Kidney International, Vol. 67 (2005), pp. 1152–1160

Impact of gastric acid suppressants on cytochrome P450 3A4 and P-glycoprotein: Consequences for FK506 assimilation

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Impact of gastric acid suppressants on cytochrome P450 3A4 and P-glycoprotein: Consequences for FK506 assimilation.

Background. Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (PGP) are important determinants of the oral bioavailability and clearance of tacrolimus. Cimetidine and omeprazole are known modulators of several CYPs in vitro. In the present study, the impact of cimetidine and omeprazole on tacrolimus exposure and on CYP3A4/PGP activity in vivo was examined.

Methods. In a cohort of 48 renal transplant recipients who switched standard ulcer prophylaxis with 400 mg of cimetidine daily to 20 mg of omeprazole, dose/weight normalized trough levels of tacrolimus during a 5-day interval before and after switch were compared and further studied using multivariate analysis. In a cohort of 6 healthy volunteers, the effect of a 5-day course of ranitidine, cimetidine, and omeprazole on overall CYP, CYP3A4, and PGP activity in vivo was assessed with the ^{13}C-aminopyrin breath test and the combined per oral and intravenous ^{14}C-erythromycin breath and urine test.

Results. Dose/weight normalized trough levels of tacrolimus decreased significantly (−15%) after switch from cimetidine to omeprazole. In healthy volunteers, a significant increase of intestinal CYP3A4 activity was observed after omeprazole, whereas no change was noted after cimetidine/ranitidine. Overall CYP activity was significantly decreased after cimetidine and remained unchanged after omeprazole/ranitidine. No effects on PGP or hepatic CYP3A4 were seen.

Conclusion. Switching treatment with cimetidine to omeprazole in renal transplant recipients is associated with a decrease of dose/weight normalized trough levels of tacrolimus. Studies in healthy volunteers suggest that this may be explained by an increase of intestinal CYP3A4 activity.

Transplant recipients receiving immunosuppressive narrow therapeutic index drugs and multiple other medications are at particular risk for potentially dangerous drug-interactions. Enteric and hepatic catabolism by cytochrome P450 (CYP) enzymes, whose most important isoform is CYP3A4, and excretion by P-glycoprotein are key determinants of oral bioavailability and clearance of several immunosuppressants and numerous other drugs [1–3]. The strong effect of well-known CYP3A4/PGP inducers and inhibitors, such as rifampin and itraconazole, on biodisposition of the calcineurin inhibitors, cyclosporine A and tacrolimus, are well documented both in vitro and in vivo [4, 5].

In addition, several other drugs have been shown to influence the activity of diverse CYP isoforms or PGP to a certain extent. Typical examples are gastric acid suppressants such as the histamine II receptor blockers, cimetidine and ranitidine, and the more powerful proton pump inhibitor, omeprazole. These drugs are frequently used in transplant recipients since several clinical studies showed a beneficial effect of ulcer prophylaxis with each of the 3 drugs [6–8]. In our country, it is common practice to initiate prophylactic treatment with cimetidine in all patients after transplantation, and to use omeprazole as a second line drug. However, numerous studies have demonstrated a modulating effect of both cimetidine and omeprazole—and to a lesser extent ranitidine—on several CYP isozymes, implicating a potential effect on bioavailability and clearance of CYP3A4 dependent immunosuppressants. Most of these studies have been done in vitro or ex vivo, which does not allow an easy extrapolation to clinical practice [9–12].

The purpose of the current study was to bridge this gap. This was done at a double level. First, the impact of switching cimetidine to omeprazole on the exposure to tacrolimus in renal transplant recipients was studied. Second, to further unravel the potential mechanisms of altered drug exposure, the specific effects of cimetidine and omeprazole on overall CYP, CYP3A4, and PGP activity in vivo were assessed in healthy volunteers. Overall CYP activity was measured by means of the aminopyrin breath test (ABT), which is also used as an indicator of liver function [13]. CYP3A4/PGP activity was quantified by means of a combined per oral and intravenous breath and urine test, using [N-methyl-^{14}C]-erythromycin as a probe for noninvasive measurement of intestinal and hepatic CYP3A4 and PGP [14].

Key words: CYP3A4, transplantation, gastric acid suppressants, tacrolimus.

