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Pharmacokinetics of TP-434 in Mouse, Rat, Dog, Monkey and Chimpanzee

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Abstract

Background: TP-434 is a broad-spectrum fluorocycline for treatment of serious hospital infections caused by multidrug-resistant bacteria.

Methods: Disposition of single IV doses of TP-434 has been determined in species relevant for safety assessment and for projection of human pharmacokinetics (PK). Plasma concentrations of TP-434 were evaluated by sensitive and selective TurboIonspray LC/MS-MS. PK parameters were calculated by noncompartmental analysis using WinNonlin.

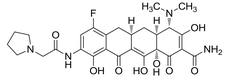
Results: Peak plasma concentrations after a single 1 mg/kg IV dose ranged from approximately 0.5-1.3 µg/mL, and declined in a multiphasic manner with estimated elimination half-lives ranging from 4-14 hrs in mice, rats, dogs, monkeys, and chimpanzees. The PK of TP-434 was species-dependent, with no notable gender differences. Systemic clearances (Cls) of low pharmacological doses in all species were low relative to hepatic blood flow, appearing somewhat higher in monkey. Cls in dogs appeared saturable at higher dosages, resulting in disproportionately higher plasma concentrations. The mechanism for this saturable clearance is unknown, but was not seen in doses evaluated in rats. Cls after a single dose in chimpanzees, a useful surrogate for the human PK of many drugs, was 0.421 L/hr/kg. TP-434 was widely distributed in extravascular tissue, with a volume of distribution ranging from 3.2-15 L/kg, demonstrating not only extensive tissue distribution but also tissue binding. When TP-434 plasma protein binding was evaluated using ultrafiltration, the percent free ranged from 10.8-59.3%. Biliary excretion is likely the major route for elimination of the dose since ~20% of the IV dose was recovered in the urine of dogs and chimpanzees. Oral bioavailability of TP-434 was 29.2% in chimpanzees and <10% in all other species.

Conclusions: PK has been adequately determined in animal models and supports the further investigation of this molecule in humans.

Introduction

TP-434 is a novel fully synthetic tetracycline-class antibiotic was designed to have a broad antibacterial spectrum with potent activity against problematic multidrug-resistant gram-negative and gram-positive bacteria. TP-434 will be used for treatment of serious hospital infections as it is unaffected by resistance mechanisms to other antibiotics and is specifically active against tetracycline-resistant strains (see posters F1-2155, F1-2157, F1-2158 and F1-2160). TP-434 has been manufactured in multi-kilo amounts and is currently in clinical trials.

TP-434



Methods

PK Analyses. All studies were performed under approved IACUC protocols and conform to OLAW standards (WuXi Apptec, Ricerca and New Iberia Research Center). The pharmacokinetics (PK) of TP-434 was determined in mice (n=10) , rats (n=3), Beagle dogs (n=3), cynomolgus monkeys (n=2), and chimpanzees (n=3). Animals were fasted overnight (minimum of 12 hrs) and given a single oral or IV dose followed by a sampling scheme for 24-48 hrs. Urine collection was done in chimpanzee. Plasma, urine, and dosing solution concentrations of TP-434 were evaluated by sensitive and selective TurboIonspray LC/MS-MS assay using appropriate standard curves, with LLOQs of 1-25 ng/mL. PK parameters were calculated by noncompartmental analysis using WinNonlin.

Protein Binding. The *in vitro* protein binding of 1 µM TP-434 in plasma collected with EDTA from mice, rats, Beagle dogs, and cynomolgus monkeys was determined in triplicate using ultrafiltration and LC/MS-MS analysis.

