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Population Pharmacokinetics of Lopinavir in Combination with Rifampicin-based Antitubercular Treatment in HIV-Infected South African Children

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**Population Pharmacokinetics of Lopinavir in Combination with
Rifampicin-based Antitubercular Treatment in HIV-Infected South African
Children**

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Running title: Lopinavir PK in children with rifampicin TB treatment

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Abstract

Objective The population pharmacokinetics (PK) of lopinavir in tuberculosis (TB)/Human immunodeficiency virus (HIV) co-infected South African children taking super-boosted lopinavir (lopinavir/ritonavir ratio 1:1) as part of antiretroviral treatment in the presence of rifampicin, were compared to the population PK of lopinavir in HIV infected South African children taking standard doses of lopinavir/ritonavir (ratio 4:1).

Methods Lopinavir concentrations were measured in 15 TB/HIV co-infected paediatric patients who were sampled during and after rifampicin-based TB treatment and in 15 HIV infected children without TB. During TB therapy, the dose of ritonavir was increased to lopinavir/ritonavir 1:1 in order to compensate the induction of rifampicin. The children received median (inter quartile range= IQR) doses of lopinavir 292 mg/m² (274, 309) and ritonavir 301 mg/m² (286, 309) twice daily. After TB treatment completion the children received standard doses of lopinavir/ritonavir 4:1 (median [IQR] lopinavir dose 289 mg/m² [286, 303] twice daily) as were those without TB (median [IQR] lopinavir dose 265 mg/m² [249, 289] twice daily).

Results Lopinavir oral clearance (CL/F) was about 30% lower in children without TB than in co-infected children treated with super-boosted lopinavir. However, the predicted lopinavir C_{min} was above the recommended minimum therapeutic concentration during TB/HIV co-treatment in the 15 children. Lopinavir CL/F increased linearly during the dosing interval.

Conclusions Increasing the ritonavir dose to achieve a lopinavir/ritonavir ratio of 1:1 when given in combination with rifampicin-based TB treatment did not completely compensate the enhancement of lopinavir CL/F caused by rifampicin. The time-dependent lopinavir CL/F might be due to a time-dependent recovery from ritonavir inhibition of lopinavir metabolism during the dosing interval.

Introduction

Human immunodeficiency virus (HIV) and tuberculosis (TB) co-infection is a major problem in sub-Saharan Africa. In South Africa, about 50% of children with TB aged between 0–12 years are HIV infected [1, 2]. Antiretroviral regimens including the lopinavir/ritonavir together with 2 nucleoside reverse transcriptase inhibitors (NRTIs) are commonly used in South African children. Lopinavir is a potent HIV protease inhibitor co-formulated with ritonavir in a ratio of 4:1. In this formulation, ritonavir acts as a booster of lopinavir concentrations due to its inhibitory effect on cytochrome P450 (CYP) enzyme 3A4 and P-glycoprotein which are involved in lopinavir metabolism and transport [3-5]. TB/HIV co-infected children should be treated with rifampicin for the whole TB treatment duration [9]. However, by inducing CYP3A4 and P-glycoprotein expression [6-8], rifampicin reduces protease inhibitor concentrations to subtherapeutic concentrations [9, 10]. In adults, rifampicin reduces the area under the-concentration-time curve (AUC) and minimum concentration (C_{min}) of lopinavir by 75% and 99%, respectively [11, 12]. Such reduction can be overcome, in healthy adults, by administering extra ritonavir (super-boosted lopinavir with lopinavir/ritonavir in a 1:1 ratio) since it results in lopinavir C_{min} similar to those obtained with a lopinavir/ritonavir (4:1) regimen without rifampicin [12]. This approach needs to be validated in children with TB/HIV co-infection since the expression of CYP enzymes and P-glycoprotein as well as protein binding may be altered by age or disease [13, 14]. The population pharmacokinetics of lopinavir in children has been published before by for example Jullien et al [15] and Rakhmanina et al [16]. However, these models do not describe or take into account the pharmacokinetic interaction between lopinavir and rifampicin. Neither is the population pharmacokinetics described when given together with the booster ritonavir. The latter has been described earlier [17, 18] but not in children. As tuberculosis and HIV are very commonly co-existing in children in developing countries, it is a great need

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3 to develop population pharmacokinetic models in order to simulate and investigate optimal
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10 The aim of this analysis was to develop a model describing the dynamic PK interactions and
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12 comparing the population pharmacokinetics (PK) of lopinavir in TB/HIV co-infected South
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14 African children taking lopinavir/ritonavir in the ratio of 1:1 in the presence of rifampicin
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16 treatment, to the population PK of lopinavir in HIV infected South African children taking
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Methods

