Effectiveness of meglumine antimoniate against *L. tropica* in a recently emerged focus of cutaneous leishmaniasis in Birjand, eastern Islamic Republic of Iran

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فعالية ميجلومين أنتيمونيات ضد الليشمانية المدارية في بؤرة لداء الليشمانيات الجلدي ظهرت مؤخّراً في بيرجاند، بشرق جمهورية إيران الإسلامية

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الخلاصة: مع محدودية خيارات معالجة داء الليشمانيات الجلدي لا بد من القيام برصد مستمر لمعدل مقاومة الأدوية التي أساسها الأنتيمون خماسي التكافؤ. وقد قامت هذه الدراسة بالتعرف على نوع الليشمانية المسببة للعدوى وتقييم نتائج المعالجة بالميجلومين أنتيمونيات (جلوكانتيم Glucantime®) في بؤرة جديدة لداء الليشمانيات الجلدي في بيرجاند، بشرق جمهورية إيران الإسلامية. فأظهرت مسحات مأخوذة من 150 مريضاً أن 141 مريضاً كانوا مصابين بالعدوى بالليشمانية المدارية و9 بالليشمانية الكبيرة. وقد لوحظ فشل المعالجة بالجلوكانتيم فقط لدى المرضى المصابين بالليشمانية المدارية. وفي الإجمال، فإن الـ 141 مريضاً المصابين بالعدوى بالليشمانية المدارية استكملوا المعالجة بالجلوكانتيم وأنهوا المتابعة؛ وقد عولج 63.8٪ منهم بالحقن داخل الآفة و36.2٪ عن طريق الحقن العضلي. وكان معدل النجاح العام بعد دورة علاجية واحدة بالجلوكانتيم 96.5٪ (136/141)، وكل حالات الفشَل (5/141) حدثت مع الحقن العضلي. فأظهر التحليل الإحصائي فرقاً كبيراً بين معدّلات فشَل الحقن العضلي والحقن داخل الآفة. وكان معدّل الفشَل لدى الأطفال الذين تقل أعمارهم عن 10 سنوات أعلى بكثير منه لدى البالغين.

ABSTRACT With limited options to treat cutaneous leishmaniasis, constant monitoring of the rate of resistance to pentavalent antimony-based drugs is needed. This study identified the infecting *Leishmania* species and evaluated the results of meglumine antimoniate (Glucantime®) therapy in a new focus of cutaneous leishmaniasis in Birjand, eastern Islamic Republic of Iran. Smears from 150 patients showed that 141 patients were infected by *L. tropica* and 9 by *L. major*. In total, 141 patients with *L. tropica* infection completed Glucantime® treatment and follow-up; 63.8% were treated intralesionally and 36.2% by intramuscular administration. The overall success rate after one course of therapy with Glucantime® was 96.5% (136/141), and all the failures (5/141) occurred with intramuscular injections. Statistical analysis showed a significant difference between the failure rates of intramuscular and intralesional injections. Children < 10 years old had a significantly higher failure rate than adults.

Efficacité de l'antimoniate de méglumine contre *Leishmania tropica* dans un nouveau foyer émergent de leishmaniose cutanée à Birjand, dans l'est de la République islamique d'Iran

RÉSUMÉ Les options thérapeutiques pour la leishmaniose cutanée étant limitées, une surveillance constante du taux de résistance aux médicaments à base d'antimoine pentavalent est nécessaire. La présente étude a identifié les espèces infectantes de *Leishmania* et a évalué les résultats d'un traitement par antimoniate de méglumine (Glucantime®) dans un nouveau foyer de leishmaniose cutanée à Birjand, dans l'est de la République islamique d'Iran. Les frottis de 150 patients ont révélé que 141 patients étaient infectés par *L. tropica* et 9 patients par *L. major*. Au total, 141 patients infectés par *L. tropica* ont achevé le traitement par Glucantime® et sont allés jusqu'au bout du suivi ; 63,8 % ont reçu un traitement intralésionnel et 36,2 % une injection intramusculaire. Le taux de succès global après un traitement par Glucantime® était de 96,5 % (136/141), et tous les échecs (5/141) ont été observés chez les patients ayant reçu des injections intramusculaires. L'analyse statistique a mis en évidence une différence significative des taux d'échec entre les injections intramusculaires et les injections intralésionnelles. Le taux d'échec chez les enfants de moins de dix ans était supérieur à celui observé chez les adultes.

