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EVALUATION OF SODIUM STIBOGLUCONATE (PENTOSTAM) AND KETOCONAZOLE IN THE TREATMENT OF AMERICAN CUTANEOUS LEISHMANIASIS

ANNUAL/FINAL REPORT

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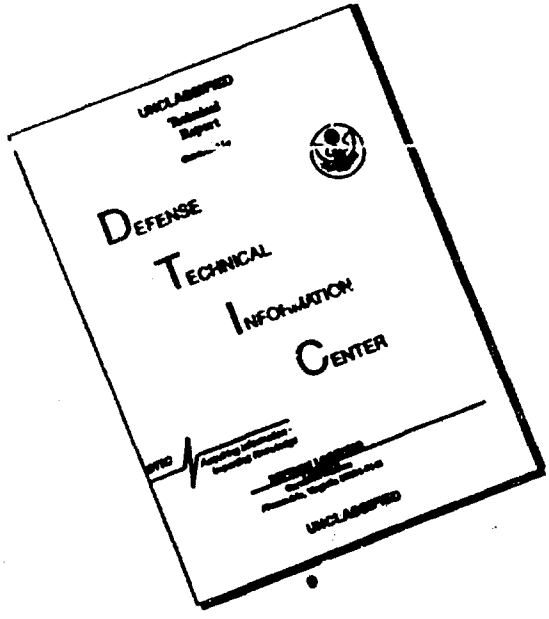

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Placebo-Controlled Clinical Trial of Sodium Stibogluconate (Pentostam) vs. Ketoconazole for Treating Cutaneous Leishmaniasis in Guatemala

88PP8801

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To determine the relative efficacy and toxicity of stibogluconate and ketoconazole for the treatment of cutaneous leishmaniasis, we conducted a comparative trial in which 120 Guatemalan men with parasitologically proven cutaneous leishmaniasis were randomly divided into three treatment groups: sodium stibogluconate (20 mg of antimony per kg per day intravenously for 20 days); ketoconazole (600 mg per day orally for 28 days); and placebo. Stibogluconate was associated with occasional moderate but manageable adverse effects, including abnormal electrocardiograms and elevated transaminase values. Treatment outcome was influenced by species. Among patients infected with Leishmania braziliensis, 24 (96%) of 25 in the stibogluconate group responded. Among L. mexicana-infected patients, only four (57%) of seven in the stibogluconate group but eight (89%) of nine in the ketoconazole group responded. These differences emphasize the importance of speciation in the treatment of leishmaniasis.

Leishmaniasis, Pentostam, Ketoconzaole, RAD 1

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FOREWORD

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INTRODUCTION

Cutaneous leishmaniasis is a vector-borne parasitic disease of the skin caused by a wide range of *Leishmania* species. In the New World, the most common infecting species are *L. braziliensis*, *L. guyanensis*, *L. panamensis*, and *L. mexicana* (formerly *L. braziliensis braziliensis*, *L. braziliensis guyanensis*, *L. braziliensis panamensis*, and *L. mexicana mexicana*, respectively). The clinical manifestations of cutaneous leishmaniasis begin with a papule at the site of inoculation by the infected vector, the phlebotomine sand fly. The papule enlarges slowly and ulcerates to form a deep, usually round, ulcer with an indurated border. The natural history of untreated cutaneous leishmaniasis is not well described, but it is known that lesions may resolve spontaneously or may persist for years.

The recommended treatment for American cutaneous leishmaniasis is one of two available pentavalent antimony compounds, sodium stibogluconate (Pentostam, Burroughs Wellcome) and meglumine antimonate (Glucantime, Specia). Despite the wide use of these antimonials, substantial confusion exists about optimum dosage regimens and toxicities. For example, the Centers for Disease Control and the World Health Organization recommend a wide range of possible daily doses, from a low of 10 to a high of 20 mg of pentavalent antimony per kg of body weight [1]. Recommendations for duration of treatment are equally vague, ranging from a minimum of a few days to a maximum of 3 weeks [1].

The lack of clear-cut treatment guidelines is a product of two factors: the scarcity of reliable information about the efficacy and toxicity of antimonials; and the large number of different *Leishmania* species. Belazzoug and Neal conducted a placebo-controlled clinical trial of meglumine antimonate for cutaneous leishmaniasis caused by *L. major* and found that the antimonial, which cured only 48% of the patients, was actually less effective than the placebo, which cured 55% [2]. Ballou et al. were the first to demonstrate a drug effect for an antimonial agent when they showed that stibogluconate at a dose of 20 mg antimony per kg body weight per day for 20 days was statistically superior to half that dose for cutaneous leishmaniasis in Panama [3]. This study, however, did not include a placebo group, and the patients were infected with only one *Leishmania* species, *L. panamensis*.

Saenz et al., also working with *L. panamensis* in Panama, compared a medium dose of stibogluconate (20 mg antimony per kg body weight with a maximum of 850 mg for 20 days) to ketoconazole (600 mg per day for 28 days) and placebo [4]. They concluded that ketoconazole, which cured 16 (76%) of 21 patients 4 months after starting treatment, was equal to medium-dose antimony, which cured 13 (68%) of 19 patients. This study included a placebo group, which was not associated with cures, but patients were not randomly allocated into the treatment groups.

In 1990 we reported that, for treatment of cutaneous leishmaniasis in Guatemala, 850 mg of antimony (equivalent in our patients to approximately 15 mg antimony per kg) for 15 days was very well tolerated and produced a clinical and parasitologic response in 73% of patients by 13 weeks [5]. Reactivation of infections in 9% of patients during 12 months of follow-up lowered the final response rate to 64%.

