Acta Dermatovenerol Croat 2008;16(2):60-64 CLINICAL ARTICLE

Clinical Efficacy of Intramuscular Meglumine Antimoniate Alone and in Combination with Intralesional Meglumine Antimoniate in the Treatment of Old World Cutaneous Leishmaniasis

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Received: November 9, 2007
Accepted: March 12, 2008

SUMMARY Treatment of cutaneous leishmaniasis is often difficult. Even though most cutaneous lesions will heal spontaneously, their duration cannot be predicted in an individual case. In general, only large, multiple or diffuse lesions of the face, head and neck need to be considered for therapeutic intervention. Pentavalent antimonials (sodium stibogluconate and meglumine antimoniate) administered intralesionally or parenterally (IM or IV) are the mainstays of systemic therapy despite the toxicity associated with their use. The objective of this study was to compare the clinical efficacy of intramuscular pentavalent antimonial compound meglumine antimoniate alone and in combination with intralesional therapy in the treatment of Old World cutaneous leishmaniasis. Study was conducted as a case controlled interventional prospective study. On the basis of demonstration of *Leishmania tropica* (LT) bodies in the skin slit smears/skin biopsies, 60 patients with cutaneous leishmaniasis were included in the study. The patients were randomly allocated to three groups of 20 patients each: group 1 treated with intramuscular injection of meglumine antimoniate (20 mg Sb/kg/day, maximum 850 mg) for 21 days; group 2 treated with intralesional injection of meglumine antimoniate (0.5 mL, 42.5 mg of Sb) into each lesion along with intramuscular injection of meglumine antimoniate (20 mg Sb/kg/day, maximum 850 mg) for 21 days; and group 3 as a control group. The patients were followed-up for therapeutic safety and efficacy at 10, 20 and 90 days. The rate of complete cure was 55% in group 1, 75% in group 2 and 10% of spontaneous cure cases in group 3. The conclusions derived from this study are limited by the relatively small number of patients. The combination of intramuscular meglumine antimoniate along with intralesional administration of the agent is superior therapy to intralesional administration of meglumine antimoniate alone.

KEY WORDS: meglumine antimoniate, intramuscular administration, intralesional administration, cutaneous leishmaniasis

INTRODUCTION

Leishmaniases represent a spectrum of several vector-borne parasitic diseases of variable severity, ranging from self-healing cutaneous papular or ulcerated lesions to life-threatening visceral disease, each caused by one of the species of the genus *Leishmania*. Leishmaniasis is endemic in

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88 countries throughout Asia, Africa, Europe and North and South America, and the population at risk is more than 350 million (1).

The parasite is transmitted to humans by the bites of infected female sandflies (*Phlebotomus* in the Old World countries and *Lutzomyia* in the New World). Leishmaniases are classified into three forms: cutaneous (oriental sore), mucocutaneous (espundia) and visceral (kala azar).

The World Health Organization estimates that at least 1.5 million cases of cutaneous leishmaniasis and 500,000 cases of visceral leishmaniasis occur each year (1). Individuals at high risk of cutaneous leishmaniasis include military personnel and those who travel to or live in areas of the tropics, subtropics and southern Europe where the disease is endemic (1,2). Approximately 90% of all cases of cutaneous leishmaniasis occur in Afghanistan, Brazil, Iran, Peru, Saudi Arabia and Syria. Cutaneous leishmaniasis is endemic along the northern areas of Baluchistan, Sindh, tribal area (refugees from Afghanistan), and western border of Pakistan. Sporadic cases have been reported from southern Punjab, Azad Kashmir, northern areas and Islamabad (3,4).

The pentavalent antimony compounds sodium stibogluconate and meglumine antimoniate have been the mainstays of antileishmanial therapy for both visceral and cutaneous leishmaniasis (5,6).

Rifampicin, ketoconazole, allopurinol, itraconazole, liposomal amphotericin B, topical paromomycin and dapsone were used in various studies, however, with conflicting results (7-11). The aim of the study was to monitor and compare clinical response to intramuscular meglumine antimoniate (MA) alone and in combination with intralesional meglumine antimoniate in cutaneous leishmaniasis.

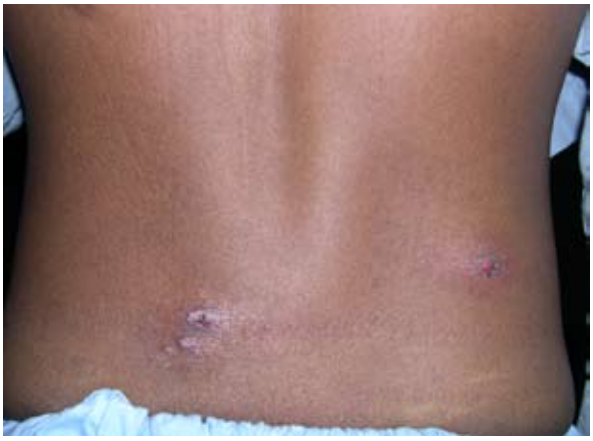

Figure 1. Excoriated crusted plaques with erythematous indurated borders on the lower back.