Study design

The data were available from a study consisting of two parallel treatment groups (Table 1), TB/HIV co-infected children and children with HIV but not TB [19]. The TB/HIV co-infected children comprised 15 children (8 females) who aged from 7 to 34 months, weighed between 5-13 kg and had body surface area (BSA) measurements between 0.28-0.54 m². The children received super-boosted lopinavir with a nominal lopinavir dose of 230 mg/m² (median [IQR] doses of lopinavir 292 mg/m² [274, 309] and ritonavir 301 mg/m² [286, 309] at the time of PK evaluation) twice daily in addition to 2 NRTIs, as well as rifampicin with a nominal dose of 10 mg/kg/day (median dose 9.4 mg/kg/day, dose range 6-12 mg/kg/day). Upon completing their TB treatment, the children received standard doses of lopinavir/ritonavir in the ratio of 4:1 with a nominal lopinavir dose of 230 mg/m² (median dose 289 mg/m² IQR 286, 303 mg/m² on the day PK was evaluated) twice daily in addition to 2 NRTIs. Ten of the 15 children returned for repeat PK sampling. The group without TB consisted of 15 children (10 females) aged from 9 to 47 months, and weighing between 5.6-16 kg with BSA measurements between 0.31-0.67 m². The children received lopinavir/ritonavir in the ratio of 4:1, with a nominal lopinavir dose of 230 mg/m² (median dose 265 mg/m², IQR 249, 289 mg/m² at PK evaluation) twice daily, in addition to 2 NRTIs. After a minimum of 4 weeks on the respective treatment regimens the children were admitted for blood sampling. Blood samples were taken just before an observed treatment dose and at 2, 3, 4, 5, 6, 8 and 12 hours after drug administration.

Data analysis

Lopinavir population PK were described using nonlinear mixed effects modelling within NONMEM version VI (GloboMax, Austin, Texas, U.S.A) [20]. The typical population pharmacokinetic parameters, interindividual variability (IIV) and residual variability were estimated by the first-order conditional estimation method with interaction.

One- and two-compartment models with first order absorption were fitted to the data.

Elimination was assumed to take place from the central compartment.

IIV was described using an exponential error model to avoid negative individual parameter estimates:

$$P_i = P \cdot \exp(\eta_i) \quad (1)$$

where P_i is the individual parameter, P is the typical parameter value and η_i is the IIV that describes the difference between the typical parameter value and the individual estimate. The variable η_i is normally distributed with mean 0 and variance ω^2 . Investigated residual error models were additive, proportional and slope-intercept models.

Model selection was achieved by the use of the objective function value (OFV) which is minus twice the log likelihood of the data. A drop in the OFV of 3.84 between two nested models corresponding to $p < 0.05$ was regarded as statistically significant. Graphical analysis using Xpose version 3.104 and version 4 [21], parameter estimates standard error, and scientific plausibility were used for model selection as well. Covariate model building was done by forward inclusion and backwards deletion using an OFV change of > 10.83 ($p < 0.001$) as the cut-off for inclusion, followed by stepwise deletion using an OFV change of > 12.12 ($p < 0.0001$) to retain the effect on the selected parameters.

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Model validation was done by bootstrap resampling [22] and visual predictive check. In the bootstrap resampling, parameter estimates were re-estimated for each of 1000 bootstrap samples. NONMEM estimates from the final model were compared with the bootstrap median and 95% confidence intervals. In the visual predictive check, the final model and parameter estimates were used to simulate 1000 datasets based on the original design. Observed concentrations were compared to the simulated median and 95% nonparametric prediction interval.

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Results

Lopinavir showed time-dependent oral clearance (CL/F) in all children. Lopinavir CL/F increased linearly during the dosing interval. Ritonavir inhibits CYP3A4 and hence the elimination of lopinavir [3]. Recovery from ritonavir inhibition during the dosing interval was described with a rate constant k_r . The final model for lopinavir oral clearance (CL/F) was:

$$(CL/F) = (CL/F)_0 \cdot (1 + [k_r \cdot TAD]) \quad (2)$$

where $(CL/F)_0$ is lopinavir CL/F at the beginning of the dosing interval and TAD is the time after dose in hours. The onset of recovery from enzyme inhibition was immediate since estimating a lag-time for the recovery did not lead to a drop in OFV. An exponential recovery from ritonavir inhibition did not offer any advantage over the linear recovery. Lopinavir $(CL/F)_0$ was 1.26, 1.17 and 0.90 L h⁻¹ in co-infected children during TB treatment, after TB treatment and in the group without TB, respectively. Recovery from ritonavir inhibition of lopinavir metabolism was linear with a k_r of 0.0582 h⁻¹ during TB treatment, and 0.0648 h⁻¹ after TB treatment and in children without TB. This leads to a gradual increase in CL/F during the dosing interval reaching, at the end of the 12-hours dosing interval, 2.14, 2.08 and 1.59 L h⁻¹ in the children during TB treatment, after TB treatment and in the group without TB, respectively. The data did not support having different k_r estimates for the co-infected group after TB treatment and the group without TB. Parameter estimates from the final pharmacokinetic lopinavir model are summarized in Table 2. None of the PK parameters were related to age, weight or gender.

