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Article title

Moxifloxacin dosing in post-bariatric surgery patients.

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Running title

Population PK of moxifloxacin in post-bariatric surgery patients

Keywords

Moxifloxacin, bariatric surgery, NONMEM, PK-PD and pharmacokinetics

Abstract

Introduction: Given the ever increasing number of obese patients and obesity related bypass surgery, dosing recommendations in the post-bypass population are needed. Using a pop-PK analysis and PK-PD simulations, we investigated whether adequate moxifloxacin levels are achieved in this population.

Methods: In this modelling and simulation study we used data from a trial on MXF pharmacokinetics. In this trial, volunteers who had previously undergone bariatric surgery (at least 6 months prior to inclusion), received 2 doses (intravenous and oral) of 400mg MXF administered on 2 occasions.

Results: In contrast to other papers, we found that MXF pharmacokinetics were best described by a 3-compartmental model using lean body mass (LBM) as a predictor for MXF clearance. Furthermore, we showed that the probability of target attainment (for bacterial eradication) against a hypothetical *Streptococcus pneumoniae* infection is compromised in patients with higher LBM, especially when targeting microorganism with MICs of 0.5 mg/L or higher (PTA approaching zero). When considering the targets for suppression of bacterial resistance formation, even at MIC values as low as 0.25 mg/L, standard MXF dosing does not attain adequate levels in this population. Furthermore, for patients with a LBM of 78 kg or higher, the probability of hitting this target approaches zero.

Conclusions: Throughout our PK-PD simulation study, it became apparent that, whenever optimal bacterial resistance suppression is deemed necessary, the standard MXF dosing will not be sufficient. Furthermore, our study emphasises the need for a lean-body mass based individualized dosing of MXF in this patient population.

What is already known about this subject

- Oral bioavailability of moxifloxacin is not altered in post-bariatric surgery patients compared to healthy controls.
- In healthy volunteers a standard 400 mg moxifloxacin dose achieves adequate plasma concentrations for the eradication of the infecting micro-organism.

What this study adds

- The standard 400 mg moxifloxacin dose is adequate to achieve optimal bacterial eradication in infections with a MIC value up to 0.5 mg/L.
- However, optimal suppression of bacterial resistance formation is not achieved with a standard 400 mg moxifloxacin dose.
- Individualization of antimicrobial therapy, using a LBM based dosing regimen, would aid in achieving the PK-PD target for optimal suppression of bacterial resistance formation.

Introduction

Recently, it was suggested that drug PK in post-bariatric surgery patients might differ significantly from PK in healthy volunteers due to, among other things, altered drug absorption.[1-3] In a previous study on the effect of roux-en-y gastric bypass surgery on moxifloxacin oral bioavailability, our group reported that non-compartmental analysis revealed no significant differences in absolute bioavailability compared to the absolute bioavailability in healthy volunteers[4]. Although our previous analysis showed that, on average, no differences exist between moxifloxacin exposure in post-bariatric surgery patients and healthy volunteers, this analysis did not address PK variability within the post-bariatric surgery cohort and its potential implications on antimicrobial therapy.

One of the types of infections where moxifloxacin therapy is deemed necessary are lower respiratory tract infections (LRTI), e.g. community acquired pneumoniae (CAP). LRTI's are the most common infectious cause of death in the world and the third most common cause of death globally[5]. The pathogens most frequently occurring in CAP[6;7] are *Streptococcus pneumoniae* and to a lesser extent *Staphylococcus aureus*, both Gram-positive bacteria.

During antimicrobial chemotherapy there is no straightforward way to monitor the pharmacological effect of the treatment. Therefore, based on data from large clinical trials and/or in-vitro (kinetic) studies, a-priori specific treatment targets are defined in terms of pharmacokinetic-pharmacodynamic (PK-PD) indices.

For fluorquinolone antibiotics it is generally accepted that bacterial eradication and clinical cure are positively correlated with the AUIC (Eq. 1).

$$\frac{\text{Area under the plasma concentration time curve (AUC)}}{MIC_{\text{invading pathogen}}} \quad (1)$$

In the absence of data from large clinical trials on moxifloxacin PK-PD targets for treating LRTI's, in-vitro (kinetic) models[8-11] are used to define AUC targets. For *Streptococcus pneumoniae* infections, Odenholt and Cars[9] advice on the use of an AUC target of 100 h to guide moxifloxacin dosing. This recommendation is in line with earlier findings by Zhanel et al.[12] and Klepser et al.[13]. They recommended targeting a free AUC between 35 h – 63 h[12] and total AUC between 50 h – 100 h[13].

Besides targets for optimal bacterial eradication, the in-vitro kinetic models provide targets for optimal suppression of bacterial resistance formation. In line with the mutant selection window hypothesis (MSW) of a.o. Zinner et al.[14] AUC targets for suppression of bacterial resistance formation are usually higher than those for optimal bacterial eradication.

