Effects of gemfibrozil and rifampicin on the pharmacokinetics of HMG-CoA reductase inhibitors

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by
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ACADEMIC DISSERTATION

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To my family

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Abbreviations

A_e	amount excreted
ADR	adverse drug reactions
Ah	aryl hydrocarbon
ANOVA	analysis of variance
ATP	adenosine triphosphate
ATPIII	3rd Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)
AUC	area under the concentration-time curve
^{14}C	radioactive isotope of carbon
CAR	constitutive androstane receptor
CK	creatine kinase
CL	clearance
C_{max}	peak concentration
cMOAT	canalicular multispecific anion transporter (*ABCC2*, MRP2)
CRP	C-reactive protein
CV	coefficient of variation
CYP	cytochrome P450
DNA	deoxyribonucleic acid
EDTA	ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FMO	flavin-containing mono-oxygenase
FXR	farnesoid X receptor
GR	glucocorticoid receptor
GST	glutathione-S-transferase
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HPLC	high-performance liquid chromatography
IC_{50}	concentration of inhibitor corresponding to a 50% decrease in reaction velocity
K^+	potassium
K_i	inhibition constant
LC/MS/MS	liquid-chromatography-tandem mass spectrometry
LDL	low-density lipoprotein

LXR	liver X receptor
m/z	mass-to-charge ratio
MAO	monoamine oxidase
MDR	multidrug resistance
mRNA	mitochondrial ribonucleic acid
MRP2	multidrug resistance protein 2 (*ABCC2*, cMOAT)
MRP3	multidrug resistance protein 3 (*ABCC3*)
Na^+	sodium
NADPH	nicotinamide adenine dinucleotide phosphate (reduced form)
NTCP	Na^+-dependent taurocholate co-transporting polypeptide
OATP-B	organic anion-transporting polypeptide B (*SLCO2B1*, OATP2B1, OATP-RP2)
OATP-C	organic anion-transporting polypeptide C (*SLCO1B1*, OATP1B1, OATP2, LST-1)
P-gp	P-glycoprotein (*MDR1*, ABCB1, PGY1, GP170)
PPAR	peroxisome proliferator-activated receptor
PPRE	peroxisome proliferator response element
PXR	pregnane X receptor
RNA	ribonucleic acid
RXR	retinoid X receptor
SD	standard deviation
SEM	standard error of mean
SNP	single nucleotide polymorphism
SULT	sulfotransferase
$t_{1/2}$	elimination half-life
t_{max}	time to peak concentration
UGT	UDP-glucuronosyltransferase
VDR	vitamin D receptor

LIST OF ORIGINAL PUBLICATIONS

I Backman JT, Kyrklund C, Kivistö KT, Wang JS, Neuvonen PJ. Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clin Pharmacol Ther* 2000;68:122-9.

II Kyrklund C, Backman JT, Kivistö KT, Neuvonen M, Laitila J, Neuvonen PJ. Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not by bezafibrate. *Clin Pharmacol Ther* 2001;69:340-5.

III Backman JT, Kyrklund C, Neuvonen M, Neuvonen PJ. Gemfibrozil greatly increases plasma concentrations of cerivastatin. *Clin Pharmacol Ther* 2002;72:685-91.

IV Kyrklund C, Backman JT, Neuvonen M, Neuvonen PJ. Gemfibrozil increases pravastatin plasma concentrations and reduces pravastatin renal clearance. *Clin Pharmacol Ther* 2003;73:538-44.

V Kyrklund C, Backman JT, Kivistö KT, Neuvonen M, Laitila J, Neuvonen PJ. Rifampin greatly reduces plasma simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 2000;68:592-7.

VI Kyrklund C, Backman JT, Neuvonen M, Neuvonen PJ. Effect of rifampicin on pravastatin pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 2004;57:181-7

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Abstract

HMG-CoA reductase inhibitors (statins) and fibrates are cholesterol-lowering drugs with complementary effects on plasma lipid levels. Although the combination of statins and fibrates is highly effective and listed in guidelines as an option in selected patient populations, it is also associated with a higher risk of severe muscle adverse effects. The risk for muscle adverse effects is known to increase with increasing statin concentrations. We carried out a series of investigations to determine whether the fibrate gemfibrozil increases plasma concentrations of four statins: simvastatin, lovastatin, cerivastatin and pravastatin. We also studied the effect of bezafibrate on lovastatin concentrations. Secondly, we studied the effects of antimicrobal drug rifampicin on the pharmacokinetics of simvastatin and pravastatin. Rifampicin is a model inducer of drug metabolism and drug transport.

All the studies were randomised, blinded and placebo-controlled, with a cross-over design in healthy human volunteers. Pretreatment with clinically relevant doses of a fibrate or rifampicin was followed by a single dose of statin, whereafter blood samples were collected to determine the plasma statin concentrations, and the pharmacokinetic parameters calculated.

Gemfibrozil significantly increased the area under the plasma concentration-curve (AUC) of all statins studied. On average, the AUC of cerivastatin, lovastatin acid, simvastatin acid, and pravastatin increased about six-fold, three-fold, three-fold and two-fold, compared to control phase values. The extent of the interactions comprised large interindividual variations, and the greatest increase in AUC by gemfibrozil was more than 10-fold for lovastatin acid and cerivastatin. Bezafibrate on the other hand, did not significantly affect the pharmacokinetics of lovastatin. Rifampicin reduced the AUC of active simvastatin acid to less than 10% of control phase values, whereas the mean AUC values of pravastatin decreased only to about 70%.

These studies reveal a clinically significant pharmacokinetic drug interaction between gemfibrozil and statins. The adverse effects of the gemfibrozil-statin combinations may at least partially result from the pharmacokinetic interaction observed, and should be taken into account when choosing an appropriate combination and dosage of a statin and fibrate. Other commonly used fibrates may be void of the pharmacokinetic interaction with statins. The interaction between simvastatin and rifampicin is significant and may result in reduced statin efficacy, whereas the effect of rifampicin on pravastatin is considerably smaller. Therefore pravastatin could be used in preference to simvastatin in patients using potent inducers of CYP3A4.

Introduction

HMG-CoA reductase inhibitors (statins) are first-choice drugs in the treatment of elevated blood cholesterol levels. Statins are powerful low-density lipoprotein (LDL) cholesterol-lowering drugs that are widely used in clinical practice. Results from clinical trials have demonstrated a decrease in coronary heart disease and all-cause mortality, reductions in myocardial infarctions, revascularisation procedures, stroke and peripheral vascular disease (Pasternak et al. 2002). Treatment of hypercholesterolemia is often lifelong, and patients often have concomitant diseases and medications that increase the likelihood of adverse drug interactions.

Although statins are well-tolerated in monotherapy, they can cause myopathy or even rhabdomyolysis as a rare side effect. Rhabdomyolysis is a potentially fatal condition resulting from destruction of skeletal muscle and leading to excretion of myoglobin in the urine and renal failure. The muscle toxicity of statins has been shown to be a dose- and concentration-dependent phenomenon (Bradford et al. 1991; Dujovne et al. 1991; 1997; Pierno et al. 1999), and the risk of muscle toxicity increases when statins are used with drugs such as intraconazole or erythromycin (Chang et al. 2002). The mechanism of these interactions is the increase in statin plasma concentration by inhibition of cytochrome P-450 (CYP) 3A4 by itraconazole or erythromycin (Neuvonen and Jalava 1996; Kantola et al. 1998a).

Fibrates, such as gemfibrozil and bezafibrate, are another class of lipid-lowering drugs. Fibrates reduce triglyceride levels and increase high-density lipoprotein (HDL) cholesterol levels, whereas statins effectively reduce low-density lipoprotein (LDL) cholesterol with usually smaller effects on triglycerides and HDL-cholesterol. Accordingly, patients with mixed lipid disorders may benefit from a combination of a statin and a fibrate.

The combination of a statin and a fibrate is highly effective in correcting blood lipid levels (East et al. 1988; Garg and Grundy 1989; Witztum et al. 1989), however the risk of rhabdomyolysis, increases in concomitant therapy (Farmer 2001; Igel et al. 2002). At the onset of these studies, whether the mechanism of the interaction between gemfibrozil and statins was similar to that of itraconazole or erythromycin with statins, or whether the increase in muscle toxicity was of a pharmacodynamic origin, was unknown.

In 1999, Murphy and Dominiczak reported a case in which the cholesterol-lowering efficacy of simvastatin substantially decreased in a patient who used phenytoin, a drug that induces CYP3A4 (Murphy and Dominiczak 1999). A handful of drugs exist that significantly induce CYP3A4, including

phenobarbital, carbamazepine and rifampicin. Rifampicin – an antimicrobal drug used in the treatment tuberculosis – is often chosen as a model inducing agent when assessing the effects of CYP induction on the pharmacokinetics of given drugs. Rifampicin also induces the expression of some drug transporters, such as P-glycoprotein (Greiner et al. 1999) and canalicular multispecific organic anion transporter (Fromm et al. 2000), and reduces plasma concentrations and the effects of several drugs (Niemi et al. 2003c).

Although assessment of the effects of fibrates and rifampicin on statin pharmacokinetics is clinically highly relevant, few controlled studies had been carried out to answer these questions. The purpose of this work was to investigate the effects of gemfibrozil on the pharmacokinetics of statins. In addition, this work aimed to investigate the effects of rifampicin on the pharmacokinetics of simvastatin and pravastatin in order to characterise their interaction potential with potent enzyme inducers.

Review of the literature

1. Pharmacokinetics

Pharmacokinetics deals with stages of a drug in the body, or rather, what the body does to the drug. Pharmacokinetics is often divided into four phases: absorption, distribution, metabolism and elimination (Rowland and Tozer 1989). The rate of absorption is indirectly described by the peak plasma drug concentration (C_{max}) and the time at which it occurs (t_{max}). Distribution initially occurs into highly perfused tissues, and depends on the ability of the drug to penetrate biological membranes. Drugs pass through cell membranes via filtration, passive or facilitated diffusion, or pinocytosis. Elimination of a drug from the body depends on blood flow, protein-binding and the intrinsic function of the eliminating organ. Most drugs are eliminated via the liver to the bile or through the kidneys to the urine. Ionised or water-soluble substances are more easily excreted though the kidneys. Disposition is the combined process of distribution and elimination, and is generally described by the terminal elimination half-life ($t_{½}$).

1.1 Drug transporters

Transport processes are increasingly acknowledged as important determinants of drug absorption, distribution and excretion, and for many drugs, hepatic uptake and efflux transport are the important routes of elimination (Ayrton and Morgan 2001; Hagenbuch and Meier 2003). Therefore, it is often appropriate that transport and metabolism be considered together when predicting *in vivo* pharmacokinetics. Increasing evidence supports the importance of a few key transporters with broad substrate specificities, rather than a large number of transporters with narrow substrate specificities (Kim 2002).

The polarised expression of uptake and efflux transporters to specific membrane domains allows for directional movement of substrates. The main currently identified uptake transporters are sodium (Na^+)-dependent taurocholate co-transporting polypeptide and the organic anion-transporting polypeptides superfamily. The main efflux transporters are P-glycoprotein (P-gp), multidrug resistance protein MRP2 (cMOAT), MRP3 and the canalicular bile salt efflux pump (Sister P-glycoprotein).

1.1.1 Uptake transporters

Na^+-dependent taurocholate co-transporting polypeptide (NTCP), characterised in 1994 (Hagenbuch and Meier 1994), is a key transporter in the hepatic uptake of bile acids (Hagenbuch et al. 1996). Bile acids have recently been identified as ligands for nuclear receptors such as pregnane X receptor (PXR) and farnesoid X receptor (FXR), both involved in CYP expression and cholesterol metabolism. NTCP is therefore likely to be important in the regulation of other transporters and CYP expression (Sinal et al. 2000; Staudinger et al. 2001; Xie et al. 2001)(Figure 1).

Organic anion-transporting polypeptides (OATPs) form a superfamily of uptake transporters with a wide spectrum of transport substrates. In contrast to NTCP, OATPs are not sodium-dependent. There are currently more than 30 mammalian members of the OATP superfamily, many of which are multispecific and transport a broad range of endo- and exobiotics (Hagenbuch and Meier 2003). Most are expressed in multiple tissues such as the liver, kidneys, intestine or brain, while some, such as OATP-C (synonyms *SLCO1B1*, OATP1B1, OATP2, LST-1), are selectively expressed in the liver. HMG-CoA reductase inhibitors pravastatin, simvastatin, lovastatin, atorvastatin, cerivastatin and rosuvastatin are transported to the liver via OATP-C (Hsiang et al. 1999; Nakai et al. 2001; Shitara et al.

2003; Schneck et al. 2004). Pravastatin is also a substrate of OATP-B (Kobayashi et al. 2003; Nozawa et al. 2004). The nomenclature of the OATP-family is currently changing. The new name for OATP-C is OATP1B1, and the new name for OATP-B is OATP2B1 (Hagenbuch and Meier 2004). However, in accordance with current practice (Kim 2004; Mwinyi et al. 2004), the names OATP-B and OATP-C will be used in this thesis.

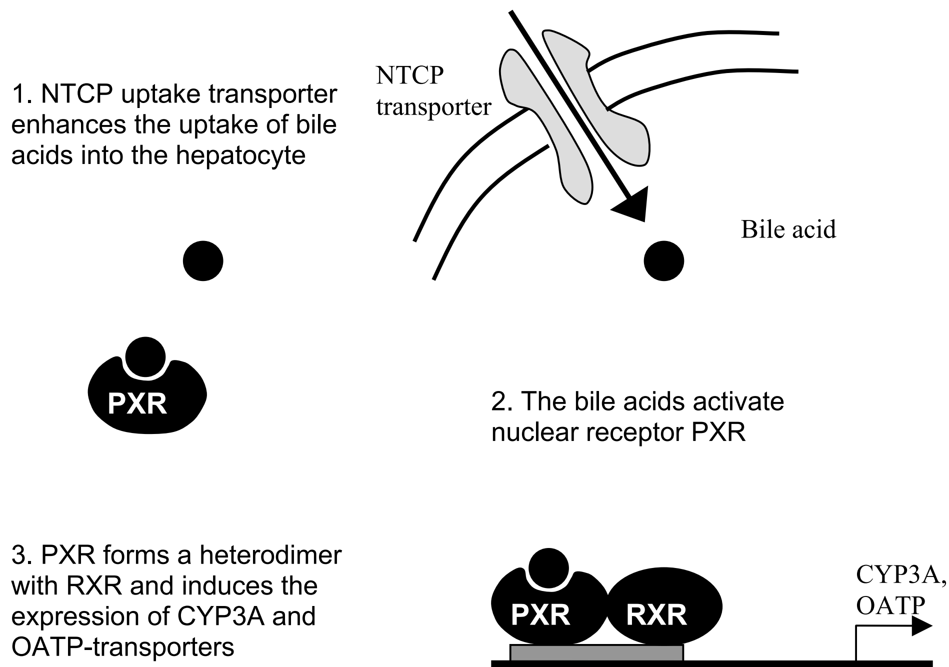


Figure 1. Na^+-dependent taurocholate co-transporting polypeptide is likely to be important in the regulation of other transporters and CYP expression.

1.1.2. Efflux transporters

P-glycoprotein (P-gp) is an ATP-dependent transmembrane transporter for a large number of hydrophobic substrates (Kim 2002). It is a part of the adenosine triphosphate (ATP)-binding cassette transporter family, and the human gene *ABCB1* (*MDR1)* encodes P-gp (Chen et al. 1986). P-gp is normally expressed in the epithelial cells and luminal surfaces of many organs with an excretory or barrier function: the liver, kidneys, small intestine, capillary endothelium of the brain and testes. Many of these cells are polarised, suggesting that P-gp can affect drug disposition by inhibiting drug absorption and facilitating drug excretion (Silverman 2000). High levels of P-gp are expressed in some

cancers, affecting the response to cytostatics. Drug substrates of P-gp include cyclosporin A, verapamil, quinidine, erythromycin, terfenadine, fexofenadine and human immunodeficiency virus (HIV)-protease inhibitors (Kim 2002). High P-gp inhibition and affinity seems to correlate with the lipid solubility of the drugs and their metabolites (Zamora et al. 1988; Ecker and Chiba 1995; Bogman et al. 2001). *In vitro* evidence suggests that at least lovastatin (Kim et al. 1999) and atorvastatin (Boyd et al. 2000; Wu et al. 2000) are substrates of P-gp, whereas fluvastatin (Lindahl et al. 1998; Scripture and Pieper 2001) and pravastatin are not (Sakaeda et al. 2002). P-gp is known to have significant substrate overlap with CYP3A. This is important to drug disposition since both CYP3A and P-gp are co-expressed in tissues such as intestinal enterocytes and hepatocytes (Kim 2002). To date, 29 isolated nucleotide differences between individuals (SNP) have been reported in the *ABCB1* gene (Marzolini et al. 2004). However, data about the effect of the polymorphisms in *ABCB1* on substrate drug pharmacokinetics are inconsistent (Marzolini et al. 2004).

MRP2 is an ATP-dependent efflux transporter found in hepatocytes, also named canalicular multiple organic anion-transporter (cMOAT). MRP2 is also expressed in the intestine and kidneys (Dean et al. 2001). In humans, absence of MRP2 is responsible for the Dubin-Johnson syndrome, a rare hereditary disorder resulting in hyperbilirubinemia (Paulusma et al. 1997). MRP2 is responsible for the biliary excretion of organic anions, gluthatione conjugates, and some antibiotics. Pravastatin is a substrate of MRP2 (Paulusma et al. 1997).

The canalicular bile salt efflux pump (Sister P-glycoprotein) has now been identified as the ATP-dependent transporter responsible for bile acid efflux (Gerloff et al. 1998).

1.2 Principles of drug metabolism

Most drugs are not readily excreted from the body unchanged and must undergo biotransformation to more hydrophilic forms before they can be excreted in the urine or bile (Meyer 1996). This biotransformation is catalysed in humans by a number of drug-metabolising enzymes and is often divided into two phases.

Phase I reactions include oxidation, reduction and hydrolysis reactions catalysed by CYP-enzymes in the endoplasmic reticulum. The metabolites produced by these reactions are polarised compounds that are usually pharmacologically less active and less toxic than the parent compound. However, there are

also examples of more toxic metabolites (Pirmohamed et al. 1994). Metabolism-activated drugs are called prodrugs.

Phase II reactions are conjugation reactions and include glucuronidation, acetylation and sulphation as well as conjugation with glutatione or amino acids. Drugs usually undergo phase I reactions to be then further metabolised in phase II reactions, but some drugs can be excreted directly after either phase I or II reactions, or even nonmetabolised (Krishna and Klotz 1994). Phase I enzymes are dealt with in more detail in section 1.3.

The phase II enzymes that catalyse conjugation reactions are broad specificity transferases such as UDP-glucuronosyltransferases (UGT), glutathione-S-transferases (GST) and sulfotransferases (SULT). The conjugation reactions are important as they prevent electrophiles from reacting with DNA and the nucleophiles from interacting with receptor proteins, and they increase the water solubility of the compounds, promoting renal and biliary excretion (Sheweita 2000). In addition to detoxification, they also activate drugs and procarcinogens (Guengerich 2000). Recent studies indicate that phase II enzymes can be induced in the same way as CYP enzymes (Sonoda et al. 2003). On such example is the induction of the glucuronidation of morphine by rifampicin (Fromm et al. 1997).

