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A comparative study between the efficacy of systemic meglumine antimoniate therapy with standard or low dose plus oral omeprazole in the treatment of cutaneous leishmaniasis

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Abstract

Background & objectives: Pentavalent antimony compounds are the first line of drugs in the treatment of cutaneous leishmaniasis. However, because of their potential toxic effects, many investigations are performed to find an effective and safe treatment for cutaneous leishmaniasis patients. Our objective in this investigation was to compare the effect of oral omeprazole and low dose systemic meglumine antimoniate (MA) and standard dose of systemic MA in the treatment of cutaneous leishmaniasis.

Methods: This was a randomized double-blinded clinical trial. In 150 patients with cutaneous leishmaniasis who were randomly divided into three groups and were treated with: (i) MA 60 mg/kg/day/IM and oral placebo for three weeks; (ii) MA 30 mg/kg/day/IM and oral omeprazole 40 mg/day for three weeks; and (iii) MA 30 mg/kg/day/IM and oral placebo for three weeks. All the patients were visited every two weeks from the beginning of the trial up to six weeks and then at 8 and 12 weeks. The effectiveness of the treatment was classified in three levels as complete response, partial response and no response. Data were analyzed by SPSS 10 using KI square, Mann-Whitney, Kaplan-Mayer and ANOVA tests.

Results: Rate of complete response for three months (12 weeks) after starting the treatments was 93% for the group treated with standard dose of glucantime and placebo, 89% for the group treated with omeprazole and low dose glucantime and 80% for the group treated with low dose glucantime and placebo and these differences were significant ($p<0.05$). The highest response rate was for the group treated with standard dose of glucantime and placebo.

Interpretation & conclusion: Although oral omeprazole and low dose of systemic MA showed less efficacy in comparison to standard dose of systemic MA in the treatment of cutaneous leishmaniasis, it still can be considered as a replacement therapy in high risk patients (such as patients with heart, kidney and/or liver disease) under close supervision of physician.

Key words Cutaneous leishmaniasis – meglumine antimoniate – omeprazole – placebo

Introduction

Leishmaniasis is one of the major health problems in the world[1]. Iran is an important foci of the cutaneous leishmaniasis and Isfahan is regarded as a hyperendemic foci of leishmaniasis as 10 to 20 thousands of new cases of leishmaniasis ulcer occur in this province annually[2].

Leishmania tropica and *Leishmania major* are the main causes of this disease in Iran and *Rhombimys opimus* is the major reservoir of this disease. The most important vectors of this disease are *Phlebotomus papatasi, P. surgenti* and *P. ansari*[2,3].

Although many therapeutic modalities are suggested for this disease, there is no definite treatment for this condition. Antimony compounds such as sodium stibogluconate or pentostam and meglumine antimony or glucantime are still regarded as the first line treatment for leishmaniasis[1,4].

Unfortunately, there are many restrictions for this kind of treatment as it is only available in parental form, expensive, has many cardiovascular, renal and hepatic complications, not completely effective and occasionally many treatment courses are needed[4]. Regarding all of these facts, many investigations are performed to find an appropriate highly effective oral or topical treatment with low side effects profile. Azole compounds and quinolone antibiotics have been used for leishmaniasis but their efficacy was lower than glucantime[5].

Omeprazole is a benzimidazole compound used for the treatment of gastrointestinal diseases, especially peptic ulcer. Omeprazole has a dual mechanism of action: H^+/K^+-ATPase inhibition and gastric mucosa carbonic anhydrase (CA) inhibition, and that these enzymes may be functionally coupled[6]. It is usually used with dosage of 20 mg B.I.D[7]. It's efficacy against intracellular parasitic infections including leishmaniasis has been suggested[8].

Acidic environment of the phagolysosomal vesicles containing parasites in the infected macrophage provide an appropriate media for proliferates of the parasites. Omeprazole can disturb in this environment through inhibition of the H^+/K^+-ATPase pump and decreasing by the environmental acidity[8]. It has shown that promastigotes cultured at acidic pH and amastigotes within infected macrophages are reduced to 90% or more with 150 μM omeprazole[8].

