COST, EFFICACY AND SAFETY OF AMINOSIDINE (PAROMOMYCIN) IN THE TREATMENT OF VISCERAL LEISHMANIASIS

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ABSTRACT

Objective: To compare Aminosidine as a single agent in the treatment of visceral leishmaniasis with antimony compounds.

Design: Open non-randomized, interventional study of three drugs used in Pakistan for visceral leishmaniasis.

Setting: Military hospitals at Muzaffarabad Azad-Kashmir and Rawalpindi (reservoir for visceral leishmaniasis in Pakistan) over a period of five years.

Patients and Methods: Children up-to 12 years of age diagnosed as visceral leishmaniasis (LD-bodies positive). Patients were divided into three groups of 30 patients each. Every patient received either sodium stibogluconate or meglumine antimonate @ 20 mg/kg/day for 28 days or the trial agent Aminosidine @15mg/kg/day for 21 days.

Results: Most patients were less than 36 months of age (82.2%) while there was male predilection (1.2:1). Fever, hepatosplenomegaly and pancytopenia were seen in 100% cases with malnutrition in 71%, cough in 51%, lymphadenopathy in 23.3% and bleeding diathesis 40% being the other common features. Three agents were found to be effective (to a different degree) as regards defervesence, reduction in size of enlarged organs, recovery of bone-marrow function manifested by improvement in hematological parameters. No major side effects were detected clinically or by laboratory studies. Cost of therapy was also remarkably lower for aminosidine as compared to the antimonials.

Conclusion: Aminosidine as a single agent is much cheaper, effective and a safe drug suitable for treatment of visceral Leishmaniasis in Pakistan.

Keywords: Visceral leishmaniasis, drug trial, Aminosidine, antimonials, Pakistan

INTRODUCTION

Visceral Leishmaniasis (VL) has long been a well-known entity to most of the health professionals in the Azad Kashmir region and Northern areas of Pakistan [1-4]. A large number of cases of VL have been diagnosed and treated in various health facilities in this region since late sixties [3]. Lack of report of these cases and a lack of a coherent national policy on this catastrophic illness has lead to the under-recognition of this medical disease in the under-privileged social set up in these areas [5]. This has lead not only to a delay in the diagnosis of this malady but also to a large number of deaths in a treatable illness so well known in these areas, with a mortality of 100% if left untreated [6].

Visceral leishmaniasis has classically been treated with Antimony compounds, Sodium-stibogluconate and Meglumine antimonate in this region [5,7] as in many other parts of the world [6-8]. Problems associated with the cost [5,6] resistance [9,10] and side effects of these therapeutic agents

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[11,12] and an unexplained sudden shortage of one or both agents in the effected regions is a well known phenomenon [4]. Alternative therapeutic options have always been eagerly sought [8,13-15] of an acceptable cheap but safe alternative [5]. An aminoglycoside Aminosidine which is structurally similar to Paromomycin [16-18], was being used in this region as an alternate agent when antimonials were either unavailable or not feasible due to their high cost [5]. Various studies recommended the drug in combination with Antimonials in the treatment of VL [19-,22]. A study from children hospital, Islamabad [5] and another from India [22,23] had recommended it as a single agent for VL in some cases also. Our study was designed to evaluate aminosidine (Paromomycin) in comparison with two antimonials being routinely used i.e.; sodium Stibogluconate and Meglumine antimonate.

AIMS AND OBJECTIVES

To compare Aminosidine as a single agent in the treatment of visceral leishmaniasis with antimony compounds Stibogluconate and Meglumine antimonate with regard to their efficacy, safety and cost. To be able to suggest it as an alternative treatment agent for visceral leishmaniasis in Pakistan and to recommend further possible avenues of research regarding visceral leishmaniasis in the light of findings of this study.

PATIENTS AND METHODS

This study was conducted between 1993 and 1997 at military hospitals Muzaffarabad (Azad Kashmir) and Rawalpindi. These hospitals drain patients from the well-known foci of disease i.e. Azad-Kashmir and Northern areas of Pakistan.

Patients less than 12 years of age were included in the study population, not suffering from any other life threatening illness or chronic infection. These patients were divided into three groups consisting of 30 patients each and treated with one of the three drugs under trial as indoor patients.

- Group-A received Pentostam (Sodium-stibogluconate) @ 20 mg / kg / day for 28 days.
- Group-B received Glucantime (Meglumine antimonate) @ 20 mg / kg / day for 28 days.
- Group-C received Gabbromicina (Aminosidine) @ 15 mg / kg / day for 21 days.

