PHARMACOKINETICS AND DRUG DISPOSITION

Disposition and sterol-lowering effect of ezetimibe are influenced by single-dose coadministration of rifampin, an inhibitor of multidrug transport proteins

Background and Aims: **The disposition and sterol-lowering effect of ezetimibe are associated with long-lasting enterosystemic circulation, which is initiated by secretion of ezetimibe and its glucuronide via intestinal P-glycoprotein (P-gp) (*ABCB1*) and the multidrug resistance-associated protein 2 (MRP2) (*ABCC2*) into gut lumen. Hepatic uptake and secretion may contribute to recycling. To obtain deeper insight into the intestinal and hepatic processes, the disposition of ezetimibe was studied in the presence of rifampin (INN, rifampicin), a modulator of P-gp, MRP2, and hepatic organic anion (uptake) transporting polypeptides (OATPs) (*SLCO*s).**

Methods: **The disposition of ezetimibe (20 mg orally) alone and after coadministration of rifampin (600 mg orally) was measured in a crossover study of 8 healthy subjects with the *SLCO1B1 *1a/*1a* genotype. Concentrations of ezetimibe and its glucuronide in serum, urine, and feces, as well as cholesterol, lathosterol, and the plant sterols campesterol and sitosterol in serum, were quantified by use of liquid chromatography and gas chromatography with mass spectrometric detection.**

Results: **After rifampin administration, the maximum serum concentrations of ezetimibe and its glucuronide were significantly elevated (12.0 ± 4.20 ng/mL versus 4.67 ± 2.72 ng/mL, $P = .017$, and 282 ± 73.8 ng/mL versus 107 ± 35.3 ng/mL, $P = .012$, respectively). The area under the curve of ezetimibe was not affected (102 ± 37.6 ng · h/mL versus 140 ± 86.3 ng · h/mL, P = not significant), whereas that of the glucuronide was markedly increased (2150 ± 687 ng · h/mL versus 1030 ± 373 ng · h/mL, $P = .012$). Renal clearance remained unchanged. Fecal excretion of ezetimibe was markedly decreased (7.6 ± 2.2 mg versus 10.4 ± 1.8 mg, $P = .036$), whereas renal excretion of the glucuronide was strongly elevated (4.8 ± 1.9 mg versus 2.0 ± 1.2 mg, $P = .049$) after coadministration. The onset of a significant sterol-lowering effect of ezetimibe was significantly shortened by rifampin coadministration.**

Conclusions: **Coadministration of rifampin increases the maximum serum concentrations of ezetimibe but reduces its enterosystemic recycling, most likely by inhibition of the secretion of ezetimibe and its glucuronide via P-gp and MRP2. (Clin Pharmacol Ther 2006;80:477-85.)**

Stefan Oswald, PhD, Thomas Giessmann, MD, Dieter Luetjohann, PhD, Danilo Wegner, Dieter Rosskopf, MD, Werner Weitschies, PhD, and Werner Siegmund, MD *Greifswald and Bonn, Germany*

From the Departments of Clinical Pharmacology, Pharmacology, and Biopharmaceutics and Pharmaceutical Technology, Ernst Moritz Arndt University of Greifswald, Greifswald, and Department of Clinical Pharmacology, University of Bonn, Bonn.

Supported by the German Federal Ministry for Education and Research (grant 01ZZ0403) and a research grant from MSD Sharp & Dohme.

Received for publication June 23, 2006; accepted July 24, 2006.

Reprint requests: Werner Siegmund, MD, Department of Clinical Pharmacology, Ernst Moritz Arndt University of Greifswald, Friedrich-Loeffler-Strasse 23d, D-17487 Greifswald, Germany.

E-mail: *siegmuw@uni-greifswald.de*

0009-9236/$32.00

doi:10.1016/j.clpt.2006.07.006

The availability of drugs on the site of their pharmacologic action depends, after oral administration, on the interplay between intestinal transit and disintegration of dosage forms, the regional conditions for drug dissolution, and the penetration of the intestinal absorption barrier, as well as the individual function of presystemic elimination mechanisms that may initiate recirculation pathways via the gut lumen.[1] The complexity of coincidental processes enables prediction of drug availability in receptor compartments if the location of pharmacologic action is along the absorption route. One example of a drug that acts within the absorption compartment is ezetimibe, which lowers serum cholesterol concentrations by inhibition of the sterol uptake transporter Niemann-Pick C1-like 1 protein (NPC1L1). NPC1L1 is located on intestinal brush border membranes, with the highest level of expression and cholesterol net absorption being observed in the jejunum, with lower levels in the duodenum and ileum.[2,3] There is some evidence from in vitro investigations, even though not undisputed, that unchanged ezetimibe binds to intracellular domains of NPC1L1.[4,5] Accordingly, the sterol-lowering effect must depend on its intracellular concentrations of brush border enterocytes.

