Clinical pharmacology in leishmaniasis: treatment optimization of a neglected disease
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Citation for published version (APA):

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Optimal dosing of miltefosine in children and adults with visceral leishmaniasis

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*Antimicrobial Agents and Chemotherapy* 2012; 56: 2864-72

*Awarded the NVKFB TOP Publication Award 2012*
*Dutch Society for Clinical Pharmacology and Biopharmacy*
Abstract

Only anecdotal data are available on the pharmacokinetics (PK) of miltefosine in children suffering from visceral leishmaniasis (VL). While failure rates were higher in children with VL, steady-state concentrations appeared lower compared to adults. We hypothesized that the current linear mg/kg dosage is too low for children and that a new dosing algorithm based on an appropriate body size model will result in an optimal exposure. A population PK analysis was performed on three historic pooled datasets, including Indian children, Indian adults and European adults. Linear and allometric scaling of PK parameters by either body weight or fat-free mass (FFM) were evaluated as body size models. Based on the developed PK model, a dosing algorithm for miltefosine in children and adults was proposed and evaluated in silico. The population PK model employing allometric scaling fitted best to the pooled miltefosine data. Allometric scaling by FFM reduced between-subject variability: e.g. for drug clearance from 49.6% to 32.1%. A new allometric miltefosine dosing algorithm was proposed. Exposure to miltefosine was lower in children than adults receiving 2.5 mg/kg/day: a $C_{\text{max}}$ of 18.8 µg/mL was reached by 90% of adults and 66.7% of children. The allometric daily dose resulted in a similar exposure to miltefosine between adults and children. The use of a new allometric dosing algorithm for miltefosine in VL patients results in optimal exposure to miltefosine in both adults and children and might improve clinical outcome in children.
Introduction

Visceral leishmaniasis (VL) or kala-azar (black fever in Hindi) has been classified as one of the worlds “most neglected diseases” [1], and of all parasitic diseases it ranks third in terms of morbidity and mortality only after malaria and lymphatic filariasis [2]. The World Health Organization (WHO) reported in 2004 around 50,000 deaths and almost 2 million disability-adjusted life years due to leishmaniasis, of which approximately half can be attributed to children from low income-countries [2,3], but in reality the burden of leishmaniasis is probably much and much larger due to massive underreporting of both cases and deaths in the often remote areas where leishmaniasis is prevalent [4].

Miltefosine (hexadecylphosphocholine; marketed by Paladin Laboratories Inc. as Impavido®) is the newest addition to the small repertory of antileishmanial drugs and until date it is the only drug that can be administered orally. It has achieved relatively high cure rates in the treatment of visceral [5–9], New World cutaneous [10–14], Old World cutaneous [15,16] and even the difficult to treat mucocutaneous leishmaniasis [17,18].

During the development of miltefosine, two clinical trials were designed to investigate efficacy and safety of miltefosine in children (<12 years of age) in which a total of 119 pediatric patients was enrolled, employing dosages linearly extrapolated from the daily ‘mg/kg’ adult dosage [19,20]. The per-protocol cure rates obtained in these trials, however, tended to be lower than was previously observed in adult patients. In a more recent large phase IV trial conducted in India and Nepal, 358 children were treated with the same daily 2.5 mg/kg dose as the adults in that trial [5]. Most notably, a significant difference in efficacy was also observed in that trial between children and adults: almost twice as much children showed therapy failure on miltefosine compared to the adults in that trial (6.4% children versus 3.4 % adults), while receiving the same mg/kg dose [5].

A reasonable explanation for the observed lower efficacy in children might be relative underdosing in children. However, little is known about the clinical pharmacokinetics of miltefosine and even less is known about the pharmacokinetics in a pediatric population. The most extensive pharmacokinetic data, from adults, were previously published by our group, in which we observed that miltefosine kept accumulating until the end of treatment and had an extremely long terminal elimination half-life of about 31 days [21]. The sparsely published pharmacokinetic data that are available from the clinical trials on miltefosine performed in India indicated that pharmacokinetics differ remarkably between adults and children. The reported miltefosine plasma concentrations in the last week of treatment were considerably higher in adults (100 mg/day for 28 days) compared to children (2.5 mg/kg/day for 28 days): 70 µg/mL in adults (median value, day 23) versus 24 µg/mL.
in children (mean value, day 26-28) [22].

