Humanization of Solithromycin Non-Human Primate Pharmacokinetic Profiles to Improve Pharmacokinetic-Pharmacodynamic Translation

Elizabeth A. Lakota[1,2], Olanrewaju O. Okusanya[1,2], Sujata M. Bhavnani[1,2], Kara Keedy[3], Amanda Sheets[3], Prabha Fernandes[3],Paul G. Ambrose[1,2], Alan Forrest[1,2]

[1]Institute for Clinical Pharmacodynamics, Latham, NY; [2] School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, SUNY, Buffalo, NY; [3] Cempra Pharmaceuticals, Chapel Hill, NC.

Presenting Author:
Elizabeth A. Lakota, Pharm.D., M.S. Candidate
Institute for Clinical Pharmacodynamics
43 British American Blvd.
Latham, NY 12110
Phone: (518) 429-2600
Email: elakota@icpd.com

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ABSTRACT

BACKGROUND: Solithromycin (SOL) is a new macrolide antibiotic with *in vitro* activity against *Bacillus anthracis and Francisella tularensis*. Pharmacokinetic-pharmacodynamic (PK-PD) modeling of non-human primate (NHP) intravenous dosing was humanized to the clinical human oral dose regimen to achieve appropriate blood levels during infections with these pathogens.

METHODS: Healthy NHP (n=32) received IV SOL (2.5 to 25 mg/kg/d) for 28 d. Pharmacokinetic (PK) data were obtained on Days 1 and 28 and fit to population PK (PPK) models. Using the final PPK model based on NHP PK data and a previously-described human PPK model (ICAAC 2012, A1269), NHP IV doses designed to achieve the same daily human free-drug AUC and concentration-time profiles similar to those in humans given 3 PO regimens over 21 d were computed.

RESULTS: NHP PPK was described by a 3 compartment linear model. Four IV doses/d were needed to mimic the human PO regimens (**Figure 1**). Despite a much faster CL in NHP (human CL=0.82 L/kg/h, NHP CL=1.5 L/kg/h), the concentration-time profiles agreed well and the concordance of cumulative free-drug AUC was excellent (98% of NHP:human cumulative AUC ratios were between 0.998 and 1.07).

CONCLUSION: This humanization method, which allows small animal PK profiles to better mimic typical human PK profiles, will allow for improved PK-PD translation from animal models to humans, which should optimize potential SOL regimens for humans.

BACKGROUND

- Solithromycin (SOL) is a fourth generation macrolide, the first fluoroketolide with potent *in vitro* activity against Gram-positive, Gram-negative, and atypical bacterial pathogens[1,2]. Given this activity, SOL is being developed for the treatment of patients with community-acquired bacterial pneumonia (CABP).
- SOL has also shown potent activity against *Bacillus anthracis* and *Francisella tularensis*, both of which are biowarfare/bioterrorism agents.[3]
- The efficacy of SOL in non-human primates (NHPs) infected with the above-described agents can be translated to humans. However, the considerable inter-species differences in metabolism can complicate this translation even when free-drug area under the concentration-time curve (*f*AUC) values are similar.
- To improve such translations, NHP intravenous (IV) dosing regimens for evaluation can be designed to not only approximate human *f*AUC values but to also mimic human plasma-concentration profiles after human oral (PO) dosing regimens. This approach is referred to as "humanization" and was undertaken to construct NHP IV dosing regimens for use in future NHP studies treating infections due to *B. anthracis or F. tularensis*.

OBJECTIVES

- To develop a NHP population PK model
- Using the NHP population PK model, to construct NHP IV dosing regimens to allow the NHP *f*AUC and free-drug concentration to closely match those predicted in humans for proposed human SOL PO dosing regimens; and
- Using data from a pilot NHP study, to evaluate the NHP population PK model and a single NHP IV dosing regimen.

