

RECENT TRENDS IN THE TREATMENT OF CUTANEOUS LEISHMANIASIS

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Leishmaniasis is caused by protozoal species and subspecies of the genus *Leishmania*. Although the infection occurs on all continents, it is endemic in tropical and subtropical countries. The World Health Organization (WHO) estimates that there are 400,000 new cases in the world each year.¹ It is transmitted to man, most often by the bites of infected female sandflies. The parasites exist in two forms: an amastigote in the mammalian host, and a flagellated promastigote in the insect vector. In increasing order of systemic involvement and clinical severity, human leishmaniasis can be classified into cutaneous (Oriental sore), mucocutaneous (espundia), and visceral (kala azar) forms. In Saudi Arabia, the most common manifestation of infection is cutaneous leishmaniasis (CL). While many cases of CL have been found in various regions such as Al Baha, Central, Qassim and the Eastern Province, CL is known to occur throughout the Kingdom.²

In the "Old World," the majority of CL is caused by one of two species of parasites: *L. tropica*, which is classically an urban disease producing relatively benign "dry" ulcers, and *L. major* (the most common cause of CL in the Kingdom), the rural type which characteristically develops large, more destructive ulcers of the "wet" type. *Leishmania aethiopica* is found in Ethiopia and Kenya. In the "New World," the parasites are *L. mexicana* (in Mexico, Guatemala, and South America), and *L. braziliensis* (in South and Central America).

The normal response to CL caused by either *L. major* or *L. tropica* is a lifelong cell-mediated immunity. While this prevents later infections from causing serious lesions, minor lesions may develop. CL manifests as self-healing ulcers, as chronic mutilating ulcers, or in rare cases, as disseminated cutaneous leishmaniasis (DCL).

The aims of therapy are two-fold, namely, clinical healing and disappearance of parasites. Very few well-documented and scientifically designed clinical trials have been carried out or have been reported. However, the main problem derives from uncertainties regarding the stage of the disease at which drug administration is initiated. A

number of published reports have been hindered by certain expectations and limitations of the number of antileishmanial drugs. This is largely because they are adhering to recommended regimens which have no sound basis in therapeutics or toxicology. Undoubtedly, misunderstanding these principles will lead to misuse of the drugs with disappointing results, and to unnecessary reliance on more toxic and less efficient drugs. Although the treatment of CL is empirical, the efficacy of anti-leishmanial drugs is controversial. Doctors have sometimes become confused when selecting the most appropriate treatment option. In this article, an attempt is made to review the classical and newly developed therapeutic agents used in the treatment of CL. Particular emphasis is placed on their efficacy and safety.

Treatment Modalities of Cutaneous Leishmaniasis

The management of CL creates a real challenge. Unfortunately, its control is usually hampered by ignorance of its true prevalence.^{1,3} Most CL lesions are self-limiting and may heal spontaneously within one to five years. In spite of this, treatment of CL is justified in a variety of cases, namely, early lesions, multiple lesions, lesions involving cosmetically sensitive sites, mucosal lesions, disseminated lesions, and patients with significant immunosuppression.⁴ In addition, the psychological impact of CL cannot be ignored. Unfortunately, to date, there is no safe, simple and effective treatment for CL and the pentavalent antimony compounds, "the best drugs of a bad bunch," still remain the mainstay of treatment in the majority of cases.⁵ In spite of many new therapeutic studies, treatment of CL is to some extent still empirical. The assessment of the efficacy of any therapeutic agent in a self-healing disease such as CL is very difficult. Cure rates have varied from zero to 100% in different areas of the world.⁶

Systemic Drugs

Antimony Compounds

Kikuth and Schmidt⁷ in 1937 reported the anti-leishmanial activity of solustibosan (sodium stibogluconate), a pentavalent antimony compound. Durand et al.⁸ in 1946 were the first to test another

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pentavalent antimony, N-methylglucamine antimoniate (glucantime) in man against leishmaniasis. Today these two pentavalent antimonials (PVAs), sodium stibogluconate (Pentostam,[®] Wellcome Foundation, UK), and meglumine antimoniate (Glucantime,[®] Specia, France), are the most widely used leishmanicides. Although it is usually reported that both have similar efficacy and toxicity, in relation to their pentavalent antimony content, sodium stibogluconate (SSG) solution (Pentostam[®]) contains about 10% antimony (100 mg Sb/mL), whereas meglumine antimoniate (MA) solution (Glucantime[®]) contains about 8.5% antimony (85 mg Sb/mL).⁹