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Introduction

Cutaneous leishmaniasis is a public health concern in more than 70 countries across the world. It can be caused by several *Leishmania* spp. and is transmitted to human beings and animals via sandflies (*1*). More than 90% of the world's cases of cutaneous leishmaniasis occur in only a few countries: Afghanistan, Algeria, Islamic Republic of Iran, Iraq, Saudi Arabia and Syrian Arab Republic in the Old World; and Bolivia, Brazil, Colombia, Nicaragua and Peru in the New World (*2*).

In the Islamic Republic of Iran the disease is endemic to over 50% of provinces (*3*), with *Leishmania major* and *L. tropica* being the primary agents of zoonotic cutaneous leishmaniasis and anthroponotic cutaneous leishmaniasis respectively (*4*). Anthroponotic cutaneous leishmaniasis caused by *L. tropica,* which tends to be more problematic for both diagnosis and treatment and lasts longer than infections caused by *L. major* (*5*), is mainly reported in urban areas of central, north east and south-east of the Islamic Republic of Iran (*6*). The main reservoir host of *L. tropica* is humans, and *Phlebotomus sergenti* is considered as main vector of anthroponotic cutaneous leishmaniasis in the country (*7*).

Birjand, the centre of South Khorasan province, is located in the eastern part of the country. In past years sporadic cases of cutaneous leishmaniasis have been diagnosed in Birjand county, but it was thought that they were imported cases from neighbouring endemic areas. Studies of increased number of cases, however, have revealed that an endemic focus of cutaneous leishmaniasis formed around 2008 and since then an annual average of 50 cases have been reported in the region. The region has a population of about 200 000 people.

The pentavalent antimony-based drugs meglumine antimoniate (Glucantime®) and sodium stibogluconate (Pentostam®, GlaxoWellcome) or generic sodium stibogluconate (Albert David Ltd, India) are the first line of treatment against both New World and Old World types of cutaneous leishmaniasis (*8–10*). However, increasing resistance of *Leishmania* spp. to these compounds has limited their usefulness in this context (*11*). Glucantime® is a commonly used pentavalent antimony-based drug for the treatment of visceral and cutaneous leishmaniasis in the Islamic Republic of Iran. However, in recent years, cases of glucantime-resistant *L. tropica* have been reported in unresponsive cutaneous leishmaniasis patients (*12*).

Because of the limited options for alternatives to treat cutaneous leishmaniasis and given that this is an endemic disease in different locations throughout the Islamic Republic of Iran, constant monitoring of the incidence of resistance to these compounds is necessary (*13*). The objective of this study was to assess the effectiveness of meglumine antimoniate on patients infected by *L. tropica* in this new focus of cutaneous leishmaniasis.

Methods

Study area and population

The study was conducted from April 2008 to March 2012 in Bijand county of Southern Khorasan province in the eastern part of the Islamic Republic of Iran. All patients selected for the study were living in Birjand and its subsidiary villages, a region of approximately 6700 km^2 (Figure 1). This region has a cold desert climate with hot summers and cool winters. This area altitude ranges between 1250 and 2050 m above sea level. The city has a dry climate with a significant difference between day and night temperatures. The average annual high and low temperatures are 25 °C and 8.5 °C respectively. The average annual rainfall is 170 mm. This region is the largest producer of saffron and barberries in the country.

A total of 188 parasitologically new confirmed cases of cutaneous leishmaniasis (i.e. Giemsa-stained smear-positive cases) who were referred to the city health centre of Birjand were recruited for this study. Of these, 154 completed the antimonial treatment course and follow-up. Out of these patients, 4 with previous treatment of cutaneous leishmaniasis were excluded from the study.

The study was approved by the ethics review committee of Birjand University of Medical Sciences.

Data collection

Collection of samples

Microscopic examination of Giemsa-stained scrapings taken from the margins of skin lesions of patients was used for diagnosis of cutaneous leishmaniasis. A questionnaire was completed for each case to record information about name, age, sex, number of lesions, patient's address, date and place of acquiring the disease, lesion sites and duration, work place and travel history.