Our objective in this study was to compare the efficacy of 'low dose systemic glucantime and oral omeprazole', 'standard dose of glucantime and placebo', and 'low dose of glucantime and placebo' so that the efficacy of omeprazole in the reduction of cutaneous leishmaniasis ulcer can be revealed.

Material & Methods

This was a double-blind, placebo-controlled clinical trial. Patients who were pregnant or lactating and patients with history of cardiac, renal, hepatic diseases or patients with any contraindication for the treatment were excluded from the study. A total of 150 patients with confirmed cutaneous leishmaniasis referred to the Skin Diseases and Leishmaniasis Research Center were selected and randomized by random allocation software into three groups. The Skin Diseases and Leishmaniasis Research Center Ethical Committee clearance was obtained. Also, informed consent was obtained from all the cases.

All the patients had positive smear for leishman body and had not received any topical or systemic therapy for leishmaniasis. The age of patients was between 7 and 70 yr and lesion was not more than three months.

Group 1 was treated with intramuscular 60 mg/kg day glucantime and placebo for three weeks while Group 2 was treated with intramuscular 30 mg/kg/day glucantime and 40 mg of the oral omeprazole for thee weeks and Group 3 was treated with intramuscular 30 mg/kg/day glucantime and oral placebo for three weeks. The oral placebo was completely similar to omeprazole capsules and was administered in the similar way; low dose of glucantime was prepared by addition of normal saline to glucantime.

At the first visit, the patients were examined by the physician and subsequently after every two weeks up to six weeks and at the end of second and third month.

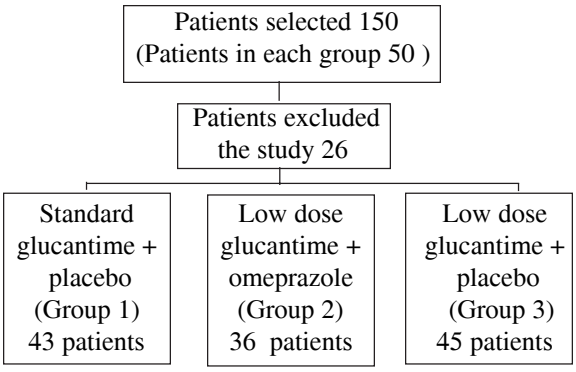
They were also visited by the physician and the questionnaires regarding response to treatment and drug side effects were filled.

At the end of study, patients were categorized according to their response in three groups. Both the investigating physicians and the patients were blinded to the type of treatment and drug codes were revealed only at the end of the study. Complete healing of the lesions was regarded as complete clinical and parasitological healing (negative direct smear).

Partial healing of the lesions was regarded as decrease of the size and indurations of the lesions and no response was regarded as no clinical change or progression of the lesions. The collected data were analyzed using SPSS 10 software. Statistical tests such as Mann Whitney, Kaplan-Mayer and ANOVA were used.

Results

In this study, out of 150 selected patients, 124 patients completed their three weeks study course and 26 patients excluded the study because of the absence at the appropriate time and one patient because of the anaphylactic shock to the glucantime as per the following chart. Demographic characteristic of the patients are shown in Table 1. Rate of complete response, three months (12 weeks) after starting treatment, was 93% for the group treated with standard dose of glucantime and placebo, 89% for the group treated with omeprazole and low dose of glucantime, and 80% for the group treated with low dose of glucantime, and placebo and these differences were significant statistically ($p < 0.05$).



The highest response rate was for the group treated with standard dose glucantime and placebo. Healing rate during the course of treatment was more in the groups treated with 'standard dose glucantime and placebo' followed by 'low dose glucantime and omeprazole than the group treated with low dose glucantime and placebo' (Fig. 1; $p < 0.05$). Except

