



POPULATION PHARMACOKINETICS AND USE OF MONTE CARLO SIMULATION TO EVALUATE CURRENTLY RECOMMENDED DOSING REGIMENS OF CIPROFLOXACIN IN ADULT PATIENTS WITH CYSTIC FIBROSIS

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ABSTRACT

PURPOSE: Pharmacodynamic data on ciprofloxacin (CP) indicate that an AUC/MIC₅₀ ≥ 125 is necessary to achieve optimal bactericidal activity for gram-negative pneumonia. The purpose of this prospective study was to 1) develop a PK model to be utilized for therapeutic drug monitoring (TDM) of CP and 2) evaluate current CP dosing for pneumonias in cystic fibrosis (CF) pts.

METHODS: 12 adult CF pts received a single 400mg dose of IV CP. Six blood samples were obtained over a 12-hour interval. Serum drug concentrations were determined by HPLC and were fitted to a 1- and 2-compartment model using IT2B. CP MIC data on *Pseudomonas aeruginosa* were obtained from 43 CF pts. Monte Carlo simulation was performed to estimate the probability of attaining an AUC/MIC₅₀ ≥ 125.

RESULTS: A 2-compartment model best describes the pharmacokinetics of CP. The fitted PK parameters are: V_d=4.39L/kg, V_d∞=11.5L/kg, CL_T=0.33L/h/kg, CL_{CR}=0.77L/h/kg, t_{1/2α}=0.17h, t_{1/2β}=2.85h. The overall probabilities of achieving an AUC/MIC₅₀ ≥ 125 against *P. aeruginosa* isolates with CP 400mg q12h and q8h were 14.1% and 20.1%, respectively; in sensitive isolates (MIC ≤ 1) the corresponding values were 26.4% and 40%, respectively. Additional higher dosage regimens will be presented. Median (interquartile range) AUC/MIC ratios were 70 (37-149) and 105 (56-225) in the q12h and q8h groups, respectively.

CONCLUSION: The pharmacokinetics of CP in adult CF pts are best described using a 2-compartment model. The recommended doses of 400mg q8h or q12h may be inadequate to treat an acute pulmonary exacerbation when given alone. The poor and variable AUC/MIC ratios support the use of TDM to monitor efficacy of CP in these pts.

STUDY DESIGN

- Single dose of ciprofloxacin 400mg iv administered to 12 adult CF patients admitted for an acute pulmonary exacerbation
- Multiple serum concentrations obtained at : 0, 0.25-, 0.5-, 1.5, 2.5-3, 7-8, and 10-12 hours following the dose
- Serum concentrations analyzed using HPLC

METHODS: INCLUSION/EXCLUSION CRITERIA

- **Inclusion Criteria:**
 - Age > 18 years
 - Most recent sputum culture positive for *P. aeruginosa*
 - Admission for treatment of an acute pulmonary exacerbation
- **Exclusion Criteria:**
 - Pregnant, attempting to conceive, or nursing an infant
 - History of a seizure disorder
 - Hypersensitivity reaction to any quinolone
 - Currently receiving theophylline

METHODS: PHARMACOKINETIC ANALYSIS/MONTE CARLO SIMULATION

- **Population pharmacokinetic analysis (USC*PACK)**
 - Measured concentrations were fitted to a 1- and 2-compartment model (IT2B)
- **Monte Carlo simulation**
 - To determine the probability of achieving an AUC/MIC ratio ≥ 125 with ciprofloxacin dosed at 400mg q12h and q8h.
 - 1000 random data vectors consisting of an AUC value at 800 and 1200 mg/day and an MIC value were sampled.

