High and Low Doses of Antimony (Sb^V) in American Cutaneous Leishmaniasis. A Five Years Follow-up Study of 15 Patients

MP Oliveira-Neto+, A Schubach, ML Araujo*, C Pirmez

Hospital Evandro Chagas, Instituto Oswaldo Cruz, Av. Brasil 4365, 21045-900 Rio de Janeiro, RJ, Brasil
*Hospital de Bonsucesso, Instituto Nacional de Assistência Médica da Previdência Social, Rio de Janeiro, RJ, Brasil

Seventeen patients proceeding from the municipality of Rio de Janeiro, Brazil presenting with the cutaneous ulcerative form of American leishmaniasis were treated with one ampoule of pentavalent antimony daily for 30 days. With this regimen the individuals doses varies greatly: from 3.8 mg/kg of body weight to 22.3 mg/kg. After five years, patients receiving either a smaller dose or a bigger one, showed the same therapeutic result: cutaneous scars and no mucosal lesions.

Key words: cutaneous leishmaniasis - therapy - antimony

Treatment of cutaneous leishmaniasis induced by *Leishmania (Viannia) braziliensis* (*L.b.*) complex is imperative in order to prevent the possibility of desfiguring mucosal lesions. Although spontaneous healing of cutaneous lesions do occur, this may take from months to many years. Spontaneous healing is well documented in Brazil (Marsden et al. 1984, Costa et al. 1987) the minimal time of healing being 6 months. Pentavalent antimonial compounds are the mainstay of therapy that has been used for more than 60 years but the best dosage has not yet been fully identified. Several therapeutic regimens have been proposed by many authors. During many years in our Hospital, treatment of cutaneous leishmaniasis was performed with one ampoule of meglumine antimoniate irrespective of body weight, for at least 25 days. Each ampoule contains 425 mg of Sb^{5+} in a 5 ml solution. With this regimen the individual dose of antimony shows a considerable variation.

In 1982, as soon as we assumed the leishmaniasis sector of the Hospital, we decided to investigate more deeply this therapeutic approach. We studied 17 patients disclosed during one of our usual active searches in the endemic areas of the suburbs of the city of Rio de Janeiro. The patients were treated at the Evandro Chagas' Hospital, Oswaldo Cruz Foundation with one ampoule of meglumine antimoniate per day for 30 consecutive days. The individual doses of antimony according to body weight varied from 3.8 mg/kg to 22.3 mg/kg. Five years later, 15 of these patients were reviewed. All of them presented with cicatricial cutaneous lesions and normal findings on examination of upper respiratory tract mucosa, suggesting the same therapeutic result with either high or low doses of antimony.

+Corresponding author.
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MATERIALS AND METHODS

Seventeen patients with active cutaneous leishmaniasis were studied. All cases were from the suburb of Campo Grande, an endemic area of the city of Rio de Janeiro. Diagnosis was established by means of clinical, parasitological (smears and biopsies) and immunological (Montenegro's test and indirect immunofluorescent test) criteria.

Clinical examination - A complete clinical examination was performed including clinical history, dermatological examination and a search for mucosal lesions by means of anterior rhynoscopy and direct examination of oropharynx with a frontal light and tongue depressor. The area of dermatological lesions was determined according to formula D1 x D2 x $\pi/4$ where D1 is the bigger and D2 the smaller diameter.

Montenegro skin test - Parasite antigens (leishmanin) containing 40 μg of protein nitrogen per ml was obtained from Institute of Biological Sciences, Federal University of Minas Gerais, Brazil. A reaction of equal or greater than 5 mm after 48 hr was considered positive.

Serological test - An indirect immunofluorescent test was used to detect specific *Leishmania* antibodies (Camargo & Rebonato 1969).

Biopsies - Incisional skin biopsy specimens from the border of the active lesion was performed after local anesthesia with Xylocaine 2%. The specimen was divided into two fragments: one was cultivated in an enriched blood agar medium (NNN) and the other was fixed in 10% buffered

formalin and embedded in paraffin to perform a histopathological examination. Before fixing, an in-print was performed and stained with Giemsa.

Therapy - Patients were submitted to pentavalent antimony therapy with N-methyl glucamine (Glucantime, Rhodia, São Paulo, Brazil). Each patient received a daily intramuscular injection of one ampoule of the drug for 30 consecutive days. Each ampoule of 5ml provides 425 mg of Sb^{5+}. With this regimen the individual dose of pentavalent antimony according to the body weight varies from 3.8 mg to 22.3 mg (Table).

TABLE

Dose of Sb^{v} per kg of body weight

Patient No.	Body weight (kg)	Dose (mg/kg of Sb^{v})
1	19	22.3
2	21	20.2
3	24	17.7
4	34	12.5
5	37	11.4
6	48	8.8
7	52	8.1
8	56	7.5
9	58	7.3
10	61	6.9
11	63	6.7
12	64	6.6
13	65	6.5
14	67	6.3
15	78	5.4
16	89	4.7
17	109	3.8

Note: only 15 patients were available for the 5 years' follow-up.