After oral administration, ezetimibe is taken up from the gut most likely in proximal segments. A minor part of the dose occurs rapidly in blood.[6] The major part is metabolized to a phenolic glucuronide by intestinal uridine diphosphate–glucuronosyltransferase 1A1, the overall activity of which is highest in the jejunum, the major site of sterol absorption.[6-9] There is evidence from in vitro studies and drug interaction studies in humans that ezetimibe and its glucuronide are substrates of P-glycoprotein (P-gp) (*ABCB1*) and multidrug resistance-associated protein 2 (MRP2) (*ABCC2*).[10-13] The long-lasting circulation and effect of ezetimibe are most likely a result of intestinal secretion of the glucuronide via MRP2, bacterial hydrolysis of the glucuronide in the colon, and absorption of the released parent drug into the systemic circulation, followed by distribution via the systemic circulation to the sterol-absorbing effect compartment in the entire small intestine.[6,9] This pathway in humans generates characteristic serum concentration peaks that have resulted in our finding of bolus-like propulsion of chyme from the terminal ileum to the hydrolytic environment of the colon triggered by a meal-induced gastroileocecal reflex.[13-15]

We have recently shown that intestinal secretion of the glucuronide of ezetimibe by P-gp and MRP2, in healthy subjects, is the rate-determining elimination route for ezetimibe from the sterol-absorbing microcompartment and, in turn, for the extent of its sterol-lowering effect.[13] Ezetimibe is also secreted into bile, as shown in bile duct–cannulated rats after intraduodenal administration of both the parent drug and the glucuronide.[9] However, it is unknown thus far by which hepatic mechanism unchanged ezetimibe or its glucuronide (or both) is extracted from sinusoidal blood. Potential carriers for hepatic uptake of ezetimibe are members of the organic anion transporting polypeptide (OATP, *SLCO*) family, particularly the liver-specific, broad substrate spectrum–acquiring OATP1B1 (*SLCO1B1*) and OATP1B3 (*SLCO1B3*).[16,17] Both uptake carriers are modulated in vitro by the antibiotic rifampin (INN, rifampicin).[18,19] However, rifampin also modulates P-gp and MRP2.[20-25] Therefore coadministration of rifampin is considered to be a suitable experimental tool by which to evaluate the complex presystemic disposition of ezetimibe in humans.

We hypothesized that inhibition of P-gp, MRP2, or OATPs (or some combination thereof) by rifampin may increase the availability of ezetimibe in the blood but decrease the extent of enterosystemic circulation of parent ezetimibe to the intestinal sterol-absorbing compartment and may, in turn, influence the sterol-lowering effect of the drug.

METHODS

Clinical study protocol

Subjects. We selected 8 healthy subjects with the *SLCO1B1 ∗1a/∗1a* diplotype (2 women and 6 men; age range, 22-36 years; body mass index range, 20.4-25.1 kg/m^2) after confirmation of good health by medical histories, physical examinations, and routine clinical-chemical and hematologic screenings. The subjects were nonsmokers and took no medications except hormonal contraceptives (2 women). Strenuous physical activity and alcoholic beverages were not allowed from 48 hours before the first administration of study medication until the last blood sampling. Intake of products containing grapefruit, orange, and poppy seed was prohibited 7 days before the first drug administration and until the last blood sampling of the study. The study protocol was approved by the local ethical committee, and all subjects gave written informed consent. Planning and performance of the study followed the regulations of the German Medical Act and the recommendations of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use–Good Clinical Practice (ICH-GCP) guidelines (Note for Guidance on Good Clinical Practice, CPMP/ICH/135/95, 1997).

Study protocol. The controlled, randomized, open crossover study was performed with washout periods between 14 and 16 days. After inclusion, the subjects were admitted to the clinical study unit in the evening before the respective pharmacokinetic study days. The study medication was given the next morning after overnight fasting for at least 10 hours. Either ezetimibe alone (two 10-mg fast-release tablets of Ezetrol; MSD Sharp & Dohme, Haar, Germany) or ezetimibe and rifampin (one 600-mg coated tablet of Rifa 600; Grünenthal, Aachen, Germany) were administered orally together with 200 mL tap water. Standard meals were served 5, 8, and 11 hours after administration and at 8:00 AM and 1:00 and 8:00 PM on the next day. Each subject had to eat meals of same size during both study periods. Drinking of tap water was also strongly standardized. Forearm venous blood sampling (5 mL) was done before and 0.33, 0.66, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours after drug intake. Urine was collected for 5 days, and feces were collected for 10 days. Serum and aliquots of urine and homogenized feces were stored at least at −80°C until quantitative analysis.

Quantitative assay of ezetimibe

As described recently, concentrations of unchanged and total ezetimibe in serum, urine, and feces were quantified by use of a liquid chromatography–tandem mass spectrometry system consisting of an XTerra MS column (C18, 2.1 × 100 mm, particle size of 3.5 μm; Waters, Milford, Mass) and PE Sciex API 2000 mass spectrometer (Applied Biosystems, Foster City, Calif).[26] The limits of quantification for serum were 0.05 ng/mL for unchanged ezetimibe and 1.0 ng/mL for total ezetimibe. The limits of quantification for urine and feces were 1.0 ng/mL and 10 ng/mL, respectively. In this study within-day and between-day accuracy for serum was within −10.1% and 5.6% and −7.3% and 6.3%, respectively, of the nominal concentrations of total and parent ezetimibe. Between-day precision in serum was 1.7% to 9.6% of mean values. For urine and feces, accuracy was −11.5% to 6.2% of nominal values, and precision was 1.4% to 10.7% of mean values.

Analysis of sterols

Cholesterol, lathosterol, and the plant sterols campesterol and sitosterol were extracted from serum after saponification and underwent derivation to trimethylsilyl ethers. Total serum cholesterol concentrations were determined by sensitive gas chromatography with flame ionization detection, which differentiates between cholesterol and side chain–substituted cholesterols, such as campesterol (24-methylcholesterol) and sitosterol (24-ethylcholesterol). Serum concentrations of the cholesterol precursor lathosterol and the plant sterols campesterol and sitosterol were assessed by use of a validated gas chromatography–mass spectrometry selective ion-monitoring method as previously described.[27] The within-day and between-day coefficients of variation for all sterols were below 4% of the respective mean values (precision). Between-day accuracy was less than 3% of the respective nominal values. The limit of quantification was 1 mg/dL for cholesterol and 0.005 mg/dL for lathosterol, campesterol, and sitosterol.

