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ZOONOTIC AND PARASITIC DISEASES

PROCEEDINGS OF THE THIRD
INTERNATIONAL AND PAN-ARAB SEMINAR
HELD IN AMMAN, JORDAN,
17-20 OCTOBER, 1989

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ZOONOTIC AND PARASITIC DISEASES

**Proceedings of the Third International and Pan-Arab Seminar
held in Amman, Jordan, 17-20 October 1989**

Edited by
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TREATMENT OF LEISHMANIASIS

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Why Treat Leishmaniasis?

Considering that 90% of primary lesions of cutaneous leishmaniasis heal spontaneously anyway and that recovering is supposed to confer lifelong immunity, this could be a pertinent question to ask.

In old world cutaneous leishmaniasis treatment is desired when there are lesions on exposed parts of the body especially on the face, the healed scars and areas of depigmentation are ugly, another reason to treat is to prevent the 10% of cases that don't heal from progressing to one of the chronic forms.

Infection with *L. aethiopica* should receive special attention since they involve large areas of the body surface and tend to have a long course. Healing of these lesions gives rise to severe fibrosis that, for example may restrict the use of fingers (5).

According to Marinkelle (20), another important reason for the need to treat is that is one of the most important methods of controlling the disease in the population.

Traditional Therapies

1. The current textbook method of treating new world cutaneous and mucocutaneous leishmaniasis but not *L. aethiopica* infection is with a pentavalent antimonials. The drugs of choice are; sodium stibogluconate and N-methylglucamine antimonate. There are various recommended dosage regimes, Bulter (6), recommended a dose of 0.1 ml of a 34% solution of the drug/kg body weight/day for 14 days. The course can be repeated after a 14 days interval, the drug can be given by intravenous or intramuscular routes.

A large number of side effects including nausea, vomiting, diarrhea, skin rashes, headache and dizziness are associated with these drugs. More importantly, the drugs are toxic to the liver, kidney and heart (15).

The mechanism of action is unclear, numerous enzymes of the parasite are inhibited selectively, of significance; phosphofructokinase which catalyses a rate limiting step of glycolysis is inhibited, in the way production of adenosine triphosphate may be blocked (12).

2. For mucocutaneous leishmaniasis, the second line of treatment is with amphotericin B, this is a toxic antibiotic used parenterally for treating systemic fungal infections. The drug should be diluted in 5% dextrose solution and given 1 mg/kg over 6 hours on alternate days. Amphotericin B is very toxic to the kidney, urea and urine protein levels should be carefully monitored. Patients often complain of fever, chills, headache, nausea and nasal swelling. Details of mechanism of action of amphotericin are not clear, it is thought to act through interaction with ergosterol in leishmania membranes.
3. Both amphotericin B and pentamidine can be used as second line drugs to treat cutaneous leishmaniasis but the severe toxic side effects should be considered, pentamidine, an aromatic diamidine is given intramuscularly at about 4 mg/kg/day for 14 days. Beside causing vomiting, hypotension and tachycardia, it is also toxic to the liver, kidney and pancreas (15).

Infections with *L. aethiopica* pose a special problem because they are refractory to the normal regimens of antimonials which may be effective only in high doses, as stated by Bryceson (5), he recommended pentamidine or amphotericin B for such infections. Treatment must be prolonged even after apparent elimination of parasites as relapses have been observed up to 15 months later. Bryceson (5) also made the interesting observation that before the patients are finally cured, they relapse in a form that has a tuberculoid histology and convert to leishmanin positive from a previously negative state, chemotherapy is usually unsuccessful until this conversion.

Chulay (7) however, recommended using high doses of sodium stibogluconate to treat *L. aethiopica* up to 40 mg/kg/day.

Drugs That Are Used For Other Conditions:

1. Ketoconazole is a new imidazole derivative which is used for antifungal therapy, it was reported in sporadic trials to be effective in vitro (3) and in vivo (18) in leishmaniasis. In one study ketoconazole was effective and curative in about 70% of *L. major* cases after 4-6 weeks of treatment with 200-400 mg daily, no connection

was found between the duration of treatment, number or size of lesions and the rate of treatment. There seemed also to be no relationship between the cure rate and the time after infection that the treatment was started.

No side effects of ketoconazole have been reported by the patients, monitoring of liver function tests is required prior to and a regular 2 weeks intervals during treatment (2).

In another study cutaneous leishmaniasis has been successfully treated by ketoconazole with permanent cure in all cases except in a small proportion (5.9%), in comparison with cases treated with rifampicin it is clearly evident that ketoconazole is a highly effective and safe drug in treatment of cutaneous leishmaniasis (1). Ketoconazole antileishmanial activity was remarkably uniform against *L. braziliensis* and *L. tropica*, but Abdel Aal et al (1), found no difference has been observed between the response of cases getting their infection in any of the endemic Arabic countries (Saudi Arabia, Iraq and Jordan).

2. Metronidazole (Flagyl) is used for treatment of amebiasis and trichomoniasis, it is also used for leishmaniasis, its selective toxicity is probably due to reduction of nitro group on the drug inside the parasite. Clinical cure of leishmaniasis has been reported by Bassiouny (2), after the use of metronidazole, the earlier reported success could be accounted for by spontaneous cure, it appeared now that it is unlikely to play a primary role in the therapy for leishmaniasis.
3. Nifurtimox is the drug of choice in American trypanosomiasis (chagas disease), with a dosage of 10 mg/kg/day for 30 days, clinical cure in 6 of 13 new world cutaneous leishmaniasis cases but only 2 of 13 mucocutaneous cases (21). At a dose level of 8-10 mg/kg/day for 120 days, nifurtimox was found to achieve clinical healing of cutaneous leishmaniasis in 5 of 8 patients, and in 6 of 10 patients on 20 mg/kg/day for 10 days (11). Side effects were more common and more severe when the higher doses were used, these include anorexia, weight loss, insomnia and personality changes.
4. Rifampicin, in one of the earlier trials with rifampicin in Middle East using 600 mg/kg/day, clinical cure was reported in 4-16 weeks, in 9 of 13 patients with cutaneous leishmaniasis (13) Rifampicin was tried with other drugs in combination, Peters et al. (25) reported a case of successful treatment of *L. mexicana amazonensis*

diffuse cutaneous leishmaniasis with rifampicin and isoniazid but showed limited therapeutic action against *L. aethiopica* compared with pentamidine which still remains the drug of choice for initial therapy of diffuse cutaneous leishmaniasis.

