INTERACTION BETWEEN FIBRATES AND STATINS - METABOLIC INTERACTIONS WITH GEMFIBROZIL

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SUMMARY

An *in vitro* study was carried out in order to examine the metabolic basis of the interaction between fibrates and statins. Metabolic inhibition of statins was noted in the presence of gemfibrozil. However, increase in the unchanged form was fairly small for pitavastatin, compared with other statins. Several CYP enzymes were shown to be principally responsible for the metabolism of gemfibrozil in contrast to other fibrates. In the presence of gemfibrozil, a focal point was obtained in Dixon plots, demonstrating that there was inhibition of CYP2C8-, CYP2C9- and CYP3A4-mediated metabolism. We propose that the increase of plasma concentration caused by co-administration of gemfibrozil and statins is at least partially due to CYP-mediated inhibition.

KEY WORDS

pitavastatin, cerivastatin, gemfibrozil, HMG-CoA reductase inhibitor, fibrates

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INTRODUCTION

Pitavastatin is a potent inhibitor of HMG-CoA reductase and causes a significant reduction in serum total cholesterol, LDL-cholesterol and triglyceride levels in animals /1-3/. In humans, a persistent effect on serum lipids and the safety of pitavastatin have been confirmed in clinical practice /4,5/. Pitavastatin is scarcely metabolized at all in the hepatic microsomes, and there is no drug-drug interaction between pitavastatin and tolbutamide, taxol, debrisoquine or testosterone *in vitro* /6-8/.

Recently, cerivastatin was withdrawn from the market because of 52 deaths attributed to drug-related rhabdomyolysis that led to kidney failure /9/. The risk was found to be higher among patients who had received cerivastatin and gemfibrozil concomitantly /10/. Previously, many researchers reported that coadministration of fibrates increased the risk of rhabdomyolysis caused by HMG-CoA reductase inhibitors (statins) /11/. In addition, the combined use of gemfibrozil and statins can result in severe myopathy and rhabdomyolysis /12,13/. In particular, gemfibrozil has been found to elevate markedly plasma levels of simvastatin acid, lovastatin acid and cerivastatin /14-16/, indicating a pharmacokinetic mechanism in the gemfibrozil-statin drug interaction. However, the mechanism of interaction between gemfibrozil and statins is still unclear. The effect of gemfibrozil on the metabolism of pitavastatin, atorvastatin and cerivastatin was examined *in vitro* using human hepatic microsomes. Moreover, the metabolic properties of fibrates and the inhibitory effects of gemfibrozil on CYP-mediated metabolism were also investigated.

MATERIALS AND METHODS

Chemicals and reagents

Pitavastatin was synthesized by Nissan Chemical Industries, (Chiba, Japan). Cerivastatin, atorvastatin and fluvastatin were synthesized and purified in our laboratory. Gemfibrozil, bezafibrate, ciprofibrate and clofibrate were purchased from Sigma (St Louis, MO, USA). Since clofibrate and fenofibrate were pro-drugs of ester form, the free acid forms of their active substances were prepared by hydrolysis of the esters. The chemical purities of obtained free acid

forms of clofibrate and fenofibrate were more than 99%. 4-Hydroxytolbutamide, 6α-hydroxypaclitaxel and 6β-hydroxytestosterone were purchased from Ultrafine Chemicals (Manchester, UK). [Fluorobenzene-U-^{14}C]-pitavastatin was synthesized by Amersham Co. (Little Chalfort, UK). The specific radioactivity of the labeled compound was 981 kBq/mg. [Ring-U-^{14}C]-tolbutamide (Amersham; 2.26 GBq/mmol), [4-^{14}C]-paclitaxel (Sigma; 2.23 MBq/mg) and [4-^{14}C]-testosterone (Amersham; 2.11 GBq/mmol) were purchased commercially. The radiochemical purities of ^{14}C-labeled chemicals were more than 99%. All other chemicals and reagents were commercially available and of guaranteed purity.

Microsomes

Human hepatic microsomes containing representative activities of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and recombinant microsomes derived from baculovirus expressing human CYPs (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) were purchased from BD-Gentest (Woburn, MA). The NADPH regenerating system (β-NADP$^+$, glucose-6-phosphate and glucose-6-phosphate dehydrogenase) was obtained commercially.

