Combined suboptimal schedules of topical paromomycin, meglumine antimoniate and miltefosine to treat experimental infection caused by Leishmania (Viannia) braziliensis

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Introduction
Leishmaniasis is one of the ten global communicable diseases given priority by the WHO. The infection, depending on the Leishmania species, may lead to different clinical diseases in humans, which are grouped as visceral leishmaniasis (VL) or tegumentary leishmaniasis (TL), which in turn comprises cutaneous leishmaniasis (CL) and mucosal leishmaniasis (ML). In the Americas, TL is mainly caused by the species Leishmania (Viannia) braziliensis, Leishmania (Leishmania) amazonensis and Leishmania (Viannia) guyanensis. The clinical form most commonly associated with infection by these species is CL, which is characterized by skin lesions on exposed areas of the body such as the face, arms and legs. Moreover, infection caused by species of the subgenus Viannia can progress to the late mucosal form, when the mucosae of the superio gastrointestinal and respiratory tracts (ML) are involved.¹

Pentavalent antimonials are largely used as first-line drugs for the treatment of CL, even after the availability of new drugs and therapeutic schemes for VL. However, their use is limited by the need for daily parenteral administration, severe side effects and treatment failures.² The development of alternative therapies, including the identification of formulations for both the oral and topical treatment of CL as well as drug combinations, continues to be urgently needed.

Paromomycin is the most widely studied drug for the topical treatment of CL caused by different species.³,⁴ An alternative paromomycin topical gel formulation, with optimal skin permeation, was shown to be effective against L. (L.) major, L. (L.) amazonensis and L. (V.) braziliensis in animal models.⁵–⁷

Miltefosine (Impavido®) was the first oral drug to be registered, in India, for the treatment of VL.⁸–¹⁰ Its efficacy for the treatment of CL has also been reported in experimental models and clinical studies.¹¹,¹² however, monotherapy with miltefosine showed variable cure rates (49%–88%) in clinical trials for the treatment of leishmaniasis where infection by L. (V.) braziliensis is frequent.¹³–¹⁷

Previous studies have shown that combination of topical paromomycin gel and oral miltefosine provided an enhanced efficacy...
in the treatment of *L. (L.) amazonensis*- and *L. (L.) major*-infected mice. Combination therapy represents an alternative strategy for the treatment of CL that offers advantages over monotherapy, such as preventing the emergence of resistance, increasing efficacy and shortening the treatment course. The possibility of using reduced doses offers the additional advantages of lowering costs, but chiefly, reducing adverse side effects.

Therefore, the purpose of this study was to compare the efficacy of the binary combination of suboptimal doses of miltefosine, meglumine antimoniate and topical paromomycin gel with the efficacy of each of these drugs as monotherapy, to treat animals infected with *L. (V.) braziliensis*, an epidemiologically relevant species causing CL in the New World.

**Materials and methods**

**Reagents and drugs**

Paromomycin sulphate (75.7 µg/mg; Olon—Antibióticos, Milan, Italy), hydroxyethylcellulose (HEC; Natrosol 250 HR, Aqualon), methylparaben (MP) and propylene glycol (PG; BASF, Ludwigshafen, Germany) were used to prepare the hydrophilic gel. Miltefosine powder was donated by Zentaris (Frankfurt, Germany). Meglumine antimoniate (Glucantine®-Sanofi-Aventis—300 mg/mL, 81 mg/mL Sb+5; Suzano, São Paulo, Brazil) was provided by the Leishmaniasis Control Program of the Brazilian Ministry of Health.

**Preparation of formulations**

The hydrophilic gel was prepared by heating 1.5% HEC, 10% PG and 0.2% MP in water to 60–70°C, under constant agitation, until a homogeneous and transparent gel had been obtained. After cooling, the paromomycin sulphate, previously dissolved in water, was incorporated into the gel to obtain a 10% concentration. Subsequently, the mixture was agitated until a homogeneous preparation was obtained. Stock solution of miltefosine (20 mg/mL) was dissolved in distilled water. Dilutions from the stock solutions were made in distilled water. Glucantine® was dissolved in water for injection and administered intramuscularly.

**Parasites and infection of animals**

Isolates of *L. (V.) braziliensis* strain WHO-MHOM/BR/75/M2903 were used throughout the study. The strain was maintained by successive passages in golden hamsters (*Mesocricetus auratus*) and amastigotes were harvested from skin lesions of infected animals. The fragments were excised, macerated in saline solution and quantified in a Neubauer® chamber. Male hamsters weighing 100–110 g were infected with *L. (V.) braziliensis* amastigotes by subcutaneous injections at the base of the tail after shaving (Pocket Pro®, Wahl Home Products).

