Ciprolexacin pharmacokinetics after oral and intravenous administration in morbidly obese and non-obese individuals; a prospective clinical study
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Plasma PK-data

Plasma samples were obtained in non-obese patients who received a 500mg oral dose of ciprofloxacin followed by a 400mg 1-hour IV infusion given three hours after the oral administration. Obese patients received a single ciprofloxacin oral or IV dose of 500mg or 400mg over 1-hour, respectively. Sampling was done according to the scheme in table 1. For non-obese and obese PO individuals, t=0 is the moment of oral administration. For obese IV individuals, t=0 is end of the 1-hour IV infusion.

Table 1: sampling scheme

| Time (min (hours)) | Non-obese | Obese IV | Obese PO |
|-------------------|-----------|----------|----------|
| 5                 |           |          |          |
| 15                |           |          |          |
| 30                |           |          |          |
| 60 (1h)           | .         | .        |          |
| 75                | .         |          | .        |
| 90                | .         | .        | .        |
| 105               | .         | .        |          |
| 120 (2h)          | .         | .        | .        |
| 135               | .         |          | .        |
| 150               | .         | .        | .        |
| 165               | .         | .        |          |
| 180 (3h)          | Start of IV infusion | . | . |
| 210               |           |          |          |
| 240 (4h)          | End of IV infusion | . | . |
| 245               | .         | .        |          |
| 270               |           |          |          |
| 300 (5h)          | .         | .        |          |
| 330               | .         |          | .        |
| 360 (6h)          | .         | .        |          |
| 420 (7h)          | .         |          | .        |
| 480 (8h)          | .         | .        |          |
| 600 (10h)         | .         |          | .        |
| 720 (12h)         | .         | .        |          |
| 960 (16h)         | .         |          |          |
| **N samples**     | 17        | 11       | 15       |
Model development

All ciprofloxacin concentration time profiles were modelled using (NONMEM; v7.4.0 with PsN; v4.7.1 (1) and Pirana v2.9.7 (2), R v4.0.3 (3), Rstudio v1.1.383, Xpose v0.4.12, VPC package v1.2.2). Model building consisted of building a structural model, statistical model and covariate model. The structural and statistical models were built simultaneously.

Nested models were discriminated by using the objective value function (OFV). A decrease in OFV >3.84 (p<0.05) was considered statistically significant for one degree of freedom. Goodness-of-fit plots (Observed versus population predicted concentrations, Observed versus individual predicted concentrations, conditional weighted residuals (CWRES) versus predicted concentration, CWRES versus time after dose, CWRES versus time), plausibility of parameter estimates, relative standard error of the estimates.

Structural and statistical model

For the oral absorption phase, a LAG-time, Erlang-type absorption, and transit compartment model was evaluated (ADVAN4, ADVAN6) in combination with a one- or two-compartment structural model. Inter-individual variability on individual parameter estimates was assumed to be log-normally distributed and modeled using equation 1 in which the individual parameter estimate for the $i$th individual is calculated using the population mean $\theta_{\text{mean}}$ and the random variable $\eta_i$ (eta) for the $i$th individual from a normal distribution with a mean of 0 and estimated variance of $\omega^2$.

$$\theta_i = \theta_{\text{mean}} \times \exp (\eta_i) \quad (1)$$

Correlation between eta’s was evaluated by creating eta-eta scatterplots. If a trend was observed that was not resolved by introduction of covariates on the concerning parameters, correlation was added using an OMEGA BLOCK in the model.

