# Effect of Fenofibrate on Plasma Concentration and Urinary Excretion of Purine Bases and Oxypurinol

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***ABSTRACT.*** ***Objective.*** To investigate whether fenofibrate increases the clearance of purine bases (hypoxanthine, xanthine, uric acid) and oxypurinol.

***Methods.*** We administered fenofibrate (150 mg) 3 times a day for 3 days, and then allopurinol (300 mg) 4 h after the last administration of fenofibrate, to 5 healthy subjects. Ten hours later, a clearance study was done.

***Results.*** Following 3 day administration of fenofibrate, fractional clearance of xanthine, uric acid, and oxypurinol increased by 41% ($p < 0.05$), 101% ($p < 0.01$), and 51% ($p < 0.01$), respectively, compared to baseline values, while the respective plasma concentrations decreased by 46% ($p < 0.05$), 46% ($p < 0.05$), and 19% ($p < 0.05$).

***Conclusion.*** Our results suggest that fenofibrate, fenofibric acid, or fenofibrate derivatives can increase fractional clearance of xanthine, uric acid, and oxypurinol by acting on their common renal pathways. It is suggested that the hypouricemic effect of combination therapy using allopurinol and fenofibrate may be less than additive. (J Rheumatol 2001;28:2294–7)

*Key Indexing Terms:*
FENOFIBRATE OXYPURINOL URIC ACID XANTHINE ALLOPURINOL

Fenofibrate is an antihyperlipidemic agent that reduces plasma lipid levels, especially triglyceride[1-3]. Fibrates are agents recognized to be clinically important, as studies[4-6] have shown that triglyceride level is an independent risk factor of coronary vascular diseases. Recently, it was found that these agents also activate peroxisome proliferator-activated receptors (PPAR), leading to a decrease in serum concentrations of triglyceride, cholesterol, and apoC-III, as well as an increase in lipoprotein lipase (LPL) activity[7]. Among fibrates, fenofibrate is one of the strongest antihypertriglyceridemic agents, which has also been shown to have a strong uricosuric action, leading to a decrease in the serum concentration of uric acid[2,8]. Since this uricosuric action is clinically significant, fenofibrate is useful for the treatment of hyperuricemia as well as hyperlipidemia. It has been reported[9-11] that glucagon, glucose, and losartan increase the renal clearance of xanthine, oxypurinol, and uric acid, suggesting that uric acid shares a renal transport pathway with oxypurinol. Oxypurinol is a metabolite of allopurinol, which has been used for the treatment of hyperuricemia. Although both allopurinol and oxypurinol are potent inhibitors of xanthine oxidase, the biological half-life of the latter is longer than that of the former. Therefore, the overall effect of allopurinol may depend on the action of oxypurinol[12-14]. As fenofibrate increases the urinary excretion of uric acid, it may also increase that of oxypurinol, and if so the concentration of oxypurinol in plasma may decrease. The hypouricemic effect of allopurinol mostly depends on the plasma concentration of oxypurinol, thus it is important to determine whether fenofibrate increases the urinary excretion of oxypurinol. We investigated the effect of fenofibrate on the urinary excretion of oxypurinol together with purine bases (uric acid, hypoxanthine, and xanthine).

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## MATERIALS AND METHODS

Fenofibrate and allopurinol were purchased from Kaken Pharmaceuticals Co. (Tokyo, Japan) and GlaxoWellcome Japan (Tokyo, Japan). Other chemicals were obtained from Wako Pure Chemical Industries (Osaka, Japan).