**Miltefosine and meglumine antimoniate monotherapy dose—effect study**

For the definition of the appropriate low doses of miltefosine and meglumine antimoniate to be used in the combination treatment and to establish the efficacy of a range of doses of these drugs, dose–effect studies were performed. Following the development of ulcerated and well-established lesions, the hamsters were divided into five groups (*n*= 3 for miltefosine and *n*= 5 for meglumine antimoniate) according to lesion size, to assure statistically similar mean lesion size among the treated groups. Miltefosine was administered by oral gavage (~0.2 mL considering the differences in body weight) at 5, 10 or 25 mg/kg/day on 10 alternate days for 20 days. Meglumine antimoniate was administered by intramuscular injection with 150 µL of a solution containing 20, 50, 100 or 200 mg of Sb+5/kg/day, for 20 consecutive days. The control group received saline via the same routes as the treatment groups. Animals receiving miltefosine were maintained with an abstinence from food for 3 h pre- and 1 h post-treatment. Treatment efficacy was evaluated by measuring the size of the lesions with calipers weekly during treatment and for 3 days (miltefosine) or 8 days (meglumine antimoniate) following completion of treatment. Parasites in the spleen were quantified 3 or 8 days following completion of treatment with miltefosine (all doses) and meglumine antimoniate (50 mg Sb+5/kg/day), respectively.

**Efficacy of the binary drug combinations**

Upon the development of ulcerated lesions, the hamsters were divided into seven groups composed of five animals according to the following treatment schedule: Group 1, untreated (control group); Group 2, once-daily application of topical paromomycin gel; Group 3, miltefosine; Group 4, meglumine antimoniate; Group 5, topical paromomycin gel and meglumine antimoniate; Group 6, topical paromomycin gel and miltefosine; and Group 7, miltefosine and meglumine antimoniate. Meglumine antimoniate and miltefosine were administered at low doses and topical paromomycin once daily when used as monotherapy or combination therapy. The different drug regimens were used: for the topical paromomycin gel administration, cutaneous lesions were covered with 100 µL of a 10% paromomycin gel that was applied with a semi-solid pipette once daily for 20 days; miltefosine was administered by oral gavage an alternate day for 20 consecutive days; and meglumine antimoniate was injected intramuscularly for 20 consecutive days.

**Lesion size and indicators of toxicity**

During and following treatment, the lesions with the largest diameter were measured weekly using digital calipers. For the dose–effect study of meglumine antimoniate, the lesions were observed for an additional 12 day period following completion of treatment. Additional evaluations, through careful observation of the base of the tails, included the appearance of nodules and metastasis in other locations on the animals’ skin. Toxicity of treatment was evaluated by determining the weight of the animals at the beginning, during and at the end of treatment. Other signs such as piloerection and number of deaths were observed as indicators of systemic toxicity. The complete healing of lesions and absence of nodules was defined as the cure criterion. The partial clinical efficacy was defined as the reduction in lesion size after the end of treatment (day 24) compared with the lesion size at the first day of treatment.

**Parasite quantification**

For the limiting dilution assay, at 3 days after the end of treatment, animals were euthanized in a CO2 chamber and the cutaneous lesions and spleens were removed. The cutaneous tissues and spleens were weighed and homogenized with an Ultra-Turrax homogenizer (IKA, Germany) in Schneider’s medium containing 100 IU/mL penicillin and 100 µg/mL streptomycin solution. Next, the tissues were centrifuged at 1620 *g* (lesion) or 45 *g* (spleen) for 2 min for removal of cell debris. The supernatants were separated and centrifuged at 1700 *g* for 15 min (lesion) or 1620 *g* for 2 min (spleen) for parasite sedimentation. The pellets were resuspended in 1 mL of Schneider’s medium containing 20% FBS, penicillin (100 IU/mL) and streptomycin (100 µg/mL). Dilutions were performed in triplicate (1:10) in successive 96-well sterile cultivation plates and incubated at 26°C for 7 days. Each well was examined using an inversion microscope for the presence of parasites and the parasite load was determined from the highest dilution at which growth was observed.
Statistical analysis

The data were processed using GraphPad Prism 4 software. To compare the parasite loads, weights of animals and lesion sizes among the groups, one-way analysis of variance followed by Tukey’s test was applied. The difference was considered significant when the P value was <0.05. The parasite load data were transformed into log10+1 and assessed for normality using the Kolmogorov-Smirnov test.

