Paper #

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POPULATION PHARMACOKINETICS OF PAROMOMYCIN SULFATE IN INDIAN VISCERAL LEISHMANIASIS PATIENTS

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INTRODUCTION

Leishmaniasis is a vector-borne disease caused by over 20 different species of the Leishmania protozoan parasite. Leishmaniasis is endemic to 88 countries, 72 of which are developing countries, with an annual incidence of 1 to 2 million new cases and an overall prevalence of 12 million. Visceral leishmaniasis (VL) is the most severe form of the disease and constitutes a major public health problem in 8 countries of the world. VL accounts for approximately 500,000 of the new cases of all leishmaniases reported annually and is endemic to Bangladesh, Brazil, India, Nepal, and Sudan. In the Indian subcontinent, VL, also known as kala-azar or Black fever, is caused by the *Leishmania donovani* species of the parasite. In the visceral form, the *Leishmania* parasites are transmitted through the bite of phlebotomine sandflies.

Paromomycin is an established drug with an extensive and well characterized safety profile, in use for over 4 decades throughout the world as a broad-spectrum aminoglycoside antibiotic. Paromomycin was approved in India in 2006 as an alternative anti-protozoal therapy for VL to overcome the declining efficacy of antimonials & pentamidine, the teratogenic potential of miltefosine, the adverse safety profile of amphotericin B, and the high cost of liposomal amphotericin B.

METHODS

Treatment Protocol/Study Design

A multi-center, randomized, controlled, Phase III clinical trial was conducted by the Institute for OneWorld Health (iOWH) to compare the safety and efficacy of paromomycin against that of amphotericin B in Indian patients with VL as follows:

(a) intramuscular (IM) paromomycin sulfate at a daily dose of 15 mg/kg/day for 21 days (n= 500) or

(b) intravenous (IV) amphotericin B as a one-time test dose and then at a dose of 1 mg/kg every other day for a total of 15 doses over 30 days (n=166).

Pharmacokinetic samples (3 per patient) were collected from the patients in the paromomycin treatment group at pre-specified times on Days 1, 8, 15, 21, or 22 for purposes of population modeling.

Study Drug

Paromomycin Sulfate Injection (Pharmamed Parenterals, Ltd., Zejtun, Malta) was formulated as a solution containing 500 mg/mL. A salt correction factor (0.7554) was used to convert the paromomycin sulfate dose to paromomycin base.

Analytical Methods

Paromomycin concentrations in plasma were determined by a validated LC/MS/MS assay with a lower limit of quantitation of 0.5 ug/mL.

Data analysis

Traditional (statistical) PK analyses were performed using SAS, version 9.1. Population analyses were performed using NONMEM Version V Level 1.1 (Globomax, Ellicott City, MD) with ADVAN2 TRANS2 (one-compartment model) or ADVAN4 TRANS4 (two-compartment model) subroutines. S-PLUS 6.2 (Insightful Corp., Seattle, WA) was used for data set creation and generation of the figures.

PK

- 1333 plasma concentration values from 453 subjects.
- 295 male subjects (5-54 years of age, 12-68 kg) and 158 female subjects (5-50 years of age, 11-55 kg).
- Assay result below the limit of quantitation (BLQ) were taken as BLQ/2.

Population Model for IM paromomycin

- 938 plasma concentration values from 448 patients were used. Only data up to 10 hours post-dose were used.
- 291 male patients (5 to 54 years of age, 12 to 68 kg) and 157 female patients (5 to 50 years of age, 11 to 55 kg).
- BLQ values were disregarded.
- 1- and 2-compartment models with first order absorption and first order elimination were fit to the data.
- A hierarchical model was used to account for inter-individual and residual variability.
- Interindividual variability was modeled with an exponential model.
- Different residual variability models were tried.
- Height, weight, serum creatinine, age and pre-treatment parasite counts were explored as covariates.
- Covariate selection was performed using a forward-selection, stepwise backward elimination method.
- Model selection was based on a comparison of the objective function value and visual inspection of goodness of fit plots.
- Model validation was based on reasonable values and precision of parameter estimates and appropriate values of the mean and standard deviation of the weighted residuals.

