The rate of gastric emptying determines the timing but not the extent of oral tacrolimus absorption: simultaneous measurement of drug exposure and gastric emptying by carbon-14-octanoic acid breath test in stable renal allograft recipients.

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Abbreviations:

GEC: gastric emptying coefficient
tlag: solid lag phase
t ½: half-emptying time
Abstract

Tacrolimus is characterised by a highly variable oral bioavailability and narrow therapeutic window. Tacrolimus absorption from the gastrointestinal tract is to a large extent determined by the genotypic, phenotypic and functional expression of P-glycoprotein and CYP3A in the gut wall and liver. It is disputed if the gastric emptying rate per se is important for determining oral bioavailability of tacrolimus and whether delayed gastric emptying is clinically relevant for therapeutic drug dosing. We conducted a pharmacokinetic study in fifty renal recipients, measuring simultaneously the rate of gastric emptying using a carbon-14-octanoic acid breath test and quantifying drug exposure by Area-Under-the-Concentration-time-Curve sampling. Gastric half emptying time (t½) significantly correlated with time to reach maximum blood tacrolimus (tmax) concentration (r²=0.30; p<0.0001) while the gastric emptying coefficient (GEC), reflecting the overall gastric emptying rate, showed a weak inverse correlation with tmax (r²=0.14; p=0.007). The time-dependent rate of gastric emptying strongly correlated with the simultaneously measured blood tacrolimus concentration over the first 4 hours following oral drug administration (r²=0.96; p<0.0001). Comparison between patients with and without delayed gastric emptying confirmed that maximum blood tacrolimus concentration was reached significantly slower in the former group (tmax: 2 ± 1 hr vs. 1.48 ± 0.68 hr; p=0.04) while the extent of tacrolimus absorption was not different.

Despite a strong association between gastric emptying rate and the timing of tacrolimus absorption from the gut in stable recipients, gastric emptying rate does not affect the total extent of drug absorption and is not responsible for significant alterations in drug exposure, even in situations of delayed gastric emptying.
Introduction

Tacrolimus (Prograft™, Fujisawa GmbH, Munich, Germany) is a potent immunosuppressive drug used effectively in clinical solid organ transplantation (Margreiter, 2002; Squifflet, 2001). Tacrolimus is a class II low-solubility, high permeability drug (Tamura, 2002) of which the absorption from the gastrointestinal tract is affected by the distribution (Shimomura, 2002), genotype (Anglicheau, 2003; Hesselink, 2003) and functional expression (Tamura, 2003; Tuteja, 2001) of P-glycoprotein (P-gp, MDR1) and cytochrome P4503A4 (CYP3A4) in the gut wall and liver. As a consequence, the oral bioavailability of the drug is characterised by a time-dependent large inter- and intra-individual variability (Venkataramanan, 1995), making continuous application of therapeutic drug monitoring post-transplantation indispensable. In addition, gastric emptying rate also appears to influence the oral bioavailability of tacrolimus while at the same time prokinetic effects of tacrolimus on gastric motility have been documented both in renal and lung transplant recipients (Maes, 1999; Verleden, 2002). This effect which tacrolimus shares with other macrolide drugs (Costa, 1996) can be advantageous for patients suffering from delayed gastric emptying and could explain why no clear differences exist in oral bioavailability of tacrolimus between fasted diabetic and non-diabetic patients awaiting combined kidney-pancreas or kidney transplantation (van Duijnhoven, 1998). However, when tacrolimus is ingested together with a high-fat meal, the rate of tacrolimus absorption (tmax, Cmax) is slowed more extensively in diabetic patients than in non-diabetic patients but without significantly affecting total drug absorption (AUC0-12h) (van Duijnhoven, 1998). Also the exact timing of a meal in relation to tacrolimus intake influences oral bioavailability of the drug, resulting in lower (AUC) and slower (tmax) absorption when administered together with a meal or 1.5 hours after a meal compared to the fasted state (Bekersky, 2001). In stable renal allograft recipients on tacrolimus therapy, the importance of the rate of gastric emptying in determining the oral bioavailability of the drug and the clinical relevance of
delayed gastric emptying, is not clear. If delayed gastric emptying significantly affects total drug exposure, under-immunosuppression (low blood levels) could lead to acute or chronic allograft rejection (Kuypers, 2004a) and ultimately graft loss in tacrolimus-treated recipients.

