Treatment of cutaneous leishmaniasis by intralesional metronidazole

Makram M. Al-Waiz, *MBChB, PhD,*
Khalifa E. Sharquie, *MBChB, PhD,*
Mohammad Al-Assir, *MBChB, DDV.*

Cutaneous leishmaniasis (CL) is a specific skin infection caused by *Leishmania* parasite and is endemic in tropical and subtropical areas.[1] Optimal treatment for the old world CL is not well established and there have been few controlled clinical trials of different therapeutic modalities of this condition. The recommendation of the use of intralesionally administered pentavalent antimony compounds by the World Health Organization,[2] as well as other substances such as zinc sulfate and hypertonic saline are the mainstay local therapy of CL. However, with these modalities there is a failure rate and always there is a need for an alternative treatment.[3] One ß-hydroxyethyl, 2 methyl and 5 nitroimidazole, now called metronidazole, was found to have particularly high activity in vitro and in vivo against *trichomonas vaginalis* and *entamoeba histolytica.*[4] Oral metronidazole had been used in the treatment of CL but the results were unsatsifactory.[5-7] The current trial was therefore designed to evaluate local infiltration of the drug in healing CL lesions. Patients with single or multiple typical lesions of CL presenting at the Department of Dermatology, College of Medicine, University of Baghdad, Baghdad, Iraq, fulfilled the following criteria, 1. confirmed cases of CL by smear and culture or in combination, 2. acute CL with history of 12 weeks or less. This criterion was applied to exclude any possibility of self-healing of lesions during the period of follow-up, 3. cases of re-infection were excluded. For each patient admitted to the study, a detailed history was taken including name, age sex and residence. Details of the lesions were recorded, including the site and size of induration, duration and type of lesion and whether it was wet or dry. Associated features such as lymphatic involvement or satellite lesions were noted. To confirm the clinical diagnosis, parasitological confirmation was sought for all cases. Thus, for a case to be admitted to the study, demonstration of the *Leishmania* organism was prerequisite. The following was conducted either alone or in combination, 1. Smear, using a dental broach, from more than one site from the lesion, smeared on a clean glass slide and stained with *Leishmania*'s stain. It was examined microscopically for amastigotes inside or outside macrophages. 2. Culture, material obtained from the lesion by dental broach was cultured on either semisolid or biphasic medium (Novy MacNeal Nicolle,) . The culture was incubated at 26°C and examined after 5 days and subsequently at close intervals to demonstrate promastigotes of *Leishmania*. A negative culture was sub passaged at 10 days interval and not discarded until after 30 days.

Seventy-three patients were included in this study. Their ages ranged from 1-66 years. Patients were divided into 3 groups, metronidazole 5% group (27 patients), CL lesions were infiltrated with 5% metronidazole solution intralesionally; metronidazole 0.5% group (31 patients), patients were injected intralesionally with 0.5% metronidazole solution. These 2 solutions were prepared by dissolving 5g and 0.5g of metronidazole powder (obtained from Samara Drugs Industry, Iraq) in 100ml of bidistilled deionized water. The solutions were then sterilized in an autoclave at 121°C for 20 minutes in suitable screw capped bottles with rubber caps to allow for sterile injection. Controls (15 patients), a few lesions on unimportant and unexposed parts of the body were left as controls after obtaining the consent of the patients. The lesion was infiltrated with the drug solution, thoroughly using disposable tuberculin syringe until complete blanching was achieved. The amount of solution required was 0.1-4ml and occasionally more, depending on the size of the lesion. No local anesthesia was added to any solution. Patients were seen at 10-15 day intervals after injection. At each visit, the lesions were re-examined and the response graded using the following system, slight (decreased erythema and edema of the lesion), mild (reduction in the size of the lesion up to 30%), moderate (reduction in the size of the lesion of more than 30% but less than 60%), marked (reduction in the size of the lesion by 60% or more and parasite not detected in the lesion by smear or culture or in combination) and total clearance of the lesion with parasites not detected in the affected area by smear or culture or in combination. Both marked improvement and total clearance were considered as a cure. In cases where there was slight or mild improvement, another injection was given. At the end of the 6-week follow-up, the lesions were reassessed and parasitological proof of cure or otherwise were obtained by smear or culture or in combination. In the 5% group, 56 lesions were treated with this concentration, 51 lesions were of the dry type while 5 lesions were of the wet one. Forty-nine lesions showed complete clearance (87%), while 7 lesions showed slight improvement. Twenty-one lesions showed marked improvement or total clearance within 10 days by a single injection. However, 22 lesions showed total clearance by 2 injections while

6 lesions required 3 injections to show complete clearance. The patients during the intralesional infiltration of the drug noticed slight pain. After healing, scarring was minimal or absent, but hyperpigmentation was noted in all patients which later disappeared. In the 0.5% group, 65 lesions were treated, 55 lesions of the dry type and 10 lesion of the wet one. Marked improvement or complete clearance was observed in 55 lesions (85%). Only 2 patients showed total clearance after a single injection. However, 24 lesions showed total clearance by 2 injections while 29 lesions required 3 injections to show complete clearance. Regarding controls, 33 lesions were included in this group and were followed-up for 45 days. After the end of follow-up, there was minimal reduction in the size of lesions. Moreover, some lesions especially on the lower limb showed signs of infection. Parasites could be still detected in smear and culture or both at the end of the follow-up period.