Glucuronidation is quantitatively the most important phase II conjugation reaction. Glucuronidation of small compounds is mediated by UGT-enzymes, themselves further divided into two families designated UGT1 and UGT2 (Mackenzie et al. 1997; King et al. 2000). UGT-enzymes are expressed in the liver, biliary tract, esophagus, stomach, intestine and colon (Tukey and Strassburg 2000). Cerivastatin, atorvastatin and simvastatin are substrates of UGT-enzymes, but the clinical relevance of glucuronidation reactions in statin metabolism is subject to debate (Prueksaritanont et al. 2002b).

Metabolism usually takes place mainly in the liver and the gastrointestinal tract, although the kidneys, skin and lungs also exhibit significant metabolic capacity (Krishna and Klotz 1994). An orally-administered drug can undergo extensive metabolism in the gut and liver during the first-pass phase and therefore have a low bioavailability (Hoppu et al. 1991; Kolars et al. 1991; Wu et al. 1995; Kivistö et al. 1996). The primary task of metabolism is to make lipophilic substances more hydrophilic and therefore easier to eliminate from the body. Metabolism often reduces the biological activity of the drug, although metabolism can also result in more active or toxic metabolites.

Metabolic capacity is influenced by numerous factors, such as polymorphisms of drug-metabolising enzymes, age, gender and possible diseases (Rowland and Tozer 1989). Also, many external factors such as drugs, alcohol or other xenobiotics, smoking and dietary factors are known to affect the capacity of the body to metabolise drugs. These partly-inherited and partly-acquired factors explain why the pharmacokinetics of a given drug can vary considerably from individual to individual.

1.3 Cytochrome P450 (CYP) enzymes

Cytochrome P450 (CYP) is a superfamily of haem-containing mono-oxygenase enzymes (Wrighton and Stevens 1992). The biological functions of CYP enzymes include metabolism of endogenous substrates, metabolism and detoxification of foreign compounds, and synthesis of endogenous hydrophobic lipids such as cholesterol, bile acids, steroid hormones and fatty acids (Wrighton and Stevens 1992; Nelson et al. 1993). CYP450 was first named in 1961, because the pigment (P) has a 450 nm spectral peak when reduced and bound to carbon monoxide (Nebert and Russell 2002).

CYP enzymes are divided into families, subfamilies and specific isoenzymes (Nelson et al. 1996). Members of a CYP family share at least 40% identity in the aminoacid sequence and are indicated by an Arabic numeral, for instance CYP**3**. Subfamilies are indicated by a capital letter (CYP3**A**) and indicate an aminoacid homology of more than 55%. The last numeral indicates the individual enzyme (CYP3A**4**).

More than 270 different *CYP* gene families have been identified, human beings having 57 *CYP* genes and 33 pseudogenes arranged into 18 families. Of these 18 families, the **CYP1**, **CYP2** and **CYP3** families are involved in drug metabolism (Nebert and Russell 2002). The families relevant in the metabolism of statins (CYP3A and CYP2C) will be discussed in more detail in the following sections.

1.3.1. CYP1 family

The CYP1 family comprises three members: CYP1A1, CYP1A2 and CYP1B1. CYP1A2 is the most important isoform in the metabolism of drugs with 10-20 different substrate drugs (Nebert and Russell 2002). CYP1A2 enzymes account for about 10% of all CYP enzymes in the liver (Shimada et al. 1994) (Figure 2). Polyaromatic hydrocarbons found for instance in grilled food and cigarette smoke induces expression of the *CYP1* gene family by binding to the aryl hydrocarbon receptor (Nebert and Russell 2002). Inhibitors of CYP1A2 include fluvoxamine and ciprofloxacin (Fuhr et al. 1992; Rasmussen et al. 1995).

1.3.2. CYP2 family

CYP2A6 is highly polymorphic with more than 11 alleles identified to date. CYP2A6 represents up to 15% of human CYP proteins (Pelkonen et al. 2000). CYP2A6 is the major nicotine oxidase, and since defective CYP2A6 variants have a reduced capacity for nicotine clearance, this polymorphism may affect smoking behaviour (Ingelman-Sundberg 2002; Oscarson et al. 2002).

CYP2B6 constitutes on average about 0.2% of total CYP content, metabolising cyclophosphamide (Chang et al. 1993), S-mephenytoin (Ko et al. 1998) and propofol (Court et al. 2001), and inhibited by fluvoxamine, sertraline and paroxetine (Hesse et al. 2000).

CYP2C enzymes account for about 20% of all CYP enzymes in the liver (Shimada et al. 1994). The subfamily has four known human members: CYP2C8, CYP2C9, CYP2C18 and CYP2C19. CYP2C enzymes are expressed mainly in the liver, but a significant amount of CYP2C enzymes is also found in the intestine, where this family appears to be the second most highly expressed CYP subfamily after CYP3A (Klose et al. 1999; Obach et al. 2001; Läpple et al. 2003).

CYP2C8 plays an important role in the metabolism of several drugs such as repaglinide, chloroquine, cerivastatin, paclitaxel, pioglitatzone and rosiglitazone (Rettie et al. 2000; Bidstrup et al. 2001; Mudaliar and Henry 2001; Wang et al. 2002; Projean et al. 2003), as well as the in metabolism of the pesticide parathion (Mutch et al. 2003). It appears that a certain degree of overlap exists between CYP2C8 and CYP3A4 substrate specificity (Ong et al. 2000; Projean et al. 2003). For example, CYP2C8 contributes in part to the metabolism of the predominantly CYP3A4 substrates carbamazepine, verapamil and zopiclone (Kerr et al. 1994; Becquemont et al. 1999; Tracy et al. 1999), and CYP3A4 contributes in part

to cerivastatin and paclitaxel metabolism (Sonnichsen et al. 1995; Wang et al. 2002). Trimethoprim and sulfamethoxazole are selective inhibitors of CYP2C8 and CYP2C9, respectively (Wen et al. 2002). CYP2C8 protein is highly expressed in the liver, but remains undetected in the intestine (Läpple et al. 2003). In the liver, CYP2C8 protein is expressed in slightly lesser quantities than CYP2C9, but in clearly greater quantities than CYP2C19 (Läpple et al. 2003).

CYP2C8, CYP2C9 and CYP2C19 are polymorphically expressed, and the polymorphisms in each isoenzyme (especially CYP2C9 and CYP2C19) seem to have clinical consequences (Goldstein 2001; Daly 2003; Niemi et al. 2003d). From 15% to 20% of Asians and from 2% to 6% of Caucasians are poor metabolisers of CYP2C19 substrates (Flockhart 1995).

Although CYP2D6 contributes about 2% to 5% of total hepatic CYP content (Shimada et al. 1994), *in vitro* studies suggest that CYP2D6 metabolises a large number of important substrates (more than 75 drugs), including many cardiac drugs and antidepressives (Wrighton and Stevens 1992; Wolf and Smith 1999). CYP2D6 is expressed in the gut wall as well as in the liver (de Waziers et al. 1990).

CYP2E1 accounts for about 7% of hepatic CYP content, and it metabolises ethanol, halothane, and paracetamol (Wrighton and Stevens 1992).

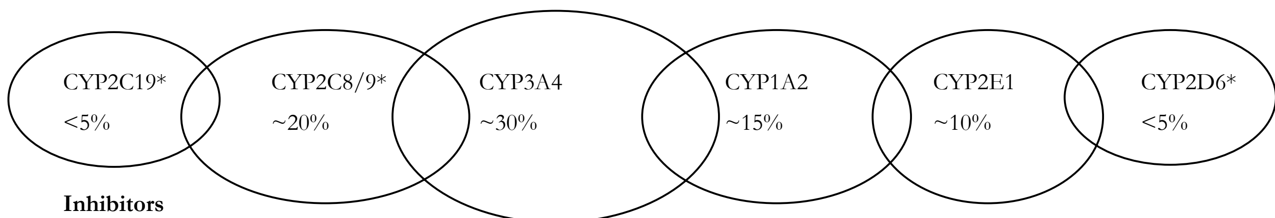
1.3.3. CYP3 family

CYP3A is the most important CYP subfamily in the biotransformation of drugs. The CYP3A subfamily includes the isoforms CYP3A4, CYP3A5, and CYP3A7. Some estimate that about half of all drugs currently on the market are at least partly metabolised by CYP3A4 (Wrighton and Stevens 1992; Shimada et al. 1994; Guengerich 1996; Wrighton et al. 2000a). CYP3A4 also metabolises endogenous substances such as testosterone and bile acid (Waxman et al. 1991; Araya and Wikvall 1999; Patki et al. 2003). CYP3A4 is the most abundant CYP enzyme in the liver, accounting for about 30% of all CYP enzymes (Shimada et al. 1994), and the main CYP enzyme in the small intestinal mucosa (Kivistö et al. 1996; von Richter et al. 2004). Hepatic and intestinal CYP3A4 can be induced by several drugs, such as carbamazepine, phenytoin, rifampicin and St John's wort (*Hypericum Perforatum*) (Backman et al. 1996a; Backman et al. 1996b; Dürr et al. 2000; Wrighton et al. 2000a). CYP3A4 can also be inhibited by a large number of structurally unrelated drugs and grapefruit juice (Pichard et al. 1990; Back and Tjia 1991; Bailey et al. 1998).

CYP3A5 displays 84% similarity in its amino acid sequence to CYP3A4 as well as a similar substrate specificity (Wrighton and Stevens 1992; Williams et al. 2002). CYP3A5 is expressed in the gastrointestinal tract, lung, pancreas, and in about 30% of adult livers (Wrighton and Thummel 2000b), and is the most abundant CYP3A enzyme in the kidney. CYP3A7 is found abundantly in fetal liver (Hakkola et al. 1998) where it accounts for half of the total expressed CYP enzymes.

Substrates

CYP2C19*	CYP2C8/9*	CYP3A4	CYP1A2	CYP2E1	CYP2D6*
mephenytoin	warfarin	simvastatin	caffeine	ethanol	metoprolol
diazepam	fluvastatin	lovastatin	theophylline	halothane	propafenone
omeprazole	cerivastatin	atorvastatin	clozapine	paracetamol	imipramine
lanzoprazole	phenytoin	midazolam	phenacetin		codeine
clomipramine	tolbutamide	triazolam			dextrometorphan
	losartan	cyclosporine			debrisoquine
	diclofenac	buspirone			



Inhibitors

CYP2C19*	CYP2C8/9*	CYP3A4	CYP1A2	CYP2E1	CYP2D6*
fluvoxamine	fluconazole	ketoconazole	furafylline	disulfiram	quinidine
fluoxetine	sulphaphenazole	itraconazole	fluvoxamine	methoxypsoralen	fluoxetine
		verapamil			paroxetine
		diltiazem			
		erythromycin			
		gestodene			

Inducers

CYP2C19*	CYP2C8/9*	CYP3A4	CYP1A2	CYP2E1	CYP2D6*
fenobarbital	fenobarbital	rifampicin	cigarette smoke	ethanol	
rifampicin	rifampicin	phenytoin	omeprazole	isoniazid	
		carbamazepine	rifampicin		

Figure 2. Schematic representation of human hepatic drug-metabolising CYP enzymes and their selected substrates, inhibitors and inducers. *) These enzymes exhibit significant polymorphism. Adapted from (Pelkonen et al. 1998) and (Bertz and Granneman 1997).

1.4 Induction and inhibition

Conversion of drugs to more easily excreted substances by oxidative and conjugating enzymes is a defence mechanism against chemicals to which our bodies are exposed. An integral part of the metabolic defence is the adaptive increase in gene expression of drug-metabolising enzymes and drug transporters during drug exposure. We call this phenomenon 'induction' (Honkakoski et al. 2003). Inhibition of drug metabolism takes place, when two substances compete for, or bind to the same metabolising enzyme.

The clinical effects of inhibition and induction are mostly deleterious. Induction of drug-metabolising enzymes can lead to an accelerated elimination of the substrate drug, changes in the metabolism of endogenous substrates (Wyde et al. 2003), and possibly the production of toxic metabolites (Zhao and Slattery 2002). Inhibition of drug-metabolising enzymes can lead to increased plasma levels, and consequently increased toxicity, of substrate drugs (Monahan et al. 1990). Occasionally, inhibition and induction of drug metabolism can also prove useful. Concomitant use of ketoconazole with cyclosporine would allow a 70% to 89% reduction in cyclosporine doses for transplant patients, resulting in cost savings (Jones 1997; Martin et al. 1999). Induction may facilitate the excretion of harmful substances from the body.

1.4.1 Mechanisms of induction of CYP enzymes

Compelling evidence suggests that induction of drug metabolism is regulated mainly by drug-activated nuclear receptors constitutive androstane receptor (CAR) and pregnane X receptor (PXR) (Honkakoski et al. 2003) (Table 1). These nuclear receptors mediate the induction of mRNA of CYP families CYP2 and CYP3 respectively, and the wide ligand specificities and overlapping DNA-binding preferences of CAR and PXR lead to complex cross-regulation of drug-metabolising enzymes (Pascussi et al. 2003).

Also, other known nuclear receptors play a role in liver CYP450 expression: peroxisome proliferator-activated receptors (PPAR), liver X receptor (LXR) and farnesoid X receptor (FXR) (Waxman 1999). These belong to the same nuclear receptor gene family (family NR1), and share a common heterodimerisation partner, retinoid X-receptor (RXR). The primary physiological role of these receptors may be to modulate hepatic CYP activity in response to endogenous dietary or hormonal stimuli. The mechanism of induction by the nuclear receptors above is essentially similar. The inducing

agent binds to CAR, PXR or PPAR, and the inducer-receptor complex forms a heterodimer with RXR, which in turn binds to a DNA response element and enhances transcription (Waxman 1999; Honkakoski et al. 2003) (Figure 3).

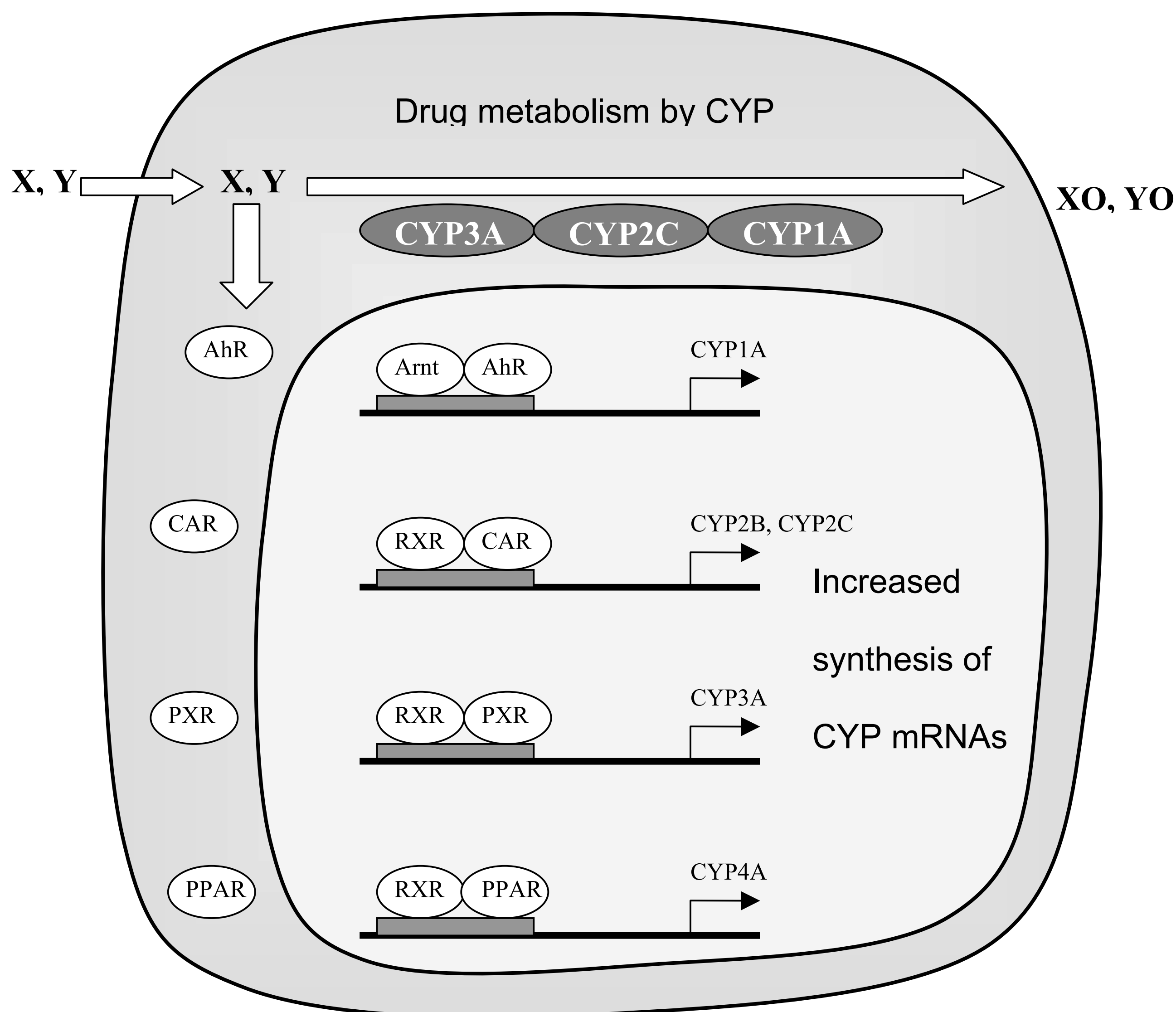


Figure 3. The intracellular mechanism of induction of CYP-enzymes.

Both CAR and PXR are abundantly expressed in the liver and intestine, with little expression in other tissues (Baes et al. 1994; Bertilsson et al. 1998; Kliewer et al. 1998; Wei et al. 2002). CAR and PXR seem to have flexible, overlapping binding specificity, which is suited to the recognition of numerous xenobiotics constantly entering our body. Besides overlapping binding specificities, CAR and PXR can also activate each other's target genes (Sueyoshi et al. 1999; Moore et al. 2000; Xie et al. 2000; Goodwin et al. 2002).

Apart from PXR, other receptors, such as the vitamin D receptor (VDR) and the glucocorticoid receptor (GR), have also been found to induce CYP3A4 enzyme activity, suggesting that there are multiple pathways by which this enzyme can be induced (Sonoda et al. 2003). Phase II enzymes are also induced via ligands binding to CAR and PXR as well as a host of other regulatory factors. Since phase I enzymes can generate toxic metabolic intermediates, simultaneous induction of phase I and phase II enzymes is not only an efficient way to eliminate xenobiotics, but also an essential means of avoiding production of excess harmful metabolic intermediates (Sonoda et al. 2003).

Nuclear receptors	Inducing agent	Enzyme	Affected substrates
Aryl hydrocarbon	cigarette smoke	CYP1A1	caffeine
	omeprazole	CYP1A2	teophylline
		some phase II enzymes	
CAR	barbiturates	CYP2B	buproprione
	antiepileptics	CYP2C	warfarin
	rifampicin	CYP3A	midazolam and other CYP3A4 substrates
		some phase II enzymes	
PXR	barbiturates	CYP3A	especially substrates of CYP3A4
	antiepileptics	CYP2B	
	rifampicin	CYP2C	
	dexamethasone	some phase II enzymes	
Unknown or no receptor	ethanol	CYP2E1	ethanol
	acetone		paracetamol
	isoniazide		halogenated anesthetics
PPAR	fibrates	CYP4A	

Table 1. List of inducing agents, nuclear receptors, CYP-enzymes and selected substrates.

