Proceedings of the Second World Conference on Clinical Pharmacology and Therapeutics

Washington, D.C., July 31–August 5, 1983

Editors

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Drugs for New World Cutaneous Leishmaniasis

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The leishmaniases are a group of several different clinical entities which are widely distributed in tropical and subtropical areas. They range in severity from self-healing skin lesions, to severely mutilating mucocutaneous involvement, and to visceral infections which are almost always fatal if not treated. Until recently the extent and severity of this group of diseases, as a major public health problem, was largely unrecognized.

The Leishmaniasis Steering Committee of the WHO Special Program for Research and Training in Tropical Diseases, has recently estimated that there are 400,000 new cases each year, but the number of people with chronic and long-standing incurable forms of the disease is unknown (1).

American cutaneous leishmaniasis includes three distinct clinico-pathologic entities: tropical ulcer, mucocutaneous leishmaniasis and the disseminated anergic cutaneous leishmaniasis. We will limit our presentation to the chemotherapy of these three entities.

Host-parasite interrelationships are intimately intertwined with approaches to chemotherapeutic management of leishmaniases. These host-parasite-drug interactions are fundamental to the successful treatment of the disease state. There is clinical and experimental evidence to indicate that treatment with pentavalent antimonials is more effective when the host's immune response is active (2).

Currently available anti-leishmanial agents have several limitations. Drug toxicity is a common limitation in patients, whose response may be compromised by both the infection and a poor nutritional state. The complexities of the disease, which may result from various strains of *Leishmania* species with different sensitivity patterns to drugs, may be complicated additionally by drug resistance. To this there must be added the fact that early treatment of leishmaniasis is rarely possible

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because the highest incidence occurs in regions where medical assistance is limited or unsophisticated and, even if diagnosed correctly, funds for effective drugs are severely limited. Moreover, the relatively long and painful course of treatment may well cause patients to leave before full and adequate treatment is complete even when it is available. It becomes increasingly apparent that a better strategy must be developed for diagnosis, treatment, management and the prevention of leishmaniases.

A meaningful strategy should include increased attention to the biology and biochemistry of the parasite and its relationships with the host. Improved methods for evaluating candidate compounds against the several types of leishmaniases are needed. The varied immune responses to infections in various hosts must be recognized as well as the differences in the pharmacokinesis of drugs selected for expanded trials. The mode of administration and frequency then become important aspects for consideration.

Cutaneous leishmaniasis extends from Mexico to Argentina with the exception of Chile and Uruguay. A decision as to treatment depends on whether one is dealing with a destructive mucous lesion, in which case treatment is absolutely necessary, or a simple cutaneous lesion, in which case the decision would be based on the type of *Leishmania* present in the area. The ulcerative lesion caused by the *L. mexicana mexicana* strain will often heal spontaneously and treatment is not always necessary. On the other hand, infections with *L. braziliensis panamensis* and *braziliensis braziliensis* are more unpredictable. They usually do not heal without treatment and occasionally, there may be complications such as mucosal lesions (nasal, oropharynx, larynx) and systemic involvement, where treatment is always necessary.

Local treatment, with antimonial infiltrations in the affected area, has been used, but this does not prevent early lymphatic dissemination and possible hematogenous dissemination. For these reasons we prefer to treat all our patients by the systemic route.

ANTIMONIAL DRUGS

The pentavalent antimonials, sodium stibogluconate and meglumine antimoniate, are the drugs of choice for treatment of cutaneous leishmaniasis. They are chemically similar and as far as is known have similar toxicity. Their mode of action against *Leishmania* has not been fully established. The polymeric character of the pentavalent antimonial drugs may provide enhanced penetration into the parasite lysosome and may also stimulate the reticuloendothelial system, but this has not been proven. There are experimental studies with infected human macrophages and mouse peritoneal macrophages which show that antimonial compounds have a direct effect against the amastigotes (3,4).

There is little information on the comparative clinical efficacy of sodium stibogluconate and meglumine antimoniate in the treatment of American cutaneous leishmaniases. At present, we are doing a comparative trial of these two drugs at Gorgas Memorial Laboratory in Panama to obtain this information. Common side

effects reported include anorexia, vomiting, nausea, malaise, myalgia, headache and lethargy. Electrocardiographic changes are dose-dependant, the most common being T wave inversion and a prolonged QT interval. A rarely reported side effect is renal damage.

Meglumine antimoniate solution (Glucantime) contains about 85 mg/ml of Sb, whereas sodium stibogluconate solution (Pentostam) contains about 100 mg/ml of Sb. Treatment regimes with these two drugs in patients with tropical ulcer is 20 mg of antimony per kg of body weight daily, intravenously or intramuscularly. However, the maximum daily dose is 850 mg for both, which is 10 ml of meglumine antimoniate and 8.5 ml of sodium stibogluconate. The rediscovery of the very short half-life and rapid renal excretion of pentavalent antimonials (5) suggests the possibility of obtaining better results by administering the antimonial in divided doses every 8 to 12 hours. The drugs should be given for a minimum of 20 days. The exact duration will vary from country to country in relation to the specific strain of parasite present. Patients who relapse after the initial recommended course should be retreated with the same drug at the same dose. Some patients may require a third course in order to obtain healing.

