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Original Article

Efficacy and Tolerability of Miltefosin for Childhood in Visceral leishmaniasis

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Abstract

Introduction: Bangladesh is a kala-azar endemic country. Previously Visceral leishmaniasis was treated with intravenous Sodium stibogluconate. But it was hazardous for the patients and associated with many adverse effects. So, doctors were searching for an oral antileishmanial drug. Miltefosin is an oral anticancer drug, but has an excellent antileishmanial activity. **Objective:** To see the effectiveness and tolerability of Miltefosin for childhood Visceral leishmaniasis. **Materials and Methods:** This is a prospective type of descriptive study. **Study setting and period:** Department of Pediatrics, Rajshahi Medical College & Hospital, Rajshahi during September 2011 to February 2012. **Study population:** Patients of Visceral leishmaniasis admitted in Pediatrics department, Rajshahi Medical College & Hospital. **Sample size:** Forty four (44) Patients of Visceral leishmaniasis admitted in Pediatrics department, Rajshahi Medical College & Hospital. **Results:** 86.4% patients of childhood Visceral leishmaniasis were cured (evidenced by absence of LD body in splenic aspirate) with Oral Miltefosin at a dose of 2.5mg/kg/day in two divided dose in the morning and evening after meal for 28 days. 65.9% became afebrile in 1-6 days, 20.5% in 7-10 days and 13.6% in >10 days. Mean weight of the patients was increased from 22.5 kg to 23.2 kg. Very few adverse effects were noted. Most of them were gastrointestinal symptoms like, nausea (29.5%), vomiting (22.7%), diarrhea (18.2%) and 11.4% patients showed transient elevation of serum transaminases. But no patient needed to discontinue the treatment with Miltefosin. **Conclusion:** This study indicates that Miltefosin is safe, well tolerable and highly effective for childhood Visceral leishmaniasis.

Key words: Otitis media, Adenoid hypertrophy, Adenoiditis, Tympanometry

Introduction

Visceral leishmaniasis (VL) or Kala-azar is a human disease caused by hemoflagellate protozoal parasite of leishmania species (Leishmania donovani) and transmitted to human by the sand fly (Phlebotomus argentipes) bites. Leishmania is distributed worldwide and 12million people are estimated to be infected with about 500,000 new cases every year[1], 90% of which occurs in India, Nepal, Bangladesh, Sudan and Brazil.[2] Approximately 50% of these patients are children[3]. In India 40% of patients are aged <13 years; in Sudan, 65% are aged <15years and in Brazil, 60% of patients are aged <5 years[4]. Furthermore, Visceral leishmaniasis is an opportunistic infection in HIV[5]. Bangladesh is a Kala-azar endemic country. At present Kala-azar cases are reported from 139 upazilas in 45 districts of Bangladesh. On an average 10,000 cases are detected and treated annually[6]. Present estimated prevalence is 45,000 cases. The present prevalence rate is 2.9/10,000 population in Bangladesh.[7] Of them most are from Mymenshingh, Pabna, Tangail, Jamalpur and Rajshahi districts.

Cardinal clinical feature of Kala-azar are: History of fever more than two weeks, residing/traveling in endemic area, splenomegaly, weight loss, anemia. Disease is confirmed by demonstration of LD body from splenic aspirate, bone marrow, buffy coat, lymph node biopsy etc. Associated laboratory changes are:

Hematological changes like- Anemia, Raised ESR, Leucopenia, Thrombocytopenia, Positive ICT for Kala-azar and Biochemical changes like- Increased Serum bilirubin, raised SGOT & SGPT, Decreased Serum albumin, increased blood urea and creatinine etc. Death occurs in >90% of patients without specific anti-leishmanial treatment[8].

All anti-leishmanial drugs are toxic and most have to be used parenterally for prolonged period. The standard drug for the treatment of VL is Pentavalent antimonial compound (SAG), that is given parenterally.The therapy has been further complicated by large number of infected children and declining effectiveness of the drug. The two usual second line agents, Pentamidine isothionate[9] and Amphotericin B deoxycholate[10] are also parenteral and are more toxic. Liposomal amphotericin B is effective and safe, but it is very expensive for developing countries[11] and prohibitively expensive for regions of endimicity. All the parenteral drugs need hospitalization for 4-6 weeks. This is very much hazardous for patients.