Metabolic inhibition of statins by gemfibrozil

The incubation conditions were as in our previous report /6/. The inhibition studies with gemfibrozil were performed at a concentration of 1 μM ^{14}C-pitavastatin, -cerivastatin and -atorvastatin as substrate and 100-1000 μM gemfibrozil as inhibitor. The substrate concentrations were selected to be less than their K_m values (pitavastatin: 45 μM, atorvastatin: 72 μM) /17,18/. Statins were co-incubated with gemfibrozil and the amounts remaining were measured up to 60 min. In the determination of *in vitro* Cl_{int}, the slope of the linear regression from the log concentration versus incubation time relationships (*-k*) was used in the calculation as follows:

$Cl_{int} = k$ x (ml incubation) / (mg microsomes).

The inhibitory effect was estimated from the amount of substrate remaining at the end of the incubation in the absence and presence of inhibitor and was expressed as an increased ratio (IR) value as follows:

IR (%) = remaining with inhibitor / remaining without inhibitor x 100

Metabolic properties of fibrates

Gemfibrozil, bezafibrate, ciprofibrate, fenofibrate and clofibrate at a concentration of 10 μM were incubated with human hepatic microsomes and the metabolic stability of fibrates was evaluated. The remaining fibrate was measured up to 120 min after the addition of microsomes.

Identification of CYP isoforms in gemfibrozil or cerivastatin metabolism

Using six recombinant human CYP-expressing microsomes, the CYP isoforms participating in the metabolism of gemfibrozil or cerivastatin were investigated. For gemfibrozil (10 and 100 μM) and cerivastatin (1 and 10 μM), the reaction mixtures were incubated for 20 and 60 min, respectively. The incubation conditions were the same as for the hepatic microsomes.

Correlation of cerivastatin metabolism

Using ten human hepatic microsome samples, the correlation between the metabolic clearance of cerivastatin and activity of CYP markers was studied for CYP1A2 (phenacetin O-deethylase), CYP2C8 (paclitaxel 6α-hydroxylase), CYP2C9 (diclofenac 4′-hydroxylase), CYP2C19 (mephenytoin 4′-hydroxylase), CYP2D6 (bufuralol 1′-hydroxylase) and CYP3A4 (testosterone 6β-hydroxylase). Cerivastatin at a concentration of 1 μM was incubated for 45 min with several human hepatic microsomes and metabolic clearance was estimated from the amount of cerivastatin remaining.

Effect of gemfibrozil on the metabolism of several model substrates

The inhibitory effect of gemfibrozil on CYP-mediated metabolism was examined using ^{14}C-taxol, ^{14}C-tolbutamide and ^{14}C-testosterone in the concentration range 2-50 μM, 40-800 μM and 25-800 μM, respectively. In the inhibition experiment for CYPs, gemfibrozil (10-500 μM) was co-incubated with these model substrates. In the presence or absence of gemfibrozil, the CYP2C9-mediated production of 4-hydroxytolbutamide, CYP2C8-mediated production of 6α-hyd-

roxytaxol and CYP3A4-mediated production of 6β-hydroxytestosterone were evaluated. The apparent inhibition constants (K_i) in each experiment were estimated by Dixon plot analysis.

Analytical methods

The measurement of pitavastatin was done by high-performance liquid chromatographic (HPLC)-radioluminography (RLG) /19,20/. The quantification of cerivastatin and atorvastatin was performed according to previous reports using liquid chromatography-electrospray tandem mass spectrometry (LC/ES/MS) /21,22/. Both statins were detected in the positive ion mode. The precursor/product ion transitions monitored were m/z 460.8/356.5 for cerivastatin and m/z 559.0/440.6 for atorvastatin. Fenofibric acid was measured according to the HPLC-UV method /23/ with some modifications. A liquid-liquid extraction-HPLC method was used for the determination of gemfibrozil, bezafibrate, cipfofibrate and clofibrate. Monitoring was performed with UV (220 nm: bezafibrate, ciprofibrate and clofibrate; 288 nm: fenofibrate) or fluorescence (Ex 242 nm, Em 300 nm: gemfibrozil) detection. Measurements of 4-hydroxytolbutamide, 6α-hydroxyltaxol and 6β-hydroxytestosterone were done by TLC-RLG methods /6,7,24/.

