The rapid emergence of macrolide resistance over the past few years has become a major problem among clinicians and public health professionals. This has limited the therapeutic options for treatment of respiratory infections. Solithromycin, a 4th generation macrolide and the 1st fluoroketolide, is being developed as oral, intravenous, and pediatric suspension formulations for the treatment of community-acquired bacterial pneumonia (CABP). Solithromycin has demonstrated potent in vitro activity against key respiratory pathogens, including Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, as well as atypical pathogens (Legionella pneumophila and Mycoplasma pneumoniae). Due to its extended spectrum of activity and pharmacological properties, Solithromycin could also be used for other indications, such as bacterial urethritis, tuberculosis, malaria, and biodefense.

Some medicinal products have been shown to have proarrhythmic potential and may induce a potentially lethal QT-prolongation associated ventricular tachycardia known as torsades de pointes [1]. Antibiotics, specifically respiratory fluoroquinolones such as moxifloxacin and levofloxacin, along with older macrolides like erythromycin, clarithromycin, and even azithromycin, can cause QT prolongation [1].

Due to the fact that solithromycin is a member of the macrolide class, the primary objective of this study was to evaluate the effects of a supratherapeutic IV dose of solithromycin on cardiac repolarization (duration of QTc interval), using the method for heart rate correction (QTcF or an optimized subject-specific QTc) chosen by a prospectively defined test.

**MATERIALS AND METHODS**

This was a Phase 1, single center, 3-way cross-over, placebo- and active controlled, double-blind, randomized trial. A total of 48 subjects (33 males, 15 females) were randomly assigned to 1 of 6 different treatment sequences. Each treatment sequence was comprised of the following 3 treatment periods: Day 1, Day 8, and Day 15, where study drugs were administered in the morning (t=0) after subjects had fasted for 8 hrs. Solithromycin was administered intravenously as an 800 mg dose over a 40 minute infusion period while Moxifloxacin was given once orally at a dose of 400 mg. The placebo control was intravenous 0.9% sodium chloride.

Continuous 12-lead ECGs were captured for 25 hours (starting 1 hour before dosing and continuing until 24 hours after time 0) using a Holter recorder. Serial ECGs and blood samples for PK analysis were collected through 24 hours after study drug administration.

The effect of study drugs (either solithromycin or moxifloxacin) on other important ECG parameters such as heart rate and PR and QRS intervals was also assessed. In addition, the relationship between plasma concentrations of Solithromycin and its effect on QTc was determined.

**RESULTS**

The geometric mean solithromycin peak plasma concentration (C_{max}) was 5.7 µg/mL (mean AUC_{tau} 23.4 µg*h/mL). For subjects randomized to receive solithromycin, the mean placebo adjusted QTcF change from baseline < 3.0 ms at all timepoints. The largest solithromycin ∆QTcF was observed at Hour 4, with an estimate of only 2.8 ms (upper bound, 90% CI, 4.9 ms) (Figure 1). On the other hand, QTc prolongation was observed after dosing with oral moxifloxacin (also Figure 1). Specifically, the ∆QTcF was 9.7 ms, 9.8 ms, and 10.9 ms at 3 pre-defined timepoints (Hour 2, 3, and 4) with the lower bound of the 90% CI above 5 ms (7.6 ms, 7.7 ms, and 8.7 ms) at each timepoint.

**CONCLUSIONS**

Unlike respiratory fluoroquinolones and other macrolide antibiotics, solithromycin does not prolong the QTc interval, even at supratherapeutic doses. In addition, solithromycin had no clinically meaningful effect on the cardiac conduction parameters, PR and QRS interval. An increase in heart rate was observed, in a recent Phase 3 trial for CABP in which solithromycin was administered orally, the mean daily heart rate in patients decreased following dosing, suggesting that this physiologic response will differ between patients with disease and healthy volunteers, and is dose related. The results from this trial constitute a definitively negative TQT study (as defined by the ICH guidance [2]). Solithromycin does not prolong QT.

**REFERENCES**


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