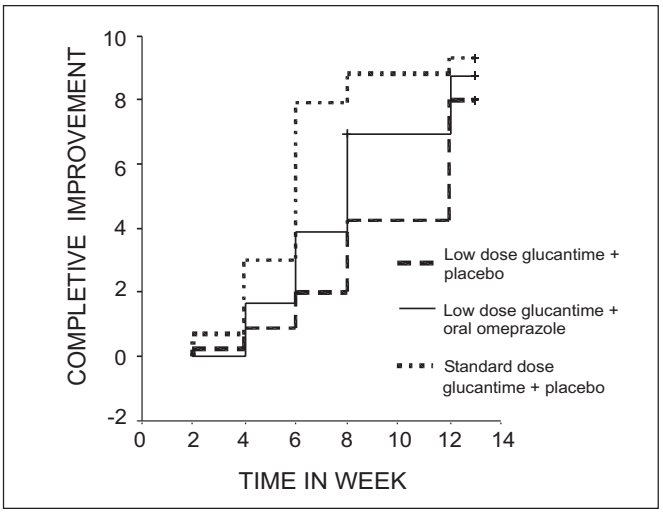


Fig. 1: Proportion of complete improvement in three groups during the course of treatment ($p<0.05$)

Table 1. Demographic characteristics of the three groups

Characteristics	Standard glucantime + placebo (n = 43)	Low dose glucantime + omeprazole (n = 36)	Low dose glucantime + placebo (n = 45)	p-value
Age (yr)	33.1 ± 17.5	27.8 ± 9.8	29.1 ± 14.7	0.23
Male	32 (74.4%)	23 (63.9%)	33 (73.3%)	0.58
Female	11 (25.6%)	13 (36.1%)	12 (26.66%)	
No. of lesions	2.86 ± 3.02	2.17 ± 1.40	2.82 ±2.41	0.37

during the first two weeks of treatment, the differences in response rate among these three groups were significant during the course of treatment and follow-up period ($p < 0.05$).

There was no significant correlation between healing rate and type of the lesions in each group of the patients. Also there was no significant difference in the prevalence and distribution of the lesions. Percent prevalence and healing rate of the lesions by type and location of the lesions are shown in Table 2.

Discussion

At the end of 12 week randomised double blind trial, the healing rate was 93, 89 and 80% in the 'standard dose glucantime + placebo', 'low dose glucantime+ omeprazole' and 'low dose glucantime and placebo', respectively. Our results showed that the effect of standard dose glucantime was more than the other two groups. The effect of low dose glucantime plus omeprazole was more than that of low dose glucantime plus placebo group. Two different studies have shown that low dose glucantime may be as effective as full dose glucantime while the side effects are less[9,10].

Table 2. Percent cure in three groups by the type and location of the lesions

Type of treatment	Standard dose glucantime and placebo	Low dose glucantime + omeprazole	Low dose glucantime + placebo
Papule	100	50	66
Nodule	NA	75	100
Plaque	93	85	81
Ulcer	89	87.5	77
Sportrichid	100	100	NA
Face	100	75	100
Neck	NA	100	NA
Upper extremity	92	75	77
Lower extremity	86	94	20
Trunk	100	100	33

NA—Not available

One recent study has shown that combination treatment with rifampicin and omeprazole is highly effective, less toxic and a cheaper alternative for the management of cutaneous leishmaniasis[11].

In vitro studies have shown that different concentrations of the omeprazole in regard with pH of culture medium has different effects on the leishman body. Although omeprazole is effective on the outer membrane of the leishman body, it is not effective at pH 7.2 even at the concentration of 150 μM. But it is able to inhibit the growth of leishman body at pH 5.5 in the concentration of 50 μM to 50%, and in the concentration of 150 μM to 90–95%[8]. It can be concluded that antileishman body effect of the omeprazole is probably because of its inhibitory effect on the K^+/H^+-ATPase pump (p-type) on the cell membrane. This pump is important in maintaining intracellular pH homeostasis and exiting the H from the leishman body membrane. In addition, the role of nitric oxide (NO) in killing of the leishman body in the macrophages has been recently suggested. Lanoprasole is another H pump inhibitor that can increase the production of nitric oxide in the mucosal cells. These two evidences are suggestive of the important role of NO in antileishmania activity of the omeprazole[12,13].

Although in the current study, the effect of oral omeprazole with low dose glucantime was more than that of low dose glucantime and placebo, but the side effects related to the latter combination causing discontinuation of the treatment was also more and further investigations are needed in this respect. Regarding the low side effect profile of the omeprazole, further studies with different doses of this drug are recommended.

Combination therapy with oral omeprazole and low dose of glucantime can be used as an alternative treatment for leishmaniasis especially in the patients with history of cardiac, renal, and hepatic disease, further studies with high dose of omeprazole with or without other treatments are recommended.

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