RESULTS

Metabolic inhibition of statins by gemfibrozil

Figure 1 shows the inhibitory effects of gemfibrozil on pitavastatin, cerivastatin and atorvastatin metabolism in human hepatic microsomes up to 60 min incubation.

Pitavastatin was poorly metabolized by human hepatic microsomes, compared with cerivastatin and atorvastatin. The metabolic clearance of each statin was 3.7, 30.9 and 44.5 μl/min/mg protein, respectively, in the absence of gemfibrozil. The metabolic clearance of pitavastatin decreased to 0.5 μl/min/mg protein at a gemfibrozil concentration of 100 μM, and was almost completely inhibited at concentrations of 300 μM or more. The IR value of pitavastatin was within 128% in the presence of gemfibrozil. A remarkable inhibitory effect and a remarkable increase of IR values were observed on the

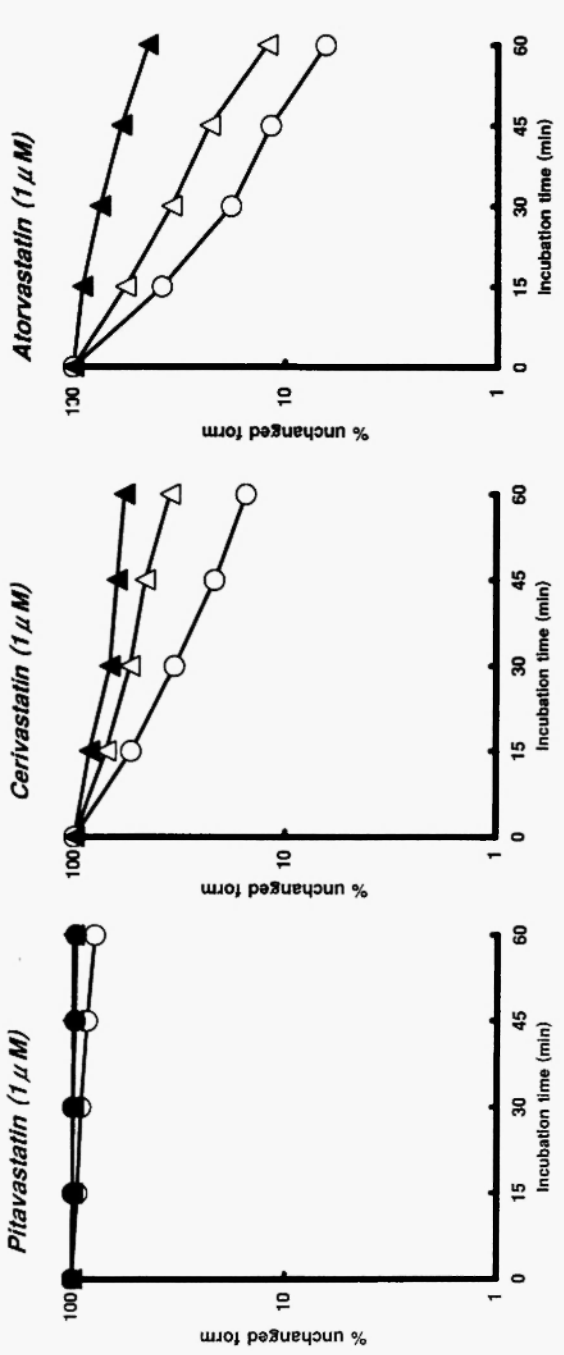

Fig. 1: Inhibitory effect of gemfibrozil on statin metabolism. o: gemfibrozil 0 μM; ●: gemfibrozil 100 μM; Δ: gemfibrozil 300 μM; ▲: gemfibrozil 1,000 μM.

metabolism of cerivastatin and atorvastatin in the presence of gemfibrozil. The metabolic clearance of cerivastatin was decreased to 16.6 and 9.0 μl/min/mg protein, and the IR values were 230% and 379% at 300 and 1000 μM of gemfibrozil, respectively. In the case of atorvastatin, the metabolic clearance decreased to 34.1 and 13.7 μl/min/mg protein, respectively. The IR values of atorvastatin were 190% at 300 μM and 702% at 1000 μM of gemfibrozil, respectively.

