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Successful therapeutic response of resistant cases of mucocutaneous leishmaniasis to a very low dose of antimony

Resposta terapêutica bem sucedida de casos resistentes de leishmaniose mucocutânea a doses muito baixas de antimônio

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ABSTRACT

Two mucocutaneous leishmaniasis cases resistant to therapy are reported here. After the failure of initial therapies (antimony, amphotericin B and/or pentamidine) patients received a low-dose schedule: one ampoule of meglumine antimoniate (405mg of pentavalent antimony [Sb^v]) by intramuscular injection, three times a week until complete healing of the lesions. One patient was cured with a total of 30 ampoules in 10 weeks and the other received 36 ampoules in 12 weeks. Both remain clinically cured after one year of follow-up.

Key-words: *Mucocutaneous leishmaniasis. Therapy-resistance. Antimony. Low dose.*

RESUMO

São relatados dois casos de leishmaniose mucocutânea resistentes ao tratamento. Depois das terapêuticas iniciais (antimônio, anfotericina B e/ou pentamidina), os pacientes receberam um esquema alternativo: uma ampola de antimoniato de meglumina (405mg de antimônio pentavalnte [Sb^v]) por via intramuscular, três vezes por semana até a cura completa das lesões. Um paciente recebeu um total de 30 ampolas durante 10 semanas e o outro, 36 ampolas durante 12 semanas. Ambos permanecem clinicamente curados até um ano após o tratamento.

Palavras-chaves*: Leishmaniose mucocutânea. Resistência a terapêutica. Antimônio. Baixa dose.*

The standard regimen of pentavalent antimony (Sb^v) recommended by the World Health Organization for mucocutaneous leishmaniasis is 20mg/kg/day parenterally applied for 3 to 4 weeks. An advantage of this regimen is its established use. Its disadvantages, however, are numerous and include cost, the requirement of daily injections and the considerable morbidity of antimony therapy. In Rio de Janeiro State, *Leishmania* (*Viannia*) *braziliensis* (*L. (V.) braziliensis*) is the only species detected so far[7]. Other drugs commonly used for the treatment are amphotericin B and pentamidine, but the former is considerably toxic and the latter seems to be less effective in controlling *L. (V.) braziliensis* infections[1]. The parenteral use of high doses of antimony for long periods of time has been shown to be highly effective for the treatment of cutaneous leishmaniasis[2 8]. A modality not previously explored, is a regimen using a low dose of antimony administered over long periods, more precisely until clinical cure. Our experience in Rio de Janeiro showed that *Leishmania* infection may be controlled with low doses of antimony. Even minimal doses applied in intralesional therapy were effective in many cases[11]. Based on the observations of one of the authors, when working in the dermatology clinic of Policlinica Geral do Rio de Janeiro about 35-years ago, we decided to try the schedule formerly used in that clinic (MP Oliveira-Neto: unpublished data). This schedule consisted in the parenteral use of one ampoule of meglumine antimoniate, applied every Monday, Wednesday and Friday, irrespective of body weight, until complete healing of the lesion. Such a schedule represented a weekly dose of 1,215mg (3x405=1,215) of antimony for a 60kg patient, which is a very low dose, since the usual recommendation for the same patient should be a weekly dose of 8,400mg.

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CASE REPORTS

Case1. Male, aged 31. This patient presented a cutaneous lesion on the left malar region extending to the tragus and left ear lobe. Histopathology was positive for amastigotes. The first treatment, in September 1999, consisted of a dose of 14mg of antimony per kilogram of body weight, by intramuscular injection, for 20 days. The lesion was still active one month after the end of therapy. A new treatment with a dose of 5mg of antimony/kg/day was applied for 30 days, but three months later the lesion was active once more. Then the patient was treated with amphotericin B, but since he presented renal insufficiency at the cumulative dose of 300mg, the treatment had to be discontinued. After an interval of ten months, pentamidine was used with a total dose of 1,500mg until lesion healing; even so reactivation occurred a few months later. The schedule of one ampoule three times a week, on Mondays, Wednesdays and Fridays, was then applied for 10 weeks, totaling 30 ampoules, and at that time the lesion was completely healed. No side effects were noted. The patient remains well up to one year and four months of follow-up after the end of this last treatment (Figure 1).

Case 2. male, aged 64. This patient, with type II diabetes mellitus, presented several cutaneous lesions. The in-print of one lesion was positive for amastigotes. He was treated initially with 10mg of antimony per kilogram of body weight for 30 days. All the lesions cleared, but one year after the end of therapy, the patient presented two vegetant lesions on the penis glands and prepuce, initially diagnosed as a venereal disease. However, the histopathology showed amastigotes. He was then treated with the same long-term schedule used in Case 1 and after a 12 week period, totaling 36 ampoules, the lesion was healed. No side effects were noted. The patient remains well up to 9 months after the end of therapy (Figure 2).