For the residual variability, which could result from model misspecification, essay errors, sampling errors and unexplained sources of variability, three different error model structures were explored using equation 2.

$$Y_{ij} = C_{\text{pred,ij}} + (C_{\text{pred,ij}} \times \varepsilon_{1ij}) + \varepsilon_{2ij} \quad (2)$$

$Y_{ij}$ is the observed concentration and $C_{\text{pred,ij}}$ is the predicted concentration for the $j$th observation of the $i$th individual. The combined error model consists of a proportional error ($\varepsilon_{1ij}$) and an additive error ($\varepsilon_{2ij}$). Both $\varepsilon_{1ij}$ and $\varepsilon_{2ij}$ are values from a normal distribution with a mean of zero and estimated variance of $\sigma^2$. Additive and proportional error models were tested by fixing $\varepsilon_1$ or $\varepsilon_2$ to 0, respectively.
Covariate analysis

Weight on $V_d$ and CL and GFR on CL were selected as covariates to be tested in the covariate analysis based on physiological plausibility. Additionally, possible correlations between pharmacokinetic parameters and covariates (sex, age, race, total body weight, lean body weight, GFR, MDRD, MDRD$_{di}$, CKD, CKD$_{di}$, CG$_{tbw}$, CG$_{lbw}$, history and duration of obesity) were assessed by plotting individual eta-values versus individual values of the covariate if shrinkage was <20%. If a trend was observed, the covariate effect was formally tested in the covariate analysis.

Continuous covariates were tested using equation 3 where $P_i$ and $P_p$ represent the individual and population parameter estimates, respectively. $COV_i$ represents the individual value of the covariate to be tested and $COV_{standard}$ represents a population standard for the concerning covariate, which represents the median value of GFR in the dataset or 70kg for TBW. $X$ represents an exponent that is being estimated.

$$P_i = P_p x \left(\frac{COV_i}{COV_{standard}}\right)^X \quad (3)$$

Covariates were entered into the model and statistical testing was performed using forward inclusion ($p<0.05$; OFV decrease $>3.84$ for one degree of freedom) and backward elimination ($p<0.001$; OFV increase $>10.8$ for one degree of freedom). Reduction of inter-individual variability, evaluation of diagnostic plots and eta-plots were used to determine if the covariate should be incorporated in the model.

Model validation

Figure 1 shows the Empirical Bayes Estimates on clearance and volume of distribution versus total body weight. Clearance shows no trend with bodyweight. Central volume of distribution does show a small trend with TBW, but inclusion of TBW as a covariate on $V_c$ did not reach statistical significance.
Figure 1

Empirical Bayes Estimates for clearance (CL), central volume of distribution (V_c) and bioavailability versus total body weight (TBW). Obese patients (n=20) are shown in teal, non-obese (n=8) are shown in red.

The visual predictive check stratified for non-obese versus obese and route of administration for the obese subgroup shows internal validity of the model (figure 2) as observations and predictions are in agreement.
Figure 2

Visual predictive check of the final model stratified by subgroup (non-obese n=8, obese PO n=10, obese IV n=10) on linear scale at the top and on logarithmic scale at the bottom. The observed data are shown as circles with the median and 2.5th and 97.5th percentile of the observed data shown as a solid black line and the upper and lower dashed lines, respectively. The blue areas represent the 95% confidence interval of the simulated median (dark blue) and 5th and 95th percentile (light blue) of the simulated concentrations based on 1000 simulations of the original dataset. Vertical lines at the top of the panels represent the bins.
Model extension

To account for reduced ciprofloxacin tissue penetration in obese patients as was reported by Hollenstein et al. (4), the ciprofloxacin model was extended with tissue concentrations from literature to explore dosing regimens leading to similar ciprofloxacin exposure in skin and soft tissue for non-obese and obese individuals.

Methods

Data
Raw pharmacokinetic data on individual plasma and tissue concentration-time curves and demographic data published by Hollenstein et al. were unavailable. The plots reported by Hollenstein et al. were digitized and concentration-time curves for plasma, adipose tissue, and skeletal muscle were obtained for the obese and non-obese subgroup. Mean concentration time-profiles in skeletal muscle and adipose tissue overlapped (figure 3). Therefore, the data from adipose and skeletal muscle were pooled to estimate mean tissue concentration for a mean obese and non-obese individual. Hollenstein et al. sampled from tissue over 20 minute intervals using microdialysis. Given the dense sampling procedure, the observed tissue concentrations were assumed to be made at the midpoint of the respective 20 minute interval.