METHODS

Subjects

Patients. A cohort of 201 Caucasian patients underwent renal transplantation at our center between July 1998 and December 2000. Standard immunosuppressive therapy consisted of corticosteroids (CS), tacrolimus, and mycophenolate mofetil (MMF) in all. Induction with 500 mg methylprednisolone iv was given at day 0, followed by 40 mg iv the next day. At days 2 to 10 the dose was 16 mg po, after which it was gradually tapered, aiming at a dose of 0 to 4 mg/day at 1 year. Tacrolimus was started at 0.2 mg/kg/day before transplantation, and thereafter adjusted to obtain blood trough levels of 10 to 15 μg/L the first 3 months and 8 to 12 μg/L afterwards. The dose of MMF was set at 2 × 500 mg a day in all patients. All patients received infection prophylaxis with trimethoprim-sulfamethoxazole (Bactrim Forte®, Roche, Basel, Switzerland) and, except for CMV-negative donors and receptors, with ganciclovir (Cymevene®, Roche) during the first 3 months after transplantation. All patients received ulcer prophylaxis with cimetidine 400 mg daily from day 0 until discontinuation of steroids. Other concomitant medications are listed in Table 1. Despite ulcer prophylaxis, 48 patients developed gastrointestinal symptoms, for which endoscopy of the upper gastrointestinal tract was performed. Reflux esophagitis was diagnosed in 39, and noncomplicated gastric or duodenal ulcer was found in 7 patients. Ulcer complicated with endoscopical stigmata of bleeding (though not requiring blood transfusion) was observed in 2 patients. In all 48 cases, cimetidine was switched to omeprazole 20 mg daily.

Mean tacrolimus dose, trough level, steroid dose, hematocrit, albumin, bilirubin, creatinine, and weight during a 5-day interval before and after date of switch (which occurred from 16 to 1095 days after transplantation) were collected from the patients' files. An oral bioavailability-clearance index (BCI) was calculated from dose, trough level, and weight [BCI = (trough level [μg/L]/dose/weight [mg/kg]) ×100], given the strong correlation between trough levels and total AUC of tacrolimus [15].

Of the 153 patients that did not switch, 102 had stopped cimetidine treatment (2–4 weeks after complete cessation of steroids) at the time of analysis. BCI before and after stop was calculated in a similar way.

Healthy volunteers. Overall CYP, CYP3A4, and PGP activity of 6 nonsmoking and drug-free healthy male Caucasians was assessed at baseline and repeated in a randomized cross-over design after completion of a 5-day course of cimetidine, 400 mg twice a day, ranitidine 150 mg twice a day, and omeprazole, 20 mg daily. Each treatment was continued during the days of testing, and washout periods of 1 to 2 weeks were respected. They adhered to a normal Western diet, from which charcoal grilled meat, Brussel sprouts, broccoli, and grapefruit or other related citrus fruits and juices were excluded, and which was not changed during the period of testing. It was also verified that the subjects did not use any herbs such as St. John's wort or other popular over the counter medications. Medical history was unremarkable for all healthy volunteers; none of them had suffered from major illness or undergone any surgery.

The Ethical Committee of the University of Leuven approved the study protocol. Written informed consent was obtained from all subjects.

Table 1. Drugs other than immunosuppressive and prophylactic (infection/ulcer) therapy in the 48 patients who switched cimetidine to omeprazole

Concomitant drug	Number of patients
Atenolol	14
Amlodipine	11
Aspirin	9
Insulin	9
Lisinopril	6
Bisoprolol	5
1,25OH vitamin D	5
Molsidomine	4
Vitamin B complex	4
Enalapril	3
Atorvastatin	2
Alprazolam	2
Gliquidone	2
Losartan	2
Terazosine	2
Allopurinol	1
Amiodarone	1
Carbamazepine	1
Chlorazepam	1
Clonazepam	1
Clopidogrel	1
Digoxin	1
Diltiazem	1
Flupentixol/melitracene	1
Furosemide	1
Isoniazide	1
Lorazepam	1
Lormetazepam	1
Moxonidine	1
Paroxetine	1
Propafenon	1
Rocephine	1
Simvastatin	1
Terbenafine	1
Thiamazole	1
Ticlopidine	1
Valsartan	1

Measuring techniques

Test procedure. Healthy volunteers were examined using the ^{13}C-aminopyrin breath test and the intravenous and per oral ^{14}C-erythromycin breath and urine test. All tests were performed after an overnight fast on 3 consecutive days. The first and second day, 74 kBq of [N-methyl-^{14}C]-erythromycin (NEN Life Science Products,

Inc., Boston, MA, USA) was administered intravenously and orally, respectively. On day 3, 100 mg of [N,N-4–4-Dimethyl-^{13}C]-aminopyrin (NEN Life Science Products, Inc.) was given orally.

After injection/ingestion of the probe, recovery of $^{14/13}CO_2$ in exhaled air was measured in breath samples taken every 10 minutes during 4 hours. Recovery of ^{14}C-labeled tracer in fractionated urine collections (at 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hours after start of the test, respectively) was followed during 24 hours. Detailed information of the technique used to obtain and analyze breath and urine samples for ^{14}C and ^{13}C recovery has been described in earlier reports [16–18]. In short, quantification of ^{14}C was done by liquid scintillation spectrometry (Packard Tri-Carb Liquid Scintillation Spectrometer, model 3375; Packard Instruments, Inc., Downers Grove, IL, USA). ^{13}C was quantified using isotopic ratio mass spectrometry (ABCA; Europa Scientific, Crewe, UK).