Dosing of miltefosine in children is, at the moment, neither rationally nor thoroughly experimentally derived. To reduce the paucity on pediatric population pharmacokinetic studies on miltefosine, we conducted a population pharmacokinetic modeling study on three existing pharmacokinetic datasets for children and adults from both the Indian subcontinent and Europe. Our objective was to identify and evaluate a new dosing algorithm which produces in children a profile of drug exposure similar to that observed in adults suffering from leishmaniasis as a first approach to establish a rational treatment design for miltefosine.

Methods

Patient populations and pharmacokinetic data

Pharmacokinetic data from three different studies and datasets were used: one pediatric study (‘Pediatric Indian’) [20] and one adult study (‘Adult Indian’) [6] with patients with relatively low body weights, both performed in India, and one adult study (‘Adult European’) [15,21] with patients with relatively high body weights, performed in Europe. In the Pediatric Indian study miltefosine was orally administered at dosages of either 1.5 or 2.5 mg/kg of body weight/day for a total of 28 days. Plasma samples were collected on day 2 and 26, 27 and 28 of treatment [20].

The Adult Indian study contained 4 dosing groups, who either received miltefosine orally in a dosage of 50 mg/day for 6 weeks, 50 mg/day for 1 week plus 3 weeks of 100 mg/day, 100 mg/day for 4 weeks, or 100 mg/day for 1 week plus 3 weeks of 150 mg/day, as reported previously. Plasma samples were taken pre-dose at various time points during and after treatment. On day 22 of treatment, samples were taken at 0, 2, 4, 6, 8, 12 and 24 h [6].

In the Adult European study miltefosine was orally administered at a dosage of 150 mg/day for a total of 28 days. Plasma samples were taken pre-dose at varying time points during and after end of treatment with a very long follow up [21].

Miltefosine concentrations were determined using validated bioanalytical methods employing liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). For the Pediatric Indian and Adult Indian studies, a validated quantitative method was used with a lower limit of quantitation (LLOQ) of 5 ng/mL, based on a previously reported method for the structural analog perifosine [23]. For the Adult European study, a previously reported validated quantitative method was used with a LLOQ of 4 ng/mL [24].
Population pharmacokinetic analysis

All calculations, simulations and estimations were performed on a dual-core desktop computer running NONMEM VI (level 2.0) [25], the R statistical software package (version 2.14; http://cran.r-project.org) [26], and Perl speaks NONMEM (PsN, version 2.3.1; http://psn.sourceforge.net) [27,28]. Pirana (version 2.4; an interface to NONMEM, PsN, and our cluster; http://www.pirana-software.com) was used for run deployment and analysis [29]. Xpose (version 4.0; http://xpose.sourceforge.net) [30], an R-based model building aid, was used for graphical model evaluation.

The first-order conditional estimation procedure with interaction between between-subject variability and residual error components was used throughout. The minimal value of the objective function (equal to minus twice the log likelihood) provided by NONMEM was used as a goodness-of-fit characteristic, in addition to comparisons of e.g. parameter values and standard errors of parameter estimates. Furthermore, performance of the models was assessed via goodness-of-fit plots using Xpose and Pirana.

**Structural model**

An open two-compartment model with first-order absorption and linear elimination from the central compartment has previously been developed on the Adult European dataset [21]. Absorption rate ($k_a$), clearance (elimination clearance [CL] and intercompartmental clearance [Q]), and volume of distribution (central [$V_2$] and peripheral volume of distribution [$V_3$]) were the primary pharmacokinetic parameters estimated. Secondary parameters, such as elimination half-life, were calculated from these primary parameters. Bioavailability ($F$) was unknown, and therefore, parameters were estimated relative to the bioavailability ($CL/F$, $V/F$, etc.).

Between-subject variability in the pharmacokinetic parameters was estimated with an exponential model. Residual variability was modeled with a proportional error model with separate estimates for each of the three different datasets (Pediatric Indian, Adult Indian, Adult European), since these datasets were obtained from three distinct clinical trials, with different populations and different analytical methods.

