Optimal dosing of miltefosine in children and adults with leishmaniasis

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Introduction

Miltefosine is the first oral drug for the treatment of visceral leishmaniasis, a fatal neglected tropical parasitic disease. According to the WHO, approximately half of the morbidity and mortality due to leishmaniasis can be attributed to children from low income countries [1].

Currently, children with visceral leishmaniasis are treated with a dose linearly extrapolated from the daily 'mg/kg' adult dosage: 2.5 mg/kg/day for 28 days. In a large phase 4 trial in India, however, the **number of treatment failures was twice as high in the pediatric population** than in adults (≥12 years): 6.4% children versus 3.4 % adults failed to cure on miltefosine [2]. Moreover, very sparse PK data from India indicate that also miltefosine PK differ between adults and children: mean/median plasma levels in the last week of treatment are twice as high in adults compared to children receiving the same 2.5 mg/kg dose (70 µg/mL in adults versus 24 µg/mL in children) [3].

Dosing of miltefosine in children is, at the moment, neither rationally nor thoroughly experimentally derived. To reduce the paucity on pediatric PK studies on miltefosine, and to evaluate the appropriateness of **allometric scaling** of PK parameters [4], all previously obtained PK data of miltefosine were pooled from studies in Indian children and adults plus European adults.

Hypothesis: The current linear mg/kg miltefosine dosage is too low for children and a dose based on allometric scaling might result in a similar exposure to miltefosine between children and adults with leishmaniasis.

Methods

The **population PK analysis** was performed with non-linear mixed effects modeling using NONMEM VI, R 2.9.0, PsN 2.3.1, XPose 4.0 and Piraña 2.0 [5].

Pharmacokinetic data from **three different studies** were pooled and analyzed: one pediatric study ('**Pediatric Indian**', *n*=39) [6], and one adult study with relatively low body weights ('**Adult Indian**', *n*=40) [7], both performed in India, and one adult study with relatively high body weights ('**Adult European**', *n*=31) [8], performed in Europe. **Linear and allometric scaling** of CL and V by either total body weight (BW) or **fat-free mass** (FFM) [9] were evaluated as body size models and a population PK model was developed. Based on this developed PK model, **a dosing-formula for miltefosine** in children was proposed.

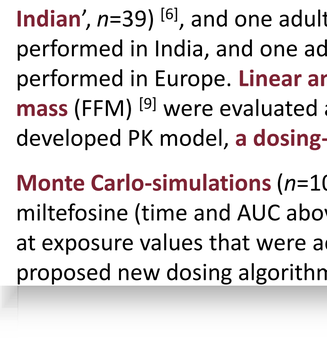
Monte Carlo-simulations (*n*=1000 per dose level) were performed with the developed PK model. Exposure to miltefosine (time and AUC above various thresholds) and the **probability of target attainment** (targets were set at exposure values that were achieved by 90% of the adults) after the currently used 2.5 mg/kg dose and the proposed new dosing algorithm were compared between Indian adults and children.

Demographics

	Pediatric Indian Study	Adult Indian Study	Adult European Study
Indication	VL	VL	CL
Ethnicity	Indian	Indian	Caucasian
Age (yr)	7 (3-11)	18.5 (12-50)	24 (19-49)
Height (cm)	108 (80-135)	152.5 (108-180)	184 (175-200)
Body weight (kg)	15 (9-23)	35.5 (16-58)	85 (70-113)
Fat free mass (kg)*	13.9 (8.58-22.6)	31.6 (15.4-49.3)	64.6 (52.9-81.2)
No. of PK measurements#	4 (4-4)	18 (16-19)	11 (8-19)

All values are median values (range) unless stated otherwise.
* Fat free mass was calculated by the formula of Janmahasatian et al.; # After start of treatment
CL, cutaneous leishmaniasis, VL, visceral leishmaniasis.

Model



A 2-compartment PK model with **fixed allometric scaling (0.75 for CL and 1.0 for V) by fat free mass** best fitted the pooled data:

PK Parameter	Estimate (RSE)	% BSV
Absorption rate (ka) (h-1)	0.39 (11.5%)	18.2%
Clearance (CL/F) (liters/day)	3.99 (3.5%)	32.1%
Volume of Central compartment (V2/F) (liters)	40.1 (4.5%)	34.2%
Intercompartmental clearance (Q/F) (liters/day)	0.0347 (18.3%)	NE
Volume of peripheral compartment (V3/F) (liters)	1.75 (8.2%)	NE
Residual variability – Indian Children (%)	54.5 (5.5%)	NE
Residual variability – Indian Adults (%)	34.3 (3.7%)	NE
Residual variability – European Adults (%)	34.8 (6.9%)	NE

*Figure 1. Final **PK-model** for miltefosine*

Acknowledgements

Pharmacokinetic and demographic data from the Pediatric Indian study [6] and the Adult Indian study [7] were kindly provided by Paladin Labs Inc (Quebec, Canada)

Comparison and evaluation of models

Model	ΔOFV	Relative BSV#	
		CL	V_2
1. No scaling	**0**	**100%**	**100%**
2. Linear scaling by WT	**32.5**	**163%**	**94%**
3. Linear scaling by FFM	**7.85**	**121%**	**72%**
4. Allometric scaling by WT	**-12.8***	**81%**	**73%**
5. Allometric scaling by FFM	**-31.4***	**68%**	**60%**

compared to the non-scaled model (Model 1).

