INTRODUCTION

Leishmaniasis is a vector-borne disease caused by over 20 different species of the Leishmania protozoon 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 leishmaniasis 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 amphotericin 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 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, and 22, or 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, Eliott City, MD) with ADVAN2/TRAN2 (one-compartment model) or ADVAN4/TRAN4 (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.

RESULTS

Table 1: Peak (C_max) and Trough (C_min) Concentrations of Paromomycin in VL Patients on Day 21.

<table>
<thead>
<tr>
<th>Group</th>
<th>C_max Value (ng/mL)</th>
<th>C_min Value (ng/mL)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male subjects</td>
<td>18.18±5.96</td>
<td>0.62±1.24</td>
<td>8.6424</td>
</tr>
<tr>
<td>Female subjects</td>
<td>19.74±7.11</td>
<td>0.58±1.37</td>
<td>7.7711</td>
</tr>
<tr>
<td>Subjects &lt;5 years</td>
<td>34.10±12.26</td>
<td>0.70±1.40</td>
<td>0.0012</td>
</tr>
<tr>
<td>Subjects 5 to 9 years</td>
<td>18.18±5.96</td>
<td>0.62±1.24</td>
<td>8.6424</td>
</tr>
<tr>
<td>Subjects 10 to 15 years</td>
<td>18.18±5.96</td>
<td>0.62±1.24</td>
<td>8.6424</td>
</tr>
<tr>
<td>Subjects &gt;15 years</td>
<td>18.18±5.96</td>
<td>0.62±1.24</td>
<td>8.6424</td>
</tr>
</tbody>
</table>

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.
• Different residual variability models were tried.
• Covariate selection was performed using a forward-selection, stepwise backward elimination method.

Parameter Estimate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SE of the ETA estimate (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance</td>
<td>CL (L/h)</td>
<td>0.383 (2.81)</td>
<td>(0.348 to 0.416)</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>V (L)</td>
<td>4.06 (2.37)</td>
<td>(3.50 to 4.64)</td>
</tr>
<tr>
<td>Residual error</td>
<td>sd</td>
<td>0.039 (3.05)</td>
<td>(0.033 to 0.047)</td>
</tr>
<tr>
<td>Proportionality</td>
<td>lambda</td>
<td>0.163 (7.59)</td>
<td>(0.114 to 0.212)</td>
</tr>
<tr>
<td>Absorption half-life</td>
<td>t1/2</td>
<td>1.41±4.32</td>
<td>(0.773 to 2.05)</td>
</tr>
</tbody>
</table>

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, offering an easy creation of age groups on severity, and was similar to the PK in healthy adult volunteers, demonstrating that the disease does not alter the pharmacokinetics of paromomycin, in particular renal excretion.
• The clearance of paromomycin in patients with normal renal function increased 3.83% for each 10% increase in body weight on Day 21, whereas it was similar to that in healthy adult volunteers, demonstrating that the disease does not alter the pharmacokinetics of paromomycin, in particular renal excretion.
• 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


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