**Body size models and descriptors**

Several body size descriptors and body size models were considered to account for the effect of body size on the pharmacokinetics of miltefosine. Fat-free body mass (FFM) in kilograms was estimated from total body weight (WT) in kilograms, height (H) in meters and weight for height standard (WHS) in kg/m² as follows [31]:

$$FFM = WT - (H^2) \times WHS$$
\[ FFM = \text{WHS}_{\text{max}} \cdot H^2 \cdot \left( \frac{WT}{\text{WHS}_{50} \cdot H^2 \cdot WT} \right) \]  
(Eq. 1)

Where \( \text{WHS}_{\text{max}} \) is 42.92 or 37.99 kg/m² and \( \text{WHS}_{50} \) is 30.93 or 35.98 kg/m² for males or females, respectively [31].

To investigate the effect of size, different models were evaluated where parameters were either scaled linearly by WT (Eq. 2) or FFM (Eq. 3), or scaled allometrically by WT (Eq. 4) or FFM (Eq. 5). E.g. for drug clearance the following equations were used:

\[ CL/F_i = \theta_1 \cdot \left( \frac{WT_i}{WT_{\text{std}}} \right) \cdot \exp(\eta_i) \]  
(Eq. 2)

\[ CL/F_i = \theta_1 \cdot \left( \frac{FFM_i}{FFM_{\text{std}}} \right) \cdot \exp(\eta_i) \]  
(Eq. 3)

\[ CL/F_i = \theta_1 \cdot \left( \frac{WT_i^{\text{PWR}}}{WT_{\text{std}}^{\text{PWR}}} \right) \cdot \exp(\eta_i) \]  
(Eq. 4)

\[ CL/F_i = \theta_1 \cdot \left( \frac{FFM_i^{\text{PWR}}}{FFM_{\text{std}}^{\text{PWR}}} \right) \cdot \exp(\eta_i) \]  
(Eq. 5)

Where \( CL/F_i \) represents the clearance of the \( i \)th individual, \( \theta_1 \) is the typical value of clearance, \( \eta_i \) is the between-subject random effect with a mean of 0 and a variance of \( \omega^2 \), \( WT_i \) is the body weight of the \( i \)th individual and \( WT_{\text{std}} \) is a standard body weight (set at 60 kg), \( FFM_i \) is the calculated fat-free body mass (see Eq. 1) of the \( i \)th individual, \( FFM_{\text{std}} \) is a standard fat-free body mass (set at 53 kg) and \( \text{PWR} \) is the allometric power exponent. For clearance the allometric \( \text{PWR} \) value was fixed at 0.75 and for volume of distribution the value was fixed at 1.0, based on the biological principles that support these values [32–35].

The ability of the body size models to reduce the unexplained between-subject variability and to improve the goodness-of-fit of the model (\( \Delta \text{OFV} \), difference in objective function value) was assessed. A visual predictive check (VPC) was used to assess the predictive performance of the models [36].
Development and evaluation of a new dosing algorithm

Based on the body size model which best described and fitted the pharmacokinetic data, a maintenance dose algorithm was developed incorporating the most appropriate body size model and descriptor.

This new dosing algorithm was evaluated by simulating pharmacokinetic curves of pediatric patients ($n = 1000$ individuals) and adult patients ($n = 1000$ individuals) with the same anthropometric properties as the subjects in the original Pediatric Indian trial and the Adult Indian trial, respectively. Final typical pharmacokinetic parameter and covariance estimates from the previous population pharmacokinetic analysis were used in the simulations. Systemic drug exposure was compared between children and adults receiving the currently used 2.5 mg/kg/day dosage or a dose according to the here proposed dosing algorithm both for a total of 28 days. All body sizes were assigned randomly from a log-normal distribution taken from the original studies, dosages were calculated from the simulated body sizes and were rounded to the nearest 10 mg (the smallest commercially available capsule of miltefosine). The simulation, thus, was consistent with the process of dosing as it should occur at the bedside. Systemic exposure to miltefosine was assessed through prediction plots, while the miltefosine plasma concentration at the end of treatment ($C_{EOT}$) and area under the plasma concentration-time curve from zero to infinity ($AUC_{0\rightarrow EOT}$) were compared between children and adults and between the two dose regimens.

Results

Demographics

In Table 1 the characteristics of the patients in the three studies are summarized. See the Methods section (Patient populations and pharmacokinetic data) for references of the studies and an overview of the exact designations used hereafter to refer to each study.