PCR–RFLP

The dermal scrapings of the patients were used to identify species of causative agents by polymerase chain reaction (PCR) assay. DNA was purified for PCR using an AccuPrep® genomic DNA extraction kit (Bioneer) according to the manufacturer's instruction. Species-specific primers, LITSR (forward, 5′-CTG GAT CAT TTT CCG ATG-3′) and L5.8S (reverse, 5′-TGA TAC CAC TTA TCG CAC TT-3′) were carried out as described by Schonian et al. to amplify the ITS1 region of the *Leishmania* ribosomal DNA (*14*). The PCR product of ITS1 was subjected to restriction fragment length polymorphism (RFLP) analysis by digesting the PCR amplified product with BsuRI (Fermentas), a HaeIII prototype, according to the manufacturer's

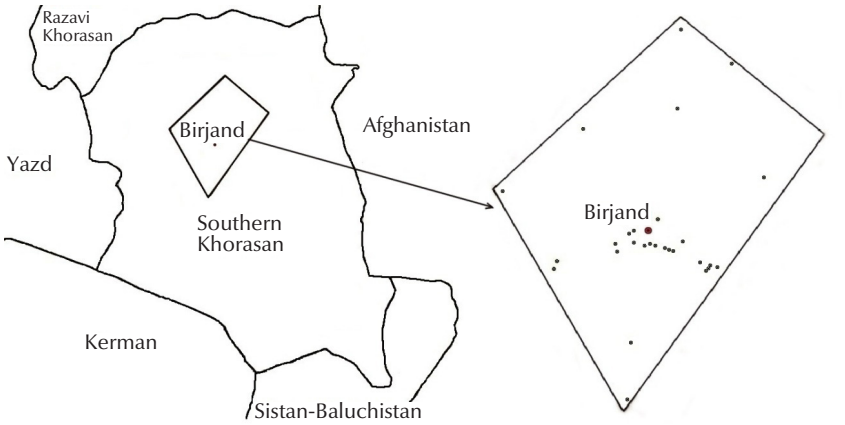

Figure 1 Geographical distribution of patients with cutaneous leishmaniasis in Birjand and its villages, southern Khorasan, Islamic Republic of Iran, 2008–2012

instructions (*15*). The restriction fragments were analysed on 2% agarose gel by electrophoresis and visualized under ultraviolet light after being stained with ethidium bromide.

Treatment

Patients were divided into 2 treatment groups: intramuscular versus intralesional administration of Glucantime®. Patients with ≤ 3 lesions and/or lesions < 3 cm in diameter were treated with Glucantime® intralesionally if the lesions were not: located on the face or neck or over the joints, sporotrichoid or superinfected with bacteria (*13*). Among 141 patients with *L. tropica*, 51 were injected intramuscular with Glucantime®, while 90 patients were treated intralesionally. Intralesional Glucantime® (Aventis; containing 81 mg antimony/mL) was injected intradermally (0.5–1 mL per lesion per week, depending on the size) in each lesion from all directions until the lesion was completely blanched (*16*). This treatment was carried out once per week until there was complete healing of the ulcer or for a maximum of 12 weeks.

All other patients were prescribed intramuscular Glucantime® at 20 mg/kg/day for 20 days according to the national guidelines distributed by the Iranian Centre for Disease Control. However, after the 10th day of intramuscular therapy, treatment was discontinued if there were increases in liver enzymes, blood urea nitrogen, creatinine or skin reactions at the injection site.

Patients who had no indications for therapy, pregnant and lactating women and those with underlying conditions (cardiac and renal diseases, etc.) were excluded from Glucantime® therapy. Healing of the cutaneous lesions was evaluated clinically and confirmed by preparation of direct smears. Successful treatment was defined as complete re-epithelialization of all lesions with no recurrence within 6 months of follow-up.

Statistical analysis

The data were analysed using Fisher exact test using *SPSS*, version 16 software. A *P*-value of < 0.05 was considered statistically significant.

Results

A total of 150 patients with cutaneous leishmaniasis entered the study. A review of the medical records of the patients showed that most of them were infected in or near their residence in Birjand county and did not stay in an endemic region of cutaneous leishmaniasis during the infection period. The majority of patients were referred to the city health centre in the autumn and winter. The lesions had been present for an average of 108 days and the mean number of lesions was 1.75.

