W5229

Assessment of a Pharmacokinetic Drug Interaction between Solithromycin and Digoxin

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Background

- Solithromycin is the first fluoroketolide in the macrolide class being developed as oral and IV formulations for the treatment of patients with community-acquired bacterial pneumonia (CABP). In patients with CABP, in a Phase II study, the results showed that solithromycin had a comparable efficacy to, and a better tolerability than levofloxacin[1]
- In a Phase III study with 860 CABP patients, oral solithromycin demonstrated statistical non-inferiority to oral moxifloxacin for treatment of CABP. Solithromycin early clinical response (ECR) rates were notably higher than moxifloxacin in the elderly and among patients with higher pneumonia severity index/PORT scores. Safety outcomes were comparable, but with more G4 ALT elevations and two episodes of *C. difficile* diarrhea in moxifloxacin-treated patients. A global P3 CABP study evaluating IV to Oral solithromycin versus IV to Oral moxifloxacin has completed enrollment[2]
- Like other macrolide antibiotics, solithromycin is both a substrate and an inhibitor of P-gp *in vitro*. It is metabolized by CYP3A4 and is also a mechanism-based inhibitor of CYP3A, which results in inhibition of its own metabolism. Solithromycin is not an inducer of CYP3A isoenzymes[3]
- Digoxin was selected as the P-gp substrate. Antibiotics may increase the bioavailability of digoxin by destroying the gut flora responsible for its metabolism. Solithromycin has minimal effect on intestinal microflora as it is well absorbed after oral administration and < 15% of unchanged solithromycin is found in the stool
- Many elderly patients (population most susceptible to CABP comorbidities) chronically take digoxin. This study evaluated whether the pharmacokinetics (PK) of digoxin is affected by the concomitant administration of solithromycin at near steady state levels of both drugs, at exposures relevant to their clinical use
- The effect of a loading dose of solithromycin on the PK of digoxin at steady state was also studied, in case a differential P-gp inhibition by solithromycin exists after a single 800 mg loading dose and subsequent 400 mg multiple doses

Objectives

The objectives of this study were as follows:

Primary:
- Evaluate the effect of oral solithromycin on oral digoxin PK at near steady-state levels of both drugs in healthy adult subjects

Secondary:
- Assess the effect of a loading dose of solithromycin on the PK of digoxin
- Evaluate the safety and tolerability of solithromycin when co-administered with digoxin

Methods

Study design
- This was an open-label, single-center, 2-period, 1-sequence crossover drug-drug interaction (DDI) study with healthy male and female subjects (19-45 years of age, with a body mass index (BMI) ≥18 and ≤32 kg/m^2 and a total body weight >60 kg)
- A total of 14 subjects were enrolled in the study. Subjects were confined at the Clinical Research Unit (CRU) from Day 1 through the duration of the drug administration (10 days) and for 24 hr after the last dose. During the first period (Days 1-5), subjects received digoxin, and during the second period (Day 6-10), subjects received both digoxin and solithromycin
- Safety (e.g. adverse events (AEs), vital signs, ECGs, clinical laboratory and concomitant medication) was assessed throughout the study, as applicable

Treatments
- **Solithromycin capsules**
  - Day 6: Oral solithromycin 800 mg (4×200 mg capsule) as a single dose
  - Day 7-10: Oral solithromycin 400 mg (2×200 mg capsule) once daily
- **Digoxin tablets**
  - Day 1: Oral digoxin 1.0 mg, given as 0.5 mg (4×0.125 mg tablet) Q12 hr
  - Day 2-10: Oral digoxin 0.125 mg (1×0.125 mg tablet) once daily

Pharmacokinetic Blood Sampling
- Blood samples for trough concentrations of digoxin were collected predose on Days 2-4, and during concomitant treatment with solithromycin (Day 7-9)
- Serial blood samples were collected for 24 hr post dose on Days 5, 6 and 10
- Plasma concentrations of digoxin were determined by a validated high performance liquid chromatography-tandem mass spectrometry method

