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Caso clínico

Topical treatment of cutaneous leishmaniasis using a nanoemulsion cream-based on generic pentavalent antimony. Case report

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RESUMEN

Tratamiento tópico de leishmaniasis cutánea con crema-nanoemulsión de un compuesto genérico antimonial pentavalente. Caso clínico.

Introducción. Vacunas contra leishmaniasis cutánea aún no han sido desarrolladas. El tratamiento de la enfermedad mediante administración intramuscular de altas dosis diarias de un compuesto antimonial pentavalente, causa dolor y otros efectos adversos. Nuevas opciones terapéuticas efectivas, de fácil aplicación, económicas y sin efectos adversos son requeridas urgentemente.

Caso Clínico. Paciente masculino de 26 años presentando úlcera facial, por presuntiva leishmaniasis cutánea, diagnóstico confirmado por intradermo-reacción de Montenegro y observación microscópica de formas amastigotes. Debido al tamaño y localización de la úlcera, fue utilizado tratamiento tópico con crema-nanoemulsión basada en compuesto antimonial. La nano-emulsión aplicada dos veces a diario fue rápidamente absorbida y, a dos meses de tratamiento, el paciente no manifestó efecto adverso alguno. La úlcera fue reemplazada con piel sana y, una suave y limpia cicatriz.

Conclusión. La crema-nanoemulsión rapidamente absorbida, efectiva, más económica que la terapia sistémica y de aplicación directa por el paciente, mostró valor potencial en el tratamiento de leishmaniasis cutánea.

ABSTRACT

Introduction. An effective vaccine against cutaneous leishmaniasis has yet to be developed. Treatment of the disease relies on painful intramuscular administration of high doses of compounds based on pentavalent antimony,

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causing adverse effects. New therapeutic options effective, easy to apply, cheap and without adverse effects are urgently required.

Case report. A 26-year-old male patient showing a large facial ulcer, presumptively by cutaneous leishmaniasis, diagnostic confirmed by Montenegro's skin test and microscopical observation of amastigote forms. Due to the ulcer's location and size, topical treatment with a nanoemulsion cream-based on a generic antimony-compound was attempted. The cream was applied twice daily and was rapidly absorbed. After 2 months of treatment, no discomfort or other adverse effects were detected. The ulcer was replaced with healthy skin tissue and a soft, clean scar.

Conclusion. The novel cream, which was rapidly absorbed, effective, cheaper than standard systemic therapy and self-applied by the patient, showed potential value in the treatment of cutaneous leishmaniasis.

INTRODUCTION

Leishmania is a genus of parasites causing neglected vector-borne parasitic diseases that range, clinically, from spontaneously healing skin ulcers to severe cutaneous, muco-cutaneous or visceral infection. In the neotropical region, cutaneous leishmaniasis (CL) is caused by *Leishmania braziliensis*, *Leishmania guyanensis*, *Leishmania mexicana* or *Leishmania amazonensis* transmitted by various species of sand flies (1-3).

Effective anti-*Leishmania* vaccines have yet to be developed. For decades the treatment of all forms of leishmaniasis has been largely reliant on intramuscular injections with meglumine antimoniate (Glucantime®), typically in relatively high doses equivalent to about 20 mg pentavalent antimony (Sb5+)/kg/day. Unfortunately, such therapy is associated with several adverse effects including discomfort, swelling, headache, myalgias, arthralgias, cardiotoxicity and/or nephrotoxicity (4-9). In addition, this treatment may be too expensive for many cases of CL and supplies of Glucantime may be poor, especially in the rural areas where CL is most common (9). There is an urgent requirement for new therapeutic options that are easier to apply, cheaper than intramuscular injections with meglumine antimoniate, and have fewer or no adverse effects (9).

During the last two decades, our research team has developed a generic Sb^{5+}-based drug that is similar, in composition and pharmacological properties, to Glucantime (4-6). When combined with a local anesthetic, weekly intralesional infiltrations with this product have been found effective in the treatment of CL, with no associated discomfort or other adverse effects and no relapses within 10 years of clinical healing (9). Recently the same product has been reformulated as a nano-emulsion, with the hope that the resultant cream could be used for the topical, pain-free treatment of patients with CL lesions on their faces and/or other particularly sensitive areas (10). Herein, we report on the successful use of this cream on a patient with a severe facial lesion.

CASE PRESENTATION

A 26-year-old male agriculture worker from El Tesoro (7°46'11''N-72°14'21''W), a rural locality in Tachira state in western Venezuela, presented with a history of an insect bite, on his nose, which led to inflammation and aggressive ulceration. Given the location and speed of his ulceration, he was hospitalized in a health-care center in Merida state, where antibiotic and steroid therapy was found to be ineffective. In December 2021, 2 months after his hospitalization, he was referred to the Center for Parasitological Research, Faculty of Science, University of Los Andes, Merida, Venezuela, with a presumptive diagnosis of CL.

The known endemicity of CL in the area where the patient resided, the presence of similar lesions on inhabitants from the same locality, the patient describing how he was frequently bitten by sand flies and the clinical presentation of his large (5 x 2.5 cm) facial ulcer all supported the presumptive diagnosis. The diagnosis was, however, confirmed by a Montenegro's skin test and, particularly, by the microscopic detection of amastigote forms in a lesion smear that had been fixed with methanol and stained with 10% Giemsa in phosphate buffer at pH 7.2.