The median sampling time (range) for the nominal 12-hour sample was 11.58 (10.50-12.07), 11.50 (9.25-12.00) and 12.00 (11.55-12.42) hours after dose administration in the children during and after TB treatment, and in those without TB, respectively. Due to the aforementioned wide ranges of the actual sampling time for the last sample, the nominal 12-

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hour sample, lopinavir concentrations were predicted at 11.9 hours after dose administration. Model predicted lopinavir concentrations, for all individuals, were above the recommended minimum therapeutic concentration (1 mg/L) [23].

The bootstrap validation results showing the medians and the 95% confidence intervals for 1000 bootstrap samples are represented in Table 2. Figure 1 shows visual predictive check plots obtained from simulation of 1000 datasets based on the final model. Figure 2 shows plots of observed and individual predicted lopinavir concentration in children with poor, typical and best goodness-of-fit, categorized by the average of the absolute weighted individual residuals.

Discussion

Increasing the dose of ritonavir to achieve a lopinavir/ritonavir ratio of 1:1 was not able to completely counteract the induction of lopinavir metabolism by rifampicin in this study as lopinavir CL/F was modestly higher during TB treatment than it was after TB treatment completion. Although giving larger doses of ritonavir may, in theory, fully compensate the effect of rifampicin on lopinavir CL/F, this needs to be evaluated in patients. When ritonavir was taken in therapeutic doses to act as HIV protease inhibitor, it induced CYP3A4 [24-26] and, *in vitro*, ritonavir activates the pregnane X receptor though it decreases microsomal CYP3A4 activity due to irreversible enzyme inhibition [27].

Even after TB treatment, CL/F in the co-infected children was greater than in children without TB, indicating increased CL or reduced bioavailability of lopinavir, or both, in the TB/HIV co-infected group. This could be attributed to a disease effect, or sampling bias as the study was small. Lopinavir V/F was 2-fold larger in children with TB/HIV compared to children without TB. Lopinavir is 98-99% bound to plasma proteins, mainly alpha-1-acid glycoprotein and albumin [4]. The larger V/F in the co-infected children might be attributed to lower albumin concentrations compared to children without TB [32, 35], or to reduced bioavailability of lopinavir since the same trend was found in CL/F.

In healthy adults, administering extra ritonavir (lopinavir/ritonavir 1:1) resulted in similar lopinavir maximum concentration and AUC as obtained with the standard lopinavir/ritonavir (4:1) regimen without rifampicin [12]. The inability of the extra ritonavir dose to completely counteract rifampicin induction of lopinavir CL/F in this study may be due to the higher hepatic enzymatic activity in children between 1-4 years compared with adults [13]. However, the clinically relevant criterion for monitoring virological efficacy is the trough sample at 12

hours after dose for drugs given twice daily [23]. The model predicted C_{\min} suggest that administering extra ritonavir (lopinavir/ritonavir 1:1) is sufficient to maintain the C_{\min} above 1 mg/L in the studied children. However, this dosing regimen needs further evaluation in a larger population of children. It is important to note that the BSA-derived doses of lopinavir/ritonavir and ritonavir were rounded up to the nearest 0.5 mL of the oral solutions, such that the doses/BSA of lopinavir and ritonavir, respectively, were 27% and 31% greater than 230 mg/m² during TB treatment.

Lopinavir showed time-dependent PK where its CL/F increased linearly during the 12-hour dosing interval probably due to recovery from inhibition by ritonavir. The recovery rate constant, k_r , was 0.0582 h⁻¹ in the co-infected children during TB treatment, while after TB treatment and in children without TB, k_r was 0.0648 h⁻¹. The estimated k_r values correspond to longer half-life values than those reported for ritonavir [29, 30] indicating that enzymatic inhibition by ritonavir is mechanism-based and not only competitive. Assuming mechanism-based inhibition and that the half-life of the inhibitor is negligible in comparison to the turnover half-life of the enzyme, the rate constant for recovery from inhibition corresponds to the rate constant of enzyme turnover [31]. The lower k_r during TB treatment, in comparison to that after TB treatment and children without TB, may be due to the fact that patients with TB/HIV co-infection have lower protein anabolism than patients with HIV infection alone [32]. Recovery from ritonavir inhibition of CYP3A4 in adults is nearly complete after 3 days of discontinuation [33]. Our estimated recovery half-life was 11.9 h during TB treatment and 10.7 h after TB treatment and in the group without TB. This means that after 3 days of discontinuation of ritonavir, the recovery in the co-infected children during TB treatment would be 98% whilst after TB treatment and in the children without TB it would be 99%. A previous attempt to link lopinavir population PK to ritonavir exposure resulted in a

time-independent inverse relationship between lopinavir CL/F and exposure to ritonavir [3]. However, since ritonavir plasma concentrations were not available from our study, there was no relationship between lopinavir PK and ritonavir PK in the model.

Noncompartmental analysis of the data showed a non-significant trend for lopinavir half-life ($t_{1/2}$) to be larger in the co-infected children during TB treatment compared to the children without TB [19]. This is consistent with the estimated population pharmacokinetic parameters since lopinavir $t_{1/2}$ at the beginning of the dosing interval and 12 hours after the dose, respectively, were 11.5 h and 6.77 h for the co-infected children during TB treatment compared to 7.98 h and 4.49 h in children without TB.