Figure 3

Digitised mean ciprofloxacin concentration-time profiles in plasma, adipose tissue and skeletal muscle of non-obese and obese individuals as obtained from Hollestein et al. (4), represented on linear (left panels) and log (right panels) scale. Ciprofloxacin mean concentration ± 95% CI for the mean.
Model building
The model was extended with an additional compartment for tissue concentrations using ADVAN9. The available data on plasma and tissue concentrations were initially modelled using a 3-compartment structure with an additional tissue-compartment. The available data proved to be too limited to simultaneously estimate parameters describing plasma and tissue pharmacokinetic parameters. Therefore, structural effects from our final model were fixed at the values presented in the publication and inter individual variability was fixed at 0 because mean data were analyzed. In this empirical approach, the compartment describing tissue concentrations was modeled as an observer compartment.

To describe the tissue concentrations, the structural model (figure 4) was used to estimate parameters for k13 and k30. The volume of the tissue compartment (V3) was set equal to the volume of the central compartment (V1).

**Figure 4**

Schematic representation of the model structure used to estimate tissue concentrations. K13 is shown as a dashed line as k13 is excluded from the differential equation describing the change in concentration in the central compartment.

V1: central volume of distribution, V2: peripheral volume of distribution, V3: tissue volume of distribution, CL: Clearance from central compartment, Q: Intercompartmental clearance, K13: rate constant for transport from central to tissue compartment, K30: rate constant for elimination from tissue.

Transport from the central (V1) to the tissue compartment (V3) was excluded in the differential equation for the central compartment, thereby implicitly assuming the amount of drug going to the peripheral compartment to be negligibly small compared to the amount of drug present in the central compartment. Different clearance functions were tested to describe the mean tissue concentration in obese and non-obese patients (table 2). Michaelis-Menten elimination was tested using equation 4.

\[ V = \frac{V_{\text{max}} \cdot c}{K_m + c} \]  

(4)
Table 2: Combinations of rate constants tested to describe tissue concentrations

| Transport from plasma to tissue (k13) | Elimination from tissue (k30) |
|--------------------------------------|-----------------------------|
| First-order                          | First-order                 |
| First-order                          | Michaelis-Menten            |
| Michaelis-Menten                     | First-order                 |
| First-order                          | Combined first- and zero-order |

Obesity was tested as a covariate on all rate constants using forward inclusion followed by backward deletion. For Michaelis-Menten kinetics both a separate $V_{\text{max}}$ and a different $k_m$ were tested for obese and non-obese patients. For forward inclusion $p<0.05$ (OFV decrease $>3.84$ for one degree of freedom) and for backward elimination $p<0.001$ (OFV increase $>10.8$ for one degree of freedom) were considered statistically significant.

For visual predictive checks, calculated tissue and plasma concentrations in obese and non-obese patient after the dosing regimen applied by Hollenstein et al. (2.85 mg/kg TBW ciprofloxacin infused over 1 hour) were plotted versus Hollenstein observations (mean ± s.e.). In order to compare exposure, the Area Under the Concentration-time curve (AUC) was calculated using the $\$\text{DES block in NONMEM}$.

Model based dosing

The extended model was used to evaluate dosing regimens for obese patients that lead to steady state exposure in tissue similar to non-obese patients. For the obese patients an estimated $\text{AUC}_{48-72h}$ at 75-125 of AUC in non-obese patients was considered acceptable. Weight based doses rounded to the nearest multiple of 400mg were evaluated for practical convenience.
Results

Model building
The data obtained from the publication by Hollenstein et al. (4) were too limited to allow simultaneous estimation of parameters describing plasma and tissue pharmacokinetics. Biologically plausible models were fitted to the available data but an acceptable fit could not be achieved.

