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Efficacy of glucantime for treatment of cutaneous leishmaniasis in Central Iran

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Summary Glucantime remains the first-line treatment for cutaneous leishmaniasis. In a prospective study, we evaluated its efficacy and side effects in patients treated in Yazd from 2010 to 2011.

Methods: Patients with lesions compatible with cutaneous leishmaniasis were considered eligible for inclusion in this study if the disease was confirmed parasitologically. The exclusion criteria were as follows: the patient preferred a treatment modality other than Glucantime; there was no indication for treatment; the patient had underlying kidney, liver, or cardiac disease; or was pregnant and lactating.

Patients with $\leq$3 lesions and/or lesions <3 cm in diameter were treated with Glucantime intralesionally if the lesions were not located on the face, neck or joints; sporotrichoid; or superinfected with bacteria. All other patients were prescribed intramuscular Glucantime at 10—20 mg/kg/day for 20 days.

Results: The failure rate for patients treated with one course of Glucantime was 22.6% overall. There were no associations between age, sex, weight, the route of administration, the number and size of lesions, the adequacy of the dose of the drug injected intramuscularly, the number of intralesional injections (<6 or $\geq$6) and the duration of therapy. The only factor associated with failure was reported previous exposure to antimony (*p* value 0.047). Adverse effects occurred in 14.2% of patients (22/155).

Conclusion: Glucantime is an effective drug for the treatment of cutaneous leishmaniasis in central Iran. However, because cutaneous leishmaniasis heals spontaneously and to prevent the acquisition of resistance, the indications for treatment in each region should be defined carefully.

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Introduction

Cutaneous leishmaniasis (CL) occurs in two forms in Iran, zoonotic cutaneous leishmaniasis (ZCL) and anthroponotic cutaneous leishmaniasis (ACL). ZCL, which is caused by *Leishmania major*, is endemic in the northeastern, southeastern and central areas of Iran [1]. ACL, which is caused by *Leishmania tropica*, is prevalent in large and medium-sized cities in Iran [2].

Pentavalent antimony is the first choice for the treatment of cutaneous leishmaniasis of both the New World and Old World types, including the type of leishmaniasis that is prevalent in Iran [3—7]. However, concerns about the resistance of parasites to Glucantime have appeared [8]. The first report of the *in vitro* resistance of *L. tropica* to Glucantime in Iran was published in 2006 [9]. Previously identified risk factors for the failure of treatment with Glucantime are body weight above 68 kg, previous anti-*Leishmania* treatment, having $\geq$3 skin lesions and failure to complete the treatment schedule [10].

A prospective study was designed to evaluate the failure rate and identify possible factors associated with failure in patients treated with Glucantime in Yazd in central Iran between March 2010 and March 2011.

Materials and methods

Patients

All patients with skin lesions compatible with CL and parasitologically confirmed disease who were referred to the Yazd Health Center from March 2010 to March 2011 were considered eligible for inclusion in this study.

Patients from known foci of either zoonotic cutaneous leishmaniasis or anthroponotic were included. The following patients were excluded: patients who preferred a treatment modality other than Glucantime (meglumine antimonite); those who had no indication for therapy; patients with underlying conditions, such as diabetes, liver disease, cardiac disease, and renal disease; and pregnant and lactating women.

Parasitological confirmation was performed by Giemsa staining (direct smear). The size of the lesion was defined as the diameter of the largest lesion measured in millimeters.

Design

Patients enrolled in the study completed a questionnaire covering age, sex, weight, number of lesions, size of the largest lesion, route of drug administration (intramuscular or intralesional), dose of Glucantime, duration of therapy, outcome (failure or cure) and adverse events.

Most patients were treated within 2—3 months after the appearance of lesions.

Patients with $\leq$3 lesions and patients who had lesions <3 cm in diameter were treated intralesionally if the lesions were not located on the face or neck or over the joints; sporotrichoid; or superinfected with bacteria. Glucantime (Aventis, Paris, France; supplied in 5 ml ampules containing 81 mg antimony/ml) was injected 2 times per week for a total number of injections from 6 to 15 [11]. Intradermal injections of 0.3—1.5 ml of drug were administered until the lesion faded.