PATIENTS AND METHODS

This case controlled interventional prospective study evaluated 60 patients admitted to Department of Medicine, Scouts Hospital Wana from January 2003 to December 2004. There were no sex differences. All patients were adults, their age ranging from 14 to 55 years and the number of lesions 2-5 *per* patient (Figures 1-10). The inclusion criteria were demonstration of *Leishmania tropica* (LT) bodies in skin slit smears/skin biopsies and

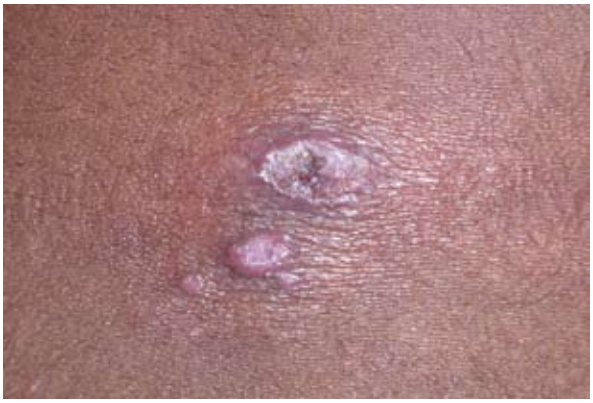

Figure 2. Close-up view of Figure 1.

lesions of less than 8-week duration to standardize the trial. The patients who had lesions more than 8 weeks old, those who had already been treated, patients with known hypersensitivity to antimonial compounds, those with cardiovascular, renal, hepatic or hematologic disorders and pregnant women were excluded from the study.

Selected patients were explained the study purpose and gave their consent for inclusion. They were randomly divided into three groups of 20 patients each: group 1 received 20 mg of Sb/kg/day by intramuscular injection daily for 21 days; group 2 received 20 mg of Sb/kg/day by intramuscular

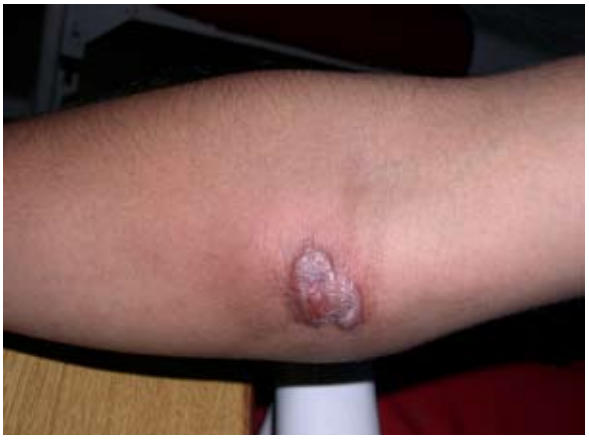

Figure 3. Erythematous indurated plaque on the back of left elbow.

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Table 1. Clinical data

	No. of patients	Mean age (yrs)	Duration (weeks)	Number of lesions
Group 1	20	25 (12-45)	6 (1-8)	4 (2-6)
Group 2	20	26 (18-50)	5 (1-8)	2 (2-6)
Group 3	20	30 (20-55)	5 (1-8)	3 (2-6)

injection along with 0.5 mL (42.5 mg of meglumine antimoniate) into each lesion, upper and mid-dermis daily; and group 3 consisting of patients unwilling to receive treatment, thus serving as a control group. The patients were evaluated at 10, 20 and 90 days. The absence of exudation, erythema, induration and LT bodies in skin slit smears/biopsies was considered as a parameter of cure. Adverse effects were also recorded during treatment. Results were analyzed using x^2 method to calculate percentage, and p value was obtained according to appropriate degree of freedom.

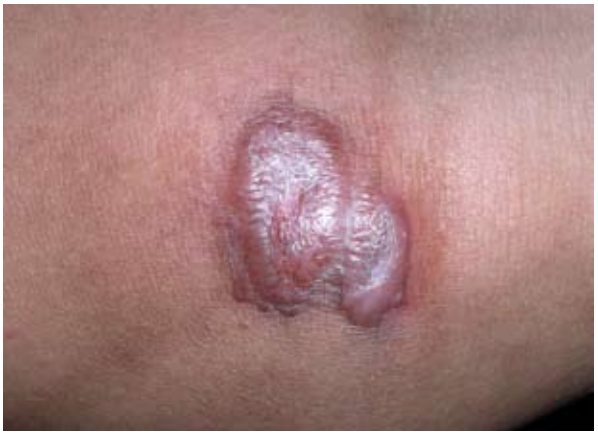

Figure 4. Close-up view of Figure 3.