In this study we will (i) use a population approach to describe pharmacokinetic variability in our post-bariatric surgery cohort and (ii) use this model in a PK-PD simulation study to assess the target attainment rate in this vulnerable patient population against a hypothetical *Streptococcus pneumoniae* infection.

Patients and methods

Model building was based on data from a randomized crossover (oral and intravenous administration) trial of moxifloxacin administration to a cohort of post-bariatric surgery patients [4] published previously. In short, 12 volunteers, who had undergone roux-en-y gastric bypass at least 6 months prior to inclusion in the study, were administered moxifloxacin. Each volunteer received two single doses of 400 mg moxifloxacin, once as a tablet and once as a 1 hour intravenous infusion, separated by a 1 week washout period. The study protocol was approved by the local institutional review board of Ghent University Hospital. [4]

For all patients venous blood samples were taken prior to administration and at serial time points up to 72h post-dose. Blood samples were collected in heparinized tubes. After centrifugation, plasma was collected and stored at -80°C until analysis. Samples were analysed by a validated HPLC-Fluorescence assay published earlier.[15] Assay characteristics were evaluated and complied with the FDA's guidance on bio-analytical method validation.[16]

Pharmacokinetic analysis

Model building

The moxifloxacin concentration versus time data, for the oral as well as the intravenous moxifloxacin administration, were analysed simultaneously using the FOCE-I estimation algorithm in NONMEM® (Version 7.2; GloboMax LLC, Hanover, MD, USA). PLT-Tools (Version 4.6; PLTsoft, San Francisco, CA, USA) was used as a graphical user interface to NONMEM®. Furthermore, R® (R foundation for statistical computing, Vienna, Austria) was used to graphically assess the model's goodness-of-fit (GOF) and to evaluate the model's predictive capabilities.

As a starting point for the development of the structural model we used a 2 compartmental model with a linear absorption into and a linear elimination from the central compartment, as published earlier by Grosjean and Urien[17] and Simon et al[18]. Subsequently several other higher-order structural models were fitted to our data and their goodness-of-fit assessed (e.g. LAG-time and TRANSIT[19] absorption models). Throughout the course of this iterative procedure of fitting and evaluating different models, the Akaike information criterion (AICc) was used to compare the goodness-of-fit of different models. In addition, graphical evaluation was used to show the goodness-of-fit according to the EMA Guideline on Reporting the Results of Population Pharmacokinetic Analyses (2007). Furthermore, the condition number was calculated on the covariance matrix of parameter estimates to detect possible ill-conditioning.

Covariate screening was empirically approached by direct incorporation of different covariates in the pharmacokinetic model and comparison of the goodness-of-fit using the AICc and graphical techniques. Shrinkage (calculated by PLT-Tools) was considered prior to incorporating patient covariates in our final structural model. When shrinkage (calculated on the post-hoc parameter estimates) was high, inclusion of patient covariates on that particular model parameter was deemed unfeasible. Finally, model parsimony was assessed by selectively removing different parameters from the model and evaluating the goodness-of-fit of the reduced model.

Internal Model Validation

R® (R foundation for statistical computing, Vienna, Austria) and PLT-Tools (Version 4.6; PLTsoft, San Francisco, CA, USA) were used for model validation. The final pharmacokinetic model was validated using different methods: (i) visual predictive check (VPC) method[20] and (ii) the normalized prediction distribution error (NPDE) method[21]. Both methods address validation through the use of simulated data. Using the final pharmacokinetic population model, with all parameters fixed at final parameter estimates, 100 concentrations were simulated for all observed time-points. These simulations were performed using the \$SIM statement in NONMEM®. Afterwards, for method (i), these simulated concentration-time profiles were analysed by non-compartmental pharmacokinetics using the PK package (version 1.2-5) for R®. The distribution of the calculated AUC's for the simulated concentration-time profiles were then compared to the observed AUC's from our dataset (similarly calculated using the PK package in R®). The validity of the model is assessed by graphically comparing the degree of similarity in the distribution of both sets of calculated AUC's. For specific details regarding method (ii), we refer to the work of Comets et al.[21]

PK-PD simulations

Using the calculated AUC_{24h} 's of the simulated concentration-time profiles for the oral data, the AUIC was assessed for typical wild-type *Streptococcus pneumoniae* MIC-values[22]. Subsequently, these AUIC's were plotted against typical AUIC thresholds to visualize the probability of target attainment (PTA) against *Streptococcus pneumoniae* MIC-values for the 400mg dosage regimen.

Based on the findings by Odenholt and Cars[9] we decided to use an AUIC target for bacterial eradication of 100h in our simulation study. Furthermore, based on the results of the in-vitro dynamic model published by Zinner et al.[14], on the emergence of resistant *Streptococcus pneumoniae*, we used, as a target for optimal suppression of bacterial resistance formation, a free AUIC target of 100 h. When accounting for plasma protein binding (approximately 50% for moxifloxacin[23]), this latter free AUIC target is equivalent to an AUIC target of 200 h (to avoid confusion with the target for bacterial eradication defined as AUIC rather than free AUIC, in our simulation study we will define both targets as (total) AUIC targets).