Results

Table 1. Mean Plasma Pharmacokinetic of TP-434 After Single IV and Oral Dose in Mouse, Rat, Dog and Cynomolgus Monkey

Species	Dosage Route	CLs	Vz	T½	C_{max}[a]	AUC_{last}	Tmax	F
	mg/kg	L/hr/kg	L/kg	hr	µg/mL	µg·hr/mL	hr	%
Mouse	2 IV	0.744	2.1	6.9	5.763*	2.639	0.083	
	10 PO			3.1	0.00624	0.0343	4	0.26
Rat	1 IV	0.564	3.2	4	0.812	1.766	0.083	
	10 PO			6.9	0.045	0.295	1.2	1.7
	1 IV	0.888	5.2	5.3	0.577	1.105	0.083	
	10 PO			nd	0.049	0.476	2.3	4.3
	1 IV	0.343	1.6	5.3	3.575*	3.022	0.083	
	10 PO			3.4	0.0341	0.208	0.88	0.77
Dog	1 IV	0.491	5.1	9.5	0.796	1.789	0.083	
	1 IV	0.247	3.9	14.2	1.213	3.087	0.083	
	10 PO			11.4	0.267	2.807	2.7	9.1
Cynomolgus Monkey	0.5 IV	1.24	14.8	8.3	0.232	0.361	0.83	
	5 PO			9.3	0.007	0.061	1.5	1.7
	1 IV	0.225	1.7	7.9	5.273*	4.39	0.083	
	10 PO			12	0.154	1.59	4	4.2

[a]Cmax: Cmax reported as the concentration at the first sampling point (typically 5 min) except indicated. In these cases the reported concentration represents Cp0, the extrapolated concentration at time 0.

Table 2. Protein Binding (% free) of 1 µM TP-434 in Plasma (EDTA) from Mouse, Rat, Beagle Dog and Cynomolgus Monkey

Replicate	Mouse	Rat	Dog	Monkey
1	57.1	11.0	56.6	19.4
2	60.8	10.5	54.0	18.7
3	60.2	11.0	52.8	17.4
Mean ± SD	59.3 ± 2.0	10.8 ± 0.3	54.5 ± 2.0	18.5 ± 1.0

TP-434 is Orally Bioavailable in the Chimpanzee

TP-434 is orally bioavailable in chimpanzees. Chimpanzees have been established as an effective surrogate for human drug disposition for a wide variety of molecules (Wong et al., Drug Metab. Dispos. 32:1359, 2004; Wong et al. Xenobiotica 36:1178, 2006). This species, which is closely related to humans genetically, physiologically, and anatomically, may provide a more relevant estimate of the human pharmacokinetics of TP-434 than studies with monkeys, dogs, or rodents.

Table 3. Mean Plasma Pharmacokinetic of TP-434 After Single IV and Oral Dose in Chimpanzee

Dosage Route	CL	Vz	T½	C_{max}	AUC_{0-24}	Tmax	F
mg/kg	L/hr/kg	L/kg	hr	µg/mL	µg·hr/mL	hr	%
1 IV	0.705	3.46	10.2	1.096	1.507	0.1	
10 PO			8.1	0.427	4.397	5.3	29.2

Figure 1. Mean (± SD, n=3) Plasma Concentrations of TP-434 in Chimpanzees Given a Single 10 mg/kg PO Dose

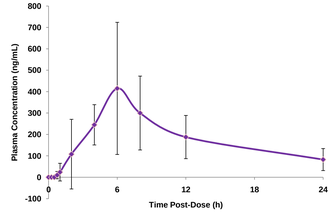


Table 4. Individual Urine Concentrations (0-24 hr) and Urinary Excretion of TP-434 By Chimpanzees Given a Single 1 mg/kg IV or 10 mg/kg PO Dose of TP-434

Animal	1 mg/kg IV					10 mg/kg PO				
	Volume mL	Concentration µg/mL	Amount mg	Dose Mg	% of Dose Excreted	Volume mL	Concentration µg/mL	Amount mg	Dose mg	% of Dose Excreted
89A007	1600	2.158	3.453	63.4	5.4	1222	7.01	8.566	644.2	1.3
89A017	3350	8.359	28.003	63.4	44.2	4022	1.68	6.757	698.3	1.0
A237H	2550	1.881	4.797	70.4	6.8	1582	1.82	2.879	758.5	0.4

Conclusions

- **TP-434 is orally bioavailable in the chimpanzee**
- **Peak plasma concentrations after a single 1 mg/kg IV dose ranged from 0.5- 1.3 µg/mL and declined in a multiphasic manner**
- **TP-434 has long estimated elimination half-lives ranging from 4-14 hrs in mice, rats, dogs, monkeys, and chimpanzees.**
- ***The results from chimpanzees warrant investigation of TP-434 in humans using an oral dosage system.***