1.4.2 Mechanisms of inhibition of CYP enzymes

Inhibiton of CYP-mediated drug metabolism mostly results in greater bioavailability or decreased elimination of drugs, resulting in increased effects of the substrate drug. Sometimes, however, the opposite may occur. If a drug is administered as an inactive prodrug, then the inhibition of the enzyme generating the active metabolites can lead to decreased pharmacological effects.

A period of time is needed for induction to take its full effect, whereas inhibition of CYP enzymes occurs rapidly, even after a single dose of inhibitor (Pelkonen et al. 1998).

Enzyme inhibition can be either reversible or irreversible. Reversible inhibition, which is more common, can be competitive, non-competitive or uncompetitive. In competitive inhibition, the inhibitor and the substrate compete for the same binding site, whereas in non-competitive inhibition the inhibitor and substrate bind to different sites on the enzyme. In uncompetitive inhibition, the inhibitor binds only to an enzyme that has formed a complex with the substrate (Ito et al. 1998). In irreversible inhibition, CYP enzymes oxidise the inhibitor to form reactive intermediates that covalently bind and irreversibly inactivate CYP. Irreversible inhibitors are often called mechanism-based inactivators or suicide substrates (Lin and Lu 1998).

1.4.3 Induction and inhibition of transporters

Although drug transporters are not directly involved in metabolism, they are critically involved in drug disposition and clearance, a notion supported by their localisation as well as their overlapping substrate specificity with phase I and II enzymes. For instance, P-gp exhibits substrate specificity which overlaps that of CYP3A enzymes (Schuetz et al. 1996; Kim et al. 1999; Lan et al. 2000). Furthermore, emerging evidence suggests that drug transport is regulated by the same nuclear receptors as the phase I and II enzymes. Several PXR activators that mediate CYP3A induction have also been shown to induce expression of *ABCB1* that encodes P-gp (Geick et al. 2001; Synold et al. 2001).

PXR activators also induce MRP2 (Dussault et al. 2001; Kast et al. 2002; Kauffmann et al. 2002) and Oatp2 (Dussault et al. 2001; Staudinger et al. 2001; Kast et al. 2002; Kauffmann et al. 2002; Guo et al. 2002a; Guo et al. 2002b). CAR and FXR also regulate MRP2 (Kast et al. 2002). This means that a single substrate, such as bile acids, may simultaneously induce phase I and II enzymes and drug transporters, all contributing to the efficient removal of the substrate (Sonoda et al. 2003).

The pathophysiological status of patients also seems to affect the activity of P-gp. Several studies indicate higher levels of *ABCB1* mRNA (producing P-gp) in atherosclerotic sections of arteries than in non-atherosclerotic arteries (Batetta et al. 1999; Batetta et al. 2001; Petruzzo et al. 2001). Expression of genes encoding P-gp is also higher in rats after limbic seizures (Volk et al. 2004), and P-gp protein is

upregulated in surgically resected human brain tissue containing epileptogenic pathologies (Sisodiya and Thom 2003).

Inhibition of the numerous transporters present in the kidney may reduce the renal excretion of the transporter substrates, whereas inhibition of intestinal transporters may increase the systemic availability of the substrate. However, very few examples of clinical interactions involving inhibition of drug transporters at the brain-blood barrier exist, possibly because of low systemic exposure at therapeutic drug levels (Ayrton and Morgan 2001). Inhibition of drug transport might prove beneficial in cancer chemotherapy, where selective P-gp-inhibitors are developed to counteract the increased expression of P-gp in some forms of cancer (Sikic et al. 1997).

2. HMG-CoA reductase inhibitors

Prevention and drug treatment of coronary disease partially relies on the lipid hypothesis, which proposes that elevated LDL cholesterol is causally related to coronary disease and that reducing it will reduce the risk of myocardial infarction and other coronary events. In the 1970s, Japanese microbiologist Akira Endo identified the first 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, compactin, in a fermentation broth of *Penicillum citrinum* (Endo et al. 1976; Tobert 2003). In 2003, with an estimated 120 million people suitable for therapy, statins were the first-choice drugs in the treatment of coronary heart disease, the leading cause of death in most of the Western world (Downton and Clark 2003).

Since 1987, when lovastatin became available for prescription as the first in its class (Tobert 2003), statins have become the most commonly used class of cardiovascular drugs (Downton and Clark 2003). In 1988, simvastatin was approved for marketing, followed by pravastatin in 1991, fluvastatin in 1994, atorvastatin in 1997, cerivastatin in 1998, and finally rosuvastatin in 2003 (Tobert 2003).

2.1. Pharmacodynamics and clinical use

Most mammalian cells can produce cholesterol. The majority of endogenous cholesterol is synthesised from dietary acetate by a complex process involving more than 30 enzymes (Figure 5). HMG-CoA reductase A is a rate-limiting enzyme subject to feedback suppression by the end-product cholesterol, catalysing the formation of mevalonate (Goldstein and Brown 1990).

All statins are competitive inhibitors of HMG-CoA reductase. In this way, statins reduce the synthesis of cholesterol in the hepatocyte (Tikkanen 1995). The number of hepatic LDL-receptors increase in response to reduced intracellular cholesterol levels. This in turn enhances the uptake of LDL-particles from the blood to the liver. The result is a reduction in plasma levels of LDL-cholesterol.

Administration of statins causes maximal reductions in LDL-cholesterol after two to three weeks of drug therapy. The reduction is sustained in most patients, but there may be a small increase in LDL-cholesterol in some patients during prolonged use of statins (Tikkanen 1996). The statins are generally administered with the evening meal or at bedtime. Somewhat greater LDL-cholesterol reductions occur when administered at night than in the morning (Wallace et al. 2003), because the rate of hepatic cholesterol synthesis is greatest at night (Miettinen 1980). Atorvastatin and its metabolites have long half-lives and therefore morning administration is equally effective (Table 4).

Results from clinical trials involving more than 50 000 individuals at risk of atherosclerotic diseases demonstrate that the reductions in LDL-cholesterol also translate into reductions in coronary heart disease and all-cause mortality, and no serious morbidity or increase in mortality are observed in the drug treatment groups (Singh and Mehta 2002). For instance, the Heart Protection study found that simvastatin 40 mg daily reduces the risk of major coronary events and all-cause mortality in high risk patients, irrespective of their initial cholesterol concentrations (HPS-Collaborative-Group 2002).

Besides lowering blood cholesterol, statins lower levels of C-reactive protein (CRP) and reduce susceptibilty to the oxidation of lipoproteins and the aggregation of blood platelets *in vitro* (Balk et al. 2003). Observational studies have suggested lower rates of fractures with statins, higher rates of obstructive airway disease at low cholesterol levels, lower rates of cataracts, and lower rates of dementia with both interventions – but these observations have yet to be confirmed by randomised trials (Yusuf 2002).

2.2. Pharmacokinetics

2.2.1. Lovastatin

Lovastatin is administered as an inactive lactone prodrug, and about 30% of the administered dose is absorbed in the intestine (Duggan et al. 1989). Ingestion with food increases the absorption of lovastatin (Garnett 1995). No data exist on the hepatic extraction ratio of lovastatin in humans, but in dogs the extraction ratio following intraportal and intravenous administration ranged from 62% to 70% (Lennernäs and Fager 1997; Hamelin and Turgeon 1998). Systemic bioavailability after absorption and first-pass metabolism is only about 5% of the ingested dose. Studies carried out in humans indicate that around 80% of an orally administered dose is eliminated in faeces, including both unabsorbed and excreted lovastatin, and 10% is eliminated in the urine (Henwood and Heel 1988). The lipophilic character of lovastatin and lovastatin acid enables them to cross cell membranes by diffusion (Hamelin and Turgeon 1998). Lovastatin is also a substrate of P-gp (Kim et al. 1999) and OATP-C (Hsiang et al. 1999).

The metabolism of lovastatin is extensive and complex (Vyas et al. 1990). The primary metabolites are formed by oxidation of the lactone, which is mediated by the CYP3A family (Desager and Horsmans 1996). The major active metabolites of lovastatin are pharmacologically active and exhibit 20% to 60% of the HMG-CoA reductase inhibitory activity of lovastatin acid (Duggan and Vickers 1990).

2.2.2. Simvastatin

The pharmacokinetics of simvastatin greatly resemble those of lovastatin (Desager and Horsmans 1996). Like lovastatin, simvastatin is also administered as an inactive lactone, and about 60% to 85% of an oral dose is absorbed from the gastrointestinal tract. The hepatic extraction ratio in dogs is around 90% for simvastatin and 80% for simvastatin acid (Vickers et al. 1990a). The absolute bioavailability of simvastatin hydroxyacid is about 5% (Todd and Goa 1990). The statin lactones are hydrolysed to their open acids chemically or enzymatically by esterases or recently identified paraoxonases (Vickers et al. 1990a; Billecke et al. 2000).

Simvastatin undergoes extensive metabolism, resulting in more than 10 metabolites (Vickers et al. 1990a; Vickers et al. 1990b). Little or no unchanged simvastatin and simvastatin acid was found in bile

(Cheng et al. 1994). Simvastatin is a substrate of OATP-C (Hsiang et al. 1999) and perhaps also of P-gp (Kim et al. 1999).

CYP3A is the major enzyme subfamily responsible for the metabolism of simvastatin by human liver microsomes, and both CYP3A4 and CYP3A5 were capable of catalysing the formation of 3'-hydroxy, 6'-exomethylene, and 3',5'-dihydrodiol metabolites (Prueksaritanont et al. 1997). Simvastatin acid undergoes oxidative metabolism to form three major oxidative products: 3',5'-dihydrodiol, 3'-hydroxy and 6'-exomethylene metabolites. The metabolism of simvastatin acid form to these metabolites was catalysed primarily (more than 80%) by CYP3A4/5, with a minor contribution (less than 20%) from CYP2C8. CYP2D6, CYP2C19, CYP2C9, CYP2A6 and CYP1A2 were uninvolved in the hepatic metabolism of simvastatin acid (Prueksaritanont et al. 2003).

2.2.3. Pravastatin

Contrary to lovastatin and simvastatin, pravastatin in not a prodrug; rather it is administered as the sodium salt of active pravastatin acid. Following an oral dose, studies indicate that about 34% of the ingested dose is absorbed, with a mean absorption time of 2.4 hours (Singhvi et al. 1990; Quion and Jones 1994). Food reduces the oral bioavailability of pravastatin by about 35% to 40% (Pan et al. 1993). The hepatic extraction ratio is 45% to 66%, and the resulting bioavailability is about 17% (Pan 1991; Lennernäs and Fager 1997). The lower hepatic extraction ratio for pravastatin as compared to lovastatin and simvastatin may in part be due to its greater hydrophilicity. The active acid forms of lovastatin and simvastatin are around 100 times more lipophilic than pravastatin, and hydrophilic substances tend to be less effectively extracted by the hepatocyte and show less affinity for oxidative metabolising enzymes (Hamelin and Turgeon 1998). In fact, pravastatin transport into hepatocytes dependens on an active uptake mechanism. Pravastatin is a substrate of the liver-specific uptake transporter OATP-C (Nakai et al. 2001) as well as the efflux transporter MRP2 (Paulusma et al. 1997). Pravastatin is also a substrate of OATP-B (Kobayashi et al. 2003; Nozawa et al. 2004).

One of the major pharmacokinetic differences between pravastatin and most other statins is that the most important elimination pathway of pravastatin is in the unchanged form. After an intravenous dose of ^{14}C-pravastatin, 67% of the radioactivity in human urine and 66% of the radioactivity recovered from faeces was attributed to the parent drug (Everett et al. 1991). Pravastatin is transformed into two major isomeric metabolites accounting for approximately 6% to 10% of a single oral dose of the drug

(Everett et al. 1991). The α-hydroxy isomeric metabolite has an activity of 3% to 10%, and the 3α-5β,6β-trihydroxy isomeric metabolite has an activity of 0.1% of the potency of pravastatin (Pan et al. 1990). At least 15 other metabolites exist, but none of these contribute to more than 6% of total radioactivity in the urine (Pan 1991). Therefore about 75% of the area under the plasma concentration-time curve for total inhibition is due to the effects of intact pravastatin (Pan et al. 1990). Pravastatin is not significantly metabolised via CYP enzymes (Jacobsen et al. 1999a; Jacobsen et al. 1999b).

2.2.4 Cerivastatin

Before its withdrawal from the market throughout the world in August 2001, the most potent statin marketed was cerivastatin. Cerivastatin is administered as the sodium salt of active cerivastatin acid. Following an oral dose, cerivastatin is completely absorbed (98% of the ingested dose) with plasma concentration reaching a peak two to three hours after administration (Mück 2000a). The absolute bioavailability of orally administered cerivastatin is about 60% because of presystemic metabolism. Food had no significant effect on the oral bioavailability of cerivastatin (Mück et al. 2000b). Cerivastatin is highly bound to human plasma proteins with an unbound fraction of 0.5% to 0.9%.

Cerivastatin is cleared exclusively via biotransformation and subsequent biliary (70%) and renal (30%) excretion of the formed metabolites; no unchanged drug is excreted in humans (Mück 1998a). Demethylation of the benzylic methyl ether leads to the formation of the major metabolite M-1, and hydroxylation at one methyl group leads to formation of the other major metabolite, M-23 (Boberg et al. 1997). Combined hydroxylation and demethylation reactions lead to the minor metabolite M-24. The HMG-CoA reductase inhibitory activity of metabolites M-23 and M-24 is equal to that of parent cerivastatin, whereas the activity of M-1 is about 30% to 50% of the activity of cerivastatin (Bischoff et al. 1997).

Recently Wang et al. reported that CYP2C8 and CYP3A4 were equally important in the formation of metabolite M-1, whereas the formation of metabolite M-23 was predominantly mediated via CYP2C8; other P450 isoforms played a negligible role (Wang et al. 2002). Lactonisation is another metabolic pathway of cerivastatin in humans: in a study on humans, concentrations of inactive cerivastatin lactone in blood were comparable to concentrations of M-1 (Kantola et al. 1999). At least cerivastatin, simvastatin and atorvastatin are converted to the corresponding lactones via an acyl glucuronide intermediate, and studies with expressed UDP glucuronosyltransferases (UGTs) revealed that UGT1A1 and UGT1A3 were capable of forming the glucuronide conjugates and the corresponding lactones for

all three statins (Prueksaritanont et al. 2002b). Cerivastatin is a substrate of the uptake transporter OATP-C *in vitro* (Shitara et al. 2003).

2.3 Adverse effects

Most patients tolerate statins well. Around 0.5% to 2.0% of patients exhibit hepatic transaminase level elevations greater than three times the upper limit of normal, and these increase in a dose-dependent fashion (Bradford et al. 1991; Hsu et al. 1995). Although cholestasis and active liver disease are listed as contraindications of statin use, it appears that liver disease would not be exacerbated by statins (Angulo 2002).

The ability of statins to cause myopathy under some circumstances is well established (Hamilton-Craig 2001; Staffa et al. 2002; Thompson et al. 2003). A common complaint describes non-specific muscle aches or joint pains that are generally not associated with significant increases in creatine kinase (CK). The incidence of these complaints is generally reported at about 5% in placebo-controlled trials. Failure to discontinue drug therapy can lead to rhabdomyolysis, myoglobinuria, and renal failure (Pierce et al. 1990). Myositis may rarely occur with statin monotherapy, but it occurs more frequently when statins are used in combination with a variety of medications, including cyclosporine, fibrates, macrolide antibiotics, certain antifungal drugs, and niacin (Thompson et al. 2003).

Because safety data from phase three clinical trials is not directly applicable to real postmarketing drug use (Martin et al. 2004), postmarketing adverse events reports are of interest when assessing drug safety. The FDA in the USA (Staffa et al. 2002) and the Medicines Control Agency in the UK (Evans and Rees 2002) have published reviews of all reports of rhabdomyolysis associated with statin use in their adverse event reporting system and obtained the number of prescriptions dispensed since marketing of each statin began (Table 2). According to these data, fatal rhabdomyolysis was very rare (less than one death/million prescriptions). The rate of fatal rhabdomyolysis for cerivastatin was 16 to 80 times higher than that for other statins.

statin	lova	prava	simva	fluva	atorva	ceriva	total
date approved	8/31/87	10/31/91	12/23/91	12/31/93	12/17/96	6/26/1997	
USA							
fatal cases of rhabdomyolysis	19	3	14	0	6	31	73
reporting rate/million prescriptions	**0.2**	**0.04**	**0.1**	**0**	**0.04**	**3.2**	**0.2**
% statin + CYP450 inhibitor	60	37	56	0	35	21	
% statin + gemfibrozil	33	11	27	0	12	58	
UK							
fatal and nonfatal cases of rhabdomyolysis		3	38	2	13	12	68
reporting rate/million prescriptions		**0.5**	**1.7**	**0.7**	**1.0**	**4.8**	**1.5**
WHO							
No. of reported ADR	21 541	6 208	15 149	2 061	3 188	387	
% rhabdomyolysis	0.2	0.3	0.4	0.5	0.5	2.1	

Table 2. Compiled postmarketing adverse event data on statins. Sources: **USA** reporting rates (Staffa et al. 2002), contributing factors (Chang et al. 2002). **UK** (Evans and Rees 2002). **WHO** (Hamilton-Craig 2001). Drugs classified as “CYP450 inhibitors” include “immunosuppressants, azole antifungals, fluoroquinolones, macrolides, anti-HIV drugs, antidepressants and anticonvulsants” (Chang et al. 2002). ADR is short for adverse drug reactions.

2.4. Possible mechanisms of statin-related myopathy and rhabdomyolysis

Statin-related myotoxicity is well documented, but the precise mechanisms behind the myotoxic effects of statins remain unclear (Evans and Rees 2002; Pasternak et al. 2002; Thompson et al. 2003). A variety of hypotheses have been put forth, but no clear consensus exists on which is the most likely mechanism.

HMG-CoA reductase catalyses the formation of mevalonate from HMG-CoA (Figure 5). Mevalonate is not only a precursor of cholesterol but also of ubiquinone (co-enzyme Q10), dolichol and isopentenyl adenine. A deficiency in these may affect myocyte duplication and cause disruption of the myocyte cell membrane (Gebhard et al. 1991). Despite some *in vitro* support for this hypothesis (Flint et al. 1997), studies on the effects of treatment with 20 mg simvastatin for four to six weeks demonstrate that simvastatin failed to reduce ubiquinone in the muscle in non-symptomatic hypercholesterolemic patients (Laaksonen et al. 1995; Laaksonen et al. 1996).

Membrane lipids are in dynamic equilibrium with plasma lipids, and low plasma cholesterol concentrations and decreased intracellular cholesterol may result in reduced membrane lipid content.

That in turn may affect the fluidity of the cell membrane and decrease cell proliferation (Levy et al. 1992; Lijnen et al. 1994; Morita et al. 1997).

Atorvastastin, lovastatin, and simvastatin also produce dose-dependent increases in apoptosis in vascular smooth muscle cells, possibly useful in preventing neointimal thickening, but simultaneously a possible factor in muscle adverse events of statins (Guijarro et al. 1998).