Pharmacokinetic Parameter Estimation
- The key PK parameters calculated for plasma digoxin data, as applicable, using a noncompartmental approach included:
  - $AUC_{0\text{-}tau}$ Area under the plasma concentration versus time curve, during the dosing interval, tau, at steady state
  - C_{max} Maximum measured plasma concentration
  - t_{max} Time of the maximum measured plasma concentration
  - CL/F Apparent total body clearance estimated at steady state after oral administration

Pharmacokinetic Parameter Statistical Analyses

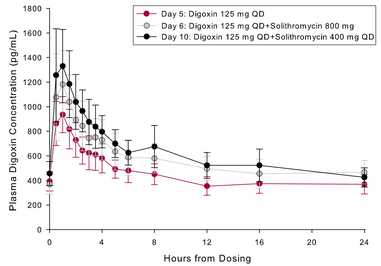
Primary:
- DDI was assessed by analyzing the natural log (ln)-transformed PK parameters $AUC_{0\text{-}tau}$ and C_{max} of digoxin with and without solithromycin at near steady state in an analysis of variance (ANOVA) using the SAS mixed model procedure (Day 10 vs Day 5)
- No interaction would be claimed if the 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) of the back-transformed PK parameters $AUC_{0\text{-}tau}$ and C_{max} of digoxin with and without solithromycin fell within 80.00% - 125.00%

Secondary:
- It was evaluated if a single 800 mg dose of solithromycin has an effect on the PK of digoxin, using ANOVA (Day 6 vs Day 5)
- It was also evaluated if a differential P-gp inhibition by solithromycin exists after a single 800 mg loading dose and subsequent 400 mg multiple doses, using ANOVA (Day 10 vs Day 6)

Results

Pharmacokinetics
- A total of 14 (100%) subjects completed the study and were included in the PK and statistical analysis populations
- Mean plasma digoxin concentrations are presented in Figure 1

Figure 1. Mean (±SD) Plasma Digoxin Concentrations Versus Time Following Oral Administration of Digoxin with or without Solithromycin (N=14).



The PK parameter results for digoxin in plasma are presented in Table 1 and the statistical comparisons of plasma digoxin PK parameters with and without solithromycin are presented in Table 2.

Table 1. Arithmetic Mean ± SD Pharmacokinetic Parameters for Plasma Digoxin (N=14).

Digoxin Pharmacokinetic Parameters	Day 5 Digoxin QD Alone	Day 6 Digoxin QD+Solithromycin Loading Dose	Day 10 Digoxin QD+Solithromycin QD
C_{max} (pg/mL)	970 ± 169	1264 ± 259	1436 ± 336
t_{max}* (hr)	1.00 (0.500, 1.99)	0.998 (0.497, 1.50)	0.968 (0.494, 1.52)
$AUC_{0\text{-}tau}$ (pg*hr/mL)	10850 ± 1880	13710 ± 2477	15050 ± 2866

* = t_{max} is presented as Median (Minimum, Maximum)
Day 5: Multiple oral administration of Digoxin (Digoxin 0.125 mg QD administered alone)
Day 6: Multiple oral administration of Digoxin (Digoxin 0.125 mg QD co-administered with a loading dose of 800 mg Solithromycin)
Day 10: Multiple oral administration of Digoxin (Digoxin 0.125 mg QD co-administered with Solithromycin 400 mg QD)

Table 2. Statistical Analysis Results for Plasma Digoxin (N=14).

Comparison	Parameters	% Geometric Mean Ratio	90% CIs	Intra-Subject CV%
Day 10 Versus Day 5	$AUC_{0\text{-}tau}$ (pg*hr/mL)	138.39	132.00-145.10	7.35
	C_{max} (pg/mL)	145.92	132.50-160.69	15.05
Day 6 Versus Day 5	$AUC_{0\text{-}tau}$ (pg*hr/mL)	126.27	120.43-132.39	7.35
	C_{max} (pg/mL)	129.61	117.69-142.74	15.05
Day 10 Versus Day 6	$AUC_{0\text{-}tau}$ (pg*hr/mL)	109.60	104.54-114.91	7.35
	C_{max} (pg/mL)	112.58	102.23-123.98	15.05