These results taken together have been interpreted to indicate that a dose of antimony of 20 mg per kg body weight per day is probably superior to 10 or 15 mg per kg and that the duration of treatment used by Ballou (20 days) is recommended until a possibly superior alternative is found [6]. Data on the efficacy of this higher dose regimen is, however, restricted to the study of Ballou, which involved only 19 patients infected with only one species of *Leishmania*.

Data on the toxicity of this higher dose regimen are also scarce. Changes in electrocardiograms are potentially the most serious adverse effects caused by antimonials. Chulay et al. found that the frequency and severity of such changes are correlated with the total dose of antimony [7]. However, these authors suggest that an antimony dose of up to 20 mg per kg per day for up to 20 days is not associated with significant cardiac toxicity. Although they studied patients who received doses of antimony both higher as well as lower than this cut-off, the authors studied no patients who actually received 20 mg per kg per day for 20 days.

Data on other potential adverse effects of antimony are limited as well, partly because most studies have dealt with small numbers of patients with visceral leishmaniasis, a disease that causes multi-organ dysfunction that can mimic drug toxicity. The information distributed with stibogluconate by the Centers for Disease Control lists as possible adverse effects jaundice, albuminuria, cough, pneumonia, nausea, vomiting, urticaria, and fever. A placebo-controlled clinical trial of stibogluconate for cutaneous leishmaniasis, which does not produce these effects, provides an opportunity to define more precisely the adverse effects associated with antimony.

Since antimonials are expensive and require parenteral injection, investigation of alternative treatments is needed. In vitro data suggest that the oral antifungal imidazole ketoconazole might be effective against *Leishmania* [8-15], and in this day of hepatitis and acquired immunodeficiency syndrome, oral drugs are attractive not only because they are easy to use but also because they do not expose patients to infectious agents that might be transmitted by contaminated needles and syringes. The study mentioned above by Saenz et al. in Panama is the only comparative study of ketoconazole for cutaneous leishmaniasis [4].

We report here the results of the first placebo-controlled, randomized comparison of the now widely recommended dose of antimony (20 mg per kg body weight for 20 days) and ketoconazole for treatment of cutaneous leishmaniasis.

Materials and Methods

Patient population. Guatemalan men who sought treatment for suspected leishmaniasis at any of our four clinics between January 1988 and November 1989 were evaluated. Eligibility for the study included a confirmed diagnosis of leishmaniasis, no previous treatment with antimonials or imidazoles, no serious concomitant medical problems, and no visible evidence of mucosal involvement. Persons who met the study requirements were offered the opportunity to enter the study. Unlike our 1990 clinical study, which involved only military personnel [5], this study included 21 civilians and 99 soldiers. Informed consent was obtained from each person.

Treatment groups. The 120 participants were assigned randomly and equally to one of three treatment groups: those receiving sodium stibogluconate (20 mg pentavalent antimony per kg of body weight per day intravenously for 20 days); those receiving ketoconazole (600 mg orally each evening for 28 days); and those receiving placebo. Half of the patients assigned to the placebo group received saline infusions similar to the stibogluconate infusions, and half received tablets similar to ketoconazole.

Parasitologic diagnosis. Cutaneous leishmaniasis was diagnosed by thin smears of lesion scrapings or culture of lesion aspirates as described before [16]. Only patients with positive cultures or clearly distinguishable amastigotes were entered into the study.

Isolates were characterized by isoenzyme electrophoresis as described before [17]. The following enzymes were used: glucose phosphate isomerase, mannose phosphate isomerase, phosphogluconate dehydrogenase, phosphoglucomutase, and peptidase D.

Patient evaluation. Patients were evaluated at 1, 2, 3, 4, 6, 9, 26, and 52 weeks after the start of therapy. If a lesion was substantially improved by the 9-week examination and the progress of healing was such that the lesion would be expected to continue to heal, the patient was also seen at 13 weeks. Aspirates for culture of all lesions and scrapings of open lesions were taken at the 9-week follow-up examination. Clinical evaluation of all lesions

was made by one physician (BAA). In addition, two other physicians (FA Neva and C Ponce) evaluated photographs of lesions before treatment and at the 9- or 13-week follow-up examination.

Before beginning treatment, on the last day of treatment, and at the 9-week examination, patients had the following tests performed: hemoglobin, hematocrit, platelet count, white blood cell count, aspartate aminotransferase, alanine aminotransferase, direct and indirect bilirubin, creatinine, and electrocardiogram. In addition, patients treated with antimony or placebo injections had the liver function tests repeated on days 7 and 14 and had electrocardiograms repeated on days 2, 4, 7, 9, 11, 14, 16, and 18. Patients who received ketoconazole or placebo tablets also had liver function tests repeated on day 14.

Definition of treatment response and reactivation. A clinical response was defined as a lesion that completely reepithelialized and had no evidence of inflammation. A reactivated lesion was defined as the appearance of an ulcer within or at the border of a previous lesion.

A patient was removed from the study and considered to be a treatment failure for any one of the following conditions: 1) increase of the size of a lesion to more than double the pretreatment size; 2) reactivation of a lesion after an initial clinical response; or 3) failure to develop a clinical response by the 13-week examination.

Patients who were removed from the study were treated with meglumine antimonate at a dose of 20 mg antimony per kg per day for 20 days. Patients with clinically healed but parasitologically positive lesions at the 9-week examination were not necessarily retreated.