All other patients were prescribed intramuscular injections of Glucantime at 20 mg/kg/day (maximum 3 ampules/day) that were administered in 2—3 divided doses for two weeks for ZCL and 20 days for ACL according to the national guidelines distributed by the Iranian Center for Disease Control. Patients who required more than 2 ampules based on their weight received less than 20 mg/kg/day. Cure was confirmed by a negative direct smear, and failure was defined as the persistence of an active lesion, the appearance of new lesions in the periphery of the primary lesion, the persistence of induration and lymphadenopathy, or positive direct smears 2—4 weeks after the completion of one course of treatment with Glucantime. The intralesional injections and the evaluation of patients were performed by four infectious disease specialists coordinated by the first author. Follow-up visits to assess patients for failure were arranged 2—4 weeks after the completion of therapy. In the case of relapse or a failure to respond to the first course of therapy, the patients were retreated as decided by the clinician.

The patients were divided into 3 treatment groups: intralesional, intramuscular, and intralesional plus intramuscular for patients who did not tolerate the IM injections because of pain or the intralesional injection because of severe inflammation and irritation.

The potential risk factors associated with a failure to respond to Glucantime were also studied. Patients were also assessed for adverse side effects of Glucantime treatment at each visit. Blood laboratory tests were not consistently requested for all patients.

Analysis

The data were analyzed with SPSS (18). Chi-square, Fisher's exact and *T* tests were used. *p* values less

than 0.05 were considered significant for differences between groups.

This study was performed as a thesis and approved by the ethical board of research deputy of our medical faculty.

3-Hypothesis

Glucantime (SbV) is the first-line treatment for cutaneous leishmaniasis in Iran. However, because resistance to this drug has been reported, its efficacy and adverse side effects should be regularly monitored.

Results

Among the 164 patients who were enrolled into the study, 9 were excluded because they refused injections with Glucantime, preferring cryotherapy (4 patients) or treatment with oral agents (5 patients). The majority of patients were referred during the autumn and winter. One hundred and fifty-five patients were treated with Glucantime, but the outcome was evaluable for only 137 patients (88.5%), who were analyzed. Seventy-six patients were male (55.5%), and the mean age of the patients was 30.8 ± 20.1 years (8 months to 84 years). The mean number of lesions was 2.2 ± 2.06 (1—15), and the mean size of the largest lesion was 29.6 ± 23.4 mm (3—120). Thirty-eight patients were treated intralesionally, and 95 patients were treated intramuscularly. Four patients were treated both intralesionally and intramuscularly and omitted from the analysis.

The overall failure rate for patients treated with one course of Glucantime was 22.6% (31/137) (Table 1). As shown in Table 1, there were no associations between age, sex, weight, the route of administration (intramuscular or intralesional), the number and size of lesions, the dose ($\geq$10 mg/kg or <10 mg/kg) of intramuscularly injected drug, an adequate number (6—15) of intralesional injections, the amount of Glucantime administered or the duration of therapy in the present study. Only 1 patient was compliant with injecting three ampules of Glucantime per day intramuscularly. The only factor associated with failure was reported previous exposure to Glucantime (p value 0.047).

Nine patients were excluded from the analysis. The lesions of 6 patients (66.6%) healed: the lesions of two pregnant women (one spontaneously and one after the use of herbal medicine and paromomycin ointment), two 30 mm lesions in 1 patient (spontaneously), one lesion after a single cryotherapy treatment session, one lesion measuring 50 mm after treatment with azithromycin (250 mg bid for 6 days), and one lesion after treatment with ketoconazole (2 tablets per day for 20 days).

Clinically observed adverse side effects of Glucantime occurred in 22/155 patients (14.2%) in the present study. These side effects included a hypersensitivity reaction in 9 patients (5.8%); cellulitis at the site of the intralesional injection in 3 patients (1.9%); syncope after injection in 2 patients (1.3%), one instance of which was associated with hypotension and required the administration of vasotonic agents; severe myalgia in 2 patients (1.3%); and dizziness, hypoglycemia, urinary retention, deep abscess formation after local injection, bullous formation following cryotherapy, severe headache after local injection and a severe generalized eczematous reaction each in 1 patient (3.9%). Shingles was observed concomitantly in three patients.

Discussion

The failure rate after one course of therapy with Glucantime administered either intramuscularly or intralesionally in central Iran in the present study was 22.6% (31/137). The failure rate evaluated 2—4 weeks after the completion of one course of treatment with intramuscular Glucantime was 24.2% (23/95). The present study included both ACL and ZCL. The reported failure rates for one course of standard intramuscular Glucantime for 14 days in Iran are 7% in the eastern region; 16%, 34.9%, and 59% in the southern region; and 16.7% in the northern region among patients treated with 20 mg/kg/day [12]. In another study in Iran, *in vitro* and *in vivo* resistance was observed in 11% of isolated *L. tropica* strains [9]. The cure rate in the present study was slightly lower than the rates reported from two clinical trials in Bolivia and Colombia (83%) [3]. Two studies from Pakistan revealed failure rates of 19% and 45% [8,13]. Two studies from South America revealed 47% and 57.9% failure rates in patients treated with 20 mg/kg/day for 20 days [10,14]. The wide range of failure rates in different studies is due to the different parasite species, different treatment schedules, and different intervals between the evaluation of the response and the termination of therapy because of the possibility of spontaneous resolution in those evaluated later [12]. We evaluated our patients 4 weeks after the completion of therapy to avoid the inclusion of patients who may have recovered spontaneously. A history of previous treatment with Glucantime was the only factor associated with failure in this study. This finding, which could be