METHODS

NHP Population Model Development

- PK data were obtained from a 28 day toxicokinetic study conducted in uninfected cynomolgus NHPs administered 2.5, 12.5, or 25 mg/kg IV SOL once daily (Q24h) for 28 days.
- Blood samples to determine SOL concentrations were collected pre-dose, 0, 0.5, 1, 4, 8, 12, and 24 hours post-infusion on Days 1 and 28.
- Candidate structural population PK models were fit to the plasma concentration data using MC-PEM as implemented in S-ADAPT[4].
  - Weighting of the plasma concentrations was based on the reciprocal of the estimated observation variance.
  - Residual error model parameters were fixed and included an additive (SDint = 0.1 mg/L) and a proportional (SDslope= 0.148) component.
  - Observations that were BLQ were modeled using the Beal M3 method.
- Model discrimination was accomplished using the corrected Akaike's Information Criterion.

Humanization

- A previously-developed human SOL population PK model based on data from 6 Phase 1 and 1 Phase 2 studies was used.[5]
  - This model was a three-compartment model with auto-inhibition of clearance.
- Using the human population PK model,[5] typical human SOL free-drug concentrations and *f*AUC values were simulated for the following SOL PO dosing regimens using ADAPT-5[6]:
  - 800 mg PO on day 1 followed by 400 mg PO Q24h for 21 days;
  - 600 mg PO on day 1 followed by 300 mg PO Q24h for 21 days; and
  - 1200 mg PO on day 1 followed by 600 mg PO Q24h for 21 days.
- Using mean parameter estimates from the NHP population PK, NHP IV doses (mg/kg) needed to mimic typical human SOL cumulative *f*AUC values for each of the 3 human dosing regimens were constructed using maximum likelihood in ADAPT 5.[6]

Evaluation of Effect of NHP Weight

- To evaluate the effect of large departures from predicted weight, *f*AUC for NHPs of 2.625 and 5.25 kg (75 and 150% of 3.5 kg, respectively) were compared to those predicted for a 3.5 kg NHP and a typical human.

Validation Study

- PK data for SOL from a pilot study of 4 cynomolgus-NHPs who received humanized SOL doses for the 800 mg PO on Day 1 followed by 400 mg PO Q24h for 14 days dosing regimens were evaluated.
  - Using the NHP population PK model, the total-drug concentrations were simulated for each of the 4 NHPs.
  - The NHP observed total-drug concentrations and AUC values were then compared to predicted values.
- Data from this validation study were then pooled with the previous NHP data and the NHP PPK model was refined.

Drug Assay

- SOL plasma concentrations were determined using reversed-phase high-performance liquid chromatography linked with mass spectrometry.
- The quantifiable limit was 0.01 mg/L and the coefficient of variation on the assay was < 5%.

RESULTS

NHP Population PK Model

- As shown in **Figure 1**, NHP population PK was described by a linear three-compartment model. The alpha, beta, and gamma half-lives were 0.5, 2.7, and 138 hours, respectively.
- Parameter estimates for the final NHP population PK model are shown in **Table 1**. All parameters were estimated with good precision.
  - The NHP weight was a covariate for volume of the central compartment (proportional) and clearance (allometric) using a typical NHP weight of 3.5 kg.

Figure 1. NHP structural population PK model for SOL

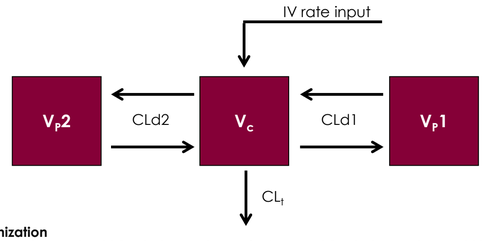


Table 1. NHP population PK model parameter estimates for SOL

Parameter	Abbreviations	Population mean		Interindividual variability (%CV)	
		Estimate	%SEE	Estimate	%SEE
Volume of the central compartment	V_c (L/3.5kg)	5.93	4.62	44.8	46.1
Distributional clearance 1	CL_d1 (L/hr)	5.51	14.7	24.8	100
Volume of the peripheral compartment 1	V_p1 (L)	6.77	6.86	36.7	35.6
Distributional clearance 2	CL_d2 (L/hr)	0.273	26.7	46.0	54.6
Volume of the peripheral compartment 2	V_p2 (L)	51.8	84.9	97.8	65.3
Total clearance	CL_t (L/hr/3.5kg)	5.30	2.29	23.0	27.7

a. Total Clearance = CL_t*(weight/3.5 kg)$^{0.75}$

Humanization

- The NHP humanized SOL dosing regimens for human SOL dosing regimens, 800 mg PO on Day 1 followed by 400 mg PO Q24h, 600 mg PO on Day 1 followed by 300 mg PO Q24h, and 1200 mg PO on Day 1 followed by 800 mg PO Q24h, are shown in **Table 2**. The first infusion of each day is a 4 hour infusion, during which the absorption phase occurs in humans. The remaining 3 doses for each day are 1 hour infusions.