The data observed by Hollenstein et al. were best described by extending the model with an observer tissue compartment with first order transport to and a combined first- and zero-order elimination from tissue for both obese and non-obese individuals. Obesity was identified as a covariate on the rate constant of transport from the central compartment to the tissue compartment (k13). Structural parameters are presented in table 3.

| Parameter | Value (% RSE) |
|-----------|---------------|
| \( CL \) (L/h) | 31.7 FIX |
| \( V1 \) (L) | 55.4 FIX |
| \( V2 \) (L) | 144 FIX |
| \( Q \) (L/h) | 87.8 FIX |
| \( K_{13} \) non-obese (h\(^{-1}\)) | 8.18 (14.8) |
| \( K_{13} \) obese (h\(^{-1}\)) | 4.3 (15.6) |
| \( K_{30} \) first order (h\(^{-1}\)) | 6.71 (16.8) |
| \( K_{30} \) zero order (h\(^{-1}\)) | 101 (14.3) |
| Proportional error (%) | 15.1 (10.8) |

\( CL \): Clearance, \( V1 \): central volume of distribution, \( V2 \): peripheral volume of distribution, \( Q \): intercompartmental clearance between \( V1 \) and \( V2 \), \( k_{13} \): rate constant of clearance from central to tissue compartment, \( k_{30} \): rate constant of elimination from tissue

A visual predictive check from the extended model is presented in figure 5. Both the high concentrations, low concentrations and trend in tissue concentration is well described over 6 hours after administration for both the obese and non-obese subgroup.
The upper panels display plasma- and tissue concentrations split for non-obese and obese patients. The lower panels display log plasma- and tissue concentration split for non-obese and obese patients. Observations and simulations are based on a 2.85mg/kg IV infusion in 1 hour.

The left panels represent observed (dashed line with shaded area) and simulated plasma concentration (black line).

The right panels represent tissue concentrations. The simulated typical concentrations are represented by the black line. The data observed by Hollenstein are presented as mean (dashed red and blue lines) and 95%CI for the mean (shaded red and blue areas).
**Tissue penetration ratio**

The model-based tissue penetration ratio from the final extended model 0-6 hours after infusion of 2.85mg/kg as dosed by Hollenstein et al. (4) was 0.41 for a typical obese individual and 0.74 for a typical non-obese individual. This is similar to the results presented by Hollenstein et al (4), where the mean tissue penetration ratio for the obese subgroup was 0.45 for skeletal muscle (9% deviation) and 0.46 for adipose tissue (11% deviation). For the non-obese subgroup tissue penetration ratio was 0.82 for skeletal muscle (10% deviation) and 0.86 for adipose tissue (14% deviation)).

**Model based dosing**

For obese patients, a dosing regimen of three or four times daily IV infusion of 400mg is expected to result on the third day of treatment in exposure in tissue similar to twice daily IV infusion of 400mg in non-obese patients. Typical exposure for the proposed dosing regimen is presented in table 4.

**Table 4**: Exposure in plasma and tissue after individualised dosing

| Dosing regimen | Non-obese 120-160kg | Obese 120-160kg | Obese >160kg |
|----------------|----------------------|-----------------|--------------|
| Plasma AUC_{day 3} (mg*h/L) | 25 | 38 | 50 |
| Tissue AUC_{day 3} (mg*h/L) | 24 | 18 | 26 |

*Exposure in plasma and tissue on day 3 after weight based dosing for typical non-obese, obese patient 120-160kg, and obese patient >160kg. Dosing regimen consists of 2-4 times daily infusion of 400mg. AUC: Area under the concentration-time curve on the third day of therapy (48-72h).*

The proposed dosing regimen results in increased exposure in plasma in obese patients. The upper limit of safety for ciprofloxacin plasma concentration is not well defined but a safety threshold of AUC<100 mg*h /L was used before (5). The typical exposure in plasma using the 4 times daily 400mg IV infusion is 50 mg*h/L which is well within that safety limit.