Results

Patient characteristics. One hundred twenty study participants were enrolled. Randomization successfully allocated patients with similar characteristics into the three treatment groups (table 1). All but two of the 120 patients completed their treatments without interruption. Both patients who prematurely interrupted their treatments were receiving ketoconazole. Data on these two patients are not included in the analysis of response rates. All the 118 patients who completed treatment were available for follow-up at 9 or 13 weeks. During the 12 months of observation, only five (4%) patients were lost to follow-up.

Clinical and parasitologic response. Figure 1 shows the response rates of patients in the three treatment groups. A number of patients had lesions that were positive by culture at 9 weeks despite being completely reepithelialized. To show both clinical response rates alone as well as clinical plus parasitologic response rates, each treatment group is represented by a range in figures 1, 2, and 3. The lower limits of the range represent the percentage of patients that had complete reepithelialization of their lesions and negative cultures at 9 weeks. The upper limit of the range represents the percentage of patients that had a complete clinical response, irrespective of the results of cultures. A single line for a treatment group indicates that all patients who had responded clinically had negative cultures.

(a) Infections with L. braziliensis. Figure 2 shows response rates for the 63 patients infected with *L. braziliensis*. Many of the 25 patients who received stibogluconate responded rapidly and by the end of 20 days of treatment eight (32%) had completely reepithelialized their lesions and had no evidence of inflammation. By 13 weeks, only one patient (4%) had not responded both clinically and parasitologically. This patient had three large ulcers; two had closed completely by the 13th week, but one was only 70% reepithelialized. Cultures of all three lesions were negative. This patient may have continued to improve without further treatment, but in compliance with the study protocol, he was removed from the study and treated successfully with additional pentavalent antimony. None of the 24 patients who responded to treatment with stibogluconate by 13 weeks had reactivations of their lesions between the 13- and 52-week examinations.

The 23 patients infected with *L. braziliensis* and treated with ketoconazole did not respond as well nor as quickly as those treated with stibogluconate (figure 2). Two patients were removed from the study prematurely

because their lesions had more than doubled in size; one at 5 weeks and the other at 7 weeks. By the end of 28 days of treatment, only two (9%) had responded clinically; by 13 weeks, 12 (52%) had responded clinically, but three of these had positive cultures at the 9-week follow-up examination. Between the 13- and the 52-week examinations, two (17%) of the 12 responders had reactivations of their lesions, one at 17 weeks and one at 11 months.

L. braziliensis-infected patients who received placebo treatment did poorly. Six (40%) of 15 were prematurely removed from the study because their lesions had more than doubled in area. At 13 weeks, only three (20%) of the 15 had responded clinically and parasitologically, and between the 13- and the 52-week examinations, two of the three responders had reactivations of their lesions, one at 14 weeks and the other at 5 months.

Statistical comparison indicated that the response rate for stibogluconate was significantly better than that for ketoconazole or placebo, whether clinical response alone or clinical and parasitologic responses were considered (table 2).

(b) Infections with L. mexicana. In contrast to patients infected with *L. braziliensis*, the 32 patients infected with *L. mexicana* responded better to ketoconazole than to stibogluconate, although this difference was not statistically significant (table 2 and figure 3). The response rate for ketoconazole was significantly higher than that for placebo only when clinical plus parasitologic response was considered (table 2). All seven patients who received stibogluconate had complete clinical responses by 6 weeks, but two had subsequent reactivations, one at 8 weeks and the other at 9 weeks. For all three treatment groups, none of the patients who had responded by 13 weeks had reactivations of their lesions between the 13-week and the 52-week follow-up examinations.

(c) Infections with both species. Two patients had dual infections with both *L. braziliensis* and *L. mexicana*; both received stibogluconate. The lesions caused by *L. braziliensis* in both patients responded rapidly to treatment. The lesion caused by *L. mexicana* in one patient deteriorated progressively, and the patient was removed from the study at 13 weeks. In the other patient, the lesion caused by *L. mexicana* responded initially but reactivated at 26 months.

To compare the evaluation made by the treating physician at the bedside with independent observers, we had 2 scientists familiar with the treatment of cutaneous leishmaniasis score the 118 patient photographs at 9 or 13 weeks as to whether the lesion or lesions had responded. In 106 cases (90%) the three observers agreed. In all 12 discordant cases, the treating physician scored the lesion as not having responded completely and at least one of the independent observers scored the lesion as having responded completely. When the median score of the three observers was considered, the clinical response rates for all patients were as follows: stibogluconate, 37 (93%) of 40; ketoconazole, 27 (71%) of 38; and placebo, 20 (50%) of 40.

Although the majority of our patients returned to a leishmaniasis-endemic area after treatment and 13 weeks of observation, none developed new lesions between the 13- and 52-week examinations.

Adverse effects, stibogluconate group. Twenty-nine adverse reactions were reported by 21 patients who received stibogluconate (table 3). The majority of the adverse reactions were minor and did not require medical attention, and none was severe enough to pose a serious threat to the patient.

Twenty (50%) of the 40 patients who received stibogluconate developed elevated transaminases (55 U/ml) at some time during their treatment, and aspartate aminotransferase and alanine aminotransferase values were in general equally elevated.

Only four patients had elevations of transaminases greater than 100 U/ml, with values for alanine aminotransferase of 102, 116, 240, and 299 U/ml, respectively. The value of 102 U/ml was obtained on the last day of treatment, and a serum sample 24 hours later gave a value of 66 U/ml. The other three values over 100 U/ml were obtained during treatment. Repeat testing within 48 hours, during which time treatment had been continued, showed that values had fallen substantially in each case, to 76, 80, and 60 U/ml, respectively. Treat-

ment in each case was continued for the prescribed duration, and values on the last day of treatment were 53, 22, and 60 U/ml, respectively. At no time did any of the patients who received stibogluconate complain of abdominal pain, jaundice, or pruritus, and values for bilirubin were always within normal limits. In all cases transaminase values were normal at the 9-week examination.