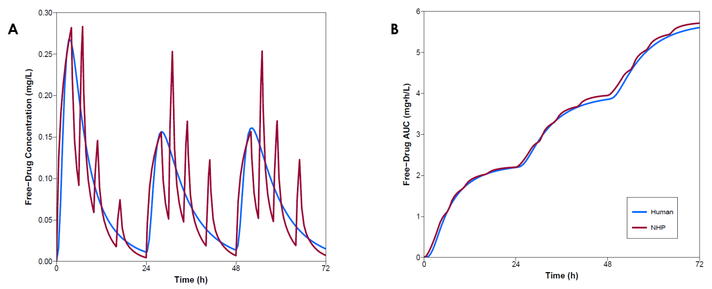
Table 2. NHP SOL humanized dosing regimens

Human SOL dosing regimens	Units for doses	NHP SOL humanized IV dosing regimens														
		Doses administered on Day 1					Doses administered on Days 2 – 7					Doses administered on Day 8 - 21				
		0 hrs[b]	6 hrs[c]	10 hrs[c]	16 hrs[c]	TDD[d]	0 hrs[b]	6 hrs[c]	10 hrs[c]	16 hrs[c]	TDD[d]	0 hrs[b]	6 hrs[c]	10 hrs[c]	1 hrs6[c]	TDD[d]
800 mg PO x 1 on Day 1 followed by 400 mg PO Q24h for 21 days[a]	mg/kg	11.1	3.66	1.73	1.03	**17.5**	6.08	3.64	2.26	1.83	**13.8**	7.10	3.52	2.44	0.93	**14.0**
	mg/3.5 kg	38.8	12.8	6.05	3.61	**61.3**	21.3	12.8	7.91	6.40	**48.4**	24.8	12.3	8.56	3.24	**48.9**
600 mg PO on Day 1 followed by 300 mg PO Q24h for 21 days	mg/kg	7.85	2.41	0.97	0.51	**11.7**	3.64	2.09	1.21	0.96	**7.90**	4.33	2.13	1.23	0.49	**8.18**
	mg/3.5 kg	27.5	8.45	3.40	1.80	**41.2**	12.7	7.31	4.24	3.37	**27.6**	15.1	7.46	4.32	1.73	**28.6**
1200 mg PO on Day 1 followed by 600 mg PO for 21 days	mg/kg	17.6	6.26	3.35	1.97	**29.2**	11.3	6.44	4.27	3	**25**	12.1	6.46	4.17	2.14	**24.9**
	mg/3.5 kg	61.5	21.9	11.7	6.9	**102**	39.6	22.5	15	10.5	**87.6**	42.3	22.6	14.6	7.48	**87**

a. This dosing regimen is under investigation for CABP; b. Infusion time of 4 hours; c. Infusion time of 1 hour; d. TDD = Total daily dose;

- **Figure 2a** shows the predicted typical NHP SOL free-drug plasma concentration versus time for the first dosing regimen in **Table 2** overlaid with the predicted human concentration versus time for 800 mg PO on Day 1 dose followed by 400 mg PO Q24h. Given that the NHP has a much faster initial elimination compared to humans, plasma concentrations for NHPs decline rapidly below predicted human concentrations at the end of each infusion. **Figure 2b shows** the predicted typical NHP SOL cumulative *f*AUC versus time for the same dosing regimen with predicted human *f*AUC overlaid. Over the course of Days 1 to 3, the predicted NHP cumulative *f*AUC matched the cumulative target human *f*AUC very well.