Genotyping of OATP1B1

The subjects were genotyped for the *SLCO1B1* polymorphisms *G−11187A*, *A388G* (Asn130Asp), and *T521C* (Val174Ala) by polymerase chain reaction–restriction fragment length polymorphism analysis as described elsewhere.[26] Haplotype *∗1a* was allocated as *−11187G*, *388A*, and *521T* as reported by Niemi et al.[28]

Pharmacokinetic and statistical evaluation

The maximum plasma concentration (C_{max}) and time to C_{max} (t_{max}) were taken from the concentration-time curves. The area under the serum concentration–time curve (AUC) from 0 to 96 hours ($AUC_{0\text{-}96}$) was calculated by use of the trapezoidal rule. Renal clearance (CL_R) was derived from the respective cumulative amounts (A_e) of ezetimibe and its glucuronide excreted into the urine over the respective $AUC_{0\text{-}96}$.

The arithmetic or geometric means and SDs were given as appropriate. Sample differences were evaluated with the nonparametric Wilcoxon test.

RESULTS

Pharmacokinetics

For several hours, oral administration of ezetimibe alone caused fluctuating serum concentrations between about 2 and 4 ng/mL and 3 to 4 distinct peaks, of which the second after lunch was eaten (5 hours after dosing) was usually the highest. The third and fourth peaks also occurred in association with meals, at 11 hours (dinner) and 24 hours (breakfast) after drug administration (Fig 1). In contrast, in most subjects the glucuronide of ezetimibe reached a single but several-fold higher maximum in an appreciably shorter amount of time. The dominating elimination route for ezetimibe was intestinal excretion. About 60% of the ezetimibe dose was eliminated via feces; about 20% of that portion was in its glucuronide form. Approximately 10% of the dose appeared in urine in the form of the glucuronide (Table I).

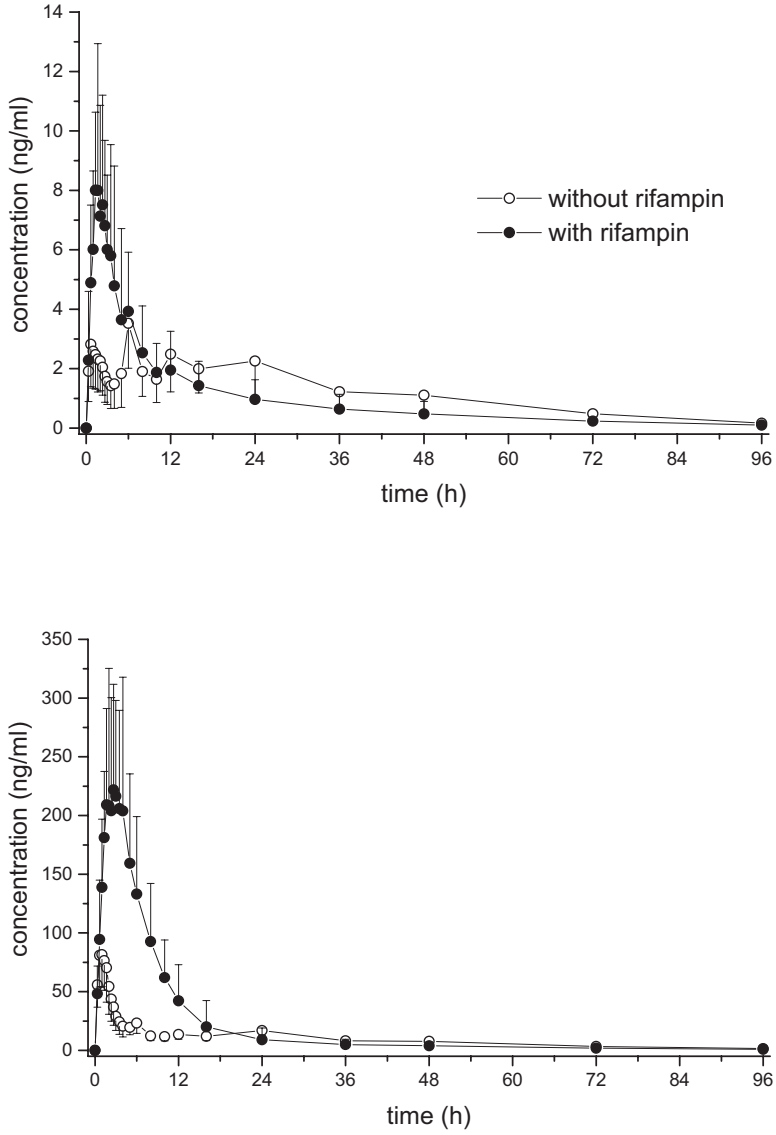

Fig 1. Serum concentration–time curves of ezetimibe (*top*) and its glucuronide (*bottom*) in 8 healthy subjects without rifampin (*open circles*) and after coadministration of 600 mg rifampin (*solid circles*). Geometric means and geometric SDs (*error bars*) are given.