Species identification of *Leishmania* spp. in the patients' smears using PCR-RFLP of the ITS1 rDNA showed that 141 patients had *L. tropica* and 9 others were infected by *L. major*. There was no statistically significant relationship between the clinical features of the cases and the infecting *Leishmania* spp. (Table 1). The overall success rate after one course of therapy with Glucantime® was 96.5% (136/141) in *L. tropica* cases and 100% in patients infected by *L. major* (Table 1).

Because of the low number of patients with *L. major* infection, and given the healing process of *L. major* lesions may be shorter than the 6 months follow-up period, only *L. tropica*-infected patients were included in the follow-up and analysis of factors associated with cure or failure.

Factors associated with cure in cases with *L. tropica*

A total of 90 *L. tropica* cases (63.8%) were treated intralesionally and 51 patients (36.2%) were treated intramuscularly (Table 2). During the treatment follow-up period, 136 patients showed a positive response to treatment, so the overall success rate of *L. tropica*-infected patients who received one course of Glucantime® was 96.5%. On the other hand, cutaneous lesions did not heal in 5 others until the end of the follow-up period.

All the 5 treatment failures occurred in the cases of intramuscular injection of Glucantime® and thus the failure rate among patients having intramuscular injections was 9.8% (5/51) versus none of the intralesionally treated cases. Statistical analysis showed a significant difference between the failure rates of intralesional and intramuscular injections ($P = 0.005$).

Table 1 Comparison of the clinical features of cases of cutaneous leishmaniasis caused by *Leishmania major* and *L. tropica* in Birjand, eastern Islamic Republic of Iran

Variable	*L. tropica* (*n* = 141)		*L. major* (*n* = 9)		*P*-value[a]
	No.	%	No.	%	
Sex					
Male	76	53.9	4	44.4	0.734
Female	65	46.1	5	55.6	
Age group (years)					
< 10	32	22.7	1	11.1	0.684
≥ 10	109	77.3	8	88.9	
Residency					
Urban	93	66.0	6	66.7	1.0
Rural	48	34.0	3	33.3	
No. of lesions					
≤ 3	130	92.2	7	77.8	0.176
> 3	11	7.8	2	22.2	
Location of lesions					
Face and neck	45	31.9	2	22.2	0.807
Extremities	90	63.8	7	77.8	
Both	6	4.3	0	0.0	
Response to Glucantime®					
Cure	136	96.5	9	100.0	1.0
Failure	5	3.5	0	0.0	

[a]*Fisher exact test.*

There was also a statistically significant difference in the cure rate by intramuscular administration of Glucantime® between the 2 patient age groups ($P < 0.05$); patients < 10 years old had a lower cure rate (77.8%) than older patients (97.0%). The overall cure rate of Glucantime® therapy was significantly lower in patients < 10 years old ($P < 0.01$) (Table 2).

In addition, the results showed that the number of lesions per patient was associated with response to treatment. In patients with > 3 lesions, the cure rate was significantly lower than those with fewer lesions (81.8% versus 97.7%) ($P < 0.05$) (Table 2). But there was no significant correlation between the improvement rate and the sex of the patients, location of the lesions, duration of therapy and patients' residency.

The maximum number of full re-epithelializations of lesions was seen within 3 months after the start of treatment.

Discussion

Monitoring resistance to pentavalent antimonials, which are the first-line treatment of cutaneous leishmaniasis, is necessary (*17*). This has become more important in the new endemic foci of cutaneous leishmaniasis such as Birjand county. In the present study, the overall success rate after one course of therapy with Glucantime® administered either intralesionally or intramuscularly was 96.5% (136/141). While the success rate of intralesional injection of the drug (maximum 12 weeks) was 100%, the intramuscular treatment of cutaneous leishmaniasis had a lower success rate of 90.2% (46/51). A wide range of success has been reported for intralesional injection of Glucantime® in other investigations conducted in the Islamic Republic of Iran (*13,18,19*). Unfortunately, in most of those studies the species of *Leishmania* was not identified, and there were variations in treatment courses.