The mean hemoglobin concentration for patients who received stibogluconate dropped from a pretreatment value of 14.9 to 14.2 g/100 ml on the last day of treatment. This decrease was statistically significant (paired samples t-test; $p = 0.048$). Anemia developed in only one patient during treatment; his pretreatment hemoglobin concentration of 12.6 g/100 ml fell to 10.0 g/100 ml on the last day of treatment.

For patients who received stibogluconate, values were always within normal limits for the following tests: creatinine; direct and indirect bilirubin; and counts for platelets, white blood cells, lymphocytes, eosinophils, and monocytes.

By far the most common change in the ECGs of patients who received stibogluconate was a decrease in the amplitude of the T wave, and this change was more common and of a greater magnitude in the precordial leads than in the limb leads. At some point during treatment, 20 (50%) of the 40 patients had decreases of 50% or more in the amplitude of their T waves measured in the limb leads, and the mean decrease from pretreatment to the last day of treatment for the entire group was 56%; 23 (58%) had such decreases in their precordial leads, and the mean decrease was 68%.

Eight (20%) patients in the stibogluconate group had inverted T waves at some point during treatment, but none had concave ST segments. One patient first developed T-wave inversion on day 7 of treatment, but the median time of first appearance was day 16. In two patients the T-wave inversion was noted only on the last day of treatment.

Only one patient treated with stibogluconate had a corrected QT interval (QTc) greater than 0.45 seconds on the last day of treatment; his pretreatment QTc was 0.43 seconds, and this measurement was prolonged to 0.46 seconds on the last day of treatment. Although in nine patients the QTc on the last day of treatment was prolonged more than 0.02 seconds compared with the pretreatment value, nine others had QTc intervals that had actually shortened by the last day of treatment. The mean QTc value for the entire group on the last day of treatment was only 0.01 seconds greater than the mean pretreatment value.

All ECG changes noted during therapy had normalized by the 9-week examination. During therapy no patients complained of shortness of breath, palpitations, or chest pain.

Adverse effects, ketoconazole group. Seven patients who received ketoconazole reported a total of eight adverse effects, of which four were moderately severe. In two patients, the adverse effect led to premature termination of treatment.

The first patient developed a generalized pruritic papular erythematous rash on the seventeenth day of treatment with ketoconazole. The patient had no urticaria or wheezing, and his blood pressure remained normal. Although the treating physician did not think the rash was severe enough to require the premature termination of ketoconazole, the patient decided to withdraw from the study. The rash spontaneously resolved 3 days after ketoconazole treatment ceased. The patient was successfully treated with meglumine antimonate. The second patient developed epigastric pain and nausea 2 hours after the second dose of ketoconazole. Two hours after the onset of these symptoms, the patient vomited several times and had diarrhea. Ketoconazole was stopped for 2 days, during which the patient had no gastrointestinal symptoms. When ketoconazole and antacids were restarted, the patient again developed moderately severe epigastric pain but did not vomit or have diarrhea. The patient was able to continue ketoconazole until the sixteenth dose, when the epigastric pain increased substantially and he again vomited once. The patient was withdrawn from the study and treated successfully with meglumine antimonate. One day after ketoconazole was stopped, the gastrointestinal symptoms disappeared.

The mean hemoglobin for patients who received ketoconazole fell from a pretreatment value of 14.4 g/100 ml to 13.9 g/100 ml on the last day of treatment. This difference approached statistical significance with the paired samples t-test ($p = 0.058$) Two (5%) of the 38 patients who received ketoconazole developed anemia during treatment. In the first, the pretreatment hemoglobin of 14.0 g/100 ml fell to 10.6 g/100 ml by the last day of treatment. In the other patient, these values were 13.5 and 10.6 g/100 ml, respectively. In both patients, values had normalized by 9 weeks.

Adverse effects, placebo group. Four patients reported a total of five adverse effects, of which only one was moderately severe. No laboratory value was ever outside of our laboratory's normal limits. Specifically, hemoglobin values rose from a pretreatment concentration of 14.4 to 14.6 g/100 ml on the last day of treatment.

All patients who received placebo treatment had normal electrocardiograms before and during treatment except for four whose QTc intervals were prolonged by more than 0.02 seconds. The maximum prolongation was 0.05 seconds, but for the group as a whole, the mean QTc interval showed no change from before treatment to the last day of treatment.

Discussion

This study was a placebo-controlled comparison of sodium stibogluconate with the oral imidazole ketoconazole in the treatment of infections caused by the two common *Leishmania* species of Guatemala, *L. braziliensis* and *L. mexicana*. Of 120 eligible patients, 118 completed treatment, and two terminated treatment prematurely due to toxicity. Because cutaneous leishmaniasis can reactivate after initial treatment, patients were followed for 12 months. With help from the Guatemalan Ministries of Health and Defence, we were able to complete 12-month follow-up on all but five of our patients.

One of the difficulties in evaluating clinical trials of cutaneous leishmaniasis has been that different investigators have used different and often ill-defined criteria to measure therapeutic response. To ensure that observer bias did not distort our measurement of clinical response, we asked two clinicians experienced in the treatment of cutaneous leishmaniasis to review in a blinded fashion photographs of our patients at 9 or 13 weeks. For each case of a difference between the bedside evaluation and that of the photographs, the physician at the bedside scored the lesion more conservatively. We suspect that it is easier to identify subtle degrees of inflammation and induration at the bedside than from photographs. Because the bedside evaluation was the more conservative, we have used these data in this report.

