A Randomized Trial of Amphotericin B alone or in Combination with Itraconazole in the Treatment of Mucocutaneous Leishmaniasis

LuisValda Rodriguez, Jean-Pierre Dedet*, Virginia Paredes, Carmelo Mendoza, Fernando Cardenas

Servicio de Dermatologia. Hospital de Clinicas Universitario, Miraflores, La Paz, Bolivia
*Instituto Boliviano de Biologia de Altura, La Paz, Bolivia

A randomized trial of amphotericin B (AB) alone and in combination with oral itraconazole (IZ) is carried out in two groups of 10 mucocutaneous leishmaniasis patients from Bolivia and Peru.

AB+IZ combination is no better than AB monotherapy, as far as efficacy and tolerability are concerned. No antagonism was detected.

Key words : mucocutaneous leishmaniasis - treatment - amphotericin B - itraconazole

Treating leishmaniasis is hampered by the toxicity and high cost of the first line antileishmanial drugs. Mucosal leishmaniasis due to *Leishmania (Viannia) braziliensis* is often resistant to antimonials. There is a need to discover new drugs or new therapeutic schedules.

Since the first use of amphotericin B (AB) in the treatment of mucocutaneous leishmaniasis (MCL) by Sampaio et al. (1960), this polyene antibiotic is the main drug for the treatment of antimonial resistant mucocutaneous leishmaniasis (MCL).

Itraconazole (IZ), an imidazole compound, exhibited, as well as powerful antifungicidal activity, an effective antileishmanial effect, mainly in cutaneous lesions, as reported by Borelli (1987), Albanese et al. (1989) and Dogra et al. (1990).

Confirming these observations, Valda Rodriguez and Calderon (1988) showed a more rapid and efficient healing in some MCL cases in which a prior IZ treatment was followed by AB. They suggested a possible synergy between the two drugs, which would permit, if confirmed, a reduced dose and duration of AB treatment in MCL.

We report a randomized open trial of the combination IZ and AB, versus AB alone, in MCL patients.

PATIENTS AND METHODS

The patients comprised 20 cases of MCL hospitalized between January 1988 and December 1990 in the Dermatology Department of the Hospital de Clinicas Universitario of the city of La Paz (Bolivia).

All patients were male, with a mean age of 40 years (range 20 - 67 years). Sixteen came from Yungas and Alto-Beni (La Paz department, Bolivia) and four from Puno province (Perú).

All patients had MCL lesions which were classified as: moderate, with localization of the lesions to nasal, buccal and pharyngeal mucosae (9 patients), or severe, with extension to the larynx in addition to nose, mouth and pharynx (11 patients). The mean age of the lesions was 9 years (range 3 - 24 years).

The diagnosis of the disease was established at the Instituto Boliviano de Biologia de Altura (IBBA) of La Paz (Bolivia). Parasites were seen in May Grünwald-Giemsa stained smears in three cases and culture was positive in six cases. In three cases, the cultivated parasites were isoenzymatically characterized and belonged to the *L. braziliensis* taxon. Histology was performed on mucosal biopsies in all cases, and processed at the Institut Pasteur (Paris, France). The parasite was detected in tissue sections in nine cases. All patients had positive Montenegro skin tests and indirect fluorescent antibody technique (IFAT).

Before, during and after the treatment, the following parameters were studied: ENT examination, full blood count, liver function tests, blood

The Instituto Boliviano de Biologia de Altura received financial support from the Ministère des Affaires Etrangères (Paris, France), the Universidad Mayor de San Andres and the Ministerio de Previsión Social y Salud Pública (La Paz, Bolivia).

*Present address: Laboratoire d'Ecologie Médicale et Pathologie Parasitaire, 163, rue Auguste Broussonet, 34000 Montpellier, France

Received 28 September 1994
Accepted 11 April 1995

glucose, urea, creatinine and electrolytes; urine examination; electrocardiogram (ECG) and chest X-ray. The laboratorial tests were repeated every ten AB perfusions.

Four patients had positive serology for *Trypanosoma cruzi*. All patients gave inform consent to participate and were randomly assigned to two groups: (a) group A comprised 10 patients (5 with moderate and 5 with severe mucosal leishmaniasis), who received AB only. AB was given as 50 mg dissolved in 500 ml 5 % dextrose with 0.25 mg dexamethasone. Infusions were administered over 8 hr, every two days until lesions healed; (b) group B comprised 10 patients (4 with moderate and 6 with severe lesions), who received the combination AB+IZ. IZ was given orally at a dose of 200 mg/day for 41 days, 10 days preceding AB treatment and then simultaneously with AB up to the 15th infusion (total dose: 8,200 mg). AB was given as above until lesions healed.

The follow-up of the patients included clinical evaluation, ENT examination and IFAT antibody detection at months 1, 3, 6, 9 and 12 after the end of the treatment.

Statistical analysis of the data was by Student's test and Mann-Whitney tests.