Finally, the effect of possible covariates identified in the final pharmacokinetic model, on PK-PD target attainment, was evaluated using graphical techniques.

Results

Patients and Data

The pharmacokinetic analysis was based on 432 observed total plasma concentrations from 12 healthy volunteers who recently underwent bariatric surgery, obtained from a study performed by De Smet et al.[4] The following patient covariates were available: age, total body weight (TBM), lean body mass (LBM) calculated according to James[24], gender, height, serum albumin, creatinine clearance estimated using the Cockcroft and Gault equation (CrCl) and estimated according to the

Modification of Diet in Renal Disease equation (MDRD). A summary of the demographic information is given in Table 1. The observed concentration-time profiles for all patients are shown in Figure 1.

Pharmacokinetic Model Building

According to Grosjean and Urien[17] and Simon et al[18], a two-compartmental model was found superior to a one-compartmental model in describing moxifloxacin pharmacokinetics for a standard 400mg dose. In their final model Grosjean and Urien[17] incorporated an allometric scaling approach to predict volume and clearance terms as a function of LBM. On the other hand, Simon et al[18] incorporated no parameter-covariate relationship in their population model. Given the thorough study conducted by Grosjean and Urien[17] on the body size effects on moxifloxacin pharmacokinetics and the number of subjects included in their population analysis relative to Simon et al.[18] (number of subjects included in the population analyses respectively 99 and 16) we decided to, as a starting point, fit the Grosjean and Urien[17] model with clearance and volume terms allometrically scaled to LBM. However, given the relatively small number of subjects in our data set, we initially simplified the Grosjean and Urien[17] model by excluding the TRANSIT absorption model and treating all model parameters as fixed effects.

Subsequently, we investigated which of the model parameters were suitable to be included in the model as random effects, using the condition number as a measure of ill-conditioning. A 2-compartmental model treating only the absorption constant (k_a), the central volume of distribution (V_c) and clearance from the central compartment (CL) as random effects, whilst estimating the random effects variance-covariance matrix using a diagonal matrix, provided us with an initial model with an acceptable condition number (approximately 10^3). The hierarchical model building procedure is depicted in Figure 2.

In their analysis, Grosjean and Urien[17] observe that including a LAG-time or TRANSIT compartment model significantly reduces the model's objective function value. Therefore, after addition of an additive error term parameter to our model (which proved to be a requisite to fit an absorption model), we fitted both absorption models. Similar to Grosjean and Urien[17], we also observed a better fit for both models. However, when our structural model was fitted with an additional peripheral compartment we observed an even higher decrease in AICc. (As seen from Figure 2) Therefore, as a starting point to append more complex absorption submodels we choose the three-compartmental model rather than the two-compartmental model as proposed by Grosjean and Urien [17].

Subsequently, the TRANSIT compartment and LAG-time absorption model were appended to our 3-compartmental model. Both significantly reduced the model's AICc. However, the condition number (approximately 10^{11} for the LAG-time model) indicated serious ill-conditioning in both cases. Although (some of) the estimated parameters for both models would suffer from poor precision, as indicated by the condition number, the estimated values (as noted in Figure 2) for the absorption model parameters point out that in our dataset little evidence is present to assume a delayed absorption of moxifloxacin (estimated LAG-time ≈ 0.19 h; estimated mean transit time (MTT) ≈ 0.19 h). Based on the potential problem of poor precision of the estimated parameters and the lack of clinical significance of an estimated absorption delay of 0.20 hours, neither the TRANSIT compartment nor the LAG-time absorption model were found feasible for inclusion in our structural model.

Finally, we (i) evaluated the feasibility of including covariates other than LBM in our model and (ii) studied whether we could simplify our model by removing, among other things, the allometric scaling component. After plotting of the post-hoc random effects estimates versus the patient covariates and calculation of the shrinkage, we decided to only evaluate CrCl and MDRD for

incorporation into our model. Hereto, CL was modelled as a linear function of CrCl or MDRD in two separate models. The first model, using CrCl as a predictor for CL resulted in a slightly lower AICc ($\Delta\text{AICc} = -2.3$), but goodness-of-fit plots (data not shown) revealed no observable difference in the fits of both models. Incorporation of MDRD into the model, as predictor for CL did not result in a decrease in AICc, and was therefore not incorporated in our final model.

By removing or substituting some of the model parameters we studied whether our final model could be simplified further. We started out by fitting a model using an allometric scaling of TBM rather than LBM as a way to predict clearance and volume terms. The resulting increase in AICc ($\Delta\text{AICc} = 27.3$) stresses the better model fit using an allometric scaling of LBM rather than TBM as a predictor of clearance and volume terms. Furthermore, leaving out the LBM covariate or the allometric exponent of 0.75 on the model's clearance terms did not result in an improved goodness-of-fit ($\Delta\text{AICc} = +56.9$ and -0.50 respectively).