Figure 2. Simulated SOL free-drug plasma concentration-time (A) and cumulative *f*AUC versus time (B) profiles for a NHP dosing regimen mimicking SOL 800 mg PO on Day 1 followed by 400 mg PO Q24h, in humans



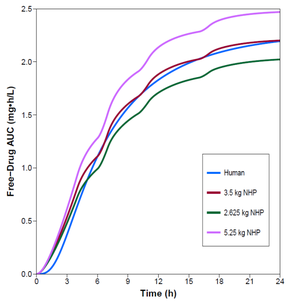
Evaluation of Effect of NHP Weight

- **Figure 3** shows the predicted SOL cumulative *f*AUC for NHPs of 2.625 kg and 5.25 kg. The *f*AUC for a typical human and a 3.5 kg NHP are also shown for comparison purposes. The small NHP (2.625 kg) showed *f*AUC values below the targeted *f*AUC while the large NHP (5.25 kg) had *f*AUC values above the target. However, as shown in **Table 3**, this deviation was less than 16% of the *f*AUC values predicted in NHP weighing 3.5 kg. As the NHP concentrations approach near steady state, the deviation was less than 11%.

Table 3. Percent of 3.5 kg NHP SOL *f*AUC achieved by NHP of varying weight

NPH of varying weight (kg)	Percent of 3.5 kg NHP SOL *f*AUC achieved by time (h) point				
	6	10	16	24	Effective steady state
2.625	89.4	90.4	91.4	91.8	93.1
5.25	115	114	113	112	111

Figure 3. Predicted SOL cumulative *f*AUC versus time for NHP of various weights compared to typical human values



RESULTS

Validation Study

- Observed (symbols) and predicted SOL total-drug plasma concentrations (lines) versus time for each NHP are shown in **Figure 4**. Predictions show good precision and accuracy.
- The 4 NHPs in the pilot study had the following weights: 5.10, 3.51, 6.68, and 3.98 kg.
  - The NHP with a weight of 6.68 kg was the largest animal studied to date. Despite this, the PK parameters for this animal were well predicted by NHP population PK model.
- The percent ratio of observed to predicted SOL cumulative total-drug AUC was calculated for selected time points for each of the 4 NHPs. The resulting range of percent ratios are shown in **Table 4**.

Figure 4. Observed and predicted NHP SOL total-drug plasma concentrations versus time on Days 1 and 2 (A) and Day 14 (B)

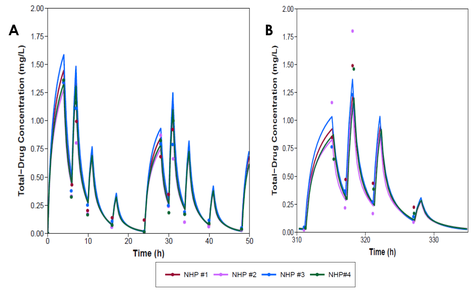


Table 4. Range of percent ratios of observed to predicted SOL cumulative total-drug AUC at selected time points

Time (h)	Range of percent ratios of observed to predicted SOL cumulative total-drug AUC (%)
6	85.7 - 122
10	87.3 - 116
16	89.2 - 112
24	90.2 - 110
30	89.3 - 113
34	89.3 - 112
40	90.0 - 111
48	90.3 - 110
318	90.2 - 106
336	90.4 - 107

DISCUSSION/CONCLUSIONS

- Humanized SOL IV regimens were developed for NHP to match target human PO PK profiles.
  - Given the differences in metabolism between NHP and humans, NHP parent and metabolite ratios after IV doses are a better match to ratios for humans after IV and PO doses, both of which would be available for humans in the event of a bioterror threat.
- The humanization approach resulted in a NHP dosing regimen for which the NHP SOL *f*AUC closely matched the human *f*AUC.
  - This method is designed to also allow the NHP free-drug concentration-time profile to resemble the typical human profiles.
  - It is important to note that the Cmax in NHP was not drastically different from that in humans (**Figure 2A).** In addition, the NHP troughs only dropped below the human trough during the last hour of each day, thereby avoiding long periods of low drug concentrations in the NHP and improving translatability.
- The simulated SOL *f*AUC for NHPs of weight 2.625 and 5.25 kg demonstrated acceptable (within 15%) *f*AUC deviations from the target. Therefore, the weight-based dosing regimen can be used for NHPs within this weight range.
- The results of the validation study demonstrated that both SOL concentration and cumulative total-drug AUC were well predicted by the NHP population PK model.
- The humanized SOL dosing regimens described herein will be considered for future IV studies in NHPs infected with *B. anthracis* or *F. tularensis*.

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