The WHO recommendations on the dosage of PVAs for CL is 20 mg Sb/kg body weight per day to a maximum of 600 mg i.m. daily for 10-14 days. The course can be repeated in resistant cases after a rest period of 14 days.^{1,3} Voller et al.¹⁰ reported that SSG can inhibit glucose uptake by promastigotes of *L. tropica*. Berman and Wyler were able to show that SSG decreases DNA, RNA and protein synthesis in a dose-dependent manner in SSG-treated *L. mexicana*.¹¹ In addition, both the anaerobic and aerobic glucose oxidation are inhibited, resulting in a reduction in ATP and GTP production in the amastigotes exposed to SSG.¹² It is not yet clear whether pentavalent antimonial drugs have to be converted to trivalent antimony to execute their antileishmanial activity.

Clinical Efficacy: When given in adequate dosage and duration, PVAs have been reported to be effective in VL in different parts of the world.^{13,14} They were also shown to have efficacy that ranged from 100%^{15,16} to 70%^{17,18} in CL when they were given daily in a dose of 10-30 mg Sb/kg for 15 days. It is reported that all patients who were given a daily dose of 20 mg/kg with no upper limit on daily dose were cured from acute CL.¹⁹ Ghosh has observed that SSG in a daily dose of 600 mg for 10 days cured 82% of cutaneous lesions in Syrian patients.¹⁷ In Saudi Arabia, the positive response of CL to PVAs varies from 50% to 100%. In a recent study we obtained a satisfactory response (lesions fully healed or improved) of 84% with MA given i.m. in a daily dose of 15 mg/kg for 15 days.²⁰ There are also various reports of treatment failure with PVAs in CL.²¹⁻²³

Side Effects: Antimonials are contraindicated in pregnancy and in patients with significant renal, hepatic or cardiac diseases. The first signs of toxicity are myalgia, joint stiffness, malaise, anorexia and bradycardia with ECG changes of prolongation of the QT interval and T-wave inversion. Hepatotoxicity, hemolytic anemia, nephrotoxicity, pancreatitis and anaphylaxis are rare occurrences.¹⁸

Other Drugs

Although the PVAs are the standard drugs used in the management of leishmaniasis, there are still controversies

and unanswered questions related to their use. In addition, treatment failures have been frequently observed.²¹⁻²³ More recently, strains of leishmania resistant to PVAs have emerged, and this has reached "alarming" proportions in some countries.²⁴ The following agents are used as second-line antileishmanial drugs in the treatment of CL that does not respond to antimony compounds, or for patients who cannot tolerate antimony.

Pentamidine

Pentamidine has been used for many years against *Trypanosoma*, *Babesia* and *Leishmania*. It acts against *Leishmania* by damaging the kinetoplast DNA-mitochondria complex.²⁵ It is effective against all forms of leishmaniasis, with the exception of DCL.^{26,27} This drug acts more slowly against *Leishmania* than PVAs, and short courses have been associated with a high relapse rate. Pentamidine in a dose of 3-4 mg/kg once or twice weekly until resolution occurs is recommended in resistant cases of CL.¹

Side Effects: Although 50% of the injected dose is excreted mainly in the urine in five days, traces can be detected in the urine up to 217 days, and in the kidney up to 240 days after a single injection.^{26,27} Cumulative effects, which often limit dose or frequency of administration, include weakness, nausea, vomiting and abdominal pain, which may indicate pancreatic damage.^{26,27} The unusually high rate of hyperglycemia (50%) associated with its use has been attributed to the high rate of pancreatic fibrosis.²⁸ Others have also attributed the observed hypotension, tachycardia and electrocardiographic changes in T waves to its cardiotoxicity.²⁵