The rate of myotoxicity for different statins may vary (Table 2), possibly due to the lipophility of the statins (McTavish and Sorkin 1991; Negre-Aminou et al. 1997; Farmer 2001; White 2002; Thompson et al. 2003). Lipophilic statins may be more myotoxic because of possible enhanced penetration of the myocyte. For instance, the highly lipophilic statin cerivastatin (Table 4) (McTaggart et al. 2001) is associated with most muscle adverse effects (Staffa et al. 2002). Statin-induced myotoxicity is a dose-dependent phenomenon, and the statin interaction with the CYP450 enzyme system may be related to myopathy (Bolego et al. 2002; Chang et al. 2002; Hodel 2002; Staffa et al. 2002; Andrejak et al. 2003; Ballantyne et al. 2003).

2.5. Interactions of statins with drugs and other factors

Lovastatin

Extensive first-pass metabolism and subsequent low bioavailability renders lovastatin prone to drug-interactions, especially with CYP3A4-inhibiting drugs. The effects of itraconazole - a potent inhibitor of CYP3A4 and P-gp - have been studied on all currently available statins. Itraconazole increased the AUC of lovastatin more than 20-fold and the AUC of lovastatin acid increased 20-fold (Neuvonen and Jalava 1996). A pretreatment with oral diltiazem 120 mg twice daily increased the AUC of lovastatin about four-fold (Azie et al. 1998), but a constant intravenous infusion of diltiazem did not significantly affect the pharmacokinetics of lovastatin (Masica et al. 2000), suggesting that the interaction is primarily due to a first-pass effect. Grapefruit juice increased the AUC of lovastatin acid about five-fold, as compared to the control phase (Kantola et al. 1998b). Downregulation of CYP3A4 may mediate the mechanism of the grapefruit juice-lovastatin interaction (Lown et al. 1997).

The effects of cyclosporine have also been studied on all currently available statins (Table 3). Cyclosporine is an inhibitor of several drug transporters including P-gp (Tamai and Safa 1990) and

OATP-C (Shitara et al. 2003). In one study with stable kidney graft patients, the lovastatin AUC values were 20-fold higher than values reported without cyclosporine (Olbricht et al. 1997), whereas lovastatin AUC values increased about five-fold in 16 patients receiving cyclosporine for different purposes, compared to 13 control patients (Gullestad et al. 1999). The mechanism of the cyclosporine-lovastatin interaction may be related to inhibition of hepatic uptake of lovastatin by OATP-C (Hsiang et al. 1999; Shitara et al. 2003), inhibition of P-gp-mediated efflux transport of lovastatin (Tamai and Safa 1990; Kim et al. 1999) or inhibition of CYP3A4-mediated metabolism of lovastatin by cyclosporine (Pichard et al. 1990; Campana et al. 1996).

Simvastatin

Itraconazole increases the AUC of simvastatin and simvastatin acid more than 10-fold and 19-fold, respectively (Neuvonen et al. 1998). The AUC of simvastatin acid increased 6-fold due to administration of cyclosporine to 20 heart transplant patients (Campana et al. 1995). Erythromycin increased the mean AUC of simvastatin acid 3.9-fold and verapamil 2.8-fold over control-phase values (Kantola et al. 1998a). Erythromycin and verapamil both inhibit CYP3A4 and verapamil is also an inhibitor of P-gp. Telithromycin, a derivative of erythromycin, increases the AUC of simvastatin 9-fold (Zhanel et al. 2002).

In a study on hypertensive patients, the cholesterol reduction for the patients using both diltiazem and simvastatin was 33% compared to 25% in the group of patients recieving simvastatin but not diltiazem (Yeo et al. 1999). The improved cholesterol-lowering response may be of pharmacokinetic origin, because diltiazem 120 mg twice daily increased the AUC of simvastatin five-fold in healthy volunteers (Mousa et al. 2000). Diltiazem is an inhibitor of CYP3A4 (Renton 1985; Ahonen et al. 1996; Varhe et al. 1996).

Dyslipidemia is one of the side effects of HIV protease inhibitors, but unfortunately protease inhibitors are prone to affect the pharmacokinetics of statins. For instance, in an open-label sequential study in which 32 healthy volunteers received first simvastatin (or atorvastatin) and then simvastatin (or atorvastastin) with nelfinavir for 14 days, nelfinavir increased the AUC of simvastatin five-fold, whereas the AUC of atorvastatin increased 74% (Hsyu et al. 2001). This combination proved fatal for a patient on nelfinavir who developed rhabdomyolysis three weeks after switching from pravastatin 40 mg daily to simvastatin 80 mg daily (Hare et al. 2002).

In a recent study, 600 mg daily of CYP3A4-inducer carbamazepine for two weeks decreased the AUC of simvastatin and simvastatin acid by 75% and 82%, respectively (Ucar et al. 2004). A two-week pretreatment with St John's wort decreased the AUC of simvastatin and simvastatin acid by 34% and 52%, respectively (Sugimoto et al. 2001). The herbal product St John's wort is an inducer of CYP3A4 as well as of P-gp.

Not all possible drug-drug interactions can be tested in controlled trials, and often case-reports can provide an indication of when care should be taken in concomitant administration. Case reports describing rhabdomyolysis in patients taking the antidepressant nefazodone, an inhibitor of CYP3A4 (DeVane et al. 2004), with simvastatin (Skrabal et al. 2003), and the antimicrobal drug fusidic acid with simvastatin (Yuen and McGarity 2003) suggest that these drugs may potentiate the effects of simvastatin.

Statin	Peroral pretreatment	Population	Change in AUC relative to placebo	Design	References
lovastatin acid	itraconazole 200 mg daily for 4 days	12 healthy volunteers	> 20x	double-blind, randomised 2-phase cross-over	(Neuvonen and Jalava 1996)
	diltiazem 120 mg daily for 14 days	10 healthy volunteers	4x (parent lova)	open, randomised, 4-phase cross-over	(Azie et al. 1998)
	grapefruit juice 200 ml x 3 daily for 2 days	10 healthy volunteers	5x	open, randomised, 2-phase cross-over	(Kantola et al. 1998b)
	cyclosporine	44 kidney graft patients	5x (parent lova)	double-blind, randomised, parallel-group multicenter	(Olbricht et al. 1997)
	cyclosporine	16 patients	20x (parent lova)	open, comparison to historical controls	(Gullestad et al. 1999)
simvastatin acid	itraconazole 200 mg daily for 4 days	10 healthy volunteers	19x	double-blind, randomised 2-phase cross-over	(Neuvonen et al. 1998)
	cyclosporine	20 heart transplant patients	6x	open, comparison to non-transplant patients	(Campana et al. 1995)
	cyclosporine	5 kidney transplant patients	3x	open, non-randomised	(Arnadottir et al. 1993)
	erythromycin 1.5 mg daily for 14 days	12 healthy volunteers	3.9x	double-blind, randomised 3-phase	(Kantola et al. 1998a)
	verapamil 240 mg daily for 14 days	12 healthy volunteers	2.8x	double-blind, randomised 3-phase	(Kantola et al. 1998a)
	orlistat 120 mg x 3 daily for 5-13 days	29 healthy volunteers	no effect	double-blind, randomised 2-phase crossover	(Zhi et al. 2003)
	imatinib 400 mg daily for 7 days	20 patients with leukemia	3.5x	open, non-randomised	(O'Brien et al. 2003)
	nelfinavir for 14 days	32 healthy volunteers	5x	open, sequential	(Hsyu et al. 2001)

	ritonavir and saquinavir	HIV-sero-negative volunteers	31x	open, randomised	(Fichtenbaum and Gerber 2002)
	telithromycin		9x (parent simva)	unspecified	(Zhanel et al. 2002)
	carbamazepine 600 mg daily for 14 days	12 healthy volunteers	0.18x	randomised, 2-phase crossover study	(Ucar et al. 2004)
	St-John's wort preparation 300 mg 3x daily for 14 days	16 healthy volunteers	0.48x	double-blind, randomised, cross-over study	(Sugimoto et al. 2001)
pravastatin	itraconazole 200 mg daily for 4 days	10 healthy volunteers	1.7x	double-blind, randomised 2-phase	(Neuvonen et al. 1998)
	cyclosporine	44 kidney graft patients	5x	double-blind, randomised, parallel-group multicenter	(Olbricht et al. 1997)
	cyclosporine	11 heart transplant patients	12x	open, comparison to non-transplant patients	(Park et al. 2002)
	digoxin 0.2 mg daily for 9 days	18 healthy volunteers	1.23x	open, cross-over trial	(Triscari et al. 1993)
	ritonavir and saquinavir	HIV-sero-negative volunteers	0.5x	open, randomised	(Fichtenbaum and Gerber 2002)
	fluconazole 400 mg on day 1 and 200 mg on days 2-4	12 healthy volunteers	no effect	double-blind, randomised 2-phase	(Kantola et al. 2000)
	diltiazem 120 mg daily for 14 days	10 healthy volunteers	no effect	open, randomised, 4-phase crossover	(Azie et al. 1998)
	St-John's wort preparation 300 mg 3x daily for 14 days	16 healthy volunteers	no effect	double-blind, randomised, cross-over study	(Sugimoto et al. 2001)
cerivastatin	itraconazole 200 mg daily for 4 days	10 healthy volunteers	1.15x	double-blind, randomised 2-phase cross-over	(Kantola et al. 1999)
	cyclosporine	12 kidney transplant patients	3.8x	open, non-randomised	(Mück et al. 1999)
	tacrolimus (individualised doses)	10 stable kidney graft patients	1.35x	open, non-randomised	(Renders et al. 2003)
	erythromycin 500 mg x 3 daily for 4 days	12 healthy volunteers	1.21x	open, randomised, cross-over	(Mück et al. 1998b)
	digoxin 0.25 mg daily for 5 days	11 healthy volunteers	no effect	open, non-randomised	(Weber et al. 1999)

Table 3. Summary of pharmacokinetic interaction studies using lovastatin, simvastatin, pravastatin or cerivastatin as a substrate.

Pravastatin

Itraconazole increased the AUC of pravastatin by 70% in a study using the same protocol as the simvastatin-itraconazole study (Neuvonen et al. 1998). Cyclosporine has been found to increase the AUC of pravastatin about 5-fold (Olbricht et al. 1997) and 12-fold (Park et al. 2002) in different patient groups. In an open cross-over trial, digoxin increased the AUC of pravastatin 23% and decreased the AUC of the α-hydroxy isomeric metabolite by 25% with no essential change in the AUC of the 3α-5β,6β-trihydroxy isomeric metabolite (Triscari et al. 1993). Both of these interactions may be the result of inhibition of pravastatin transport by cyclosporine (Chen et al. 1999; Shitara et al. 2003) and digoxin (Kodawara et al. 2002; Mikkaichi et al. 2004), respectively.

Coadministration of ritonavir and saquinavir to HIV-seronegative volunteers resulted in a 31-fold increase in simvastatin acid exposure, a three-fold increase in atorvastatin exposure but a decrease of 50% in pravastatin exposure (Fichtenbaum and Gerber 2002). A single 201 mg dose of fenofibrate did not significantly affect the plasma concentration of pravastatin (Pan et al. 2000). A 300 mg preparation of St John's wort three times daily for 14 days did not significantly affect the plasma concentration of pravastatin (Sugimoto et al. 2001).

Cerivastatin

A four-day pretreatment with itraconazole 200 mg daily increased the AUC of cerivastatin by 15%, whereas the AUC of cerivastatin lactone increased by 160%, the AUC of the M-1 metabolite decreased by 28% and the AUC of the M-23 metabolite increased by 36% (Kantola et al. 1999). Pretreatment with erythromycin 500 mg three times daily increased cerivastatin AUC by 21% (Mück et al. 1998b). Digoxin (0.25 mg daily for 5 days) did not affect the pharmacokinetics of cerivastatin, nor did cerivastatin (0.2 mg daily for 14 days) affect the pharmacokinetics of digoxin (Weber et al. 1999).

As compared to 12 healthy controls in an open, nonrandomised study, cyclosporine increased the AUC of cerivastatin 4-fold in 12 kidney transplant patients. The AUC of metabolites M-1 and M-23 increased 4.6- and 3.9-fold, respectively (Mück et al. 1999). Based on *in vitro* studies, Shitara and colleagues have suggested that the mechanism behind this interaction is inhibition of OATP-C by cyclosporine (Shitara et al. 2003).

Statin	lovastatin	simvastatin	atorvastatin	cerivastatin	pravastatin	fluvastatin	rosuvastatin
absorption (%)	31	60 to 85	30	> 98	35	> 90	~50
t_{max} (h)	2.8	1.3 to 2.4	2 to 4	2.5 to 3.0	0.9 to 1.6	0.5 to 1.5	3
hepatic extraction (% of abs. dose)	62 to 69	78 to 87	> 70	N.A	45 to 66	68	63 to 90
bioavailability (%)	< 5	< 5	12	60	18	10-35	20
lipophilicity	+++++	+++++	++++	++++++	+	++++	++
protein binding (%)	> 95	> 95	> 95	> 99	48 to 50	> 95	88 to 90
elimination half-life (h)	2.5 to 15	1.9 to 15.6	14	1.7 to 2.7	1.3 to 2.6	0.5 to 3.1	20
transporters (substrate)	OATP-C, P-gp	OATP-C, P-gp?	OATP-C, P-gp	OATP-C	OATP-B, OATP-C, MRP2		OATP-C
major metabolic enzymes	CYP3A4, CYP2C8?	CYP3A4, CYP2C8	CYP3A4	CYP2C8, CYP2A4		CYP2C9	CYP2C9
active metabolites	yes	yes	yes	yes	mainly inactive	mainly inactive	mainly inactive
equipotent dosage (mg)	40	20	10	0.4	40	40	N.A
max FDA approved dose (mg)	80	80	80	0.4 to 0.8	80	80	40

Table 4. Summary of the pharmacokinetic variables of statins. Mainly from (Igel et al. 2002; White 2002), for other references see text.

3. Fibrates

Gemfibrozil, bezafibrate and fenofibrate, and clofibrate and ciprofibrate belong to the fibrate class. The first three of these five are currently on the market in Finland. Fibrates are primarily used in the treatment of hypertriglyceridemia and as second-line agents in patients intolerant of statins, and contraindications include severe hepatic or renal insufficiency (ATPIII 2001).

3.1. Pharmacodynamics and clinical use

The mechanism of action of fibrates is complex. Recent studies indicate that fibrates are agonists for the nuclear transcription factor named peroxisome proliferator-activated receptor-alpha (PPAR-alpha) (Schoonjans et al. 1996) (Figure 4). After heterodimerisation with the Retinoid X Receptor, PPAR-alpha affects the expression of numerous genes important in lipid regulation (Staels et al. 1998; Bishop-Bailey 2000). Fibrates reduce triglycerides by increasing fatty acid oxidation and upregulating genes for

lipoprotein lipase as well as downregulating the apolipoprotein C-III gene (Staels et al. 1995; Vu-Dac et al. 1995; Fruchart et al. 1998).

Fibrates reduce triglycerides by about 25% to 50%, LDL-cholesterol levels in patients with combined hyperlipidemia decrease only slightly (Leaf et al. 1989; Pauciullo et al. 1990). Fibrates usually raise HDL-cholesterol levels by 10% to 15%, and somewhat more in severely hypertriglyceridemic patients. Because fibrates lower triglyceride levels, fibrate therapy is also used to reduce the risk for acute pancreatitis in patients with elevated triglyceride levels (Leaf et al. 1989).

Therapy with gemfibrozil reduced the risk for fatal and non-fatal myocardial infarction in a large primary prevention trial (Frick et al. 1987), and gemfibrozil therapy reduced the risk for fatal and non-fatal myocardial infarction and stroke in a secondary prevention trial (Rubins et al. 1999). This beneficial effect on cardiovascular outcomes has not been observed in all large fibrate trials (Coronary-Drug-Project-Research-Group 1975; Bezafibrate-Infarction-Prevention-Study-Group 2000), and fibrates do not significantly seem to reduce all-cause mortality. In fact in a study with clofibrate, total mortality increased, while the incidence of fatal heart attacks in the clofibrate and control groups was similar (Committee-of-Principal-Investigators 1978). Also, in a follow-up to the Helsinki Heart Study, non-cardiac death and all-cause mortality were higher in the group that had received gemfibrozil, but this increase was statistically insignificant (Huttunen et al. 1994). The increase in mortality with clofibrate was mainly related to diseases of the liver, biliary tract, and intestine (Committee-of-Principal-Investigators 1978), and to a higher cancer mortality in the gemfibrozil group in the Helsinki Heart Study follow-up (Huttunen et al. 1994).

Fibrate	gemfibrozil	bezafibrate	fenofibrate	clofibrate	ciprofibrate
absorption (%)	100	100		100	
t_{max} (h)	1-2	2	4-6	3	
protein binding (%)	98%	95%	>99%	96%	99%
bioavailability (%)	100	100	60	100	
volume of distribution		0.29 l/kg	0.89 l/kg	0.24 l/kg	
elimination half-life (h)	1.5	1.5-3	19-27	15	81
usual daily dosage (mg)	1200	400	200	1000	100

Table 5. Pharmacokinetic properties of fibrates. Mainly from (Abshagen et al. 1980; Monk and Todd 1987; Todd and Ward 1988; Goa et al. 1996).

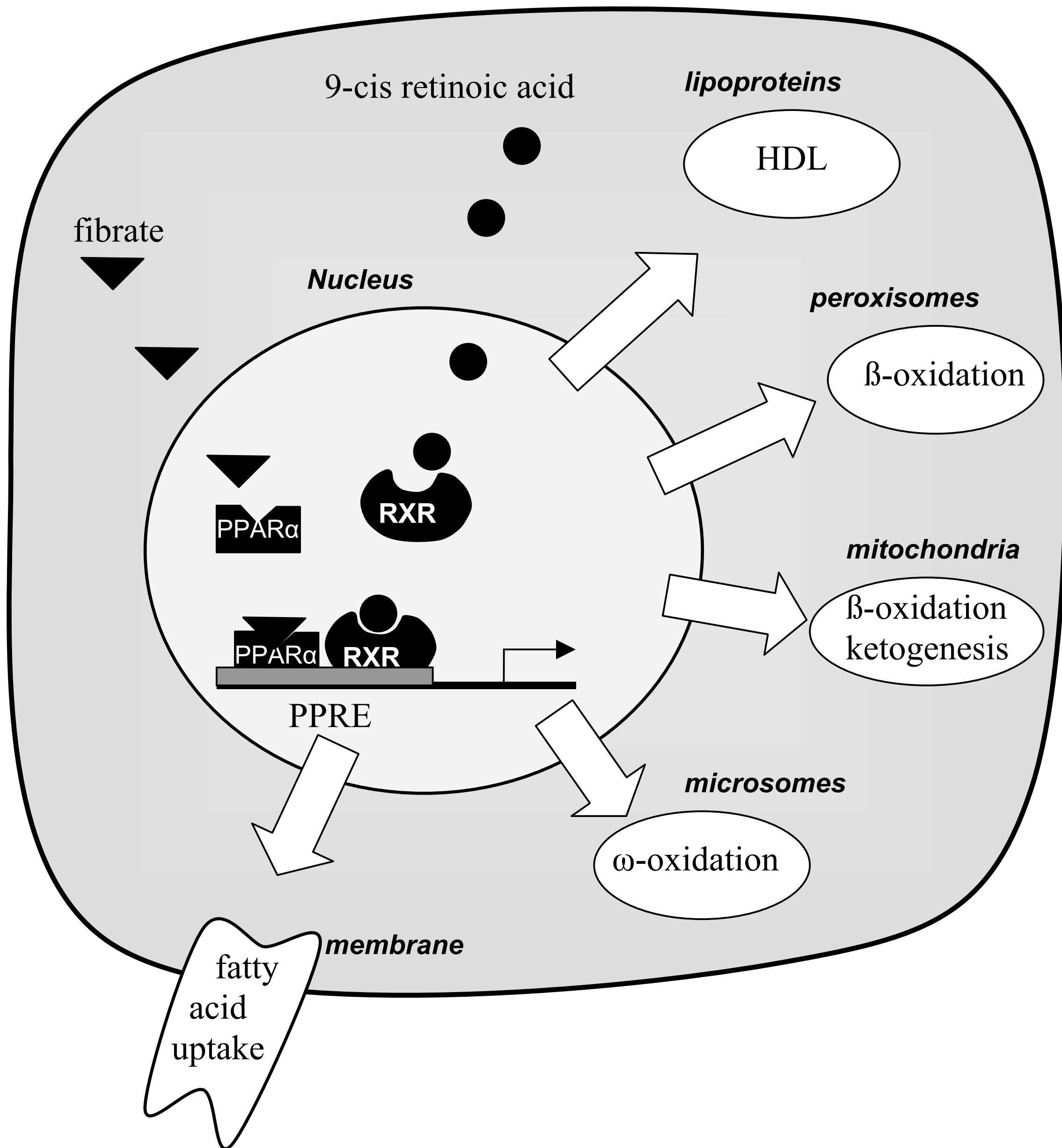


Figure 4. Fibrates act by forming a ligand with PPAR-alpha. PPAR-alpha in turn forms a heterodimer with RXR and binds to the peroxisome proliferator response element (PPRE) that enhances the gene expression of apolipoproteins A-I and A-II, lipoprotein lipase, SR-BI and ABC-1 genes.

