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Original Article

Rifampicin in cutaneous leishmaniasis – a therapeutic trial in Saudi Arabia

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Abstract

Objectives The aim of the present work is to evaluate the efficacy of oral rifampicin in the treatment of cutaneous leishmaniasis in a double-blind, placebo-controlled study.

Patients and methods This randomized, double-blind, placebo-controlled trial assessed the efficacy of oral rifampicin in a dose of 10mg/kg/day for four to six weeks, in the treatment of smear or biopsy confirmed cutaneous leishmaniasis. The study was carried out at Dermatology Department, Prince Abdullah Bin Abdul Aziz Hospital, Bisha (Aseer region), Saudi Arabia from January, 1999 to January, 2000. Sixty-two patients suffering from single or multiple lesions of cutaneous leishmaniasis were studied, out of which 46 were given rifampicin and 16 received placebo. The results were also studied and compared in two age groups as group I - children (3 to 11 years) and group II - adults (12 to 65 years).

Results Out of 62 patients, a total of 46 were assigned to receive rifampicin, and 16 to receive placebo. Follow up data were available for 34 (73.9%) and 7 (43.7%) patients, respectively. At the three months follow up, healing of the lesion was complete for 21 out of 34 patients in rifampicin group (61.8 percent) and 3 out of 7 patients in the placebo group (42.9%; relative risk of complete healing 1.44). According to intention to treat analysis, the rates of healing were 45.7% and 18.8% in the rifampicin and placebo group, respectively (relative risk of complete healing 2.43). The difference was statistically significant in favour of rifampicin ($p<0.01$). Amongst the two age groups, the results were more impressive in the group I - children. In group I, 24/32 patients and in group II, 22/30 patients received rifampicin. Fifteen (83.4%) out of 18 followed up patients amongst group I while 6 (37.5%) out of 16 followed up patients in group II, receiving rifampicin showed marked improvement. Eight patients served as control in each group to receive placebo. For the control group, 2 (66.6%) out of 3 followed up in group I and only one patient (25%) of the 4 followed up in group II, showed complete healing.

Conclusion Systemically administered rifampicin 10 mg/kg for 4-6 weeks may prove to be a valuable, safe, easy to administer and cheap modality for the treatment of cutaneous leishmaniasis. The results were more encouraging in children where other conventional injectable treatments are not acceptable, feasible or may be toxic. The study also suggested that rifampicin is worthy of a more extensive trial.

Key words
Cutaneous leishmaniasis, rifampicin, therapeutic trial.

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Introduction

Leishmaniasis designates a human disorder produced by protozoan species and subspecies of genus *Leishmania*. According to WHO, **a**pproximately 400,000 new cases

occur each year and 400 million people are at risk of the disease.[1] The cutaneous form of the disease i.e. cutaneous leishmaniasis (CL) is endemic in more than 80 countries, notably those of Southwest Asia[2] and is an important public health problem in Saudi Arabia.[3] The disease is usually a self-limiting benign one that remains limited to the skin. However, it usually takes several months before complete healing occurs with residual disfiguring scars. It can present itself as hard indurated plaques, nodules, scabby papules, or warty tumor like lesions. Leishmaniasis is transmitted by the sandflies of the genus *Phlebotomus*, commonly *Phlebotomus papatasii*. The average time for incubation is about 2 months.[4] The clinical features of the disease differ according to the immunologic reaction of the host to the parasite.[5]

Clinically, the disease is seen in dry and wet forms. The dry, urban or late ulcerative form is generally attributed to *L. tropica*. It consists of a single 1-3 cm ulcer which heals in the course of 1 year. The wet, rural, or early ulcerative form is caused by *L. major* and consists of ulcers that are frequently multiple and also heal in the course of 1 year.[6] The rare forms of the disease are diffuse cutaneous leishmaniasis, mucocutaneous leishmaniasis, and leishmaniasis recidivans.