*Subjects and protocol.* Five healthy men aged 36 to 42 years (body weight 61 to 73 kg) participated in the study after giving informed consent. Each had normal laboratory data including ALT, AST, and creatine phosphokinase. Baseline measurements of the plasma concentrations and urinary excretion of hypoxanthine, xanthine, and uric acid were performed in each using the following protocol. Allopurinol (300 mg) was given orally at 10:00 PM. The next day, 10 h after the allopurinol administration (at 8:00 AM), urine was completely voided and 1 hour urine samples were collected twice serially (first and second period). Blood samples were also drawn with heparinized syringes at the midpoint of the respective 1 hour urine collection periods (first and second period). Two weeks later, fenofibrate (150 mg) was administered orally 3 times a day (8:00 AM, 12:00 PM, and 6:00 PM) for 3 days (total amount 1350 mg), and then allopurinol (300 mg) was given orally 4 h after the last administration of fenofibrate. The next day, urine and blood sample collections were performed as described in the baseline measurement study. In the fenofibrate loading study, 450 mg/day fenofibrate (more than a usual dose) was administered to observe the short term effects on urinary excretion of purine bases and oxypurinol. Both sample collections were performed during a fast, except for water, after the allopurinol administration. The subjects had regular diets and did not drink alcohol or take medication, except the test drugs, during the baseline measurement and fenofibrate loading studies. ALT, AST, and CPK values in plasma, determined from samples taken during the

second period of the fenofibrate loading study, were within normal ranges, as were their reference values.

*Blood and urine analyses*. The concentrations of hypoxanthine, xanthine, and oxypurinol in plasma and urine were determined using high performance liquid chromatography (HPLC) as described[9]. In brief, the chromatographic system consisted of an LC-6A high performance liquid chromatograph (Shimadzu, Kyoto, Japan), an SPD-6AV UV-VIS (Shimadzu), and a C-R3A chromatopac recorder (Shimadzu). The column was a Wakosil 5C-18-200 (4.6 × 250 mm) (Wako), with a flow rate of 1 ml/min, a mobile phase of 0.02 M $KH_2PO_4$ (pH 2.2), and a wavelength of 254 nm. To measure the plasma concentrations of hypoxanthine, xanthine, and oxypurinol, plasma was immediately separated after drawing blood with a heparinized syringe. The concentrations of uric acid and creatinine in plasma and urine were measured by the uricase method using a Uric Acid B test kit (Wako), and by the enzymatic method using a Diacolor Liquid CRE kit (Toyobo, Osaka, Japan), respectively. Other measurements were performed in our hospital laboratory.

The percentage ratios of uric acid clearance/creatinine clearance (fractional uric acid clearance), hypoxanthine clearance/creatinine clearance (fractional hypoxanthine clearance), xanthine clearance/creatinine clearance (fractional xanthine clearance), and oxypurinol clearance/creatinine clearance (fractional oxypurinol clearance) were calculated.

*Statistical analysis*. Data are presented as the mean ± SD. The significance of difference between variables was analyzed by 2 tailed Student t test.

## RESULTS

*Effect of fenofibrate on plasma concentrations of purine bases and oxypurinol*. After the 3 day administration of fenofibrate, plasma concentrations of xanthine, uric acid, and oxypurinol decreased by 46% ($p < 0.05$), 46% ($p < 0.05$), and 19% ($p < 0.05$), respectively, in the first period, and by 38% ($p < 0.05$), 36% ($p < 0.05$), and 20% ($p < 0.05$), respectively, in the second period, compared with each respective reference value (Table 1). However, the plasma concentration of hypoxanthine did not change in either period (Table 1).

*Table 1*. Effect of fenofibrate on plasma concentrations of purine bases and oxypurinol (n = 5). Values are expressed as mean ± SD.

| | Baseline | | With Fenofibrate | |
|---|---|---|---|---|
| | 1st Period | 2nd Period | 1st Period | 2nd Period |
| Hypoxanthine, μM | 1.34 ± 0.82 | 1.26 ± 0.72 | 1.20± 0.74 | 1.04 ± 0.50 |
| Xanthine, μM | 3.36 ± 0.84 | 3.20 ± 0.68 | 2.16 ± 0.64* | 2.00 ± 0.62* |
| Uric acid, μM | 318 ± 65 | 315 ± 65 | 202 ± 60* | 202 ± 60* |
| Oxypurinol, μM | 23.96 ± 1.12 | 23.8 ± 1.22 | 19.38 ± 3.27* | 19.14 ± 3.84* |

First period and second period denote the first 1 hour urine collection period and the second 1 hour urine collection period. * $p < 0.05$ compared with the respective period.

