The uric acid clearance/creatinin clear-

ance ratio ($CUA/Ccr = R$) was calculated from serum and urine UA and creatinin levels.

Statistics

The lipid profiles and uric acid metabolic markers were compared before and after the Fenofibrate treatment by student-*t* test using Statcel software (OMS, Tokorozawa, Japan). *p* values less than 0.05 were regarded as significant.

Results

Effects of fenofibrate on lipid profile

As previously described the 12-week fenofibrate treatment decreased the T-Cho and TG level with statistical significance. Changes of the lipid profiles after the fenofibrate treatment are shown in Table 2. There is no difference of lipid profile response to fenofibrate between male gender and female gender (data not shown). The body weight and other physical conditions were not changed by the treatment (data not shown). In the case of hyperuricemia, the same result was observed (Table 2).

Effects of fenofibrate on serum UA level

The uric acid level decreased from 7.0 ± 1.58 mg/dl to 5.2 ± 1.57 mg/dl ($p < 0.0001$) in all the cases. In the hyperuricemic group the uric acid level decreased from

Table 1. Clinical characteristics of patients.

				(min, max)		
All cases (<i>n</i> = 40)				Male gender (<i>n</i> = 24)		
Age	year	56.9 ± 12.40		Age	year	56.2 ± 13.2
Gender	M/F	24/16		T-cho	mg/dl	220 ± 45.9 (134–304)
T-cho	mg/dl	224 ± 41.9	(134–304)	TG	mg/dl	219 ± 114.2 (152–494)
TG	mg/dl	205 ± 71.7	(152–494)	HDL-c	mg/dl	53.8 ± 19.56 (21–81)
HDL-c	mg/dl	55 ± 16.1	(21–81)	Uric acid	mg/dl	7.1 ± 1.62 (3.2–10.4)
Uric acid	mg/dl	7.0 ± 1.58	(3.2–10.4)	CUA/Ccr (<i>R</i>)	mg/dl	6.3 ± 2.92 (2.1–9.1)
CUA/Ccr (<i>R</i>)	mg/dl	6.2 ± 2.58	(2.1–9.1)			
Hyperuricemic group (UA > 7.0 mg/dl, <i>n</i> = 18)				Female gender (<i>n</i> = 16)		
Age	year	53.9 ± 11.32		Age	year	57.9 ± 10.6
Gender	M/F	14/4		T-cho	mg/dl	231 ± 35.7 (162–290)
T-cho	mg/dl	216 ± 39.4	(134–304)	TG	mg/dl	183 ± 51.2 (158–243)
TG	mg/dl	224 ± 92.7	(152–494)	HDL-c	mg/dl	56.7 ± 13.8 (39–76)
HDL-c	mg/dl	52 ± 18.4	(21–78)	Uric acid	mg/dl	6.9 ± 1.61 (4.1–9.4)
Uric acid	mg/dl	8.0 ± 0.96	(7.2–10.4)	CUA/Ccr (<i>R</i>)	mg/dl	6.1 ± 1.87 (4.5–9.1)
CUA/Ccr (<i>R</i>)	mg/dl	5.4 ± 1.97	(2.1–9.1)			

8.0 ± 0.96 mg/dl to 5.9 ± 1.48 mg/dl ($p < 0.001$). For the purpose of clarifying that the effect of fenofibrate on uric acid level is attributed to the decrease of uric acid synthesis or increase in uric acid excretion, the xanthine and hypoxanthine levels and uric acid clearance/creatinin clearance ratio (CUA/Ccr = R) were measured before and after the treatment. R was increased both in the all cases and the hyperuricemic group with statistical significance after treatment. The fenofibrate treatment did not cause statistically significant change in xanthine and hypoxanthine levels. There is no difference of fenofibrate effect

on uric acid metabolism between male gender and female gender (Table.3).

Discussion

Fibrates belong to the antihyperlipidemic agents that reduce a plasma lipid concentration, especially TG (18, 19). The agents act as a PPAR alpha agonist to reduce a lipid concentration, change a lipid profile to anti-atherogenic state, increase an HDL-c concentration, and improve insulin sensitivity (20–23). Fibrates have been

Table 2. Effects of fenofibrate on lipid profile.

All cases		Before	After	% of change	<i>p</i> value
T-cho	mg/dl	224 ± 41.9	199 ± 35.2	– 11%	$p < 0.001$
TG	mg/dl	205 ± 71.7	134 ± 67.5	– 34%	$p < 0.001$
HDL-c	mg/dl	55 ± 16.1	63 ± 19.2	+ 14%	$p < 0.001$
LDL-c	mg/dl	113.9 ± 46.4	100.7 ± 43.2	– 12%	NS
Hyperuricemic group		Before	After	% of change	<i>p</i> value
T-cho	mg/dl	215 ± 44.1	197 ± 42.1	– 8%	$p < 0.001$
TG	mg/dl	223 ± 102.8	165 ± 105.6	– 23%	$p < 0.001$
HDL-c	mg/dl	52 ± 18.4	61 ± 19.2	+ 17%	$p = 0.004$
LDL-c	mg/dl	96 ± 22.4	93 ± 31.2	– 3%	NS

Table 3. Effects of fenofibrate on uric acid metabolism.