3.2. Pharmacokinetics

3.2.1. Gemfibrozil

Gemfibrozil is almost completely absorbed after oral administration (Table 5). C_{max}-values are attained in one to two hours following intake of a 600 mg gemfibrozil immediate release tablet. Plasma drug concentrations are directly proportional to dose. Gemfibrozil is highly bound to plasma proteins (about 98%). Most studies indicate that the elimination half-life of gemfibrozil is 1.5 hours (Knauf et al. 1990). The principal metabolite of gemfibrozil is a benzoic acid derivative (metabolite III) and is the only metabolite excreted in unconjugated form. All metabolites of gemfibrozil form glucuronide conjugates. The majority (66%) of gemfibrozil is excreted into urine, most within 48 hours (Todd and Ward 1988). About half of the radioactivity in urine following a radiolabelled gemfibrozil dose represented unchanged gemfibrozil, and 20% of the radioactivity represented metabolite III (Todd and Ward 1988).

3.2.2. Bezafibrate

Bezafibrate is chemically related to clofibrate. Bezafibrate is almost completely absorbed after oral administration. C_{max}-values are attained within about two hours following a 300 mg dose in healthy volunteers (Monk and Todd 1987). Bezafibrate is highly protein-bound (about 95%) and the volume of distribution is 0.29 l/kg (Abshagen et al. 1980). Renal excretion in its unchanged form is the main route of elimination of bezafibrate (Goa et al. 1996). After a 300 mg dose, 94% of the drug was recovered in the urine within 24 hours (43% to 52% unchanged drug), and 1.7% in faeces. The elimination half-life of bezafibrate is 1.5 to 2 hours, but extends to about 9 hours in patients with renal insufficiency. The AUC_{0-10} of bezafibrate after ingestion of a single bezafibrate 300 mg tablet in healthy volunteers is 37 mg/l·h (Monk and Todd 1987). Bezafibrate potentiates the effects of warfarin and other anticoagulants, and the doses of warfarin may need to be reduced (Monk and Todd 1987; Goa et al. 1996). Hypoglycemia has sometimes been described in patients taking both sulfonylureas and fibrates concurrently (Girardin et al. 1992).

3.3. Adverse effects and drug interactions

Fibrates are generally well tolerated, and only mild adverse effects are observed in 5% to 10% of patients. Gastrointestinal complaints are the most common, including abdominal pain, diarrhoea, nausea, flatulence and vomiting. Fibrates can also lead to an increased incidence of cholesterol

gallstones as well as occasionally increased transaminase levels (Todd and Ward 1988). According to the Helsinki Heart Study, the occurence of gemfibrozil adverse effects diminishes with time (Frick et al. 1987). A very rare side-effect is myopathy, but it mostly occurs when fibrates are used concomitantly with statins (Miller and Spence 1998; Hodel 2002). Although a tendency for some fibrates showed towards an increase in non-cardiac deaths in some large randomised trials, no evidence of specific toxicity that enhances mortality has emerged (ATPIII 2001).

At the time of planning of this study, few pharmacokinetic studies with gemfibrozil had been carried out, and Todd and Ward concluded that "the only significant drug interaction seen so far is an enhancement of the effect of anticoagulants", such as warfarin (Todd and Ward 1988). The mechanism of the interaction may involve alteration in the synthesis of clotting factors or changes in the disposition of vitamin K by gemfibrozil (Lozada and Dujovne 1994). In 1991, Ahmad reported on an interaction between gemfibrozil and glyburide resulting in hypoglycemia (Ahmad 1991). Studies carried out after Study I indicate that gemfibrozil increases the AUC of repaglinide and rosiglitazone 8-fold and 2-fold, respectively (Niemi et al. 2003a; Niemi et al. 2003b).

3. Combination treatment with HMG-CoA reductase inhibitors and fibrates

Numerous lipid researchers have put forth the combination of a statin and a fibrate as an option in the treatment of patients with both high cholesterol and triglyceride levels (Goa et al. 1996; Shek and Ferrill 2001; McKenney 2002; Wierzbicki et al. 2003). After initial reports of an increased risk for myopathy using lovastatin and gemfibrozil, the use of this combination declined considerably. More recently, it has been used increasingly with apparent safety in the majority of patients (ATPIII 2001). The ATPIII report now presents this combination is as an option, with careful monitoring, for some forms of dyslipidemia (ATPIII 2001).

Fibrates and statins have complementary effects on blood lipid levels, as fibrates primarily lower plasma triglycerides and increase HDL-cholesterol, while statins primarily lower plasma LDL-cholesterol. But there is also a molecular rationale for the use of the statin-fibrate combination (Farnier 2003), because statins and fibrates synergistically activate PPAR-alpha via different molecular mechanisms (Martin et al. 2001) (Figure 5).

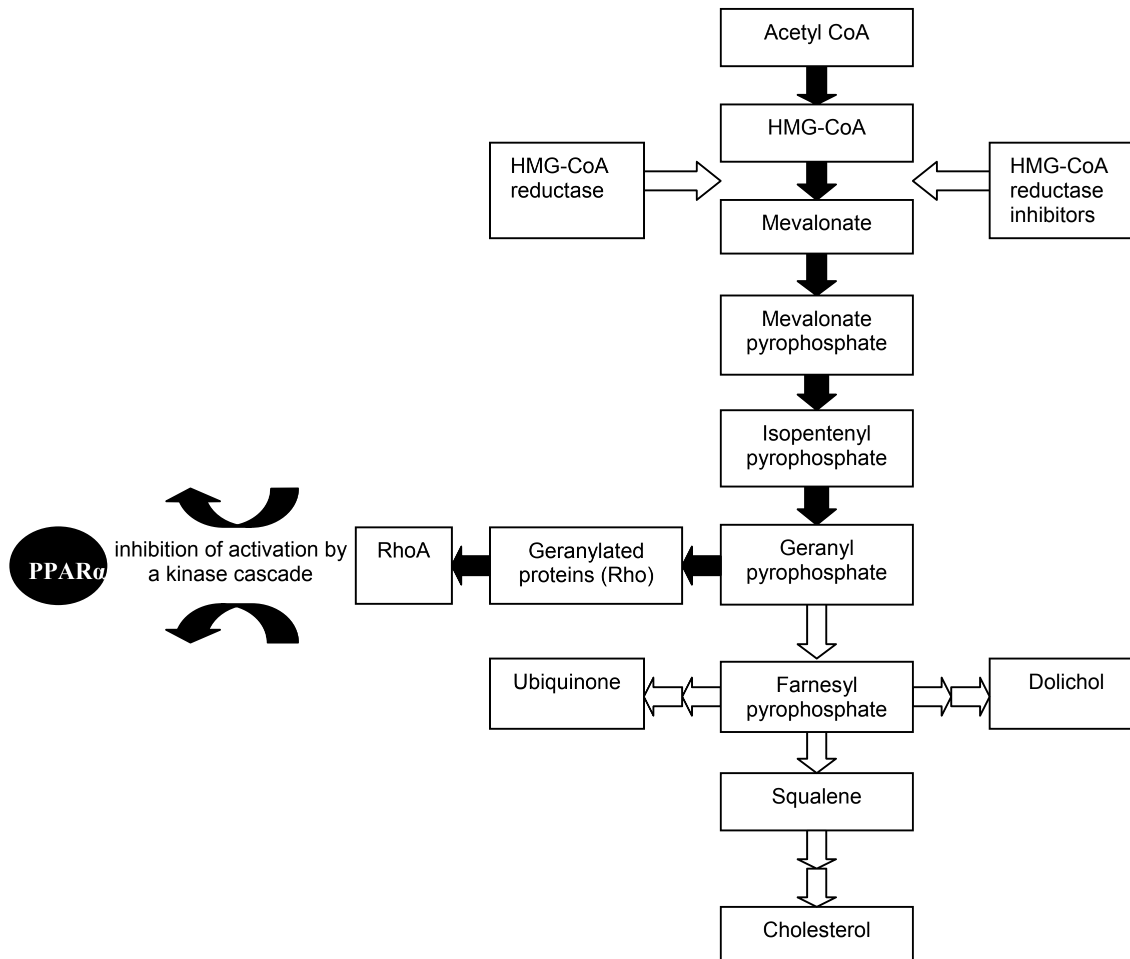


Figure 5. Cross-talk between statin and PPAR-alpha pathways. Rho-proteins repress activation of PPAR-alpha, and statins inhibit the formation of Rho-proteins, leading to the activation of PPAR-alpha. Statins are not direct ligands of PPAR-alpha as are fibrates, and therefore statins and fibrates synergistically activate PPAR-alpha. Freely adapted from Martin et al. 2001 and Goldstein and Brown 1990.

No large-scale randomised trials using hard endpoints have been published, although one such study, due to report in 2008, will investigate the effects of the combined use of simvastatin and fenofibrate (Wierzbicki et al. 2003). However, the pooled data from tens of smaller studies, mainly carried out in patients with combined hyperlipidemia, indicate that statin-fibrate combinations are highly effective in correcting blood lipid values and better than either agent used alone (Table 6). Studies on other risk factors such as CRP, homocysteine or other surrogate endpoints of coronary heart disease are yet to be published.

In these controlled statin-fibrate clinical trials, 0.1% have experienced a CK greater than 10 times the upper normal limit with myalgia (Shek and Ferrill 2001), and 1% have been withdrawn from therapy

because of muscle discomfort (ATPIII 2001). These values are no substantially higher than those of statin monotheraphy (Pasternak et al. 2002). No cases of rhabdomyolysis or myoglobinuria have been encountered in these clinical trials (ATPIII 2001; Shek and Ferrill 2001). However, safety data from controlled trials are not directly applicable to clinical use because of strict inclusion and exclusion criteria and rigorous follow-up (Martin et al. 2004). Although no cases of rhabdomyolysis were recorded in the trials, numerous case reports have been published on rhabdomyolysis related to concomitant use of a statin and a fibrate (Marais and Larson 1990; Pierce et al. 1990; Raimondeau et al. 1992; Knöll et al. 1993; van Puijenbroek et al. 1996; Duell et al. 1998; Oldemeyer et al. 2000; Ozdemir et al. 2000; Plotkin et al. 2000; Hendriks et al. 2001; Kind et al. 2002). Most cases of rhabdomyolysis have occured with the gemfibrozil-statin combination (Shek and Ferrill 2001), although a few cases have also occurred with the bezafibrate-statin (Plotkin et al. 2000) and fenofibrate-statin combinations (Raimondeau et al. 1992). In the USA, the use of gemfibrozil has been greater than the use of other fibrates, which may explain why many cases of rhabdomyolysis have occured with the gemfibrozil-statin combination (Shek and Ferrill 2001).

Study	Duration	Statin (mg/day)	Fibrate (mg/day)	No of patients on combination treatment	Mean change vs. baseline			
					Total C.	LDL	HDL	TG
(Leitersdorf et al. 1994)	3 months	Fluvastatin 20	Bezafibrate 400	20	-24%	-30%	+27%	-18%
(Leitersdorf et al. 1994)	3 months	Fluvastatin 40	Bezafibrate 400	20	-29%	-35%	+27%	-25%
(Pauciullo et al. 2000)	6 months	Fluvastatin 20	Bezafibrate 400	85	-20%	-23%	+21%	-36%
(Pauciullo et al. 2000)	6 months	Fluvastatin 40	Bezafibrate 400	82	-20%	-24%	+22%	-38%
(Farnier et al. 1999)	4 months	Fluvastatin 20	Fenofibrate 200	33	-27%	-32%	+14%	-39%
(Farnier et al. 1999)	4 months	Fluvastatin 40	Fenofibrate 200	31	-35%	-41%	+3%	-40%
(Esper et al. 1999)	2 months	Cerivastatin 0.3	Bezafibrate 400	116	-29%	-43%	+34%	-44%
(Farnier and Dejager 2000)	2 months	Cerivastatin 0.3	Fenofibrate 200	115	-30%	-41%	+12%	-37%
(Eliav et al. 1995)	7.5 months	Fluvastatin 80	Bezafibrate 400	22	-33%	-39%	+9%	-31%
(Papadakis et al. 1999)	2-3 months	Fluvastatin 40	Ciprofibrate 100	13	-32%	-36%	+19%	-53%
(Papadakis et al. 1999)	2-3 months	Fluvastatin 40	Bezafibrate 400	10	-21%	-26%	+19%	-46%
(Spieker et al. 2000)	1 month	Fluvastatin 20	Bezafibrate 400	71	-15%	-9%	+5%	-47%
(Ellen and McPherson 1998)	2.1 years	Pravastatin 20/ Simvastatin 10	Fenofibrate 200/ 300	63	-26%	-28%	+22%	-41%
(Athyros et al. 1997)	2.4 years	Pravastatin 20	Gemfibrozil 1200	135	-31%	-35%	+14%	-48%
(Athyros et al. 1997)	2.4 years	Simvastatin 20	Gemfibrozil 1200	130	-35%	-39%	+25%	-54%
(Athyros et al. 1997)	2.4 years	Simvastatin 20	Ciprofibrate 100	124	-38%	-42%	+17%	-57%
(Murdock et al. 1999)	2.4 years	Various statins (first gemfibrozil only)	Gemfibrozil 1200	148	-18%		+20%	-41%
(Murdock et al. 1999)	2.4 years	Various statins (first statin only)	Gemfibrozil 1200	104	-22%		+15%	-42%
(Iliadis and Rosenson 1999)	3.7 years	Pravastatin (mean) 22	Gemfibrozil (mean) 1154	26	-25%	-14%	+20%	-53%
(Zambon et al. 1999)	1 year	Lovastatin 40	Gemfibrozil 1200	25	-32%	-34%	+19%	-51%
(Kiortisis et al. 2000)	1.5 months	Atorvastatin 40	Fenofibrate 200	12	-42%	-42%	+28%	-46%
(Kehely et al. 1995)	3 months	Simvastatin 20	Bezafibrate 200	49	-28%	-31%	+19%	-45%
(Hutchesson et al. 1994)	3 months	Simvastatin 20	Bezafibrate 400	22	-20%	-35%	+18%	-31%
(Gavish et al. 2000)	1 year	Simvastatin 20	Bezafibrate 400	148	-23%	-29%	+25%	-42%
(Athyros et al. 2002)	6 months	Atorvastatin 20	Fenofibrate 200	40	-37%	-46%	+22%	-50%
(Durrington et al. 2004)	4.5 months	Rosuvastatin 5	Fenofibrate 200	60	-30%	-34%	+11%	-41%
(Durrington et al. 2004)	4.5 months	Rosuvastatin 10	Fenofibrate 200	60	-36%	-42%	+12%	-47%

Table 6. Efficacy of combination therapy with fibrates and statins on lipid parameters in clinical trials in patient groups at high risk for coronary heart disease. Freely adapted from (Farnier 2003) with some additions.

4. Rifampicin

Rifampicin, a synthetic derivative of rifamycin B, inhibits bacterial RNA polymerase by forming a stable drug-enzyme complex (Wehrli 1983). Rifampicin remains one of the most effective and broad spectrum antimicrobals. It is mainly used in the treatment of tuberculosis (Venkatesan 1992), but also in methicillin-resistant as well as methicillin-sensitive staphylococcal infections (Turnidge and Grayson 1993), and its dosage in adults is usually between 450 mg and 600 mg once daily (Douglas and McLeod 1999).

Pharmacokinetics. The bioavailability of oral rifampicin after a single dose is 93%, but after a three-week treatment, its oral availability falls to 68% (Loos et al. 1987). This probably occurs because of autoinduction of rifampicin metabolism (Venkatesan 1992). After administration of a single 600 mg dose, peak plasma serum concentration occurs in two hours, and the $t_{1/2}$ is about 2.5 hours (Acocella 1978). Rifampicin is mainly metabolised via desacetylation and hydrolysis. Desacetylrifampicin and unchanged rifampicin are excreted in the bile and urine, and unchanged rifampicin is reabsorbed into the enterohepatic circulation. About 80% of rifampicin is bound to protein (mainly albumin) in plasma (Acocella 1978). Because the capacity of the liver is saturated with 300 mg to 450 mg doses, further increases in dosage therefore result in a more than proportional increase in serum concentrations (Acocella 1978).

Interactions. Rifampicin is a potent inducer of hepatic and intestinal CYP3A4 (Combalbert et al. 1989; Kolars et al. 1992) and therefore reduces the plasma concentrations and effects of several CYP3A4 substrates (Backman et al. 1996; Villikka et al. 1997; Lamberg et al. 1998). Rifampicin can also induce CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, and CYP3A5 enzymes, but their inducibility is less than that of CYP3A4 (Niemi et al. 2003c). Induction of CYP3A4 by rifampicin is mediated by a nuclear receptor PXR (Lehmann et al. 1998). PXR also regulates members of the UPD-glucuronyltransferase (UGT), sulfotransferase and carboxylesterase families (Goodwin et al. 2002). Correspondingly, studies in cell cultures indicate that rifampicin induces some phase II enzymes, such as UGTs and sulfotransferases (Doostdar et al. 1993; Kern et al. 1997), as well as non-cytochromal drug-metabolising enzymes, such as monoamine oxidase B (MAO-B) and flavin-containing mono-oxygenases four and five (FMO4 and FMO5) (Sumida et al. 2000).