Table 1 shows that both the adult and pediatric Indian patients were smaller and had a much lower relative fat mass than the adult European patients. The estimated fat-free mass to total body weight ratio was around 95% for the Indian children and around 90% for Indian adults, while for the European adults this value was around 75%. The Indian adult patients were also younger in age (minimal age of 12 years) compared to the European adult patients (Table 1).
Population pharmacokinetic analysis

The observed miltefosine plasma concentrations-versus-time data that were used in the population analysis are shown in Figure 1, stratified by the different dosing regimens in the three distinct clinical studies. Out of a total of 1196 observations, only one sample was below the LLOQ, which was ignored in the analysis.

The base model (Eq. 2) with linear scaling by WT could successfully be fitted to the pooled miltefosine pharmacokinetic data. The model with pharmacokinetic parameters scaled linearly by FFM (Eq. 3) performed better in terms of relative change in objective function value ($\Delta$OFV) and reduction of between-subject variability than the linear model scaled by WT (Eq. 2) (see Table 2). However, both allometrically scaled models (Eq. 4 and 5) did perform much better than both the linear models (Eq. 2 and 3): the allometric scaling reduced the between-subject variability of both clearance ($CL$) and central volume of distribution ($V_2$) compared to the linear models.

Table 1. Baseline characteristics of patients in three distinct clinical trials included in the population pharmacokinetic analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pediatric Indian ($n = 53$) [20]a</th>
<th>Adult Indian ($n = 26$) [6]a</th>
<th>Adult European ($n = 17$) [21]a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>VL</td>
<td>VL</td>
<td>CL</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Indian</td>
<td>Indian</td>
<td>Caucasian</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>7 (3-11)</td>
<td>18.5 (12-50)</td>
<td>24 (19-49)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>108 (80-135)</td>
<td>152.5 (108-180)</td>
<td>184 (175-200)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>15 (9-23)</td>
<td>35.5 (16-58)</td>
<td>85 (70-113)</td>
</tr>
<tr>
<td>Fat-free mass (kg)b</td>
<td>13.9 (8.58-22.6)</td>
<td>31.6 (15.4-49.3)</td>
<td>64.6 (52.9-81.2)</td>
</tr>
<tr>
<td>Body mass index (kg m⁻²)</td>
<td>12.8 (9.57-15.7)</td>
<td>15.2 (11.0-23.2)</td>
<td>25.1 (20.0-28.8)</td>
</tr>
<tr>
<td>No. of PK measurementsc</td>
<td>4 (4-4)</td>
<td>18 (16-19)</td>
<td>11 (8-19)</td>
</tr>
</tbody>
</table>

*a All values are median values (range) unless stated otherwise.

*b Fat-free mass was calculated by the formula of Janmahasatian et al. [31].

Table 2. Comparison of the performance of miltefosine population pharmacokinetic models: differences in objective function values and relative between-subject variabilities.

<table>
<thead>
<tr>
<th>Model</th>
<th>Corresponding equation</th>
<th>$\Delta$OFVb</th>
<th>% BSV [relative % change]b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>CL/F</td>
</tr>
<tr>
<td>1. Linear scaling by WT</td>
<td>(Eq. 2)</td>
<td>0</td>
<td>49.6 [0%]</td>
</tr>
<tr>
<td>2. Linear scaling by FFM</td>
<td>(Eq. 3)</td>
<td>-22.7</td>
<td>42.8 [-13.8%]</td>
</tr>
<tr>
<td>3. Allometric scaling by WT</td>
<td>(Eq. 4)</td>
<td>-42.0</td>
<td>35.1 [-29.3%]</td>
</tr>
<tr>
<td>4. Allometric scaling by FFM</td>
<td>(Eq. 5)</td>
<td>-63.9</td>
<td>32.1 [-35.3%]</td>
</tr>
</tbody>
</table>

*a $\Delta$OFV, difference in objective function value, was calculated as [(OFV Model) - (OFV Model 1)], where model 1 was used as the base model. A negative $\Delta$OFV indicates a better fit of the model.