We therefore conducted a prospective pharmacokinetic study in stable renal recipients on tacrolimus therapy, simultaneously measuring the rate of gastric emptying through a carbon-14-octanoic acid breath test while at the same time quantifying drug exposure by Area-Under-the-Concentration-time-Curve (AUC) blood concentration sampling. The aim of the study was to determine the concurrent effect of gastric emptying on the rate and extent of tacrolimus absorption in stable renal recipients.
Methods

Immunosuppressive drugs. Thirty-one male and nineteen female recipients of a cadaveric renal allograft (median age 52.4 years) consented to participate in this study. Recipients were treated with a standard maintenance immunosuppressive drug regimen of oral tacrolimus (Prograf®, Fujisawa GmbH) in combination with mycophenolate mofetil (MMF: CellCept®, Roche) and oral methylprednisolone (Medrol®, Upjohn). The daily tacrolimus dose was adjusted to achieve target 12-hour trough blood concentrations between 8-15 ng/ml.

Inclusion and exclusion criteria. Patients who had received a single cadaveric donor kidney and were clinically stable were eligible for inclusion. Exclusion criteria were medical or surgical hepatic and gastrointestinal disorders, -including active peptic ulcer disease and diabetes mellitus-, that could interfere with the absorption, distribution, metabolism or excretion of tacrolimus. Patients had to be free from biopsy-proven acute rejection for at least 6 months prior to the study and any acute illness in the last 6 weeks was a contraindication for enrollment. Drugs known to affect gastric emptying were prohibited by the study protocol. Patients with a history of non-compliance were also excluded as were recipients known with a current drug, nicotine or alcohol addiction. Finally, since this was a primary pharmacokinetic study, all substances documented to have a significant clinical effect on the absorption, distribution, metabolism and excretion of tacrolimus, were prohibited (Christians, 2002). If patients required one of the latter drugs as maintenance therapy, they were excluded from the study. Approval was obtained from the ethics committee from the University of Leuven, Faculty of Medicine and each patient gave his/her written informed consent.

Safety parameters. Standard safety evaluation during this study included physical examination with systolic and diastolic blood pressure measurement, body weight, vital signs and laboratory tests. The use of any concomitant medication was noted. Renal allograft function was assessed using serum creatinine determinations and creatinine clearance calculated by the Cockcroft-Gault formula.
Pharmacokinetic and gastric emptying studies. Tacrolimus blood samplings were performed while simultaneously gastric emptying rate was measured using a radio labeled octanoic acid breath test (Maes, 1994) for all patients who consented. These measurements were done at 12 (n=24) or 24 (n=26) months post-transplantation. Patients had to adhere to an overnight fast for at least 10 hours and the morning dose of tacrolimus was ingested at the start of the test meal (see below), twelve hours after the previous dose.

The abbreviated 4-hour tacrolimus blood sampling profile consisted of consecutive blood samples taken through an intravenous catheter, from pre-dose (time point zero: C₀) up until 4 hours post-dosing. Concomitant medication that could interfere with the absorption and metabolism of tacrolimus, including over-the-counter drugs, and the validity of the dose-interval was double-checked. Whole blood tacrolimus concentrations were determined using a microparticulate enzyme immunoassay (Tacrolimus II™ MEIA/IMx analyser, Abbott Laboratories).

Gastric emptying of a standard mixed solid-liquid meal was measured by means of the combined ¹⁴C-octanoic acid/¹³C-glycine gastric emptying breath test (Maes, 1994). In short, a test meal composed of an egg omelette labeled with 74 kBq of ¹⁴C-octanoic acid (Dupont, NEN Research, Boston, MA, USA), 60 grams of white bread and 150 mL of water labeled with 91 mg of ¹³C-glycine (Isotec, Miamisburg, OH, USA) was consumed in less than 10 minutes. The meal consisted of 14 grams proteins, 26 grams of carbohydrates and 9 grams (18.4%) of fat. The ¹³CO₂ and ¹⁴CO₂ excretion in breath was subsequently measured every 15 minutes for a total duration of 4 hours and expressed as percentage dose per hour in order to calculate a gastric emptying coefficient (GEC), a half-emptying time (t½) and a solid lag phase (tₗ₉) as described in detail elsewhere (Maes, 1994). A correlation exists between GEC, t ½, and tₗ₉ determined by the breath test technique and radioscintigraphic techniques (respectively r=0.88, r=0.92 and r=0.89; p<0.0001) (Maes, 1994). The gastric emptying parameters calculated from the ¹⁴C-octanoic acid data, reflecting the solid phase gastric emptying rate, were used for further analysis and are reported here. No
additional information was obtained from measuring the $^{13}$CO$_2$ excretion in breath ($^{13}$C-glycine reflecting the liquid phase of gastric emptying) and therefore these data are not shown.

