A Phase 1 Study Of The Effects Of Itraconazole On The Pharmacokinetics Of Oral And IV Sulopenem In Healthy Adult Subjects

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ABSTRACT

Background: Sulopenem is a novel thiopenem antibiotic available in oral prodrug and intravenous formulations being studied for urinary tract and intra-abdominal infections. The oral formulation of sulopenem is coformulated with probenecid. In this study we investigated the effects of itraconazole, a cytochrome P450 (CYP3A4) and P-glycoprotein (Pgp) inhibitor, on the pharmacokinetic profile of sulopenem, administered alone or with probenecid. While sulopenem is not expected to be a CYP3A4 or Pgp substrate, the prodrug, sulopenem etzadroxil, is an *in vitro* substrate for Pgp and probenecid, while primarily an OAT inhibitor, may have effects on other relevant metabolic pathways.

Materials/methods: 64 healthy adult subjects were dosed in four cohorts over two study periods with a single dose of either: 1.0 gm of IV sulopenem, 500 mg sulopenem etzadroxil/500 mg probenecid in a bilayer tablet (fasted and, in a separate cohort, in the fed state) or 500 mg sulopenem etzadroxil tablet (fed) without and then with multiple-doses of 200 mg itraconazole over four days.

Results:

Effect of itraconazole on Plasma Sulopenem Pharmacokinetic Parameters

Sulopenem		N	Alone	+ Itraconazole	Ratio	90% CI
$AUC_{0\text{-}Inf}$ (h*ng/mL)						
1.0 gm IV sulopenem	Fasted	15	30,699	31,606	103	99-107
500 mg sulopenem etzadroxil +	Fed	16	6,146	6,844	111	105-118
500 mg probenecid	Fasted	15	4,167	4,296	103	93-113
500 mg sulopenem etzadroxil	Fed	15	4,816	4,849	101	95-106
C_{max} (ng/mL)						
1.0 gm IV sulopenem	Fasted	15	10,165	10,522	104	99-108
500 mg sulopenem etzadroxil +	Fed	16	2,254	2,816	125	106-149
500 mg probenecid	Fasted	15	1,771	1,602	91	77-106
500 mg sulopenem etzadroxil	Fed	15	1,988	2,077	105	91-119

Conclusions: Overall, itraconazole had no significant effect on the pharmacokinetics of sulopenem with a small increase in sulopenem oral exposure observed only when oral sulopenem etzadroxil was combined with both probenecid and food. Sulopenem does not appear to be a significant substrate for cytochrome CYP3A4 or Pgp.

INTRODUCTION

- Sulopenem is a novel thiopenem antibiotic available in oral prodrug and intravenous formulations being studied for urinary tract and intra-abdominal infections.
- The oral formulation of sulopenem is coformulated with probenecid.
- In this study we investigated the effects of itraconazole, a cytochrome P450 (CYP3A4) and P-glycoprotein (Pgp) inhibitor, on the pharmacokinetic profile of sulopenem, administered alone or with probenecid.
- While sulopenem is not expected to be a CYP3A4 or Pgp substrate, the prodrug, sulopenem etzadroxil, is an *in vitro* substrate for Pgp and probenecid, while primarily an OAT inhibitor, may have effects on other relevant metabolic pathways.

METHODS

- 64 healthy adult subjects were dosed in four cohorts over two study periods with a single dose of either: 1.0 gm of IV sulopenem, 500 mg sulopenem etzadroxil/500 mg probenecid in a bilayer tablet (fasted and, in a separate cohort, in the fed state) or 500 mg sulopenem etzadroxil tablet (fed) without and then with multiple-doses of 200 mg itraconazole over four days.

