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From Mouse to Man: the Pharmacokinetics of CEM-102 (Fusidic acid)

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Abstract

Background: The pharmacokinetics (PK) of CEM-102 (fusidic acid) have been studied in animals and in human clinical trials. The notable differences between humans and other animals are presented.

Methods: Mouse, rat, dog, micropig and human plasma samples were obtained following single doses of CEM-102. Samples were also obtained from multiple dose studies of 28 days in rats and dogs and following 5.5 days of dosing in healthy human subjects. Plasma samples containing K_3EDTA as the anticoagulant were extracted via liquid/liquid extraction and analyzed by LC/MS/MS.

Results: Single doses of 100 mg/kg yielded maximum plasma concentrations (C_{max}) of 0.6-1.2, 1.3-4.1, 0.7, and 25.6-29.1 µg/mL in mice, rats, micropigs, and dogs, respectively, and were reached 0.25-4 hours following drug administration. Single doses of 550 mg in a Phase 1 trial resulted in a mean plasma C_{max} of 33.4 µg/mL 2 hours post-dose. The 100 mg/kg dose administered to animals equates to respective human equivalent doses of 488 (mouse), 968 (rat), 4286 (micropig), and 3333 mg (dog). The PK in rat and dog did not change after 28 days of dosing and drug did not accumulate. In contrast, twice daily dosing of 550 mg in humans resulted in significant accumulation of CEM-102 in plasma until steady state was approached after 5.5 days (C_{max} 130 µg/mL). Total exposure (AUC_{0-t}) increased from 242 µg·h/mL (single dose) to 1150 µg·h/mL (multiple dose). Gender differences were observed in rats and mice but not in dogs or humans.

Conclusions: The PK of CEM-102 in animals was compared to that in human subjects. Plasma exposure to CEM-102 differed notably between species, with very limited exposure in rodent species in contrast to greater exposure in dogs and highest exposure in humans.

Species	Single Dose (100 mg/kg)			Multiple Dose (100 mg/kg/d)		
	C_{max} (µg/mL)	T_{max} (h)	$AUC_{(0-t)}$ (µg·h/mL)	C_{max} (µg/mL)	T_{max} (h)	$AUC_{(0-t)}$ (µg·h/mL)
Mouse	0.6-1.2	1-4	ND	ND	ND	ND
Rat	1.3-4.1	0.25-0.5	2.81-18.2	0.5-2	0.25	1.7-10.7
Micropig	0.7	0.5-2	ND	ND	ND	ND
Dog	25.6-29.1	1	74-81	25.6-26.5	2	76.7-87.2
Human (550 mg)	33.4	2	242	130	3	1150

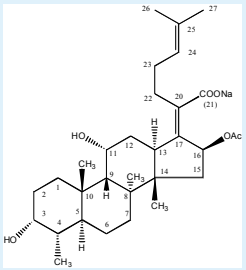
Introduction

CEM-102 (Figure 1) is fusidic acid, an antibiotic of the fusidane class that is under development in the US by Cempra Pharmaceuticals for treatment of patients with acute bacterial skin structure infections. CEM-102 has shown excellent microbiological activity against *Staphylococcus aureus*, including methicillin resistant *S. aureus* (MRSA) (MIC_{90} 0.12 µg/mL). Coagulase-negative staphylococci (CoNS) with or without oxacillin-resistance were all highly susceptible to CEM-102 (MIC_{90} 0.12 µg/mL). The MIC range of CEM-102 against Group A streptococci was 2 to 8 µg/mL.

In animal pharmacology and toxicology studies we have found that the exposure of CEM-102 in rodent species is very low and variable, thus providing a challenge for the conduct of meaningful studies of efficacy in animal models.

In this presentation, we compare the exposures of CEM-102 following single and, where available, multiple doses of CEM-102 in rodent and non-rodent species to exposures observed at relevant therapeutic doses in humans.

Figure 1. Chemical Structure of CEM-102



Study Design and Methodology

- **Blood collection**
  - Blood was collected from an appropriate vein at specified timepoints from mice, rats, dogs, micropigs and humans.
  - Blood samples were stored refrigerated or on ice until centrifugation at 4°C within 2 hours of collection. The resulting plasma was collected into polypropylene tubes containing K_3EDTA as anticoagulant and stored at -70°C until analysis.
- **Sample analysis**
  - Extraction: Plasma samples (50 uL) containing tetrahydrofusidic acid as internal standard were extracted by liquid/liquid extraction with dichloromethane: hexane:MTBE, 1:1:1).
  - HPLC Analysis: Samples were analyzed by reverse phase HPLC using a Hydro-RP column. Samples containing CEM-102 and tetrahydrofusidic acid as internal standard were nebulized with heated nitrogen using a Z-spray source/interface and the ionized compounds were detected by quadrupole tandem mass spectrometry.
  - The analytical methods used for measurement of CEM-102 in mouse, rat, micropig, dog and human plasma were fully validated.
- **Human Equivalent Doses**
  - Respective human equivalent doses (HED, based on body surface area)

Species Dosed (100 mg/kg)	HED (mg/60kg)
Mouse	488
Rat	968
Micropig	4286
Dog	3333

Results

Mouse

- Following a single oral (gavage) dose of 100 mg/kg, CEM-102 plasma levels were low and variable, reaching 0.6 to 1.2 µg/mL at 1 hour post-dose and 0.9 to 1.9 µg/mL after 4 hours.

Rat

- In a 28-day study, Sprague-Dawley rats were administered single doses of 50, 100, or 250 mg/kg (10/sex/group) of CEM-102 by oral gavage on Day 1 (Table 1).
- Plasma levels following the 50 mg/kg dose were low and variable. At 100 mg/kg, maximum mean plasma levels of 1.3 and 4.1 µg/mL were determined for males and females, respectively.
- Higher exposures were observed in female rats compared to male rats.