Our study may have been too small to detect any effects of age or sex within the 6-month to 4-year age range of the study. Very young children (≤ 6 -months) require increased doses/BSA of lopinavir/ritonavir in order to achieve the same lopinavir concentrations as those in older children and adults [28, 36, 31], and a 39% increase in CL/F has been reported for boys compared to girls in children older than 12 years [37].

In conclusion, our study suggests that super-boosted lopinavir (lopinavir/ritonavir in the ratio of 1:1) in children treated concomitantly with rifampicin-based TB treatment results in therapeutic concentrations of lopinavir ($C_{\min} > 1$ mg/L). However, larger studies including younger and older children are needed to evaluate the pharmacokinetics, safety and efficacy of the combination of lopinavir, ritonavir and rifampicin in children. Lopinavir PK was time-dependent probably due to recovery from ritonavir inhibition of lopinavir metabolism during the dosing interval.

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Figure legends

Figure 1

Observed lopinavir concentrations (filled circles) versus time compared to simulated median (dashed line) and 5-95% prediction interval (dotted lines) based on 1000 simulations from the final model in (a) TB/HIV group during TB treatment, (b) TB/HIV group after TB treatment and (c) in HIV group.

Figure 2

Observed (open circles) and individual predicted (solid lines) lopinavir concentration-time curves from the final lopinavir pharmacokinetic model in (a) TB/HIV group during TB treatment, (b) TB/HIV group after TB treatment and (c) in HIV group (c). 'Poor', 'Typical' and 'Best' denote goodness-of-fit, categorized by the average of the absolute of weighted individual residuals.

Table 1 Study design

<i>TB/HIV group</i>	<i>HIV group</i>
<i>During TB treatment (n=15)*</i>	<i>n=15*</i>
lopinavir:ritonavir (1:1)	lopinavir:ritonavir (4:1)
230 mg/m ² x 2: 230 mg/m ² x 2	920 mg/m ² x 2: 230 mg/m ² x 2
2 NRTIs	2 NRTIs
Rifampicin 10 mg/kg/day	
<i>After TB treatment (n=10)*</i>	
lopinavir:ritonavir (4:1)	
920 mg/m ² x 2: 230 mg/m ² x 2	

*Blood sampling for PK determination was done after minimum 4 weeks of treatment

Table 2 Parameter estimates from the final pharmacokinetic lopinavir model

Parameter	Typical value		Interindividual variability	
	Estimate (RSE)	Bootstrap median (95% CI)	Estimate (RSE)	Bootstrap median (95% CI)
(CL/F) ₀ in TB/HIV group during TB treatment (L·h ⁻¹)	1.26 (0.11)	1.26 (1.06-1.5)	0.39 (0.24)	0.14 (0.081-0.21)
(CL/F) ₀ in TB/HIV group after TB treatment (L·h ⁻¹)	1.17 (0.14)	1.16 (0.933-1.48)	0.5 (0.29)	0.23 (0.11-0.36)
(CL/F) ₀ in HIV group (L·h ⁻¹)	0.895 (0.14)	0.904 (0.703-1.13)	0.5 (0.29)	0.23 (0.11-0.36)
k _r in TB/HIV group during TB treatment (h ⁻¹)	0.0582 (0.71)	0.06 (0.018-0.17)	1.9 (0.58)	3.1 (0.91-7.7)
k _r in TB/HIV group after TB treatment and in HIV group (h ⁻¹)	0.0648 (0.29)	0.064 (0.035-0.105)	0.7 (0.51)	0.48 (0.15-1.1)
V/F in TB/HIV group (L)†	20.9 (0.13)	20.5 (15.5-27.1)	0.86 (0.29)	0.74 (0.39-1.2)
V/F in HIV group (L)	10.3 (0.17)	10.0 (7.03-15.2)	0.44 (0.5)	0.17 (0.059-0.39)
k _a (h ⁻¹)	0.338 (0.076)	0.338 (0.244-0.403)	-	-
Proportional residual variability	0.155 (0.092)	0.154 (0.13-0.178)	-	-

TB= tuberculosis, HIV= Human immunodeficiency virus, RSE= relative standard error which is the ratio of the estimated standard error of the parameter relative to its value, CI= confidence interval, (CL/F)₀ = lopinavir oral clearance at the beginning of the dosing interval, k_r= rate constant for the dissipation of ritonavir enzyme inhibition, (CL/F)= oral clearance in a typical individual $(CL/F)_0 \cdot (1 + [k_r \cdot \text{Time After Dose}])$, V/F= volume of distribution, k_a= absorption rate constant

†Interindividual variability in V/F in TB/HIV group was only estimated during TB treatment.