*b The between-subject variability (BSV) was calculated using the between-subject variance ($\omega^2$). BSV values from the base model (Model 1) were used as reference values to calculate the % change between the models of the respective parameters.
Figure 1. Visual predictive checks for the population pharmacokinetic model employing allometric scaling based on fat-free mass. The dots represent the observed concentrations; the black line indicates the median observed concentration and the dotted lines show the 5th and 95th percentiles of the observations (indicating the 90% observation interval). The dark gray line indicates the median predicted concentration from 1000 simulated individuals and the gray area shows the 90% prediction interval of the model predicted values. The plots are stratified for each different dosing regimen that was used in the respective clinical trials (Adult Indian study: 4 regimens, plot A-D; Pediatric Indian study: 2 regimens, plot E and F; Adult European study: 1 regimen, plot G).
and had a better goodness-of-fit to the data (the OFV decreased by 31.4). Allometric scaling by FFM reduced the between-subject variability by 35.3% for CL (from 49.6% to 32.1%, Table 2) and by 40% for \( V_2 \) (from 42.7% to 34.1%, Table 2), thereby adding explanatory power to the model. When estimated, the allometric power exponent for CL yielded a value of 0.667, with the value for \( V_2 \) fixed to 1. However, in comparison to using a fixed value for CL of 0.75, there was only a very slight decrease in both OFV (-1.2 ΔOFV) and between-subject variabilities of CL (29.4% vs 32.1%) and \( V_2 \) (33.2% vs 34.1%) and thus little improvement of model fit. Given the body of knowledge on the biological principles behind the allometric power exponents, the fixed values of 0.75 for CL and 1 for \( V_2 \) were therefore preferred in the final model.

Conventional goodness-of-fit plots (observed versus individual and model predicted concentrations, conditional weighted residuals versus time and model predicted concentrations) did not show any obvious trends, indicating that the model fit was adequate (plots not shown).

Figure 1 shows the VPC of the final model with allometric scaling by FFM plotted over the observed values. The VPC indicated a sufficiently predictive performance of the two-compartment model for the two dosing regimens in the Pediatric Indian study, the four regimens in the Adult Indian study and the single regimen in the Adult European study. Table 3 shows the final parameter estimates of the model with allometric scaling by FFM.

Residual variability was estimated separately for the three different studies and appeared to be higher in the Pediatric Indian study (54.5%) than in both Adult studies (34.3% and 34.8% for the Adult Indian and European study, respectively), which is also illustrated by the variability of observed values depicted in Figure 1. The individual parameter estimates were used to calculate the elimination half-lives for the pediatric Indian population, the adult Indian population and the adult

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**Table 3.** Final parameter estimates from the population PK model with allometric scaling by fat-free mass.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (RSE [%])</th>
<th>% Between-subject variability (RSE [%])&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption rate ((k_a)) (h&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.416 (11.5)</td>
<td>18.2 (115.5)</td>
</tr>
<tr>
<td>Clearance ((CL/F)) (liters/day/53 kg FFM)</td>
<td>3.99 (3.5)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>32.1 (18.4)</td>
</tr>
<tr>
<td>Volume of Central compartment ((V_2/F)) (liters/53 kg FFM)</td>
<td>40.1 (4.5)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>34.1 (27.3)</td>
</tr>
<tr>
<td>Intercompartmental clearance ((Q/F)) (liters/day)</td>
<td>0.0347 (18.3)</td>
<td>NE</td>
</tr>
<tr>
<td>Volume of peripheral compartment ((V_3/F)) (liters)</td>
<td>1.75 (8.2)</td>
<td>NE</td>
</tr>
<tr>
<td>Residual variability Pediatric Indian Study (%)</td>
<td>54.5 (5.5)</td>
<td>NE</td>
</tr>
<tr>
<td>Residual variability Adult Indian Study (%)</td>
<td>34.3 (3.7)</td>
<td>NE</td>
</tr>
<tr>
<td>Residual variability Adult European Study (%)</td>
<td>34.8 (6.9)</td>
<td>NE</td>
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</table>

<sup>a</sup> FFM, fat-free mass  
<sup>b</sup> NE, not estimated  
<sup>c</sup> Estimates are given for a standard person with a fat-free mass of 53 kg
European population. The typical initial elimination half-lives were estimated to be 4.99, 5.86 and 7.18 days, for the Pediatric Indian, Adult Indian and Adult European study respectively, while the typical terminal elimination half-life was similar for all three study populations and was estimated at 35.5 days.