These patients were regularly monitored for therapeutic as well as side effects of three agents at the end of first week, second week, end of treatment period and ultimately evaluated at the completion of a 90-day period.

Inclusion and Exclusion Criteria:

All patients with a positive bone marrow smear for LD bodies under the age of 12 years were included in this study. Patients outside this age bracket or those who were critically ill or had a major accompanying illness like tuberculosis were excluded from the study.

Main Outcome Measures:

The main outcome measures were studied under four headings.

- To compare cost of these drugs.
- To asses efficacy defined as reduction of fever (defervesence), reduction in size of enlarged organs along with an improvement in weight.
- To collect laboratory evidence of improvement in hematological criteria i.e. hemoglobin, platelet count, Total red blood cell count and total white blood cell count were monitored.
- To study safety of drugs by estimation of urea and creatinine for renal involvement and study audiological status by clinical methods.

Ethics:

A study protocol was approved by College of Physicians and Surgeons of Pakistan. as a requirement for dissertation.

A verbal informed consent was obtained and documented. Strict randomization could

not be maintained as all three agents were not available simultaneously through most period of study. The trial had to be limited to 30 patients in each group as Aminosidine was suddenly withdrawn from the market when 30 patients in our study had received this agent.

STATISTICAL METHODS

Descriptive statistics were used to describe the pattern of age, sex and clinical features at presentation. Chi-square test was applied to compare the efficacy i.e defervesence, reduction in size of enlarged organs. ANOVA was applied to compare the improvement in hematological variables and safety of drugs.

RESULTS

Clinical Findings at Presentation:

Fever, splenomegaly, hepatomegaly and bone marrow suppression were seen in all (100%) cases diagnosed as visceral leishmaniasis. Other symptoms like cough (51%), lymphadenopathy (23.3%), malnutrition (79%), bleeding diathesis (46.6%) and overt bleeding were seen in gradually decreasing number of our patients (table-1).

Age and Sex:

Age of patients in our study ranged from 7 months to 6 years. A large proportion, 74 (82%), was between 12-36 months of age. Gp A had 24 patients between 12-36 months and 5 patients below 12 months of age. Gp B had 24 patients between 12-36 months and 4 patients were below 12 months. GP C had 26 patients below 36 months and 4 patients were less than 12 months. Age distribution was similar in three groups (fig. 2 a).

Patients were seen from both sexes. Males were 48 (53.3%) p-value < 0.042. GP A had 15 males; Gp B had 14 males while Gp C had 19 males.

Fever and Defervesence:

Prolonged fever was the main presenting complaint. At presentation 36 (40%) patients had fever of less than 2 months duration while 12 (13.3%) had it for more than 6 months duration. In another 42 (46.7%) patients duration of fever was between 2 and 6 months. When defervesence was studied in Stibogluconate group 21 patients were afebrile within 7 days while 4 patients remained pyrexial for more than 14 days. In Meglumine antimonate group 19 patients were afebrile within 7 days while in 3 patients fever persisted for more than 14 days. In Aminosidine group only 6 patients were afebrile within 7 days while in 6 patients fever persisted for more than 14 days (p-value <0.05) (table-2).

Spleen and Liver Size:

Spleen and liver were palpable in all cases on admission. Spleen was less than 5 cm in 12 cases, between 5-10 cm in 65 cases and more than 10 cm in only 13 cases. The size was monitored throughout the study. Liver was decreased more rapidly as compared to spleen.

Malnutrition:

On admission 18 (20%) patients had PCM grade-I (Gomez), a greater number in Gp C with a palpable liver at 90 day follow up was probably due to the younger age group of patients in this category (table-3). After applying chi-square test for each time separately we got p-value <0.05. Therefore there is no significant difference in the 3 groups at each time. Another 36 (40%) had PCM grade-II while 19 (21.1%) were in PCM grade-III while 17 were not malnourished. At the end of 90 day study period 35 (40%) patients were in PCM grade-I while 19 (21.1%) were in PCM grade-II. There was a visible change in the nutritional status of our patients as none was in PCM grade-III at the end of our study. Weight gain was again similar in all the groups.

Laboratory Evaluation:

Hematological Indices

Hematological level, white-blood cell, red-blood cell and platelet counts were monitored throughout the study as criteria for recovery of bone-marrow function. After

applying ANOVA separately for each time we got p-value >0.05 at different times. With minor variations at different times of the study the results were almost similar in all the three group at the end of the study period at 90 days (table-4 & fig. 1).