Different values have been reported as success rates for one course of standard intramuscular Glucantime® in patients treated with 20 mg/kg/day in endemic areas of cutaneous leishmaniasis in the Islamic Republic of Iran. In studies conducted in the southern and northern parts of the country on patients infected by *L. major*, the rate of treatment success was 65.1% and 83.3% respectively (*9,20*). In 2 other investigations which were done in the central provinces of the country, intramuscular treatment by Glucantime® had success rates of 75.8% (*13*) and 93.0% respectively (*21*), although the causative agents of the disease were not identified. In another study in the eastern area, which included cutaneous leishmaniasis patients infected by *L. tropica*, intramuscular injection of Glucantime® had a success rate at 95.3%

Table 2 Demographic and clinical characteristics of cutaneous leishmaniasis patients with *Leishmania tropica* and their responses to Glucantime®

Variable	Cure		Failure		*P*-value[a]
	No.	%	No.	%	
Sex					
Male	74	97.4	2	2.6	0.662
Female	62	95.4	3	4.6	
Age group (years)					
< 10	28	87.5	4	12.5	0.01
≥ 10	108	99.1	1	0.9	
Type of injection					
Intramuscular	46	90.2	5	9.8	0.005
Intralesional	90	100.0	0	0.0	
Intramuscular injection by age group (years)					
< 10	13	77.8	4	22.2	0.037
≥ 10	33	97.0	1	3.0	
Duration of intramuscular- therapy (days)					
< 10	1	100.0	0	0.0	0.416
10–14	3	75.0	1	25.0	
≥ 15	42	91.3	4	8.7	
No. of intralesional injections					
1–4	5	100.0	0	0.0	1.0
5–8	18	100.0	0	0.0	
9–12	118	100.0	0	0.0	
No. of lesions					
≤ 3	127	97.7	3	2.3	0.049
> 3	9	81.8	2	18.2	
Location of lesions					
Face and neck	42	93.3	3	6.7	0.465
Extremities	88	97.8	2	2.2	
Both	6	100.0	0	0.0	
Residency					
Urban	89	95.7	4	4.3	0.661
Rural	47	97.9	1	2.1	

[a]*Fisher exact test.*

(*12*). So the efficacy of treatment with intramuscular injection of Glucantime® in the present study is consistent with the survey conducted in eastern Islamic Republic of Iran.

Comparison of response rates between the 2 age groups of the patients (< and ≥ 10 years of age) revealed that the cure rate of intramuscular Glucantime® was significantly lower in children < 10 years of age ($P < 0.05$). A number of other studies have yielded similar results. Layegh et al. showed that systemic Glucantime® has a significantly lower efficacy in treating acute cutaneous leishmaniasis in children than in adults (*22*). In another study performed on *L. viannia* species, cutaneous treatment by systemic Glucantime® also had a clinically significant lower response in children when compared with the same regimen dosage and duration in adults (*23*). Several reasons for this have been proposed: a weaker immune response in children, differences in the pharmacokinetics of the drug in different age groups and differences in exposure to parasite antigens and sandfly saliva (*24*).

The cure rate of intralesional therapy in our study was significantly higher than intramuscular therapy. In the study by Alkhawajah and Larbi intralesional treatment method also has better results compared with intramuscular Glucantime®, although there was no statistically significant difference between the 2 routes of administration (*25*). Uzun et al. obtained a high cure rate (97.2%) of cutaneous leishmaniasis by intralesional

injection of Pentostam®, another pentavalent antimonial agent (*26*).

Patients with > 3 lesions had significantly higher failure rate than the patients with fewer lesions ($P < 0.05$). This may have resulted from the significantly higher percentage of intramuscular versus intralesional Glucantime® in patients with > 3 lesions ($P < 0.05$). Sex, location of lesions, self-reported previous treatment with Glucantime® and patients' residency (urban/rural) had no effect on the response rate to the treatment.

Identification of causative agents of cutaneous leishmaniasis using an ITS1 PCR–RFLP assay showed that all the patients with no response to treatment in this study were infected by *L. tropica*. In contrast, no treatment failures were observed in the patients who identified as being infected by *L. major*.

Conclusion

In conclusion, we found a higher rate of success with standard Glucantime® therapy than other studies conducted in the Islamic Republic of Iran. Furthermore, the study results indicated that systemic treatment with meglumine antimoniate was less successful in children compared with adults. We recommend further research to evaluate the efficacy of cutaneous leishmaniasis drugs due to the differences in pathogenesis and treatment processes between these agents.

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