After rifampin administration, maximum serum concentrations of ezetimibe and its glucuronide were significantly elevated (12.0 ± 4.20 ng/mL versus 4.67 ± 2.72 ng/mL, $P = .017$, and 282 ± 73.8 ng/mL versus 107 ± 35.3 ng/mL, $P = .012$, respectively). The area under the curve of ezetimibe was not affected (102 ± 37.6 ng · h/mL versus 140 ± 86.3 ng · h/mL, P = not significant), whereas that of its glucuronide was markedly increased (2150 ± 687 ng · h/mL versus 1030 ± 373 ng · h/mL, $P = .012$). Renal clearance remained unchanged. Under the influence of rifampin, a significantly lower portion of the ezetimibe dose was excreted via feces (7.6 ± 2.2 mg versus 10.4 ± 1.8 mg, $P = .036$), whereas the amount of its glucuronide excreted via urine was more than doubled (4.8 ± 1.9 mg versus 2.0 ± 1.2 mg, $P = .049$) after coadministration (Table I).

Drug effects

The single 20-mg dose of ezetimibe produced a long-lasting cholesterol-lowering effect that was significantly different from baseline for time points later than

Table I. Pharmacokinetic characteristics of ezetimibe after single oral dose of 20 mg given either alone or concomitantly with single oral dose of 600 mg rifampin in 8 healthy subjects

	Ezetimibe		*Glucuronide*	
	Without rifampin	*With rifampin*	*Without rifampin*	*With rifampin*
$AUC_{0\text{-}96}$ (ng · h/mL)	140 ± 86.3	102 ± 37.6	1030 ± 373	2150 ± 687 (*P*=.012)
C_{max} (ng/mL)	4.67 ± 2.72	12.0 ± 4.20 (*P*=.017)	107 ± 35.3	282 ± 73.8 (*P*=.012)
t_{max} (h)	4.83 ± 3.85	1.89 ± 0.90	1.12 ± 0.47	2.73 ± 1.06 (*P*=.012)
Ae_{feces} (mg)	10.4 ± 1.81	7.59 ± 2.22 (*P*=.036)	1.81 ± 2.73	0.88 ± 1.01
Ae_{urine} (mg)	0.015 ± 0.033	0.015 ± 0.014	2.04 ± 1.18	4.84 ± 1.93 (*P*=.049)
CL_R (mL/min)	5.40 ± 13.6	2.46 ± 2.17	38.4 ± 26.1	44.2 ± 29.2

Data are given as mean ± SD. *P* values indicate significance levels for comparisons to values without rifampin coadministration (Wilcoxon test).
$AUC_{0\text{-}96}$, Area under serum concentration–time curve from 0 to 96 hours; C_{max}, maximum serum concentration; t_{max}, time to maximum serum concentration; Ae_{urine}, cumulative amount excreted into urine; Ae_{feces}, cumulative amount excreted into feces; CL_R, renal clearance.

48 hours after administration (Fig 2). Similar changes were found for campesterol and sitosterol (Fig 3). The effects on the ratios between campesterol and cholesterol and between sitosterol and cholesterol, which are established surrogates for cholesterol absorption, were quite similar. The ratio between lathosterol and cholesterol, a surrogate of cholesterol synthesis, was not significantly influenced by ezetimibe.

After comedication of rifampin, the onset of the plant sterol–lowering effect was generally faster; the campesterol and sitosterol serum levels and the campesterol/cholesterol and sitosterol/cholesterol ratios were already significantly different from baseline at 24 hours after administration. However, the initial ratio between lathosterol and cholesterol was also significantly lowered after rifampin coadministration (Figs 2 and 3).

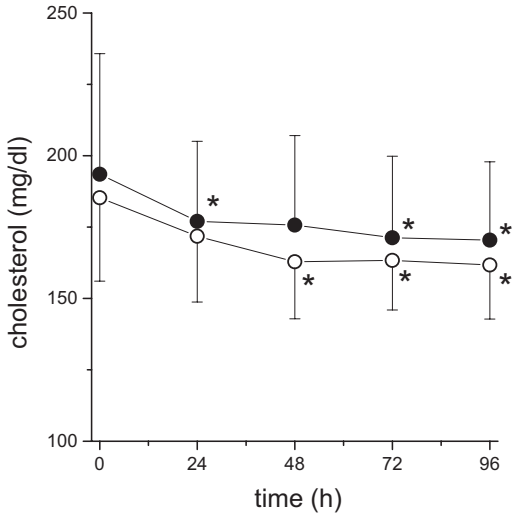

Fig 2. Serum concentrations of cholesterol after administration of 20 mg ezetimibe in 8 healthy subjects without rifampin (*open circles*) and after coadministration of 600 mg rifampin (*solid circles*). Geometric means and geometric SDs (*error bars*) are given. *Asterisk*, $P < .05$ for comparison with initial values (Wilcoxon test).

DISCUSSION

In this clinical study it has been shown that coadministration of rifampin yields more than 2-fold higher serum concentrations of ezetimibe. The systemic exposure, however, remained unchanged. The serum levels and the area under the curve of the glucuronide were also increased by more than 2-fold, whereas the renal clearance remained unchanged. Consequently, a dose fraction of about 15% was also excreted in the form of the glucuronide via urine, rather than via feces, as in the absence of rifampin.