L. braziliensis. Treatment with high-dose (20 mg per kg per day for 20 days) stibogluconate in this clinical trial proved very effective against infections due to *L. braziliensis*. Only one of 25 patients infected with *L. braziliensis* and treated with high-dose stibogluconate had not completely responded by 13 weeks, and even this patient had improved substantially with treatment and responded completely to additional treatment with antimony.

In our clinical trial in Guatemala in 1990, we reported that only 64% of patients infected with *L. braziliensis* had a clinical and parasitologic response to 850 mg of antimony per day for 15 days [5]. In that study, all patients completely reepithelialized their lesions at some point. The major difference in the results of the two studies, therefore, are the rates of reactivation (36% in [5] vs. 0% in this study) rather than the initial response rate (100% in [5] vs. 96% in this study).

Treatment of *L. braziliensis* infections with ketoconazole was statistically more effective than placebo. The drug, however, was associated with a clinical response in less than half the patients, a rate significantly less than that for stibogluconate.

L. mexicana. In contrast to the impressive results with stibogluconate for infection caused by *L. braziliensis*, we were surprised to find that stibogluconate was not significantly better than placebo for infections caused by

the other major species of *Leishmania* in Guatemala, *L. mexicana*. Although all seven patients infected with *L. mexicana* had responded clinically to stibogluconate by 6 weeks, two had reactivations and another had a positive culture at 9 weeks. These results are similar to our results with 850 mg of antimony, where three of four patients with *L. mexicana* infections responded by 6 weeks, but two of the three responders had reactivations by 9 weeks [5]. The two studies together suggest that antimony has an initial effect against *L. mexicana*, but this effect is transient and associated with relapses.

Ketoconazole proved more effective than either stibogluconate or placebo in the treatment of infections caused by *L. mexicana*, although the number in each group was small and the difference between ketoconazole and placebo was statistically significant only when clinical plus parasitologic response was considered.

Adverse effects. The randomized, placebo-controlled nature of this study permitted for the first time the determination of the toxicity of these regimens of stibogluconate and ketoconazole for cutaneous leishmaniasis.

Although complaints by patients of adverse reactions, abnormal electrocardiograms, and elevated transaminase values were common in patients who received stibogluconate in this study, these problems were never more than moderately severe and never necessitated discontinuing treatment.

The two adverse effects that posed the biggest potential problems were elevated transaminases and abnormal ECGs. The abnormal transaminases we observed in patients were difficult to interpret because they were inconsistently elevated. In two patients, values over 200 U/ml fell to near normal levels within 48 hours even though therapy was continued. Our suspicion is that these patients drank alcohol during treatment despite having been warned against it and that the combined hepatotoxicity of antimony and alcohol caused intermittent elevations of transaminase tests.

Although ECG changes developed in a large percentage of our patients, our results were actually reassuring in light of previous reports of serious cardiotoxicity associated with higher doses of antimony [7]. Chulay et al. suggested that dangerous cardiotoxicity was indicated by the presence of concave ST segments or QTc values greater than 0.50 seconds. We observed no concave ST segments, and the most prolonged QTc in our patients was 0.46 seconds. We agree with Chulay et al. that routine ECG monitoring of young, otherwise healthy individuals with no history of heart disease is not necessary if the antimony dose does not exceed 20 mg per kg per day for 20 days.

When evaluating our data on adverse effects, however, one must keep in mind that our patient population is young and in good enough physical shape to withstand the hardships of making a living or conducting military patrols in a tropical jungle. Cutaneous leishmaniasis is, in general, a disease of young males, so our results should be applicable to most other geographic settings. When the disease occurs in older patients, however, or in patients with underlying hepatic or cardiac disease, the hepatic and cardiac toxicity of stibogluconate may present a greater problem.

CONCLUSIONS

Although no study has directly compared medium-dose antimony (850 mg) and the high-dose regimen used in this study (20 mg per kg), our results and those from Panama [3,4] now strongly suggest that the high-dose regimen is superior in efficacy to the medium-dose regimen for infections due to *L. braziliensis*. Little is known about the proper duration of this high dose regimen. Our results and those of Ballou et al. [3] show that 20 days of treatment is associated with excellent results. Future studies should be designed to test whether this duration can be shortened. Adverse effects were more frequent with the higher dose, but these effects were manageable and never required the premature termination of the drug.

We recommend, therefore, that cutaneous leishmaniasis caused by *L. braziliensis* be treated with one of the two available pentavalent antimonial agents (sodium stibogluconate or meglumine antimonate) at a dose of 20 mg antimony per kg body weight per day intravenously for 20 days.

Recommendations for treatment of infections caused by *L. mexicana* are more difficult to formulate, since we were able to study only a small number of patients with this infection. This is our second study, however, in which antimonial agents have not proved superior to placebo [5]. Because our results show that ketoconazole at a dose of 600 mg per day orally for 28 days gave better results than did either stibogluconate or placebo, this is our recommendation for treatment of infections with *L. mexicana* until more information becomes available.

In most endemic regions of the New World, several species of *Leishmania* coexist. We were unable to differentiate infections caused by *L. braziliensis* from *L. mexicana* on clinical grounds. In addition, although there are certain characteristics, such as amastigote size and concentration, that can predict infection with one species or the other, such predictions are not sufficiently accurate to be of great help to the clinician. Differentiating species by biochemical methods is very accurate, but available techniques, such as monoclonal antibody binding, cellulose acetate electrophoresis, and DNA hybridization, are not commercially available and are often not rapid enough to guide the initial therapeutic choice.

