Assessment of a Pharmacokinetic Drug Interaction between Solithromycin and Digoxin

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Authors: S. Ciric[1], K. Dunnington[2], M.R. Gartner[2], R. Hernandez[3] and P. Fernandes[3]

1. Celerion, Montreal, QC Canada; 2. Celerion, Lincoln, NE USA; 3. Cempra, Chapel Hill, NC USA

Background/Purpose: Solithromycin is the first fluoroketolide in the macrolide class and is being developed as oral and IV formulations for the treatment of patients with community-acquired bacterial pneumonia (CABP). Like other macrolide antibiotics, solithromycin is both a substrate and an inhibitor of P-gp in vitro. This study assessed whether the PK of digoxin was affected by concomitant administration of solithromycin.

Methods: Fourteen healthy adult participants received two 0.5 mg doses of digoxin Q12h (Day 1) followed by 0.125 mg QD doses of digoxin for 9 days (Days 2-10). Solithromycin was co-administered with digoxin as a single 800 mg oral dose (Day 6) followed by 400 mg solithromycin QD doses for 4 days (Days 7-10). The PK of digoxin was evaluated when administered alone and when co-administered with solithromycin, at near steady state levels of both drugs, based on trough plasma concentrations measured for 4 days, followed by a serial 24-hour sampling day following the last dose (Day 10 for co-administration versus Day 5 for digoxin alone). The effect of a loading dose of solithromycin on the PK of digoxin at steady state was also studied (Day 6 for co-administration versus Day 5 for digoxin alone). Analysis of PK samples was performed using a validated high performance liquid chromatography - tandem mass spectrometry method. Safety and tolerability of co-administration of the 2 drugs were evaluated by closely monitoring participants for adverse events, changes in blood pressure, vital signs, clinical laboratory evaluations, and electrocardiograms.

Results: Compared to serum digoxin concentrations with digoxin alone, serum concentrations following co-administration with solithromycin were increased (Day 10 AUC_{tau} 38%, and C_{max} 46%). No differential P-gp inhibition by solithromycin was observed between the multiple QD dosing and the loading dose administration. Despite a somewhat higher exposure following co-administration of solithromycin, none of digoxin C_{max} values ever exceeded 2 ng/mL (concentration typically associated with toxicity) and digoxin C_{trough} levels were similar. Study medications were well tolerated. With the exception of mild, self-limited tachycardia in one subject, there were no clinically significant findings in the clinical laboratory tests, vital signs, or ECGs.

Conclusion: Although the results of this study suggest a potential for a pharmacokinetic interaction between digoxin and solithromycin (increased levels of digoxin following co-administration), the safety and tolerability of digoxin were preserved during concurrent administration of solithromycin in the study population. This was consistent with the fact that digoxin C_{max} never exceeded 2 ng/mL (digoxin level typically associated with toxicity symptoms). In addition, there was a lack of effect on serum trough levels of digoxin. When solithromycin is given concomitantly with digoxin, digoxin levels should be monitored, especially in elderly and patients with decreased renal clearance.

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