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Original Article

Chloroquine in cutaneous leishmaniasis

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Abstract

Background Chloroquine is an antiprotozoal drug that has shown a favorable therapeutic index for cutaneous leishmaniasis.

Objective A clinical trial was conducted to determine the efficacy of oral chloroquine in patients with cutaneous leishmaniasis and its comparison with the most effective standard treatment, pentavalent antimony compounds.

Patients and methods This non randomized, open-label comparison study was conducted in department of dermatology, Pakistan Institute of Medical Sciences, Islamabad, from August 2006 to January 2007. 30 patients, 12 years of age or older were enrolled in the study. Diagnosis was made on the basis of clinical features and histopathological examination. 15 patients received orally administered chloroquine 250mg tds for 20 days and remaining 15 patients received injectable pentavalent antimony 20mg/kg for 28 days. Pre-treatment complete physical examination was done along with necessary laboratory investigations in all cases. They were repeated after 2 weeks and then at the end of treatment to note any abnormality developing. Groups were almost matched in terms of age, duration of lesions and number of lesions. The efficacy was evaluated by the appearance of the lesion and healing with or without scar formation. Patients were followed up for 3 months.

Results All patients completed the study without any complication. Lesions healed completely with only minimal scarring or post-inflammatory hyperpigmentation at the site of lesion. The cure rate at 3-month follow-up was 100% in group A (chloroquine) and 93% in group B (antimony compound) at the end of treatment period.

Conclusion Chloroquine seems to be a safe and effective alternative to antimony compounds. The striking advantage of chloroquine being its benefit of oral administration, and low cost along with easy availability which is of particular importance in underdeveloped countries like Pakistan.

Key words
Cutaneous leishmaniasis, chloroquine, antimonials

Introduction

Leishmaniasis is a major health problem worldwide.[1,2] It is also a particular problem in the rural areas of Pakistan.[3,4] The disease occurs in varying presentations, from the self-limited and even self-healing cutaneous forms to fatal systemic disease. The disease has a very long history and lesions like leishmaniasis have been described dating back to the ninth century (Balkan sore). Cutaneous leishmaniasis has been given various names in different civilizations such as "Delhi boil" in India, "Baghdad boil" in Iraq, and "saldana" in Afghanistan. The organism responsible for leishmaniasis was discovered 100 years ago but the disease has not been eradicated; rather it is on rise in many parts of the world. If control measures

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are not taken, it might emerge as a major health problem. The predominant mode of transmission is the bite of sandfly.[5] Different species of sandfly act as vectors in different parts of the world. In the Old World the main species are *Leishmania tropica, L. major, L. infantum,* and *L. aethiopica.*

Careful review of the literature reveals that cutaneous leishmaniasis is present in almost all parts of Pakistan but is more prevalent in the hilly areas. It is endemic in Baluchistan, Interior Sind, and Multan.[7] It has also been reported in Pakistanis working abroad. In Pakistan, the disease has been described in its classic form and as variants of the classic variety. Some rare manifestations have also been described. These include acute paronychial, chancriform, annular, palmoplantar, zosteriform and erysipeloid forms.

Because of the diverse and varied presentation, there is no single optimal treatment for all forms of cutaneous leishmaniasis.[8] The situation is complicated by the self-healing nature of cutaneous leishmaniasis. Adequately controlled therapeutic trials are, therefore, essential to assess the efficacy of any new treatment. Unfortunately, the trials done on drugs are few, inconsistent, uncontrolled, and sometimes biased. Furthermore, the drugs that work reasonably well in one endemic area may not be efficacious in another area. Natural healing is so common that it is uncertain whether therapy will be justified at some stage.

Many treatment options have been tried. Although the treatment of cutaneous leishmaniasis is empirical, the efficacy of antileishmanial drugs is controversial and also the choice of drug is affected by the price of drug especially in underdeveloped countries like Pakistan.

Different treatment options are available at the moment. Unfortunately, to date, there is no safe, simple, effective and affordable treatment for cutaneous leishmaniasis and the pentavalent antimony compounds "the best drug of bad bunch" still remains mainstay of treatment in majority of cases. Other treatment options are pentamidine given systemically and imidazole compounds.[9,10] Drugs such as allopurinol, rifampicin, dapsone, chloroquine[11] and nifurtimax have found favor in some studies. Cryotherapy and intralesional antimonials[12] are also found to have beneficial role. Physical methods to control transmission of CL as a preventive measure have also been tried with some success.[13] For simple lesions which are few in number and where there is no risk of disfigurement or joint mobility restriction, the treatment options which involve parenteral injections and which expose the patient to untoward side effects are not only inconvenient but also expensive.

