New Insights into the Most Commonly Studied Drug Interaction with Antibiotics: Pharmacokinetic Interaction between Ciprofloxacin, Gemifloxacin and Probenecid at Renal and Non-renal Sites

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Introduction

Probenecid interacts with transport processes of drugs at several sites in the body. Little is known about the time course and mechanism of the quinolone-probenecid interaction. We used plasma and urine data and modelled the full time course of following interactions:

A) Ciprofloxacin, its metabolite (CIP-M1), and probenecid

(Data from Clin Pharmacol Ther. 1995 58:532-41, NCA only)

B) Gemifloxacin and probenecid

Objectives

1) To assess the extent, time course, and mechanism of the quinolone probenecid interaction at the renal and nonrenal sites.

2) To study the effect of probenecid on the formation of CIP-M1.

Methods

Clinical studies

Two randomized, two-way crossover studies in healthy volunteers:

Study 1: 200 mg ciprofloxacin as 30 min iv infusion without and with 3 g probenecid divided in five oral doses (6M / 6F)

Study 2: 320 mg oral gemifloxacin without and with 4.5g probenecid divided in eight oral doses (n=17 subjects, 9M / 8F)

Pharmacokinetic and statistical analysis

Non-compartmental analysis (NCA) and ANOVA + equivalence statistics to assess the extent of interaction.

Standard-two-stage (STS) approach was used to model the full time course of gemifloxacin and probenecid as well as of ciprofloxacin, CIP-M1 and probenecid in plasma and urine simultaneously. We used descriptive statistics on the PK parameters from STS to derive population PK parameters and their variance-covariance matrix.

Individual Akaike values, residual plots and visual predictive checks were used for model discrimination.

Software

We used WinNonlin(R) Professional (Version 4.0.1, Pharsight Corporation, USA) for NCA, STS and statistics, NONMEM V (level 1.1, GloboMax LLC, Hanover, MD, USA) and validated Perl scripts for visual predictive checks.
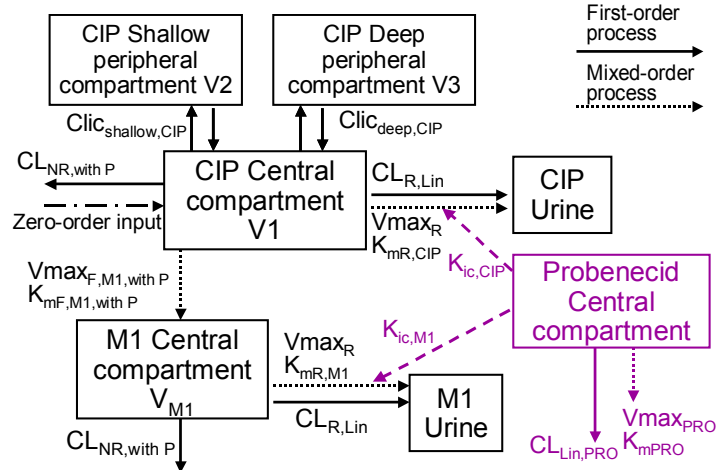
Results

Table 1 shows the extent of the interaction of ciprofloxacin, CIP-M1, and gemifloxacin with probenecid. The rate and extent of absorption of gemifloxacin were not affected by the interaction. The average distributional clearances were also not affected by probenecid.

Table 1: PK parameters from NCA and ANOVA

	Median [25%-75% percentile]		Point estimate (90% Conf. Int.)	p-value
	With PRO	Without PRO	With / without PRO	
Ciprofloxacin				
Total clearance (L h^{-1})	21.4 [16.4-25.6]	37.4 [30.3-44.3]	58% (55 - 61%)	<0.01
Renal clearance (L h^{-1})	8.25 [6.87-9.85]	23.8 [18.6-25.4]	**35% (29 - 41%)**	<0.01
Nonrenal clearance (L h^{-1})	14.1 [8.82-18.9]	13.5 [10.7-18.4]	92% (84 - 102%)	0.19
CIP-M1				
Renal clearance (L h^{-1})	8.26 [4.90-9.88]	20.5 [18.7-24.6]	**36% (31 - 42%)**	<0.01
Gemifloxacin				
Total clearance (L h^{-1})	26.0 [20.1-29.7]	35.2 [30.7-43.8]	69% (65 - 73%)	<0.01
Renal clearance (L h^{-1})	6.49 [4.92-8.15]	13.1 [9.91-16.2]	**49% (47 - 51%)**	<0.01
Nonrenal clearance (L h^{-1})	19.0 [15.4-22.3]	24.2 [19.0-26.4]	81% (74 - 88%)	<0.01