Figure 1 a

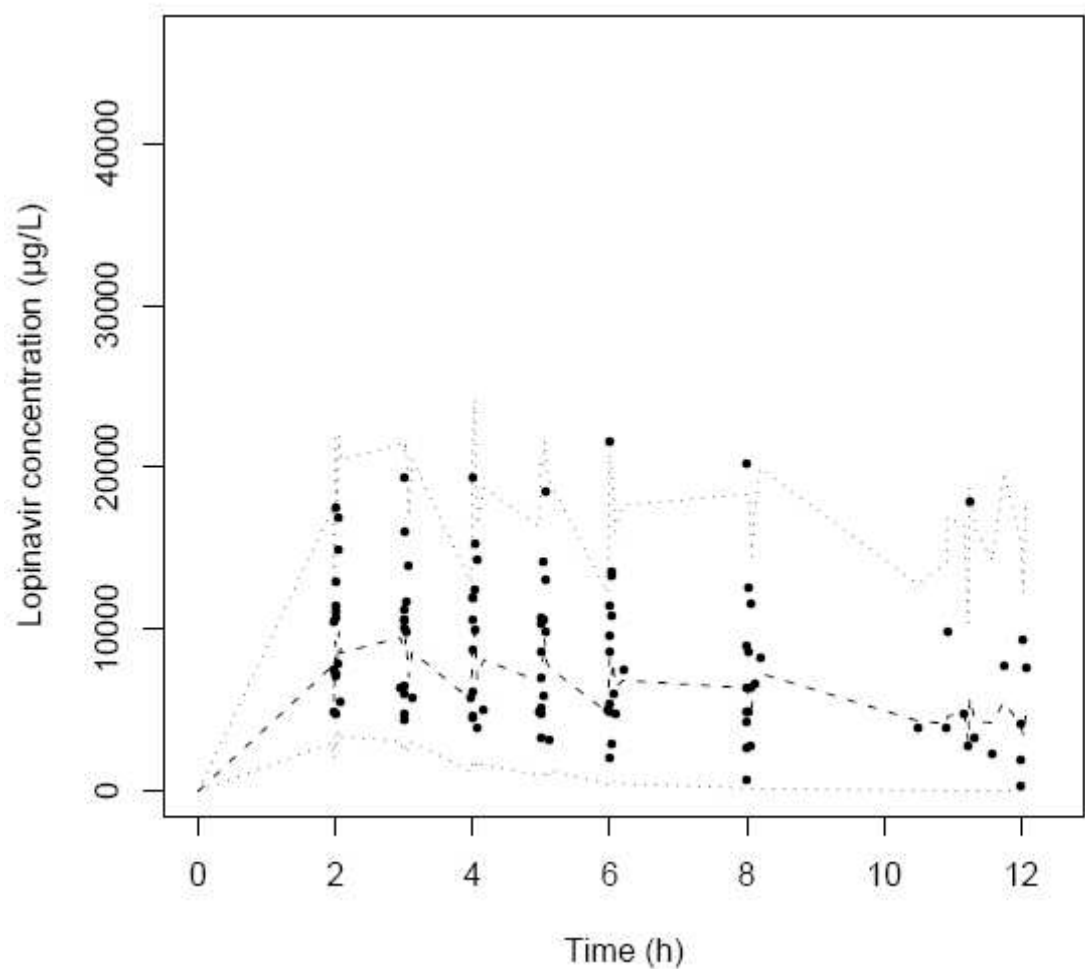


Figure 1 b

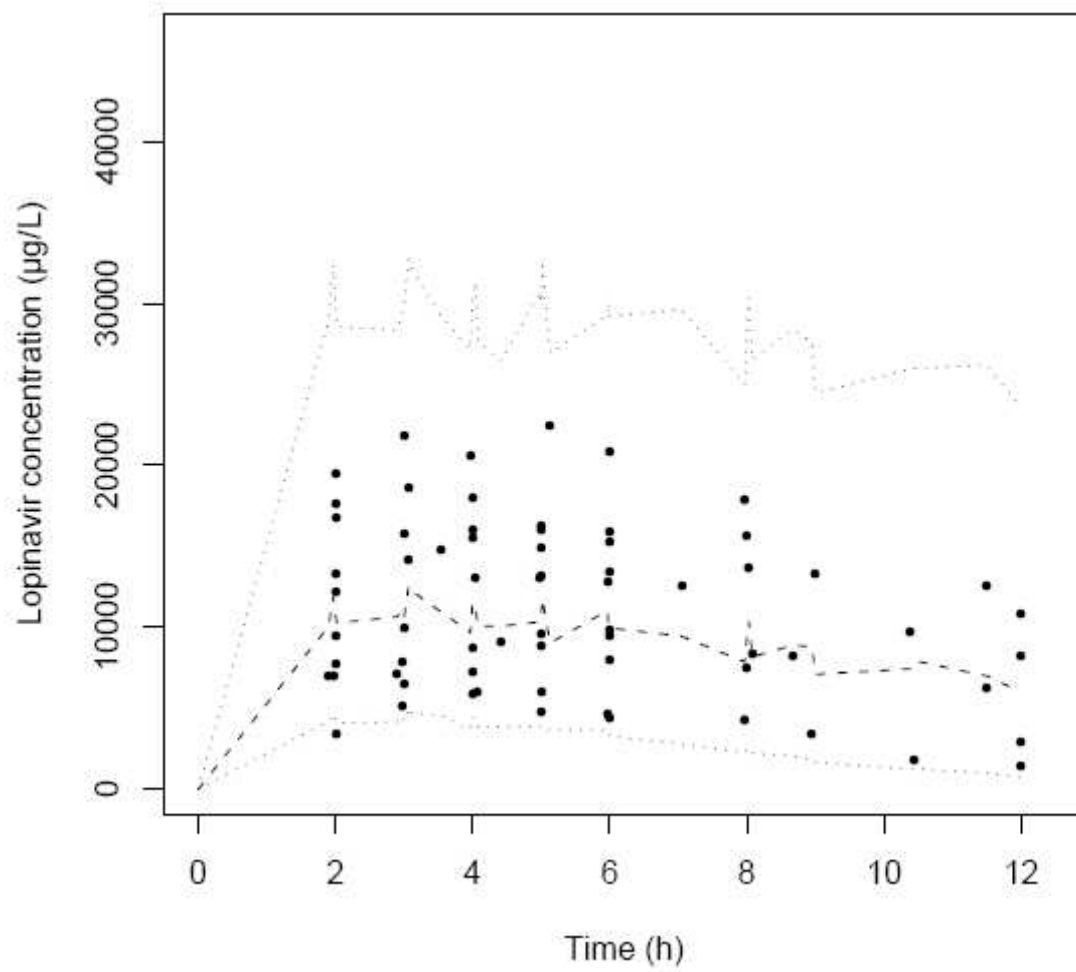


Figure 1 c