Coadministration of rifampin caused significantly faster lowering of plant sterol serum levels. The ratios between the plant sterols campesterol and sitosterol and cholesterol were used as surrogates for changes in cholesterol absorption because plant sterols, unlike cholesterol, are not endogenously formed.[29] On the other hand, the lathosterol/cholesterol ratio is an accepted surrogate for the influence on endogenous cholesterol synthesis.[30] Rifampin coadministration has obviously also modulated cholesterol synthesis for about 24 hours after administration. Lathosterol is the end product of a long chain of biochemical reactions, some of which are cytochrome P450–dependent.[31] Because rifampin also modulates cytochrome P450 enzymes (eg, 3A4 and 2C8), cholesterol serum levels in our study may have been decreased by inhibition of the endogenous synthesis via lathosterol.[32]

The single-dose effects of rifampin on the disposition and pharmacologic effect of ezetimibe are, to our interpretation, best explained by inhibition of the intestinal efflux of ezetimibe and its glucuronide because

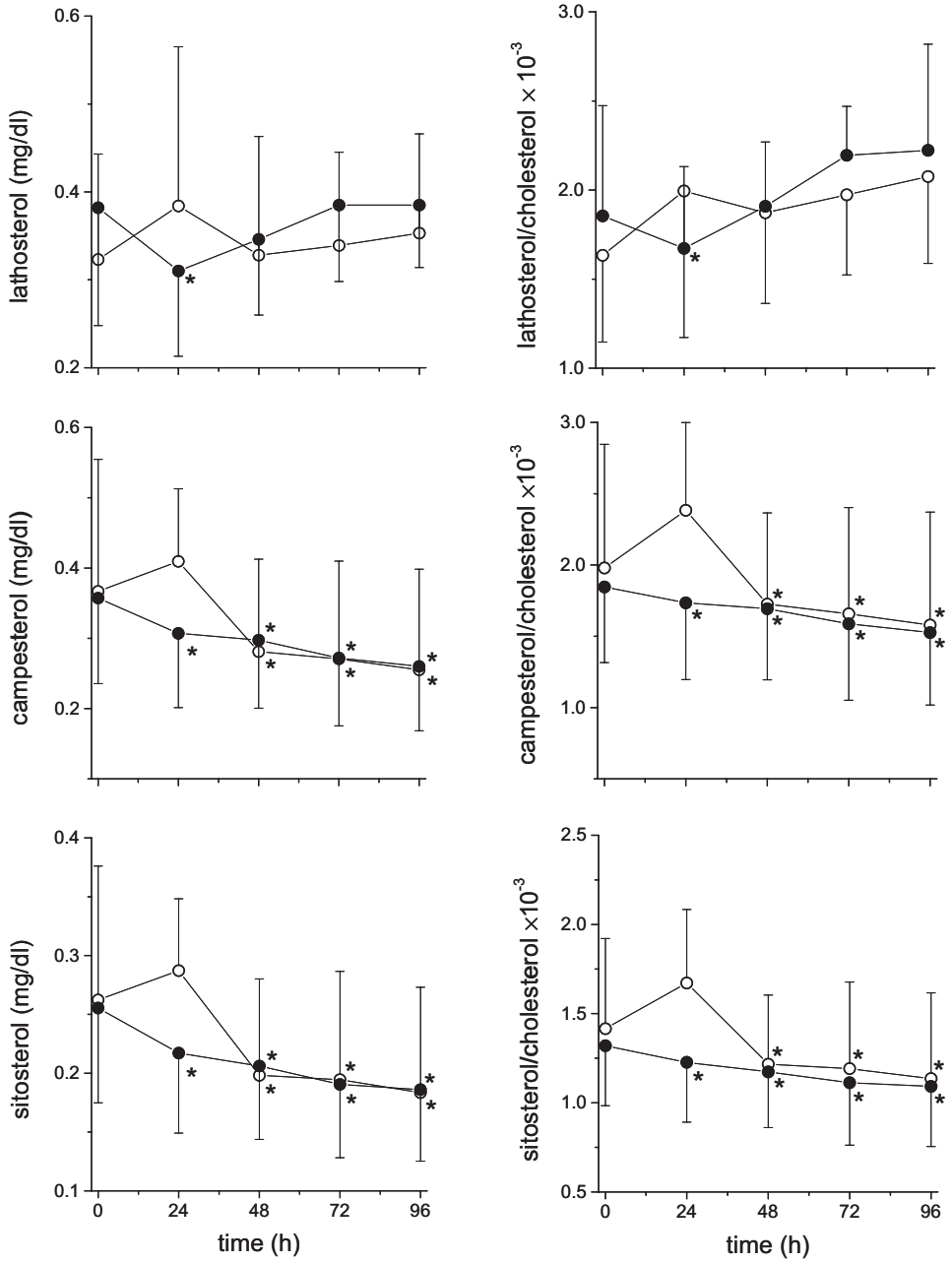

Fig 3. Serum concentrations of lathosterol, campesterol, and sitosterol (*left*) and lathosterol/cholesterol, campesterol/cholesterol, and sitosterol/cholesterol ratios (*right*) after administration of 20 mg ezetimibe in 8 healthy subjects without rifampin (*open circles*) and after coadministration of 600 mg rifampin (*solid circles*). Geometric means and geometric SDs (*error bars*) are given. *Asterisk*, $P < .05$ for comparison with initial values (Wilcoxon test).

rifampin is an inhibitor of P-gp and MRP2 in vitro and in animals.[20-25] After oral administration of the modulator, highly active concentrations at the binding sites of P-gp and MRP2 are temporarily expected in the absorbing enterocytes during the short absorption period. Sustained inhibition of the efflux in the sterol-absorbing receptor compartment of ezetimibe along the entire small intestine, however, seems to result from

intense enterohepatic circulation of rifampin via hepatic uptake by OATPs and biliary secretion via MRP2.[18,19,24,25] Active intestinal secretion of rifampin may also contribute to distribution of rifampin to the sites of the intestinal efflux carriers for ezetimibe and its glucuronide.[33] However, rifampin is markedly more quickly eliminated than ezetimibe (half-life, 3-4 hours versus 20-25 hours). Furthermore, systemic availability of ezetimibe is also prolonged by the long-lasting enterointestinal circulation. Therefore single-dose rifampin may influence ezetimibe disposition only during absorption and the early phases of elimination.