Our experience in Guatemala suggests that the treatment of choice for cutaneous leishmaniasis when *L. braziliensis* and *L. mexicana* coexist is the antimony regimen recommended above for *L. braziliensis*. If subsequent identification of *L. mexicana* is made, or the patient fails to respond or responds but then reactivates, additional treatment with ketoconazole at a dose of 600 mg per day orally for 28 days should be considered.

Table 1. Characteristics of patients by treatment group.

Characteristic	Treatment group		
	Stibogluconate (n=40)	Ketoconazole (n=38)	Placebo (n=40)
Age (years)	19.1 ± 0.6*	20.2 ± 1.2	21.3 ± 1.4
Number lesions/patient	1.6 ± 0.2	1.5 ± 0.1	1.5 ± 0.2
Mean area of ulceration (cm^2)	1.5 ± 0.3	2.2 ± 0.4	2.0 ± 0.4
Mean age of lesions (days)	73.7 ± 34	68.3 ± 10	59.1 ± 7
Infecting species			
L. mexicana	7	9	16
L. braziliensis	25	23	15
Both (*L.m.* and *L.b.*)	2	0	0
Unknown	6	6	9

* Mean ± standard error.

Table 2. Statistical comparison of responses rates at 52 weeks by treatment group and by infecting species of *Leishmania*.

	Response rates (%)	Chi square**	p value
CLINICAL RESPONSE*			
All patients			
Stibogluconate vs ketoconazole	88 vs 58	7.24	0.007
Stibogluconate vs placebo	88 vs 33	22.97	< 0.001
Ketoconazole vs placebo	58 vs 33	4.11	0.043
Patients infected with *L. braziliensis*			
Stibogluconate vs ketoconazole	96 vs 43	13.55	< 0.001
Stibogluconate vs placebo	96 vs 7	28.22	< 0.001
Ketoconazole vs placebo	43 vs 7	FE	0.026
Patients infected with *L. mexicana*			
Stibogluconate vs ketoconazole	71 vs 89	FE	0.560
Stibogluconate vs placebo	71 vs 56	FE	0.657
Ketoconazole vs placebo	89 vs 56	FE	0.182
CLINICAL + PARASITOLOGIC RESPONSE*			
All patients			
Stibogluconate vs ketoconazole	85 vs 50	9.41	0.002
Stibogluconate vs placebo	85 vs 25	26.72	< 0.001
Ketoconazole vs placebo	50 vs 25	4.20	0.040
Patients infected with *L. braziliensis*			
Stibogluconate vs ketoconazole	96 vs 30	19.74	< 0.001
Stibogluconate vs placebo	96 vs 7	28.22	< 0.001
Ketoconazole vs placebo	30 vs 7	FE	0.114
Patients infected with *L. mexicana*			
Stibogluconate vs ketoconazole	57 vs 89	FE	0.262
Stibogluconate vs placebo	57 vs 38	FE	0.650
Ketoconazole vs placebo	89 vs 38	FE	0.033

* Patients with "clinical responses" had lesions that were clinically healed by 13 weeks, irrespective of post-treatment culture results. Patients with "clinical + parasitologic responses" had clinical responses and negative cultures at 9 weeks.

** Chi square calculated with Yates' correction. For cells with expected values less than 5, Fisher's exact test, 2-tailed (FE) was used.

Table 3. Number of adverse effects reported by patients.

Treatment group/ Adverse reaction	Severity * Mild	Moderate	Severe	Total
Stibogluconate				
Nausea	3	2	0	5
Anorexia	4	0	0	4
Headache	1	2	0	3
Rash	1	0	0	1
Arthralgias	5	1	0	5
Phlebitis	8	2	0	10
TOTAL	22	7	0	29
Ketoconazole				
Nausea	1	1 **	0	2
Abdominal pain	1	1	0	2
Headache	1	1	0	2
Dizziness	1	0	0	1
Rash	0	1 **	0	1
TOTAL	4	4	0	8
Placebo				
Nausea	1	0	0	1
Anorexia	1	0	0	1
Abdominal pain	2	1	0	3
TOTAL	4	1	0	5

* Mild: No need for medical attention
Moderate: Required medical attention, but posed no danger to patient
Severe: Required immediate medical attention to prevent danger to patient

** Adverse reaction led to the premature termination of the study drug

Figure 1. Percent of patients who responded to treatment with sodium stibogluconate, ketoconazole, or placebo by week of follow-up examination.