In vitro sensitivity studies of clinical isolates of *Leishmania* to pentavalent antimony suggest that in only a few cases is inherent drug resistance of the parasite responsible for treatment failures (6). Our clinical studies also show that the majority of the patients who do not respond to one course of antimonial will improve after a second or third course.

Pentavalent antimony compounds are still the drugs of choice for nasal-oral-pharyngal lesions (espundia). The daily recommended dose is 40 mg of antimony per kg of body weight, with a maximal daily dose of 20 ml of meglumine antimoniate and 17 ml of sodium stibogluconate for a period of 20 days. Cure rates have been unsatisfactory and in some regions of South America recurrence has been reported to be as high as 50% within one year of treatment (7). The drug of second choice in those patients who do not respond to multiple courses of pentavalent antimony is amphotericin B. Many patients are hypersensitive to *Leishmania* antigen and desensitization before specific treatment could be helpful.

Disseminated anergic cutaneous leishmaniasis is very difficult to treat because of the severe cellular immune defect of the patient. Pentavalent antimony and amphotericin B have been used with poor results. Dialyzable leukocyte extract, obtained from healthy donors with previous acute cutaneous leishmaniasis, given in high doses, at constant intervals and at the earliest time possible could be helpful in some of these patients (8). Total immersion in hot water twice daily may be helpful in some cases (7).

OTHER ANTILEISHMANIAL DRUGS

Amphotericin B

This is the second line treatment for patients refractory to antimonial drugs. Amphotericin B binds to steroles in the plasma cell membranes of eukaryotic cells

and this interacts with both the amastigotes and the host cell. The drug is administered by slow intravenous drip in a 5% dextrose solution. A total dose of 1.5 to 2 g for cutaneous lesions is recommended and 2.5 to 3 g for the mucosal disease. Since this drug is inconvenient to administer and has a number of toxic side effects, its use should be limited to those cases with ulcerative lesions localized near vital areas of the face, extensive and multiple skin lesions and the mucocutaneous cases that have failed to respond to antimony.

Cycloguanil Pamoate

In the treatment of cutaneous leishmaniasis, cycloguanil pamoate (Camolar) is administered by the intramuscular route in an oily medium of 40% benzyl benzoate and 60% castor oil as a repository drug containing 140 mg of base per ml. The advantage of cycloguanil pamoate is that it can be given in a single dose of 350 mg (2.5 ml) to adult patients, and a second dose can be given after six to eight weeks, if required. Thus, it is well suited in situations where patients travel long distances for treatment and treatment cannot be controlled adequately. The complete absence of adverse side effects is another advantage of this drug (9). Healing of lesions produced by *L. braziliensis* has been reported to take one to three months or more, and viable parasites have been demonstrated in lesions up to 15 weeks after treatment (9,10). Camolar is now recommended only for use in *L. mexicana* infections because of the high cure rate and shorter healing period (11) than that observed in cases of *L. braziliensis* (12).

Pyrimethamine (Daraprim)

This drug is a structural analogue of *p*-amino benzoic and folinic acids with antileishmanial activity. In Panama, C. M. Johnson (personal communication) giving pyrimethamine 25 to 50 mg daily for three to five weeks has obtained healing in 65 of 72 (90%) patients with cutaneous leishmaniasis. Because of bone marrow toxicity, the use of this drug has been discontinued for the treatment of leishmaniasis; however, it should be kept in mind as an alternative which could be used in cases of therapeutic failures with pentavalent antimony.

EXPERIMENTAL ANTILEISHMANIAL DRUGS

Nifurtimox (Lampit)

An oral nitrofuran compound with some effect on cutaneous lesions, this drug is ineffective in mucosal disease (13). In Brazil it has been used at dosage levels of 8 to 10 mg/kg body weight daily for 120 days and 20 mg/kg body weight for ten days (13). Neither schedule appears appropriate for treatment of patients under field conditions since treatment is prolonged and because it is associated with severe side effects which precludes its use in outpatients. The adverse effects include anorexia, weight loss, nausea, vomiting, abdominal pain and mental changes.

Benznidazole

An oral nitroimidazole derivative which has been employed in the treatment of mucocutaneous leishmaniasis by Texeira (14) with promising results. Fava, in a small series given 3 to 5 mg/kg body weight during 45 days, observed that patients with cutaneous lesions responded better than those with mucosal lesions (15). However, the recurrence rate, after 30 days of follow-up, was high in both groups of patients.

Ketoconazole

In vitro studies by Berman (16) showed that hydrolyzed ketoconazole was effective against *Leishmania* in human mononuclear cell cultures by achievable concentration in vivo. Clinical experience by Urcuyo (17) in Nicaragua and Saenz (unpublished observations) in Panama, giving ketoconazole 400 mg daily for 3 months, revealed antileishmanial activity in cutaneous and mucocutaneous disease but the time required to obtain healing of the lesions was between two and three months. This slow response to treatment increases the cost, makes it impractical in the field, and increases the risk of toxicity.