On the one hand, inhibition of P-gp and MRP2 by rifampin leads to better absorption of ezetimibe and, consequently, to serum concentrations that are increased by more than 2-fold at 2 to 3 hours after oral administration. In contrast, inhibition of MRP2, the major intestinal and hepatic efflux carrier for the glucuronide, leads to interruption of the enterosystemic recycling of the active drug (ezetimibe) and, consequently, shorter residence of the drug in blood. The AUC values remain unchanged with rifampin coadministration, as shown by our data.

The nonsecreted portion of the glucuronide is available in venous blood via the portal vein, yields higher serum concentrations, and undergoes increased urinary excretion by renal filtration than in the absence of rifampin. Renal clearance is consequently not influenced; the dose fraction excreted via feces is significantly reduced, in our study by about 15%.

Despite the marked pharmacokinetic changes after rifampin administration, the sterol-lowering effect of ezetimibe has changed negligibly; the only influence was earlier onset of sterol-lowering. The recommended therapeutic dose in patients is 10 mg/d. In the presence of rifampin in our study, 20 mg is obviously still enough to produce the full, long-lasting cholesterol-lowering effect, even though the mean residence of the parent drug was markedly decreased.

In contrast to single-dose administration, long-term treatment with rifampin increases intestinal elimination associated with markedly lower serum concentrations of ezetimibe and its glucuronide and nearly abolished the sterol-lowering effects.[13] The characteristic fluctuating concentration-time profiles remain undisturbed. The rationale behind these phenomena is, to our interpretation, acceleration of the enterosystemic circulation as caused by up-regulation of intestinal and hepatic efflux particularly of the glucuronide via MRP2 because rifampin is a ligand of the nuclear pregnane X receptor.[34-36]

The influence of rifampin on serum concentration–time curves of ezetimibe and its glucuronide in our single-dose study was very similar to the effects that were measured after comedication of gemfibrozil and fenofibrate. Long-term treatment of hypercholesterolemic patients with gemfibrozil (600 mg) and ezetimibe (10 mg) increased plasma concentrations of ezetimibe and its glucuronide without changing the characteristic meal-associated fluctuations.[12] A similar influence was obtained with comedication of fenofibrate, though to a lower extent, which was not of statistical significance in the case of the parent drug (ezetimibe).[11] Gemfibrozil and polysorbate 80, which were part of the tested gemfibrozil formulation (Lopid; Pfizer, Freiburg, Germany), as well as fenofibrate, are modulators of P-gp or MRP2 (or both).[37-40] Furthermore, plasma levels of total ezetimibe and therapeutic efficacy are also markedly increased by comedication of cyclosporine (INN, ciclosporin), which is an inhibitor of P-gp and, to a minor extent, of MRP2.[10,41-44]

Rifampin, cyclosporine, and gemfibrozil are also inhibitors of OATP1B1, an uptake transporter for many drugs and endogenous substances, such as pravastatin, methotrexate, thyroid hormones, and bilirubin glucuronide, which is selectively expressed in the basolateral membrane of human hepatocytes.[16-19,40,45,46] To our knowledge, no information are available so far on whether ezetimibe and its glucuronide are substrates of hepatic OATPs. Pravastatin and pitavastatin, which are substrates of OATP1B1 in vitro, with demonstrated dependence of their disposition on the *OATP1B1* genotype, lacked a significant influence on the AUC and C_{max} of ezetimibe and its glucuronide in hypercholesterolemic patients.[28,47-50] Furthermore, the OATP1B1 substrate rosuvastatin did not interact with the disposition of ezetimibe.[49,51] In our study, however, we cannot exclude that inhibition of hepatic OATPs by rifampin has contributed to the overall changes in ezetimibe disposition and sterol-lowering effect.

In conclusion, single-dose coadministration of rifampin increases maximum serum concentrations of ezetimibe but reduces its enterosystemic recycling, most likely by inhibition of the secretion of the parent drug and its glucuronide via P-gp and MRP2.

We thank Hannelore Kreher, Sabine Bade, Gitta Schumacher, and Anja Kerksiek for excellent technical assistance.

The authors have no conflict of interest.

References

1. Kunta JR, Sinko PJ. Intestinal drug transporters: in vivo function and clinical importance. Curr Drug Metab 2004; 5:109-24.

