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Pharmacokinetics of Intravenous WCK 771 in Healthy US Adults

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Background & Objective

- WCK 771, a novel broad-spectrum fluoroquinolone with enhanced activity against MRSA and quinolone-resistant staphylococci, is being developed by Wockhardt as a parenteral anti- MRSA agent [1-3]
- Objective: To evaluate the pharmacokinetics (PK) of multiple doses of 600, 800 and 1000 mg of WCK771 administered twice daily for 5 days by IV infusion in healthy adult subjects

Data & Methodology

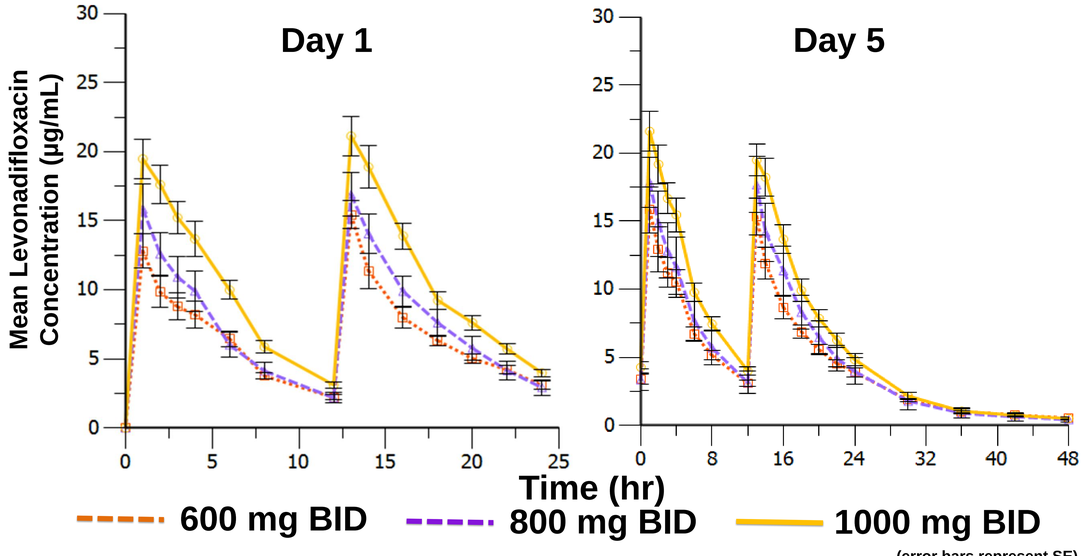
- A phase I, single-center, prospective, randomized, double-blind, comparative, placebo controlled study in healthy subjects was conducted to evaluate safety, tolerability and PK of multiple doses of 600, 800 and 1000 mg WCK 771
- PK was available from 10 subjects on 600 mg BID, 9 subjects on 800 mg BID and 10 subjects on 1000 mg BID. A total of 10 doses over 5 days were administered as 1 hr infusion
- Rich PK samples were collected on Day 1 and Day 5. The PK analysis was conducted after 1st and 2nd dose on Day 1 and 9th and 10th dose at Day 5. A total of 435 observations from 29 subjects on Day 1 and 531 observations from 28 subjects on Day 5 were included in analysis
- WCK 771 is converted to levonadifloxacin as the active drug *in vivo*
- Non compartmental analysis was conducted in Phoenix WinNonlin version 6.4 to characterize PK of WCK 771

Results

Table 1: Mean PK Parameters of Levonadifloxacin

Day of Study	Parameter	Units	Dose Level: 600 mg (n=10)		800 mg (n=9)		1000 mg (n=10)*	
Day 1			Mean	SD	Mean	SD	Mean	SD
	$AUC_{(0-12)}$	µg·hr/mL	74.26	20.44	86.89	31.63	118.34	24.31
	$AUC_{(12-24)}$	µg·hr/mL	85.59	20.02	101.45	32.58	129.80	26.21
	$AUC_{(0-24)}$	µg·hr/mL	159.86	40.18	188.34	63.73	248.14	49.46
	$AUC_{(0-\infty)}$	µg·hr/mL	187.62	45.22	211.97	76.93	275.92	52.76
	C_{max}	µg/mL	15.82	3.41	17.82	4.98	22.39	4.62
	T_{max}	hr	1		1		1	
Day 5								
	$C_{max,ss}$	µg/mL	16.67	5.33	19.57	6.38	22.09	4.47
	$C_{min,ss}$	µg/mL	3.57	1.17	3.95	2.45	4.41	1.22
	$T_{max,ss}$	hr	1		1		1	
	$AUC_{(0-12),ss}$	µg·hr/mL	94.75	24.26	111.68	54.31	133.89	25.35
	$AUC_{(12-24),ss}$	µg·hr/mL	92.15	22.17	114.08	48.45	130.92	24.67
	$AUC_{(0-24),ss}$	µg·hr/mL	186.89	46.25	225.77	102.32	264.81	49.71
	λ_z	1/hr	0.064	0.019	0.086	0.032	0.094	0.032
	$t_{1/2}$	hr	12.01	4.60	9.05	3.12	8.48	3.80
	CL_{ss}	L/hr	6.69	1.61	8.20	2.58	7.69	1.32
	V_z	L	111.49	34.11	101.71	34.95	94.52	46.5
	V_{ss}	L	145.34	39.10	172.00	50.00	155.83	33.11
	Accumulation Ratio (NCA)		2.01	0.54	1.67	0.35	1.61	0.43
	Accumulation Ratio (Obs)		1.05		1.10		0.99	

Figure 1: Mean Levonadifloxacin concentration-time profiles



Conclusions

- With a 1.7 fold increase in dose from 600 mg to 1000 mg, the $C_{max,ss}$ and $AUC_{(0-24),ss}$ increased 1.3 and 1.4 fold, respectively
- The volume of distribution (V_{ss}) and the clearance (CL_{ss}) were estimated to be similar across the three dose levels. The V_{ss} ranged from 145.34 to 172.0 L while the CL_{ss} ranged from 6.7 to 8.2 L/hr.
- Terminal half-life ranged from 8.5 to 12.0 hrs.
- Based on the observed AUC and Cmax comparison at day 1 and day 5, the accumulation factor ranged from 0.99 to 1.1 representing no or minimal accumulation
- The doses were well tolerated at all levels

References

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