Allometric scaling by fat-free mass reduced unexplained between-subject variability by 32% for CL and by 40% for V2.

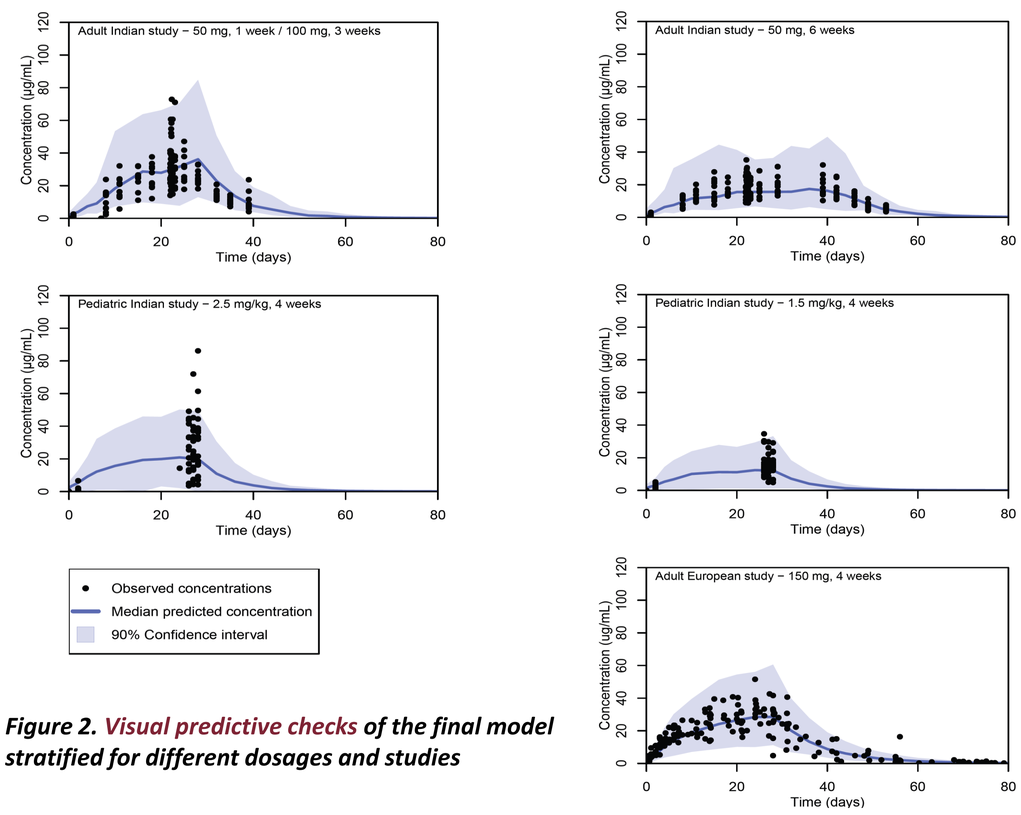


***Figure 2. Visual predictive checks** of the final model stratified for different dosages and studies*

Monte Carlo simulations

The following **dose**, based on a standard adult of 60 kg receiving 150 mg, was proposed to achieve similar exposure between children and adults:

$$Dose_{allometric} = 150\ \text{mg} \times \left(\frac{BW_{individual}}{60\ kg} \right)^{0.75}$$

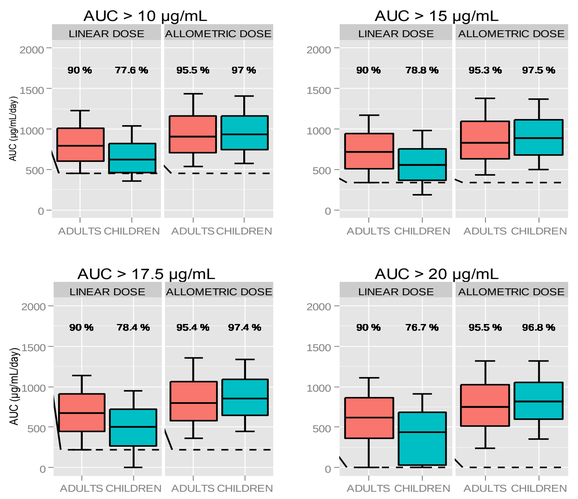


***Figure 3. Comparison of systemic exposure:** amount of AUC above various threshold values - linear vs allometric dose*

Simulated exposure to miltefosine was **similar between adults receiving 2.5 mg/kg (the current linear dose) and children receiving the new allometric dose.**

Only 74-78% of the children receiving the currently used linear dose of 2.5 mg/kg achieved a similar minimal systemic exposure as 90% of adults receiving 2.5 mg/kg or children receiving the allometric dose.

Conclusion & Discussion

- The currently applied linear dose of 2.5 mg/kg results in a **significantly lower exposure** to miltefosine in children compared to adults.
- An **allometric dose formula** is recommended, especially in children with leishmaniasis, resulting in **similar exposure to miltefosine between adults and children**. Whether this dosage is tolerable and improves clinical outcome in children should be investigated.
- More data are urgently needed on both PK and PD of miltefosine in leishmaniasis, certainly in children, to further improve the treatment of this fatal neglected disease.

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