Imidazole Compounds

The antifungal imidazole compounds, such as ketoconazole, clotrimazole, miconazole, fluconazole and itraconazole, have been reported to have antileishmanial activity.^{29,30} Of these, ketoconazole and itraconazole are the only ones that have been used systemically for cutaneous leishmaniasis. The others are used topically. Experimental and clinical studies have demonstrated possible antileishmanial action of ketoconazole.³¹⁻³³ The clinical studies have demonstrated beneficial effects in CL when ketoconazole is administered orally at a dose of 200-400 mg/day.^{29,30} In Saudi Arabia, oral ketoconazole was found to be an effective treatment for CL caused by *L. major*. In a study by Kubba et al., 17 out of 20 patients responded successfully to oral ketoconazole.²⁹ However, in another study from Saudi Arabia, it was found to be ineffective when applied topically in the form of 2% cream.³⁴ In all studies, however, prolonged therapy, varying from 8-16 weeks, was necessary to achieve the desired results. Furthermore, although the treatment was fairly well tolerated, side effects, particularly gastrointestinal and hepatotoxicity, were observed.³⁵

Ketoconazole must be used with extreme caution, because of the possibility of idiosyncratic hepatitis, which may be severe or fatal.³⁵ Itraconazole (200 mg/day for 4-8 weeks) cured 15 (79%) of 19 patients from India who had CL, and was reported to be more easily tolerated than ketoconazole.³⁶

Metronidazole (another imidazole derivative) is mainly used for amebiasis, trichomoniasis and anaerobic infections. There are conflicting reports regarding its activity in leishmaniasis. Pearson and Sawick³⁷ have used it successfully in CL, but others have found it ineffective in infections with *L. braziliensis*³⁸ and *L. aethiopica*.³⁹

Amphotericin B

This is one of the polyene antibiotics effective against various fungi and leishmania. *In vitro*, as well as *in vivo* (both animal and human), studies have demonstrated the leishmanicidal activity of amphotericin B. It is indicated in MCL when one or more courses of PVAs have failed to cure the disease.⁴⁰⁻⁴² The use of amphotericin B for CL in humans has been limited, and there is no experience with this drug in Saudi Arabia. It is administered over a period of 4-6 hours by slow intravenous infusion, starting at 0.1 mg/kg dose and gradually increasing to 1 mg/kg. In addition to nephrotoxicity, other side effects include anemia, thrombophlebitis, and hypokalemia.

Miscellaneous Drugs

Drugs such as allopurinol, rifampicin, dapsone, chloroquine, and nifurtimox,⁴³⁻⁴⁷ have found favor in some studies, but the experience with these drugs is not widely accepted.

Local Treatment

The standard treatment of CL consists of parenteral administration of pentavalent antimony. For simple lesions which are few in number and where there is no risk of disfigurement or restriction of joint mobility, such treatment regimens which involve parenteral injections and which expose patients to untoward side effects may not only be inconvenient but also unnecessary. Topical application or local treatment of cutaneous lesions, therefore, would be valuable. Such a therapeutic measure has always been the dream of all experts in the field of CL. It is believed that this type of treatment must have been in use in endemic areas.^{1,3} Local therapy is of value if a number of criteria are met: 1) no dissemination to local lymph nodes; 2) the therapeutic measures must ensure that most of the organisms in the lesion are eradicated; and 3) local therapy should be simpler to administer and less toxic than systemic ones.^{1,3}

Physical Methods

Physical methods such as scraping the lesions with a sharp spoon or cauterization have been employed to treat

CL since the earliest times.⁴⁸ The most common physical methods used for the treatment of CL include:

Curettage and Surgical Excision

Plastic surgery has had an important role in treating disfiguring scars. Currie treated 78 patients with CL in Pakistan by curettage under local anesthetic. He noticed that small sores responded especially well and heal within three weeks with good cosmetic results.⁴⁹ Azab et al. treated 35 lesions in Saudi Arabia with skin flaps or free grafting. The author claimed good cosmetic results with no scars.⁵⁰ However, surgical curettage is not recommended, in view of the risk of dissemination along lymphatics.⁵¹

Cryosurgery and Heat Application

Leishmania parasites are thermosensitive. In *in vitro* study, *L. tropica* multiplied best at 35°C and was completely eliminated at 37°C.⁵² In view of this feature, both heat and cold treatment have been tried. In Iraq, infrared heat was used to raise the temperature of CL lesions to 55°C for 5 minutes, and all lesions healed in 5 to 6 weeks.⁵³ Mutinga and Mingola successfully treated three cases of acute CL by combined ultraviolet light and infrared therapy.⁵⁴ Bassiony et al. reported the successful treatment of 30 Saudi patients using cryosurgery with a CO₂ cryomachine.⁵⁵ In this study, the probe-tip was applied for less than 60 seconds. With this method, there is little scarring because cryotherapy leaves an intact collagenous framework. However, the efficacy of cryosurgery was questioned in a large study in which only 27% of patients with CL caused by *L. major* who were treated with a nitrous oxide cryomachine were cured.⁵⁶ Cryotherapy can result in dissemination (satellite papules and lymphatic subcutaneous nodules) and permanent pigment changes in dark-skinned patients.⁵⁶