RESULTS

In group A B, healing of the lesions occurred at a mean dose of 1,640 mg (range 1,250 - 2,500 mg). The mean duration of the treatment to heal lesions was 70 days (range 51 - 109) (Table).

Adverse effects were seen in six patients and consisted of slight anaemia (3 cases), reversible renal impairment (2 cases) and ECG changes (ventricular extra systoles and sub-endocardial ischaemia: 2 cases). These latter side-effects occurred in two patients with associated chagasic cardiopathy. All side-effects were transitory and disappeared after completion of the treatment.

Relapse of the MCL occurred in a single patient, nine months after the end of the treatment.

In group A B + I Z, healing of the lesions was achieved with a mean dose of 1,400 mg of A B (range 750 - 2,500 mg). The mean duration of the treatment to heal the lesion was 66 days (range 36 - 117) (Table).

Adverse effects were seen in seven patients and consisted of slight anaemia (3 cases), reversible renal impairment (2 cases), nausea and vomiting (2 cases) and sub-endocardial ischaemia (1 case). All these disappeared after completion of the treatment.

Relapse of the MCL occurred in two patients, two and six months after the end of treatment.

DISCUSSION

A B is considered by several authors, such as Martins Castro (1972), as the most effective drug for treating MCL, including antimonial resistant cases, because of a low relapse rate. An optimal therapeutic effect is generally obtained with doses less than 2 g (Llanos-Cuentas et al. 1988). In few cases, the doses have nevertheless to be increased to 3 - 4 g, above which irreversible renal damages may occur (Wolff & Régnier 1984). Renal, cardiac and haematological toxicity limites large scale A B utilization.

The combination of AB with other drugs, mainly antifungicidal products, has been proposed, with the hope of obtaining synergistic effects. This strategy could prevent the development of resistance and could reduce toxic side effects by a decrease in doses or duration of treatment.

The most commonly used combination is of AB and flucytosine and has been used in the treatment of systemic infections due to *Candida* and *Cryptococcus* (Bennet et al. 1979, Dismukes et al. 1987, Sarosi 1990) and of chromomycosis (Bopp 1976, Valda 1978).

The AB-fluocytosine combination is generally considered as an additive synergy, which may be due to an increase of flucytosine penetration resulting from increased permeability of the fungal cell membranes produced by AB (Sande & Mandell 1988).

However, the combination of AB and imidazoles, mainly ketoconazole, showed contradictory results. Medoff and Kobayashi (1980) describe a theoretical antagonism between the two drugs,

TABLE

Summary of results of the efficacy and tolerability of the amphotericin B alone (AB) and amphotericin B in combination with itraconazole (IZ)

Groups	AB	AB+IZ
Dose to produce healing	1.64 g.(1.25-2.5 g)	1.4 g (0.75-2.5 g)
Time to healing	75 days (51-109 days)	66 days (36-117 days)
Adverse effects	6/10	7/10
Relapse (months)	1 (9)	2 (2, 6)

resulting from common mechanisms of activity. Experimental studies showed a synergy between AB and ketoconazole against *Cryptococcus neoformans* (Graybill et al. 1980, Odds 1982). The combination against *Candida* and *Aspergillus*, was either synergistic (Odds 1982) or antagonic (Jitsud & Feingold 1983).

Drug combinations including IZ are rarely described, probably because of the superiority of this product to other imidazoles and/or because of its recent commercialization. The IZ-flucytosine combination was effective in patients infected with cryptococcosis (Viviani et al. 1990) and with chromoblastomycosis (Pradinaud & Bolzinger 1991).

An AB-IZ combination showed inconclusive results in the few trials available. Among a group of 15 patients suffering with invasive aspergillosis, Dupont (1990) observed that the combination of IZ, AB and flucytosine resulted in disappearance of the symptoms, and was well tolerated with minor side effects, which did not limit treatment.

To our knowledge, the combination of AB and IZ in the treatment of leishmaniasis has not been previously tested. The present study showed that AB plus IZ was neither antagonic nor synergistic. It resulted in healing at slightly lower doses of AB and in slightly less time than in patients treated with AB alone, but, in both cases, the results were not significatively different. The relapse rate was better after AB alone than after the combination.

Drug tolerance was similar in both groups of patients. In the combined schedule, cumulative side-effects were not observed. ECG changes can occur in patients infected simultaneously with leishmaniasis and Chagas' disease, and require close assessment of cardiac function when treated with AB.

In conclusion, the AB-IZ combination is no better than AB monotherapy for MCL. The lack of antagonism suggests however that the combination should be studied in other infections, particularly in severe systemic fungal infections.