Increased plasma C_{max} has also been proposed as a marker for increased side effects (4). Figure 6 shows ciprofloxacin C_{max} is increased from 3.6 (upper limit 95% prediction interval 5.0mg/L) to 4.3 (upper limit 95% prediction interval 5.9mg/L). The mild increase in plasma C_{max} is not considered clinically relevant.
Figure 6:

Ciprofloxacin plasma concentration versus time profiles for twice daily 400mg IV which is currently used as standard dose in obese and non-obese (red) and 400mg four times daily in individuals with TBW >160kg (blue). Plasma concentrations are shown as median (line) and 95% prediction interval (PI) (shaded area). The median peak concentration at steady state for the twice daily regimen is 3.6mg/L (upper limit 95% PI 5.0mg/L) and 4.3mg/L (upper limit 95% PI 5.9mg/L) for the four time daily regimen. Data are based on a stochastic simulation with n=5000 per dosing regimen.
Model code
Base model

:: 1. Based on: run003a0
:: 2. Description: Ciprofloxacin oral absorption and plasma concentration model
:: 3. Author: KvR
:: 4. Label:

$PROBLEM PK
$INPUT ID TIME AMT RATE DV CMT MDV TAD

$data.data.prn IGNORE=@
$SUBROUTINES ADVAN6 TOL9
$MODEL
COMP=(ABS)
COMP=(CENT)
COMP=(PERI)

$PK
IF(AMT.GT.0.AND.CMT.EQ.1)PODO=AMT ; ORAL DOSING
IF(AMT.GT.0.AND.CMT.EQ.2)PODO=0   ; IV DOSING

; DISPOSITION MODEL
CL  = THETA(1) * EXP(ETA(1))    ; CLEARANCE
V2  = THETA(2) * EXP(ETA(2))     ; CENTRAL VOLUME OF DISTRIBUTION
Q   = THETA(3) * EXP(ETA(3))     ; INTERCOMPARTIMENTAL CLEARANCE
V3  = THETA(4) * EXP(ETA(4))    ; PERIPHERAL VOLUME OF DISTRIBUTION

; BIOAVAILABILITY MODEL
F1  = 0                     ; THE AMOUNT IS USED IN THE ABSORPTION PROCESS
F2  = 1
BIO = THETA(5) * EXP(ETA(5))     ; BIOAVAILABILITY

; ABSORPTION MODEL
KA  = THETA(6)     ; ABSORPTION RATE CONSTANT
MTT = THETA(7) * EXP(ETA(6))             ; MEAN TRANSIT TIME
NN  = THETA(8)    ; NUMBER OF TRANSIT COMPARTMENTS
KTR = (NN+1)/MTT                  ; TRANSIT RATE CONSTANT
K23 = Q/V2
K32 = Q/V3
K20 = CL/V2                      ; ELIMINATION RATE CONSTANT
NFAC =SQRT(2*3.1415)*NN**(NN+0.5)*EXP(-NN)  ; STERLING APPROXIMATION
S2 = V2
S3 = V3

$DES
DADT(1)=BIO*PODO*KTR*(KTR*T)**NN*EXP(-KTR*T)/NFAC-KA*A(1)
DADT(2)=KA*A(1)-K20*A(2)-K23*A(2)+K32*A(3)
DADT(3)=K23*A(2)-K32*A(3)

$ERROR
IPRED= A(2)/S2 ; INDIVIDUAL PREDICTION
Y = IPRED + IPRED*EPS(1)
IRES=DV-IPRED
$THETA
(0, 31.7) : CL
(0, 55.4) : V2
(0, 87.8) : Q
(0, 144) : V3
(0, 0.567) : BIO
(0, 1.25) : KA
(0, 0.363) : MTT
(0, 19.9) : NN

$OMEGA
0.0389 ; IIV CL
0.457 ; IIV V2
0.0916 ; IIV Q
0.120 ; IIV V3
$OMEGA BLOCK(2)
0.0542 ; IIV BIO
0.0848 0.335 ; IIV MTT