In the design of this trial, only acute lesions, which had been present for 12 weeks or less, were included, and the follow up period was 6 weeks. This gave a total of 18 weeks, which is less than the healing time reported for lesions caused by both *L. major* (9 months or more) and *L. tropica* (one year or more).[8] In addition, a number of lesions were left untreated and followed-up as controls to demonstrate that no self healing took place within the follow-up period. It can therefore be assessed that the healing which occurred after drug administration in this trial is due to the effect of the drug and not due to self-healing lesions. The results of this trial show that intralesional infiltration with metronidazole gives high cure rate using low concentration (0.5%) or high concentration (5%). However, with higher concentration, healing occurs faster and requires less frequent injections. Metronidazole had been reported as an effective treatment of CL when the drug is orally administered. However, the cure rate is not high and there is the controversy regarding its use.[5,6] This is probably due to the low concentration of this antiprotozoal drug at lesional site following oral route of administration. In case of intralesional infiltration the high cure rate is owed to high concentration of the active ingredient at tissue level.

On the basis of this trial, the use of 5% metronidazole solution, injected intralesionally, in the treatment of CL is highly recommended. The treatment is safe with no serious side effects, gives high cure rates and the final cosmetic effect is very good. Local injections for the treatment of CL are advised when there are few lesions, to avoid systemic side effects, to increase the concentration of drug at the lesional site and to increase its effectiveness and reduce the cost of therapy.

Received 10th February 2004. Accepted for publication in final form 11th May 2004.

From the Department of Dermatology and Venereology, College of Medicine, University of Baghdad, Baghdad, Iraq. Address correspondence and reprint requests to Prof. Makram Al-Waiz, Department of Dermatology and Venereology, College of Medicine, University of Baghdad, PO Box 61369, Postal Code 12114, Medical Collection Post Office, Bab Al-Mua'dham, Baghdad, Iraq. Fax. +964 (1) 4250243. E-mail: makram552000@yahoo.com

References

1. Pringle G. Oriental sore in Iraq. Historical and epidemiological problems. ***Bulletin of Endemic Diseases (Baghdad)*** 1959; 2: 42-67.
2. World Health Organization. The leishmaniasis, report of WHO report of expert committee. Technical report series, WHO No. 701. Geneva: World Health Organization, 1984.
3. Sharquie KE, Najim R, Farjou IB. A comparative controlled trial of intralesionally administered zinc sulfate, hypertonic sodium chloride and pentavalent Antimony compound against acute cutaneous leishmaniasis. ***Clinical and Experimental Dermatology*** 1997; 22: 169-173.
4. Cosar C, Ganter P, Julou L. Etude experimental du metronidazole, 8823 R.P., activities trichomonacide et amoebicide. Toxicite et prietes pharmacologiques generales. ***Presse Med*** 1961; 69: 1069-1972.
5. Wahba A, Cohen H. Cutaneous leishmaniasis: inefficacy of treatment with metronidazole. ***Arch Dermatol*** 1977; 113: 1299-?
6. Belehu A, Naafs B, Touw-langendijk E. Failure of metronidazole treatment in Ethiopian mucocutaneous leishmaniasis. ***Br J Dermatol*** 1978; 99: 421-422.
7. Pedersen JK, Sawicki S. Metronidazole therapy for cutaneous leishmaniasis. ***Arch Dermatol*** 1975; 111: 1343-1344.
8. Griffiths WA, Croft SI. Cutaneous leishmaniasis. ***Postgraduate Doctor Middle East*** 1980; 3: 338-340.

Comparison of intravenous aminoglycoside therapy with switch therapy to cefixime in urinary tract infections

Salmieh Noorbakhsh, *MD,* ***Abdolaziz R. Lari,*** *MSc, PhD,* ***Faramarz Masjedian,*** *BSc, MSc,* ***Hamid Mostafavi,*** *PharmD,* ***Reza Alaghehbandan,*** *MD.*

Urinary tract infections (UTI) cause acute morbidity and may result in severe problems, including hypertension and reduced renal function. Diagnosis of UTI is extremely important as prompt treatment could prevent damage. As intravenous (IV) antibiotic therapy is associated with side effects, toxicity, high cost, and long hospitalization period in treatment of UTIs, switch therapy (IV-to-oral antibiotic) is considered to reduce above-mentioned harms. In the present study, we compared the efficacy of IV aminoglycoside