RESULTS

PK

- The mean (SD) peak plasma concentrations at 1-hour post dose ranged from 20.5 µg/mL (7.01) on Day 1 to 18.3 µg/mL (8.86) on Day 21; and the concentrations at 24-hour post dose ranged from to 4.53 µg/mL (6.71) on Day 1 to 1.31 µg/mL (4.16) on Day 21 (Figure 1).
- Plasma concentrations on Days 1, 8, 15, 21, and 22 were similar, and there was no evidence of drug accumulation or induction of metabolism over the 21-day course of therapy.
- Day 21 mean peak (C_{max}) or trough (C_{trough}) plasma concentrations were similar in children less than 15 years of age vs. subjects aged 15 years and older and in male vs. female subjects (Table 1).

Figure 1: Mean (SD) Plasma Concentrations of Paromomycin on Days 1 and 21.

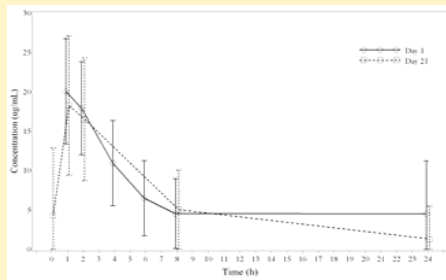


Table 1: Peak (C_{max}) and Trough (C_{trough}) Concentrations of Paromomycin in VL Patients on Day 21.

Group	Mean (±SD) C_{max} (µg/mL)[1]	p-value[2]	Mean (±SD) C_{trough} (µg/mL)[3]	p-value[2]
Male subjects	18.7±9.45 (N=43)	0.6028	1.41±4.32 (N=49)	0.7771
Female subjects	17.6±8.07 (N=31)		1.11±3.89 (N=24)	
Subjects 5 to 14 years	18.3±8.26 (N=28)	0.7312	1.40±4.12 (N=25)	0.9005
Subjects 15 to 29 years	17.0±8.63 (N=18)		1.01±3.81 (N=25)	
Subjects ≥30 years	19.1±9.75 (N=28)		1.55±4.71 (N=23)	

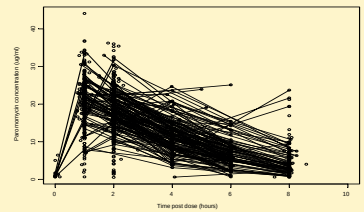
[1] At 1-hour post dose.
[2] General linear model for continuous data.
[3] At 24-hours post dose.

Population Model for Paromomycin

The population model was fit to the data shown in Figure 2.

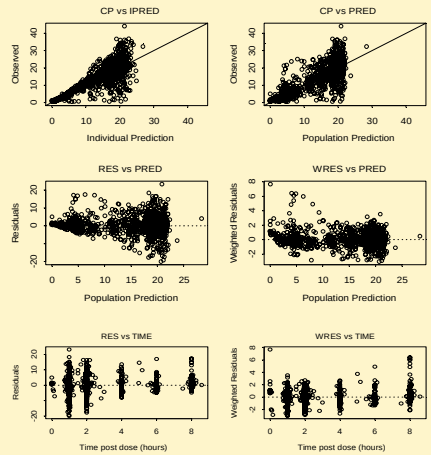
- 1-compartment model with first order absorption and first order elimination with no lag time for absorption was found to fit the data best.
- Interindividual variability on clearance (CL) was modeled with an exponential model.
- Residual variability was modeled with additive and proportional components.
- Weight was a statistically significant covariate for both CL and V.
- Sex was a statistically significant covariate for CL.
- Bayesian individualization was accomplished using the FOCE INTERACTION option.
- The estimates were compared to those obtained in 7 healthy adult volunteers who received a single 15 mg/kg IM dose of PS[1]. In both patients and healthy volunteers, the PK data following IM administration were described by a 1-compartment model with first-order absorption and first-order elimination.The parameter estimates for CL/F, V/F, Ka, Ke, and $t_{1/2}$ were comparable.