Final PK model & Internal model validation

The final parameter estimates and the estimated standard errors (SE) for our 3-compartmental model are shown in Table 2. Figures 3 and 4 illustrate the model's goodness-of-fit. In Figure 3 the observed plasma concentrations are contrasted with the plasma concentrations predicted by the final model, whilst in Figure 4 the observed plasma concentrations are plotted along with the median, 5% and 95% percentile of the simulated plasma concentrations for every observed time-point. As seen from Figure 4, the model gives a good prediction of the mean response at every time-point. Furthermore, it adequately describes the variation around this mean response (this is seen by comparing the observed variation in plasma concentrations at every time-point versus the percentiles of the simulated distributions at these time-points.) Alternatively, Figure 5 presents the results of the VPC method as described earlier. Again, it is noted that our model provides a good

estimation of the mean observed AUC, as well as the observed variation around this mean AUC. The goodness-of-fit of our model was further confirmed by inspection of the distribution of the NPDE's (Data not shown). Upon comparison against the standard normal distribution, no deviations were observed, hence demonstrating the goodness-of-fit of our model.

PK-PD simulations

The distribution of simulated AUIC's for the standard 400 mg daily dose of moxifloxacin against typical *Streptococcus pneumoniae* MIC-values is depicted in Figure 6. To evaluate the expected efficacy of this treatment at every MIC-value, we simultaneously plotted the AUIC targets for bacterial eradication (AUIC > 100 h) and suppression of bacterial resistance formation (AUIC > 200 h). For MIC-values up until 0.5 mg/L, the distribution of simulated AUIC's remains well above the indicated targets for bacterial eradication. However, MIC-values in excess of 0.5 mg/L, the median of the predicted AUIC's is smaller than the proposed target of AUIC >100 h, leading to a PTA (bacterial eradication) below 50%. Furthermore, when comparing the simulated AUIC's versus the proposed target[14] for the control of antimicrobial resistance formation, it stands out that even at MIC values as low as 0.25 mg/L the proposed target is attained for only a very small fraction of the simulated population (< 25%, given that the 75% percentile of the simulated distribution is below the AUIC threshold).

To elucidate the effect of LBM on moxifloxacin PK-PD target attainment rate, we simulated two patient subpopulations. On one hand we simulated 100 plasma concentration-time profiles for a patient population with a LBM of 42 kg (for a person of average height, this would correspond to a TBM of around 60 kg, this is the lowest observed LBM in our cohort). On the other hand, simulations were performed for a population with a LBM of 78 kg (corresponding to a TBM of approximately 100 kg, highest observed LBM in our cohort). Figure 7 provides the information on the simulated AUIC's

as a function of *Streptococcus pneumoniae* MIC-values. From this graph it is apparent that, for patients with a higher LBM, the PTA at every MIC-value is lower as compared to patients with a lower LBM (on average, the AUC_{24h} in the high LBM group is 40.5 % lower than the AUC_{24h} in the low LBM group).

Furthermore, , all simulated AUC's from the high LBM group drop below the recommended AUC target of 100 h when targeting a microorganism with an MIC of 0.5mg/L, and hence the PTA for bacterial eradication for those patients approaches zero. Furthermore, when evaluating the PTA for suppression of bacterial resistance formation, for patients with a higher LBM, this PTA approaches zero at MIC values as low as 0.25 mg/L.

Discussion

Many authors reported in literature that moxifloxacin pharmacokinetics were best described using a 1-compartmental [25] or a two-compartmental [17;18] model, with[17;25] or without[18] additional parameters to account for the observed absorption delay. In contrast to these observations, we found that a three-compartmental model produces a superior fit as compared to a two-compartmental model. This discrepancy is explained by the difference in sampling times between our study (up until 72 hours post-dose) and the studies reported in literature earlier (restricted to 24 hours post-dose). Given the relatively short sampling schemes of the foregoing studies, it would have been nearly impossible for these authors to reliably identify this third compartment. Although this third compartment might not have a significant impact on the single dose simulations performed in our study, it is expected to have an impact whenever trying to simulate moxifloxacin exposure after repeated doses. Moreover, not taking into account this 3rd compartment when simulating moxifloxacin PK will result in an underestimation of a subjects true (unobservable) AUC.

As opposed to Florian et al. [25] and Grosjean and Urien [17] our study, as well as the study reported by Simon et al. [18], found no evidence in favour of a (clinically significant) delayed absorption and therefore no LAG-time nor TRANSIT-model was fitted. These differences are likely explained by the fact that Florian et al. [25] and Grosjean and Urien [17] used data originating from double-blinded trials in which moxifloxacin tablets were overencapsulated, thereby most likely prolonging the absorption phase.