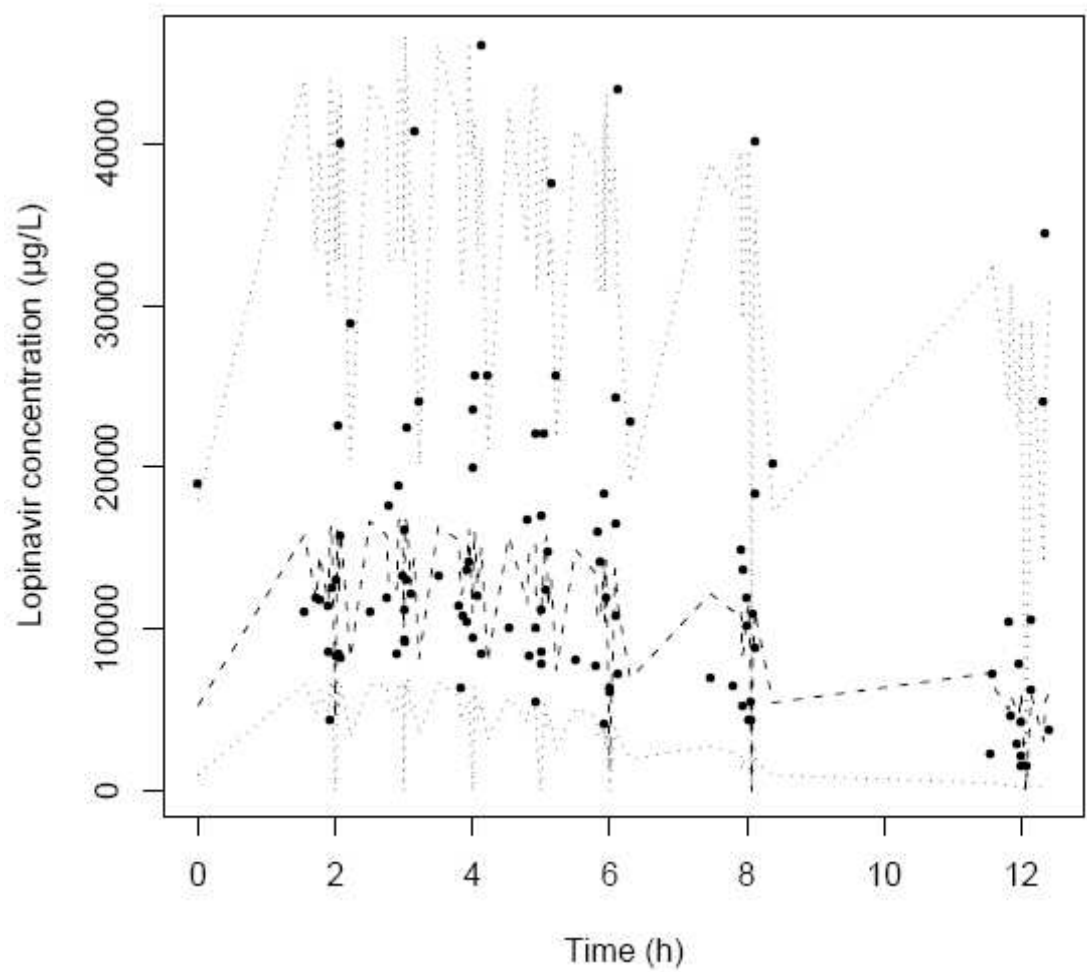
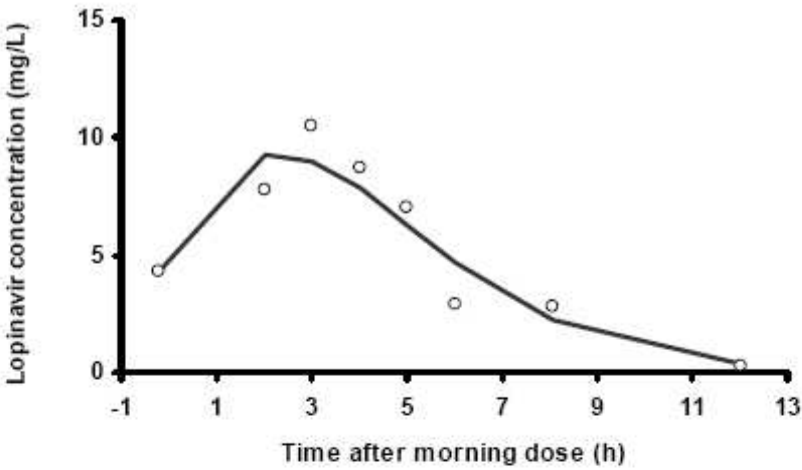
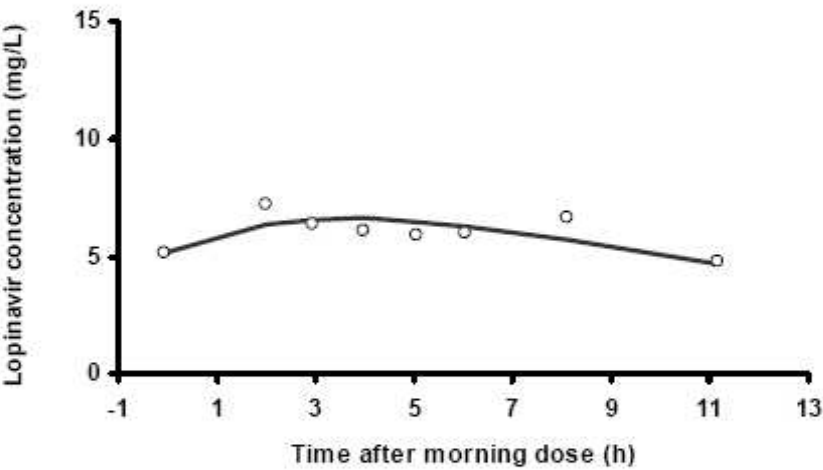