Rifampicin also induces PXR-regulated P-gp (Geick et al. 2001). P-gp is induced mainly in the liver and the intestine, but significantly less if at all in the kidneys (Greiner et al. 1999). Fromm et al. recently showed that MRP2 that is involved in the efflux of some drugs and drug conjugates (König et al. 1999) is indused by rifampicin (Fromm et al. 2000).

Becase of its broad spectum of effects, rifampicin can cause clinically significant interactions with a number of important drugs, including verapamil, dihydropyridine calcium-channel antagonists, sulfonureas, itraconazole, ketoconazole, midazolam, triazolam, indinavir, nelfinavir, saquinavir, cyclosporine, methadone, warfarin and digoxin (Niemi et al. 2003c).

AIMS OF THE STUDY

No controlled studies about the effect of gemfibrozil on the pharmacokinetics of simvastatin, lovastatin, cerivastatin, atorvastatin and pravastatin had been published when we carried out the original studies of this thesis. Nor did any published studies on the effects of potent CYP inducers on statin pharmacokinetics exist.

The specific aims of the studies were:

I To investigate the effect of gemfibrozil on the pharmacokinetics of four HMG-CoA reductase inhibitors: simvastatin, lovastatin, cerivastatin and pravastatin (Study I-IV), and to characterise the magnitude of these interactions. To investigate the effect of bezafibrate on the pharmacokinetics of lovastatin and to compare it to the effect of gemfibrozil on lovastatin (Study III), to determine if the effects of bezafibrate and gemfibrozil on lovastatin pharmacokinetics differ.

II To study the effects of rifampicin on the pharmacokinetics of simvastatin and pravastatin (Study V and VI).

MATERIALS AND METHODS

1. Subjects

A total of 53 (23 female and 30 male) healthy volunteers participated in the studies. Their health was assessed beforehand based on their medical history, a physical examination, and routine laboratory tests. None of the subjects received continuous medication, except two female subjects in Study I who were using oral contraceptive steroids. None of the subjects were frequent smokers. Pregnant, lactating, obese, or volunteers under 18 years old were excluded. Intake of other drugs or grapefruit or grapefruit juice was prohibited two weeks prior to each study day. Subjects that had donated blood within one month or participated in other trials were excluded. Details of the subjects appear in Table 7.

Study no.	Gender (male/female)	Age (years)	Weight (kg)	Height (cm)	Body Mass Index (kg/m^2)	No. of users of oral contraceptives
I	5/5	22 ± 3	62 ± 13	172 ± 11	21 ± 2	2
II	5/6	22 ± 2	68 ± 11	173 ± 10	23 ± 2	0
III	5/5	23 ± 2	69 ± 11	175 ± 7	22 ± 2	0
IV	5/5	23 ± 3	70 ± 10	176 ± 5	22 ± 3	0
V	10/0	24 ± 3	71 ± 8	178 ± 6	22 ± 2	0
VI	6/4	22 ± 2	70 ± 15	172 ± 9	23 ± 3	0

Table 7. Characteristics of the subjects. Age, weight, height and Body Mass Index data are mean ± SD

2. Study design

All six studies used a similar randomised, placebo-controlled crossover-design. All studies consisted of two phases and had a washout period of four weeks, except Study III, which consisted of three phases and had a washout period of two weeks. Details of the studies appear in Table 8. The studies were carried out at the Department of Clinical Pharmacology, University of Helsinki.

The Pharmacy of the Helsinki University Central Hospital supplied, packaged and labelled the pretreatment medications and matched placebos according to a randomisation list for each subject.

Details of the drugs appear in Table 9. Drug doses were chosen to reflect current use and to facilitate determination of plasma drug concentrations.

Following ingestion of the statin, timed blood samples were taken for up to 12 or 24 hours to determine plasma drug concentrations. In each study, the volunteers fasted overnight before administration of the statin and received a warm meal three hours, and a standard meal seven hours afterwards. No volunteers were allowed to drink alcohol during the study days or during the previous 24 hours. The statins were administered orally with 150 ml water.

Study No.	Pretreatment medication and dose	Duration of pretreatment	Washout period (weeks)	Study drug and dose	Administration of study drug
I	gemfibrozil 600 mg x 2 placebo x 2	3 days (at 8:00 and 20:00)	4	simvastatin 40 mg	on day 3 at 9:00
II	gemfibrozil 600 mg x 2 bezafibrate 400 mg x 1 placebo x 2	3 days (at 8:00 and 20:00)	2	lovastatin 40 mg	on day 3 at 9:00
III	gemfibrozil 600 mg x 2 placebo x 2	3 days (at 8:00 and 20:00)	3	cerivastatin 0.3 mg	on day 3 at 9:00
IV	gemfibrozil 600 mg x 2 placebo x 2	3 days (at 8:00 and 20:00)	4	pravastatin 40 mg	on day 3 at 9:00
V	rifampicin 600 mg x 1 placebo x 1	5 days (at 16:00)	4	simvastatin 40 mg	on day 6 at 9:00
VI	rifampicin 600 mg x 1 placebo x 1	5 days (at 16:00)	4	pravastatin 40 mg	on day 6 at 9:00

Table 8. Structure of the studies.

3. Blood sampling

On the days of administration of the study drug, a cannula was inserted into a forearm vein of each subject and kept patent with an obturator. Timed blood samples were drawn just before administration of the study drugs and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours later in studies I, II and V and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours later in studies III, IV and VI. In studies II-IV, a final blood sample was collected 24 hours after administration of the study drug.

In all studies, blood samples (10 ml each) were collected in tubes that contained

ethylenediamintetraacetic acid. In study III, additional 5-ml samples were drawn before and 24 hours after administration of cerivastatin for measurement of serum creatine kinase values. Plasma samples were separated by centrifugation with a relative centrifugal force of 1900g within 30 minutes after blood sampling, and stored at -70ºC until analysis.

In studies IV and VI, urine was collected cumulatively to determine renally excreted pravastatin.

Study No.	Pretreatment drug	Study drug
I	gemfibrozil: Lopid 600 mg tablet, Gödecke/ Parke Davis, Germany	simvastatin: Zocor 40 mg tablet, Merck Sharpe & Dohme, the Netherlands
II	gemfibrozil: Lopid 600 mg tablet, Gödecke/Parke Davis, Germany bezafibrate: Bezalip 400 mg slow-release tablet, Orion Pharma, Finland	lovastatin: Lovacol 40 mg tablet, Orion Pharma, Finland
III	gemfibrozil: Lopid 600 mg tablet, Parke Davis, Warner Lambert Nordic AB, Germany	cerivastatin: Lipobay 0.3 mg tablet, Bayer, Germany
IV	gemfibrozil: Lopid 600 mg tablet, Parke Davis, Germany	pravastatin: Pravachol 40 mg tablet, Bristol-Myers Squibb, USA
V	rifampicin: Rifarm 600 mg tablet, Pharmacal, Finland	simvastatin: Zocor 40 mg tablet, Merck Sharpe & Dohme, the Netherlands
VI	rifampicin: Rifarm 600 mg tablet, Pharmacal, Finland	pravastatin: Pravachol 40 mg tablet, Bristol-Myers Squibb, USA

Table 9. Details of the drugs used in the study.

4. *In vitro* study (Study I)

Professor Olavi Pelkonen of the University of Oulu provided the liver microsomal samples. The microsomes were prepared as described previously (Meier et al. 1983). After determination of protein concentration (Lowry et al. 1951), the suspended microsomes were divided into alignots, frozen and stored at -80ºC until use.

The incubations were performed in duplicate and within the linear range with respect to incubation time. The incubation volume was 0.2 ml. Gemfibrozil was dissolved in acetonitrile, and acetonitrile was removed by evaporation. Gemfibrozil 0 to 1200 µmol/l was reconstituted with an incubation medium containing 0.13 mol/l sodium phosphate buffer (pH 7.4), 5.0 mmol/l magnesium chloride, 1.0 mmol/l

NADPH and 6.25 μmol/l midazolam. After incubation at 37°C for two minutes, the reaction was started by adding microsomal protein (100 μg/0.2 ml). In an additional experiment, gemfibrozil was first preincubated together with the incubation medium and microsomes for 15 minutes, after which the reaction was started by adding midazolam. The reaction was stopped after eight minutes by adding 200 μl ice-cold methanol containing 25 ng/ml methoxydiazepam as an internal standard. The samples were centrifuged, and the supernatant was analysed for 1'-hydroxymidazolam by HPLC (Ha et al. 1993).

5. Determination of plasma drug concentrations

5.1. HMG-CoA reductase inhibitors

Simvastatin and simvastatin acid

Concentrations of simvastatin and simvastatin acid in plasma (Studies I and V) were measured with liquid chromatography-ion spray tandem mass spectrometry using the Perkin Elmer Sciex API 3000 LC/MS/MS system, as described previously (Mulvana et al. 2000). The ion transitions monitored were *m/z* 436 to *m/z* 285 for simvastatin and *m/z* 437 to *m/z* 303 for simvastatin acid. The limit of quantification was 0.1 ng/ml, and the standard curves were linear from 0.1 ng/ml to 100 ng/ml for simvastatin and simvastatin acid. In Study V, the day to day coefficients of variation (CV) were 4.9% at 0.10 ng/ml and 4.1% at 0.52 ng/ml for simvastatin (n=7), and 8.1% at 0.11 ng/ml and 11.0% at 0.52 ng/ml for simvastatin acid (n=7). In Study I, the CVs were 1.8% at 0.12 ng/ml, 4.6% at 5.4 ng/ml, and 0.8% at 49.7 ng/ml for simvastatin (n=3) and 12.9% at 0.097 ng/ml, 9.8% at 5.1 ng/ml, and 3.9% at 51.0 ng/ml for simvastatin acid (n=3).

Lovastatin and lovastatin acid

The concentrations of lovastatin and lovastatin acid in plasma (Study II) were measured with liquid chromatography-ionspray tandem mass spectrometry using the LC/MS/MS system (Mulvana et al. 2000). Simvastatin served as an internal standard. The ion transitions monitored were *m/z* 405 to *m/z* 199 for lovastatin, *m/z* 423 to *m/z* 285 for lovastatin acid, and *m/z* 419 to *m/z* 285 for simvastatin. The limit of quantification was 0.1 ng/ml for lovastatin and lovastatin acid. The CVs were 7.8% at 0.19

ng/ml and 3.5% at 11 ng/ml for lovastatin (n=6), and 12% at 0.20 ng/ml and 4.8% at 12 ng/ml for lovastatin acid (n=6).

Cerivastatin and metabolites

The concentrations of cerivastatin and its major metabolites in plasma (Study III) were measured with liquid chromatography-ionspray tandem mass spectrometry using the LC/MS/MS system as described previously, with some modifications (Jemal et al. 1999). Fluvastatin served as an internal standard. The ion transitions monitored were m/z 460 to m/z 356 for cerivastatin (acid), m/z 442 to m/z 354 for cerivastatin lactone, m/z 446 to m/z 342 for M-1 acid, m/z 476 to m/z 340 for M-23 acid, and m/z 412 to m/z 224 for fluvastatin. These transitions represent the product ions of $[M+H]^+$ ions. The limit of quantification for cerivastatin was 0.01 ng/ml, and the CVs were 3.7% at 5 ng/ml (n=5), 3.9% at 0.5 ng/ml (n=5), and 13% at 0.05 ng/ml (n=5).

Pravastatin

The concentrations of pravastatin in plasma and urine (Studies IV and VI) were measured with liquid chromatography-ionspray tandem mass spectrometry using of the LC/MS/MS system (Mulvana et al. 2000). The ion transition monitored was m/z 442 to m/z 269, and the limit of quantification was 0.25 ng/ml for pravastatin. In Study V, the CVs were 7.8% at 1 ng/ml, 3.7% at 10 ng/ml, and 10.9% at 100 ng/ml for pravastatin (n=6). In Study VI, the CVs were 9.0% at 1 ng/ml, 2.6% at 10 ng/ml, and 3.3% at 100 ng/ml (n=7).

5.2. Fibrates

Plasma concentrations of gemfibrozil and bezafibrate were determined with HPLC with ultraviolet detection (Hengy and Kölle 1985). Ibuprofen served as an internal standard. In Studies I-IV, the limit of quantification for gemfibrozil was 0.1 mg/l, and the between-day CV was less than 12% at relevant plasma gemfibrozil concentrations (approximately 0.5-30 mg/l). The limit of quantification for bezafibrate was 0.05 mg/l, and the between-day CV was less than 8% at relevant plasma bezafibrate concentrations (approximately 0.3-9 mg/l).

6. Pharmacokinetic calculations

The pharmacokinetics of the study drug were characterised by peak concentration in plasma (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve from time 0 to t or infinity ($AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ respectively) and elimination half-life ($t_{½}$). The terminal log-linear phase of the plasma drug concentration-time curve was identified visually for each subject. The C_{max} and t_{max} values were taken directly from the original data. The elimination rate constant (k_{el}) was determined by a linear regression analysis with use of at least three points on the plot of the natural logarithm of the plasma concentration-time curve. The $t_{½}$ was calculated from the equation:

$$t_{½} = \ln 2 / k_{el}$$

AUC values were calculated by the linear trapezoidal rule for the rising phase of the plasma concentration-time curve and by the log-linear trapezoidal rule for the descending phase, with extrapolation to infinity, when appropriate by division of the last measured concentration by k_{el}. AUC_{0-12} values were calculated in Studies I and V-VI, wheras AUC_{0-24} values were used in studies II-IV.

Renal clearance ($CL_{ren\ 0-12}$) was calculated as:

$$CL_{ren\ 0-12} = A_e / AUC_{(0-12)}$$

where A_e is the amount of study drug excreted into urine within 12 hours.

The pharmacokinetics of gemfibrozil and bezafibrate were characterised by C_{max} and AUC. The pharmacokinetic analysis was carried out with the program MK model, version 5.0 (Biosoft, Cambridge, UK).

7. Statistical analysis

Results were expressed as mean values ± SEM or ± SD. T_{max} data were expressed as median with range. Mean values ± SEM were used in the figures. C_{max} and AUC values were log-transformed before statistical analysis as appropriate. In Studies I, III, IV, and VI, 95% confidence intervals were calculated for the mean differences of selected variables.

Statistical comparisons between the two phases in Studies I, III, and V were carried out using repeated measures analysis of variance (ANOVA), with fixed effects for period, treatment sequence, and treatment - except for t_{max} values. Statistical comparisons of the continuous pharmacokinetic variables between the two phases in Studies IV and VI were carried out with the Student *t*-test for paired values (two-tailed). The Wilcoxon-signed rank test was used in all studies for analysis of t_{max}.

Analysis of the results in Study II was carried out using two-way ANOVA and *a posteriori* testing with the Tukey test. The t_{max} values in Study II were compared with Friedman's two-way ANOVA and the Wilcoxon-signed rank test.

Pearson's product-moment correlation coefficient was used to test linear correlations between selected variables in Studies I, II, III and IV, and the Mann-Whitney U-test was used to compare the effects of rifampicin on AUC values of simvastatin acid and pravastatin.

All data were analysed with the statistical program Systat for Windows, version 6.0.1 (SPSS Inc, IL, USA). The level of statistical significance is $p < 0.05$.

8. Ethical considerations

All the study protocols were approved by the appropriate ethics committees according to current regulations. The study protocols of Studies I and V were approved by the Ethics Committee of the Department of Clinical Pharmacology, University of Helsinki, and protocols of Studies II, III, IV and VI were approved by the Ethics Committee for Studies in Healthy Subjects, Hospital District of Helsinki and Uusimaa. In addition, all the study protocols were approved by the Finnish National Agency for Medicines. All subjects received both oral and written information and provided their written informed consent. Study III was initiated before the withdrawal from the market of cerivastatin, which occurred before the study was completed. The ethics committee and the volunteers in Study III were informed of the withdrawal of cerivastatin.

RESULTS

1. Effects of gemfibrozil and bezafibrate on HMG-CoA reductase inhibitor

1.1 Effect of gemfibrozil on simvastatin

Pretreatment with gemfibrozil 600 mg twice daily for three days increased the mean $AUC_{(0-\infty)}$ of simvastatin to 140% (range 60% to 240%, $p < 0.01$) and the mean $AUC_{(0-\infty)}$ of simvastatin acid to 290% (range 100% to 860%, $p < 0.001$) of control phase values. The mean C_{max} of simvastatin saw no statistically significant increase, while the C_{max} of simvastatin acid increased to 210% ($p < 0.01$) of control phase values. During the gemfibrozil phase the $t_{½}$ of simvastatin was 170% ($p < 0.05$) and the $t_{½}$ of simvastatin acid was 150% longer ($p < 0.01$) than that of the control phase. Gemfibrozil more than doubled the $AUC_{(0-\infty)}$ ratio of simvastatin acid to simvastatin ($p < 0.05$).

1.2 Effect of gemfibrozil and bezafibrate on lovastatin

Pretreatment with gemfibrozil raised the mean $AUC_{(0-24)}$ of lovastatin acid to 280% (range 130% to 1180%, $p < 0.001$) and the mean C_{max} of lovastatin acid to 180% ($p < 0.05$) of control phase values (Figure 6). The mean $AUC_{(0-24)}$ or C_{max} of lovastatin failed to increase. The $t_{½}$ of lovastatin or lovastatin acid could not be determined because of rebound increases at 24 hours. Gemfibrozil raised the $AUC_{(0-24)}$ ratio of lovastatin acid to lovastatin more than three-fold.

Pretreatment with bezafibrate 400 mg once daily for three days had no significant effect on the mean $AUC_{(0-24)}$ of lovastatin or of lovastatin acid or on the mean C_{max} of lovastatin. Bezafibrate raised the mean C_{max} of lovastatin acid by 40%, but the $t_{½}$ could not be determined.

Effect of gemfibrozil on simvastatin acid, lovastatin acid, cerivastatin and pravastatin pharmacokinetics

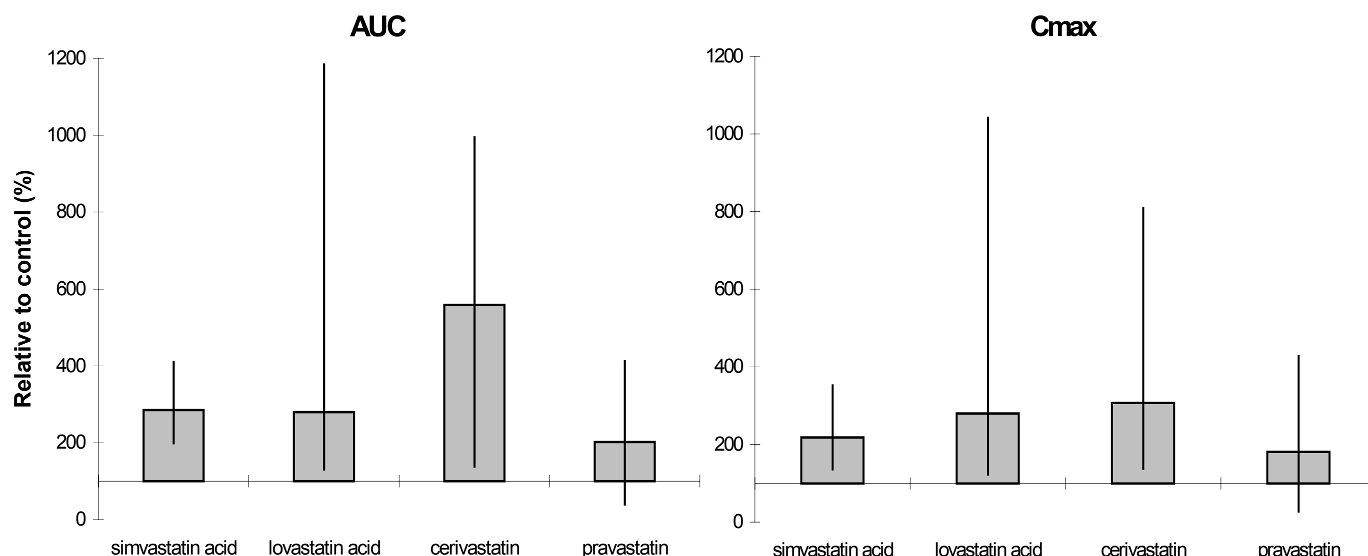


Figure 6. Pharmacokinetic changes in simvastatin acid, lovastatin acid, cerivastatin and pravastatin due to administration of gemfibrozil 600 mg twice daily. The mean AUC and mean C_{max} values are expressed relative to control (gray bars), and the smallest and largest values appear as black lines.