Based on our data, it seems that allometric scaling of LBM by an exponent of 0.75 is superior, compared to a simple linear regression model, for the prediction of moxifloxacin clearance terms. Furthermore, in concordance with the findings of Grosjean and Urien [17] we found that LBM rather than TBM should be used in the prediction of moxifloxacin pharmacokinetics. However, since it is well known [26] that the James [24] equation tends to overestimate the subjects' percentage body fat, thereby underestimating the true LBM, care has to be taken when using this model to estimate PK parameters in the morbidly obese ($BMI > 30 \text{ kg/m}^2$).

Although the appropriate PK-PD targets to pursue when trying to optimise moxifloxacin treatment are still under debate, our PK-PD simulations show that, when taking into account currently propagated AUIC thresholds, in this population the PTA for bacterial eradication against a *Streptococcus pneumoniae* organism with a MIC-value of 0.5 mg/L is already below 50%. When we look at the PTA for the simulated population with LBM of 78 kg, this probability approaches zero at the MIC value of 0.5 mg/L. Furthermore, when evaluating the PTA of suppression of bacterial resistance formation it is apparent that at standard 400mg doses of moxifloxacin, even at MIC values of 0.25 mg/L this PTA is unacceptably low.

Given the relatively low prevalence of MIC-values of 0.50 mg/L for the wild type *Streptococcus pneumoniae* species [22], at first glance, our results do not seem to have an important impact on the average PTA for bacterial eradication of moxifloxacin therapy in this population.

However, as indicated in Figure 7, for subjects with a LBM of 78 kg, approximately 25 % will attain AUC values below the recommended target of 100 h. (as seen by the near-overlap of the 25 % percentile of the simulated distribution and the dashed line for the AUC target of 100 h) Moreover, although not included in our simulated population, from our model it is apparent that post-bariatric surgery patients with a LBM higher than 78 kg are likely to fail in achieving an AUC of 100 h.

When considering an AUC target of 200 h, as proposed in literature[14] to optimally suppress bacterial resistance formation, we see that the overall PTA is low (well below 50 %) even at MIC values of 0.25 mg/L for the entire simulated population. Furthermore, when considering the effect of LBM on this particular PTA, we observe that for subjects with a higher LBM (78 kg) the PTA for suppression of bacterial resistance formation approaches zero at this MIC value.

This study has a number of limitations. At first, changes induced in the PK of moxifloxacin by the infection are not captured. Furthermore, given that the subjects in our study were included after having stabilised from their bariatric surgery, i.e. they were in a generally good condition, the observed PK variability might underestimate the variability seen in infected patient populations. The consequence of this limitation is that both PK and the probability of target attainment are likely to be even more variable in a patient population treated with moxifloxacin.

Conclusions

This analysis demonstrates that for antimicrobial dosing the “one dose fits all” paradigm is not correct. Throughout this simulation study, it was clear that optimization of moxifloxacin dosing should take into account the effect LBM on PK and, ultimately, the PK-PD endpoints. Our study results show that in order to optimize moxifloxacin chemotherapy, both in terms of bacterial eradication and optimal suppression of resistance development during therapy, individualized dosing strategies should be developed.

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Conflicts of interest

All authors have completed the Unified Competing Interest form at

http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and

declare: no support from any organisation for the submitted work, no financial relationships with any

organisations that might have an interest in the submitted work in the previous 3 years, no other

relationships or activities that could appear to have influenced the submitted work.

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Tables

TABLE 1

Table 1 Summary of patient demographics.

Characteristic	median [range]
Age (years)	41 [25 – 57]
TBM (kg)	78.1 [57.4 – 104.0]
LBM (kg)	51.7 [41.9 – 77.6]
Height (m)	1.68 [1.58 – 1.99]
Sex (# males / # females)	4 / 8
Serum albumin (g/dL)	3.96 [3.54 – 4.40]
CrCl _{Cockcroft-Gault} (mL/min)	131.9 [100.4 – 221.5]
CrCl _{MDRD} (mL/min)	101.5 [91.9 – 134.9]

TABLE 2

Table 2 Population parameter estimates of the final pharmacokinetic model and the associated 95% bootstrap confidence intervals calculated on 100 bootstrap samples. All model parameters except k_a were centered for a typical subject with a LBM of 60 kg.