Development and evaluation of a new dose algorithm

The final population pharmacokinetic model with allometric scaling by FFM which best fitted the data was used to perform Monte Carlo simulations. Following from this, an allometric maintenance dose was adapted from the adult ‘standard’ dose resulting in the following allometric dose algorithm:

\[
Dose_{\text{allometric}} = Dose_{\text{std}} \cdot \left( \frac{FFM_i}{FFM_{\text{std}}} \right)^{PWR}
\]  

(Eq. 6)

Where, standard FFM is set at 53 kg and the standard dose is 150 mg, which is the maximal tolerable daily dose in adults. This allometric dose algorithm was transformed to a dosing table (Table 4) according to body weight and height and resulting FFM according Eq. 1. The dose was rounded to the nearest 10 mg, based on the smallest available miltefosine capsules.

Pharmacokinetic curves were simulated of: (i) 1000 Indian adults receiving 2.5 mg/kg/day of miltefosine, (ii) 1000 Indian children receiving 2.5 mg/kg/day, (iii) 1000 Indian adults receiving a new allometric dose (Table 4), and (iv) 1000 Indian children receiving the new allometric dose (Table 4); all with the same mean and variance of body weights as the subjects in the respective original trials included in the population pharmacokinetic analysis but with their own estimates of between-subject variability. The prediction intervals and predicted median concentrations resulting from these simulations (Figure 2) clearly demonstrate the discrepancy in exposure between children and adults when administrated a similar linear mg/kg dose (2.5 mg/kg/day). Consistent with the results from the population pharmacokinetic analysis, the mg/kg dose led to underexpose to miltefosine in children compared to adults as both median values and 90% prediction interval boundaries were lower in children. Conversely, the proposed allometric dose led to a comparable miltefosine exposure in children and adults (Figure 2). This is corroborated by the relative probability of reaching a minimal miltefosine exposure. An AUC_{\text{0-EOT}} value of 412 µg/mL/day or higher is achieved by 90% of adults receiving 2.5 mg/kg/day, while only 71.4% of children on this dose reach this level of exposure (Figure 3). In contrast, 95.6% and 97.3% of the adults and children, respectively, receiving the here proposed allometric dose reach this minimal target-value of exposure (Figure 3). Comparison of the miltefosine C_{\text{EOT}} shows similar results (Figure 3). When administrated the linear mg/kg dose, only 66.7% of children reached the C_{\text{EOT}} that is reached by 90%
of adults (18.8 µg/mL), while the allometric dose led to comparable proportions of both children and adults reaching this concentration (95.7% and 96.6%, respectively, above the target concentration).

**Figure 2.** Comparison of miltefosine exposure in children and adults: predicted miltefosine concentrations following different dosage regimens. In the left plot are shown the predicted miltefosine concentration-time curves and intervals for the currently recommended linear 2.5 mg/kg/day miltefosine dose for 28 days, while in the right plot these are shown for the here proposed allometric daily miltefosine dose for 28 days. The areas show the 90% prediction intervals (90% PI, 5th and 95th percentiles) for adults (in blue) and children (in red), the lines indicate the median predicted concentrations for adults and children.

**Figure 3.** Comparison of miltefosine exposure in children and adults: predicted concentration at the end of treatment and the area under the plasma concentration-time curve. These boxplots represent distributions of the central miltefosine exposure following from Monte Carlo simulations of 1000 adults (in blue) and 1000 children (in red) receiving either the linear miltefosine dose (2.5 mg/kg/day) or the here proposed allometric daily miltefosine dose (Table 4, Eq. 6). In plot A is depicted the concentration at the end of treatment (C\text{\text{EO}}), while in plot B is shown the area under the concentration-time curve from start to end of treatment (AUC\text{\text{EO}}). The pharmacokinetic target to be attained was the minimal adult exposure set at the value that was attained by 90% of the adults receiving the linear dose (indicated by the dashed line); the percentages above the boxplots show the proportion of individuals reaching this target.
### Table 4A. Daily allometric miltefosine dose for males based on fat-free mass

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<th>Weight (kg)</th>
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*The total daily dose is calculated with Eq. 6 and rounded to the nearest 10 mg (smallest available capsule)

To reduce the risk on gastrointestinal side effects upon intake, daily doses are best divided into three and given with an 8h interval.

150 mg is currently considered to be the maximal tolerable dose that can be administered on a daily basis to a patient.

### Table 4B. Daily allometric miltefosine dose for females based on fat-free mass

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Discussion

The presented population pharmacokinetic model for miltefosine adequately predicts miltefosine exposure in Indian children, Indian adults and European adults. The differences in body dimensions between these highly heterogeneous populations were high, with respective median body weights of 15, 35.5 and 85 kg. The differences in pharmacokinetics could best be explained with allometric scaling by FFM. This body size descriptor was found to be the best related to drug clearance and volume of distribution. Following from this a new dose algorithm was developed resulting in similar systemic exposure to miltefosine between Indian children and Indian adults.