RESULTS

Data on 60 study patients, mean age 27 years and a mean of 3 lesions, are shown in Table 1. Complete cure was ascertained by clinical and laboratory parameters already discussed. The patients on combination therapy with intramuscular and intralesional meglumine antimoniate showed better response (Table 2). At the end of follow up, complete cure was achieved in 11 of 20 (55%) patients in group 1 (p-0.001), 15 of 20 (75%) patients in group 2 (p-0.00001) and only two of 20 (10%) patients in group 3 as a control group.

Adverse effects recorded in study patients are presented in Table 3. Myalgia, arthralgia, headache, nausea, urticaria and cardiomyopathy were common in group 2 (combination therapy), while cellulitis and pain at the injection site were common in group 1. Cardiomyopathy was observed in only one group 2 patient, with tachycardia and nonspecific ECG changes at 3 weeks of treatment, however, these changes reverted to normal upon therapy discontinuation.

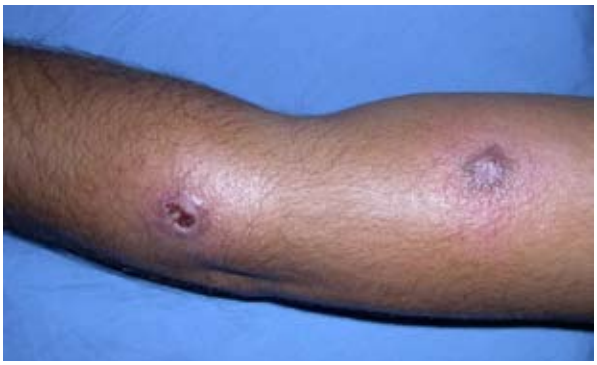

Figure 5. A crusted ulcer with indurated borders on the left forearm, and an indurated erythematous plaque on the left arm.

DISCUSSION

The treatment of cutaneous leishmaniasis is still controversial despite the fact that a wide variety of oral, parenteral, topical, surgical, combination and cryotherapy had been tried in the past with conflicting results in various studies. Pentavalent antimonial compounds, sodium stibogluconate and meglumine antimoniate, are still the drugs of first choice. The two compounds have almost similar efficacy and toxicity. Parenteral administration of meglumine antimoniate showed variable efficacy from 65% to 95% in various studies (12-16).

In our study, group 1 administered only intramuscular therapy showed 55% cure rate that

Table 2. Response to intramuscular meglumine antimoniate alone and in combination with intralesional therapy

	10 days	20 days	90 days
Group 1	7/20 (35%)	10/20 (50%)	11/20 (55%)
Group 2	9/20 (45%)	10/20 (50%)	15/20 (75%)
Group 3	1/20 (5%)	3/20(15%)	2/20 (10%)

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Table 3. Adverse effects of treatment

Adverse effect	Group 1	Group 2	Group 3
Arthralgia	1 (5%)	3 (15%)	-
Myalgia	1 (5%)	3 (15%)	-
Headache	-	2 (10%)	-
Urticaria	-	1 (5%)	-
Cardiomyopathy	-	1 (5%)	-
Cellulitis	2 (10%)	1 (5%)	-
Pain at injection site	4 (20%)	1 (5%)	-
Renal toxicity	-	-	-
Hepatic toxicity	-	-	-
Drug fever	-	-	-

increased to 75% when intramuscular treatment was added to intralesional therapy which was in conformity to previous studies (12). A minor difference may have been due to different or resistant parasite strain or technique of intralesional treatment; however, in group 2 the efficacy was enhanced and the cost of few adverse effects (Table 3) as compared with group 1. Therapeutic

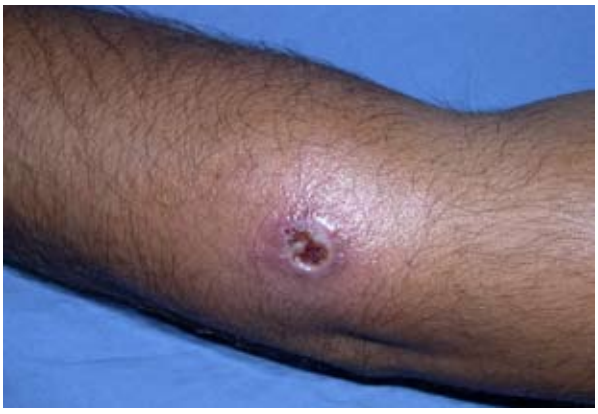

Figure 6. Close-up view of Figure 5.