Figure 2 a

Poor fit



Typical fit



Best fit

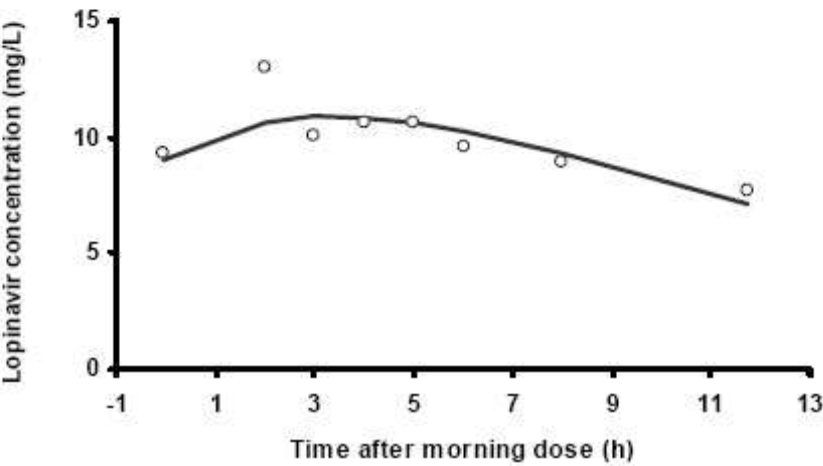
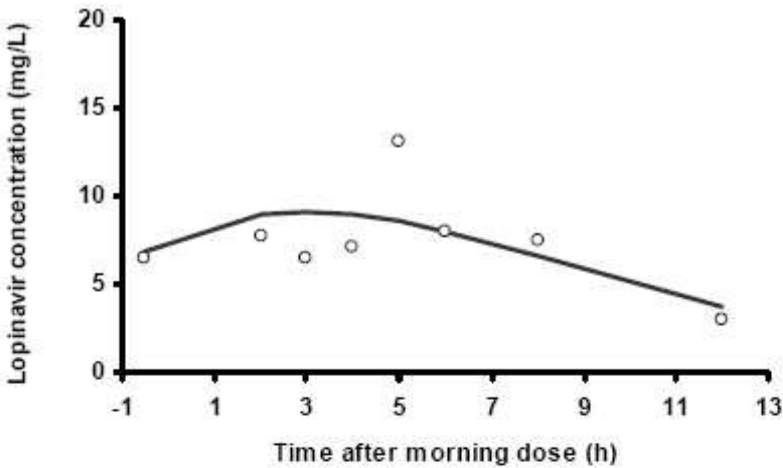
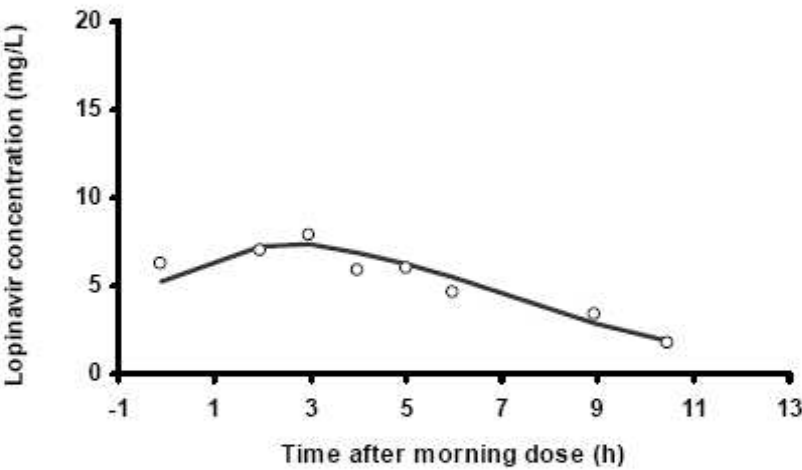