Metabolic stability of fibrates in human hepatic microsomes

Figure 2 shows the metabolic stability of several fibrates in human hepatic microsomes at a concentration of 10 μM. No remarkable metabolism was found for bezafibrate, ciprofibrate, fenofibrate or clofibrate. In contrast, gemfibrozil was metabolized extensively in human hepatic microsomes and the linearity of the metabolic reaction was maintained up to 20 min. The metabolic clearance of gemfibrozil was 71.5 μl/min/mg protein.

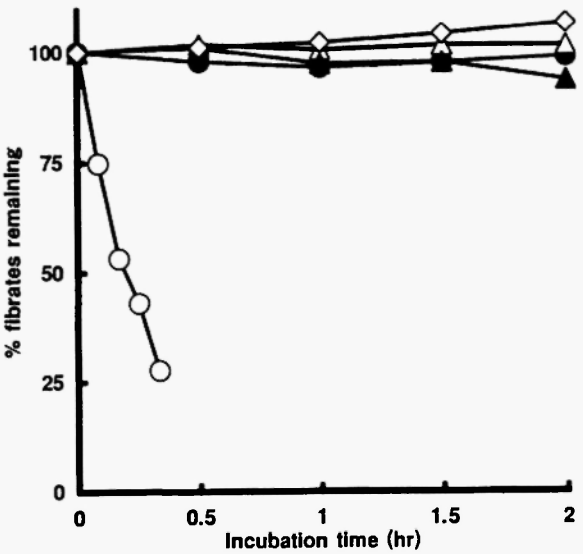

Fig. 2: Metabolic stability of several fibrates in human hepatic microsomes. Each fibrate (concentration: 10 μM) was incubated in the presence of an NADPH regenerating system. o: gemfibrozil; ●: bezafibrate; Δ: ciprofibrate; ▲: fenofibrate; ◇: clofibrate.

Identification of CYP isoforms involved in the metabolism of gemfibrozil and cerivastatin

Six human CYP-expressing microsomes were used to investigate gemfibrozil and cerivastatin metabolism (Fig. 3). Among the recombinant CYPs examined, CYP2C9 showed the highest activity at lower concentrations. CYP1A2 was also capable of catalyzing the metabolism of gemfibrozil, though other CYP isoforms, such as CYP2C19, were also involved. In addition, the metabolic clearance of gemfibrozil in human hepatic microsomes decreased in the presence of fluvastatin as a positive CYP2C9 inhibitor /25/ (data not shown). In contrast, little metabolism occurred in the presence of other CYP isoforms (CYP2C8, CYP3A4 and CYP2D6) up to a concentration of 100 μM. In the case of cerivastatin, CYP3A4 and CYP2C8 catalyzed its metabolism. Metabolite formation was not observed in the presence of the other CYPs tested (CYP1A2, CYP2C9, CYP2C19 and CYP2D6).

Correlation between P450 activities and cerivastatin metabolism

Figure 4 illustrates the correlation between the metabolism of cerivastatin and several CYP markers in ten human hepatic microsomes. A good correlation was observed for testosterone 6β-hydroxylase (CYP3A4; $R^2 = 0.893$), whereas a lower correlation ($R^2 = 0.357$) was observed between cerivastatin metabolism and CYP2C8-mediated paclitaxel 6-hydroxylase activity. Only low correlations ($R^2 < 0.064$) were observed for the markers of CYP1A2, CYP2C9, CYP2C19 or CYP2D6 isoforms.

Effect of gemfibrozil on CYP2C8-, CYP2C9- and CYP3A4-mediated metabolism

Figure 5 shows Dixon plots of tolbutamide 4-hydroxylation, taxol 6α-hydroxylation and testosterone 6β-hydroxylation. In the presence of gemfibrozil, focal points were obtained in all experiments, demonstrating that there was inhibition of CYP2C9-, CYP2C8- and CYP3A4-mediated metabolism by gemfibrozil. The Dixon plot indicated that gemfibrozil competitively inhibited CYP2C9 activity with an apparent K_i value of 18.6 μM. On the other hand, the pattern of inhibition of CYP2C8 and CYP3A4 by gemfibrozil was compatible with mixed