Parameter	Final pharmacokinetic model
Fixed effects	
k_a (h^{-1})	0.95 [0.72 – 1.21]
$V_1 \times \left(\frac{LBM}{60}\right)^1$ (L)	47.7 [31.6 – 78.6]
$Cl \times \left(\frac{LBM}{60}\right)^{0.75}$ (L/h)	8.60 [7.80 – 9.70]
$V_2 \times \left(\frac{LBM}{60}\right)^1$ (L)	61.5 [37.6 – 75.7]

$Q_2 \times \left(\frac{LBM}{60}\right)^{0.75}$ (L/h)	105.3 [55.2 – 140.0]
$V_3 \times \left(\frac{LBM}{60}\right)^1$ (L)	48.4 [34.4 – 92.9]
$Q_3 \times \left(\frac{LBM}{60}\right)^{0.75}$ (L/h)	1.35 [1.23 – 1.56]
Inter-individual variability	
ω^2 (k_a)	0.24
ω^2 (V_1)	0.14
ω^2 (Cl)	0.04
Residual error	
σ^2 (Proportional)	0.03

k_a : absorption constant; V_1 : Volume of distribution for the central compartment; Cl: Clearance from central compartment; V_2 & V_3 : Volume of distribution for the first and second peripheral compartment; Q_2 & Q_3 : Inter-compartmental clearance from the central compartment to the first and second peripheral compartment; ω^2 : Variance terms describing inter-individual variation in a particular model parameter; σ^2 : Variance term describing residual unexplained error

Legends to figures

Figure 1 Observed moxifloxacin plasma-concentration time profiles after oral dosing (left graph) and after a 1 hour i.v. infusion (right graph) The LLOQ of the assay is depicted by the dashed line.

Figure 2 Overview of the structural model building: V_c : Volume of distribution for the central compartment; CL: Clearance from central compartment; V_p & V_{p2} : Volume of distribution for the first and second peripheral compartment; Q_p & Q_{p2} : Inter-compartmental clearance from the central compartment to the first and second peripheral compartment; θ_{lag} : Absorption lag time; θ_{MTT} : Mean transit time; θ_N : Number of transit compartments; σ_{Add} : Residual error variance explained by the additive error term.

Figure 3 Goodness-of-fit plots for our final PK model, insets show the first 3 hours post dosing. The black line represents a LOESS smoother.

Figure 4 Observed moxifloxacin plasma concentrations after a standard 400 mg oral dose (open circles). The model simulated median moxifloxacin plasma concentration (solid line) along with the 5% and 95% percentile (dashed lines) from the simulations are shown to assess the model's goodness-of-fit.

Figure 5 Visual predictive check comparing the distribution of the 100 model simulated AUC_{72} values (histogram on top) against the observed AUC_{72} values (open circles) after a standard 400 mg oral dose of moxifloxacin.

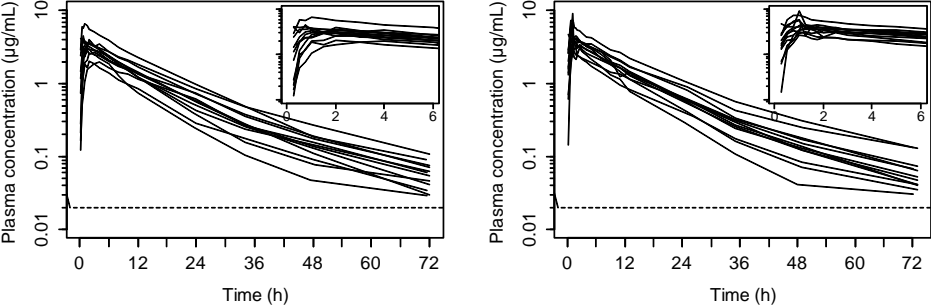
Figure 6 AUIC values calculated as the ratio of the model simulated moxifloxacin AUC_{24} values after a standard 400mg oral dose versus the theoretical *Streptococcus pneumoniae* MIC-values. Simultaneously the AUIC cut-off values for bacterial eradication as well as suppression of bacterial resistance formation, as proposed in literature, are shown. (long dashes: AUIC = 100; short dashed lines: AUIC = 200)

Figure 7 AUIC values calculated as the ratio of the model simulated moxifloxacin AUC_{24} values for subjects with a LBM of 42 kg (open squares) and 78 kg (solid squares) after a standard 400mg oral dose versus the theoretical *Streptococcus pneumoniae* MIC-values. Simultaneously the AUIC cut-off values for bacterial eradication as well as suppression of bacterial resistance formation, as proposed in literature, are shown. (long dashes: AUIC = 100; short dashed lines: AUIC = 200) Overall, AUIC values for the high LBM group are 40.5 % lower than those for the low LBM group.

