S. Ciric1, K. Dunnington2, M.R. Gartner2, R. Hernandez3 and P. Fernandes3

Secondary:

Primary:

Objectives

Evaluate the safety and tolerability of solithromycin when co-administered with digoxin

Assess the effect of a loading dose of solithromycin on the PK of digoxin

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.

Solithromycin capsules was assessed throughout the study, as applicable

Safety (e.g. adverse events (AEs), vital signs, ECGs, clinical laboratory and concomitant medication) in case 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)

Dermatitis and nausea were the most commonly reported AEs, occurring after digoxin+solithromycin. Notably, this degree of interaction is less marked than that reported for clarithromycin which caused a 1.7-fold increase in the AUC(0,24) of digoxin5 consistent with an interaction between solithromycin and digoxin. This effect is notably less than that observed previously between clarithromycin and digoxin3.

Methods

Note: This was an open-label, single-center, 2 period, 3 sequence crossover drug-drug interaction (DDI) study with male and female subjects (18-75 yrs of age), with a body mass index (BMI) of 18-30 kg/m2 and a total body weight of 50 kg or more.

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 4 hours after the last (Day 10) dose. The subjects were randomly assigned to receive solithromycin 800 mg (4×200 mg capsule) as a single dose.

Safety, (e.g. adverse events (AEs), vital signs, ECGs, clinical laboratory and concomitant medication) observed throughout the study, as applicable

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 3.

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Conclusions

Administration of multiple once-daily doses of solithromycin resulted in an increase in exposure parameters of digoxin in plasma (AUC0-tau and Cmax) by ~50% and ~60%, respectively, consistent with a drug-drug interaction between solithromycin and digoxin. This effect is notably less than that observed between clarithromycin and digoxin3.

Table 3. Statistical Analysis Results for Plasma Digoxin (N=14)

<table>
<thead>
<tr>
<th>Digoxin QD+Solithromycin</th>
<th>Digoxin QD</th>
<th>Mean Ratio</th>
<th>90% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 5</td>
<td>130.41 ± 20.43</td>
<td>1.00 (0.90, 1.09)</td>
<td>1.00 (0.90, 1.09)</td>
</tr>
<tr>
<td>Day 10</td>
<td>185.97 ± 29.17</td>
<td>1.00 (0.90, 1.09)</td>
<td>1.00 (0.90, 1.09)</td>
</tr>
</tbody>
</table>

References


5. LAMIN® (sulfonilamide) Tablets, Coarse Pharmaceuticals, Inc., 1-yr continuing information August 2014.