Chloroquine is an antiprotozoal drug and has much less side effects and cost as compared to antimony compounds. It is widely used orally as an antimalarial. It is worth while to compare the efficacy of this cheap antiprotozoal with the current standard therapy i.e. pentavalent antimony in CL.

Patients and methods

A randomized, open-label comparison of injectable pentavalent antimony compounds

and oral chloroquine was carried out in dermatology department of Pakistan Institute of Medical Sciences, Islamabad from August 2006 to January 2007.

Patients were of either sex, aged 12 years or older, mostly belonging to Islamabad and Azad Kashmir, had histopathologically-confirmed cutaneous leishmaniasis. They did not have any other significant concomitant disease. They had normal blood counts, liver and renal function tests before starting treatment. Patients who were pregnant or lactating were excluded from the study.

30 patients fulfilling the inclusion criteria were finally enrolled and were divided into two equal groups of 15 patients each, who were almost matched in terms of age, weight and duration of lesion. Group A patients received chloroquine treatment orally in the dose of 250 mg tds, for 20 days while in group B, pentavalent antimony compound was administered intramuscularly in the dose of 20 mg/kg/day for 28 days. Pretreatment complete physical examination was done, including fundoscopy, along with necessary laboratory investigations in all cases. Patients received medicine with meals. Patients were reviewed weekly for adverse events. Blood samples were obtained at 2 weekly intervals for blood cell count, liver function tests, and renal function tests.

Efficacy was evaluated by healing of lesion clinically with or without scarring. Healing was defined as disappearance of signs of inflammation, complete repitheliazation with or without post-inflammatory hyperpigmentation. Relapse was defined by signs and symptoms suggestive of leishmaniasis and appearing after an initial cure (1 month). Treatment failure was defined as either lack of initial cure or relapse, or appearance of new lesions. Chi-square test was used to compare response (categorical variables) while t-test was used to compare regression in size of lesion (numerical variables) for significance of difference.

Results

A total of 30 patients were enrolled in the study, which belonged to both sexes and aged over 3 years. Group A (chloroquine) had a mean and S.D of age 25.93±13.53 years, while group B (sodium stibogluconate) had mean age of 27.80 with standard deviation of 12.79 years (**Table 1**). In group A (chloroquine) 53.3% patients were male and 46.6% patients were females while in group B (sodium stibogluconate), 70% patients were males and 30% were females. In group (A), 76% of patients had 1 lesion, 13% of patients had 2 lesions, and 10% had 3 lesions. While in group (B), 76% of patients had 1 lesion, 13% had 2 lesions, 6% had 3 lesions and 3% had 4 lesions. So in both groups majority of patients had 1 lesion.

At the final follow-up, chloroquine group showed a cure rate of 100% (**Figures 1** and **2**) whereas in antimony group it was 93%. At 3 months follow-up visit none in group A while 1 patient in antimony group came with relapse with appearance of a nodular lesion at the site of initial lesion which was confirmed to be leishmaniasis on biopsy of lesion.

Table 1 Demographic characteristics of study population

	Group A (Chloroquin)	*Group B (Sodium stibogluconate)*
Age (years)	25.93±13.53	27.80±12.79
Male:female ratio	8:7	10:5

In group A, no side effect was noted while in group B, 2 (13.3%) patients had myalgias, and 1 (6.66%) patient developed increase in liver enzymes. but treatment was not stopped prematurely in any patient.