Figures

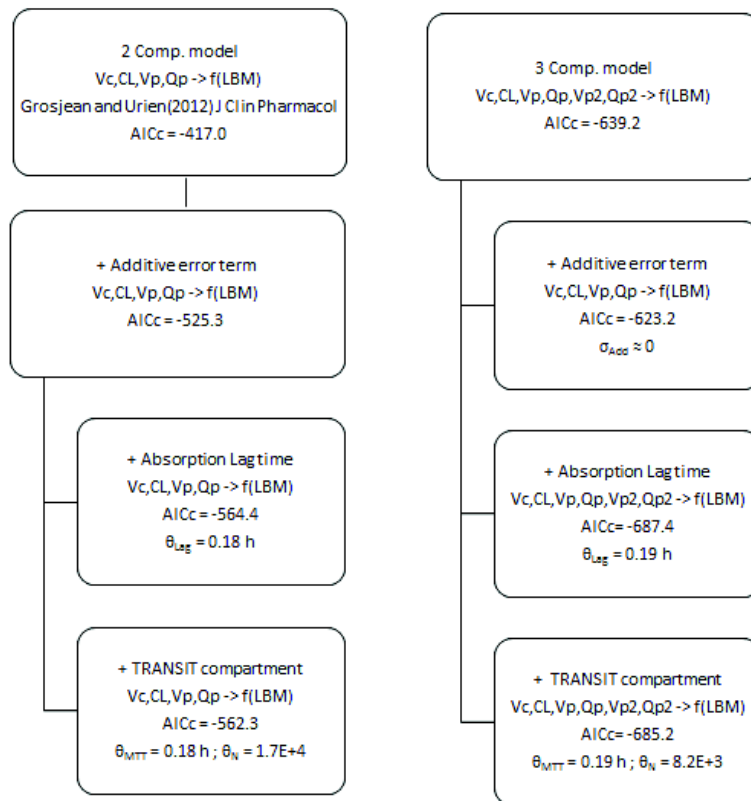
FIGURE 1

Figure 1 Observed moxifloxacin plasma concentration time profiles after oral dosing (left graph) and after a 1 hour i.v. infusion (right graph). The LLOQ of the assay is depicted by the dashed line.



□

FIGURE 2



V_c : Volume of distribution for the central compartment; CL : Clearance from central compartment; V_p & V_{p2} : Volume of distribution for the first and second peripheral compartment; Q_{p1} & Q_{p2} : Inter-compartmental clearance from the central compartment to the first and second peripheral compartment; t_{lag} : Absorption lag time; t_{MTT} : Mean transit time; N : Number of transit compartments; σ_{Add} : Residual error variance explained by the additive error term.

FIGURE 3

Figure 3 Goodness-of-fit plots for our final PK model, insets show the first 3 hours post dosing. The blackline represents a LOESS smoother.

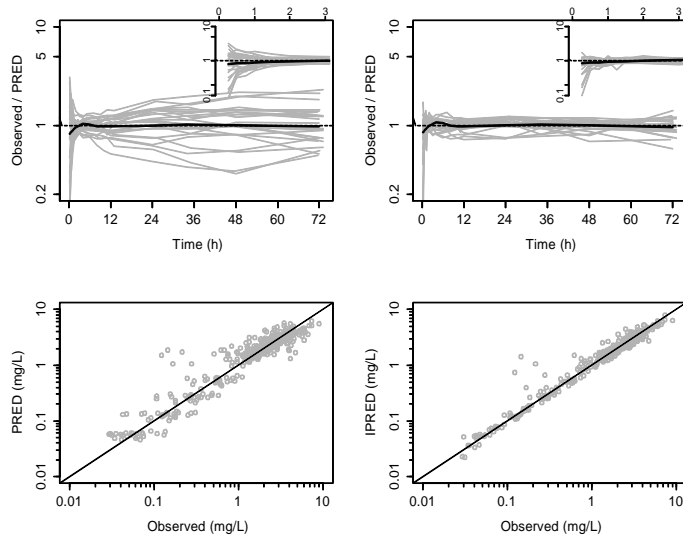


FIGURE 4

Figure 4 Observed moxifloxacin plasma concentrations after a standard 400 mg oral dose (open circles). The model simulated median moxifloxacin plasma concentration (solid line) along with the 5% and 95% percentile (dashed lines) from the simulations are shown to assess the model's goodness-of-fit.

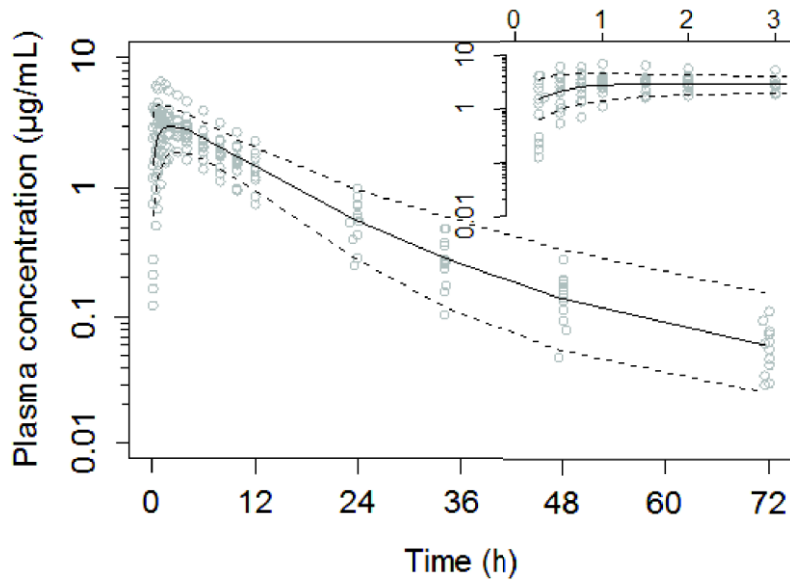


FIGURE 5

Figure 5 Visual predictive check comparing the distribution of the 100 model simulated AUC_{72} values (histogram on top) against the observed AUC_{72} values (open circles) after a standard 400 mg oral dose of moxifloxacin.