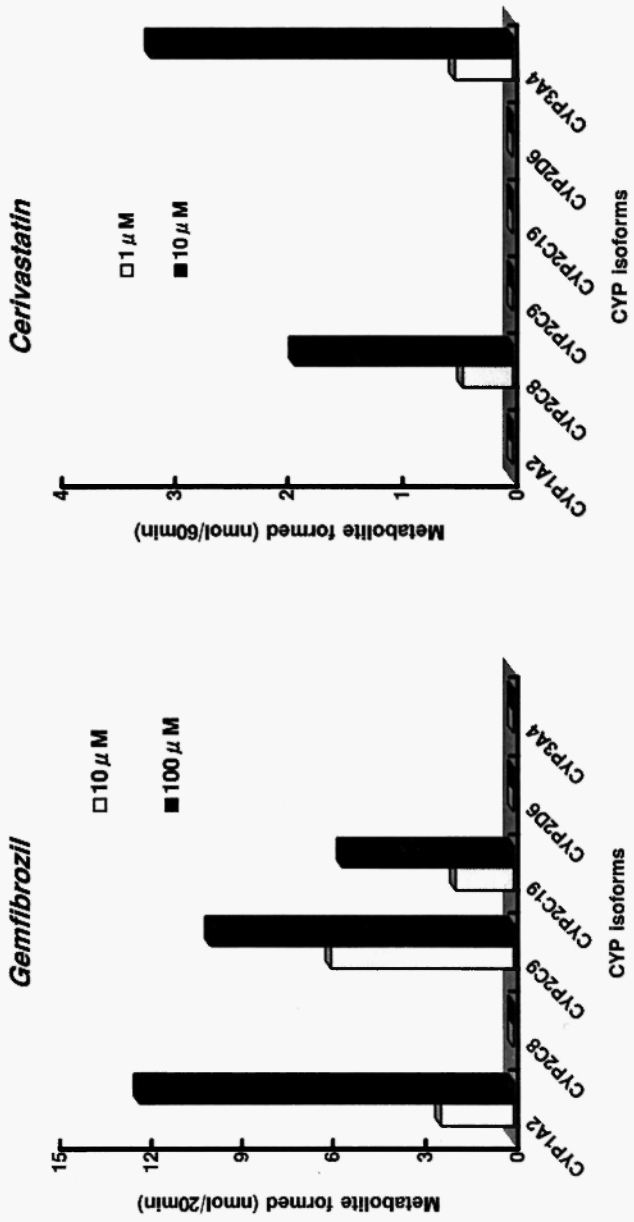

Fig. 3: Identification of CYP isoforms involved in gemfibrozil or cerivastatin metabolism.