2. Altmann SW, Davis HR Jr, Zhu LJ, Yao X, Hoos LM, Tetzloff G, et al. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. Science 2004;303:1201-4.
3. Hui DY, Howles PN. Molecular mechanisms of cholesterol absorption and transport in the intestine. Semin Cell Dev Biol 2005;16:183-92.
4. Davies JP, Scott C, Oishi K, Liapis A, Ioannou YA. Inactivation of NPC1L1 causes multiple lipid transport defects and protects against diet-induced hypercholesterolemia. J Biol Chem 2005;280:12710-20.
5. Yu LQ, Bharadwaj S, Brown JM, Ma YY, Du W, Davis MA, et al. Cholesterol-regulated translocation of NPC1L1 to the cell surface facilitates free cholesterol uptake. J Biol Chem 2006;281:6616-24.
6. Patrick JE, Kosoglou T, Stauber KL, Alton KB, Maxwell SE, Zhu Y, et al. Disposition of the selective cholesterol absorption inhibitor ezetimibe in healthy male subjects. Drug Metab Dispos 2002;30:430-7.
7. Ghosal A, Hapangama N, Yuan Y, Achanfuo-Yeboah J, Iannucci R, Chowdhury S, et al. Identification of human UDP-glucuronosyltransferase enzyme(s) responsible for the glucuronidation of ezetimibe (Zetia). Drug Metab Dispos 2004;32:314-20.
8. Tukey RH, Strassburg CP. Genetic multiplicity of the human UDP-glucuronosyltransferases and regulation in the gastrointestinal tract. Mol Pharmacol 2001;59:405-14.
9. van Heek M, Farley C, Compton DS, Hoos L, Alton KB, Sybertz EJ, et al. Comparison of the activity and disposition of the novel cholesterol absorption inhibitor, SCH58235, and its glucuronide, SCH60663. Br J Pharmacol 2000;129:1748-54.
10. Bergman AJ, Burke J, Larson P, Johnson-Levonas AO, Reyderman L, Statkevich P, et al. Interaction of single-dose ezetimibe and steady-state cyclosporine in renal transplant patients. J Clin Pharmacol 2006;46:328-36.
11. Kosoglou T, Statkevich P, Fruchart JC, Pember LJ, Reyderman L, Cutler DL, et al. Pharmacodynamic and pharmacokinetic interaction between fenofibrate and ezetimibe. Curr Med Res Opin 2004;20:1197-207.
12. Reyderman L, Kosoglou T, Statkevich P, Pember L, Boutros T, Maxwell SE. Assessment of a multiple-dose drug interaction between ezetimibe, a novel selective cholesterol absorption inhibitor and gemfibrozil. Int J Clin Pharmacol Ther 2004;42:512-8.
13. Oswald S, Haenisch S, Fricke C, Sudhop T, Remmler C, Giessmann T, et al. Intestinal expression of P-glycoprotein (*ABCB1*), multidrug resistance associated protein 2 (*ABCC2*), and uridine diphosphate–glucuronosyltransferase 1A1 predicts the disposition and modulates the effects of the cholesterol absorption inhibitor ezetimibe in humans. Clin Pharmacol Ther 2006;79:206-17.
14. Ezzet F, Krishna G, Wexler DB, Statkevich P, Kosoglou T, Batra VK. A population pharmacokinetic model that describes multiple peaks due to enterohepatic recirculation of ezetimibe. Clin Ther 2001;23:871-85.
15. Schiller C, Frohlich CP, Giessmann T, Siegmund W, Monnikes H, Hosten N, et al. Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging. Aliment Pharmacol Ther 2005;22:971-9.
16. Chandra P, Brouwer KL. The complexities of hepatic drug transport: current knowledge and emerging concepts. Pharm Res 2004;21:719-35.
17. Hagenbuch B, Meier PJ. The superfamily of organic anion transporting polypeptides. Biochim Biophys Acta 2003;1609:1-18.
18. Tirona RG, Leake BF, Wolkoff AW, Kim RB. Human organic anion transporting polypeptide-C (SLC21A6) is a major determinant of rifampin-mediated pregnane X receptor activation. J Pharmacol Exp Ther 2003;304:223-8.
19. Vavricka SR, Van Montfoort J, Ha HR, Meier PJ, Fattinger K. Interactions of rifamycin SV and rifampicin with organic anion uptake systems of human liver. Hepatology 2002;36:164-72.
20. Fardel O, Lecureur V, Loyer P, Guillouzo A. Rifampicin enhances anti-cancer drug accumulation and activity in multidrug-resistant cells. Biochem Pharmacol 1995;49:1255-60.
21. Zong J, Pollack GM. Modulation of P-glycoprotein transport activity in the mouse blood-brain barrier by rifampin. J Pharmacol Exp Ther 2003;306:556-62.
22. Furusawa S, Nakano S, Wu J, Sasaki K, Takayanagi M, Takayanagi Y. Potentiation of pirarubicin activity in multidrug resistant cells by rifampicin. Biol Pharm Bull 1997;20:1303-6.
23. Cui Y, Konig J, Keppler D. Vectorial transport by double-transfected cells expressing the human uptake transporter SLC21A8 and the apical export pump ABCC2. Mol Pharmacol 2001;60:934-43.
24. Lau YY, Okochi H, Huang Y, Benet LZ. Multiple transporters affect the disposition of atorvastatin and its two active hydroxy metabolites: application of in vitro and ex situ systems. J Pharmacol Exp Ther 2006;316:762-71.
25. Spears KJ, Ross J, Stenhouse A, Ward CJ, Goh LB, Wolf CR, et al. Directional trans-epithelial transport of organic anions in porcine LLC-PK1 cells that co-express human OATP1B1 (OATP-C) and MRP2. Biochem Pharmacol 2005;69:415-23.
26. Oswald S, Scheuch E, Cascorbi I, Siegmund W. A LC-MS/MS method to quantify the novel cholesterol lowering drug ezetimibe in human serum, urine and feces in healthy subjects genotyped for SLCO1B1. J Chromatogr B Analyt Technol Biomed Life Sci 2006;830:143-50.
27. Sudhop T, Lutjohann D, Kodal A, Igel M, Tribble DL, Shah S, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation 2002;106:1943-8.
28. Niemi M, Schaeffeler E, Lang T, Fromm MF, Neuvonen M, Kyrklund C, et al. High plasma pravastatin concentrations