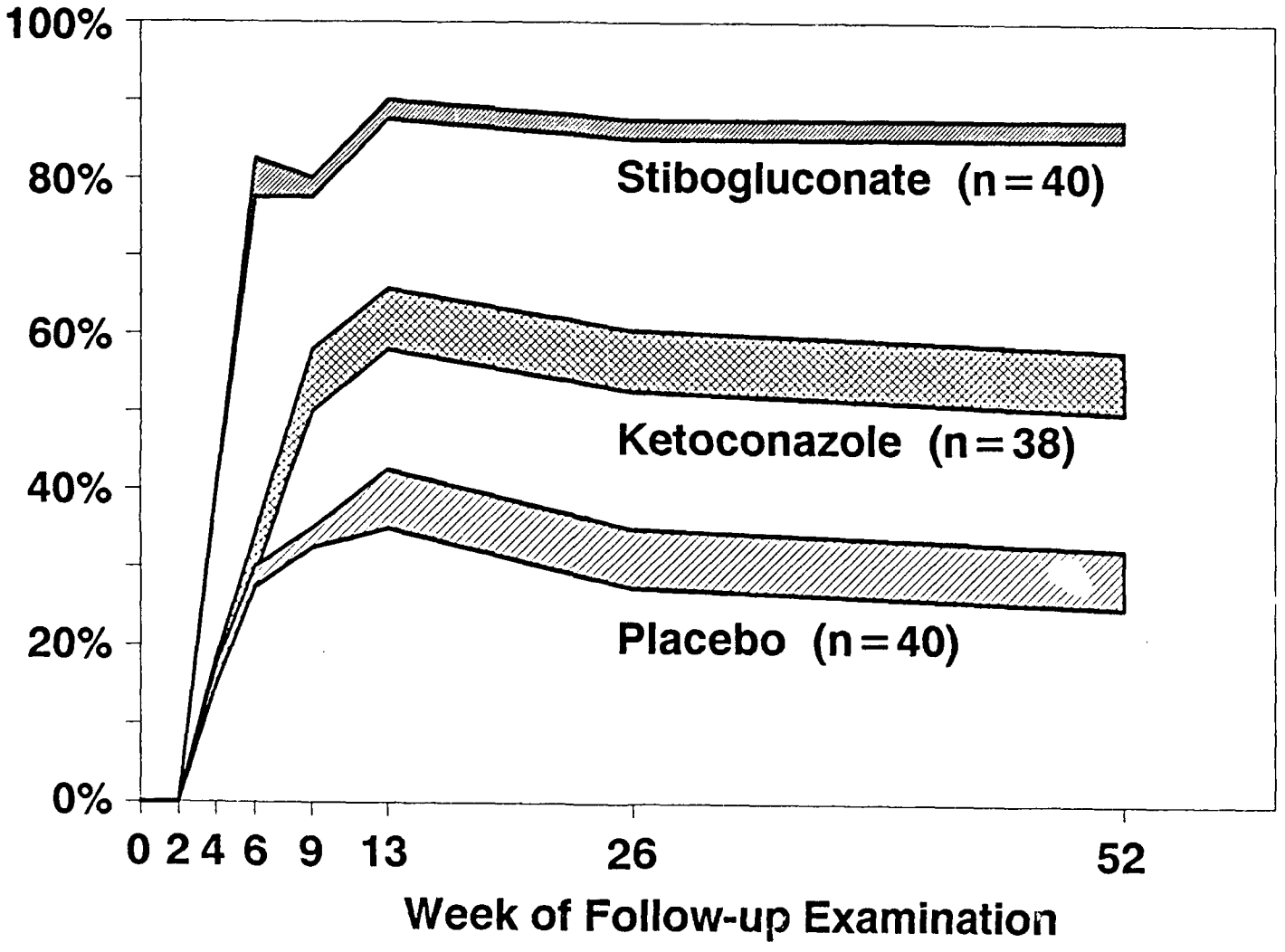


Figure 2. Percent of patients infected with L. braziliensis who responded to treatment.