The treatment of VL patients has improved over the past years, as the international scientific attention has increased and several not-for-profit organizations have made it their priority to develop new chemical entities, drugs and combination treatments for this fatal neglected disease [37–40]. Unfortunately, the currently available drugs for VL featured several lacunas during their development, which may in part be due to the difficulty of performing clinical trials in the resource-limited settings where VL is present. For instance, for miltefosine, the pharmacokinetic studies during the clinical development were inadequate and remained largely unpublished. Although significant deviations in drug accumulation were detected between children and adults, no further research was done on dosage requirements and pharmacokinetic-pharmacodynamic relationships in children [20,22]. The first pediatric studies with miltefosine, however, already indicated differences in efficacy between children and adults. These pediatric trials employed dosages linearly extrapolated from the ‘mg/kg’ adult dose. In the phase I/II dose-finding study 21 patients were treated with 1.5 mg/kg/day and 18 patients with 2.5 mg/kg/day of miltefosine for a total of 28 days. The per-protocol cure rates in both treatment groups were lower than was previously observed in adult patients receiving 2.5 mg/kg/day (90% and 88%, respectively, versus 97%) [6,9,19,20]. This difference in efficacy was confirmed in a large phase IV trial, where compared to adults twice as much children failed to cure while receiving an equal 2.5 mg/kg dose [5]. The mg/kg dosing of miltefosine can be regarded as biologically inappropriate scaling over a wider range of body weights as it apparently does not result in a similar efficacy and a similar systemic exposure to miltefosine [41].

It is scientifically widely accepted that the relationship between size and metabolic functions (such as drug clearance) in organisms can appropriately be scaled by an allometric power model [35,42,43]. Such allometric models have widely been used to investigate and explain the effect of size on the pharmacokinetics of a variety of compounds, including analgesics and antimicrobial agents [33,34,44–47], and imply that the metabolism of these drugs is not linearly related to changes in size.
Notwithstanding that the value of the allometric power exponent remains a point of discussion [48], in this study a fixed value of 0.75 for clearance and 1 for volume of distribution was chosen based on the biological principles that support these values [33,35,42]. Moreover, estimating the allometric power exponent for clearance of miltefosine improved only marginally the performance of the model. In this study we showed that allometric scaling of clearance and central volume of distribution resulted also for miltefosine in adequate fit of a population pharmacokinetic model to data from pediatric and adult patients with very diverse body weights.

During model development we have considered as well the application of allometric scaling of the peripheral volume of distribution and intercompartmental clearance, however, we have chosen not to incorporate this due to the peculiar distribution of miltefosine. Miltefosine is amphipathic and structurally similar to membrane lipids. Incorporation of miltefosine in cell membranes has been demonstrated in vitro [49–51] and would explain the extremely slow uptake and release from the (small) peripheral compartment. Therefore, we expect that a relationship between these peripheral distribution parameters and measures of body size is unlikely and not well supported. When applied in our PK model, allometric scaling resulted in a small and probably not very relevant decrease in goodness-of-fit. More importantly, the results of the simulation study were not altered (data not shown). Ultimately, we have chosen not to incorporate allometric scaling for these distribution parameters.

Not only total body weight was very different between the Indian children, Indian adults and European adults included in our analysis, but also the relative contribution of fat to WT. Allometric scaling by FFM reduced the interindividual differences in clearance more than allometric scaling by WT (Table 2). Fat contributes only little to the metabolic capacity of the body and thus FFM might be the best descriptor for size in allometric models, certainly when there is a high variability in leanness between patients [33]. On the other hand, miltefosine is a relatively lipophilic compound and at least in rats there is to a small degree distribution of miltefosine in fat tissue [52]. Nevertheless, allometric scaling by FFM reduced also between-subject variability of the central volume of distribution more than any other scaling method (Table 2), also when e.g. clearance was scaled by FFM and volume of distribution by WT (data not shown). Another alternative approach to assess the influence of the relative contribution of fat to body size on the pharmacokinetic parameters would be the estimation of normal fat mass (NFM) per individual parameter (P) as body size descriptor, using a parameter-specific fat-factor \((F_{fat, p})\) which accounts for different contributions of fat mass, as described previously by Anderson and Holford [53]:

\[
NFM_p = FFM + F_{fat, p} \cdot (WT - FFM)
\]

(Eq. 7)

In this particular study, \(F_{fat}\) was estimated to be 0 for each parameter (data not shown) and thus FFM alone was the most appropriate body size descriptor. However, in
other cases the use of NFM would allow for a continuous parameter to distinguish between body size models based on FFM and WT.