Animal research ethical aspects

Animals were handled according to local and federal regulations and the research protocols were approved by the Fiocruz Committee on Animal Research (protocol P-0321/06; licence L-0024/8). The research adhered to the Brazilian Guidelines for Care and Utilization of Animals from the Conselho Nacional de Controle e Experimentação Animal.

Results

Dose–effect studies of intramuscular meglumine antimoniate and oral miltefosine

Hamsters infected with an amastigote suspension of L. (V.) braziliensis were treated with different doses of meglumine antimoniate (20, 50, 100 and 200 mg Sb+5/kg/day) or miltefosine (5, 10 and 25 mg/kg/day). As shown in Figure 1(a), a typical dose–response curve was observed, with lesion size decreasing as the dose of intramuscular meglumine antimoniate increased. The lesions of animals treated with the highest doses of meglumine antimoniate diminished progressively until complete healing, which was observed at 14 and 21 days after the start of therapy for the doses of 200 and 100 mg Sb+5/kg/day, respectively (P<0.05). The differences between these two doses were not significant (P>0.05). For animals treated with meglumine antimoniate at 50 mg Sb+5/kg/day, a significant reduction in lesion size, compared with the control group, was observed 14 days after initiation of treatment, but complete healing was not reached for this group. In contrast, animals treated with meglumine antimoniate at 20 mg Sb+5/kg/day did not show a significant decrease in lesion size, which suggested this dose was ineffective. The number of viable parasites in the group of animals treated with 50 mg Sb+5/kg/day meglumine antimoniate was statistically lower compared with the number of parasites in the control group in lesions (Figure 1b) and spleen (Figure 1c) (P<0.05), but this treatment regimen did not result in complete clearance of parasites. Based on these findings, the dose of 50 mg Sb+5/kg/day meglumine antimoniate was selected for the combination assays, as this dose led to a significant reduction in lesion size after the 14th day of treatment and a reduction in the number of parasites in the lesion and spleen, but did not promote complete healing of the lesion or clearing of parasites.

Figure 1. Meglumine antimoniate monotherapy dose–effect study. Evaluation of the activity of meglumine antimoniate (Gluconatime®) (Glu) in male golden hamsters infected with L. (V.) braziliensis. Animals (n=5) were treated via intramuscular injection with different doses of meglumine antimoniate for 20 consecutive days. (a) Vertical bars represent the standard deviation of lesion size (greater diameter) for each group. (b and c) Horizontal bars represent the average number of viable parasites in the lesion (b) or spleen (c) for control and meglumine antimoniate at 50 mg Sb+5/kg/day. For lesion size, significant differences were observed for meglumine antimoniate (100 and 200 mg Sb+5/kg/day) on the 14th day after initiation of treatment (P<0.05) compared with the control group. The number of viable parasites in the group of animals treated with 50 mg Sb+5/kg/day meglumine antimoniate was significantly lower than the number of parasites in the control group (P<0.05) for both lesion and spleen. *P<0.05 versus the control.
The animals treated with oral miltefosine did not present a significant reduction in lesion size during the period of evaluation (P > 0.05) (Figure 2a), thus the monitoring of lesions was determined 3 days after the end of treatment to avoid unnecessary discomfort for the animals. The viable parasites in the lesion and spleen were the parameter used to select the dose of miltefosine for further combination studies. Parasites in the lesion and spleen were assessed 3 days following completion of treatment, as shown in Figure 2 (b and c). The viable parasites in the site of infection (lesion) were not reduced in animals treated with miltefosine at 5, 10 or 25 mg/kg/day and there was no significant reduction in the parasite burden in comparison with the control group (P > 0.05) (Figure 2b). However, statistical analysis showed a significant reduction in parasite number in the spleens of animals treated with miltefosine at 25 mg/kg/day when compared with the control group (P < 0.05) (Figure 2c). This dose was selected for the combination schemes.