Calculations. Assuming a stable CO_2 production of 300 mmol/m^2 body surface area per hour at rest, the quantity of ^{14}C and ^{13}C in each sample of breath could be expressed as %dose/h recovery of administered tracer. By plotting this as a function of time, a recovery rate curve was obtained. In addition, the trapezoidal rule was used to construct a cumulative recovery curve (%dose). For each urine collection, the %dose recovery of ^{14}C was measured and a cumulative recovery curve was made.

In the erythromycin breath test (EBT), the amount of exhaled $^{14}CO_2$ directly reflects CYP3A4-mediated oxidative demethylation of the administered probe. In the erythromycin urine test (EUT), urinary recovery of ^{14}C reflects the portion of labeled probe that escaped efflux toward the intestinal lumen and, hence, correlates inversely with intestinal/hepatic PGP activity. Measurements obtained after iv administration of the tracer are principally determined by hepatic activity, whereas those obtained after po administration result from both hepatic and intestinal enzyme activity. To isolate intestinal activity, mathematic deconvolution was applied to the ^{14}C recovery curves as previously reported [14]. This yielded new curves for both breath (recovery rate and cumulative recovery) and urine (cumulative recovery) tests. The curves obtained by deconvolution of the breath test curves after iv and po administration of the tracer represent the fraction of tracer that eventually entered the enterocyte and were metabolized by intestinal CYP3A4. The curves obtained by deconvolution of the urine test curves after iv and po administration of the probe represent the fraction of tracer that was absorbed along the gastrointestinal tract and escaped excretion by the intestinal PGP system.

In order to make mathematic deconvolution feasible, the curves from the po and iv EBT and EUT were fitted according to the least square method with Excel-Visual Basic software (Microsoft, Seattle, WA, USA) by varying the parameters *m, k*, and β in the following formulas:

$$\%\ \text{dose recovery} = m.(1 - e^{-kt})^{\beta} \quad \text{for cumulative recovery}$$

$$\%\ \text{dose/h recovery rate} = m.k.\beta.e^{-kt}.(1 - e^{-kt})^{\beta-1} \quad \text{for recovery rate}$$

where *t* is the time in hours, and *m* equals the total cumulative ^{14}C recovery when time is infinite [14, 16–18]. The curves obtained by deconvolution were fitted the same way.

The derived parameter *m* of the iv and deconvolved curves was used for statistical comparison of hepatic and intestinal CYP3A4 and PGP activity between different groups of subjects. Relative differences of activities were expressed as% change from the value of *m* obtained in healthy volunteers at baseline.

For the ABT, $^{13}CO_2$ recovery in breath directly reflects overall CYP activity [13, 20]. In order to statistically compare different groups, the cumulative ^{13}C dose recovery after 4 hours (cum 4h) was used. Relative differences of activities were expressed as% change from the value of cum 4h obtained in healthy volunteers at baseline.

Statistics

For statistical analysis, SAS software version 8.02 (SAS Institute, Cary, NC, USA) was used.

The paired *t* test was used for comparison of patients before and after switching cimetidine to omeprazole or before and after stopping cimetidine. In addition, multivariate analysis of variance (ANOVA) was used to analyze the difference of BCI before—after switch (ΔBCI) with the following independent variables: sex, days of follow-up at the moment of switching, Δsteroid dose, Δhematocrit, Δalbumin, Δbilirubin, and Δcreatinine.

Nonparametric ANOVA was used to compare the test results of the healthy volunteers obtained in different conditions. Subsequent Wilcoxon signed rank tests with Bonferroni correction were used to compare each modulation with baseline. A P value < 0.05 was considered significant.

RESULTS

Renal transplant patients

Patient demographics of the 48 studied patients did not differ from the total renal transplant population at our center (Table 2). Mean age at transplantation was 54 (±12) years. The male/female ratio was 29/19. Renal diagnosis, duration (34 ± 58 months), and modality (44/48 hemodialysis, 4/48 peritoneal dialysis) of renal replacement therapy prior to transplantation were similar to the general population of transplanted patients, as was outcome after transplantation. Patient survival at 1 and 3 years after transplantation was 100% and 92%, respectively. Graft survival at 1 and 3 years was 100% and 84%,

Table 2. Clinical data before and after switch to omeprazole in 48 renal transplant recipients

	Before	After	*P* value
Tacrolimus: trough μg/L	13.5 (±6)	11.5 (±3.5)	0.02
Tacrolimus: dose/weight *mg/kg*	0.14 (±0.07)	0.15 (±0.11)	0.54
Tacrolimus: BCI	13 (±7)	11 (±7)	0.02
Hematocrit	0.33 (±0.05)	0.32 (±0.06)	0.25
Albumin *mg/dL*	35 (±7)	36 (±7)	0.14
Bilirubin *mg/dL*	0.47 (±0.37)	0.51 (±0.41)	0.66
Creatinine *mg/dL*	2.38 (±2.31)	1.76 (±1.53)	0.01
Steroid dose *mg/day*	14 (±2)	13 (±2)	0.48

BCI, [(trough level)/(dose/weight)]×100; data are expressed as mean (±SD) and are compared with two-sided paired *t* test.