*Effect of fenofibrate on urinary excretion of purine bases and oxypurinol*. After the 3 day administration of fenofibrate, urinary excretion of uric acid was increased by 21% and 22% in the first and second periods, respectively. However, the urinary excretion of oxypurines (hypoxanthine and xanthine) and oxypurinol were not significantly different from their respective values in either period (Table 2).

*Effect of fenofibrate on fractional clearance of purine bases and oxypurinol, and clearance of creatinine*. After the 3 day administration of fenofibrate, fractional clearance of xanthine, uric acid, and oxypurinol increased by 41% ($p < 0.05$), 101% ($p < 0.01$), and 51% ($p < 0.01$), respectively, in the first period, and by 45% ($p < 0.01$), 101% ($p < 0.01$), and 49%, respectively, in the second period, compared with each reference value (Table 3). However, neither the fractional clearance of hypoxanthine nor the clearance of creatinine changed in either period (Table 3).

*Effect of fenofibrate on plasma concentrations of triglyceride and cholesterol*. The plasma concentration of triglyceride decreased from 1.38 ± 0.22 mM in the first period of the baseline study to 0.99 ± 0.24 mM after the same period of the fenofibrate loading study ($p < 0.05$), while the plasma concentration of cholesterol did not decrease significantly (4.60 ± 0.51 mM in the baseline first period vs 4.24 ± 0.56 mM in the fenofibrate loading study first period).

## DISCUSSION

Studies[15,16] have shown that as plasma concentrations of purine bases (hypoxanthine, xanthine, uric acid) and oxypurinol increase, the renal clearance of purine bases and oxypurinol also increases. We observed that the fractional clearance of xanthine, uric acid, and oxypurinol increased following a 3 day administration of fenofibrate, while their plasma concentrations decreased. These results indicate that fenofibrate was the agent that caused the fractional clearance of xanthine, uric acid, and oxypurinol to increase in spite of their decrease in plasma. Since the overall effect of allopurinol mostly depends on oxypurinol, a decrease in the plasma concentration of oxypurinol by fenofibrate may affect plasma concentrations of uric acid, xanthine, and hypoxanthine.

In xanthine metabolism, fenofibrate increased the fractional clearance of xanthine but did not increase its urinary excre-

*Table 2*. Effect of fenofibrate on urinary excretion of purine bases and oxypurinol (n = 5). Values are expressed as mean ± SD.

| | Baseline | | With Fenofibrate | |
|---|---|---|---|---|
| | 1st Period | 2nd Period | 1st Period | 2nd Period |
| Hypoxanthine, μmol/h | 5.88 ± 2.68 | 5.70 ± 2.52 | 6.51 ± 3.50 | 6.07 ± 3.04 |
| Xanthine, μmol/h | 16.96 ± 2.93 | 16.20 ± 2.03 | 15.20 ± 5.71 | 14.47 ± 4.11 |
| Uric acid, μmol/h | 183 ± 17 | 183 ± 24 | 222 ± 26* | 223 ± 30* |
| Oxypurinol, μmol/h | 32.01 ± 8.34 | 30.68 ± 7.45 | 37.70 ± 11.54 | 36.89 ± 9.28 |

First period and second period denote the first 1 hour urine collection period and the second 1 hour urine collection period. * $p < 0.05$ compared with the respective period.