**Efficacy of the combinations**

The efficacies of the combinations of a single daily application of topical paromomycin gel with miltefosine at 25 mg/kg/day or meglumine antimoniate (Glucantime®) at 50 mg Sb\(^{15}\)/kg/day for the treatment of *L. (V.) braziliensis*-infected hamsters were investigated. The efficacy of the combination of the two systemic drugs, miltefosine at 25 mg/kg/day and meglumine at 50 mg Sb\(^{15}\)/kg/day, was also evaluated. Figure 3 shows the lesion size at the beginning and 3 days after the end of treatment. The lesion sizes of animals treated with monotherapy regimens were slightly reduced during the evaluation period, but the differences when compared with the control group were not significant (P > 0.05). The average lesion size (mm) and standard deviation at the beginning and 3 days following completion of treatment were, respectively: control, 14.0 \(\pm\) 4.3 and 17.1 \(\pm\) 4.5; meglumine antimoniate at 50 mg Sb\(^{15}\)/kg/day, 13.6 \(\pm\) 5.7 and 10.1 \(\pm\) 2.8; miltefosine at 25 mg/kg/day, 10.6 \(\pm\) 5.1 and 13.7 \(\pm\) 3.3; paromomycin gel at 10%, 12.9 \(\pm\) 2.7 and 14.8 \(\pm\) 4.5 (Figure 3). In contrast, the lesion sizes of animals treated with combination regimens were significantly reduced during the evaluation period. The average lesion size (mm) and standard deviation at the beginning and 3 days following completion of treatment for animals treated with combination regimens were, respectively: paromomycin gel combined with meglumine antimoniate, 11.5 \(\pm\) 4.4 and 0.9 \(\pm\) 1.9; paromomycin gel combined with miltefosine, 12.6 \(\pm\) 2.5 and 3.7 \(\pm\) 4.6; and meglumine antimoniate combined with miltefosine, 11.3 \(\pm\) 5.4 and 5.6 \(\pm\) 2.1 (Figure 3). Only the treatment with paromomycin gel combined with meglumine antimoniate (Glucantime®) resulted in a significant lesion size reduction compared with all of the monotherapy regimens (P < 0.05). Table 1 shows the percentage clinical efficacy of monotherapy and combination treatments for animals infected with *L. (V.) braziliensis*.
Drug combinations for cutaneous leishmaniasis

Figure 3. Monitoring the size of the lesion in response to treatments. Evaluation of treatment efficacy (lesion size) for combinations of meglumine antimoniate at 50 mg Sb⁵/kg/day with a 10% paromomycin gel (Glu + PA), oral miltefosine at 25 mg/kg/day with a 10% paromomycin gel (Milt + PA) or meglumine antimoniate at 50 mg Sb⁵/kg/day with oral miltefosine at 25 mg/kg/day (Glu + Milt) compared with the untreated group (control). Male golden hamsters (n = 5) were infected with L. (V.) braziliensis amastigotes in the base of the tail and treated for 20 days. Vertical bars represent the standard deviation of lesion size (greater diameter) for each group. Comparisons between the monotherapy regimens and the control group were not statistically significant (P > 0.05). For comparisons between the combination regimens and the control group, significant differences were observed 3 days after the end of treatment for all combinations (P < 0.05). The differences between the meglumine antimoniate and paromomycin combination and all monotherapy regimens were significant (P < 0.05).

Table 1. Clinical efficacy of monotherapy and combination treatments in animals infected with L. (V.) braziliensis

<table>
<thead>
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<th>Treatment</th>
<th>Clinical efficacy reduction in lesion size (%)</th>
<th>complete healing of the lesion (%)</th>
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<tr>
<td>Paromomycin gel</td>
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<td>0</td>
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<tr>
<td>Miltefosine</td>
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<td>0</td>
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<tr>
<td>Meglumine antimoniate (Glucantime®)</td>
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<td>50.0</td>
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<td>80.0</td>
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<tr>
<td>miltefosine</td>
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<td></td>
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<tr>
<td>Control</td>
<td>0</td>
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*Calculated as the percentage of the reduction in lesion size 3 days after the end of treatment (day 24) compared with the lesion size before treatment (day 1).

The viable parasites in the lesions were assessed 3 days after the end of treatment, as depicted in Figure 4(a). The viable parasites in the site of infection (lesions) were significantly reduced (P < 0.05) in animals treated with each of the three combination schemes compared with the control group. Monotherapy regimens with a low dose of miltefosine or a suboptimal use of paromomycin gel did not reduce the levels of viable parasites in comparison with the control group (P > 0.05); only meglumine antimoniate (Glucantime®) at 50 mg Sb⁵/kg/day showed a significant difference (P < 0.05). All of the combinations that employed the topical treatment (paromomycin gel) as one of the drugs resulted in a larger reduction in the number of viable parasites in lesions compared with the monotherapy regimens (P < 0.05). However, the combination treatment that used both systemically administered drugs [miltefosine and meglumine antimoniate (Glucantime®)] did not result in a smaller number of viable parasites in the skin lesions compared with the monotherapy regimen using meglumine antimoniate (Glucantime®) at 50 mg Sb⁵/kg/day (P > 0.05) (Figure 4a).

