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Therapeutic and Adverse Effects of Glucantime Used for Treatment of Cutaneous Leishmaniasis.

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Abstract:

Introduction: Cutaneous leishmaniasis is endemic in Iran. Fasa region (Southern west of Iran) is one of the hot spots. The most popular drug for treatment of cutaneous leishmaniasis is glucantime.
Aims: To study the therapeutic and adverse effects of Glucantime in cutaneous leishmaniasis patients and also comparing the intramuscular and intralesional administration routes.
Methods and Material: All new cutaneous leishmaniasis cases (880) that were diagnosed within two years of study were ruled in. Intralesional injection was used for solitary non-facial wounds, for maximum of 10 doses, injected every other day. For multiple lesions or facial lesions, intramuscular injection was performed, in daily manner for maximum of three 10 day periods, apart by 10 days of drug free intervals. Injections were done according to WHO guidelines.
Results: The recovery rate was 84.03 % and 75.98% in intramuscular and intralesional injection groups, respectively. The most common side effect was skin hypersensitivity and urticaria, which was more seen in those with intralesional injection (10.92% in comparison with 2.59% in IM group). No cardiac or renal complication was observed.
Conclusions: Complete recovery is higher in intramuscular injection compared to intralesional injection of Glucantime for cutaneous leishmaniasis. Side effects are also less seen in the intramuscular injection.

Key Words: Cutaneous leishmaniasis, Glucantime.

Introduction:

Cutaneous leishmaniasis is endemic in Iran [1], however, it is hyperendemic in Fasa, South Iran. Fasa region has a population of about 300'000. Most people especially those living in villages (more than 60 villages and also many nomad inhabitants) do farming or animal husbandry. Annually, more than 400 new cases are diagnosed and most of them, receive glucantime for treatment. The scar of the disease leads to cosmetic and psychologic problems in many patients (Figures 1, 2, 3 and 4). Therefore, treatment the lesions, especially those located in the face is important but unfortunately, it is still a major health concern. Some available therapeutic modalities available include cryotherapy [2], thermotherapy [3], and chemotherapic agents such as Dapsone [4], Levamizole [5], Rifampin [6], Ketoconazole [7], local Paramomycin [8], Itraconazole [9], Emetin [10], Mepacrin [11], Amphotericin [12] and Allopurinol [13], however it seems that pentavalent antimony (e.g., glucantime), although not completely effective, is the drug of choice. There are a few reports regarding the side effects of glucantime [14, 21, 22], but it is considered generally a safe medication. This study is designed to assess the therapeutic and adverse effects of Glucantime in cutaneous leishmaniasis patients and also comparing the intramuscular and intralesional administration routes.

Figure 1.

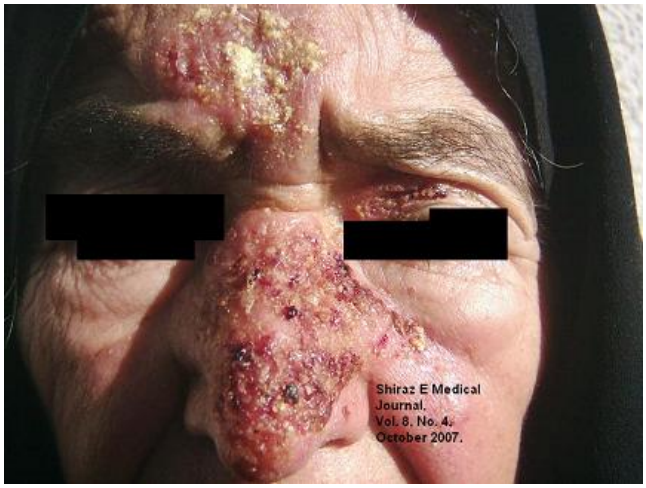


Figure 2.