Micropig

- As part of a cardiovascular safety study in Yucatan Micropigs®, plasma levels of CEM-102 were measured during the MTD phase following single doses of 100, 250, 500, and 800 mg/kg (2 males).
- Following a single dose of 100 mg/kg, plasma levels were low and variable with a mean C_{max} of 0.7 µg/mL after 0.5 to 2 hours. At 250 and 500 mg/kg doses, C_{max} values of 28.5 and 40 µg/mL were reached after 4 and 2 hours, respectively. These data show a more than dose proportional increase in exposure from the 100 to 250 mg/kg dose.

Dog

- As part of a 28-day study in Beagle dogs, plasma levels of CEM-102 were evaluated following doses of 40, 100, or 250 mg/kg (4/sex/group) (Table 2).
- Following a single 40 mg/kg dose on Day 1, C_{max} values of 11.0 and 12.4 µg/mL were observed in males and females, respectively. After the 100 mg/kg dose, the respective C_{max} values were 25.6 and 29.1 µg/mL. T_{max} was reached between 0.75 and 1 hour at both doses.

Table 1. Plasma concentrations of CEM-102 following single oral doses in SD rats

	Male			Female		
Dose (mg/kg)	50	100	250	50	100	250
C_{max} (µg/mL)	0.782	1.32	1.23	7.22	4.08	12.60
T_{max} (h) (Range)	0.250 (0.25-0.5)	0.250 (0.25-0.5)	0.5 (0.25-0.5)	0.500 (0.5-0.5)	0.500 (0.25-0.5)	0.5 (0.25-1)
$AUC_{(0-T)}$ (µg·h/mL)	1.20	2.81	3.54	9.34	18.2	58.4
C_{max} Ratio	0.982	0.383	1.72	0.135	0.487	1.31
AUC Ratio	1.02	0.587	0.921	0.607	0.588	0.760

C_{max} Ratio: C_{max} (Day 28) / C_{max} (Day 1)
AUC Ratio: AUC (Day 28) / AUC (Day 1

Table 2. Plasma concentrations of CEM-102 following single oral doses in dogs

	Male			Female		
Dose (mg/kg)	40	100	250	40	100	250
C_{max} (µg/mL)	11.0	25.6	30.8	12.4	29.1	22.7
T_{max} (h) (Range)	0.75 (0.5-2)	1.0 (0.5-1)	2.0 (1-2)	0.75 (0.5-1)	1.0 (1-2)	2.0 (1-4)
$AUC_{(0-T)}$ (µg·h/mL)	21.4	74.0	131.0	28.8	81.1	120.0
C_{max} Ratio	1.23	1.00	0.581	1.12	0.911	0.868
AUC Ratio	1.20	1.04	1.14	0.847	1.08	1.18

C_{max} Ratio: C_{max} (Day 28) / C_{max} (Day 1)
AUC Ratio: AUC (Day 28) / AUC (Day 1

Human

- Human PK data was obtained from a Phase 1, randomized, double-blind, placebo-controlled, escalating-dose, single and multiple dose study in healthy adult male and female subjects (Table 3).
- 32 subjects were enrolled in 4 cohorts of 8 subjects (6 active, 2 placebo).
- C_{max} and AUC showed more than dose proportional increases from 550 mg to 1100 mg, then approximately dose proportional increases from 1100 mg to 2200 mg.
- Accumulation occurred from Day 1 to last day of dosing at all dose levels.

Table 3. Plasma concentrations of CEM-102 following single or bid doses (5.5 days) in humans

	Cohort 1 550 mg	
Parameter	Mean	SD
Period 1 Day 1		
C_{max}, µg/mL	33.4	12.2
T_{max}, h[a]	2.00	(2-3)
K_{el}, h^{-1}[b]	0.0564	0.0130
$T_{1/2}$, h[c]	12.3	2.98
$AUC_{(0-24)}$, µg·h/mL	242	102
$AUC_{(0-inf)}$, µg·h/mL	441	269
CL/F, L/h	1.69	1.00
V_d/F, L	28.4	10.8
Period 2 Day 6		
C_{max}, µg/mL	130	30.5
T_{max}, h[a]	3.00	(1.5-4)
K_{el}, h^{-1}[b]	0.0554	0.0131
$T_{1/2}$, h[c]	12.5	3.05
$AUC_{(0-12)}$, µg·h/mL	1,150	433
CL/F, L/h	0.553	0.255
V_d/F, L	9.88	3.05
C_{max} accumulation ratio[d]	3.89	-
$AUC_{(0-12)}$ accumulation ratio	2.61	-

a Expressed as median and range
b Apparent first-order terminal elimination rate constant
c Expressed as harmonic mean and pseudo SD

Conclusions

- In a comparative analysis of the pharmacokinetics of CEM-102 in various animal species and humans, plasma concentrations of CEM-102 were significantly higher in humans.
- CEM-102 plasma concentrations were lowest in rodents; better exposure was achieved in larger animals such as dogs.
- No significant accumulation was observed following multiple doses of up to 28 days in the animal species tested; in contrast, CEM-102 accumulated significantly in human plasma.
- The discrepancy in achievable plasma exposures between humans and species that are suitable for pharmacology studies, particularly rodents, produces challenges for extrapolation of data from studies in standard models of infection.
- Traditional drug discovery methods of testing for microbiological activity in rodent models are not appropriate for CEM-102. Repeated dosing was required to achieve marginal efficacy in rodent models (Turnidge, 1999).

References

- Turnidge (1999), Int. J. Antimicrob Agents, S23-S34.