RESULTS

Of the 17 patients, 9 were male and 8 female. Ages varied from 4 years to 59 years old. Duration of lesions varied from 27 to 103 days, with a mean duration of two and a half months. The 17 patients showed a total of 24 lesions: 12 patients with single lesions, 3 patients with two lesions and 2 patients with three lesions. All lesions were of the ulcerative type and the areas varied from 1.19 cm^2, the smallest one, to 10.80 cm^2 the biggest one. The legs were affected 10 times (42%), the arms 7 times (29%), the face 5 times (21%) and the trunk 2 times (8%). Montenegro's test was positive in all patients and the immunofluorescent test positive in only 7 patients. Parasite demonstration was positive with at least one of the 3 methods employed (in-prints, histological examination and culture) in all patients. The legs showed both: the largest lesions and the more prolonged time of healing, clearly not related with individual doses of antimony: patient number 4 had an area lesion of 10.80 cm^2, the biggest one, and received a dose of 12.5 mg/kg; patient number 16 whose lesion measured 9.76 cm^2 received a dose of 4.7 mg/kg. Both patients healed in 58 and 53 days respectively. Mean time of cure in all patients was 43 days.

Follow-up studies - In about two months after therapy, all patients presented healed lesions. Five years later, 15 of these patients were reviewed. At that time, clinical dermatological and otolaryngological examination disclosed cicatricial cutaneous lesions and no mucosal lesions in all patients. Montenegro's test was again positive and immunofluorescence negative in all patients.

DISCUSSION

The drug of choice for leishmanial disease is pentavalent antimony, but the important question about the more effective dosage has not been yet clearly determined. The initially proposed schedules were the same that were used somewhat empirically for the treatment of visceral leihmaniasis in China, India and East Africa during World War II (Tuckman 1949, Sen Gupta 1953, Manson-Bahr & Heisch 1956). This recommended schedule was of 600 mg of Sb^{v} per day during 10 days and at equal intervals another 10 days series could be added. Pentavalent antimony is rapidly excreted (Rees et al. 1980, Sampaio et al. 1980, Chulay et al. 1988) resulting in sub-therapeutic blood levels in a few hours (Oster et al. 1985) and so such rest periods are regarded as pharmacologically unsound. Chulay et al. (1988) exposed the view point that treatment with pentavalent antimony depends on maintenance of a inhibitory drug concentration for most of the day. The same author (Chulay et al. 1983) however, have established that treatment of visceral leishmaniasis with sodium stibogluconate at a dose of 10 mg/kg every 8 hr for 10 days showed to be equally effective as 10mg/kg once a day for 30 days. For cutaneous disease the dose of 10 to 20 mg/kg/day during at least 3 weeks is recommended by WHO in cases of *L. b.* infections. The same dose is also recommended for cutaneous leishmaniasis by the Center for Disease Control and Prevention in Atlanta, Georgia, USA (Herwaldt & Berman 1992). In Brazil a dose of 20 mg/kg/day for 30 days is recommended in cutaneous cases by some authors (Marsden 1983). According to Berman (1988) the time for spontaneous healing in cutaneous leishmaniasis varies from a month to a few years. Therefore, for a therapeutical agent to be considered active, this agent must produce a cure in a very high percentage of patients in a very short period, about 2 months. Both conditions were found in our patients since all of them cured in a short period.

With the schedule employed in our observation the mean dose was 9.5 mg/kg, very close to the dose recommended by WHO. However we have had patients receiving doses larger than 20 mg/kg, as well as patients with a dose lower than 10 mg/kg.

Management of American cutaneous leishmaniasis must achieve two goals: healing of cutaneous lesions and prevention of later mucosal involvement. Mucosal lesions are not frequent in Rio de Janeiro. In 479 cases of American cutaneous leishmaniasis observed in our Service of Evandro Chagas' Hospital from 1987 to 1994, only 16 (3.3%) were mucosal cases proceeding from periphery of Rio de Janeiro city. Mendonça et al. (1988) working in Jacarepaguá, another endemic area of the state, estimate a frequency of 2% of mucosal cases. Nevertheless, the only species of *Leishmania* until now identified in this region of Brazil is *L.b.* (Grimaldi et al. 1989) and so, to the actual level of our knowledge, the risk of mucosal involvement is to be considered. Our observation suggests that a low dose of Sb^v may be equally effective than a higher one, both dosages achieving the goals after a five years follow-up. This time of follow-up seems to be sufficient since some studies indicate that in two years the great majority of patients who would develop mucosal disease have clinical evidence of this type of metastasis (Marsden et al. 1984 a,b). We think that with the clinical presentation usually seen in Rio de Janeiro, namely: few or - more frequently - single cutaneous lesions, a short evolution time of illness, small number of parasites in lesions and a good immune response, a low dose could be effective. To try and develop a more suitable regimen for outpatient treatment we intend to investigate the therapeutical effect of a low antimony dose in a greater number of patients.

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