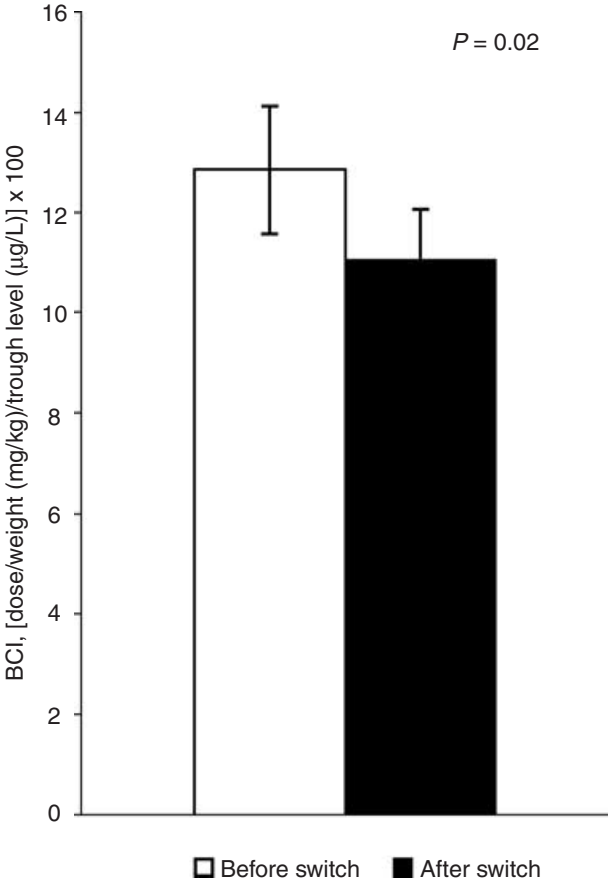

Fig. 1. Difference of mean (±SEM) dose/weight normalized tacrolimus trough level (BCI) before (white box) versus after (black box) switch from cimetidine to omeprazole in 48 renal transplant recipients in whom ulcer prophylaxis with cimetidine was changed to omeprazole.

respectively. During the first 3 years after transplantation, 16/48 patients experienced 1 or more episodes of acute rejection. Mean serum creatinine during the first 3 years after transplantation amounted to 1.59 (±0.67) mg/dL. Mean systolic and diastolic arterial tension during the first 3 years after transplantation was 139 (±15) mm Hg over 78 (±5) mm Hg. Mean hematocrit was 0.38 (±0.06) during the first 3 years after transplantation. Cimetidine was switched to omeprazole at a median of 44 days after transplantation (range 16–1095 days). None of the patients studied had undergone major gastrointestinal surgery, and except for diabetes mellitus in 11 patients, treated with insulin in 9, and oral hypoglycemics in 2, no other endocrine or metabolic disorders were present.

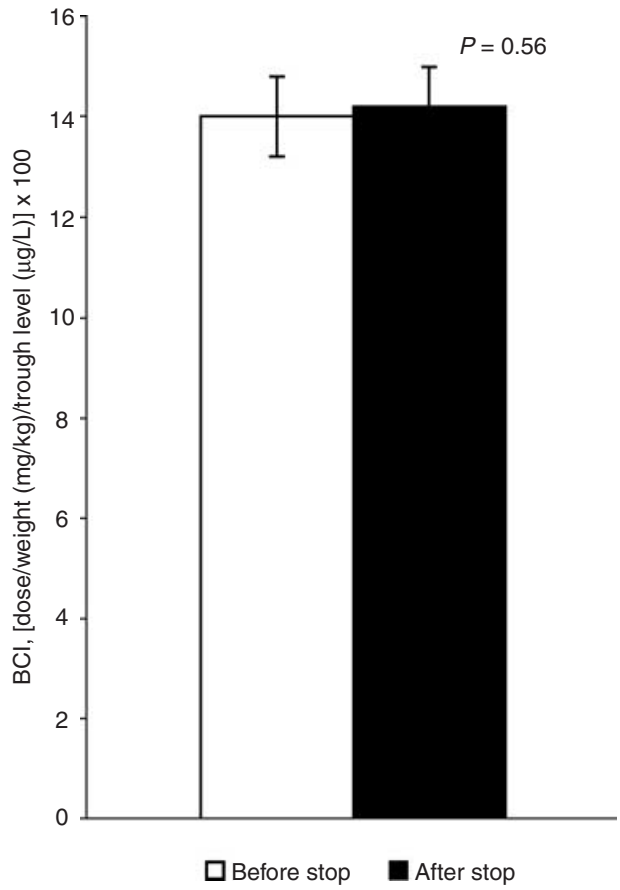

Fig. 2. Difference of mean (±SEM) dose/weight normalized tacrolimus trough level (BCI) before (white box) versus after (black box) cessation of cimetidine in 102 renal transplant recipients in whom ulcer prophylaxis with cimetidine was never switched to omeprazole.

Paired comparison of BCI before versus after switch from cimetidine to omeprazole showed a significant decrease of 15% (Fig. 1). Serum creatinine also decreased significantly with 26% after switch. Mean steroid dose, hematocrit, serum albumin, and bilirubin did not change (Table 2).