Intralesional Infiltration

Intralesional injection of PVA would seem to be a means of delivering high concentrations of antimony to the infected lesions. Although some investigators have questioned the effectiveness of this method, Sharquie et al. obtained good results (94.6% cure rate) after injecting CL lesions with SSG once or twice every 8 days.⁵⁷ Excellent results were also obtained by Kellum, who injected each lesion 18-20 times with SSG, and followed up for two months.⁵⁸ In a recent study in Saudi Arabia, we found that intralesional injection is as effective as daily intramuscular therapy, and leads to faster improvement.²⁰ Lesions should be injected with antimony (0.2-0.8 mL) into the upper- and mid-dermis on alternate days, for a total of 15 injections. Infiltration must be thorough and produce complete blanching of the base of the lesion.²⁰ Intralesional antimony is recommended for early lesions and limited disease, particularly in those who have cardiac, liver or renal diseases for whom toxic, parenteral antimonials are contraindicated. It is more economical than intramuscular

treatment, since a much lower total dose of antimony is required, and less likely to cause the side effects associated with high doses of systemically administered antimony.⁵⁹ However, it is not practical for multiple or disseminated lesions and is not suitable if the lesions are located in highly sensitive sites such as the face, unless a local anesthetic is used to reduce the local pain induced by intralesional injection. Inadequate infiltration of lesions is probably the reason for the reported failure with this mode of therapy in some studies.⁵⁷

Topical Therapy

The results of topical treatment of CL with some imidazole compounds have been encouraging. Brenner⁶⁰ used clotrimazole in seven patients and miconazole in two patients with CL of 2-9 months' duration and found clinical improvement in all patients within seven days to two months. The lesions disappeared in all patients within a maximum period of two months when the solution was applied three times daily. In Saudi Arabia, we compared clotrimazole with miconazole creams for the treatment of CL. The results indicated that 15.7% of lesions treated with clotrimazole fully healed, and none of the lesions treated with miconazole healed when assessed at 30 days.⁶¹ On the other hand, ketoconazole cream was shown to be ineffective when it was used for the treatment of Saudi patients with CL.³⁴

El-On et al.^{62,63} carried out clinical trials on 100 patients with CL of 4-6 years' duration. After 10 days of treatment with an ointment consisting of 15% paromomycin plus 12% methylbenzathonium chloride (MBCL) in soft paraffin (P-ointment) applied twice daily, there was complete disappearance of parasites from the lesions in 72% of patients, and another 15% became completely free of parasites in 20 days. Thirteen percent failed to respond to this form of treatment. This ointment is not yet available commercially.

Combination Therapy

Attempts have been made to increase the efficacy and reduce the side effects of antileishmanial drugs by using combination therapy. Rifampicin in combination with intralesional SSG was reported to produce good results in CL in Saudi Arabia.⁶⁵ A combination of SSG 600 mg i.m. and ketoconazole 200 mg three times daily was superior in CL caused by *L. major*, compared with either drug alone.²⁹ Isoniazid (INH) was also effective in patients with CL caused by *L. mexicana* and *L. major*⁶⁶ when it was combined with rifampicin (isoniazid 300 mg + rifampicin 1200 mg daily) for 4-7 weeks.

Experimental Treatment

Liposome-encapsulated PVA and amphotericin B,

recombinant interferon, cyclosporine, and monoclonal antibodies are some of the modalities under evaluation.⁶⁷⁻⁶⁹

Conclusion

Pentavalent antimonials are the drugs of choice for the treatment of lesions involving cosmetically sensitive sites, and multiple or disseminated lesions of CL. However, for simple lesions which are few in number, and where there is no risk of disfigurement or restriction of joint mobility, local therapy is simple, economic, quick, safe, appears effective and offers an attractive alternative to systemic therapy. Other drugs, such as pentamidine, amphotericin B and oral ketoconazole, are used for resistant cases of CL. In all cases of CL caused by *L. major* (wet type), secondary bacterial infections should be treated with the appropriate antimicrobial agent.

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