$AUC_{0\text{-}tau}$ and C_{max} parameters were in-transformed prior to analysis
Day 5: Multiple oral administration of Digoxin (Digoxin 0.125 mg QD administered alone)
Day 6: Multiple oral administration of Digoxin (Digoxin 0.125 mg QD co-administered with a loading dose of 800 mg Solithromycin)
Day 10: Multiple oral administration of Digoxin (Digoxin 0.125 mg QD co-administered with Solithromycin 400 mg QD)

- Digoxin pharmacokinetics were altered by the co-administration of multiple-dose digoxin with both multiple-dose and loading-dose solithromycin. The digoxin $AUC_{0\text{-}tau}$ and C_{max} were 38% and 46% higher, respectively, with multiple-dose solithromycin co-administration, suggesting an interaction via P-gp systemically at the clinical solithromycin daily dose of 400 mg
- Similarly, the digoxin $AUC_{0\text{-}tau}$ and C_{max} were 26% and 30% higher with a solithromycin loading dose, respectively, suggesting an interaction following a loading dose of solithromycin of 800 mg
- Digoxin C_{trough} levels were generally similar for digoxin alone and when co-administered with solithromycin
- In the case of narrow therapeutic index drugs like digoxin, the potential for an interaction due to P-gp is possible as demonstrated by the number of subjects with C_{max} >2 ng/mL (digoxin level associated with toxicity symptoms [LANOXIN® (digoxin) Tablets, Covis Pharmaceuticals, Inc[4]])
- Although there were no subjects in this study with C_{max} >2 ng/mL, an interaction between solithromycin and digoxin cannot be excluded due to the increase of 46% in C_{max} following co-administration of multiple-dose solithromycin with digoxin. Notably, this degree of interaction is less marked than that observed previously between clarithromycin and digoxin[5]

Safety
- Of the 28 AEs reported during the study, 26 were mild in severity and 2 were moderate. Mild contact dermatitis and nausea were the most commonly reported AEs, occurring after digoxin+solithromycin. The most frequently occurring treatment emergent adverse events (TEAEs) (experienced by >1 subject [>7%]) are summarized in Table 3

Table 3. Treatment Emergent Adverse Events (>7%).

Adverse Event*	Treatment		Overall
	Day 1-5 (Digoxin)	Day 6+ (Digoxin+Solithromycin)	
Number of Subjects Dosed	14 (100%)	14 (100%)	14 (100%)
Number of Subjects With Adverse Events	4 (29%)	9 (64%)	9 (64%)
Nausea	0 (0%)	4 (29%)	4 (29%)
Dermatitis contact	0 (0%)	5 (36%)	5 (36%)

Note: Adverse events are classified according to MedDRA Version 17.1.

- No subject discontinued the study due to an AE
- There were no safety concerns regarding the clinical laboratory, vital signs, physical examination, or ECG assessments in this study

Conclusions

- Administration of multiple once-daily doses of solithromycin resulted in an increase in exposure parameters of digoxin in plasma ($AUC_{0\text{-}tau}$ and C_{max} increased by ~38% and ~46%, respectively), consistent with an interaction between solithromycin and digoxin. This effect is notably less than that reported for clarithromycin which caused a 1.7-fold increase in the $AUC_{[0,24]}$ of digoxin[5]
- Similar increases and potential for an interaction were observed following administration of a single loading dose of solithromycin ($AUC_{0\text{-}tau}$ and C_{max} increased by ~26% and ~30%, respectively). However, digoxin C_{trough} levels were similar for digoxin alone and digoxin co-administered with solithromycin
- No differential P-gp inhibition effect on digoxin exposures attributed to solithromycin was observed when comparing a single 800 mg loading dose and subsequent 400 mg multiple dose solithromycin administrations
- Multiple oral doses of 400 mg solithromycin capsules appeared to be safe and well tolerated when co-administered with multiple doses of 0.125 mg digoxin tablets in this group of healthy adult male and female subjects. There were no safety concerns regarding the clinical laboratory, vital sign, physical examination, or ECG assessments in this study

References

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