Monitoring for Side Effects

a) Renal Functions:

This was done monitoring serum urea and creatinine levels on admission as well as through the study period and at the end. Serum urea showed an initial rise with all agents initially but showed complete recovery at the end of therapy in all the groups ($p<0.05$) (table-5 and graph-II).

b) Hearing Assessment:

Audiology assessment was carried out by age appropriate methods throughout our study. No deterioration in hearing for any of the drugs was detected by us or reported by the parents during this period. Aminosidine group behaved in a similar manner to other groups in this regard too.

Cost of Therapy

A course of therapy for a 10-kg child with antimony compound Stibogluconate costed Rs.6000, Meglumine therapy costed Rs.4500 while treatment with Aminosidine costed only Rs: only 300, (table-3).

DISCUSSION

Age of patients in our study was similar to the other studies in the country as it showed the disease to be more prevalent in the younger (less than five years) age group [1-3,5,24-26]. It differed from the other major study in Kenya, which went to the extent of excluding children less than 36 months [23]. In total 74 out of 90 patients in our study were below 36 months of age. Other 16 cases also were below 72 months of age. Another Pakistani study at Pakistan Institute of Medical Sciences [5] also confirmed the impression that younger patients with lack of immunity and exposure to disease due to malnutrition were the worst effected. These earlier studies reported a similar predisposition to the illness with a mean age of 3.5 years [5,26].

Males were seen to be more afflicted by the disease and the ratio was 1.1:1. Earlier studies showed varying figures ranging from 1:1 through 3.7:1[3]. A slightly increased exposure of male children to the vector may be responsible for this statistical difference. This may also explain the incidence of male predominance in African studies.

Most of the children in our study had some degree of malnutrition at the start. Only 17 patients (18.9%) were having weight in the normal range while 19 patients (21.1%) suffered from severe malnutrition (PEM – III).This finding was similar to other local studies [5]. Rapid recovery in the state of nutrition was appreciated by the researchers as well as the parents as none of our patients belonged to the extremely malnourished group PCM grade-III at the end of 90 days period.

Fever was seen in all cases of VL and considered to be an integral component of the disease. Double-spike of fever noted in the Kenyan study [23] was not detected in our series. In Stibogluconate group 70% of patients were afebrile before 7 days while 63% in Meglumine group and only 20% in Aminosidine group were afebrile before 7 days of treatment. If fever was to be taken as sole criterion of efficacy then Aminosidine took significantly longer before fever settled (p-value < 0.05).

All patients had splenomegaly. Eighty percent had a spleen size less than 10-cm. Spleen size was not mentioned in centimeters in other studies [5]. A few cases treated with Aminosidine showed persistence of spleen although significance of this finding needs to be further explored.

Hepatomegaly was also seen in all our patients. It is however normally palpable in young age group. Aminosidine group showed a comparatively rapid regression in liver size to that of spleen.

Cough was seen in 46 cases (51.1%) at presentation although clinical or x-ray evidence of pneumonia was seen only in 14 cases (15.5%) which was significantly less than reported in earlier studies [5,23]. Additional antibiotics were prescribed in these cases.

Significant lymphadenopathy was noted in 21 (23.3 %) cases in our series. Cough is a significant feature in Chinese, African and Mediterranean forms of visceral leishmaniasis [6].

Bleeding tendency with petechiae, bruises and overt bleeding was seen in 42 (46.6%) cases. Actual bleeding was seen in 19 patients (21.1%) all of them received platelet concentrates (or whole blood when platelets

Table-1: Clinical features at presentation.

Clinical Feature	No. of Patients
Fever	90 (100 %)
Splenomegaly	90 (100 %)
Hepatomegaly	90 (100 %)
Malnutrition	64 (71.1 %)
Cough	46 (51.1 %)
Lymphadenopathy	21 (23.3 %)
Bleeding diathesis	36 (40 %)
Overt bleed	19 (21.1 %)

Table-2: Patterns of defervesnce.

	Defervesence <7 days	Defervesence 7-14 days	Defervesence >14 days
Gp a (n=30)	21	5	4
Gp b (n=30)	19	8	3
Gp c (n=30)	6	18	6

Table-3: Organ enlargement and response.