*Table 3*. Effect of fenofibrate on fractional clearance of purine bases and oxypurinol, and clearance of creatinine (n = 5). Values are expressed as mean ± SD.

| | Baseline | | With Fenofibrate | |
|---|---|---|---|---|
| | 1st Period | 2nd Period | 1st Period | 2nd Period |
| Fhx | 66.4 ± 20.6 | 67.6 ± 14.5 | 77.1 ± 13.9 | 81.2 ± 16.2 |
| Fx | 69.2 ± 13.6 | 69.9 ± 10.0 | 97.8 ± 23.5* | 101.5 ± 18.1** |
| Fua | 7.9 ± 1.4 | 8.0 ± 1.4 | 15.9 ± 3.3** | 16.1 ± 3.5** |
| Fox | 17.8 ± 4.0 | 17.4 ± 3.6 | 26.8 ± 4.0** | 25.9 ± 1.5** |
| Ccr | 104 ± 4.7 | 102.6 ± 3.2 | 99.5 ± 3.7 | 99.6 ± 3.4 |

Fua: percentage ratio of uric acid clearance/creatinine clearance (fractional uric acid clearance), Fhx: percentage ratio of hypoxanthine clearance/creatinine clearance (fractional hypoxanthine clearance), FX: percentage ratio of xanthine clearance/creatinine clearance (fractional xanthine clearance), Fox: percentage ratio of oxypurinol clearance/creatinine clearance (fractional oxypurinol clearance), Ccr: clearance of creatinine (ml/min). * $p < 0.05$, ** $p < 0.01$ compared with the respective period. First period and second period denote the first 1 hour urine collection period and the second 1 hour urine collection period.

tion despite the decrease in plasma concentration of xanthine. These findings suggest that a fenofibrate induced decrease in the plasma concentration of oxypurinol may play a role in a decrease in plasma concentration of xanthine in addition to a fenofibrate induced increase in its fractional clearance. On the other hand, in hypoxanthine metabolism the plasma concentration, urinary excretion, and fractional clearance of hypoxanthine did not change significantly after administration of fenofibrate, suggesting that a decrease in the plasma concentration of oxypurinol does not significantly affect the plasma concentration of hypoxanthine. Both hypoxanthine and xanthine are substrates for xanthine dehydrogenase; however, xanthine dehydrogenase has a higher Km value for xanthine than for hypoxanthine. Therefore, the plasma concentration of hypoxanthine may not be affected as much as that of xanthine by a decrease in the plasma concentration of oxypurinol.

In uric acid metabolism, the decrease we observed in plasma concentration of uric acid seems to have been due mainly to a fenofibrate induced increase in the fractional clearance of uric acid, although the effect of allopurinol on uric acid must also be considered, because allopurinol (300 mg) has been found to decrease the plasma concentration of uric acid by about 30 to 60 $\mu$mol/l at 10 h after administration (unpublished data). As a result, the 1 h urinary excretion of uric acid was significantly increased by fenofibrate.

Finally, in oxypurinol metabolism, we observed that fenofibrate enhanced the urinary excretion of oxypurinol, suggesting that the hypouricemic effect of combination therapy using allopurinol and fenofibrate may be less than additive, although our study was for a short term with a higher than usual dose.

Recent studies[9-11,17] have revealed that glucagon, glucose, and losartan sodium increase the clearance of uric acid, xanthine, and oxypurinol, while furosemide causes them to decrease, suggesting that uric acid, xanthine, and oxypurinol share a renal transport pathway. We found that fenofibrate increased the fractional clearance of uric acid, xanthine, and oxypurinol, further suggesting that these 3 share a renal transport pathway, although the mechanism remains undetermined. A recent study[18] using brush border membrane vesicles showed that losartan, probenecid, and benzbromarone act on a urate/anion transport pathway, thus fenofibrate, fenofibric acid (the active metabolite), or other metabolites may also act on the urate/anion transport pathway and increase the urinary excretion of uric acid. Regardless of the means by which fenofibrate induces uricosuria, attention must be paid to the formation of calculi containing uric acid in the urinary tract, as the uricosuric action of fenofibrate may increase their frequency.