The currently recommended mg/kg dose resulted in a substantially lower miltefosine exposure in children compared to adults, while on the other hand the allometric dose led to a similar minimal miltefosine exposure in both patient groups. The probability of attaining a similar minimal exposure in children as in adults with the here proposed allometric dose was evaluated making use of Monte Carlo pharmacokinetic simulations. Monte Carlo pharmacokinetic simulations are a useful approach for the identification of pharmacokinetic-pharmacodynamic breakpoints of e.g. antibiotics [54–60], however, the minimum inhibitory concentration (MIC) values used for antibiotics are difficult to establish for *Leishmania* parasites because of their intracellular nature and the difficulty of drug sensitivity testing [61,62]. Intracellular concentrations, within the macrophages, to which the *Leishmania* parasites are exposed in these *in vitro* experiments have never been reported, which should deserve more attention in future experiments. In this study, only miltefosine regimens for monotherapy were evaluated and compared. Nevertheless, also for combination therapies that include miltefosine relative underexposure to miltefosine of children compared to adults can be expected when miltefosine is similarly dosed on an mg/kg basis.

The allometric dosage algorithm that we advise on results in a higher absolute daily dose in children or adults with very low body weights than the currently advised 2.5 mg/kg dosage. An easy-to-use table to be used in clinical practice following from the proposed allometric miltefosine dosing algorithm is presented in Table 4. For the lowest weight category (9-12 kg) this would result in a 1.7 to 1.5 times higher daily absolute amount of miltefosine compared to the current 2.5 mg/kg dose. Main side-effects of miltefosine are mild to moderate vomiting and diarrhea which are related to a direct effect of miltefosine on the gastrointestinal tract upon administration of the miltefosine dose, instead of a systemic effect of the drug. However, to minimize the risk of gastrointestinal side-effects we suggest dividing the dose as much as possible over the day, while the current 2.5 mg/kg dosage is often administered as a single daily dose. Intake of (fatty) food concurrently with the administration of the miltefosine dose also minimizes the gastrointestinal side-effects during miltefosine administration and is therefore recommended [63]. Systemic toxic effects of miltefosine are most notably reversible hepatotoxicity and, to a lesser degree, nephrotoxicity [5]. These drug effects are related to the systemic drug exposure and thus are not thought to differ between lower and higher weight categories using the allometric dosing algorithm since drug exposure in both categories is similar, as shown in this study. On the contrary, hepato- and nephrotoxicity seem to be lower in pediatric patients: e.g. in a large phase 4 trial reversible elevation of creatinine was seen in ~20% of the adults (including severe cases with CTC-3 increases), while this was observed in only ~10% of the children in the trial (no severe cases) [5]. This
observation is in line with the hypothesis and outcome of our study that the systemic exposure to miltefosine is lower in children than in adults given the similar 2.5 mg/kg daily dosage. It is therefore important to investigate whether this presented optimal allometric dosage of miltefosine improves clinical outcome in children with VL, similar to that of adult patients. This trial will also reveal whether the higher absolute dose from our allometric dosing algorithm will lead to toxicities in the lower body weight categories and whether these toxicities limit the applicability of this dosing algorithm.

In conclusion, the currently applied dose of 2.5 mg/kg/day results in a substantially lower exposure to miltefosine in children than in adults. We recommend the use of an allometric dosing table for miltefosine in VL patients, which results in a similar exposure to miltefosine between adults and children and might improve clinical outcome in children. An easy-to-use table is available for implementation of this dose in the clinic. More data are urgently needed on the pharmacokinetics of miltefosine in VL, specifically in children, to better define the role and dosing of miltefosine in (combination) therapy regimens and further improve the treatment of this fatal neglected disease.

**Acknowledgements**

We thank Paladin Labs Inc. (Montreal, Canada) for making the pharmacokinetic data from the Adult Indian and Pediatric Indian studies available to us for the specific purpose of this study.
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