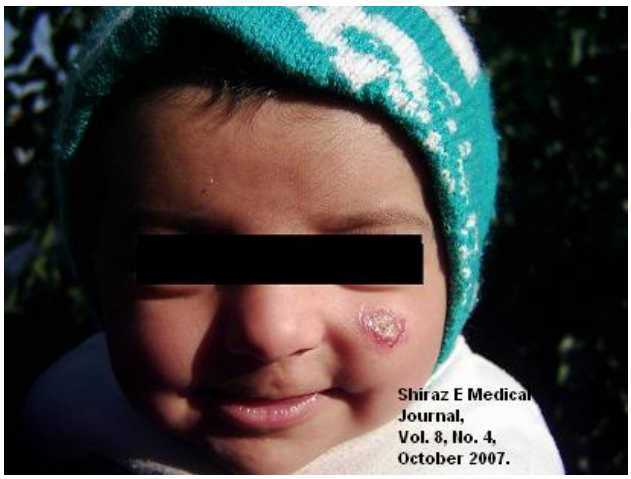


Figure 3.

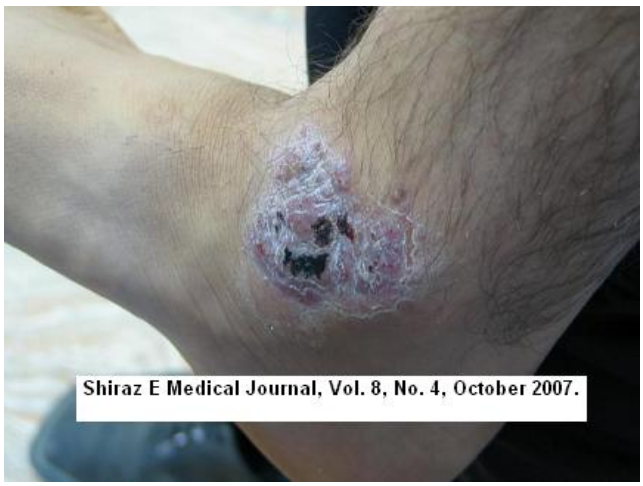
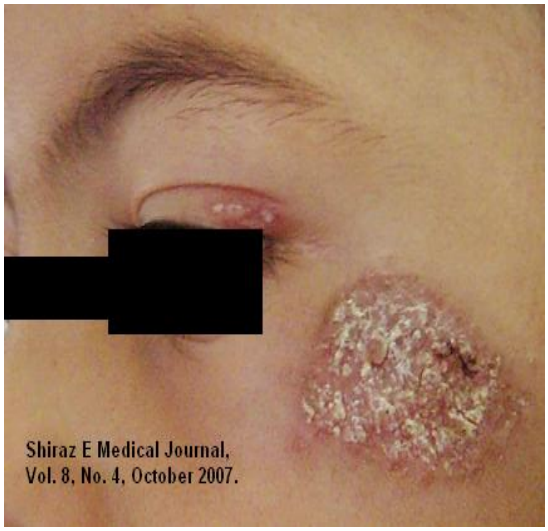


Figure 4.



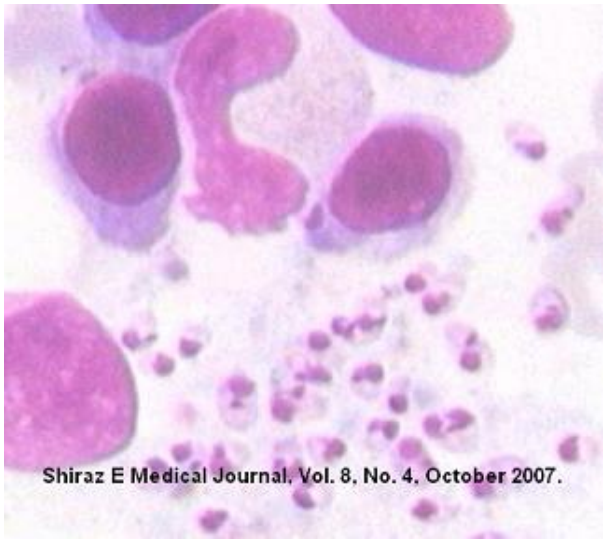
Materials and Methods:

This is a prospective study. All patients referred to Clinic number 1 of Fasa Medical School (the referral clinic of cutaneous leishmaniasis in Fasa Medical School which all medical services presented to these patients (including medication) are free.) for cutaneous leishmaniasis between December 2004 and November 2006 are included.

