LACK OF EFFICACY OF MEFLOQUINE IN THE TREATMENT OF NEW WORLD CUTANEOUS LEISHMANIASIS IN COLOMBIA

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*Abstract.*In a nonblinded, therapeutic trial conducted in Colombia, 1.25–1.5 grams of mefloquine base given as a single oral dose or as 250 mg a day for 5–6 consecutive days was not efficacious in the treatment of New World cutaneous leishmaniasis. The drug had cured only 30.8 % of patients with leishmaniasis skin lesions by the 10th week after start of therapy as compared with a 27.9% complete cicatrization rate in historical controls treated with placebo tablets and an 86.3% cicatrization rate in historical controls who received meglumine antimoniate, 20 mg/kg/day intramuscularly for 20 days, with no upper limit to daily dose. It is concluded that a single course treatment with mefloquine is not indicated as monotherapy in the treatment of Colombian cutaneous leishmaniasis primarily due to *L. panamensis.*

New world cutaneous leishmaniasis (CL), caused by parasites of the *Leishmania (viannia)* subgenus, classically presents as skin ulcers, nonulcerated nodules, or plaques that heal spontaneously over a period of a few to many months.[1] Since the infection occasionally spreads to the mucous membranes of the nose and throat, systemic treatment is an official guideline in Colombia.[2]

Pentavalent antimonial has been the first line treatment for various forms of leishmaniasis for more than 40 years although this requires systemic injection and frequently induces malaise, nausea, headache, myalgias, arthralgias, anorexia, disturbed liver enzyme levels, and electrocardiographic changes. Very high doses may cause fatal arrhythmias.[3–6] Increasing unresponsiveness and relapse rates in India and Kenya when treating kala-azar suggest gradually increasing secondary resistance, a hypothesis also supported by *in vitro* findings for the New World mucocutaneous forms.[7–9] Amphotericin B and pentamidine are more toxic and should be restricted to severe disease unresponsive to antimony.[1,7] Thus, there is still a need for research on therapeutic alternatives.

Recently, a healing rate of 100% over an eight-week period was achieved in Ecuador with oral administration of mefloquine (4.2 mg/kg/day for six days to a maximum of 1.5 grams, if necessary repeated after three weeks) in 16 volunteers with parasitologically proven CL primarily due to *Leishmania panamensis.*[10] The present study was conducted to determine if similar rates could be accomplished in Colombian CL.

PATIENTS AND METHODS

Since there is only one study reporting efficacy of mefloquine in the treatment of CL,[10] and because of the lack of known biologically plausible mechanisms, a preliminary trial using a nonrandomized, nonblinded intervention design was started. The objectives were to verify the effectiveness of the drug as well as the reported cicatrization rates before designing a partially blinded clinical trial with concurrent placebo and meglumine antimoniate controls. The necessary sample size for the mefloquine group was calculated to be 15 patients using the following criteria: a significance level of 0.05, a power of 0.80, a provision to allow for a continuity correction in significance testing; an estimated cicatrization rate of 80% at 10-weeks follow-up for mefloquine-treated patients (in contrast to the 100% reported), and a 23.3% cicatrization rate for placebo-treated patients.[10,11]

Patients from the predominantly *L. panamensis*-endemic regions of Antioquia, Choco, and Tolima attending the outpatient service of the Programa de Estudio y Control de Enfermedades Tropicales between January and December 1996 were recruited into the study. Clinical diagnosis was parasitologically confirmed by staining of ulcer scrapings with Giemsa and/or by culture of fine needle aspirates of the border of at least one lesion in NNN medium. Cultures were maintained at 26°C for three weeks before discarding them as negative. *Leishmania* species in culture-positive isolates were identified by the use of monoclonal antibodies.[12]

Before therapy, all patients provided a complete medical history and underwent a physical examination that included photographing of all lesions. Both induration (with the ballpoint technique[13]) and ulceration of each lesion were measured in two directions to the nearest millimeter (D_1 = maximal diameter, D_2 = diameter perpendicular to D_1) with the patient assuming a standard posture. Areas were calculated using the formula $\pi \times \frac{1}{2}D_1 \times \frac{1}{2}D_2$.

Exclusion criteria included a body weight less than 15 kg, an age greater than 60 years, treatment with recognized antileishmanial agents in the previous six months, cutaneous lesions within 2 cm of the mucosal skin borders, mucosal involvement, diffuse or disseminated CL, severe concomitant disease, pregnancy, lactation, or an impossibility of ensuring follow-up. Informed written consent was obtained from all participants. The trial was approved by the Ethical Review Committee of the Faculty of Medicine of the University of Antioquia.