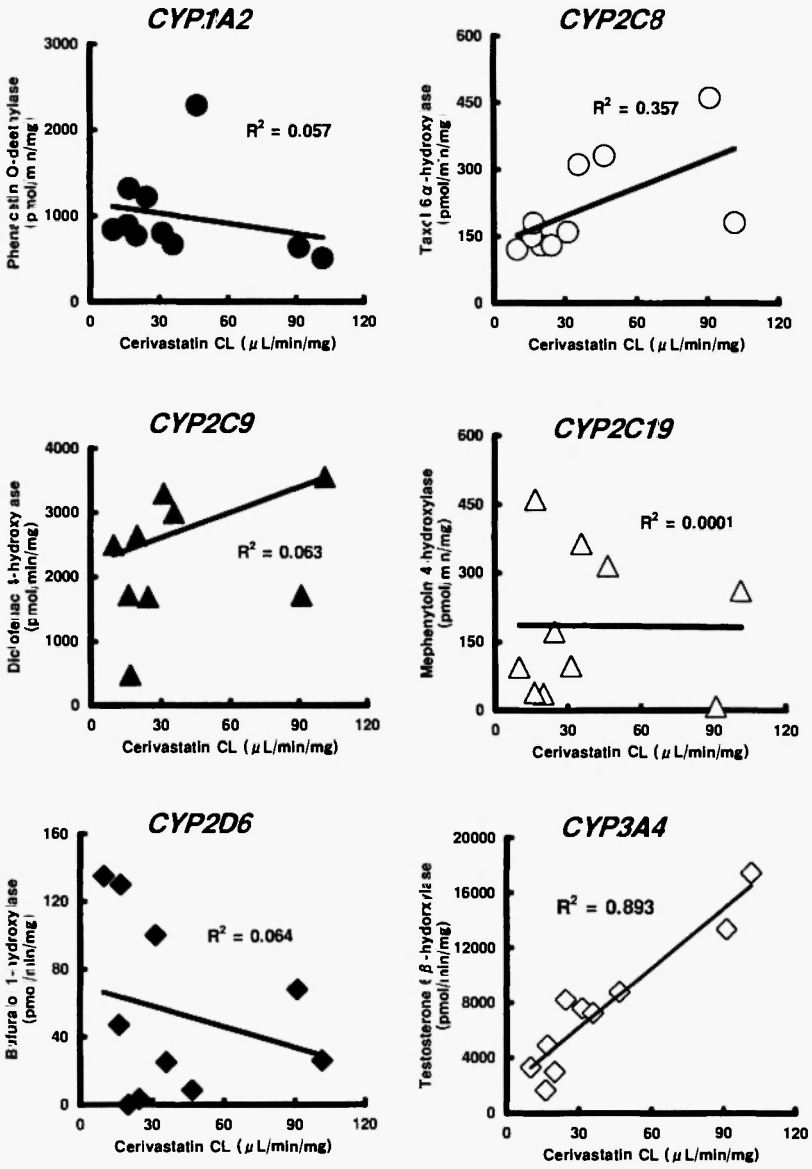

Fig. 4: Correlation between CYP activities and cerivastatin metabolism in human hepatic microsomes.

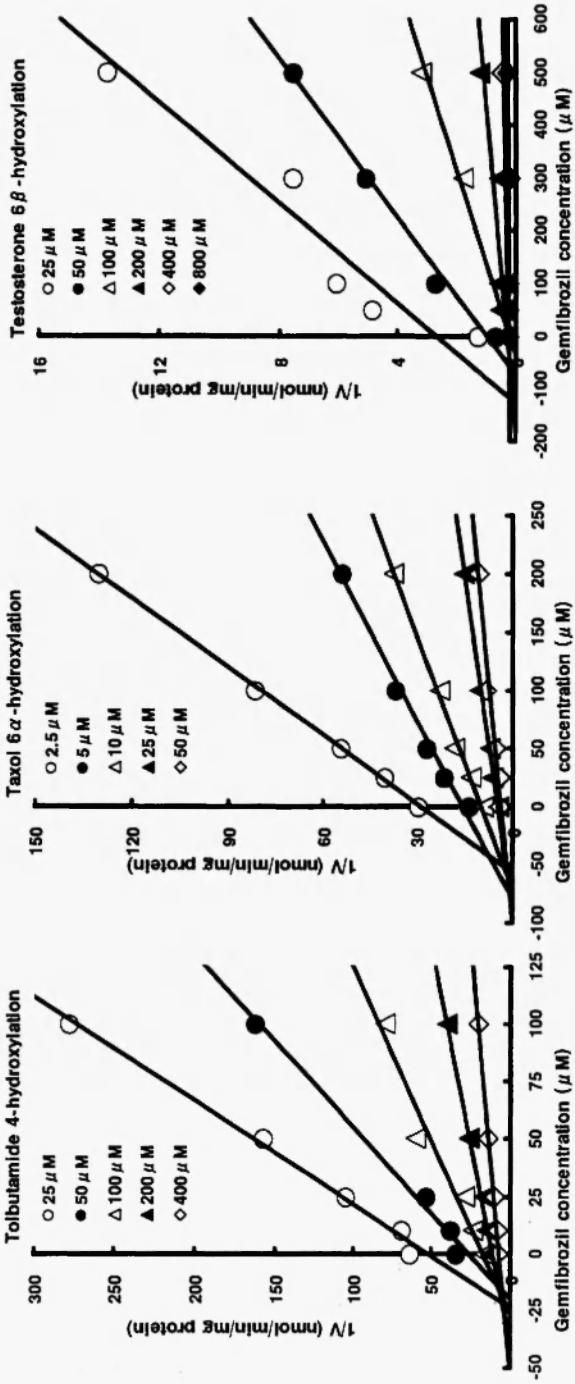

Fig. 5: Dixon plot analysis of CYP model substrates (CYP2C9, CYP2C8 and CYP3A4) in the presence of gemfibrozil.

inhibition and the apparent K_i values were 55.4 and 171 μM, respectively.

