Exploring variability in paromomycin pharmacokinetics in Eastern African visceral leishmaniasis patients

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Introduction

- There is a high need for new therapies for the neglected tropical parasitic disease visceral leishmaniasis (VL), as effective, safe and affordable treatments are still lacking.
- Paromomycin (PM) is effective in Eastern African VL patients and is deemed affordable and reasonably safe.
- Efficacy differences were observed between Eastern African VL patient populations for PM 15 mg/kg/day for 21 days, with notably worse efficacy in Sudan (14.3% and 46.7%) and better efficacy in Kenya (80.0%) and Ethiopia (75.0% and 96.6%).[1]

Objectives

- To characterize PM PK in VL patients and explore the observed variability in pharmacokinetics (PK).
- To identify and explain differences in PK between Eastern African patient populations.

Methods

PM PK data was available from a multi-centre randomized controlled trial (RCT) in VL patients from Kenya, Sudan, and Ethiopia.[2]

Treatment arms:

- Intramuscular PM monotherapy (20 mg/kg/day for 21 days)
- Intramuscular PM plus intravenous sodium stibogluconate (SSG) combination therapy (PM 15 mg/kg/day and SSG 20 mg/kg/day for 17 days)

- PK was sampled on the first and last day of treatment.
- A population pharmacokinetic (PK) model of PM was developed using NONMEM (v 7.3).
- Tested covariates included study site, country, treatment group (monotherapy or combination therapy with SSG), creatinine plasma levels, glomerular filtration rate (GFR), albumin plasma levels, and time after first dose.

Data & Results

Table 1. Data summary and patient characteristics

	Kenya	Sudan	Ethiopia	Total
n				
Subjects	16	16	42	74
Male/female	13/3	13/3	34/8	60/14
Observations	200	215	125	540
Observations BLQ	46	55	10	111
mean (range)				
Age (years)	23.1 (15–45)	25.4 (12–40)	19.9 (8–60)	21.8 (8–60)
Body weight (kg)	47.3 (37–56)	49.1 (34–73)	39.4 (15–62	43.2 (15–73)
Height (m)	1.67 (1.55–1.79)	1.64 (1.00–1.99)	1.55 (0.89–1.85)	1.0 (0.89–1.99)

Figure 1. Creatinine levels (Kenya and Ethiopia) and albumin levels (all patients)

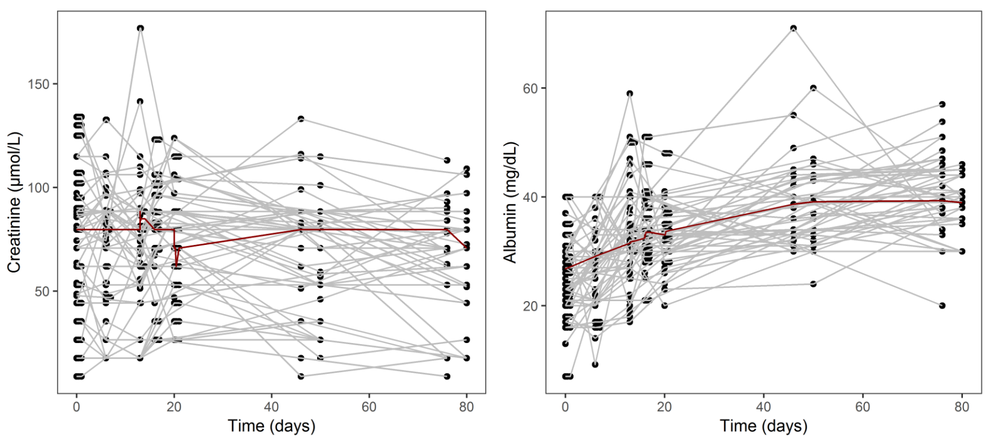
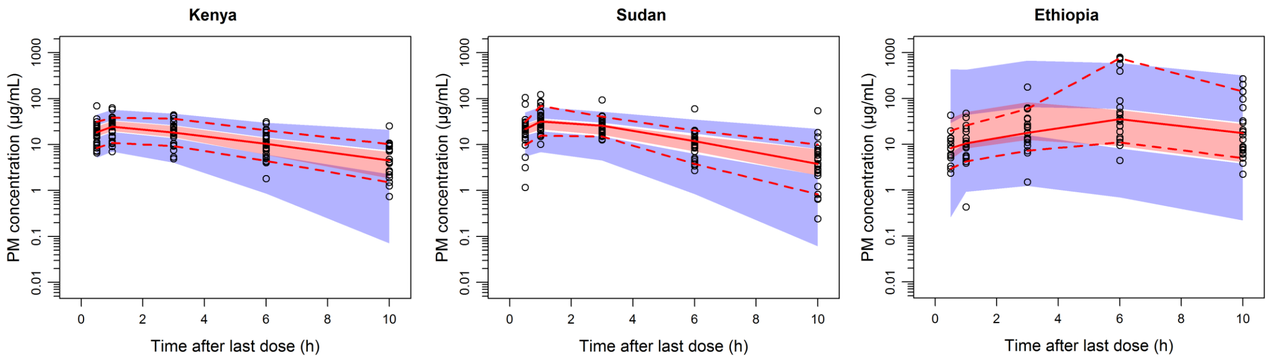


