A THIRTY DAY COURSE OF SODIUM STIBOGLUCONATE FOR TREATMENT OF KALA-AZAR IN NEPAL

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Abstract. Twenty-seven cases of Kala-azar were treated with sodium stibogluconate at a dose of 20 mg/kg/day for 20 days (group A) and an equal number of cases were treated with the same dose but for a longer duration of 30 days (group B). Clinical and laboratory evaluation of these cases were carried out before and after therapy, during a follow up of cases every month, upto 6 months. Renal and liver function tests and electrocardiography were carried out of monitor any toxic effect of the drug during therapy. The cure rates of patients were 77.78% and 92.59% in group A and B cases respectively. Six and two patients in group A and B respectively were unresponsive to the treatment and showed relapse. Results of the study show that treatment of cases of Kala-azar with sodium stibogluconate in a dosage of 20 mg/kg/day for a longer period of 30 days is effective with a higher cure rate and minimum side effects, for treatment of cases of Kala-azar in this eastern part of Nepal, endemic for the disease.

INTRODUCTION

Kala-azar caused by *Leishmania donovani* is a major public health problem in Nepal. The condition affects mostly the rural population living in Southern terai (plain areas) of 11 districts which border Kala-azar endemic areas of Bihar state of India. Approximately, 5.5 million people are estimatd to be at risk to suffer from the disease in Nepal (WHO, 1984; HMGN, Nepal, 1995).

Sodium stibogluconate, the classical antimonial compound, is widely used for treatment of the condition in Nepal. The protocol recommended initially by the World Health Organization (WHO) was 20 mg/kg/day (maximum 850 mg/day) intramuscularly (IM) every day for a minimum period of 20 days or two weeks after the anticipated parasitological cure. Since this regimen often was associated with the cases of unresponsiveness to the therapy and relapse, it was suggested that a 40 days regimen would be more effective than a 20 or 30 days regimens (WHO, 1982). However, the major disadvantage of a 40 days regimen, when the treatment was extended beyond 3 days was the occurrence of cardiac toxicity due to cumulative effect of the drug (Thakur, 1986).

The main objective of the study was to determine the optimum duration of sodium antimony gluconate therapy that would achieve a high rate of cure, and reduce the rate of relapse/unresponsiveness. In this study we evaluated two different regimens of sodium stibogluconate; one regimen given in a dosage of 20 mg/kg/day for twenty days and another in the same dosage but for thirty days.

MATERIALS AND METHODS

This study was an randomized and open label clinical trial, carried out in BP Koirala Institute of Health Sciences, Dharan, situated in the Eastern part of Nepal (the endemic zone for kala-azar), over a period of 3 years from March 1994 to March 1997. All patients with typical signs and symptoms of Kala-azar (fever, hepatosplenomegaly, weight loss, etc) confirmed by the presence of amastigotes of *Leishmania donovani* (LD bodies) in the stained bone marrow smears were included in the study. Informed consent was obtained from each patient. Patients who had received treatment earlier with sodium antimony gluconate, pentamidine or amphotericin B were excluded from the study. Patients with severe complications like renal failure, cardiac or liver diseases and pregnant women were also excluded from the study.

These patients were randomly allocated into two groups of 27 patients, each receiving sodium stibogluconate at 20 mg/kg/day for 20 days (Group A) and 20 mg/kg/day for 30 days (Group B). These drugs were administered intramuscularly.

Before starting therapy, clinical and laboratory

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evaluation of each case was carried out. The clinical details were recorded on a proforma for every patient. Laboratory tests included total differential white blood cell (WBC) count, hemoglobin estimation, total erythrocyte count, and estimation of liver and renal function tests. Electrocardiography was also carried out before treatment and during follow up of cases after treatment. Bone marrow smears were aspirated and stained by Giemsa for the LD bodies. Sodium stibogluconate (Albert David Limited, Calcutta, India, 100 mg antimony pentavalent per ml) was given by intramuscular route into the buttock for 20 (Group A) and 30 (Group B) days. The study was approved by ethical committee of BP Koirala Institute of Health Sciences, Dharan.