decision depends on the site of lesion, e.g., face, which is too sensitive to be treated by intralesional route. Single lesions, especially on the extremities, may be treated exclusively by intralesional

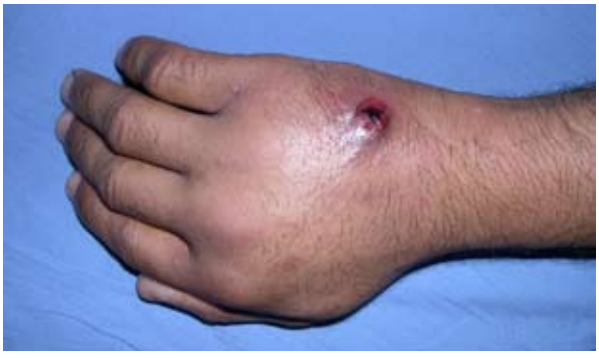

Figure 7. An erythematous indurated plaque with crusted ulcer.

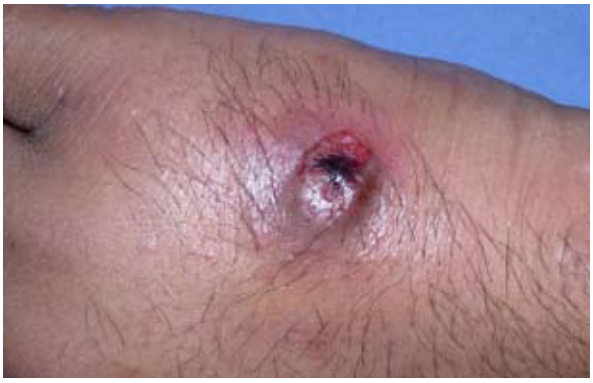

Figure 8. Close-up view of Figure 7.

therapy, whereas for multiple and extensive lesions intramuscular therapy combined with intralesional therapy will be more effective than either therapy alone.

In group 3, three (15%) patients showed spontaneous healing, one of them developing relapse at six months; the overall cure of 10% indicates that most patients require therapy, especially if the lesions are multiple, extensive, disfiguring, disseminating, and located at cosmetically unacceptable sites and joints.

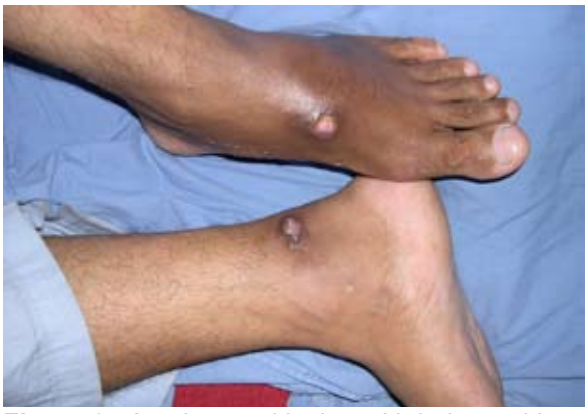

Figure 9. An ulcerated lesion with indurated borders on the left foot and a similar lesion on the right lower leg.

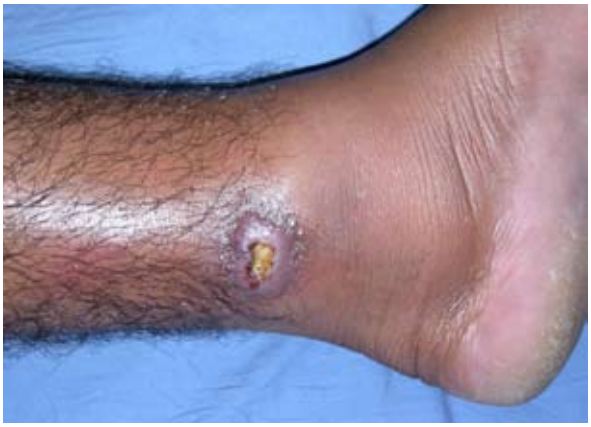

Figure 10. An ulcerated plaque with yellowish base on the left lower leg.

Adverse effects commonly reported were mylagias, arthralgias, headache, urticaria, cellulitis and pain at injection sites. These were transient and disappeared upon treatment discontinuation, however, regular follow up for cardiac, hepatic, renal and hematologic toxicity was performed; only one patient developed early cardiotoxicity at the end of the 3rd week of treatment that normalized upon treatment discontinuation.

CONCLUSION

Treatment of cutaneous leishmaniasis with combination therapy consisting of intramuscular and intralesional meglumine antimoniate showed high efficacy at the cost of few side effects. However, intralesional therapy should only be administered in case of multiple, extensive and disseminating lesions.

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