Figure 2 b

Poor fit



Typical fit



Best fit

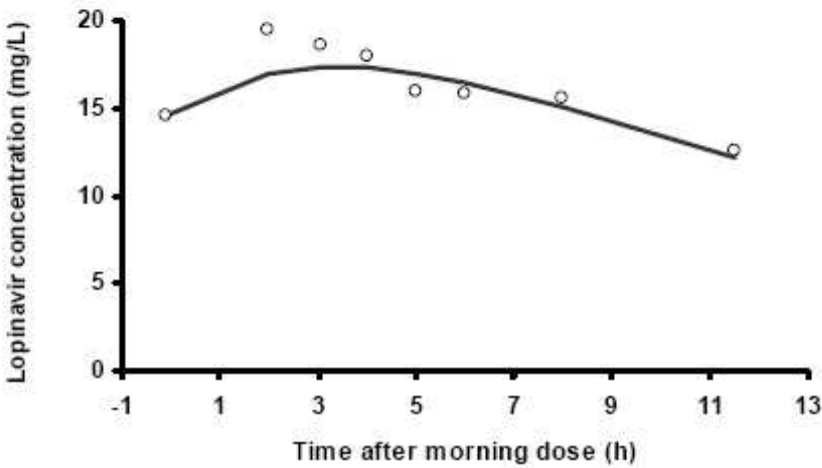
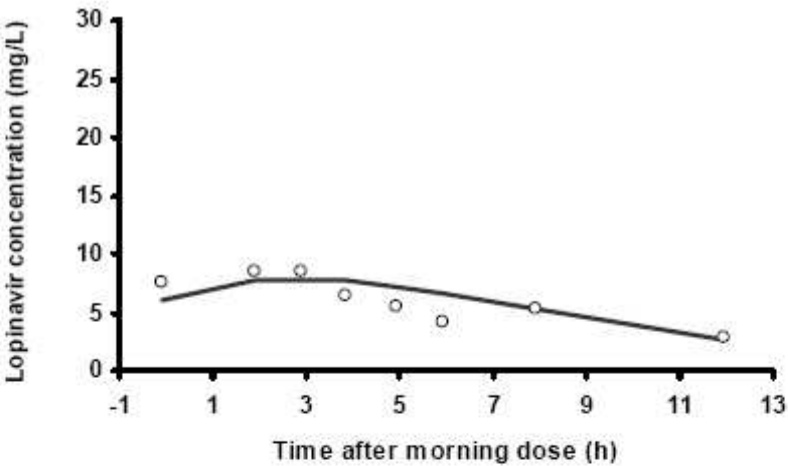
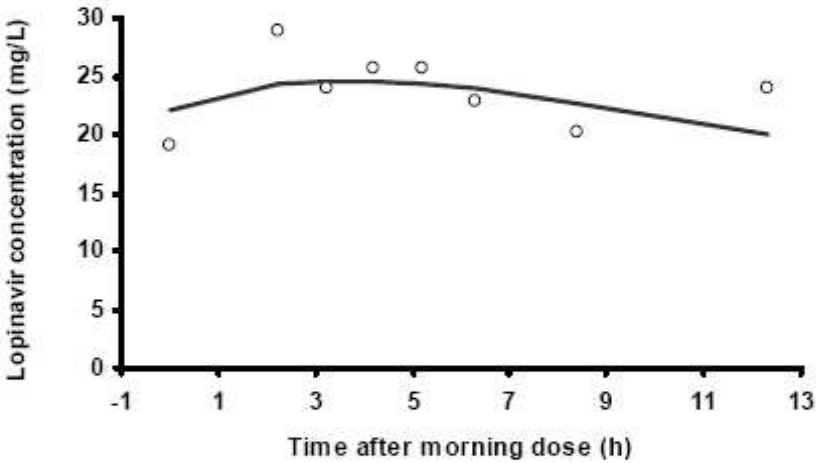


Figure 2 c

Poor fit



Typical fit



Best fit