Patients included in the study were admitted in the hospital for a minimum period of 10 days or more if needed. They were evaluated with special attention to : a) spleen and liver size, b) fever, c) disappearance of clinical symptoms, d) improvement of laboratory parameters, e) parasitological cure and f) adverse reactions. To detect the latter, special attention was given to liver and renal functions, ECG changes and occurance of any other toxic manifestations.

After discharge from the hospital, the patients were advised to attend monthly follow up examinations for 6 consecutive months. They were considered to be clinically cured if temperature returned to normal, spleen and liver decreased in size, and general condition and hematological parameters improved. They were considered to be parasitologically cured when their bone marrow smears were negative for LD bodies. The data were statistically analysed by Student's *t*-test.

RESULTS

The important clinical features at the time of admission were intermittent fever with chills and rigors, loss of weight, dark coloration of skin, leucopenia, anemia and hepatosplenomegaly. None of the patients had lymphadenopathy. Two groups (Group A and B) did not differ with respect their clinical and laboratory findings at the time of admission before starting therapy (Table 1).

The over all cure rate at end of therapy was 21/27 patients (Group A) treated with sodium stibogluconate at 20 mg/kg/day for 20 days while it was 25/27 with the same dosage for 30 days. The response to treatment varied. Four patients became afebrile just after three injections of the drug and sixteen during the first week of treatment, they were the fast responders. Slow responders took as long as four or five weeks to respond. The mean fever clearance time being 10.74 days (SD± 8.93). At the time of admission, 27 patients in group A and 23 in group B had a palpable spleen. By the end of the treatment, the spleen was no longer palpable in 21 and 23 cases in group A and group B respectively. Similarly, 17 and 16 had palpable liver. However, at the end of 6 months 13 in group A and 16 patients in group B had non-palpable livers. All the patients who were slow reponders had their illness for a long time and their spleens were more than 8 cm beyond the costal margin. In fast responders, the spleen size regressed quickly and became impalpable by the 20th to 30th day. In slow responders, the spleen size regressed slowly. Pentamidine was effective in the treatment of unresponsive patients in our study.

WBC count and other hematological parameters improved in most of the patients in both the groups (Table 2). Renal function tests remained normal in all the patients during treatment and follow up period. The pre and post therapy ECG was normal. There were no cardiovascular, respiratory or any other side effects reported during the trial.

Few patients had side effects such as arthralgia in five patients, and cellulitis and abscess only in 2 patients. The major complain was pain at the site of injections in 16 patients in group A and in 15 patients in group B. All the patients tolerated longer duration and higher dosage of drug without any major side effects. Table 3 shows the outcome of patients who were not cured at six months after they had been treated with extended regimens of sodium stibogluconate or pentamidine.

Twenty-one patients in group A were cured at six months. Three patients in group A were cured with an extended ten days and one patient with 15 days of treatment. Two patients at the follow up of examination had their spleens enlarged. The aspirate from bone marrow of these cases was found to be positive for LD bodies. They were subsequently treated with pentamidine and were eventually cured.

Twenty-five patients in group B were cured. One patient in group B was cured with an extended

Table 1

Admission clinical and laboratory data of Kala-azar patients to treatment with sodium stibogluconate in two different regiments.

	Group A sodium stibogluconate 20mg/kg/day × 20 days	Group B sodium stibogluconate 20mg/kg/day × 30 days
Total no. of patients	27	27
no. of men	19	16
no. of women	8	11
Mean age (Years)	25.78 (12.05)[a]	27.04 (15.03)[a]
Age range (Years)	9-62	6-61
No. of patients with fever	27	26
Duration of fever (months)	2.78 (1.30)[a]	2.83 (2.82)[a]
No. of patients with splenomegaly	27	23
Mean splenic size (cm)	8.02 (2.73)[a]	8.61 (3.41)[a]
Splenic size range (cm)	2-12	3-15
No. of patients with hepatomegaly	17	16
Mean liver size (cm)	2.76 (1.61)[a]	2.58 (1.30)[a]
No. of patients with hepato-splenomegaly	14	16
No. of patients with pigmentation of skin	9	8
Mean hemoglobin (g/dl)	7.86 (1.81)[a]	8.16 (1.82)[a]
Mean WBC/mm^3	4,792 (2,432.61)[a]	4,100 (1,029.94)[a]
Mean platelet counts	130,000 (70,326.16)[a]	106,865 (45,427)[a]

[a] = No. in parenthesis indicates standard deviation

Table 2

Therapeutic response of patients with Kala-azar.