In the multivariate analysis, none of the variables, including sex, presence of diabetes, duration of follow-up, Δsteroid dose, Δhematocrit, Δalbumin, Δbilirubin, and Δcreatinine had any significant impact on ΔBCI.

Comparison of BCI before versus after cimetidine stop in 102 patients that eventually stopped ulcer prophylaxis showed no statistically significant difference (Fig. 2).

Healthy volunteers

Figure 3A shows the recovery rate and cumulative recovery curves of the ABT, which reflects overall CYP

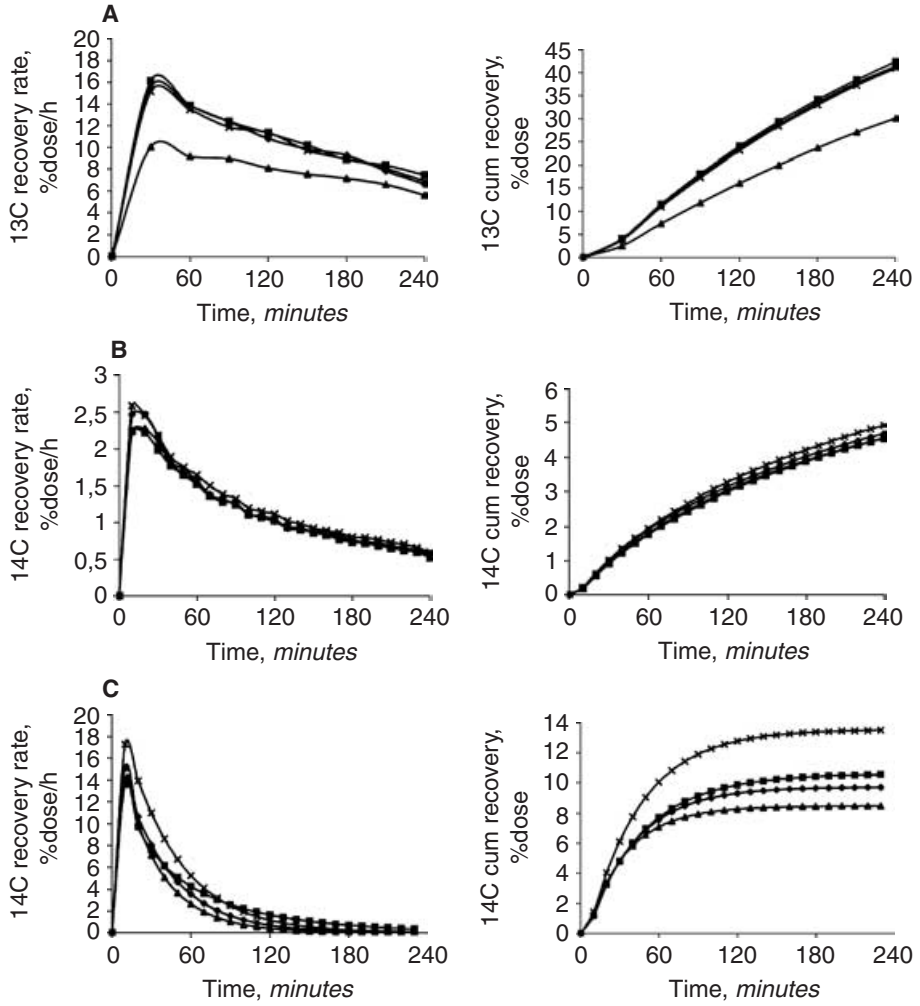

Fig. 3. Median breath recovery curves of $^{13/14}$C after ^{13}C-aminopyrin (reflecting overall CYP, *A*), after intravenous ^{14}C-erythromycin (reflecting hepatic CYP3A4, *B*), and after deconvolution of measurements obtained by per oral and intravenous administration of ^{14}C-erythromycin (reflecting intestinal CYP3A4, *C*), at baseline (◆), after cimetidine (▲), omeprazole (x), and ranitidine (■). Left side: $^{13/14}$C recovery rate (dose%/h); right side: cumulative $^{13/14}$C recovery (dose%).

activity, at baseline and after treatment with cimetidine, ranitidine, and omeprazole. The visible decline of the curves after cimetidine indicates an inhibitory effect. Results after treatment with ranitidine and omeprazole did not differ from baseline.

Figure 3B depicts the recovery rate and cumulative recovery curves of the iv EBT, reflecting hepatic CYP3A4 activity at baseline and after the different treatments. No difference was observed in shape of the curves neither in total ^{14}C recovery.

The isolated intestinal CYP3A4 curves, obtained by deconvolution of the po and iv EBT, are displayed in Figure 3C. Whereas cimetidine and ranitidine did not produce any alterations, a clear increase of intestinal CYP3A4 activity was observed after treatment with omeprazole.