		Size in cm	Day 1	Day 14	Day 28	Day 90
Spleen size (cm)	Gp a	<5cm	7	20	22	7
		5-10 cm	18	9	1	0
		>10 cm	5	1	0	0
	Gp b	<5cm	2	20	24	12
		5-10 cm	25	9	1	1
		>10 cm	3	1	0	0
	Gp c	<5cm	3	17	3	1
		5-10 cm	22	13	0	0
		>10 cm	5	0	0	0
Liver size (cm)	Gp a	<5cm	15	25	14	5
		5-10 cm	12	3	0	0
		>10 cm	3	0	0	0
	Gp b	<5cm	10	27	16	6
		5-10 cm	19	3	0	1
		>10 cm	1	0	0	0
	Gp c	<5 cm	12	23	15	8
		5-10 cm	14	6	0	0
		>10 cm	4	0	0	0

Table-4: Lab parameters of efficacy.

Hemoglobin (gm/dl)	GP A	6.4	9.1	10.6	12.4
	GP B	6.8	8.8	10.2	12.2
	GP C	6.8	9.3	10.5	12.5
TWBC 1000/mm 3	GP A	3.69	4.30	4.73	4.21
	GP B	3.86	4.78	5.01	4.24
	GP C	4.26	4.94	4.67	4.50
TRBC 1000/mm 3	GP A	2.90	3.32	3.90	4.34
	GP B	2.88	3.41	4.04	4.42
	GP C	3.02	3.32	3.93	4.21
Platelets 1000/mm 3	GP A	82.2	123.6	224.3	275
	GP B	65.5	115.2	245.2	267.3
	GP C	94.0	128.9	299.9	281.1

Table-5: Lab parameters for safety.

Urea (N=3.3-6.7 mmol/l)	GP A	5.16	5.86	5.04	4.56
	GP B	5.36	5.79	5.18	4.52
	GP C	5.17	5.72	4.81	4.27
Creatinine (N=53-176 mmol/l)	GP A	130.2	140.5	121.4	105.6
	GP B	137.7	134.4	121.9	105.9
	GP C	129.8	145.3	114.3	95.2

were not available). No evidence of increased bleeding diathesis was observed in Stibogluconate group as seen in Kenyan study [23].

All features indicating bone marrow recovery like hemoglobin, total white blood cell count, total red blood cell count and platelet counts showed gradual improvement with comparable results in the end, with minor differences in counts in some patients at earlier stages of the study.

Results of treatment were similar and comparable in all the groups treated with three different agents. All patients were afebrile for more than a week in hospital before they were discharged. Patients took a significantly longer time for defervesence in Aminosidine group ($P<0.05$). Visceromegaly had markedly regressed. Bone marrow exam that was kept as an inclusion criterion was not maintained as an evidence of remission because a large number of patients refused to undergo this invasive procedure after the signs and symptoms of disease had abated. This lack of compliance to repeat bone marrow was also confronted by researchers in another local study [5].

Lack of relapses and recurrences was a pleasant surprise especially in the absence of a lab criterion of remission like a negative bone marrow smear at the end of treatment. Only one case that had received Meglumine antimonate @ 20 mg / kg / day for 28 days relapsed (treated successfully with Stibogluconate later). Follow up was initially planned till 6 months [28], it could not be done due to lack of compliance, education, financial resources and logistic constraints (patients came from far flung areas with extreme weather conditions).

Table-6: Comparison of cost of drugs.

Trial agent	Cost of a course of therapy for a 10 kg child (Average)
Sodium stibogluconate	Rs-6000
Meglumine antimonite	Rs-4500
Aminosidine / paromomycin	Rs-300