The disease presents a therapeutic problem and management of CL is still a challenge.[7] Both parenteral e.g. sodium stibogluconate, antimony-N-methyl-glutamine,[8] pentamidine and amphotericin-B[9,10] and oral e.g. dapsone, ketoconazole, itraconazole, fluconazole and allupurinol,[11-14] drugs are available against the disease, each has its own efficacy and attendent toxicity. According to Hafez *et al*.[15] oral rifampicin, which is a systemic bactericidal antibiotic, may be effective in the treatment of cutaneous leishmaniasis. Recently, Kochar *et al*.[16] quoted rifampicin as effective treatment in cutaneous leishmaniasis. It may be an appropriate substitute of antimony and other antileishmanial drugs, with less toxicity and easy administration where the treatment modalities may be restricted.

Materials and methods

A total of 62 patients with active localized lesions of cutaneous leishmaniasis served as subjects for this study. All patients were subjected to a thorough clinical examination. Liver function tests, renal function tests, and complete blood profile were done for all of them before, during, and after completion of treatment.

Informed consent was taken from patients. They were told about the harmless orange discoloration to urine, sweat and tears including contact lenses. Women of childbearing age were also warned about the reduced efficacy of oral contraceptives.

Diagnosis of cutaneous leishmaniasis was made by a direct smear taken from the lesions, which was then stained with Giemsa stain, or via biopsy of the lesion in difficult cases. Only those cases that proved positive for leishmania parasites (amastigotes) on microscopic examination or biopsy were included further in the study. Sixty two patients were randomly divided either to receive oral rifampicin (46 patients) or placebo (n=16). Rifampicin was given orally in a dose of 10 mg/kg per day in two equally

divided doses during meals for 4-6 weeks. The drug was supplied in capsules for adults, each containing l00 mg of rifampicin, and in the form of suspension for children containing 100mg/5ml. Each subject in the control group was given placebo, which was supplied, in capsules/ suspension identical in shape and colour to that given in the rifampicin group.

The patients were assessed at the end of two, four, six and eight weeks. The primary outcome measure was the time to complete healing of the lesions at the end of three months. The study was also split up to observe the effect separately in children and adults. Two groups were analysed; Group I – children from 3-11 years of age (mean age, 7.5 years) and group II – adults from 12-65 years (mean age, 33 years). Thirty-two patients were enrolled in group I and 30 in group II to make a total of 62 patients. Out of these 8 patients in each group (16 in total) served as a control to receive the placebo.

The statistical analysis was done using percentage and X^2 charts after which appropriate calculations of p value was done to asses the efficacy of rifampicin in the trial.

Results

Sixty-two patients (32 children - group I; 30 adults - group II) with male to female ratio of 2.3:1 (43 males and 19 females) were studied. Forty-six received rifampicin and 16 served as control. Their ages ranged between 3-65 years with the mean age of 20 years. The duration of the lesions varied between 1 and 12 months (mean, 2.6 months). The lesions of cutaneous leishmaniasis were single or multiple and were mostly over the extremities (upper limbs 51% and lower limbs 38%), and to a lesser extent on the face 30% (**Table 1**). Most of the lesions were active being nodular, nodulo-ulcerative, or ulcerative. Two of the patients included in the study were members of the same family. However, the rest of the patients had a negative family history.

Out of total 62 patients, 46 received rifampicin, 34 (73.9%) were followed up till the end of three months. Of 34, 21 (61.8%) showed excellent clinical response, where the lesions showed either marked reduction in size or complete healing with minimal scarring and pigmentation. Thirteen (38.2%) cases showed no change in the lesions. One patient (2.1%) had significant elevation in his liver enzymes during treatment, which returned back to normal upon discontinuation of the drug. Follow-up of the patient in the group treated with rifampicin for a period up to 12 weeks after suspension of the drug did not show any reactivation of the lesions. In the control group 7/16 patients were followed up where only 3 (42.9%) showed improvement and the rest (57.1%) had no signs of improvement in their cutaneous lesions after 12 weeks (**Table 2**). The relative risk of complete healing between the rifampicin and placebo group is 1.44. When the intention to treat analysis was done, the rates of healing were 45.65 percent and 18.75 percent in the rifampicin and placebo group, respectively (relative risk 2.43). The difference was statistically significant in favour of response to rifampicin ($p<0.01$). The 17 patients (13 in rifampicin and 4 in