RESULTS

Table 1: Demographic and Baseline Characteristic for All Cohorts Combined – Safety Population

Statistic/Category	All Cohorts Combined
Age at informed consent (years)	
n	64
Mean (SD)	38.2 (8.99)
Sex – n (%)	
Female	6 (9.4)
Male	58 (90.6)
Race – n (%)	
White	20 (31.3)
Black or African American	42 (65.6)
Other	2 (3.1)
Ethnicity – n (%)	
Hispanic or Latino	4 (6.3)
Not Hispanic or Latino	60 (93.8)
Height (cm)	
n	64
Mean (SD)	175.74 (7.495)
Body weight (kg)	
n	64
Mean (SD)	81.43 (11.412)
BMI (kg/m^2)	
n	64
Mean (SD)	26.31 (2.743)

Baseline was defined as the measurement at Screening. BMI = body mass index = 10,000 x weight (kg)/height (cm^2). Percentages were calculated using the number of subjects of the Safety Population as the denominator. SD = standard deviation.

Table 2: Effect of Itraconazole on Plasma Sulopenem Pharmacokinetic Parameters for Cohort 1: Paired T-Test Pharmacokinetic Parameter Population

PK Parameter (unit)	Study Period 1 1.0 g IV Sulopenem Fasted		Study Period 2 1.0 g IV Sulopenem + Itraconazole Fasted		Ratio GM (Itraconazole + IV Fasted)/IV Fasted (%)	90% CI for Ratio (%)[2]
	n	GM[1]	n	GM[1]		
C_{max} (ng/mL)	15	10164.95	15	10521.55	103.5	(99.33, 107.86)
$AUC_{0\text{-}t}$ (h·ng/mL)	15	30647.96	15	31549.80	102.9	(99.09, 106.95)
$AUC_{0\text{-}\infty}$ (h·ng/mL)	15	30698.96	15	31605.52	103.0	(99.08, 106.97)
$T_{free}>MIC_{0.5}$ (h)	15	5.71	15	5.73	100.4	(96.83, 104.19)

Note: A paired t-test was performed on logarithm-transformed PK parameters. A subject must have a calculable PK parameter in both treatments (test and reference) in order to be included in the analysis of that parameter.
1. Geometric means were the means after back transformation to the original scale.
2. The 90% CIs were presented after back transformation to the original scale. Note the study was not powered for statistical inferences, but these ranges are a useful tool for comparison.

AUC = area under the plasma concentration curve; $AUC_{0\text{-}\infty}$ = AUC from time 0 extrapolated to infinity; $AUC_{0\text{-}t}$ = AUC from time 0 to time of the last quantifiable concentration; CI = confidence interval; C_{max} = maximum observed plasma concentration; GM = geometric mean; IV = intravenous(ly); PK = pharmacokinetic(s); $T_{free}>MIC_{0.5}$ = time above minimum inhibitory concentration.

RESULTS

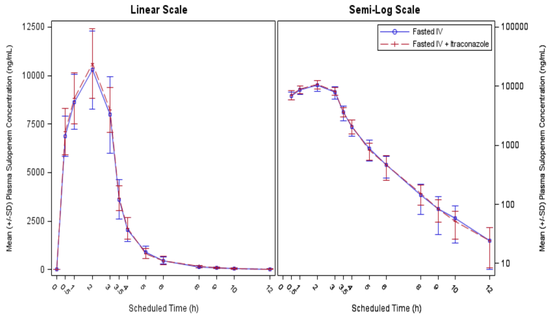
Table 3: Effect of Itraconazole on Plasma Sulopenem Pharmacokinetic Parameters after Dosing with Bilayer Tablet

PK Parameter (unit)	Study Period 1 Bilayer Tab Fed		Study Period 2 Itraconazole + Bilayer Tab Fed		Ratio GM (Itraconazole + Bilayer Tab Fed)/Fed Bilayer Tab (%)	90% CI for Ratio (%)[2]
	n	GM[1]	n	GM[1]		
C_{max} (ng/mL)	16	2253.77	16	2815.85	124.9	(105.58, 147.85)
$AUC_{0\text{-}t}$ (h·ng/mL)	16	6117.37	16	6813.44	111.4	(105.19, 117.93)
$AUC_{0\text{-}\infty}$ (h·ng/mL)	16	6145.91	16	6843.79	111.4	(105.21, 117.86)
$T_{free}>MIC_{0.5}$ (h)	16	3.89	16	3.90	100.4	(94.32, 106.82)