All cases		Before	After	% of change	<i>p</i> value
Uric acid	mg/dl	7.0 ± 1.58	5.2 ± 1.57	– 25%	$p < 0.01$
CUA/Ccr (R)	mg/dl	6.1 ± 2.56	9.9 ± 3.78	+ 62%	$p = 0.02$
Xanthine	μg/dl	0.20 ± 0.057	0.16 ± 0.022	– 0.8%	NS
Hypoxanthine	μg/dl	0.52 ± 0.236	0.47 ± 0.317	– 9%	NS
Hyperuricemic group		Before	After	% of change	<i>p</i> value
Uric acid	mg/dl	8.0 ± 0.96	5.9 ± 1.48	– 26%	$p < 0.01$
CUA/Ccr (R)	mg/dl	5.4 ± 1.99	9.5 ± 2.01	+ 75%	$p < 0.01$
Xanthine	μg/dl	0.3 ± 0.291	0.28 ± 0.101	– 6%	NS
Hypoxanthine	μg/dl	0.47 ± 0.223	0.56 ± 0.452	+ 19%	NS
Male gender		Before	After	% of change	<i>p</i> value
Uric acid	mg/dl	7.0 ± 1.61	5.4 ± 1.59	– 23%	$p < 0.01$
CUA/Ccr (R)	mg/dl	5.8 ± 2.90	8.9 ± 4.51	+ 53%	$p = 0.02$
Xanthine	μg/dl	0.26 ± 0.277	0.15 ± 0.079	– 42%	NS
Hypoxanthine	μg/dl	0.54 ± 0.241	0.46 ± 0.318	– 14%	NS
Female gender		Before	After	% of change	<i>p</i> value
Uric acid	mg/dl	6.9 ± 1.61	4.9 ± 1.83	– 28%	$p < 0.01$
CUA/Ccr (R)	mg/dl	6.8 ± 1.88	11.8 ± 0.67	+ 73%	$p = 0.02$
Xanthine	μg/dl	0.25 ± 0.125	0.29 ± 0.78	+ 16%	NS
Hypoxanthine	μg/dl	0.49 ± 0.250	0.47 ± 0.353	– 0.9%	NS

thought to be good candidates to treat metabolic syndromes; because basic pathophysiologic conditions of the syndromes are hyperinsulinemia and insulin resistance (24–26). Although fenofibrate belongs to fibrates with similar types of efficacies as mentioned above, it is noticeable that this drug additionally has a unique antihyperuricemic effect that other fibrates do not have (14–16). The antihyperuricemic effect of fenofibrate is reversible and is observed in healthy volunteers and hyperuricemic patients (27, 28). It has been already reported that fenofibrate increases the renal uric acid clearance and improve hyperuricemia (29).

In this study, we evaluated the antihyperlipidemic and antihyperuricemic effects of fenofibrate on hyperlipidemic patients. Subjects of this evaluation were selected by the usual indication of fenofibrate and not by special viewpoints of uric acid metabolism. The T-Cho and TG concentrations decreased, while HDL-C concentrations increased with statistical significance. Fenofibrate decreased the serum uric acid concentrations for both hyperuricemic and normouricemic patients at the usual clinical dose. There are three types of hyperuricemia from the viewpoints of pathogenesis; with the first type, the uric acid production increases, in the second type the urinary excretion of uric acid decreases and in the third type these two pathogeneses combine. In this study we could not evaluate the types of pathogenesis of hyperuricemia precisely, because we only obtained spot urine for analysis. The clearance ratio of uric acid to creatinin (*R*) can be, however, used as indicator of the type of hyperuricemia. Mean *R* is 8.68 in the first type 5.66 in the second type, and 6.42 in the third mixed type (29). The mean *R* in this study was 6.1 in all the cases and 5.4 in the hyperuricemic group. Hence, the patients with hyperuricemia in this study were most likely to be categorized to the second type in which the urinary excretion of uric acid decreases. In Japan the incidence of this type of hyperuricemia is higher than the first type in which uric acid production increase (1). After the fenofibrate treatment mean *R* increased to 9.9 in all the cases and 9.5 in the hyperuricemic group; this result thus indicating fenofibrate increased uric acid excretion to a much higher level than the normal one (*R* = 7.4) (29). It is consequently necessary to be careful for the uric acid level in urine to be allowed to prevent renal stone formation or renal dysfunction when fenofibrate is used to any patients.

Recently hyperuricemia has been thought to be one of the metabolic abnormalities that lead to metabolic syndrome (30, 31). Especially in women, there is positive correlation between serum uric acid level and leptin concentration (7). Some authors report that serum uric acid level is well correlated to prognosis of patients with type 2 diabetes and coronary heart disease (32–34). On the other hand, other authors report no correlation between serum uric acid concentration with mortality from car-

diovascular disease, and another author reports that uric acid in the systemic blood flow works as an antioxidant to prevent atherosclerosis (35, 36). It is not clear whether decreasing the uric acid concentration improves the prognosis of patients with metabolic syndrome; as a result, whether we have to prescribe one more medicine to reduce the serum uric acid concentration in the patients with metabolic syndrome remains a difficult question. It can be, however, thought of as a favorable-side profile that the treatment of hyperlipidemia causes a mild decrease of a uric acid level. Fibrates decrease a serum T-Cho concentration and improve a serum lipid profile, *e.g.* the increase in HDL-C concentration. Fenofibrate can improve a lipid profile and uric acid abnormalities, and hence, it improves many metabolic abnormalities at once by one medicine. It is also reported that fenofibrate suppresses experimental autoimmune myocarditis in rats (37). Use of fenofibrate can be a good choice for the treatment of metabolic syndrome with hypercholesterolemia, hypertriglyceridemia and hyperuricemia.

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