Oral medications have an obvious appeal with ease of administration, domiciliary treatment, no hospital cost; no limitation by bed capacity etc.Thus the quest for an effective oral anti-leishmanial drug has been ongoing for a long period. Drugs such as Allopurinol, ketoconazole, Triazoles (fluconazole), Atovaquone have been tested either alone or in combination for the treatment of Visceral leishmaniasis; however, they had either no effect or only a partial effect[12].

Miltefosin (1-0-hexadecylphosphocholine) is a membrane active synthetic ether-lipid analogue, was developed as an oral anti-cancer drug against solid tumor, but due to treatment-limiting gastrointestinal adverse events, its development as a synthetic anti-neoplastic agent was abandoned. Although later it was approved as a topical formulation for treatment of cutaneous metastasis of breast cancer[13]. It was discovered in both in vitro and in animal studies that Miltefosin has excellent anti-leishmanial activity[14].

There were several studies on effectiveness of Miltefosin against leishmania in India. Bangladesh is also a Kala-azar endemic country. In Bangladesh some studies are going on. But very few studies have been done with Miltefosin in children suffering from Visceral leishmaniasis. But we have already mentioned that about 50% patients of Visceral leishmanisis are children. So it is desirable that a study should be done to see the effectiveness and tolerability of Miltefosin on children. This study was designed to see the efficacy, tolerability, safety and drug related adverse reaction of Meltifosin in pediatric age group.

Materials and Methods

This is a prospective type of descriptive study. It was an observational study. This study was conducted in Department of Pediatrics, Rajshahi Medical college hospital, Rajshahi. Study period was six months from September 2011 to February 2012. All the admitted patients of visceral leishmaniasis in Rajshahi Medical College Hospital pediatric words during the study period. Age group: 1-14 years. Forty four (44) patients were admitted during the study duration. Oral Miltefosin was given at a dose of 2.5mg/kg/day in two divided dose in the morning and evening after meal for 28 days. Before treatment, visceral leishmaniasis was diagnosed by positive ICT for kala-azar. Convenient sampling method was followed in this series. Ethical measures were taken. After all necessary correction, the data was compiled and analyzed in the computer based software (SPSS).

Results

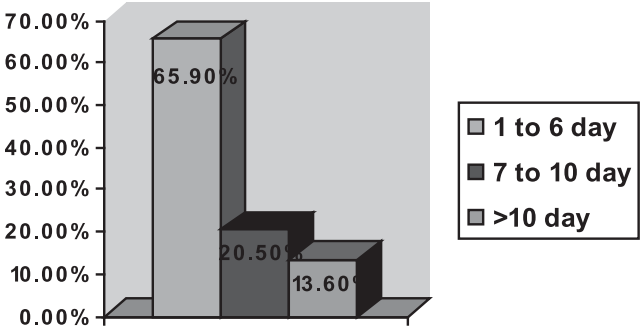

Figure-I: Time for temperature normalization.

The above figure shows that 65.9% patients became afebrile in 1-6 days, 20.5% in 7-10 days and 13.6% in more than 10 days.

	Before treatment	After treatment
Weight of the patients	22.5kg	23.2kg

Table-I: Weight of the patients before and after treatment of the study patients.

Above table shows that, the mean weight of the patients was 22.5 kg before treatment. But the mean weight is increased to 23.2 kg after the end of treatment.

	Before treatment	After treatment
Size of the spleen	7.3cm	1.8cm

Table-II: Size of the spleen before and after treatment of the study patients.

Above table shows that, the mean size of spleen of the study patients was 7.3 cm before treatment. But it was reduced to 1.8 cm after completion of therapy.

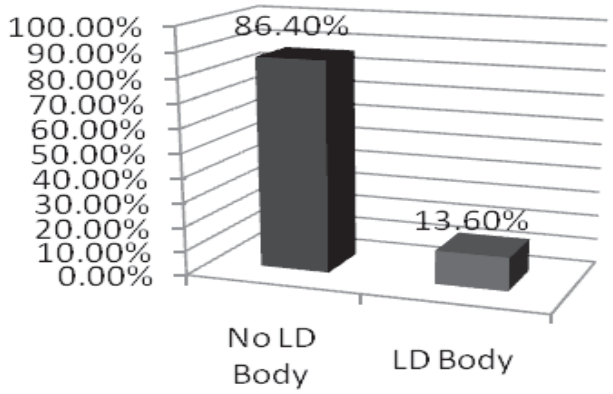

Figure-2: Status of LD body in splenic aspirate after end of treatment of the study patients.