Discussion

Regarding cutaneous leishmaniasis, antimonials are the mainstay of treatment. These compounds have the disadvantage of both toxicity and clinical resistance in at least 40% of cases in certain regions where they have been used for a long time. The other well known problems with these compounds are increasing frequency and severity of adverse events, and increasing cost, which is especially important in underdeveloped countries like Pakistan, in addition to the fact that the disease is prevalent in rural areas where people have limited resources of income. Another important problem is availability of drug. Most of the rural areas do not have drug available, an important cause of which again is cost. Even in developed areas of Pakistan like Islamabad has to face the problem of shortage of drug very often. Common adverse effects of antimonials are myalgias, arthralgias, increase in liver function enzymes, arrhythmias and repeated parenteral injections. These events can be particularly a problem in old age group

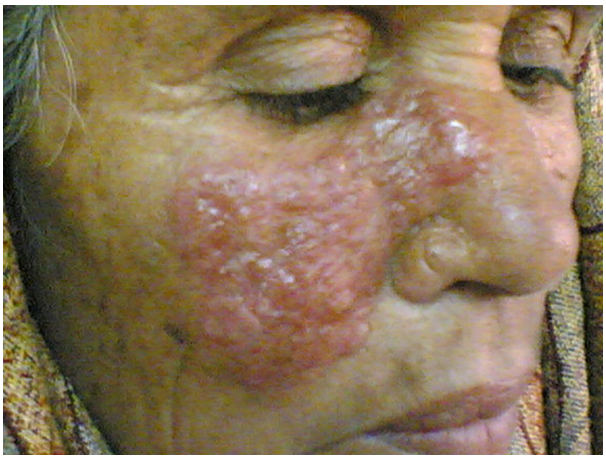

Figure 1 Cutaneous leishmaniasis before treatment.

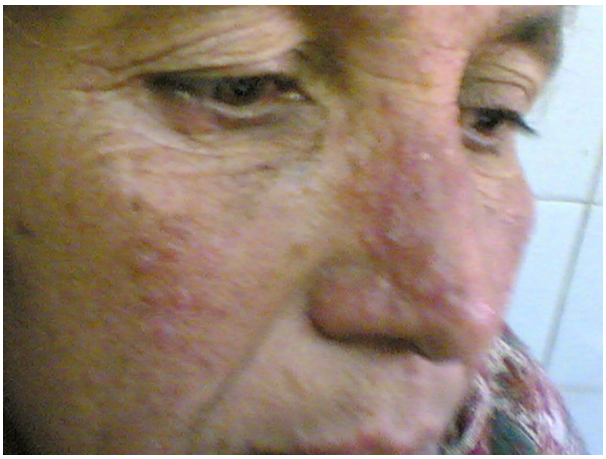

Figure 2 Almost completely healed lesion after chloroquine treatment.

when people are already friable and are suffering from many systemic illnesses. These limitations have stimulated the search for new drugs to treat this disease.

In the past decade, there have been several advances with the introduction of new therapies liposomal amphotericin, paromomycin and oral miltefosine. Chloroquine is an antimicrobial drug which is used as an antimalarial, but never has been tried as antileishmanial. This study was planned to find out the efficacy of the drug, and to compare the results with antimonials compounds.

Our present trial in immunocompetent patients, 12 years of age or older, shows that oral chloroquine is effective and safe treatment for cutaneous leishmaniasis. At the end of trial period all the patients in this treatment group recovered with complete healing of lesion. At the three months follow-up, none of the patients showed signs of recurrence. No side effect was noted in this group. In antimony group recurrence was noted in one patient and there were few side effects. Significantly higher cure rates were seen in our trial. We compared chloroquine with conventional antimonials and found it equally effective than antimonials.

Previously chloroquine has been used intralesionally in Pakistan in a small study and is found to be very effective.[11] To our knowledge, no clinical trial has been published so far describing the clinical efficacy of this drug, when taken orally in Old World disease and results of our study are very promising. Therapeutic agents may be compared with respect to efficacy, tolerance, convenience and cost of administration. Very high cure rate of 100% in our study clearly surpass the efficacy of other antileishmanial drugs and side effects profile also shows that it is more tolerable than other agents used in the treatment of leishmaniasis. Moreover, chloroquine is free of any side effects as compared with antimonials. Cost-effectiveness is another important plus point of chloroquine especially in underdeveloped counties like Pakistan. Oral treatment with chloroquine is very easy to take as compared to daily painful injections of antimony compounds and also duration of treatment is less than antimony compounds. Regarding availability of drug it is easily available even in small towns and villages because of its low cost.

Conclusion

The assessment of the efficacy of any therapeutic agent in a self limiting disease such as cutaneous leishmaniasis is very difficult. However, in this study, chloroquine appears to be a safe and effective alternative to currently available therapies. It is administered orally and it may also be helpful in areas where parasites are resistant to current agents.

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