Table 1 Demographic and clinical characteristics of patients with cutaneous leishmaniasis and their responses to Glucantime.

Variable	Cure *N* (%)	Failure *N* (%)	*p* value	Test applied
Age group (years)				
<18	26 (24.5)	9 (29.1)	0.261	Chi-square
18—59	72 (67.9)	17 (54.8)		
>60	8 (7.5)	5 (16.1)		
Sex				
Male	59 (77.6)	17 (22.4)	0.935	Chi-square
Female	47 (77)	14 (23)		
Type of injection				
Intramuscular (IM)	72 (75.8)	23 (24.2)	0.470	Chi-square
Intralesional (IL)	31 (81.6)	7 (18.4)		
Previous treatment with Glucantime				
Yes	5 (50)	5 (50)	0.047	Fisher's exact
No	101 (79.5)	26 (20.5)		
Number of lesions				
≤3	94 (79.7)	24 (20.3)	0.139	Chi-square
>3	12 (63.1)	7 (36.9)		
Lesion size (mm)				
≤30	76 (76.8)	23 (25.2)	0.785	Chi-square
>30	30 (78.9)	8 (21.1)		
Weight of patient (kg)				
≤40	18 (69.2)	8 (30.8)	0.270	Chi-square
>40	88 (79.3)	23 (20.7)		
Dose of Glucantime (IM)				
≥10 mg/kg/day	61 (78.2)	17 (21.8)	0.551	Fisher's exact
<10 mg/kg/day	13 (72.2)	5 (17.8)		
Number of IL injections				
6—15	20 (66.6)	5 (35.4)	1.000	Fisher's exact
<6	10 (76.9)	3 (23.1)		
Amount of Glucantime/kg/day (mg)	12.9 ± 3.97	12.37 ± 3.48	0.601	*T*-test
Duration of therapy in intramuscularly treated patients (days)				
<10	12 (80)	3 (20)	0.910	Chi-square
10—14	31 (75.6)	10 (24.4)		
≥15	29 (74.3)	10 (25.7)		

due to acquired resistance, has been observed in two other studies [3,10]. Practices that expose the parasites to drug pressure lead to the selection of species of the parasite that are resistant to SbV [15]. Resistance to Glucantime is an important issue because there are few other drugs available for the treatment of cutaneous leishmaniasis [16]. Cross-resistance has been observed between Pentostam (SSG) and Glucantime, which further limits the treatment options available in Iran [9].

Regarding the clinical adverse side effects observed in the present study, hypersensitivity was the most frequent and was primarily observed following local injection. In another study in Iran comparing the intralesional injection of Glucantime with zinc sulfate, 8.52% of patients treated with Glucantime developed pruritus, erythema and peripheral scaling [17]. Severe pain associated with local injection and resulting in syncope and hypotension, which was observed in one of our patients, was a potentially serious adverse effect. For this subgroup of patients, other treatment modalities, such as an alternative antimony schedule, can be used [18]. Myalgia, which was reported by 2 patients in the present study, was reported in up to 68% of patients in a trial in which patients were treated with 20 mg/kg/day Glucantime intravenously for 20 days [19]. In a retrospective study performed in Tunisia, myalgia was the third most frequent side effect of Glucantime [20]. Although pentavalent antimonials, such as Glucantime, have been used since 1911 [21], some of the adverse side effects observed in the present study, including hypoglycemia in a diabetic patient, urinary retention, deep abscess formation, severe headache, and concomitant shingles, have not been mentioned in previous reports [8,12,17,19]. Therefore, the side effects

of Glucantime should be monitored repeatedly, and because of the self-limiting nature of cutaneous leishmaniasis in the majority of cases and to prevent the development of resistance to Glucantime, this drug should be reserved for the treatment of severe, progressive or disfiguring disease.

Conflict of interest

Funding: No funding sources.
Competing interests: None declared.
Ethical approval: Not required.

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