Note: A paired t-test was performed on logarithm-transformed PK parameters. A subject must have a calculable PK parameter in both treatments (test and reference) in order to be included in the analysis of that parameter.
1. Geometric means were the means after back transformation to the original scale.
2. The 90% CIs were presented after back transformation to the original scale. Note the study was not powered for statistical inferences, but these ranges are a useful tool for comparison.

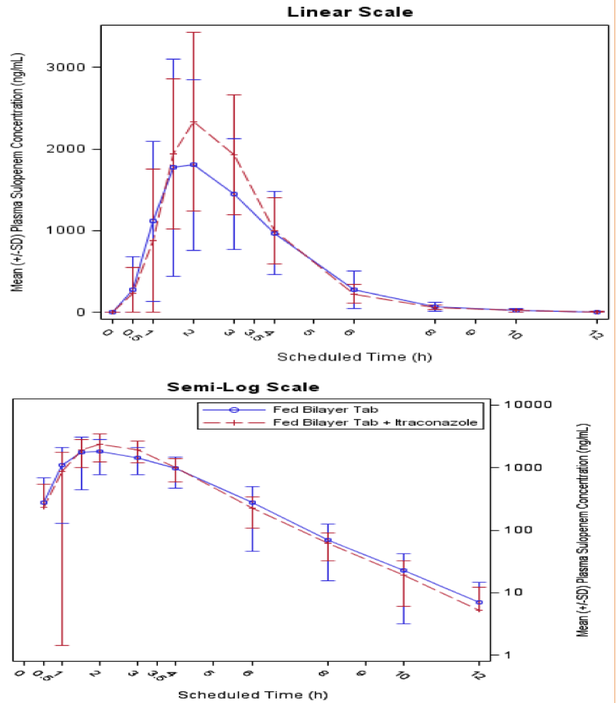
AUC = area under the plasma concentration-time curve; $AUC_{0\text{-}\infty}$ = AUC from time 0 extrapolated to infinity; $AUC_{0\text{-}t}$ = AUC from time 0 to time of the last quantifiable concentration; bilayer tab = sulopenem etzadroxil 500 mg + probenecid 500 mg film-coated, fixed-dose combination, bilayer tablet; CI = confidence interval; C_{max} = maximum observed plasma concentration; GM = geometric mean; PK = pharmacokinetic(s); $T_{free}>MIC_{0.5}$ = time above minimum inhibitory concentration.

Figure 1: Plot of Mean Plasma Sulopenem Concentrations by After IV Dosing with and without Itraconazole



Note: Cohort 1 = Fasted IV sulopenem vs daily itraconazole + fasted IV sulopenem.
Note: If the actual sampling time (measured from dosing) was outside of the collection window for nominal time points, the corresponding concentration was excluded from concentration versus time descriptive summaries and plots, but was still used in the calculation of PK parameters.
The lower limit of quantification for sulopenem = 10.0 ng/mL.
IV = intravenous(ly); PK = pharmacokinetic(s); SD = standard deviation; Semi-Log = semi-logarithmic; vs = versus.

Figure 2: Mean Plasma Sulopenem Concentrations after Dosing of Bilayer Tablet with and without Itraconazole



Bilayer tablet = sulopenem etzadroxil 500 mg + probencid 500 mg
SD – standard deviation; lower limit of quantification = 10 ng/ml

CONCLUSIONS

- Overall, itraconazole had no significant effect on the pharmacokinetics of sulopenem with a small increase in sulopenem oral exposure observed only when oral sulopenem etzadroxil was combined with both probenecid and food.
- Sulopenem does not appear to be a significant substrate for cytochrome CYP3A4 or Pgp.