1.3. Effect of gemfibrozil on cerivastatin

Pretreatment with gemfibrozil raised the mean $AUC_{(0-\infty)}$ of cerivastatin (acid) to 560% (range 140% to 1000%, $p < 0.001$) of control phase values. Gemfibrozil increased the C_{max} of cerivastatin was to 310% (range 140% to 810%, $p < 0.005$), and the mean $t_{½}$ of cerivastatin raised to 270% ($p < 0.001$) of control values.

Gemfibrozil raised the $AUC_{(0-\infty)}$ of cerivastatin lactone on average to 440% of control values (range 90% to 590%, $p < 0.005$) and that of metabolite M-1 to 440% (range 220% to 800%, $p < 0.001$) of control phase values, but lowered the $AUC_{(0-24)}$ of metabolite M-23 to 20% (range 10% to 70%, $p < 0.005$) (Figure 7).

On study day three (before cerivastatin administration), the mean serum creatin kinase (CK) values were 87 ± 20 U/l during the placebo phase, and 111 ± 49 U/l during the gemfibrozil phase. On day four (at 24 hours from cerivastatin administration), the mean CK value was 77 ± 16 U/l during the placebo phase and 109 ± 81 U/l during the gemfibrozil phase. The slight tendency to higher CK-values during the gemfibrozil phase was statistically insignificant.

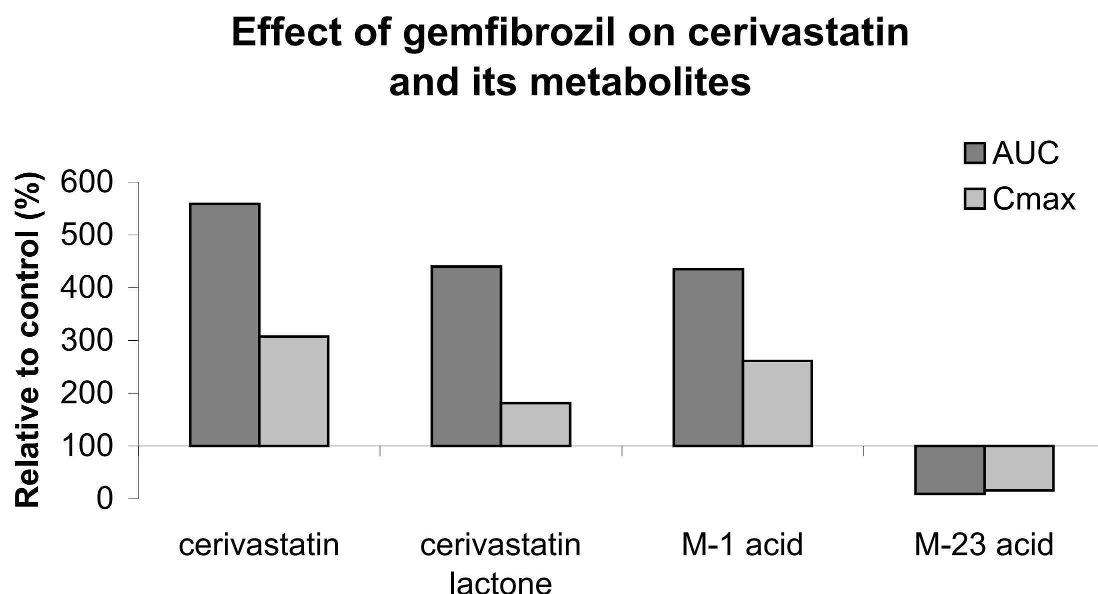


Figure 7. Effect of gemfibrozil on mean AUC and C_{max} values of cerivastatin and its metabolites.

1.4 Effect of gemfibrozil on pravastatin

During pretreatment with gemfibrozil the mean $AUC_{(0-\infty)}$ of pravastatin was 200% (range 40% to 410%, $p < 0.05$) of control phase values. Gemfibrozil raised the AUC in 9 of 10 subjects. During the gemfibrozil phase, the mean C_{max} of pravastatin was 180% (range 30% to 430%, $p = 0.09$) of control phase values, but the change was statistically insignificant. No difference existed in the $t_{½}$ of pravastatin between phases. Gemfibrozil reduced the renal clearance of pravastatin from 25 l/h to 14 l/h ($p < 0.001$), and a significant correlation existed between the increase in the $AUC_{(0-24)}$ of pravastatin and the decrease in its renal clearance ($r = 0.72$; $p < 0.05$).

1.5 Effect of gemfibrozil on CYP3A4 activity *in vitro*

Gemfibrozil in concentrations up to 1200 μmol/l showed no significant effect on midazolam 1'-hydroxylation, a probe CYP3A4 reaction in human liver microsomes either with or without preincubation.

2. Effects of rifampicin on HMG-CoA reductase inhibitors

2.1 Simvastatin

Pretreatment with rifampicin 600 mg once daily for five days lowered the mean $AUC_{(0-\infty)}$ of simvastatin to 13% (range 6% to 44%, $p < 0.001$), and the mean $AUC_{(0-\infty)}$ of simvastatin acid to 7% (range 3% to 18%, $p < 0.001$) of control phase values (Figure 8). The mean C_{max} of simvastatin and simvastatin acid fell to 10% ($p < 0.001$), of control phase values. Rifampicin had no effect on the $t_{½}$ of simvastatin and simvastatin acid.

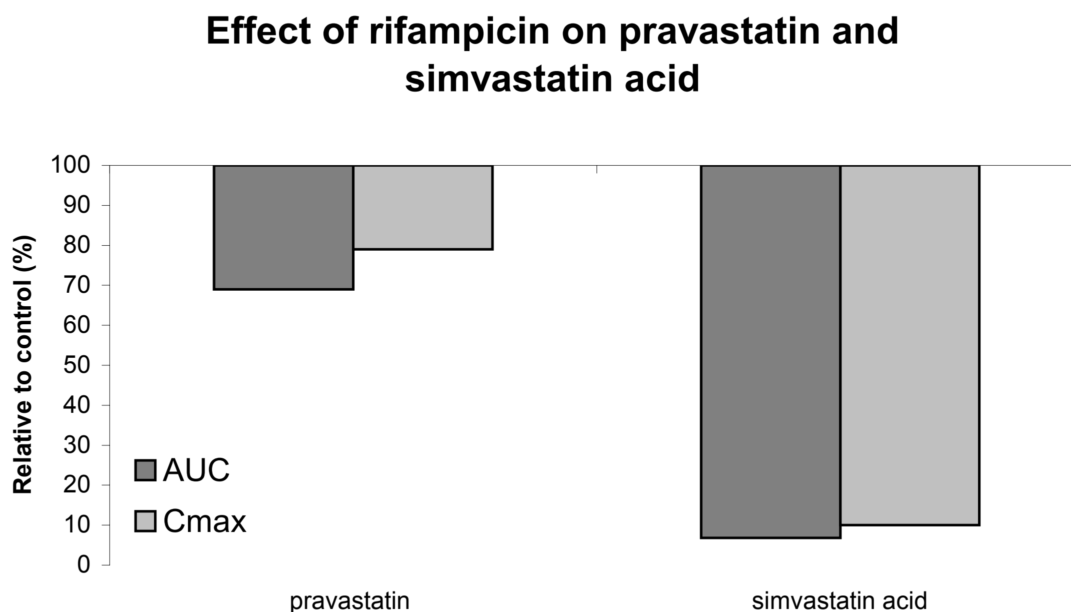


Figure 8. Effect of rifampicin on AUC and C_{max} values of pravastatin and simvastatin acid

2.2 Pravastatin

Pretreatment with rifampicin lowered the mean $AUC_{(0-\infty)}$ of pravastatin to 69% (range 24% to 220%, $p < 0.05$) of control phase values. Although the $AUC_{(0-\infty)}$ markedly decreased in seven subjects, the other three subjects showed a moderate increase. Rifampicin lowered the mean C_{max} of pravastatin to 79% of control phase values, but this change was statistically insignificant ($p = 0.13$). Rifampicin had no significant effect on the $t_{½}$ of pravastatin compared to control phase. Rifampicin had no significant effect on the renal clearance of pravastatin or on the amount of pravastatin excreted in urine.

DISCUSSION

1. Methodological considerations

A randomised, placebo-controlled cross-over study design was used in all six studies. Because a cross-over design was used, the variation in the parameters studied was smaller, and also fewer subjects were required than in a parallel group design. Balanced randomisation and adequate wash-out periods (two to four weeks) reduced the risk of possible carry-over effects. The number of subjects included in the studies (10 to 11) was sufficient to ascertain an interaction large enough to be clinically significant.

All the subjects in the studies were young, healthy volunteers. The activity of CYP3A4 is quite constant during adulthood, but the pharmacokinetics of drugs can change with increasing age and liver or kidney failure (Schmucker et al. 1990; Le Couteur and McLean 1998; Pichette and Leblond 2003). Therefore care must be taken when extrapolating the results for elderly subjects. Variations in drug interaction size may be greater in the actual patient-population than in our healthy subjects.

A longer period of concomitant medication could have been chosen to reflect clinical use more closely. However, steady state plasma levels of gemfibrozil and bezafibrate were likely reached in the three-day treatment. The elimination half-life of gemfibrozil and bezafibrate is 1.5 hours (Monk and Todd 1987; Todd and Ward 1988). Enzyme induction by rifampicin requires the synthesis of new enzyme protein and therefore a five-day pretreatment with rifampicin was used. On the basis of the ratio of 6β-hydroxycortisol to cortisol, the inducing effect of rifampicin reaches a plateau after six days, and after five days, the extent of induction remains close to this level (Tran et al. 1999). The length of pretreatments used was a compromise between the opposing goals of preventing unnecessary exposure to drugs in healthy volunteers on one hand, and of revealing clinically significant interactions on the other. The selected doses were clinically relevant and reflect current use.

Because alcohol intake can affect drug metabolism and exercise may predispose subjects to muscle toxicity (Carroccio et al. 1994), alcohol and strenuous exercise was prohibited for two days prior to the study and during the study days. Grapefruit juice, which is an inhibitor of CYP3A4 (Bailey et al. 1998), was prohibited for two weeks prior to each study. To standardise absorption, the volunteers fasted overnight before intake of the statin, and meals during the phases were standardised.

Some of the conclusions about the clinical relevance of the results drawn in these studies rely on the finding that a linear dose-response relationship exists in statin pharmacokinetics (Jones et al. 1998; White 2002; Jones et al. 2003). Numerous studies indicate that both efficacy and adverse effects increase with increasing plasma levels (Bradford et al. 1991; Dujovne et al. 1991; Anonymous 1997; Murphy and Dominiczak 1999; Ballantyne et al. 2003).

2. Effects of gemfibrozil and bezafibrate on pharmacokinetics of HMG-CoA reductase inhibitors

Gemfibrozil 600 mg twice daily increased the AUC and C_{max} of all four statins studied. All statin-gemfibrozil interactions displayed considerable interindividual variation, and at most the increase was 12-fold for lovastatin acid, 10-fold for cerivastatin, 7-fold for simvastatin acid, and 4-fold for pravastatin. Those individuals at the upper ends of the distribution curves probably run the highest risk for adverse effects.

In contrast to the effect of gemfibrozil, bezafibrate 400 mg once daily did not statistically or clinically affect the pharmacokinetics of lovastatin. Accordingly, the risk for developing myopathy may be somewhat lower with the bezafibrate-lovastatin combination than with the gemfibrozil-lovastatin combination. In two small clinical trials, no adverse effects occured more frequently with bezafibrate-simvastatin coadministration than with monotherapy of either drug (Hutchesson et al. 1994; Kehely et al. 1995).

It appears that gemfibrozil is the only fibrate bearing a documented pharmacokinetic interaction with statins. Pharmacokinetic studies indicate that fenofibrate does not seem to affect the pharmacokinetics of rosuvastatin (Martin et al. 2003) or pravastatin (Pan et al. 2000). Gemfibrozil, on the other hand, raises the AUC of both rosuvastatin (Schneck et al. 2004) and pravastatin (Study IV). Studies on the effects of other fibrates on the pharmacokinetics of statins appear not to have been published, but a similar interaction was observed with repaglinide. Gemfibrozil raised the AUC of repaglinide eight-fold (Niemi et al. 2003a), but fenofibrate had no significant effect on the pharmacokinetics of repaglinide (Kajosaari et al. 2004).

Two research groups have studied the effects of different fibrates on metabolism *in vitro* using human hepatocytes. Prueksaritanont et al. reported that while gemfibrozil inhibited the glucuronidation of simvastatin, cerivastatin, atorvastatin and rosuvastatin, fenofibrate did not affect the glucuronidation of simvastatin *in vitro* (Prueksaritanont et al. 2002c). Fujino et al. found that gemfibrozil inhibited metabolism via CYP2C8 to a greater extent than did fenofibrate, bezafibrate, clofibrate and ciprofibrate (Fujino et al. 2003). These *in vitro* studies indicate that inhibition of statin metabolism may occur in the presence of gemfibrozil – and considerably more than with the other fibrates studied.

Most cases of rhabdomyolysis have occurred in combination with gemfibrozil rather than with some other fibrate (Farmer 2001; Shek and Ferrill 2001; Farnier 2003). This suggests that gemfibrozil showed greater propensity for pharmacokinetic drug-drug interactions with statins than does bezafibrate. Therefore, the risk for myopathy in concomitant use of bezafibrate with a statin may be smaller than in concomitant use of gemfibrozil with a statin. Because rhabdomyolysis occurs in statin and fibrate monotherapy, the possibility of a pharmacodynamic interaction cannot be excluded.

3. Possible mechanisms of the gemfibrozil - statin pharmacokinetic interactions

It is remarkable that gemfibrozil raises the plasma concentrations of lovastatin acid, simvastatin acid, cerivastatin, pravastatin and rosuvastatin (Schneck et al. 2004), even though they differ in their extent of absorption as well as in their routes of excretion (Lennernäs and Fager 1997; Christians et al. 1998). *In vitro* studies that show that gemfibrozil inhibits CYP2C8 and CYP2C9 (Wen et al. 2001; Wang et al. 2002), glucuronidation-mediated lactonisation of statins (Prueksaritanont et al. 2002a; Prueksaritanont et al. 2002c), and OATP-C-mediated uptake transport of substrate statins (Schneck et al. 2004). The gemfibrozil-statin interaction mechanism may vary from statin to statin.

One of the most plausible mechanisms for all statins is the inhibition of drug transporters by gemfibrozil (Figure 9). The statins studied are all substrates of OATP-C (Hsiang et al. 1999; Nakai et al. 2001; Shitara et al. 2003), and gemfibrozil is known to inhibit OATP-C (Schneck et al. 2004). Cyclosporine, an inhibitor of drug transporters P-gp (Tamai and Safa 1990), MRP2 (Chen et al. 1999), and OATP-C (Shitara et al. 2003) also markedly raises the plasma levels of these statins (Campana et al. 1995; Olbricht et al. 1997; Mück et al. 1999; Hedman et al. 2004).

Especially in the case of pravastatin, which is not metabolised by CYP enzymes to a significant extent (Jacobsen et al. 1999a; Jacobsen et al. 1999b), the most probable explanation is that gemfibrozil inhibits OATP-C-mediated uptake of pravastatin (Schneck et al. 2004). Gemfibrozil or some of its metabolites may also inhibit MRP2-mediated efflux transport of pravastatin. At least lovastatin and probably also simvastatin is a substrate of P-gp (Kim et al. 1999), but gemfibrozil does not inhibit P-gp *in vitro* (Ehrhardt et al. 2004). The role of P-gp however, cannot be completely excluded on the basis of *in vitro* studies, because some of the untested metabolites of gemfibrozil may inhibit P-gp.

Another likely mechanism of the interaction is the inhibition of CYP2C8 by gemfibrozil. Trimethoprim, a selective inhibitor of CYP2C8 (Wen et al. 2002), also raised the AUC of cerivastatin, although not as much as did gemfibrozil (Backman et al. 2003). Cerivastatin metabolite M-23 has been shown to be formed mainly by CYP2C8 (Wang et al. 2002). The decrease in the formation of the CYP2C8-mediated metabolite M-23 in Study III suggests that inhibition of CYP2C8 by gemfibrozil is an important factor in the interaction. Furthermore, an *in vitro* study shows that gemfibrozil inhibits CYP2C8-mediated metabolism (Wang et al. 2002). Besides cerivastatin, CYP2C8 is also involved in the metabolism of simvastatin acid (Prueksaritanont et al. 2003), and perhaps in the metabolism of lovastatin acid as well. Gemfibrozil also raises the plasma concentrations of other substrates of CYP2C8 such as repaglinide (Niemi et al. 2003a) and rosiglitazone (Niemi et al. 2003b).

It is highly unlikely that inhibition of CYP3A4 would cause the observed effects of gemfibrozil on statin pharmacokinetics. Gemfibrozil raised the AUC of the acid form of simvastatin and lovastatin more than the AUC of the parent lactone (Study I and II). This is contrary to the effects of CYP3A4 inhibitors on simvastatin or lovastatin pharmacokinetics, where the parent lactone AUC increases more than does the acid (Kivistö et al. 1998; Kantola et al. 1998a; Kantola et al. 1998b). Moreover, gemfibrozil did not affect the CYP3A4-mediated 1'-hydroxylation of midazolam (Study I), even though the gemfibrozil concentrations used were 10 times as high as the peak concentration in the *in vivo* study. Potent inhibitors of CYP3A4, such as itraconazole and erythromycin, produce only modest increases in cerivastatin pharmacokinetics, suggesting a limited role for CYP3A4 in the elimination of cerivastatin (Mück et al. 1998b; Kantola et al. 1999). Gemfibrozil, on the other hand, raised cerivastatin AUC-values on average six times more than control values.

A third, though less important explanation could be that gemfibrozil inhibitios statin glucuronidation. Glucuronidation by phase II enzymes is not, however, a major pathway of simvastatin or lovastatin

elimination (Prueksaritanont et al. 2002a; Prueksaritanont et al. 2002b), and therefore its inhibition may not be the main contributor to the mechanism of interaction.