DISCUSSION

Remarkable increases in the plasma concentrations of lovastatin, simvastatin and cerivastatin have been reported with the concomitant use of gemfibrozil /14-16/. From these reports, it has generally been accepted that the risk of myopathy is due primarily to a drug-drug interaction, and recent studies have suggested that the increased risk might have a pharmacokinetic origin. To gain a better understanding of the mechanism of drug-drug interaction between fibrates and statins, we undertook a number of *in vitro* investigations using human hepatic microsomal preparations.

In the current study, we showed that metabolic clearance by human liver microsomes of cerivastatin and atorvastatin was about 31 and 45 μl/min/mg protein, respectively, some 10 and 15 times higher than that of pitavastatin, indicating that metabolic inhibition caused the remarkable increase in the unchanged form. The IR values of cerivastatin and atorvastatin reached 379% and 702%, respectively, due to inhibition by gemfibrozil. On the other hand, the metabolism of pitavastatin was inhibited completely by gemfibrozil, but the IR value was less than 128%. These results indicated that a remarkable increase in the plasma concentration of pitavastatin may not occur concomitantly with gemfibrozil compared with other statins. In addition, these findings indicate that the drug-drug interaction caused by the co-administration of gemfibrozil and statins is partially due to metabolic inhibition.

Extensive metabolism of gemfibrozil was noted in human hepatic microsomes in contrast to other fibrates. We also demonstrated that CYP2C9 is mainly involved in the metabolism of gemfibrozil. In addition, it has been reported that gemfibrozil inhibits the activity of CYP2C9 at clinically relevant concentrations /26/. Previously, we reported that CYP2C9 was involved in the metabolism of pitavastatin /8,17/. These findings indicate that gemfibrozil competitively inhibits the CYP-mediated metabolism of pitavastatin.

We next investigated the metabolic properties of cerivastatin using CYP-expressing microsomes and the correlation between CYP activities. CYP2C8 and CYP3A4 have previously been reported to be

involved in the formation of two major metabolites of cerivastatin /27/, and these results are consistent with our findings. On the other hand, CYP1A2, CYP2C9, CYP2C19 and CYP2D6 were not involved in the metabolism of cerivastatin. There was no competitive relationship of CYP isoforms between gemfibrozil and cerivastatin. These findings caused confusion over the hypothesis of CYP-mediated inhibition by the concomitant use of gemfibrozil and cerivastatin. In the current study, we found that gemfibrozil inhibited CYP2C8-mediated taxol 6α-hydroxylation. CYP2C8 is one of the isoforms involved in the metabolism of cerivastatin. However, since the expression level of CYP2C8 in human liver was much lower than that of CYP3A4 /28/, it is difficult to explain all the metabolic inhibition of cerivastatin as CYP2C8-mediated. We also confirmed the contribution of CYP isoforms are involved in the metabolism of cerivastatin by correlation studies. The metabolic clearance of cerivastatin showed a good correlation with CYP3A4 activity, whereas no good correlation was found for CYP2C8 activity. These findings suggest that CYP3A4 is mainly involved in the metabolism of cerivastatin with some contribution by CYP2C8.

In the Dixon plot analysis, gemfibrozil was shown to be a potent competitive inhibitor of CYP2C9-mediated metabolism with an apparent K_i value of 18.6 μM. In contrast, gemfibrozil inhibited CYP2C8- and CYP3A4-mediated metabolism non-competitively with apparent K_i values of 55.4 and 171 μM, respectively. The K_i value of gemfibrozil for CYP2C9 and CYP2C8 was almost equal to the clinical concentration, and for CYP3A4 was equivalent to the plasma C_{max} (about 100 μM) in a clinical study /29/. A remarkable inhibitory effect on CYP3A4-mediated atorvastatin metabolism was observed in the presence of gemfibrozil, also supporting our findings. Based on the present *in vitro* results, we hypothesize that gemfibrozil inhibited the CYP2C9- and CYP2C8-mediated metabolic pathway of pitavastatin and cerivastatin at a relatively low concentration, and also inhibited the CYP3A4-meditated metabolic pathway of atorvastatin and cerivastatin at a relatively high concentration.

In conclusion, we propose that the increase of plasma concentration caused by co-administration of gemfibrozil and statins is at least partially due to a CYP-mediated inhibition.

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