In this study, 3 day administration of fenofibrate decreased the plasma concentration of triglyceride together with uric acid, suggesting that this agent is useful for the treatment of patients with gout with hypertriglyceridemia. Indeed, it is occasionally used in patients with gout, as they frequently experience hypertriglyceridemia[19]. Fibrates, including fenofibrate, are widely used to decrease plasma triglyceride and cholesterol concentrations, and to increase plasma HDL-cholesterol concentration, and the mechanism by which fibrates lower serum triglyceride have been recently described[7]. The effects of fibrates on lipids are mediated, in part, through alterations in the transcription factors of genes encoded for proteins that control lipoprotein metabolism. Fibrates activate peroxisome proliferator-activated receptor $\alpha$ (PPAR$\alpha$), resulting in increased expression of apoA-I and apoA-II. Further, they increase the expression of LPL, decrease that of apoC-III, and increase the expression of genes for fatty acid transport protein and acyl-CoA synthetase via PPAR. In addition, fibrates increase peroxisomal and mitochondrial beta-oxidation, decrease the synthesis of fatty acids and triglyceride, and decrease the production of very low density lipoprotein (VLDL). These effects lead to a decrease in the plasma concentration of triglyceride via enhanced catabolism of triglyceride-rich particles and reduced secretion of VLDL, and an increase in the plasma concentration of HDL-cholesterol.

Recently, it was reported that hypertriglyceridemia is an independent risk factor for cardiovascular diseases, while treatment for it decreases their frequency of onset[4-6]. Several other studies[20-22] have suggested that uric acid is an independent risk factor for coronary vascular diseases, especially in patients with hypertension. Therefore, antihypertriglyceridemic agents with strong uricosuric action may provide greater protection against cardiovascular diseases in patients with both hypertriglyceridemia and hyperuricemia compared with other antihypertriglyceridemic agents, although an intervention study must be undertaken before concluding that the treatment for hyperuricemia reduces the rate of coronary vascular disease in hyperuricemic patients with hypertension.

From our results, it remains undetermined whether fenofibrate acts directly on the renal transport of uric acid, xanthine, or oxypurinol. However, this agent seems to be effective for the treatment of hyperuricemia, since the longterm hypouricemic effect of fenofibrate, described in several studies[23,24], is comparable to that of probenecid. A study[25] using benzbromarone, available in Europe and Japan but not in Canada or the USA, revealed that the hypouricemic effect of combination therapy of benzbromarone and allopurinol is less than additive, since benzbromarone increases the urinary excretion of oxypurinol. The same result may also be obtained with a combination of fenofibrate and allopurinol as in our study, although a longterm and usual-dose study is needed to confirm whether the effect of combination therapy of fenofibrate and allopurinol on plasma concentration of uric acid is less than additive. Since fenofibrate is occasionally used together with allopurinol in patients with gout with hypertriglyceridemia, this type of longterm study is important.