Table 1 Sites of lesions of cutaneous leishmaniasis

Site of lesions	*n (%)*
Upper limbs	30 (51)
Lower limbs	21 (28)
Face	16 (30)

Table 2 Overall efficacy of rifampicin

Total patients (n = 62)	*Rifampicin (n = 46)*	*Control (n = 16)*
Follow-up	34 (73.9%)	7 (43.7%)
Improved	21(61.8%)	3 (42.9%)
Not improved	13 (38.2%)	4 (57.1%)

Table 3 Response to therapy with rifampicin in adults and children (n= 62)

	Group I Children (n=32)		*Group II Adults (n=30)*	
	Rifampicin (n=24)	Control (n=8)	Rifampicin (n=22)	Control (n=8)
Followed up	18 (75%)	3 (37.5%)	16 (72.7%)	4 (50%)
Improved	15 (83.4%)	2 (66.6%)	6 (37.5%)	1 (25%)
Not improved	3 (16.6%)	1 (33.4%)	10 (62.5%)	3 (75%)

control group) who did not improve after three months with the above treatment were given the standardized injection of sodium stibogluconate (pentostam®) in the dose of 20 mg/kg/day, either intramuscular or intralesional, showed 96% improvement. Two cases who finally did not improve with sodium stibogluconate were biopsied further for reconsideration of other differential diagnoses.

Comparison of the results in patients taking rifampicin and placebo (**Table 3**) was also done in two age groups i.e. children vs. adults. In group I (children) 24/32 patients and group II (adults) 22/30 patients received rifampicin. Fifteen (83.4%) out of 18 followed up cases in group I and only 6 (37.5%) out of 16 followed up in group II were improved. Out of 8 patients in each group who served as control, 2/3 (66.6%) followed up in group and 1/4 (25%) followed up in group II showed improvement.

Discussion

Therapy for any disease should be effective and should entail less morbidity than that due to the disease itself. A wide variety of therapeutic agents, either systemic or local, have been used for the treatment of cutaneous leishmaniasis. Its management poses a real problem. The most widely used leishmanicides i.e. pentavalent antimonials namely, sodium stibogluconate (pentostam®) and meglumine antimonite (glucantime®), have significant toxic effects on renal, hepatic and cardiac tissue.[17] Recently, treatment resistance has also been reported with these antimonials.[18] The second line drugs like pentamidine, imidazole compounds like ketoconazole, itraconazole and fluconazole, terbinafine[19] and amphotericin B have been tried and have variable results and side effects, which has made it important to look for a new drug without side effects or with minimal side effects and at the same time show efficiency. Intralesional sodium stibogluconate[20,21] or bleomycin[22] showed promising results in the studies. Topically paromomycin ointment (leshcutan®)[23,24] is also effective. Physical methods such as cryotherapy, heat therapy, scraping and curettage are also used with encouraging success.[25-27]

In addition to oral antibiotics like metronidazole and cotrimoxazole,[28-30] which are reported to be successful in the treatment of cutaneous leishmaniasis, rifampicin was also reported as a possibly promising antileishmanial agent.[31-33]

The results of the present controlled study support this conclusion. Rifampicin seems to be a suitable antileishmanial drug with good efficacy, with minor side effects in comparison to placebo and in patients treated with pentavalent antimonials,[34] the mainstay of leishmania treatment. Although it has not been reported to be associated with hepatic dysfunction, it should not be given to patients with known liver disease. A course of 6 weeks in the doses of 10mg/kg/day is likely to be sufficient for treatment of cutaneous leishmaniasis in most cases. Children in whom the treatment modalities are restricted, rifampicin can be given in doses of 10 mg/kg/day for 4-6 weeks with considerable efficacy. The study also suggested that rifampicin is worthy of a more extensive trial.

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