At all time points during the study the investigators were blinded for the results of the tacrolimus pharmacokinetic studies and the gastric emptying data; adjustments of tacrolimus dose were made strictly based on single pre-dose 12-hour trough blood concentrations.

Clinical interpretation of $^{14}$C-octanoic acid gastric emptying breath test results.

All results of $^{14}$C-octanoic acid gastric emptying breath test were independently assessed by either of two investigators who were not involved in the study and who remained blinded at all times for the results of the pharmacokinetic studies and the clinical characteristics of the patients as well as their drug therapy. Gastric emptying was defined as delayed based on: visual inspection of the $^{14}$CO$_2$ breath excretion curve; a gastric half emptying time ($t_{1/2}$) of more than 75 minutes and/or a gastric emptying coefficient (GEC) value below 3.3 in comparison with gastric emptying data obtained in healthy volunteers described in detail elsewhere (Maes, 1994; Maes, 1997). In order to control for a possible interpretation bias, the GEC, $t_{1/2}$, and $t_{lag}$ were compared post hoc between those recipients determined by the blinded investigators as having delayed gastric emptying (=24) and patients determined as having normal gastric emptying (n=26). All gastric emptying parameters (GEC, $t_{1/2}$, $t_{lag}$) differed highly significantly between both groups (GEC: 3.82 ± 0.44 vs. 3.28 ± 0.32; p<0.0001, $t_{1/2}$: 56.8 ± 16.3 min vs. 102.4 ± 21.5 min; p<0.0001, $t_{lag}$: 28.7 ± 12.9 min vs. 57.7 ± 18.1 min; p<0.0001).

Determination of pharmacokinetic parameters. Pharmacokinetic modeling was performed using WinNonLin 3.2 Pro software (Pharsight Inc.™) and SAS 8.02 statistical program (The SAS institute™). Model-independent pharmacokinetic parameters for tacrolimus were calculated and dose-corrected when appropriate. The corresponding tacrolimus dose-interval area-under-the-concentration curve (AUC$_{0-12h}$) was calculated from the abbreviated 4-hour AUC, using an algorithm previously validated in de novo renal recipients (Kuypers, 2004b) that explained 96% of the variance in AUC$_{0-12h}$ with a mean percent prediction
error of -0.57 ± 5.6% (range: -13.6% to +15.1%) and a mean absolute prediction error of 4.7 ± 3.2% (range: 0.1% to 15.1%). Maximum blood concentration (Cmax), pre-dose trough blood concentration (C0) and time to reach maximum blood concentration (tmax) were determined. An estimate of total steady-state body clearance (CL) was obtained from the calculated dose-interval AUC and tacrolimus dose.

Statistical Analysis

A sample size of 44 recipients was calculated (α=0.05 and power of 80%) assuming that delayed gastric emptying would result in a clinically relevant decrease of tacrolimus exposure by 30% and taking into account a 10% drop-out rate.

Distribution for continuous data was evaluated (Kolmogorov-Smirnov) and consequently parametric tests and non-parametric tests were applied when appropriate. Data are always expressed as mean ± standard deviation (SD) except when stated differentially (median + range). Non-parametric statistics were used (Kruskall-Wallis and Wilcoxon rank sum test; SAS 8.2 software) for comparison. Simple regression analysis (Pearson's and Kendall's tau) for correlation of gastric emptying data with PK-parameters, demographic and laboratory variables, were performed as appropriate. Multiple linear regression analysis of PK-parameters as dependent variables was applied with backward elimination and stepwise selection models for the different gastric emptying parameters and clinical variables. A p-value < 0.05 was considered statistically significant.
Results

Patient demographics, transplantation-related characteristics, allograft function and laboratory tests at the time of pharmacokinetic studies are summarized in Table 1.