Figure 4A and B shows the cumulative recovery curves of the iv EUT and of the deconvolution product of the iv and po EUT, corresponding inversely with hepatic and intestinal PGP activity, respectively. Comparison of total ^{14}C recovery revealed no changes of relative intestinal and hepatic PGP activity after treatment with any of the 3 gastric acid suppressants studied.

Figure 5 and Table 3 summarize the changes relative to baseline observed after treatment with the different gastric acid suppressants. The median value of total $^{13/14}$C recovery at baseline was considered as the reference (100%) to which the values obtained after different treatments were normalized. Nonparametric ANOVA retained a significant decrease (−28%) of overall CYP activity after cimetidine and a significant increase (+63%) of intestinal CYP3A4 activity after omeprazole.

DISCUSSION

The present study of 48 renal transplant recipients revealed that switching of ulcer prophylaxis from

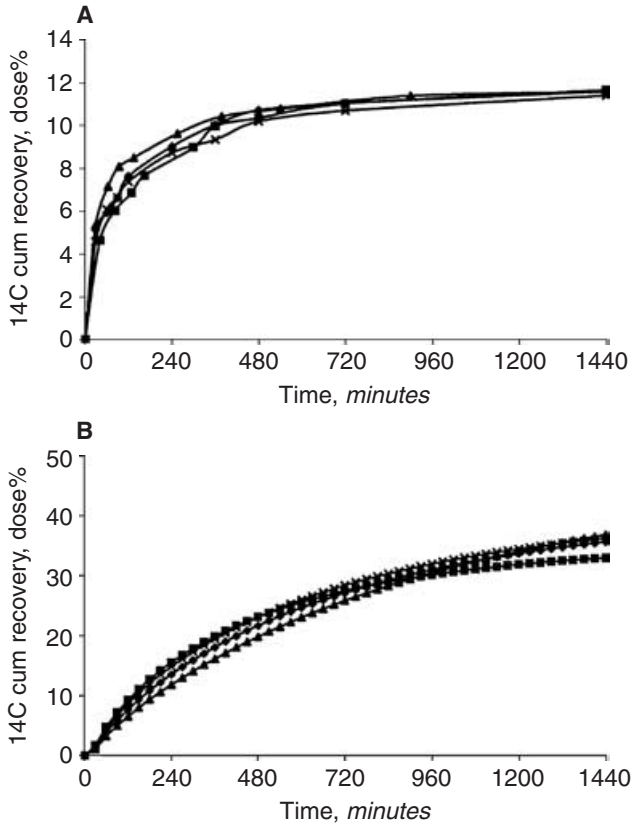

Fig. 4. Median cumulative ^{14}C recovery (dose%) in urine (inversely reflecting PGP activity), after intravenous (*A*) and after deconvolution of measurements obtained by oral and intravenous ^{14}C-erythromycin (*B*) at baseline (◆), after cimetidine (▲), omeprazole (x), and ranitidine (■).