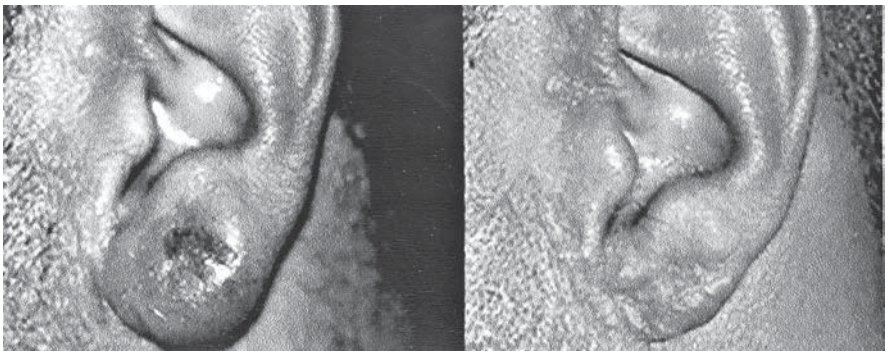

Figure 1 - Aspect of the lesion before (left) and after (right) long-term therapy.

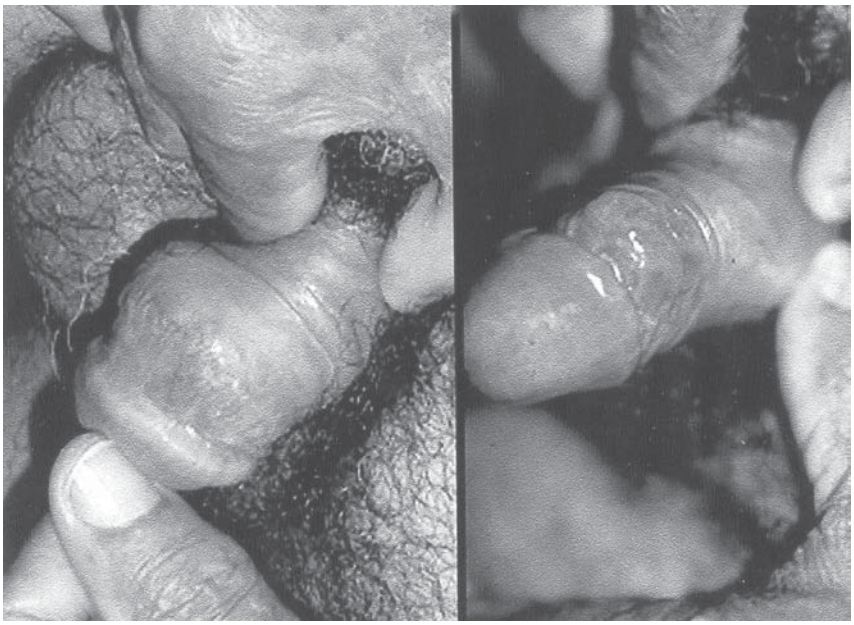

Figure 2 - Aspect of the lesion before (left) and after (right) long-term therapy.

DISCUSSION

Although used for more then 50 years and considered, even now, as the first-choice drug for the treatment of leishmaniasis[4], antimony is far from ideal. Several papers have been published during this time searching for a more suitable schedule of antimony therapy that is either less toxic and/or easier to apply[5 11 12 14 17]. In Rio de Janeiro State, an endemic area of *Leishmania (V.) braziliensis* transmission as the sole agent for tegumentary leishmaniasis[7], the efficacy of low doses of antimony have been regularly demonstrated[10 15], even in the treatment of mucosal lesions[13]. The majority of proposed antimony schedules are based on the antimony dose, not on the treatment period. In a few cases, prolonged treatment period with high doses has been tested[2 8]. The application of low doses of antimony over an extended treatment period has already been used in leishmaniasis, though in association with interferon-ν[6]. The schedule used here was established after the observation of the efficacy of low doses associated with a prolonged treatment period. A protracted treatment period was regularly used at the beginnings of antimonial therapy[3]. A prolonged treatment period is used for many diseases induced by intracellular pathogens such as leprosy, tuberculosis, Chagas' disease and paracoccidiodomycosis. We believe that the recommended treatment period for leishmaniasis, of three to four weeks using high doses, might be replaced for a more prolonged period using low doses of antimony. In a study designed to identify the criteria of cure, time was identified as an important factor for cure[9]. The schedule of one ampoule three times a week improved not only the acceptance of the treatment by the patients, but also regarding drug tolerance and, consequently, revealed a reduction in undesirable side effects. Although failure in antimonial therapy has sometimes been associated with parasite acquired resistance to low doses[16], the reported cases disclosed an undisputed fact: an extremely low dose of antimony applied after the use of high doses was effective and led to patient cure. We believe that low and intermittent doses for prolonged periods should be further evaluated in the treatment of mucocutaneous leishmaniasis.

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