The diagnosis is made by direct smear for leishman (Donovan) body (Figure 5). Before starting treatment, all patients had complete history and physical examination. A questionnaire was filled in, containing detailed questions regarding age, sex, occupation, residence (home and environment), number and morphology of the lesions, duration of disease, history of previous treatments for the lesions, history of drug hypersensitivity, and history of any medical disease.

All of the patients, received glucantime 60 mg/kg (intralesional for solitary wounds, not in the face and intramuscular for multiple or facial lesions). Intramuscular injection was done in 10 day periods (everyday), apart by 10 days of no medication interval and continued until recovery or three injection courses. For intralesional injection Insulin syringe was used for subcutaneous injection. According to WHO (15, 21), the injections were done to whiten the lesion. For large lesions, injection was done in all surrounding parts to cover the wound surface completely. The injection was done every other day until the recovery of the lesion or 10 doses without recovery. Each week, patients were asked about any side effect of the medication and ECG, Cardiac enzymes and renal function tests were requested in case of any cardiac or renal problems.

Figure 5. Donovan Bodies.



Results:

During 24 months of the study, 880 new cases of cutaneous leishmaniasis were referred to the clinic. All of them received glucantime (357 intralesional and 523 intramuscular). Patients were classified

into three groups according to the response to the medication:

1- Complete clinical and laboratory recovery. (complete recovery "CR" group)

2- Relative Recovery ("RR" Group). In this group, either clinical recovery was achieved despite of positive laboratory findings, or laboratory recovery was associated with non-responding lesion.

3- No clinical or laboratory recovery "NR".

271 out of 357 patients who received intralesional medication had complete recovery (75.98%), 34 had relative recovery (9.6%) and 13 had no recovery (3.5%). In 39 patients (10.93%) the medication was discontinued due to side effects.

The average number of injection in the intralesional group was 8. If no recovery was achieved after 10 injections, no further intralesional medication was administrated and treatment was switched to another category (usually Rifampin or Ketoconazole). Unfortunately, due to some reasons especially seasonal migration of the nomad patients, it was impossible to determine the drug sensitivity pattern in Glucantime resistant group.

In intramuscular injection group, there were 523 patients, which 22 where omitted from the study because they did not want to continue with the protocol, 421 (84.03%) had complete recovery, 40 (7.98%) had relative recovery and 27 (5.38%) had no recovery. Medication of 13 patients (2.59%) was discontinued due to side effects.

The treatment in the IM injection group was administrated in three 10 day periods, separated with 10 days of drug free intervals. Table 1 summarizes the results of therapy in the two groups.

Side Effects:

In intralesional group these effects include redness, edema, local pruritus (dose dependant) and urticaria. Other rare untoward effects were local swelling, nausea and vomiting, diffuse erythema and shock. (Table 2)

In the intramuscular group, the side effects were less in comparison to the intralesional group and they were urticaria, muscle pain, diffuse erythema, headache, edema or wound in the injection site, chills and fever (in one patient, she developed chills and fever after each injection, which finally her medication was discontinued and was switched to another group of drugs.), unilateral transient hemiparesis (Table 2).

In neither groups, no cardiac or renal complication was seen.

Discussion:

Pentavalent antimony, including Sodium Stibogluconate and Meglumine antimoniate (glucantime) is used for treatment of leishmaniasis for the past 80 years. The mechanism of action of these agents is suppression of the phosphofructokinase (PFK) activity, resulting in blocked ATP production [(14)]. Trivalent antimony components were used to be prescribed but they were replaced with pentavalent antimony in 1920's because of severe renal and cardiac side effects. Additionally, the pentavalent agents reach the therapeutic serum level much earlier and is excreted in the urine (95 % as pentavalent

Table 1: Therapeutic effects of the Glucantime.

Group	Number	CR: N(%)	RR: N(%)	NR: N(%)	Complications: N(%)
IL	357	271 (75.98)	34 (9.6)	13 (3.5)	39 (10.93)
IM	501	421 (84.03)	40 (7.98)	27 (5.38)	13 (2.59)

IL: Intralesional, IM: Intramuscular, CR: Complete Recovery, RR: Relative Recovery, NR: No Recovery, N: Number, %: Percent.