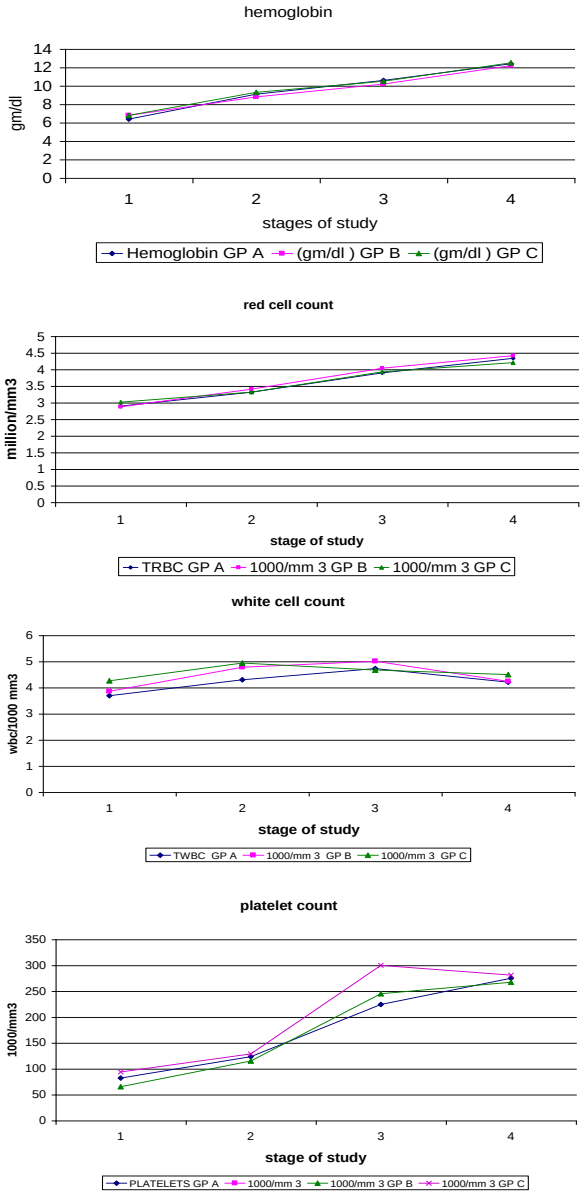

Fig. 1: Various haematological parameters during the various stages of study.

The drugs under trial being antimonials and an aminoglycoside, it was encouraging that none of our patients needed stoppage or change of therapeutic agent due to side-effects during whole of our study. This was especially notable with Aminosidine which being an aminoglycoside was feared to affect the renal functions and hearing. Lack of any significant lab evidence of deterioration in renal functions (urea and creatinine levels) or any clinical evidence of deterioration in hearing assessed by age appropriate methods [11,27] were consistent with similar findings in the local [5] as well as international studies [18].

CONCLUSION

Aminosidine @15 mg/kg/day for 21 days was found to be as effective as antimony compounds (Stibogluconate and Meglumine antimonate) in the treatment of visceral leishmaniniasis in Pakistan. Lack of any significant side effects in addition to a remarkably low price i.e. Rs.4500-6000 for antimonials for a 10-kg child as compared to Rs.300 for Aminosidine was considered a significant factor to recommend Aminosidine as first line drug for the treatment of Visceral Leishmaniasis in a third world country like Pakistan.

RECOMMENDATIONS

Emergence of resistance to antimonials [10,22,29] and association of disease with malnutrition and dysfunction of immune function like AIDS reported in some recent studies [29] would immediately point to the need for immediate work in this field. Fresh studies should be immediately undertaken to study the old drugs in new doses and combinations [22]. New drugs like oral agent Miltefosine being currently under trial in India [30], another trial of Aminosidine (Paromomycin) under W.H.O. currently being carried out in India [32] and possibility of a vaccine for VL [31] are other positive developments being perused. With already scarce health resources in the developing countries fight against a disease of this

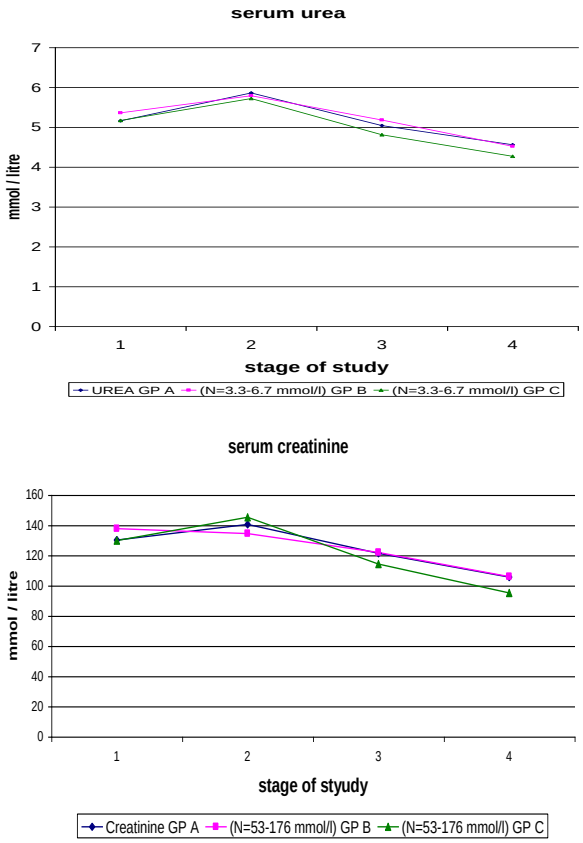

Fig. 2: Urea and creatinine levels during study period.

magnitude can prevent a potential loss of precious life and effort. The disaserous earth-quake in this region has increased the possibility of sudden rise in the number of patients due to massive changes in the risk of exposure to this disease. This endeavor could well provide the starting point for collaboration in field of health research between the neighbouring countries of SAARC region.

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