*Gastric emptying parameters and tacrolimus pharmacokinetics.* Gastric half emptying time (t½) significantly correlated with time to reach maximum blood tacrolimus concentration (r²=0.30; p<0.0001). In patients with delayed gastric emptying, gastric half emptying time (t½) correlated significantly with time to reach maximum blood tacrolimus concentration (r²=0.18; p=0.03), albeit weaker than for patients with normal gastric emptying (r²=0.37; p=0.0009) (Figure 1). Gastric half emptying time did not correlate significantly with any of the other dose-uncorrected or dose-corrected tacrolimus pharmacokinetic exposure parameter including AUC₁₄ₐₜ, AUC₀-₁₂ₐₜ, Cₘₐₓ, C₀, oral clearance and weight-corrected daily dose. The gastric emptying coefficient (GEC), reflecting the overall gastric emptying rate for solids, showed a weak but significant inverse correlation with tₘₐₓ (r²=0.14; p=0.007) (Figure 2). Again GEC did not correlate with other tacrolimus exposure parameters. The lag phase for solids (tₗₐ₉) was found not to correlate with tacrolimus exposure nor with tₘₐₓ. Using multiple linear regression analysis (backward and stepwise elimination model) with tₘₐₓ as dependent variable and gastric emptying parameters as explanatory variables, only t ½ was withheld as significant variable in the model.

The mean rate of gastric emptying strongly correlated with the simultaneously measured mean blood tacrolimus concentration over the first 4 hours following oral drug administration (r²=0.96; p<0.0001). This significant correlation was present both in recipients with (r²=0.81; p=0.0003) and without (r²=0.97; p<0.0001) delayed gastric emptying, albeit weaker in the former group (Figure 3). The ¹⁴CO₂ excretion curve in recipients with delayed gastric emptying, reflecting gastric emptying rate, clearly demonstrates a diminished ascending slope of the curve, a diminished and prolonged descending part with a lower peak excretion rate of ¹⁴CO₂, appearing significantly later (time to peak excretion rate: 1.90 ± 0.28 hr vs. 1.42 ±
0.22 hr, p<0.0001) in comparison with patients without delayed emptying. The blood tacrolimus concentration over time very closely follows a similar pattern as the gastric emptying rate in both patient groups. Comparison of tacrolimus pharmacokinetic parameters between stable patients with (n=24) and without delayed gastric emptying (n=26), confirms that the maximum blood tacrolimus concentration is reached significantly slower in the former group (tmax: 2 ± 1 hr vs. 1.48 ± 0.68 hr; p=0.04) while the extent of tacrolimus absorption and exposure is not different as reflected by Cmax, AUC or C0 (Table 2). The dose of tacrolimus necessary to obtain comparable drug exposure did not differ between groups, even after correction for body weight.

No significant correlation was detected between gastric emptying parameters (GEC, t1/2, tlag) and recipient age, weight, allograft function; albumin and haemoglobin concentration; neither could an effect of gender be demonstrated (data not shown).
Discussion

We have demonstrated in stable renal allograft recipients treated with a tacrolimus based maintenance immunosuppressive drug regimen, that the rate of gastric emptying influences the rate of tacrolimus absorption from the gut, as reflected by the time to reach maximum blood tacrolimus concentration (tmax). However, the rate of gastric emptying does not affect the extent of tacrolimus absorption and exposure as measured by Cmax, AUC and C₀. More so, patients suffering from delayed gastric emptying obtain similar tacrolimus exposure as recipients with normal gastric emptying using the same drug dose. This finding illustrates that oral bioavailability of tacrolimus is not primarily affected by the rate of gastric emptying in the absence of other gastrointestinal disorders. Being able to use the ¹⁴C-octanoic breath test for measuring gastric emptying rate in real-time, at consecutive time points after drug dosing and simultaneously determine tacrolimus exposure, opens new opportunities for clinical investigations. Alternative methods like radioscintigraphy and radiological techniques are less sensitive tools for this purpose as the latter only allow to calculate an overall coefficient (e.g. t ½) reflecting gastric emptying rate.

Tacrolimus, due to its macrolide structure, exhibits intrinsic prokinetic properties, as opposed to cyclosporin, as was clearly demonstrated in renal and lung transplant recipients (Maes, 1999; Verleden, 2002). It is possible that extreme delays in gastric emptying rate, as for example encountered in some cases of severe diabetic gastroparesis, were not detected in the present study because primary diabetic patients were excluded from the trial and the prokinetic effects of tacrolimus on gastric motility could have masked (ameliorated) strongly delayed emptying in some patients. In fact, three patients in the present study developed post-transplantation diabetes mellitus but their gastric emptying parameters did not differ significantly from that of the non-diabetic patients, neither were there any significant differences in tacrolimus exposure parameters (data not shown). When we considered only those recipients with a strong delay in gastric emptying, in the upper quartile of gastric half emptying times, again no differences in
tacrolimus exposure \((\text{AUC}_{0-12h}, \text{Cmax})\) could be established (data not shown). Of course, very early after successful transplantation, gastric motility might be even more extensively disturbed than in chronic stable recipients; possibly resulting in more marked alterations of tacrolimus absorption.