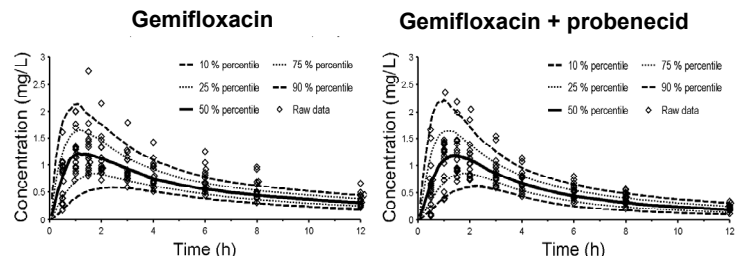**Figure 1:** Model for ciprofloxacin, CIP-M1 & probenecid

Our final models included a competitive inhibition of renal clearance by probenecid for ciprofloxacin, CIP-M1 and gemifloxacin. The formation of CIP-M1 was described by a mixed order process which was not affected by probenecid (see Figure 1). For final parameter estimates see Table 2. The visual predictive checks for gemifloxacin are shown in Figure 2.

Table 2: PK parameter estimates from STS approach

Parameter	Unit	Median [25% - 75% percentile]		
		Gemifloxacin	Ciprofloxacin	CIP-M1
Km_R	mg L^{-1}	9.24 [7.78 - 10.9]	4.66 [2.74 - 7.58]	5.83 [3.98 - 9.82]
K_{ic} (probenecid)	mg L^{-1}	69.3 [55.2 - 79.2]	12.3 [5.76 - 22.6]	18.5 [9.23 - 31.0]
K_{ic}/Km_R (derived)	-	7.2 [5.8 - 8.6]	3.8 [1.7 - 6.2]	3.2 [2.1 - 4.6]
$Vmax_R$	mg h^{-1}	118 [96.2 - 121]	106 [65.0 - 183]	
$CL_{R,Lin}$	L h^{-1}	2 (fixed to $f_u \cdot$ GFR)	5.04 [4.40 - 5.37]	
$CL_{NR,without P}$	L h^{-1}	24.7 [20.3 - 29.2]	12.6 [9.69 - 15.9]	
$CL_{NR,with P}$	L h^{-1}	19.3 [17.9 - 23.8]	11.9 [8.48 - 13.0]	
$Km_{F,M1,without P}$	mg L^{-1}		0.608 [0.327 - 0.826]	
$Km_{F,M1,with P}$	mg L^{-1}		0.481 [0.422 - 1.41]	
$Vmax_{F,M1,without P}$	mg h^{-1}		1.94 [1.29 - 2.70]	
$Vmax_{F,M1,with P}$	mg h^{-1}		1.89 [1.34 - 3.45]	

Figure 2: Visual predictive checks for gemifloxacin

Conclusions

1) Probenecid inhibited the renal clearance of ciprofloxacin and CIP-M1 by about 65% and renal clearance of gemifloxacin by 51%. Probenecid reduced non-renal clearance of gemifloxacin by 19%.

2) A competitive inhibition of renal clearance by probenecid was the most likely mechanism for all three compounds.

3) Relative affinity to the renal transporter was 7.2 times higher for gemifloxacin, 3.8 times higher for ciprofloxacin, and 3.2 times higher for CIP-M1 compared to probenecid. Probenecid inhibited the renal tubular secretion, as its average plasma concentration was about 100-150 fold higher than for gemifloxacin & ciprofloxacin.

4) The formation of CIP-M1 and the average rate and extent of absorption of gemifloxacin were not affected by probenecid.