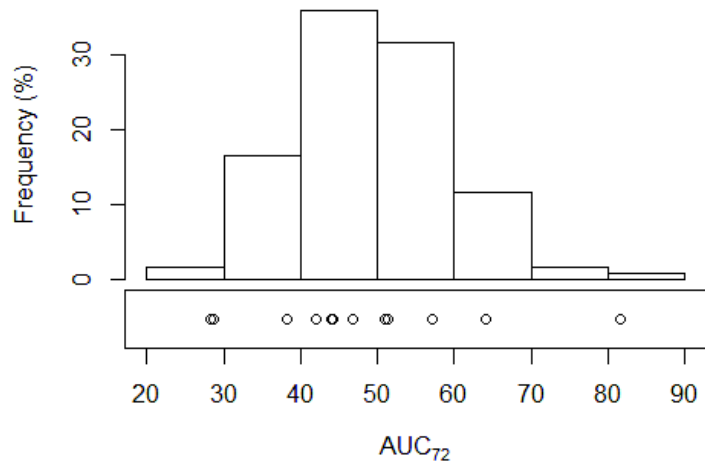


FIGURE 6

Figure 6 AUC values calculated as the ratio of the model simulated moxifloxacin AUC values after a standard 400mg oral dose versus the theoretical *Streptococcus pneumoniae* MIC-values. Simultaneously the AUC cutoff values for bacterial eradication as well as suppression of bacterial resistance formations as proposed in literature, are shown. (long dashes: AUC = 100; short dashed lines: AUC = 200)

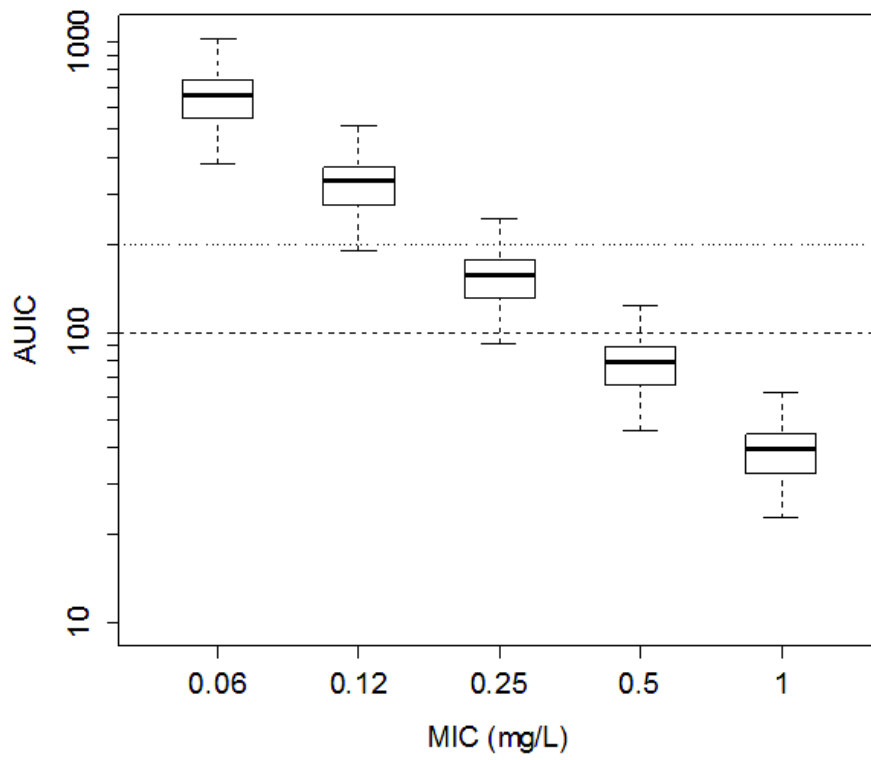


FIGURE 7

Figure 7 AUC values calculated as the ratio of the model simulated moxifloxacin AUC values for subjects with a LBM of 42 kg (open squares) and 78 kg (solid squares) after a standard 400mg oral dose versus the theoretical Streptococcus pneumoniae MIC-values. Simultaneously the AUC cutoff values for bacterial eradication as well as suppression of bacterial resistance formation, as proposed in literature, are shown. (long dashes: AUC = 100; short dashed lines: AUC = 200) Overall, AUC values for the high LBM group are 40.5 % lower than those for the low LBM group.