RESULTS: SUSCEPTIBILITY OF PSEUDOMONAS AERUGINOSA ISOLATES (N=42)

- 45.2% of the isolates were susceptible to ciprofloxacin
- MIC₅₀ = 2 μg/ml; MIC₉₀ = 4 μg/ml
- Isolates were tested against 9 agents
- MIC susceptibility ranged from 45.2 to 78.6

RESULTS: PATIENT CHARACTERISTICS

Characteristic	Mean ± S.D.	Range
Age (yr)	31 ± 6.8	22-42
Male/female (n)	10/2	
Height (inches)	66 ± 3.7	59-74
Weight (kg)	54.5 ± 8.9	41.5-72
Lean Body Mass (kg)	46.0 ± 7.4	33.1-60.4
CL _{CR} (mL/min/1.73 m ²)	11.5 ± 22.8	86.3-150.4
Genotype (n)		
ΔF508/ΔF508	2	
ΔF508/Other	6	
Other/Other	4	

RESULTS: POPULATION PHARMACOKINETIC PARAMETER VALUES

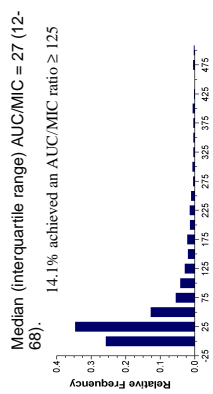
Parameter	Median	Range
V _d (L/kg)	0.37	0.02-0.97
V _d ∞ (L/kg)	1.2	0.0-1.6
CL _T (L/h/kg)	0.33	0.04-0.55
CL _{CR} (L/h/kg)	0.70	0.07-1.50
k ₁₀ (hr ⁻¹)	1.16	0.34-1.84
t _{1/2α} (h)	0.17	0.11-0.36
t _{1/2β} (h)	3.0	2.1-3.7
AUC _{0-∞}		
400mg q12h	42.1	27.9-284.2
400mg q8h	63.2	41.9-426.2

SUMMARY OF CIPROFLOXACIN PHARMACOKINETIC STUDIES IN CF PATIENTS

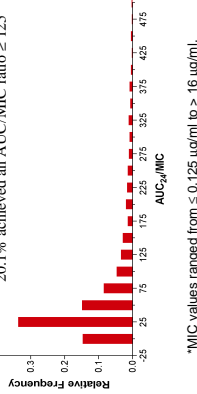
Study	V _d (L/kg)	V _d ∞ (L/kg)	CL _T (L/kg/hr)	T _{1/2} (h)
Davis et al ¹	0.42 ± 0.38	2.21 ± 0.89	0.308	4.3 ± 1.9
Steen et al ²			0.62 ± 0.31	3.21 ± 1.27
Ohen et al ³			0.61 ± 0.17	2.81 ± 1.42
Christenson et al ⁴	0.69 ± 0.179	1.2 ^a	2.71 ± 0.705	6.5 ± 3.25
Forrest et al ⁵			0.243 ± 0.148	
Current Study	0.37 ± 0.29	1.2 ± 0.62	0.33 ± 0.15	3.0 ± 0.52

^aV_d = V_d + V_p, where V_p = volume of the peripheral compartment.

FREQUENCY DISTRIBUTION OF AUC/MIC₅₀ TO CIPROFLOXACIN 400 MG Q12H & Q8H



RESULTS



REFERENCES

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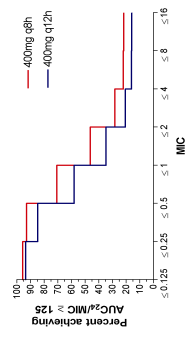
STUDY OBJECTIVES

- Develop a compartmental pharmacokinetic model to be utilized for therapeutic drug monitoring (TDM) and dosage adjustment of ciprofloxacin in adult cystic fibrosis patients.
- Evaluate the appropriateness of current ciprofloxacin dosing regimens for acute pulmonary exacerbations in CF patients using Monte Carlo simulation.

SUMMARY

- The pharmacokinetics of ciprofloxacin in adult CF patients are well described using a 2-compartment model.
- The recommended doses of 400 mg q8-12h may be inadequate to treat an acute pulmonary exacerbation when given as monotherapy.
- An individualized approach to optimize therapy according to each patients' pharmacokinetics and organism susceptibility may be necessary.

RESULTS: PROBABILITY OF ACHIEVING THE GOAL AUC_{0-∞}/MIC RATIO OF 125 AT SPECIFIC MIC SUBSETS



The clinical breakpoint is 0.25 μg/ml, using currently recommended doses.