Is paromomycin an effective and safe treatment against cutaneous leishmaniasis? A meta-analysis of 14 randomized controlled trials

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CRD summary
This well-conducted review concluded that topical paromomycin was effective only when combined with methylbenzethonium chloride for cutaneous leishmaniasis. It was as effective as intrallesional pentavalent antimony compounds in Old World leishmaniasis, but inferior to parenteral pentavalent antimony compounds in New World leishmaniasis. In light of the small number and methodological limitations of the included studies, the authors' caution is justified.

Authors' objectives
To evaluate the safety and efficacy of paromomycin compared to placebo or pentavalent antimony compounds (SbV) in the treatment of cutaneous leishmaniasis.

Searching
PubMed, Scopus and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to August 2007 for articles in any language. Search terms were reported. The search was expanded through use of the Related Articles function in PubMed and a manual search of the bibliography of retrieved articles.

Study selection
Randomised controlled trials (RCT) that compared paromomycin to placebo or pentavalent antimony compounds in patients with cutaneous leishmaniasis were eligible for inclusion if they reported clinical or safety outcomes. The primary outcome was clinical cure, defined as complete healing, disappearance or reepithelialization of all lesions. Secondary outcomes were clinical improvement and local or systemic side effects.

Included studies were of topical paromomycin, parental paromomycin, topical paromomycin with methylbenzethonium chloride, topical paromomycin with methylbenzethonium chloride and parental meglumine antimoniate. Comparison groups were placebo, meglumine antimoniate or sodium stibogluconate. Where reported, mean duration of lesion ranged from 15 to 105 days. Duration of treatment ranged from 10 to 45 days. Duration of follow-up ranged from 27 to 455 days. The species of parasite that caused the cutaneous leishmaniasis were *Leishmania major* (Old World cutaneous leishmaniasis), *L. braziliensis*, *L. panamensis* and *L. chagasi* (New World cutaneous leishmaniasis). Where reported, average age of patients ranged from 5.5 years to 24 years. The proportion of males ranged from 41% to 100%. The studies were conducted in the Middle East, North Africa and Central and South America.

Two reviewers independently selected the studies for review; disagreements were resolved by consensus.

Assessment of study quality
The methodological quality of the included studies was assessed according to double-blinding, concealment of treatment allocation, blinding of outcome assessment and use of intention-to-treat analysis. Where insufficient information was provided, quality was assumed to be inadequate. Two reviewers independently assessed study quality and disagreements were resolved by consensus.

Data extraction
The number of events in each group for each outcome were extracted and used to calculate relative risks (RR) with 95% confidence intervals (CI). Two reviewers independently extracted data; any disagreements were resolved by consensus.

Methods of synthesis
Pooled RRs with 95% CI were calculated using the inverse-variance weighted random-effects model according to intention-to-treat principles. Studies were analyzed separately according to whether paromomycin was compared to
placebo or pentavalent antimony compounds. Heterogeneity was assessed using the $X^2$ and $I^2$ statistics. Potential sources of heterogeneity were investigated by meta-regression analysis. A sensitivity analysis was conducted with each trial excluded in turn. Publication bias was assessed using Begg's test and Egger's test.

**Results of the review**

Fourteen RCTs (<1,200 patients) were included for the review. One RCT was a cross-over design (39 patients). Seven RCTs were double-blinded; two were double-blinded only to topical treatment. Six trials adequately concealed treatment allocation. Five trials blinded outcome assessment. Five trials used intention-to-treat analysis. There was no evidence of publication bias using Egger's or Begg's tests.

Any paromomyocin regime significantly increased the likelihood of clinical cure compared to placebo (RR 1.49, 95% CI 1.04 to 2.13, $p=0.031$; eight RCTs; 730 patients). There was evidence of significant statistical heterogeneity ($p=0.002$); meta-regression analyses revealed that type of paromomyocin regimen was the main source of heterogeneity ($p=0.024$).

Paromomyocin significantly improved the chances of clinical cure in New World cutaneous leishmaniasis (RR 2.34, 95% CI 1.48 to 3.71, $p<0.001$; two RCTs; 129 patients) but not Old World cutaneous leishmaniasis when compared to placebo.

Paromomyocin significantly improved the chances of clinical cure when combined with methylbenzethonium chloride (RR 2.58, 95% CI 1.76 to 3.76, $p<0.001$; three RCTs; 198 patients) but not when used alone compared to placebo.

Any paromomyocin regimen was significantly less likely than pentavalent antimony compounds to result in clinical cure (RR 0.77, 95% CI 0.59 to 0.99, $p=0.043$; six RCTs; 491 patients). There was evidence of significant statistical heterogeneity ($p=0.007$).

Topical paromomyocin was significantly less effective than parenteral meglumine antimoniate (RR 0.67, 95% CI 0.54 to 0.82, $p<0.001$; two RCTs; 270 patients) but not significantly different from parenteral pentavalent antimony compounds in the treatment of New World cutaneous leishmaniasis. There were no significant differences between paromomyocin and intralesional meglumine antimoniate in the treatment of Old World cutaneous leishmaniasis.

The authors reported that similar results were observed for the outcome of clinical improvement, but did not present the results. The authors reported that local side effects were more common with topical treatments and that systemic side effects were more common with parenteral treatment.

**Authors’ conclusions**

Topical paromomyocin was only effective when combined with methylbenzethonium chloride, but this also increased the likelihood of local reactions. Topical paromomyocin was as effective as intralesional pentavalent antimony compounds in Old World cutaneous leishmaniasis, but inferior to parenteral pentavalent antimony compounds in New World cutaneous leishmaniasis. The findings should be interpreted with caution due to the small number and varying quality of the included studies.

**CRD commentary**

The review addressed a clear question with well-defined inclusion criteria. Three relevant databases were searched for articles in any language, thereby the risk of language bias was minimised. No search appeared to have been carried out for unpublished data, but publication bias was assessed and no evidence of it was found. Appropriate steps were taken in the review process to minimise the risk of reviewer error and bias.

The methodological quality of included studies was assessed. The decision to combine the studies in a meta-analysis was appropriate. However, it was unclear whether necessary steps were taken to include a study with a cross-over design and this may have influenced the reliability of the results.

This was a generally well-conducted review. In light of the small number and methodological limitations of the available studies, the authors’ caution is justified.

**Implications of the review for practice and research**
**Practice:** The authors stated that the evidence did not support use of topical paromomycin in the treatment of New World cutaneous leishmaniasis, but topical paromomycin combined with methylbenzethonium chloride could be a viable therapeutic alternative in the treatment of Old World cutaneous leishmaniasis where there was a low risk of mucocutaneous involvement.

**Research:** The authors stated that future research into topical paromomycin in the treatment of Old World cutaneous leishmaniasis should evaluate the efficacy in species of parasites not included in the current review, compare topical paromomycin alone with topical paromomycin plus methylbenzethonium chloride, evaluate topical paromomycin combined with different concentrations of methylbenzethonium chloride and focus on the development of new formulations.

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