ACKNOWLEDGEMENTS

To Dr Cauwenberth (Division of Investigation, Janssen Pharmaceutica, Belgium) for providing the itraconazole, Dr P Ravisse (Institut Pasteur, Paris, France) for the pathological revision of all biopsy material, Dr J Fernandez (CHU Montpellier, France) for statistical analysis, and Dr RN Davidson for kindly assisting with the english version. To the following physicians or biologists for collaboration in the development of the trial: Pr G Antezana, Pr R Bustillos, Dr C David, Dr L Dimier-David, Dr P Lyevre, Dr F Rollano, Dr A Quintela, Dr N de Nallar, Dr R Peñaloza, Mrs H Miguez, Mrs C Camacho and Dr M Munoz.

REFERENCES

Albanese G, Giorgetti P, Santagostino L, Crippa D, Sala G 1989. Cutaneous Leishmaniasis treatment with itraconozole. *Archs Derm 125*: 1540-1542.

Bennet JE, Dismukes WE, Duma J, Medoff G, Sande MA, Gallis H, Leonard J, Fields BT, Bradshaw M, Haywood H, Mc Gee ZA, Cate TR, Cobbs CG, Warner JF, Alling DW 1979. A comparison of Amphoterin B alone and combined with Flucytosine in the treatment of Cryptoccal Meningitis. *New Engl J Med 301*: 126-131.

Bopp C 1976. Cura da Cromoblastomicose por novo método de tratamento. *Med Cutanea Ibero-Latino-america 4*: 285-292.

Borelli D 1987. A clinical trial of Itraconazole in the treatment of Deep Mycoses and Leishmaniasis. *Rev Infect Dis 9*: 557-563.

Dismukes WE, Cloud G, Gallis HA, Kerkering TM, Medoff G, Graven PC, Kaplowitz LG, Fisher JF, Gregg CR, Bowles CA, Shadomy S, Stamm LM, Diasio RB, Kaufman L, Soong SJ, Blakwelder WC 1987. Treatment of Cryptococcal Meningitis with combination of Amphotericin B and Flucytosine for four as compared with six weeks. *New Engl J Med 317*: 334-341.

Dogra J, Aneja N, Lal BB, Mishra SN 1990. Cutaneous leishmaniasis in India. Clinical experience with Itraconazole (R51 211 Janssen). *Int J Derm 29*: 661-662.

Dupont B 1990. Itraconazole therapy in aspergillosis: Study in 49 patients. *J Am Acad Derm 23*: 607-614.

Graybill JR, Williams DM, Vancutsem E, Drutz DJ 1980. Combination therapy of Experimental Histoplasmosis and Cryptococcis with Amphotericin B and Ketoconazole. *Rev Infect Dis 2*: 551-558.

Jitsud I, Feingold DS 1983. Effect of Ketoconazole on the fungicidal action of Amphotericin B in *Candida albicans. Antimicrob Ag and Chemotherapy 23*: 185-187.

Llanos-Cuentas A, Cieza J, Cabezas J, Alvarez H, Echevarria J 1988. Eficacia de Anfotericina B en el tratamiento de Leishmaniasis mucosa. V Jornadas Cient Univ Peruana Cayetano Heredia.

Martins Castro R 1972. Tratamento da Leishmaniose Tegumentar pela Anfotericina B. A propósito de 70 casos. *Anais bras Derm 47*: 229-233.

Medoff G, Kobayashi GS 1980. Strategies in the treatment of systemic fungal infections. *New Engl J Med 302*: 145-155.

Odds FC 1982. Interactions among Amphotericin B, 5 Flucytosine, Ketoconazole, and Miconazole against pathogenic fungi *in vitro. Antimicrob Ag and Chemotherapy 22*: 763-770.

Pradinaud R, Bolzinger T 1991. Treatment of chromoblastomycosis. *J Am Acad Derm 25*: 869-870.

Sampaio SAP, Godoy JT, Paiva L, Dillon N, Lacaz CS 1960. The treatment of American (mucocutaneous) Leishmaniasis with Amphotericin B. *Archs Derm 82*: 627-635.

Sande MA, Mandell GL 1988. Agentes Antimicrobianos. In *Bases Farmacológicas en Medicina*, Goodman Gilman, México: Edición Médica Panamericana, 1160 pp.

Sarosi GA 1990. Amphotericin B. Still the "gold standard" for antifungal therapy. *Postgrad Med 80*: 151-166.

Valda Rodriguez L 1978. A propósito de la cromomicosis y de su tratamiento. *Archos Argent Derm 28*: 159-168.

Valda Rodriguez L, Calderon Valle SW 1988. Itraconazole en el tratamiento de la Leishmaniasis tegumentaria americana. *Actual Terap Derm 1*: 376-381.

Viviani MA, Tortorano A M, Pagano A, Vigevani GM, Gubertini G, Cristina S, Assaisso ML, Suter F, Farina C, Minetti B, Faggian G, Caretta M, Di Fabrizio N, Vaglia A 1990. European experience with Itraconazole in Systemic mycoses. *J Am Acad Derm 23*: 587-593.

Wolff M, Régnier B 1984. Amphotericin B en 1984. *Méd Mal Infect 14*: 538-549.