Prior to his treatment with the nano-emulsion cream, a written informed consent was obtained from the patient, in order to comply with the criteria

established by the Biomedical Committee of the National Research Council of Venezuela.

The patient was initially briefly treated systemically, according to the protocol established, by our research team, for CL: an intramuscular injection of 2.5 mL of the generic meglumine antimoniate compound in solution (90 Sb^{5+} mg/mL), repeated 3 days later. This treatment was based on the known endemicity of CL in El Tesoro and the possibility that the patient, given his frequent exposure to sand-fly bites, had had a subclinical or inapparent *Leishmania* infection prior to the symptomatic infection with which he had presented. The patient's ulcer was cleaned following a surgical debridement before topical treatment with the nano-emulsion cream began.

The cream, which contained 10% (w/v) meglumine antimoniate, was stored in small plastic pots, with 10 g in each pot (Figure 1). The basic characteristics of the cream, including its formulation, transdermal passage, antimony analysis, preparation, human sensory testing, droplet size, pH and stability, have been reported previously (10). The cream is white, smooth and homogenous, with a pleasant smell.

Figure 1. Pentavalent antimony nanoemulsion-based cream used during topical treatment. (Note the small plastic containers, which were labelled with the Sb5+ concentration and mode of use).

The topical treatment, which was applied by the patient, consisted of two daily applications, each of about 150 mg of the cream. For each application, the patient was instructed to wash his ulcer with a neutral soap solution in warm water, and dry it before spreading the cream over all the borders of the ulcer. As a complementary treatment, to avoid bacterial infection, 10 days of twice daily 80mg trimethoprim and 400 mg Sulphametoxazol (Bactrimel®) were prescribed. In addition, to help soften any scarring after lesion healing, the patient was asked to apply fresh *Aloe vera* gel to the ulcer once a day (9) midway between the applications of the nano-emulsion cream.

During the first 10 days of topical treatment, the patient was evaluated every 3-4 days to check for skin-tissue regeneration and to check that he was using the cream as instructed. After 28 and 36 days of topical treatment, the ulcerated area had reduced to 12% and 0.02% of its initial size, respectively. After 67 days, when the topical treatment was halted and the remaining cream was weighed so that the total used (20.1 g) could be determined, the previously ulcerated area had totally epithelized and all that was left was apparently healthy skin tissue and a small area of soft and clean scar tissue. The lesion-regeneration process is graphically illustrated in Figure 2, which includes photographs of the patient taken 1 month and 12 months after completing treatment. The patient reported no adverse effects.

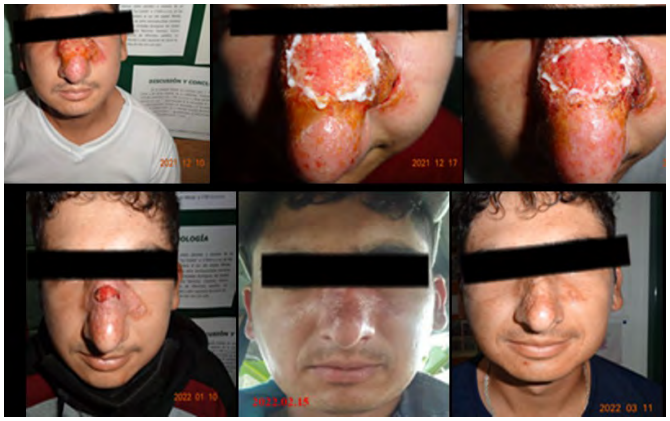

Figure 2. Graphical sequence showing the healing process during and after treatment with the nano-emulsion-based cream.

DISCUSSION

We report a serious facial CL lesion that appears to have been successfully and safely treated with a

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generic nano-emulsion-based cream containing 10% (w/v) meglumine antimoniate as active ingredient.

During the 67 days of topical treatment, the patient applied a total of 20 g of the cream, equivalent to about 2 g of meglumine antimoniate. The systemic treatment recommended for CL by the World Health Organization (11) is 20 mg Sb^{5+}/kg/day. If given this systemic treatment, the patient described here, who weighed about 75 kg, would receive 1.5 g Sb^{5+}/day, i.e., 75% Sb^{5+} in a day of the total given over 67 days of topical treatment. The cream clearly has potential in the treatment of CL lesions and, given the relatively low dose of Sb^{5+} required to effect an apparent cure in our case, may represent considerable cost-savings compared with the more conventional systemic treatments. The absence of reported adverse effects and the ability for self-application are also encouraging.

Although based on a single case, the present observations are so positive that they may justify the mass production of the nano-emulsion-based cream as an antileishmanial topical therapy that is easily applicable, apparently safe and cheap and one that could be particularly useful among poor people suffering CL who live in rural areas far from the nearest health center.

The cream's rapid absorption into the skin may facilitate quick contact between the active ingredient and the *Leishmania* parasites. In our research team, Bullón *et al.* (10) found that up to 50% of the active ingredient in the cream passed across a transdermal diffusion (Strat-M) membrane (Figure 1) within 15 mins. If topical use of the cream allows fast drug–parasite contact, delays associated with the hepatic metabolism that normally occur with systemic treatments may be avoided. The cream may satisfy some, if not all, of the characteristics previously defined for an effective system for transdermal drug delivery (12-15).

CONFLICT OF INTEREST

The authors declare they have not conflict of interest.

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