Mode of treatment. Patients admitted into the trial were administered 1.25 (bodyweight = 45 to less than 60 kg) to 1.5 g (bodyweight = 60 kg or more) of mefloquine after food intake in the form of tablets containing 250 mg base/tablet.[14] The drug was administered as a single dose under direct medical supervision for the first five study participants. Because this single dose proved to be poorly tolerated, the remaining patients were prescribed 250 mg base once a day for 5–6 consecutive days. Loss due to early emesis was verified for all patients through questioning at the four-week

TABLE 1
Patient characteristics

Characteristic*	Mefloquine group	Historical meglumine group	Historical placebo group
No. of patients recruited	14	66	56
Mean ± SD age, years	33 ± 14	25 ± 14	26 ± 13
Male sex, %	79	62	63
Mean ± SD no. of lesions per patient	2.0 ± 1.2	2.9 ± 3.8	3.3 ± 3.4
Patients with lesion, %			
Head and arms only	43	38	45
Trunk and legs only	36	44	29
Upper and lower body	21	18	27
Mean ± SD no. of ulcers, %†	96 ± 13	90 ± 23	91 ± 21
Mean ± SD age of lesion, months‡	2.9 ± 2.7	2.6 ± 1.6	2.7 ± 1.9
No. (%) of patients culture positive	11/14	37/51	28/43
	(78.6)	(72.5)	(65.1)
Leishmania panamensis	10/11	29/37	25/28
	(90.9)	(78.4)	(89.3)
L. braziliensis	0/11	6/37	3/28
	(0.0)	(16.2)	(10.7)
Identification uncertain	0/11	1/37	0/28
	(0.0)	(2.7)	(0.0)
Not done	1/11	1/37	0/28
	(9.1)	(2.7)	(0.0)

* None of the differences were significant (analysis of variance, chi-square, $P < 0.05$).
† Percentage of lesions of a patient presenting as ulcers, with the remaining lesions being nonulcerated nodules or plaques.
‡ At the time of the first medical evaluation.

follow-up visit. Intensive wound hygiene was prescribed for all ulcerated lesions. Treatment with mefloquine was not repeated in cases of insufficient clinical responses.[15]

Lesions were re-evaluated as described and photographed again during the follow-up visits scheduled at 3–4 and 9–10 weeks after the start of therapy. Adverse effects were recorded at each control visit. The response of lesions was determined clinically since the correlation between results of post-treatment parasitologic examination and ultimate clinical outcome is not clear.[5,16] Each lesion was evaluated for changes in both ulcerated and indurated areas and the response was determined according the least favorable outcome recorded. A patient was considered a treatment failure if at least one of his or her lesions had grown by more than 50% in four weeks, if at least one of the lesions had diminished by less than or equal to 50% at 2.5 months compared with the four-week evaluation, if reactivation, induration, and/or ulceration of any lesion occurred after complete healing, or if mucosal involvement developed. If none of these criteria applied, follow-up continued. Clinical amelioration was defined as the least healed still active lesion having decreased its area by more than 50% compared with the previous evaluation, and total re-epithelialization and disappearance of induration of all lesions constituted complete cicatrization. All patients classified as treatment failures received a additional treatment with meglumine antimoniate.

The cure rates obtained with mefloquine were compared with those of randomized controls treated between April 1992 and November 1995 who were selected and evaluated using the same methods: 66 receiving meglumine antimoniate, 20 mg/kg/day intramuscularly for 20 consecutive days, with no upper limit on the daily dose and 56 taking placebo tablets for 28 days.[2,11]

Data were analyzed by means of the chi-square test, *t*-test, analysis of variance, or Fisher's exact test as appropriate. A *P* value < 0.05 was regarded as significant.

RESULTS

During the study period, 55 patients were parasitologically diagnosed. Fourteen of them, 17–59 years of age, were recruited for the trial. Forty-one patients were excluded due to the impossibility of reporting for follow-up (n = 26), age (n = 3), mucosal involvement (n = 2), disseminated CL (n = 1), a lesion within 2 cm of a mucosal skin border (n = 1), pregnancy (n = 1), failure to seek treatment after diagnosis (n = 2), and refusal (n = 5). This excluded group showed no statistically significant differences compared with the study group for the characteristics shown in Table 1 except for age (mean ± SD = 21.3 ± 12.9 years; *P* = 0.004, by two-tailed *t*-test). One study participant and 28 controls did not return for follow-up and were excluded from analysis. After the evaluation of the therapeutic efficacy of mefloquine in the 14th patient was completed, it was clear that a significant difference between the treated patients and those receiving placebo was not evident and the study was stopped. The characteristics of the patients and controls is shown in Table 1. None of the differences were statistically significant.

Mefloquine therapy was no more efficacious than the nonconcurrent placebo control treatment (Table 2). Treatment failures were recognized at four weeks as a greater than 50% enlargement of lesions (eight patients) or at 10 weeks as a less than 50% diminution of lesions (one patient). Three patients healed completely by the fourth week and one showed a greater than 50% reduction in size of his lesions. This patient healed by the 10th week.

The mefloquine cicatrization rate at 10 weeks follow-up did not differ statistically from the combined cicatrization and clinical amelioration rate in the noncurrent placebo group (30.8% versus 37.2%; *P* = 0.75, by Fisher's two-tailed exact test), while the difference with the historical meglumine antimoniate group was highly significant (30.8% versus 90.2%; *P* < 0.001, by Fisher's two-tailed exact test).