To investigate the systemic effect of the combination treatments, the viable parasites in the spleen were evaluated. The number of viable parasites in the spleen was significantly reduced (P < 0.05) in animals treated with the combinations when compared with the control group (Figure 4b). In monotherapy regimens, only meglumine antimoniate (Glucantime®) at 50 mg Sb⁵/kg/day showed a significant reduction in the number of viable parasites in comparison with the control group (P < 0.05). All combinations showed reduced numbers of residual viable parasites in the spleen compared with topical paromomycin gel and oral miltefosine as monotherapy (P < 0.05). This difference was not observed with meglumine antimoniate (Glucantime®) at 50 mg Sb⁵/kg/day as monotherapy (P > 0.05).

At the end of treatment, compared with time zero, the animals did not present a significant loss of body weight (P > 0.05) for all groups. Other indicators of systemic toxicity were also absent.

Discussion

In the present study, topical paromomycin was selected as one modality of treatment for the combination schemes. The combination using two routes of administration (topical and systemic) has advantages over the combination of two systemically administered drugs for CL treatment, such as fewer side effects, lower cost and one of the drugs is administered directly at the site of infection, which increases its local concentration. In fact, CL often develops into an ulcer with the loss of epidermis, the principal barrier to skin penetration of drugs; this favours the percutaneous absorption of paromomycin. In the hydrophilic gel, paromomycin is dissolved, allowing its prompt release and penetration across the skin. Since there are no previous reports on dose–effect studies of pentavalent antimonials and/or oral miltefosine for L. (V.) braziliensis in animal models, the first step of this study was to evaluate their efficacy in experimentally infected hamsters through a dose–effect analysis.

Hamsters (M. auratus) are susceptible to dermotropic Leishmania (Vianna) species, developing skin lesions that are very similar to the ulcers observed in humans. The development of infection with L. (V.) braziliensis in hamsters is not limited to skin lesions, but also includes the spleen and lymphoid organs. The doses of 100 or 200 mg Sb⁵/kg/day meglumine antimoniate led to complete healing of the lesions and the dose of 50 mg Sb⁵/kg/day practically kept the size of the lesion stable throughout the study period. Aiming for the evaluation of a reduced therapeutic dose of meglumine antimoniate (Glucantime®) for the combination studies, the suboptimal dose of 50 mg Sb⁵/kg/day was selected. None of...
the dosages of miltefosine (5, 10 and 25 mg/kg/day) led to healing and the highest dose (25 mg/kg/day) was selected. Animals treated with miltefosine at the dose of 50 mg/kg/day showed signs of toxicity with a significant loss of body weight.18 A previous study conducted with paromomycin for the topical treatment of hamsters infected with \( L. (V.) \) braziliensis showed the efficacy of using paromomycin twice daily; therefore, in this study a once-daily dose was selected.5

One issue about topical treatment as monotherapy for CL in the New World concerns its safety due to the risk of persistence of disseminated parasites. In fact, the risk of persistence of parasites cannot be ruled out even after systemic therapy, as suggested by the risk of late development of mucosal lesions after systemic treatment. Clinical trials with long follow-up periods are needed to clarify this issue. Data concerning dose–effect studies of oral miltefosine revealed a clear relationship between