	Group A sodium stibogluconate 20mg/kg/day × 20 days	Group B sodium stibogluconate 20mg/kg/day × 30 days
Total no. of patients	27	27
no. of men	19	16
no. of women	8	11
Mean age (Years)	25.78 (12.05)[a]	27.04 (15.03)[a]
Age range (Years)	9-62	6-61
Fever clearance (days)		
Mean	11.56 (9.76)[a]	10.74 (8.93)[a]
No. of patients with splenomegaly	6	0
Mean splenic size (cm)	0.52 (1.09)[a]	0
Splenic size range (cm)	1-4	0
No. of patients with hepatomegaly	4	0
Mean liver size (cm)	0.19 (0.48)[a]	0
No. of patients with hepato-splenomegaly	4	16
Mean hemoglobin (g/dl)	10.73 (0.82)[a]	10.91 (1.86)[a]
Mean WBC/Cu mm	6,038.15 (569.97)[a]	7,164.93 (775.39)[a]
Mean platelet counts	244,703.70 (68,309.71)[a]	259,148.15 (54,256.30)[a]
Cure rate at 6 months (%)	77.78	92.59

[a] = No. in parenthesis indicates standard deviation

Table 3

Patients who are not cured at six months follow up.

Group	No. of patients who were not cured	No. of patients with extended course of antimony	No. of patients cured with pentamidine
A	6	4	2
B	2	1	1

15 days of treatment. One patient in group B was unresponsive to treatment with antimony but was cured with pentamidine.

DISCUSSION

Results of the study shows that administration of sodium stibogluconate in a dosage of 20 mg/kg/day for 30 days was effective in achieving a high cure rate with minimum side effects and only few cases were unresponsive to the treatment. The higher efficacy of this regimen was demonstrated by cure of 25 patients suffering from Kala-azar. The bone marrow smear collected at 6 month follow up was negative for LD bodies. The patients also showed improvements in their clinical and laboratory parameters soon after therapy (Table 2). Results of other studies have shown that when duration of treatment of antimonials increased, the rates of relapse and unresponsiveness also declined further (Thakur *et al*, 1984). It has also been seen that by increasing the dosage and duration of treatment, the need for therapy with other drugs such as pentamidine and amphotericin B which were more toxic and had caused sudden death, could be avoided (Thakur, 1986).

In our study, some of the patients who did not respond to full course of treatment for 30 days, were cured with an extended course of treatment by sodium stibogluconate for an additional period for 10-15 days. Similar observations have also been noted in earlier studies (Anabwani *et al*, 1983; Kager *et al*, 1984; Jha and Sharma 1986). Kager *et al* (1984) demonstrated better results with an extended course of treatment with antimony in Kenya (Kager *et al*, 1984). It was also demonstrated by Awabwani *et al* (1983) that Kenyan patients who has relapses responded to a higher dose given for a longer time (Awabwani *et al*, 1983). In a similar study, Jha and Sharma (1986) reported better results with 30 days treatment in new patients, 60 days in those who relapsed and 42 days in slow responders. Our data clearly demonstrate that longer duration is important in achieving a high rate of cure. Patients in group B administered with sodium stibogluconate in a dosage of 20 mg/kg/day for 30 days had a better cure rate.

To conclude, results of the study show that the longer duration of treatment with an adequate dose of sodium stibogluconate will minimise the relapses and unresponsiveness to chemotherapy. We therefore recommend sodium stibogluconate in a dosage of 20 mg/kg/day at least for 30 days for effective treatment of patients with kala-azar in this part of Nepal.

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