Population Pharmacokinetics and Use of Monte Carlo Simulation To Determine Optimal Dosing Regimen of Oral Ciprofloxacin in Paediatric Patients with Severe Malnutrition

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Background and Objectives

Oral ciprofloxacin has been considered as an alternative antimicrobial agent for severely malnourished children. However, to date, there are no pharmacokinetic data in this patient population and an appropriate dosage regimen is not well defined.

The aims of the present study were to determine the influence of clinical characteristics on the population pharmacokinetics of oral ciprofloxacin in paediatric patients with severe malnutrition and to define the optimal dosage regimen.

Patients and Methods

The study was conducted in Kilifi District Hospital, Kenya. All children received oral ciprofloxacin 10 mg/kg 12 hourly for 48 hours. Up to four blood samples were collected at various times after the first dose.

Data were analysed with NONMEM [1] version VI using FOCE with interaction. First order, zero order, and transit compartment absorption models were compared. Allometric relationships between oral clearance (CL/F) and oral volume of distribution (V/F) and weight were included in the basic model. A wide range of clinical characteristics was then examined for their influence on ciprofloxacin pharmacokinetics.

The final model was validated using bootstrap, prediction corrected Visual Predictive Check (pc-VPC), and normalised prediction distribution error (npde). Monte Carlo simulations of 10,000 patients were performed to determine the probability of attaining a target AUC/MIC ratio (AUIC) of 125 (gram negative organisms) or 35 (gram positive organisms) and cumulative fraction of response (CFR) for a range of organisms [2].

Results

A total 202 ciprofloxacin concentration measurements were available from 52 infants and children aged 8 to 102 months; weight ranged from 4.1 to 14.5 kg. A one compartment model with first order absorption and a lag adequately described the data.

A combination of high mortality risk (HIGH) and serum sodium concentration provided the best fit for CL/F and serum sodium concentration for V/F . Inclusion these factors reduced between subject variability (BSV) in CL/F from 50% to 38% and in V/F from 49% to 43%. Absorption rate was poorly estimated and highly variable.

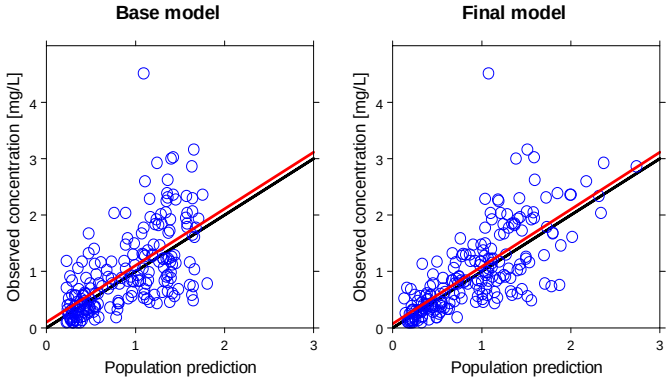

Figure 1 Scatterplots of observed concentrations versus population predicted concentrations obtained from the base model (left) and the final model (right).

References

[1] BEAL, S. L., SHEINER, L. B. & BOECKMANN, A. J. 1989-2006. *NONMEM user's Guides*, Icon Development Solutions, Ellicott City, Maryland, USA.

[2] DRUSANO, G. L., PRESTON, S. L., HARDALO, C., HARE, R., BANFIELD, C., ANDES, D., VESGA, O. & CRAIG, W. A. 2001. Use of preclinical data for selection of a phase II/III dose for evernimicin and identification of a preclinical MIC breakpoint. *Antimicrob Agents Chemother*, 45, 13-22.

The final population model describing ciprofloxacin pharmacokinetics:

Population CL/F (L/h) = 42.7 x $(WT/70)^{0.75}$ x (1+0.0368*(Na^+ -136)) x (1-0.283*(High))

Population V (L) = 372 x (WT/70) x (1+0.0291*(Na^+ -136))

Absorption rate constant = 2.97 h^{-1}

Absorption lag time = 0.742 h (~45 mins)

Table 1 Parameter estimates from the final model

Parameter	Population estimate	Bootstrap estimate	95% CI
CL/F	42.7	42.6	37.0, 49.3
Na^+ on CL/F	0.0368	0.0352	0.0217, 0.0446
High risk on CL/F	-0.283	-0.280	-0.412, -0.118
V/F	372	368	316, 429
Na^+ on V/F	0.0291	0.0280	0.0155, 0.0388
Ka	2.97	3.91	1.32, 8.86
ALAG	0.742	0.733	0.168, 0.924
BSV in CL/F	38.1	37.8	28.7, 45.8
BSV in V/F	43.0	42.8	32.4, 51.8
BSV in Ka	102	112	56.2, 159
Residual error Additive (SD)	0.0273	0.0254	0.0040, 0.0438
Proportional (%CV)	18.6	17.9	14.0, 22.6

BSV = between subject variability expressed as a % coefficient of variation; CL/F = oral clearance; V/F = oral volume of distribution; TVCL = typical value of oral clearance (L/h); TVV = typical value of oral volume of distribution (L); Ka = absorption rate constant (h^{-1}); ALAG = absorption lag time (h); WT = body weight (kg); Na^+ = serum sodium concentration (mmol/L)

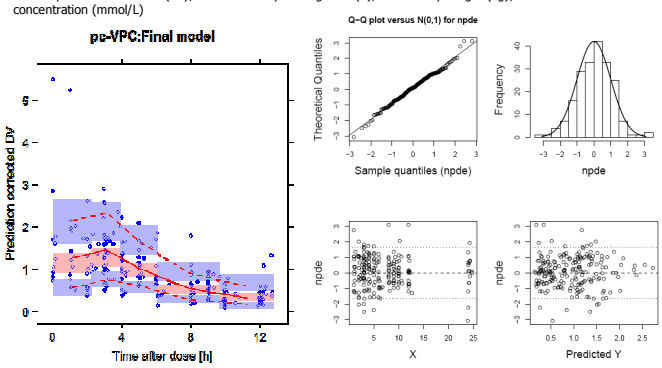

Figure 2 Graphical outputs from pc-VPC and npde based on 10,000 simulation datasets

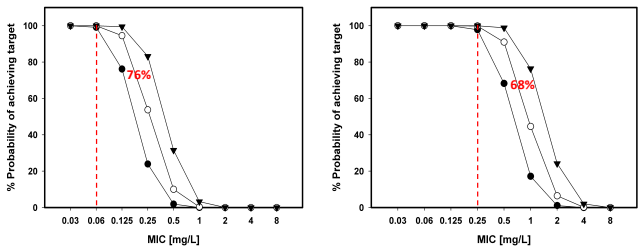

Figure 3 Percentage probability of achieving target AUIC ≥125 for gram-negative organisms (left) and ≥35 for gram positive organisms (right) for three daily dosage regimen (●= 20 mg/kg/day, O = 30 mg/kg/day, ▼=45 mg/kg/day) at each MIC value

Table 1 Cumulative fraction of response

Pathogens	Target AUIC	CFR (%)		
		20 mg/kg/day	30 mg/kg/day	45 mg/kg/day
Salmonella spp.	125	96	98	99
E. coli	125	85	87	88
K. pneumoniae	125	76	80	83
P. aeruginosa	125	43	55	64
S. pneumoniae	35	23	44	67

Conclusions

- The pharmacokinetics of oral ciprofloxacin in malnourished children are influenced by weight, sodium concentration, and presence of high mortality risk
- A dose of 20 mg/kg/day achieves adequate concentrations for some organisms
- Other drugs should be considered for *P. aeruginosa* and *S. pneumoniae*

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