Evans and Rees have offered a fourth possible mechanism: that fibrates might downregulate the expression of the enzymes that metabolise statins, thus resulting in greater statin exposure (Evans and Rees 2002). It is known that fibrates activate PPAR, and the PPAR family of receptors have been shown to influence regulation of CYP enzymes. However, this mechanism seems an unlikely explanation for the effects of gemfibrozil on statins, as studies on PPAR activation involve CYP4A6 rather than CYP3A4 or CYP2C8 (Palmer et al. 1994), and other PPAR activators such as pioglitazone and troglitazone, do not inhibit statin metabolism. On the contrary, plasma levels of HMG-CoA reductase inhibitors decreased during coadministration of simvastatin and troglitazone in healthy volunteers, and remained unchanged during coadministration of pioglitazone and simvastatin (Prueksaritanont et al. 2001).

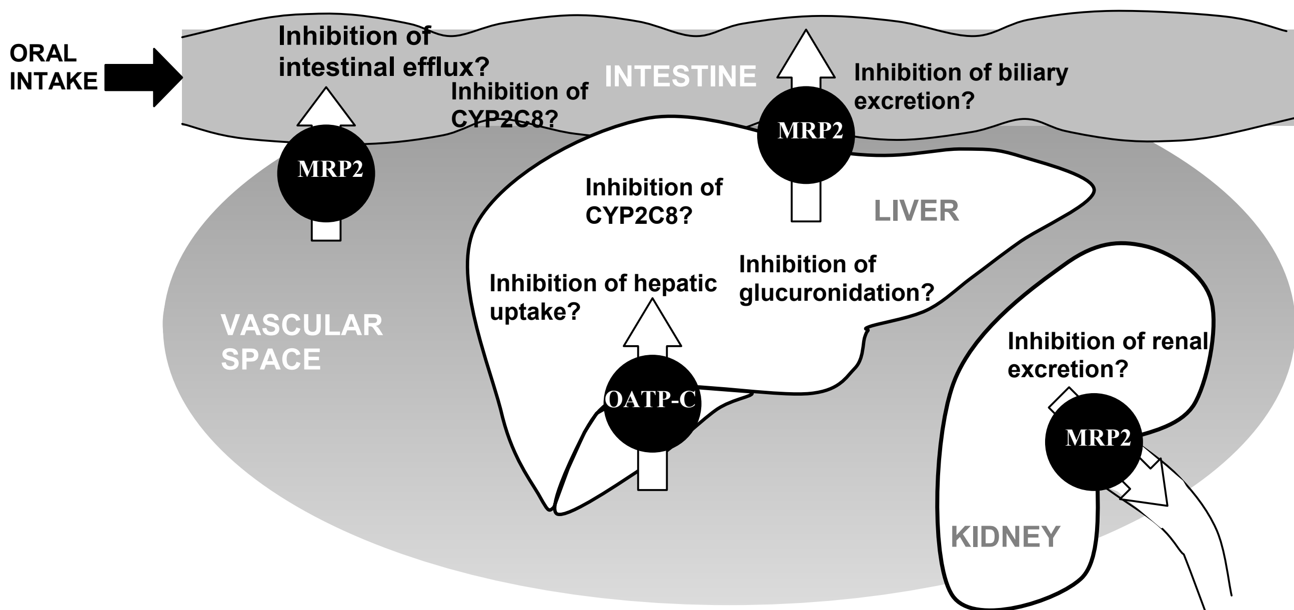


Figure 9. Simplified drawing of possible mechanisms of the gemfibrozil-statin pharmacokinetic interaction.

4. Clinical relevance of the results with gemfibrozil and bezafibrate

The risk for rhabdomyolysis with statins depends on the plasma concentration (Bradford et al. 1991; Dujovne et al. 1991; Anonymous 1997; Ballantyne et al. 2003) and lipophilicity of the statin (McTavish and Sorkin 1991; Negre-Aminou et al. 1997; Farmer 2001; White 2002; Thompson et al. 2003). It is now well established that the pharmacokinetic interaction leading to elevated statin concentrations raises the risk for rhabdomyolysis in concomitant use of statins and azole antifungals such as itraconazole (Böger 2001). However, the causality between pharmacokinetic interaction and rhabdomyolysis is not as straightforward in the gemfibrozil-statin combination, because both agents are also known to cause rhabomyolysis in monotherapy.

The FDA has published data on the percentages of gemfibrozil use in 866 statin-related cases of rhabdomyolysis (Table 2) (Chang et al. 2002). If pharmacokinetic interaction is responsible for at least part of the increased frequency of rhabdomyolysis in statin-gemfibrozil coadministration, one could reasonably assume that out of all cases of statin-related rhabdomyolysis as the size of the pharmacokinetic interaction increases, so does the percentage of cases of statin-related rhabomyolysis involving concomitant use with gemfibrozil. Such a positive correlation between gemfibrozil cotreatment and the mean size of pharmacokinetic interaction seems to exist ($p < 0.005$, $r = 0.98$). Although correlation does not mean causality, this result may indicate that the pharmacokinetic interaction between gemfibrozil and a statin is a major explanatory factor for the increased risk for muscle damage (Figure 10). This however, does not rule out the possibility of a pharmacodynamic interaction.

That reporting rates of rhabdomyolysis differ for different statins does not skew this comparison, if the likelihood of reporting a case of statin-related rhabdomyolysis is as likely in combined use with gemfibrozil as when gemfibrozil is not used. Nor does the withdrawal of cerivastatin (8 August 2001) distort the data that extend to the end of July 2001. One confounding factor is, however, that the percentage of patients using gemfibrozil together with a statin may vary from statin to statin. It appears that elevated plasma levels of HMG-CoA reductase inhibitors is at least one factor in the risk for myopathy and rhabdomyolysis.

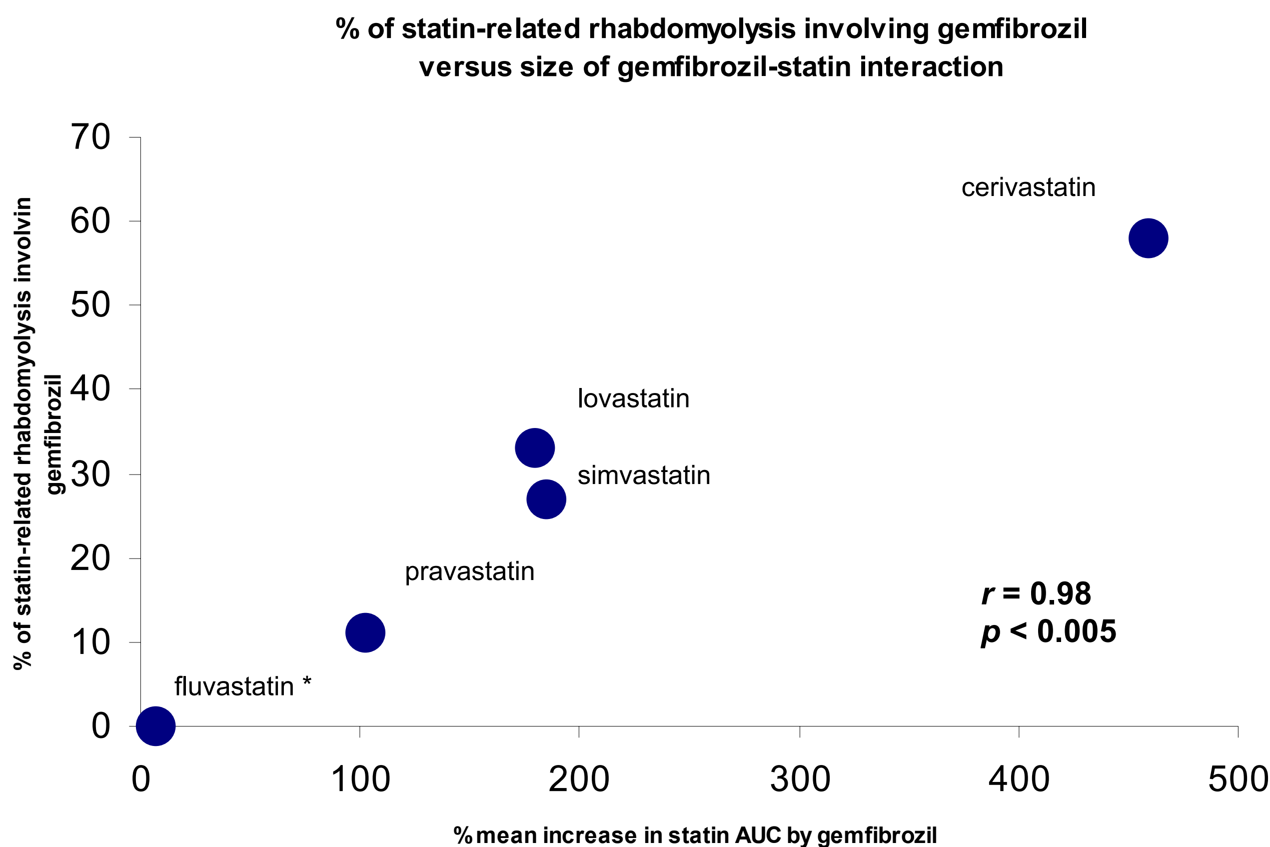


Figure 10. From onset of marketing through 31 July 2001, 866 cases of statin-related rhabdomyolysis were reported to the FDA (Chang et al. 2002). Of these 866 cases, gemfibrozil was used concomitantly with a statin in 384 cases. The y-axis values indicate the percentage of statin-related cases of rhabdomyolysis involving concomitant use of gemfibrozil of all statin-related cases of rhabdomyolysis, and the x-axis values indicate the percentage of the mean increase in statin AUC by gemfibrozil (Studies I-IV). *) No cases of statin-related rhabdomyolysis were observed with fluvastatin, and the percentage of cases involving concomitant use of gemfibrozil appear as zero. Of atorvastatin-related cases of rhabdomyolysis, 12% involved concomitant use of gemfibrozil (pharmacokinetic interaction unknown).

If the elevated plasma level of HMG-CoA reductase inhibitor is a factor in the risk for myopathy and rhabdomyolysis, it follows that the risk for myopathy is lower in combinations of fibrate and statin that lack a pharmacokinetic interaction. However, the observed increases in statin plasma concentrations by gemfibrozil may also explain the effectiveness of the statin-gemfibrozil combination in clinical trials in the treatment of dyslipidemia (Wierzbicki et al. 2003). The clinical effects of an elevated statin plasma level due to a pharmacokinetic interaction may be comparable to the clinical effects of using higher doses of statin (Jones et al. 1998; Yeo et al. 1999; White 2002; Jones et al. 2003). However, because gemfibrozil inhibits OATP-C-mediated statin uptake into hepatocytes (Schneck et al. 2004), the resulting statin concentration in the liver, which is the target organ of statins, may differ from plasma statin concentrations. Theoretically, gemfibrozil may even reduce the concentrations of some statins in the liver by blocking their active uptake via OATP-C while simultaneously increasing statin concentrations in plasma. This, however, seems unlikely as clinical trials indicate that the statin-gemfibrozil combination is highly effective (Athyros et al. 1997; Zambon et al. 1999; Vergoulas et al. 2000).

As a class, statins are very safe overall and exhibit a favourable effect on all-cause mortality in the treatment of hypercholesterolemia (Shepherd et al. 1995; HPS-Collaborative-Group 2002). Because bezafibrate and fenofibrate, in contrast to gemfibrozil, have not been shown to affect the pharmacokinetics of statins, one may prefer them to gemfibrozil when the statin-fibrate combination is indicated. However, because the lack of a pharmacokinetic interaction does not preclude the lack of a pharmacodynamic interaction, the maximal dose of statin can be lowered when statins are used together with fibrates. Overall, care should be taken when fibrates and statins are used concomitantly, and this especially applies if gemfibrozil is combined with a statin.

5. Effects of rifampicin on pharmacokinetics of simvastatin and pravastatin

Simvastatin

The five-day pretreatment with rifampicin lowered simvastatin AUC by 56% to 94%, and simvastatin acid by 82% to 97% (Study V). This means that a substantial interaction was observed in all subjects. The main mechanism of the interaction is most probably the induction of CYP3A4 in the intestinal wall and the liver. CYP3A4 is expressed in the intestine and liver (Kivistö et al. 1996); simvastatin and simvastatin acid are substrates of CYP3A4 (Prueksaritanont et al. 2003), and rifampicin induces

CYP3A4 (Backman et al. 1996; Fromm et al. 1996; Holtbecker et al. 1996). The elimination half-life of simvastatin or simvastatin acid by rifampicin remained unchanged. This suggests that the interaction occurred during first pass rather than during elimination. It is also possible that rifampicin induced the expression of some transport protein, such as P-gp (Greiner et al. 1999), thus contributing to the mechanism of the interaction. Simvastatin may be a substrate for P-gp as is lovastatin (Kim et al. 1999). Rifampicin lowered the concentrations of simvastatin acid more than simvastatin itself (Study V). This implies that, besides the induction of simvastatin metabolism, the metabolism of simvastatin acid was also induced.

In a recent study, 600 mg daily of another CYP3A4 inducer, carbamazepine for two weeks lowered the AUC of simvastatin and of simvastatin acid by 75% and 82%, respectively (Ucar et al. 2004). As with rifampicin, the change was greater with simvastatin acid than with simvastatin, but carbamazepine also shortened the elimination half-life of simvastatin acid from 5.9 hours to 3.7 hours. The herbal product St John's wort is an inducer of CYP3A4 as well as of P-gp. A 14-day pretreatment with St John's wort reduced the AUC of simvastatin and of simvastatin acid by 34% and 52%, respectively, but left the elimination half-life unchanged (Sugimoto et al. 2001). Of these three inducers, rifampicin seems to induce the metabolism of simvastatin most potently.

Pravastatin

The effect of rifampicin on pravastatin pharmacokinetics differed considerably from the effect of the same pretreatment on simvastatin pharmacokinetics. Although the mean AUC of pravastatin decreased by 31%, substantial interindividual variation existed. AUC was more than halved in five subjects, but actually increased in three subjects.

Although the induction of CYP3A4 by rifampicin is probably a major determinant in its pharmacokinetic interaction with simvastatin, induction of CYP3A4 or P-gp is not a plausible mechanism in the interaction with pravastatin, as pravastatin is a substrate of neither P-gp nor of CYP3A4 (Jacobsen et al. 1999a; Sakaeda et al. 2002). On the other hand, pravastatin is a substrate of OATP-C and of MRP2 (Yamazaki et al. 1997; Hsiang et al. 1999), and rifampicin can at least induce MRP2 (Fromm et al. 2000). Fromm and colleagues found that rifampicin induced duodenal MRP2 expression in 10 of 16 subjects (Fromm et al. 2000), and in Study VI, rifampicin reduced the AUC of pravastatin in 7 of 10 subjects. However, the increase in AUC during the rifampicin phase in some subjects might also be due to the inherent intraindividual variability of pravastatin.

The same pretreatment with St John's wort that reduced simvastatin AUC did not significantly affect pravastatin pharmacokinetics (Sugimoto et al. 2001). This is consistent with the results of our induction studies on simvastatin and pravastatin, and confirms that pravastatin is less susceptible to induction of metabolism than is simvastatin.

6. Clinical relevance of the results with rifampicin

When assessing the effects of induction of drug metabolism on statin pharmacokinetics, it is useful to remember a rule of thumb: that a doubling in statin dose will further reduce blood cholesterol levels by about 5% (Olsson 2001; White 2002), and by analogy the halving of a statin dose (comparable to a drop in AUC of 50%) will reduce the cholesterol lowering effect by the same amount. For instance, as little as 1 mg of rosuvastatin provides over half the beneficial effect of an 80 mg dose of rosuvastatin (Olsson 2001). In a patient using both simvastatin and the CYP-inducer phenytoin (325 mg daily), the cholesterol-lowering effect of simvastatin was substantially reduced, raising total plasma cholesterol from below 10 mmol/l before and after phenytoin to 16 mmol/l during phenytoin treatment (Murphy and Dominiczak 1999).

In a meta-analysis of the large statin trials, each 10% reduction in blood-cholesterol level was associated with a 15% drop in the risk for coronary artery disease mortality, and an 11% drop in total mortality (Gould et al. 1998). However, the inducing effects resulting from pharmacokinetic interactions are often temporary, and even though a reduction in blood cholesterol levels is probable, effects on mortality are impossible to forecast on the basis of statin AUC-values alone. On the other hand, induction of drug metabolism, for example can last for several years in long-term treatment with antiepileptics that induce CYP enzymes. If the statin dose is raised to compensate for reduction in AUC, and the dosage is not returned to baseline, exposure to statins may increase when the effects of induction wear off. According to the results of Study V, the AUC of simvastatin acid increases on average 14-fold when the effects of induction wear off.

It appears that simvastatin (Study V) is more susceptible to enzyme induction by rifampicin than are atorvastatin (Backman et al. 2002), fluvastatin (Jokubaitis 1994) or pravastatin (Study VI). The effect of rifampicin on pravastatin pharmacokinetics seems to be the smallest of these statins. Because the pharmacokinetic profile of lovastatin is similar to that of simvastatin (Vickers et al. 1990b; Lennernäs

and Fager 1997), the effects of rifampicin on the pharmacokinetics of lovastatin and simvastatin are probably of the same magnitude. And since the pharmacokinetic profile of pravastatin is similar to that of rosuvastatin (Igel et al. 2002; White 2002), the effects of rifampicin on the pharmacokinetics of pravastatin and rosuvastatin are likely also of the same magnitude.

When potent inducers of CYP enzymes are used with statins, the loss off statin efficacy is best taken into account when choosing the appropriate statin and dosage. When the effects of induction wear off, the plasma concentrations of for instance simvastatin acid may increase by a factor of 10. It therefore seems sensible to refrain from using simvastatin or lovastatin with potent inducers of CYP3A4, such as rifampicin. If the statin dose is increased due to induction of statin metabolism, care is warranted when the effects of induction wear off.

CONCLUSIONS

The following conclusions can be drawn on the basis of the results from studies I to VI:

1. Gemfibrozil increases plasma concentrations of cerivastatin, lovastatin acid, simvastatin acid, and pravastatin. On average, cerivastatin is most susceptible to interaction with gemfibrozil, while pravastatin is least affected. All of these interactions are clinically significant, which means that the interaction must be taken into consideration when choosing the most appropriate drug and dose for the statin-fibrate combination. A larger pharmacokinetic interaction due to gemfibrozil also seems related to a higher risk for rhabdomyolysis, than with a smaller interaction.

2. On the basis of *in vitro* results and the changes of the concentrations of statin metabolites caused by gemfibrozil, the mechanism of the gemfibrozil-associated interactions seems unrelated to inhibition of CYP3A4. On the other hand, inhibition of CYP2C8 and drug transporting proteins may play a role in the interactions.

3. Bezafibrate exhibits no clinically significant pharmacokinetic interaction with lovastatin. Therefore fibrates seem to differ in their propensity to cause pharmacokinetic interactions when taken with a statin. The use of bezafibrate in concomitant treatment with statins may be associated with a lower risk for myopathy than is the use of gemfibrozil with statins, although the possibility of a pharmacodynamic interaction remains.

4. Rifampicin, and probably other potent inducers of CYP3A4 as well, greatly reduces plasma concentrations and probably the effects of simvastatin also. The effect of rifampicin on pravastatin is relatively small and highly variable. If long-term treatment with rifampicin or other potent inducers of CYP3A4 is needed, the loss of effect is probably less for pravastatin than for simvastatin. Therefore pravastatin may be used in favour of simvastatin in concomitant treatment with rifampicin or other potent inducers of CYP3A4.

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