TABLE 2
Comparison of treatment efficacy

	Mefloquine group	Historical meglumine group	Historical placebo group
No. of patients recruited	14	66	56
No. (%) of evaluable patients	13/14 (93)	51/66 (77)	43/56 (77)
No. (%) of treatment failures*			
At 4 weeks	8/13 (61.5)	1/51 (2.0)	21/43 (48.8)
At 10 weeks	1/13 (7.7)	4/51 (7.8)	6/43 (14.0)
No. (%) with clinical amelioration*			
At 10 weeks*	0/13 (0.0)	2/51 (3.9)	4/43 (9.3)
No. (%) with complete cicatrization*			
At 4 weeks	3/13 (23.1)	24/51 (47.1)	4/43 (9.3)
At 10 weeks	1/13 (7.7)	20/51 (39.2)	8/43 (18.6)
Cumulative totals at 10 weeks, no. (%)*			
Treatment failure	9/13 (69.2)	5/51 (9.8)	27/43 (62.8)
Clinical amelioration	0/13 (0.0)	2/51 (3.9)	4/43 (9.3)
Complete cicatrization	4/13 (30.8)	44/51 (86.3)	12/43 (27.9)

* Relative to start of therapy.

The difference in cicatrization rates at 10 weeks follow-up would still not be significant (mefloquine versus placebo group; P = 0.30, by Fisher's two-tailed exact test) or would remain significant (mefloquine group versus meglumine antimoniate group; $P = 0.03$, by uncorrected chi-square test) if it is assumed that the one patient in the mefloquine group who could not be evaluated would heal and that treatment with meglumine antimoniate in the controls who could not be evaluated as well as in those who showed only clinical amelioration would fail.

Dizziness occurred in four (one mild, one severe, and two incapacitated) of the five patients (80.0%) on the single-dose regimen and in four (three mild and one of unknown intensity) of the nine patients (44.4%) taking one mefloquine tablet a day. Dizziness lasted for 2–28 days after the start of therapy without a difference in duration between the two groups. Vomiting was reported by one patient (30 min after starting the single-dose regimen). The same adverse events and their reduction in incidence and severity when the dose was split have been previously reported.[14,15,17]

DISCUSSION

When used to treat Colombian CL, a single course of 1.25–1.5 g of mefloquine was as effective as placebo in controls, with cicatrization rates of 30.8% and 27.9%, respectively. In comparison, meglumine antimoniate, 20 mg/kg/day for 20 days, showed an 86.3% cicatrization rate by the 10th week after start of therapy.

Although noncurrent controls in most cases do not allow for the drawing of inferences, we believe that their use here is justified because of the identical selection, diagnostic, and evaluation criteria and the large difference in the cure rate observed with meglumine antimoniate. Also, changes in the virulence of leishmaniasis in Colombia have not been reported and the outpatient population attending our clinic remained similar.

The difference between the results obtained in this study compared with those obtained in Ecuador remains to be explained. Evaluation of treatment efficacy was done at similar follow-up times. Patients in both studies came from predominantly *L. panamensis*-endemic regions. Patients in Ecuador were similar with respect to the sex ratio (81% males), lesions per patient (mean ± SD = 1.75 ± 1.07), type of lesions (all ulcerated) and age of lesions prior to therapy (3.6 ± 3.1 months), but were younger (22 ± 19 years) and more had their lesions located on the head, neck, and arms (81%).[10] Also, we did not repeat the dose, as was done for some patients in Ecuador, since up to seven-fold increases of serious central nervous system events have been reported when mefloquine (25 mg/kg) was again given within one month.[14,17]

The results of this study do not rule out the possibility of differences in age being a possible explanation for the lack of efficacy of mefloquine. Moreover, the subjects excluded from the trial also differed significantly in this aspect from the study participants. However, such a conclusion would suggest that the use of mefloquine should be restricted to a subgroup of patients.

Early vomiting (30 min after starting the single-dose regimen), a risk factor for malaria treatment failure, occurred in one of our cases but this patient healed completely by the fourth week.[18] Lack of compliance cannot be excluded, although we supervised drug intake in four patients, but this was not mentioned in the Ecuadorian report. Lesions on the limbs may heal more slowly due to superinfection, but our patients were prescribed intensive wound hygiene. In Ecuador, Mephaquin® (Mepha Ltd., Basel, Switzerland) was administered while we used Lariam® (F. Hoffmann-La Roche, Basel, Switzerland), which has a higher bioavailibility.[15] Lesions might initially enlarge considerably before healing, which constituted therapeutic failure in our study, but this phenomenon was not reported in Ecuador where 11 patients (68.8% versus 23.1% in our study; P = 0.038, by Yates' corrected chi-square) had cured in four weeks or less.[10,16] Five of our patients took their treatment as a single dose while in Ecuador all patients took 250 mg a day for six days. However, the cure rates we obtained with the two dosage regimens were comparable (25% cure at four weeks with the single dose versus 22% with the one tablet a day regimen; at 10 weeks 0% versus 11%, respectively). Lastly, it should be noted that the Ecuadorian study did not include controls and that spontaneous cure rates of up to 75% in nine weeks have been reported in this country.[16]

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