## REFERENCES


1. Brown WV. Potential use of fenofibrate and other fibric acid derivatives in the clinic. Am J Med 1987;83:85-9.
2. Bastow MD, Durrington PN, Ishola M. Hypertriglyceridemia and hyperuricemia: effects of two fibric acid derivatives (bezafibrate and fenofibrate) in double-blind, placebo-control trials. Metabolism 1988;37:217-20.
3. Genest J Jr, Nguyen NH, Theroux P, Davignon J, Cohn JS. Effect of micronized fenofibrate on plasma lipoprotein levels and hemostatic parameters of hypertriglyceridemic patients with low levels of high-density lipoprotein cholesterol in the fed and fasted state. J Cardiovasc Pharmacol 2000;35:164-72.
4. Patsch JR, Miesenbock G, Hopferweiser T, et al. Relation of triglyceride metabolism and coronary artery disease. Studies in the postprandial state. Arterioscler Thromb 1992;12:1336-45.
5. Manninen V, Elo MO, Frick MH, et al. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. JAMA 1988;260:641-51.
6. Austin MA. Plasma triglyceride and coronary heart diseases. Arterioscler Thromb 1991;11:2-14.
7. Schoonjans K, Staels B, Auwerx J. Role of the peroxisome proliferator-activated receptor (PPAR) in mediating the effects of fibrates and fatty acids on gene expression. J Lipid Res 1996;37:907-25.
8. Desager JP, Hulhoven R, Harvengt C. Uricosuric effect of fenofibrate in healthy volunteers. J Clin Pharmacol 1980;20:560-4.
9. Yamamoto T, Moriwaki Y, Takahashi S, Tsutsumi Z, Hada T. Effect of losartan potassium, an angiotensin II receptor antagonist, on renal excretion of oxypurinol and purine bases. J Rheumatol 2000;27:2232-6.
10. Moriwaki Y, Yamamoto T, Takahashi S, Suda M, Higashino K. Effect of glucose infusion on the renal transport of purine bases and oxypurinol. Nephron 1995;69:424-7.
11. Yamamoto T, Moriwaki Y, Takahashi S, et al. Effect of glucagon on renal excretion of oxypurinol and purine bases. J Rheumatol 1997;24:708-13.
12. Appelbaum SJ, Mayersohn M, Dorr RT, Perrier D. Allopurinol kinetics and bioavailability: intravenous, oral and rectal administration. Cancer Chemother Pharmacol 1982;8:93-8.
13. Hande K, Reed E, Chabner B. Allopurinol kinetics. Clin Pharmacol Ther 1978;23:598-605.
14. Elion GB, Kovensky A, Hitchings GH. Metabolic studies of allopurinol, an inhibitor of xanthine oxidase. Biochem Pharmacol 1966;15:863-80.
15. Goldfinger S, Klinenberg JR, Seegmiller JE. The renal excretion of oxypurines. J Clin Invest 1965;44:623-8.
16. Elion GB, Yu TF, Gutman AB, Hitchings GH. Renal clearance of oxypurinol, the chief metabolite of allopurinol. Am J Med 1968;45:69-77.
17. Yamamoto T, Moriwaki Y, Takahashi S, Tsutsumi Z, Hada T. Effect of furosemide on renal excretion of oxypurinol and purine bases. Metabolism 2001;50:241-5.
18. Roch-Ramel F, Guisan B, Schild L. Indirect coupling of urate and p-aminohippurate transport to sodium in human brush-border membrane vesicles. Am J Physiol 1996;270:F61-8.
19. Takahashi S, Yamamoto T, Moriwaki Y, Tsutsumi Z, Higashino K. Impaired lipoprotein metabolism in patients with primary gout — influence of alcohol intake and body weight. Br J Rheumatol 1994;33:731-4.
20. Freedman DS, Williamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-up Study. Am J Epidemiol 1995;141:637-44.
21. Ward HJ. Uric acid as an independent risk factor in the treatment of hypertension. Lancet 1998;352:670-1.
22. Alderman MH, Cohen H, Madhavan S, Kivlighn S. Serum uric acid and cardiovascular events in successfully treated hypertensive patients. Hypertension 1999;34:144-50.
23. Elisaf M, Tsimichodimos V, Bairaktari E, Siamopoulos KC. Effect of micronized fenofibrate and losartan combination on uric acid metabolism in hypertensive patients with hyperuricemia. J Cardiovasc Pharmacol 1999;34:60-3.
24. Bastow MD, Durrington PN, Ishola M. Hypertriglyceridemia and hyperuricemia: effects of two fibric acid derivatives (bezafibrate and fenofibrate) in a double-blind, placebo-controlled trial. Metabolism 1988;37:217-20.
25. Von Löffler W, Grobner W, Zöllner N. Harnsauresenkende wirkung einer kombination von benzbromaron und allopurinol — untersuchungen unter standardiserten ernahrungsbedingungen [Hypouricemic effect of a combination therapy with benzbromarone and allopurinol: investigation under standard dietary conditions]. Arzneimittelforschung 1983;33:1687-91.