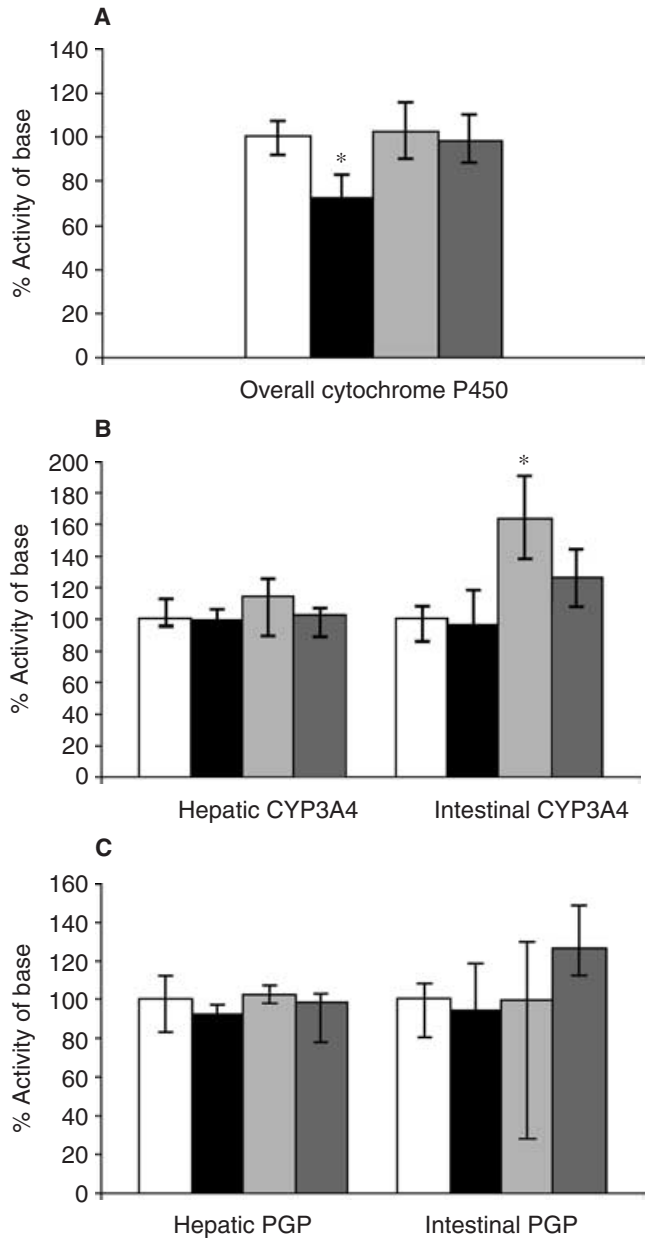

Fig. 5. Relative changes in overall CYP (*A*) and hepatic (left) and intestinal (right) CYP3A4 activity (*B*) and hepatic (left) and intestinal (right) PGP activity (*C*) based on comparison of total ^{13}C recovery from the ABT and total ^{14}C recovery from the iv and deconvolved EBT and EUT observed at baseline (= 100%, white), and after cimetidine (black), omeprazole (light shade), and ranitidine (dark shade). Bars represent interquartile range. $^{*}P < 0.05$ for comparison with baseline by means of nonparametric ANOVA and subsequent Wilcoxon signed rank test.

cimetidine to omeprazole was associated with a significant decrease of dose/weight normalized trough levels of tacrolimus (BCI). Although the study was retrospective, it is strengthened by the completeness of the data analyzed, and the fact that each patient could be used as his/her control before and after switch. Moreover, the observed effects on tacrolimus trough levels remained valid after thorough control for possible confounding factors. Hematocrit and albumin, known to influence whole blood levels of tacrolimus [20–21], and dose of steroids, known to induce CYP3A4-mediated catabolism [21–22], did not change before versus after switching. In addition, multivariate analysis did not retain any impact of the individual changes of these parameters on the individual change of BCI. The significant decrease of serum creatinine, seen after the switch, was not associated with the change of BCI either and was most probably due to the known inhibitory effect of cimetidine on tubular excretion of creatinine [23]. Further analysis also eliminated sex, duration of follow-up, and bilirubin as explaining variables for the observed change of BCI.

Not unexpectedly, the majority of the patients were taking multiple concomitant drugs beside the standard immunosuppressive and prophylactic regimen. In 4 cases, a well-known inducer (carbamazepine) or inhibitor (amiodarone, isoniazide, diltiazem) of CYP/PGP was involved. However, all concomitant drugs were started at least a month before switching the acid suppressant and were not altered during the studied period in all patients. When analysis of BCI was repeated after exclusion of the

Table 3. Relative% change of overall CYP, CYP3A4, and PGP activity in vivo after intake of cimetidine, omeprazole, and ranitidine compared to baseline

	Overall CYP	Hepatic CYP3A4	Intestinal CYP3A4	Hepatic PGP	Intestinal PGP
Cimetidine	−28%[a]	−1%	−4%	−8%	−6%
Omeprazole	+2%	+14%	+63%[a]	+2%	−1%
Ranitidine	−2%	+2%	+26%	−2%	+26%

Relative changes are expressed as% increase/decrease of the median activity at baseline after 5 days of treatment with the studied drugs.

[a] $P < 0.05$ for comparison with baseline by means of nonparametric ANOVA and subsequent Wilcoxon signed rank test.

4 mentioned patients, the observed decrease of BCI after switch to omeprazole was confirmed and the level of significance was even slightly higher.

Subsequent exploration of the observations made in patients with studies in healthy volunteers showed that treatment with cimetidine caused a decrease of overall CYP activity, according to in vitro findings [9, 10]. However, no specific effect on CYP3A4 activity in vivo was noted. Since the main human CYPs involved in the demethylation of aminopyrin are CYP1A2, 2C/D, and 3A4 [24], this suggests that the observed effect was mainly mediated by inhibition of CYP1A2 and/or 2C/D. In vivo measurement of the effects on CYP1A2, measured by a caffeine breath test, showed no influence of cimetidine [25]. Theophylline, a CYP1A2-dependent drug, has been shown to interact with cimetidine in one study [26], whereas no effects were seen in another [27]. Pharmacokinetic studies in humans mainly point toward interactions with drugs that are CYP2C9 and CYP2D6 dependent, such as warfarin and propranolol [28, 29]. Omeprazole did not change overall CYP, but selectively and significantly augmented intestinal CYP3A4 activity. This is in contrast with reported inhibitory effects on liver microsomes in vivo, but confirms in vitro studies on cultured human hepatocytes. In these studies, after 48 hours' incubation with the compound an enhanced expression of CYP3A4 and its most important transcription activator, the human nuclear pregnane X receptor was clearly demonstrated [30, 31]. Moreover, a recent ex vivo study of CYP expression in human duodenal biopsies showed a significant up-regulation of CYP3A4 encoding mRNA in association with intake of omeprazole [11]. The fact that the observed induction of CYP3A4 was limited to the intestinal site might be explained by the relatively higher concentrations of omeprazole to which the enterocyte gets exposed after oral intake. No significant effects on either CYP or PGP in vivo were noticed with ranitidine, which may favor its use in multimedicated patients in order to minimize the risk for drug interactions. Although in vitro tests and pharmacokinetic studies comparing cimetidine and ranitidine seem to confirm this [30, 31], additional clinical data are needed. Unfortunately, the present clinical study could not provide any extra information on this topic because the analyzed patient cohort did not use ranitidine.