are associated with single nucleotide polymorphisms and haplotypes of organic anion transporting polypeptide-C (OATP-C, SLCO1B1). Pharmacogenetics 2004;14:429-40.
29. Miettinen TA, Tilvis RS, Kesaniemi YA. Serum plant sterols and cholesterol precursors reflect cholesterol absorption and synthesis in volunteers of a randomly selected male population. Am J Epidemiol 1990;131:20-31.
30. Reihner E, Rudling M, Stahlberg D, Berglund L, Ewerth S, Bjorkhem I, et al. Influence of pravastatin, a specific inhibitor of HMG-CoA reductase, on hepatic metabolism of cholesterol. N Engl J Med 1990;323:224-8.
31. Nebert DW, Russell DW. Clinical importance of the cytochromes P450. Lancet 2002;360:1155-62.
32. Kajosaari LI, Laitila J, Neuvonen PJ, Backman JT. Metabolism of repaglinide by CYP2C8 and CYP3A4 in vitro: effect of fibrates and rifampicin. Basic Clin Pharmacol Toxicol 2005;97:249-56.
33. Mariappan TT, Singh S. Evidence of efflux-mediated and saturable absorption of rifampicin in rat intestine using the ligated loop and everted gut sac techniques. Mol Pharm 2004;1:363-7.
34. Fromm MF, Kauffmann HM, Fritz P, Burk O, Kroemer HK, Warzok RW, et al. The effect of rifampin treatment on intestinal expression of human MRP transporters. Am J Pathol 2000;157:1575-80.
35. Geick A, Eichelbaum M, Burk O. Nuclear receptor response elements mediate induction of intestinal MDR1 by rifampin. J Biol Chem 2001;276:14581-7.
36. Kast HR, Goodwin B, Tarr PT, Jones SA, Anisfeld AM, Stoltz CM, et al. Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor. J Biol Chem 2002;277:2908-15.
37. Ehrhardt M, Lindenmaier H, Burhenne J, Haefeli WE, Weiss J. Influence of lipid lowering fibrates on P-glycoprotein activity in vitro. Biochem Pharmacol 2004;67:285-92.
38. Seral C, Carryn S, Tulkens PM, Van Bambeke F. Influence of P-glycoprotein and MRP efflux pump inhibitors on the intracellular activity of azithromycin and ciprofloxacin in macrophages infected by Listeria monocytogenes or Staphylococcus aureus. J Antimicrob Chemother 2003;51:1167-73.
39. Shono Y, Nishihara H, Matsuda Y, Furukawa S, Okada N, Fujita T, et al. Modulation of intestinal P-glycoprotein function by cremophor EL and other surfactants by an in vitro diffusion chamber method using the isolated rat intestinal membranes. J Pharm Sci 2004;93:877-85.
40. Yamazaki M, Li B, Louie SW, Pudvah NT, Stocco R, Wong W, et al. Effects of fibrates on human organic anion-transporting polypeptide 1B1-, multidrug resistance protein 2- and P-glycoprotein-mediated transport. Xenobiotica 2005;35:737-53.
41. Bohme M, Jedlitschky G, Leier I, Buchler M, Keppler D. ATP-dependent export pumps and their inhibition by cyclosporins. Adv Enzyme Regul 1994;34:371-80.
42. Koshman SL, Lalonde LD, Burton I, Tymchak WJ, Pearson GJ. Supratherapeutic response to ezetimibe administered with cyclosporine. Ann Pharmacother 2005;39:1561-5.
43. Payen L, Courtois A, Campion JP, Guillouzo A, Fardel O. Characterization and inhibition by a wide range of xenobiotics of organic anion excretion by primary human hepatocytes. Biochem Pharmacol 2000;60:1967-75.
44. Tamai I, Safa AR. Competitive interaction of cyclosporins with the Vinca alkaloid-binding site of P-glycoprotein in multidrug-resistant cells. J Biol Chem 1990;265:16509-13.
45. Shitara Y, Itoh T, Sato H, Li AP, Sugiyama Y. Inhibition of transporter-mediated hepatic uptake as a mechanism for drug-drug interaction between cerivastatin and cyclosporin A. J Pharmacol Exp Ther 2003;304:610-6.
46. Shitara Y, Hirano M, Sato H, Sugiyama Y. Gemfibrozil and its glucuronide inhibit the organic anion transporting polypeptide 2 (OATP2/OATP1B1:SLC21A6)-mediated hepatic uptake and CYP2C8-mediated metabolism of cerivastatin: analysis of the mechanism of the clinically relevant drug-drug interaction between cerivastatin and gemfibrozil. J Pharmacol Exp Ther 2004;311:228-36.
47. Chung JY, Cho JY, Yu KS, Kim JR, Oh DS, Jung HR, et al. Effect of OATP1B1 (SLCO1B1) variant alleles on the pharmacokinetics of pitavastatin in healthy volunteers. Clin Pharmacol Ther 2005;78:342-50.
48. Hirano M, Maeda K, Shitara Y, Sugiyama Y. Contribution of OATP2 (OATP1B1) and OATP8 (OATP1B3) to the hepatic uptake of pitavastatin in humans. J Pharmacol Exp Ther 2004;311:139-46.
49. Kosoglou T, Statkevich P, Johnson-Levonas AO, Paolini JF, Bergman AJ, Alton KB. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. Clin Pharmacokinet 2005;44:467-94.
50. Nakai D, Nakagomi R, Furuta Y, Tokui T, Abe T, Ikeda T, et al. Human liver-specific organic anion transporter, LST-1, mediates uptake of pravastatin by human hepatocytes. J Pharmacol Exp Ther 2001;297:861-7.
51. Simonson SG, Raza A, Martin PD, Mitchell PD, Jarcho JA, Brown CD, et al. Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine. Clin Pharmacol Ther 2004;76:167-77.