The effect of diurnal variation in tacrolimus exposure (Tada, 2003) and ethnicity (Mancinelli, 2001) could not have played a role in the current study as all measurements were performed in the morning, after an overnight fast, and all participants were of Caucasian origin. Also, concomitant drugs that could have influenced gastric emptying were excluded per protocol and double-checked on every visit. It is therefore unlikely that concomitant medication would have caused a systematic bias. Mycophenolate mofetil, administered routinely in this study, does not affect gastric emptying as was demonstrated in renal recipients (Maes, 2003) and could therefore not have altered our findings.

The ingestion of tacrolimus together with a low-fat test meal might of course have influenced our results but at the same time probably reflects more accurately real life. It is known that the exact timing of tacrolimus intake in relation to a meal is important in terms of \(t_{\text{max}}\) and \(C_{\text{max}}\) but not for total drug exposure (Kimikawa, 2001). In contrast, in healthy volunteers, timing of a single 5 mg tacrolimus dose immediately after a meal does affect drug exposure significantly (Bekersky, 2001). Extrapolating pharmacokinetic data from healthy volunteers and pre-transplantation (uraemic) circumstances to chronic stable transplant recipients is however prone to error (Satoh, 2001). Furthermore, the fat content of a meal also influences tacrolimus absorption, at least in healthy volunteers (Bekersky, 2001). In the current study, tacrolimus was administered exactly timed with a standardized test meal containing 18% of fat and this methodology was strictly adhered to throughout the study for all participants. In contrast to van Duijnhoven et al (van Duijnhoven, 1998) who used a high fat (43%) meal in diabetic uremic transplant candidates, we could not demonstrate an effect of the low fat test meal on the extent of tacrolimus absorption \((C_{\text{max}})\) in patients with delayed gastric emptying compared to patients with normal gastric emptying. Similarly, Christiaans et al
could not find a significant effect of a high fat meal on tacrolimus absorption in renal recipients at different time points after transplantation (Christiaans, 1998).

Considering tacrolimus as a poorly water-soluble drug with low dissolution characteristics in its current formulation (Yamashita, 2003), it could be argued on theoretical grounds that gastric emptying rate \textit{per se} will have less impact on drug absorption (Kaus, 1999). Furthermore, the intrinsic prokinetic effect of tacrolimus - as opposed to cyclosporin A (Maes, 1999) - could ameliorate mild to moderate delays in gastric emptying to such a degree that the extent of drug absorption remains unaffected. Nevertheless, it appears that tacrolimus absorption and subsequent exposure in stable recipients is mainly determined at more distal parts of the gastrointestinal tract (jejunum, ileum, colon) and regulated through the activity of P-glycoprotein and CYP3A4 in the gut wall and liver (Shimomura, 2002; Tamura, 2003; Tuteja, 2001).

In conclusion, despite the fact that there exists a strong correlation between the rate of gastric emptying in stable renal allograft recipients and the timing of tacrolimus absorption from the gut, gastric emptying rate does not affect the total extent of drug absorption and is therefore not responsible for significant alterations in drug exposure, even in situations of delayed gastric emptying.
References


Legends to the figures

Figure 1: Gastric half emptying time ($t_{1/2}$) and time to reach maximum tacrolimus concentration ($t_{\text{max}}$) in recipients with normal gastric emptying (□, n=26) and patients with delayed gastric emptying (♦, n=24). Univariate regression analysis on paired data, the R-squared values for the regressions are respectively 0.37 and 0.18 ($p < 0.0001$).

Figure 2: Gastric emptying coefficient (GEC) and time to reach maximum tacrolimus concentration ($t_{\text{max}}$) in 50 stable renal recipients (♦). Univariate regression analysis on paired data, the R-squared value for the regression is 0.14 ($p < 0.0001$).

Figure 3: Simultaneous mean gastric emptying rate (solid lines) and mean blood tacrolimus concentration (dotted lines) over time in patients with normal gastric emptying (□, n=26) and delayed gastric emptying (♦, n=24).
Table 1: Recipient demographics, transplantation characteristics, allograft function and laboratory data (n=50).