Some therapeutic effect of rifampin/isoniazid may be expected in patients with very mild parasite load (some scanty parasites in the skin biopsy but no parasites in the skin smear) (28).

5. 8-Aminoquinoline is found to have exceptional efficacy in the *L. donovani* hamster model of visceral leishmaniasis as reported by Kimmamonk et al. (19), but no convincing clinical trials have been reported. Dihydroemetine and emetine was for leishmaniasis by some authors, Cohen (8), reports adding emetine to steroids to treat chronic leishmaniasis.
6. Levamisole, an antihelmenthic drug, can be used for leishmania as well, its use is dependant on a separate property of the drug which is its potentiating effect on T cells. Bulter (6), observed that even in an endemic area the prevalence of cutaneous leishmaniasis is low, probably due to inoculation with the parasite in early life by sandflies which leads to subclinical infections and long term immunity, he proposes that clinical disease in late life is due to declining cell mediated immunity which can be potentiated by levamisole, in his trial 28 patients were cured with levamisole only, but his proposal requires further investigation.
7. Furazolidine, Berman and Lee (3), reported a high antileishmanial activity of furazolidine against amastigotes in human macrophages. In vitro it was found to be more effective than nifurtimox (11).
8. Phenothiazines which are psychoactive drugs for psychiatric disorders, were found to have antileishmanial and antitrypanosomal activity. Henriksen and Lenden (14), treated 3 patients with *L. aethiopica* diffuse cutaneous leishmaniasis with topical chlorpromazine, inflammation was improved and parasites smears were after one month of treatment. Although this method of treatment is attractive, its efficacy has to be investigated further. However scars and skin discolouration were not altered and it is important that treatment is started early (21).

9. Allopurinol which is used in hyperuricaemia is observed to prevent growth of leishmania and Trypanosoma cruzi in vitro. It also augments the antileishmanial effects of sodium stibogluconate in vitro. Allopurinol was successful in curing 6 of 10 patients with visceral leishmaniasis who has failed with sodium stibogluconate (17).

Rational Approaches For Better Antileishmanial Agents:

1. Difluoromethylornithine (DFMO) inhibit growth of leishmania by blocking polyamine synthesis through inhibiting ornithine decarboxylase essential for polyamine synthesis (22).
2. Antipain and leupeptin, the peptide analogues, lead to inhibition of cysteine proteinases, and stop the in vitro multiplication of the parasite (9).
3. Clomipramine inhibits the H⁺ATP in the membrane of the parasites leading to disruption of the parasite surface membrane proton electrochemical gradient (28).
4. Transfer factor is a dialysable extract of leucocytes obtained from healthy donors who have recovered from cutaneous leishmaniasis. This factor is injected subcutaneously near the skin lesion of the patient (15).

Treatment of Leishmaniasis Recidivans:

Many of the drug therapies that are effective for cutaneous leishmaniasis are less effective for leishmaniasis recidivans, it is believed that this is due to, in part, the structure of the tuberculoid lesions. These have a dense cellular infiltrate and later dense scar tissue, surrounding small islands of the parasites, these pockets are not penetrable by the drug (15).

Steroids have been injected near or at the lesion to shift the hypernergic activity towards a normogenic response (8). This treatment is very painful, Cohen (8), reported adding emetine to steroids to treat a case that failed with amphotricin B.

Non Medical Treatment of Leishmaniasis:

Plastic surgery has had an important role to play in treating disfiguring scars especially scars of leishmaniasis recidivans, in these cases the patients already would have received medical treatment for some time, Currie (10), treated 78 lesions in 50

patients by surgical curettage under local anaesthetic, there were 73 success with wound healing within 4 weeks. Surgical treatment is quick, cheap and simple with few side effects and in simple cases, it requires only one or two visits to the clinic (15).

Leishmania organism are very thermo sensitive, both heat and cold treatment have been tried. Local heat treatment was tested and found effective in 3 patients with diffuse leishmaniasis, a water bath with circulating water through a pad wrapped around the lesion provided a temperature of 39°C to 41°C for a cumulative time of at least 20 hours over a period of several days, beneficial effect documented by pre and post treatment biopsies and cultures, but several other patients with ordinary cutaneous leishmaniasis did not respond to the same form of treatment. It was concluded that different strains and/or species of leishmania vary in their sensitivity to elevated temperatures (23).

Cold treatment has an advantage over heat treatment in that it tends to cause less inflammation to the surrounding tissues. Bassiouny (2), reported the successful treatment of 30 south American patients using cryotherapy with carbon dioxide cryomachine, the cosmetic result is good, there is little scarring because cryotherapy leaves an intact collagenous framework.

Cryotherapy is simple rapid effective once treatment for cutaneous leishmaniasis. It can be as alternative to antimonial therapy but it is not alone curative for mucosal leishmaniasis due to *L. braziliensis*, which needs systemic treatment and cryosurgery is suggested to be used as an adjunctive or palliative measure (2). This is because there is usually early systemic spread of the parasite to the mucosa although the mucosal lesions may not appear until much later. (16).

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