$SIGMA
0.0165 ; Proportional error PK

$EST METHOD=1 INTER MAXEVAL=999 NOABORT SIGL=9 NSIG=3 PRINT=5 POSTHOC
$COV PRINT=E

$TABLE ID TIME DV MDV EVID IPRED ETAS (1;LAST) CWRES CL V2 TAD ONEHEADER
NOPRINT FILE=sdtab003a21
Extended model

;; 1. Based on: run008c6
;; 2. Description: First order transport to tissue. Combined zero- and first-order elimination from tissue (Obesity on K13)
;; 3. Author: KvR

$PROBLEM PK
$INPUT ID TIME AMT RATE DV CMT MDV GRP ; GRP==0; obese, GRP==1; non-obese
$DATA data.pnr IGNORE=@
$SUBROUTINES ADVAN9 TOL9
$MODEL
COMP=(CENT)
COMP=(PERI)
COMP=(TISSUE)

$PK
; BASE MODEL
CL = THETA(1) * EXP(ETA(1)) ; CLEARANCE
V1 = THETA(2) * EXP(ETA(2)) ; CENTRAL VOLUME OF DISTRIBUTION
Q = THETA(3) * EXP(ETA(3)) ; INTERCOMPARTMENTAL CLEARANCE
V2 = THETA(4) * EXP(ETA(4)) ; PERIPHERAL VOLUME OF DISTRIBUTION
K10 = CL/V1 ; ELIMINATION RATE CONSTANT
K12 = Q/V1
K21 = Q/V2

; HOLLENSTEIN EXTENSION
V3 = V1
TVK13 = THETA(5) ; FIRST ORDER TRANSPORT TO TISSUE NON-OBESE
IF(GRP.EQ.0) TVK13 = THETA(6) ; FIRST ORDER TRANSPORT TO TISSUE OBESE
K13 = TVK13
K301 = THETA(7) ; FIRST ORDER ELIMINATION FROM TISSUE
K300 = THETA(8) ; ZERO ORDER ELIMINATION FROM TISSUE
S1 = V1
S2 = V2

$DES
DADT(1)=-K12*A(1)+K21*A(2)-K10*A(1)
DADT(2)=K12*A(1)-K21*A(2)
DADT(3)=K13*A(1)-K301*A(3)-K300

$ERROR
IPRED=F
IF (CMT.EQ.1) Y=IPRED+IPRED*ERR(1)
IF (CMT.EQ.3) Y=IPRED+IPRED*ERR(2)
IRES=DV-IPRED

$THETA
(31.7) FIX ; CL
(55.4) FIX ; V1 CENT
(87.8) FIX ; Q
(144) FIX ; V3 PERI
(8.18) ; K13 NON-OBESE
(4.30) ; K13 OBESE
(6.71) ; K30 FIRST ORDER
(101) ; K30 ZERO ORDER
$OMEGA
0 FIX
0 FIX
0 FIX
0 FIX

$SIGMA
0.0165 ; PROPORTIONAL ERROR PK PLASMA
0.0224 ; PROPORTIONAL ERROR PK TISSUE

$EST METHOD=1 INTER MAXEVAL=999 SIGL=9 NSIG=3 PRINT=5 POSTHOC
References

(1) Beal S, Sheiner L, Boeckmann A. NONMEM Users Guide - Part IV. 2018.

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(3) R Core Team. R: A language and environment for statistical computing. 2015.

(4) Hollenstein UM, Brunner M, Schmid R, Müller M. Soft tissue concentrations of ciprofloxacin in obese and lean subjects following weight-adjusted dosing. Int J Obes Relat Metab Disord 2001;25(3);354-358.

(5) Gieling EM, Wallenburg E, Frenzel T, de Lange DW, Schouten JA, ten Oever J, et al. Higher Dosage of Ciprofloxacin Necessary in Critically Ill Patients: A New Dosing Algorithm Based on Renal Function and Pathogen Susceptibility. Clin Pharmacol Ther 2020;108:770-774.