Data are expressed as mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs):</strong></td>
<td>52.4 ± 12.6</td>
</tr>
<tr>
<td><strong>Sex (M/F):</strong></td>
<td>31 / 19</td>
</tr>
<tr>
<td><strong>Weight (kg):</strong></td>
<td>74.9 ± 14.8</td>
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<tr>
<td><strong>Height (cm):</strong></td>
<td>170.5 ± 9.8</td>
</tr>
<tr>
<td><strong>Time on renal replacement therapy (mo):</strong></td>
<td>29.9 ± 20.4</td>
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<td><strong>Retransplantation:</strong></td>
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<td><strong>HLA-mismatches per patient:</strong></td>
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<tr>
<td><strong>Donor age (yrs):</strong></td>
<td>42.6 ± 17.8</td>
</tr>
<tr>
<td><strong>Donor sex (M/F):</strong></td>
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<tr>
<td><strong>Serum creatinine (mg/dL):</strong></td>
<td>1.77 ± 1.06</td>
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<tr>
<td><strong>Creatinine clearance (mL/min/1.73 m²):</strong></td>
<td>54.7 ± 20</td>
</tr>
<tr>
<td><strong>Serum albumin (g/L):</strong></td>
<td>39.9 ± 2.65</td>
</tr>
<tr>
<td><strong>Hemoglobin (g/L):</strong></td>
<td>126 ± 1.5</td>
</tr>
</tbody>
</table>

M: male; F: female; *creatinine clearance calculated by the Cockcroft-Gault formula
Table 2: Comparison of tacrolimus model-independent (and dose-corrected) pharmacokinetic parameters at the time of measurement of gastric emptying (n=50) and between recipients with normal gastric emptying (n=26) and patients with delayed gastric emptying (n=24). Data are expressed as mean ± SD. Differences between patients with normal and delayed gastric emptying were statistically evaluated by Student's t test of Wilcoxon rank test. A p-value < 0.05 was considered statistically significant.

<table>
<thead>
<tr>
<th>PK-parameter</th>
<th>All patients (n=50)</th>
<th>Normal gastric emptying (n=26)</th>
<th>Delayed gastric emptying (n=24)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-4h (ng.h/mL)</td>
<td>59.0 ± 20.7</td>
<td>59.9 ± 18.7</td>
<td>57.9 ± 23</td>
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<tr>
<td>AUC0-12h (ng.h/mL)</td>
<td>145.0 ± 46.7</td>
<td>142.4 ± 38.3</td>
<td>147.7 ± 54.1</td>
<td>0.92</td>
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<tr>
<td>AUC0-12h (ng.h/mL/mg)</td>
<td>53.7 ± 26.5</td>
<td>52.9 ± 25.4</td>
<td>54.4 ± 28.2</td>
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<tr>
<td>C0 (ng/mL)</td>
<td>9.4 ± 3.7</td>
<td>8.8 ± 3</td>
<td>10 ± 4.3</td>
<td>0.40</td>
</tr>
<tr>
<td>C0 (ng/mL/mg)</td>
<td>3.5 ± 2.0</td>
<td>3.3 ± 1.9</td>
<td>3.8 ± 2.1</td>
<td>0.46</td>
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<tr>
<td>Cmax (ng/mL)</td>
<td>19.1 ± 7.1</td>
<td>20.0 ± 6.5</td>
<td>18.1 ± 7.8</td>
<td>0.24</td>
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<tr>
<td>Cmax (ng/mL/mg)</td>
<td>6.9 ± 3.5</td>
<td>7.3 ± 3.5</td>
<td>6.4 ± 3.4</td>
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<td>tmax (hr)</td>
<td>1.76 ± 0.9</td>
<td>1.48 ± 0.68</td>
<td>2.00 ± 1.00</td>
<td>0.04</td>
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<tr>
<td>Clearance (L/h/kg)</td>
<td>0.32 ± 0.17</td>
<td>0.31 ± 0.13</td>
<td>0.33 ± 0.20</td>
<td>0.84</td>
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<tr>
<td>Daily dose (mg/day)</td>
<td>6.3 ± 4.0</td>
<td>6.0 ± 3.4</td>
<td>6.5 ± 4.7</td>
<td>0.85</td>
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<td>Weight-corrected daily dose (mg/kg/day)</td>
<td>0.08 ± 0.05</td>
<td>0.07 ± 0.03</td>
<td>0.09 ± 0.06</td>
<td>0.80</td>
</tr>
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</table>
Figure 2

Gastric emptying coefficient (GEC) versus tmax (n=50)

\[ r^2 = 0.14 \]
Figure 3

![Graph showing tacrolimus concentration over time with normal and delayed gastric emptying](image-url)