P1267
Paper Poster Session
Levonadifloxacin

Plasma and intrapulmonary pharmacokinetics of levonadifloxacin in healthy adult subjects

Rakesh Chugh*[1], Ashima Bhatia[2], Mugha Gupta[3], Nitin Sharma[2], Mark H. Gotfried[4], Keith Rodvold[5]

[1]*Wockhardt, Global Clinical Development, Mumbai, India*

[2]*Wockhardt, Mumbai, India*

[3]*Wockhardt Ltd, Global Clinical Development, Mumbai, India*

[4]*Pulmonary Associates, Phoenix, United States*

[5]*University of Illinois at Chicago, College of Pharmacy, Pharmacy Practice , Chicago, United States*

Background: WCK 2349 is a novel L-alanine ester prodrug of levonadifloxacin being developed as an oral fluoroquinolone antibacterial agent that displays excellent coverage for methicillin-resistant *Staphylococcus aureus*. In addition, levonadifloxacin has an *in vitro* spectrum of activity for commonly encountered respiratory organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. For pulmonary infections, concentrations of antibiotics in epithelial lining fluid (ELF) for extracellular pathogens and in alveolar macrophage (AM) cells for intracellular pathogens are thought to reflect antibiotic activity in pneumonia. The primary objective of this study was to determine and compare plasma, ELF, and AM concentrations of levonadifloxacin following oral administration of WCK 2349 in healthy adult male and female subjects.

Material/methods: Levonadifloxacin concentrations in plasma, ELF, and AM of 30 healthy subjects were measured by LC-MS/MS following repeat oral dosing of WCK 2349 (1000 mg twice daily for 5 days). Subjects were enrolled into 5 groups with 6 subjects assigned to each bronchoalveolar lavage (BAL) sampling time. Noncompartmental pharmacokinetic (PK) parameters were determined from serial plasma samples collected over a 12-hour interval following the first and ninth oral doses. BAL samples were collected once in each subject, at 2, 4, 6, 8 or 12 hours after the ninth oral dose. To determine penetration ratios, the $AUC_{0–12}$ for plasma, ELF, and AM were calculated using mean and median concentrations at the BAL sampling times. Unbound plasma concentrations were used to determine penetration ratios since plasma protein binding of levonadifloxacin is high (~85%).

Results: Mean (± standard deviation) PK parameters, based total plasma levonadifloxacin concentrations, after the first dose included maximum concentration (C_{max}) of 16.5 ± 5.1 µg/mL, time to C_{max} (t_{max}) of 1.8 ± 0.7 h, apparent volume of distribution (V/F) of 58.0 ± 14.7 L, clearance (CL/F) of 9.11 ± 2.23 L/h, and elimination half-life ($t_{½}$) of 4.5 ± 0.9 h. Steady-state was achieved by the fifth oral dose and PK parameters after the ninth dose were C_{max} of 20.0 ± 4.3 µg/mL, t_{max} of 2.1 ± 1.4 h, V/F of 59.2 ± 16.0 L, CL/F of 8.17 ± 2.05 L/h, $t_{½}$ of 5.1 ± 1.3 h, and AUC_{0-12} of 129.8 ± 31.6 µg•h/mL. The respective AUC_{0-12} values based on mean and median ELF concentrations were 172.6 and 161.2 µg•h/mL, whereas AUC_{0-12} values based on AM concentrations were 35.3 and 30.6 µg•hr/mL.

Conclusions: The ratio of ELF to unbound plasma levonadifloxacin concentrations based on the mean and median AUC_{0-12} values were 7.66 and 7.58, respectively, whereas the AUC_{0-12} ratios of AM

to unbound plasma levonadifloxacin concentrations were 1.58 and 1.44, respectively. These data support further study of WCK 2349 for treatment of lower respiratory tract bacterial infections caused by susceptible pathogens.