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**Figure 4.** Parasite load of the lesion and spleen in response to treatment. In vivo efficacy of the combinations of meglumine antimoniate (50 mg Sb\(^{3+}\)/kg/day) with once daily administration of 10% paromomycin gel (Glu+PA), oral miltefosine (25 mg/kg/day) with 10% paromomycin gel (Milt+PA) and meglumine antimoniate (50 mg Sb\(^{3+}\)/kg/day) with oral miltefosine (25 mg/kg/day) (Glu+Milt) compared with the monotherapy regimens and the control group (untreated). Male golden hamsters \((n=5)\) were infected with \( L. (V.) \) braziliensis amastigotes in the base of the tail and treated for 20 days. Three days after the interruption of treatment, the parasite loads recovered from the lesions and spleen were evaluated by limiting dilution assay. Horizontal bars represent the mean viable parasites in the lesion (a) or spleen (b). (a) A significant difference was observed for all combinations and for monotherapy with 50 mg Sb\(^{3+}\)/kg/day compared with the control group \((P<0.05)\). All of the combinations with paromomycin gel topical treatment showed a higher efficacy when compared with the monotherapy regimens \((P<0.05)\). The combination using two systemically administered drugs (miltefosine and meglumine antimoniate) was not significantly different from the efficacy of monotherapy with 50 mg Sb\(^{3+}\)/kg/day meglumine antimoniate \((Glucantime\textsuperscript{w})\) \((P>0.05)\). (b) A significant difference was observed for all combinations and the control group \((P<0.05)\). Among the monotherapy regimens, only meglumine antimoniate at 50 mg Sb\(^{3+}\)/kg/day showed a significant difference in comparison with the control group \((P<0.05)\). All combinations showed a higher efficacy compared with once daily administration of topical 10% paromomycin gel monotherapy and oral miltefosine monotherapy \((P>0.05)\). There was no significant difference between the groups treated with all combinations and with meglumine antimoniate \((Glucantime\textsuperscript{w})\) monotherapy \((P>0.05)\). \(^*P<0.05\) versus the control; \(^#P<0.05\) versus monotherapy; \(^\times P<0.05\) versus paromomycin or miltefosine as monotherapy.
the drug dose and parasite number within the spleen, but this was not observed at the site of infection (lesion). In this case, only a dose of 25 mg/kg/day showed a significant reduction in the parasite number within the spleen and, based on these findings, this dose was selected for the studies involving combination treatments. The higher activity of miltefosine in the spleen, compared with skin, might be explained by a favourable distribution of the compound in the reticuloendothelial system.33

Miltefosine or meglumine antimoniate (Glucantime®) and topical paromomycin combinations showed high efficacy in infected hamsters, resulting in statistically significant reductions in lesion size and parasite burden in lesions and spleens as compared with the control group. When comparing parasite burdens in lesions and lesion sizes of animals treated with combined and monotherapy regimens, significant differences were only observed for the two combination treatments that included topical paromomycin.

In this study, treatment with topical paromomycin alone, only once daily, was not effective in reducing lesion size. Previous studies evaluating the same formulation in animals that were experimentally infected with L. (L.) amazonensis or L. (V.) braziliensis showed a significant reduction in lesion size when animals were treated twice daily, suggesting that the optimum dosing is at least twice daily.5,6,19 In the present study, potentiation of the suboptimal application of topical paromomycin once daily was obtained by combination with low doses of pentavalent antimonial or miltefosine, which significantly reduced lesion sizes in animals infected with L. (V.) braziliensis.

The combination of oral miltefosine and subcutaneous paromomycin was ineffective against L. (L.) donovani in a mouse model of VL.24 Synergism between paromomycin and meglumine antimoniate was previously observed in murine macrophages infected with L. (V.) braziliensis.25

In this study, the improved systemic efficacy of the topical paromomycin plus miltefosine combination may well be attributable to the effects of both drugs, since enhanced percutaneous absorption of paromomycin after topical application was observed in previous studies.18 Studies were also performed using pig ear skin, a more relevant model for human skin. Paromomycin permeation across intact pig skin was low, regardless of the formulation tested (gel and ointment). In contrast, paromomycin permeation across dermal membranes from hydrophilic gel was higher than that observed for other formulations.5

Soto et al.26 evaluated the efficacy of combining the topical formulation 15% paromomycin sulphate/12% methylbenzethonium chloride (MBCL) ointment (10 days) and a short course (7 days) of parenteral meglumine antimoniate as treatment of American CL caused by L. braziliensis panamensis. Initial cure was defined as complete healing of all lesions by the end of therapy or by the 1.5 month follow-up.26 Local reactions such as inflammation after the application of topical formulation paromomycin/MBCL were described and may increase the time for complete healing of the lesions.27,28 These reactions are related to the presence of MBCL.

In summary, our data show that combinations of suboptimal topical paromomycin administration with a low dose of oral miltefosine or intramuscular meglumine antimoniate (Glucantime®) present higher activity than observed for monotherapy regimens for L. (V.) braziliensis species. Furthermore, the reduction in the effective dose for systemic treatment may diminish the incidence of side effects and the cost of treatment. These results suggest that the combination of a systemic treatment (miltefosine or meglumine antimoniate) with a topical treatment (paromomycin) may be an alternative to increase drug efficacy in the treatment of CL caused by L. (V.) braziliensis.

References

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Transparency declarations
None to declare.