The observed increase of intestinal CYP3A4 activity with omeprazole is the most plausible mechanism for the decrease of dose-normalized trough levels for tacrolimus seen in the patients that switched cimetidine to omeprazole. However, this could also be attributed to the cessation of cimetidine (Fig. 6) because the application of a washout period at switching gastric acid suppressants in the patients was not feasible. This possibility seems less likely for 2 reasons. First, catabolism of tacrolimus depends mainly on CYP3A4 activity, whereas cimetidine appeared to exert its inhibitory effects on other CYP isozymes. Second, additional analysis in patients who did not switch to omeprazole and eventually stopped ulcer prophylaxis with cimetidine failed to show any decrease of trough/dose levels before versus after stop.

Cyclosporine A is also extensively eliminated by CYP3A4 and PGP. Clinical studies on interactions with gastric acid suppressants are scarce and conflicting. Most studies failed to demonstrate any effect of cimetidine or omeprazole on oral bioavailability [32–36]. This apparently different interaction pattern of cyclosporine versus tacrolimus may result from a different impact by the 2 calcineurin inhibitors themselves on CYP3A4 and PGP activity, as was recently shown in transplant patients and healthy volunteers. Clinically relevant doses of tacrolimus and also sirolimus did not alter CYP3A4/PGP activity in vivo, whereas cyclosporine was associated with decreased intestinal and hepatic PGP activity and increased intestinal CYP3A4 activity [37]. Subsequently, it can be expected that administration of moderate CYP3A4 and PGP modulators are more likely to affect tacrolimus/sirolimus assimilation because these immunosuppressants do not seem to affect CYP3A4/PGP activity in vivo themselves. Cyclosporine levels will probably not be influenced, as this drug itself already strongly influences CYP3A4/PGP activity in vivo.

CONCLUSION

The present study showed that switching therapy from cimetidine to omeprazole was associated with a decrease of dose/weight normalized tacrolimus trough levels in a clinical setting. This observation is most likely explained by the demonstrated enhancement of intestinal CYP3A4 activity by omeprazole in vivo. Since different gastric acid suppressants have different effects on oral bioavailability, differential patterns of drug interactions might be expected, and cautious drug monitoring is warranted when switching such drugs.

ACKNOWLEDGMENTS

The ever-continuing support and enthusiasm of the clinical nurses A. Herelixka, H. Wieland, R. Eerdekens, and G. Melis, and the excellent technical support of S. Rutten, A. Luypaerts, and L. Swinnen and the

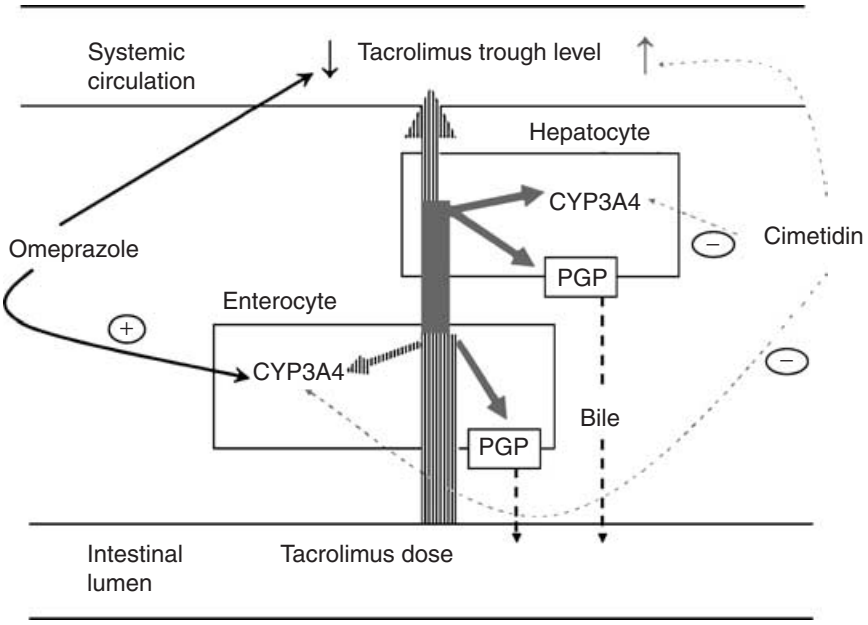

Fig. 6. Potential interaction mechanisms of tacrolimus and omeprazole or cimetidine. Full arrows: effects of omeprazole; dashed arrows in light shade: effects of cimetidine.

other members of the Gastrointestinal Research Center UZ Gasthuisberg is greatly acknowledged. This work was partially supported by a Fujisawa GmbH grant. Part of this work has been presented as abstract No. 1481 at the ATC, Boston, Massachusetts, May 2004.

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