Table 2: Side effects of the Glucantime

Group	Number	Complicated cases: N(%)	Nausea	Local Reaction	Urticaria	Diffuse Erythema	Muscle Pain	Headache	Others
IL	357	39 (10.29)	1	21	10	1	0	2	7
IM	501	13 (2.59)	1	2	5	2	3	2	3

IL: Intralesional, IM: Intramuscular, N: Number, %: Percent.

components and 5% as trivalent antimony). These agents were first introduced to treat schistosomiasis but today, they are drugs of choice for treatment of leishmaniasis, used as intralesional or intramuscular injections [14, 15, 20, 21, 22, 23, 24, 25, 26].

The intralesional injection was first experienced in Algeria and was reported to be effective and approved by the world health organization [15, 21]. The WHO also recommended the daily or every other day injection [15, 21]. This route is used in treatment of lesions with severe inflammation. For large lesions, the injection should be performed in several directions to cover the surface of the wound completely. In two studies, performed in Syria (1979) and Costa Rica (1984), the recovery rate was reported to be 75% and 65% respectively using intralesional injection. In our study, the recovery rate is 75.98%. The WHO recommended dosage is 75 mg/kg/day of Glucantime. It is also recommended to inject the drug in a q12h manner (divided dose). The drug is recommended to be used in 10 to 15 day periods apart from each other by 10 to 15 days. For non-responding or recurring lesions, dose and length of treatment may be increased (up to 35 days).

The recovery rate with intramuscular injection is reported to be 70% to 85% in different studies [16 - 26]. Our recovery rate in IM injection group is similar to WHO report and is 84.03%.

Side effects: It is estimated that more than 200'000 patients are treated with pentavalent antimony in the past 80 years [22], however, there are just two reports of death following drug administration which is not clear whether it is because of the drug side effects or the process of the disease [17]. It means that these components are relatively safe agents. The most frequently seen adverse effects include nausea, vomiting, abdominal pain, diarrhea, cough, pneumonia, bleeding tendency, skin reactions (e.g., erythema and urticaria), albuminurea, convulsion, bradycardia, ECG changes such as prolonged QT interval and flat T wave, myositis and muscle pain [15, 22]. It should be noted that most

side effects are reported in patients treated with high doses of glucantime for visceral leishmaniasis (Kala Azar). It is also suggested that many of these effects is a sequel of the disease and not an untoward effect of the medication. There is no report of complications such as cough, pneumonia, bleeding tendency, diarrhea, albuminurea and convulsion in treating cutaneous leishmaniasis. In a study in Nairobi (1983), Glucantime was used as 70 mg/kg for 20 days and no hematologic or cardiac side effects were seen, however, some slight and reversible changes in liver enzyme were observed [(18)].

The probable adverse effects of glucantime on the fetus is still unknown and since there is no report of untoward effects in experimental animal studies, it seems to be safe for use in pregnant women, however, it should not be considered as a completely safe drug and clinical benefits should be weighted against the possible complications.
The dosage of the drug should be reduced in patients with cardiac and renal disease [(22)].

In our study, no case of renal or cardiac complication was observed; however, the high rate of skin reactions which is not so common in the earlier studies was seen. 10.92% of intralesional injection group patients had local swelling and pruritus which got worse with repeated administration of the drug. In intramuscular injection group, generalized urticaria was a major concern (Table 2). It is not clear why these complications are seen more in our population. It is postulated that the preparations used in our setting may contain some allergens. It would be our next study to compare two different preparations in order to assess the possibility of presence of allergens.

Conclusion:

Although many drugs are used in treatment of cutaneous leishmaniasis, there is no completely effective medication available, however, Glucantime is the best available agent, which if used with recommended dosage protocol, complete recovery would be achieved in many cases. The most important side effect of the drug in our study is skin reactions, which is dose dependant and the cause is unclear. It is also concluded that complete recovery is seen more frequently in intramuscular drug administration compared to the intralesional injection.

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