Allopurinol

(4-Hydroxypyrazolo-[3,4-d]-pyrimidine), a structural analog of hypoxanthine, was reported by Pfaller and Marr (18) to have antileishmanial activity at concentrations that can be obtained in humans. Marr and his associates have since shown that allopurinol is effective in vitro against *L. braziliensis*, *L. mexicana*, *L. donovani*, and *T. cruzi* (19). It was determined by in vitro studies that the key step is the metabolic conversion by the parasite of allopurinol to allopurinol riboside and to allopurinol ribonucleoside 5'-monophosphate (HPPR-MP) followed by the unique amination of 4-aminopyrazolo-(3,4-d)-pyrimidine 5'-ribonucleotide (APPR-MP) which is converted to a triphosphate and is incorporated into RNA of the parasite (20,21).

In humans allopurinol is converted largely to oxipurinol, a less effective antileishmanial agent, and approximately 10% is converted to allopurinol riboside. This ribonucleoside is more active than allopurinol against *L. braziliensis* and *L. donovani*. It has the advantage of being minimally metabolized in humans, because it is not oxidized by xanthine oxidase but by aldehyde oxidase, which in humans is present only in low levels. For this reason allopurinol riboside seems promising as an oral therapy for the treatment of leishmaniasis (23).

Peters et al. (22) demonstrated the effectiveness of allopurinol in the treatment of the visceral disease caused by *L. tropica major* in mice. In a limited clinical study of patients who had pentostam-resistant visceral leishmaniasis, Kager (23) found allopurinol effective in the treatment of this disease. More recently Jha (24) giving allopurinol 300 to 1,200 mg per day for at least 14 days produced cures on clinical grounds in 14 of 17 hospitalized patients with kala azar. Walton (25) reported pronounced antileishmanial activity of allopurinol against experimentally

induced cutaneous lesions of *L. braziliensis panamensis* in *Aotus trivirgatus* monkeys. Clinical trials with allopurinol riboside in humans with cutaneous leishmaniasis have been programed to begin as soon as the Phase I safety and tolerance studies are completed.

Antituberculous drugs

There are some reports on the effectiveness of rifampin (26) and isoniazid (27) therapy in cutaneous leishmaniasis, including the disseminated anergic form. Also, a synergistic effect was observed when these two drugs were administered in combination (27). Further clinical trials of this combination are necessary, as well as experimental studies on other antimycobacterial agents, alone and in various combinations.

Therapy with liposome-entrapped pentavalent antimony

A new development in experimental chemotherapy is the selective targeting of antileishmanial drugs by incorporation into liposomes. These are synthetic phospholipid bilayer vesicles (25 nm in diameter), which are taken up by the reticuloendothelial cell. Alvin et al. (28) reported that pentavalent antimony encapsulated within liposomes was 700 times more active than the free (unencapsulated) drug. Although the system is primarily designed for the visceral form, experimental studies indicate that i.v. administration was also effective for cutaneous leishmaniasis (29). Liposomes, as vehicles for drugs, may not be totally innocuous, since experimental administration of empty liposomes can exacerbate a leishmanial infection, aggravating the concomitant underlying pathologic condition of the reticuloendothelial system (28).

Local application of heat

The local application of heat was reported first by Ribeiro and Brenner (30), tried experimentally by Pereira et al. (31) and reviewed by Zeledon (32). Berman (33) recently observed the marked effect of temperature on multiplication of amastigotes of *L. tropica* within human macrophages with their almost complete elimination at 39°C.

Neva (34) has used pads through which warm water circulates to produce temperatures of 39.5 to 41°C at the skin surface for periods of 2 to 3 h at a time. After a total of 25 to 36 h of local heat treatment, disappearance of viable organisms and subsequent clearing of lesions have been documented in several cases. This method of treatment may be applicable to those leishmanial species that are sensitive to elevated temperatures and grow only in the skin. In addition, there is clinical evidence that immunity is not expressed adequately in the cooler parts of the skin, as the lobe of the ears and the tip of the nose, whereas in the same patient lesions heal on the trunk.

SUMMARY

Over the past 70 years antimonial drugs remain the preferred method of treatment for leishmaniasis despite limitations, such as the need for their parenteral administration, the necessity of prolonged therapy, of toxicity, and the fact that a significant number of patients have a poor therapeutic response or recurrence, necessitating two and sometimes even three therapeutic courses. The development of a relatively fast-acting, effective oral drug with minimal toxicity is the vision of every clinician involved in the treatment of leishmaniasis.

We should also bear in mind that in leishmaniasis an adequate immunological response is essential and that the development of a method for immuno-stimulation would be a valuable complement to attain a therapeutic response in those cases where a depression of the cellular immunity exists.

A better identification of the different New World subspecies of *Leishmania* through the use of monoclonal antibodies and improved sensitivity of in vitro studies, is fundamental to a better definition of the patterns of susceptibility in the different geographical areas, and a better choice of the ideal drug for the patient.

Lastly, once treatment is completed, a serological follow-up of the patient is advisable to ensure that a parasitological cure has been effected and that there will be no relapse or late mucosal complications. However, we also need longitudinal studies which will define better the real value of serological tests in evaluating the effectiveness of the treatment.

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