Figure 2. Visual predictive check stratified by country



- PM in plasma was best described by a one-compartment model with first-order absorption.
- Body weight was included on clearance and V_c, with fixed powers of 0.75 and 1.00, respectively.
- SSG co-medication did not affect the PK of PM.
- The deviating Ethiopian concentration-time profiles were best characterized by a 2.04 times higher bioavailability (F_{Eth}) and a 3.85 times slower k_a. An additional BSV for F_{Eth} described the overall higher variability in Ethiopian patients.
- Accordingly, estimated daily exposure in Ethiopian patients was on average 26% higher than in Sudanese/Kenyan patients.
- A decrease in clearance over time was identified, amounting to -33.2% between start and end of treatment (day 21). This effect could not be explained by either GFR, creatinin or albumin, even though patients showed an increase in albumin over time (figure 1).

Table 2. Parameter estimates in the final population PK model

Parameter	Value (CV)
CL (L/h)	3.97 (10%)
V_c (L)	15.1 (9%)
k_a (h^{-1})	1.71 (12%)
$\alpha_{Ethiopia}$ Ka	0.26 (18%)
F1	1 (fixed)
$\alpha_{Ethiopia}$ F1	2.04 (26%)
ɣ (time effect)	-0.0008 (27%)
BSV (CL)	45.7% (19%)
BSV (V_2)	32.6% (17%)
BSV ($F1_{Eth}$)	153.9% (14%)
Prop. res error (sd)	0.41 (5%)

$$k_a = 1.71h^{-1} * \alpha_{Ethiopia}$$

$$F1 = 1 * \alpha_{Ethiopia}$$

$$CL = CL_{pop} * \left(\left(\frac{BW}{BW_{med}}\right)^{0.75}\right)^{\gamma * time}$$

$$V_c = V_{c,pop} * \left(\frac{BW}{BW_{med}}\right)^{1.00}$$

Table 3. $AUC_{0\text{-}tau,SS}$ by treatment and country

Country	Dose	Med (sd) µg·h/mL	Dose	Med (sd) µg·h/mL
Kenya	15 mg/kg	180.5 (69.5)	20 mg/kg	204.1 (168.2)
Sudan		149.6 (24.6)		279.6 (351.5)
Ethiopia		227.6 (1754.4)		243.0 (1881.9)

Conclusions

For the first time paromomycin PK was characterized in VL patients:

- Differences in PK were found among Eastern African countries
- Exposure in Ethiopia was higher compared to Kenya and Sudan
- Slower absorption and higher bioavailability were identified in Ethiopian patients
- For all patients, a decrease in CL over time was identified, which could not be explained by any of the time-varying covariates

References

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2. Musa, A. *et al.* Sodium Stibogluconate (SSG) & Paromomycin Combination Compared to SSG for Visceral Leishmaniasis in East Africa: A Randomised Controlled Trial. PLoS Negl. Trop. Dis. 6, (2012).

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Disclosure

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