Figure 2: Data used for population modeling.



Observed concentrations are shown as circles, concentrations taken after the same dose are connected by lines.

Figure 3: Diagnostic plots for assessing the goodness-of-fit of the final model.



CP= observed concentration-time points; PRED= population predictions from the model; IPRE= individual predictions from the model; WRES= weighted residuals.
The upper left panel is a plot of the observed plasma concentrations of paromomycin (mg/L) *vs.* individual concentration predictions (IPRED) from the model. The line is the line of unity.
The upper right panel is a plot of observed plasma concentrations *vs.* population values predicted by the model (PRED).
The middle left panel is a plot of residuals (RES) *vs.* predictions (PRED). The dotted line indicates zero residuals.
The middle right panel similarly plots the weighted residuals (WRES) *vs.* PRED.
The lower left and right panels are plots of RES and WRES, respectively, *vs.* time.

Table 2. Population PK Parameters for Paromomycin.

Parameter	Population Mean		Inter-subject Variability	
	Estimate (95% confidence interval)	SE of the estimate (%CV)[a]	ETA estimate (%CV)[b]	SE of the estimate (%)[c]
Clearance, CL/F (L/h)	4.06 (3.82 to 4.30)	0.124 (3.05)	0.094 (30.7)	0.015 (39.3)
Volume of distribution, V/F (L)	15.3 (14.6 to 15.9)	0.347 (2.27)	-	-
Absorption rate constant, Ka (h^{-1})	2.11 (1.79 to 2.43)	0.162 (7.68)	-	-
Effect of weight on CL/F	0.383 (0.273 to 0.493)	0.056 (14.6)	-	-
Effect of weight on V/F	1.00 (0.924 to 1.08)	0.039 (3.90)	-	-
Effect of SEX on CL	-0.348 (-0.667 to -0.029)	0.163 (46.8)	-	-
Residual error[d] Proportional[e]	0.098 (0.083 to 0.112)	0.007 (7.59)	-	-
Additive ug/ml (SD)	0.400 (0.084 to 0.716)	0.161 (40.3)		
Elimination rate constant, Ke (h^{-1})[f]	0.265	-	-	-
Absorption half-life, $t_{1/2}$ (h)[g]	0.33	-	-	-
Elimination half-life, $t_{1/2}$ (h)[h]	2.62	-	-	-

[a] Percent coefficient of variation of the estimates (100×$SE_{estimate}$/estimate).
[b] Estimates of variability expressed as approximate percent coefficient of variation (%CV,).
[c] Percent square root of the relative standard error of the coefficient of variation().
[d] Residual intrasubject variability.
[e] Proportional component of residual variability is 31.2 (%CV).
[f] Computed as CL/V.; [g] Computed as 0.693/Ka; [h] Computed as 0.693/Ke.
Mean weight of patients was 38 kg.

SUMMARY

- The PK of paromomycin remained linear with time, and there was no evidence of drug accumulation or induction of metabolism over the 21-day course of therapy.
- The PK in VL patients was not influenced by age, gender, height, serum creatinine values, or disease severity, and was similar to the PK in healthy adult volunteers, demonstrating that the disease does not alter the pharmacokinetics of paromomycin, in particular its renal excretion.
- The clearance of paromomycin in patients with normal renal function increased 3.83% for each 10% increase in body weight (kg). The effect of SEX on CL/F was estimated with low precision (47%CV), and the difference is considered clinically minimal (~9%); therefore, dosage adjustment by gender is unnecessary.
- V/F was directly proportional to body weight, with a proportionality factor of 0.40 L/kg.

CONCLUSION

PS can be safely and effectively administered on a body weight (mg/kg) basis to male and female VL patients, who have normal renal function, without the need for therapeutic monitoring or dose adjustment. Children should receive the same mg/kg dose as adults.

REFERENCE

(1) T. P. Kanyok, A. Killian, K. Rodvold, L. Danziger. Pharmacokinetics of Intramuscularly Administered Aminosidine in Healthy Subjects. Antimicrob. Agents. Chemother. 41: 982-986, 1997.

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