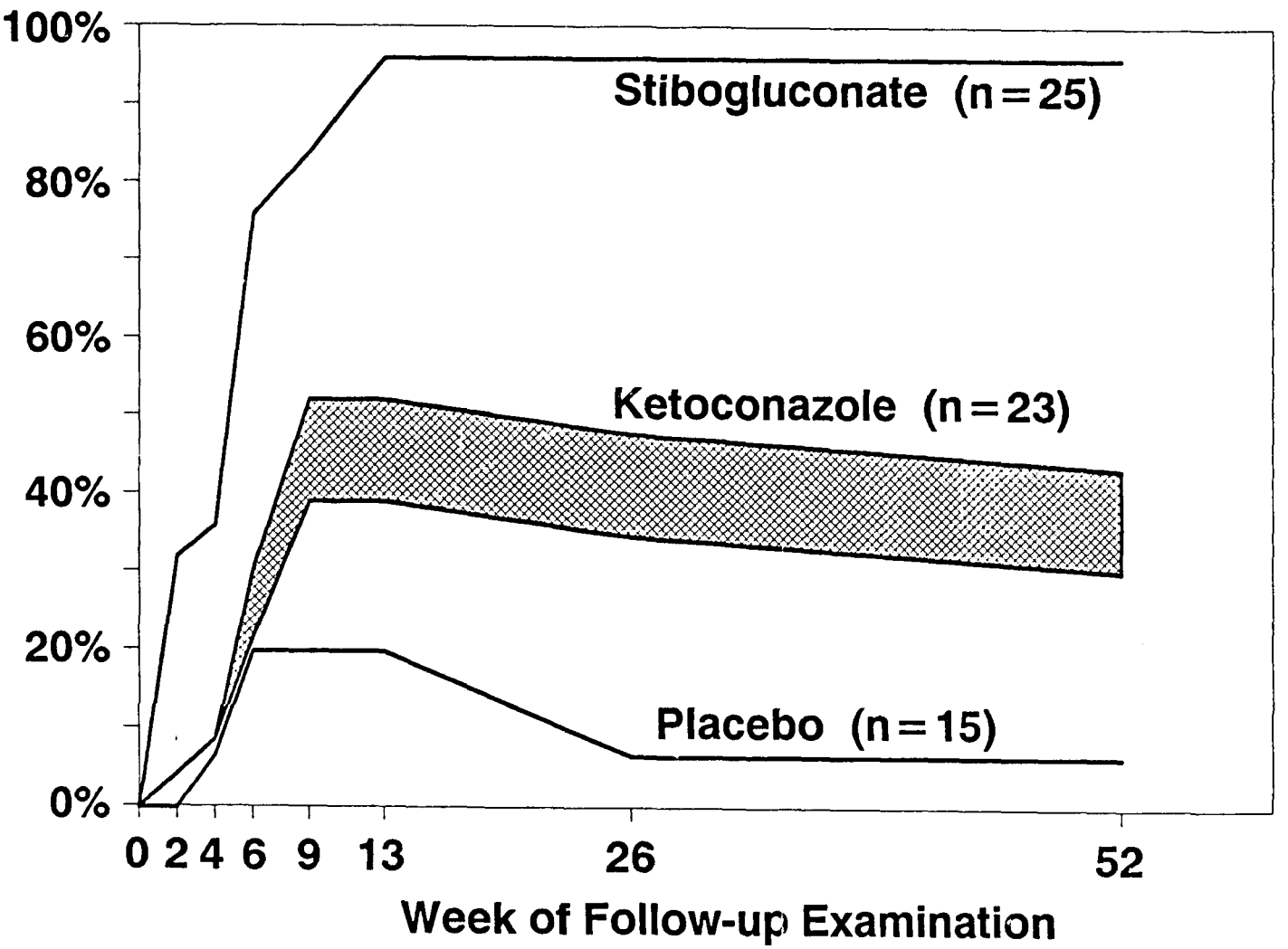
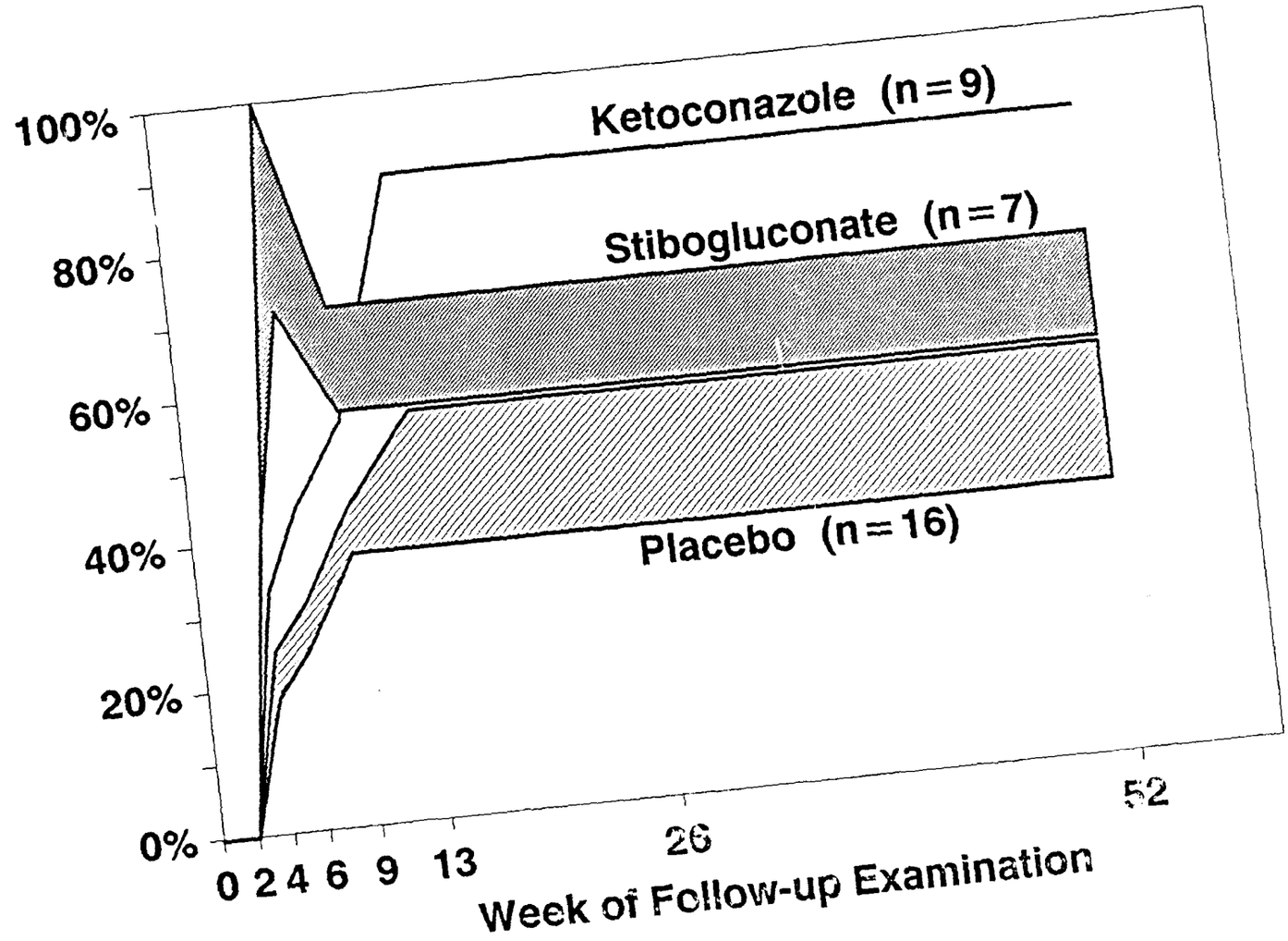


Figure 3. Percent of patients infected with L. mexicana who responded to treatment.



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BIBLIOGRAPHY OF PUBLICATIONS FROM PROJECT:

EVALUATION OF PENTOSTAM AND KETOCONAZOLE
IN THE TREATMENT OF AMERICAN CUTANEOUS LEISHMANIASIS

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1. Navin TR, Arana BA, Arana FE, Berman JD. Placebo-controlled Clinical Trial of Pentostam vs. Ketoconazole for Cutaneous Leishmaniasis in Guatemala. Abstract presented at the 39th annual meeting of the American Society of Tropical Medicine and Hygiene, New Orleans, November 4-8, 1990. Abstract number 327.