The above figure shows that, after end of treatment, no LD body was found in splenic aspirate in 86.4% patients and LD body was present in splenic aspirate in 13.6% patients

Investigations	Before treatment	After treatment
Hemoglobin	7.91 gm/dl	9.81 gm/dl
Total count of WBC	3240 /cumm	4927 /cumm
Platelet count	1,24,477 /cumm	2,04,522 /cumm
S.creatinine	0.70 (mg/dl)	0.79 (mg/dl)
Blood urea (mg/dl)	33.16 (mg/dl)	34.29 (mg/dl)

Table-III: Mean value of different investigations before and after treatment of the study patients.

The above table shows that, after treatment Hb level raised from 7.91gm/dl to 9.81gm/dl,total count of WBC raised from 3240/cumm to 4927/cumm and Platelet count from 1,24,477/cumm to 2,04,522/cumm. Blood urea and S. creatinine level remained almost static.

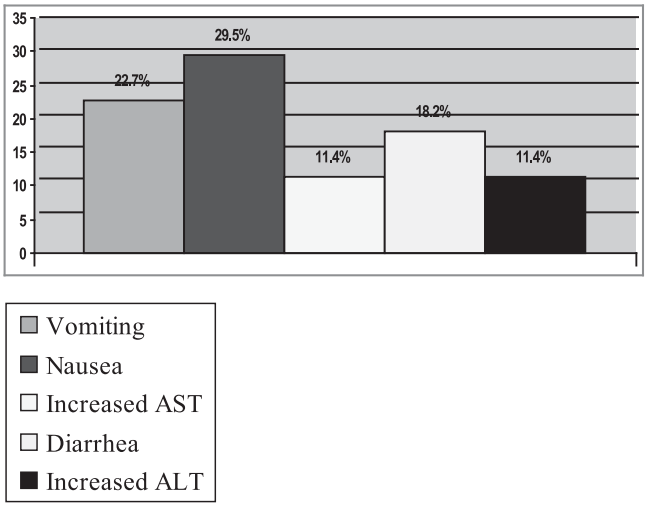

Figure-3: Adverse effects of Miltefosin therapy.

The above diagram shows that, 29.5% patients had nausea, 22.7% vomiting, 18.2% diarrhea, 11.4% had increased ALT and AST level after initiation of Miltefosin therapy.

Discussion

In this study the majority (61.4%) of the patients was male and 38.6% patients were female. Male: female ratio was 1.6:1. A study by Sunder et al (2004) showed male: female ratio 1.3:115.The present study shows that, majority (65.90%) of the study patients became afebrile in [1-6] days (Figure no.1). Rahman et al (2011) had shown in their study that, 85% patients were LD body negative in splenic aspirate after 28 days treatment with Miltefosin16. The present study closely resembles with the above study. In this study 86.4% patients became LD body negative in splenic aspirate after end of therapy (Figure no-2). This result indicates that Miltefosin is highly effective in treating childhood Visceral leishmaniasis. Regarding the weight of the

study patients, before treatment mean weight was 22.5 kg and after completion of treatment the mean weight increased to 23.2 kg (Table no-1). It means that Miltefosin could stop the disease process of and by taking adequate nutrition the patients were able to increase their weight.

Bhattacharya et al (2004) in their study showed that, mean size of spleen was 6.8cm at the time of enrollment and 1.5 cm at the end of treatment[15]. The present study closely resembles the above study, where the mean size of spleen was 7.3 cm at the time of enrollment and 1.8 cm after completion of treatment with Miltefosin (Table no-2).

Singh et al (2006) had shown in their study that, formed elements of blood (RBC, WBC, Platelet) are increased and no significant change in S.creatinine and Blood urea value after treatment with Miltefosin[18]. This study shows mean value of hemoglobin level 7.91 gm/dl, Total count of WBC 3240/cumm, Platelet count 1,24,477/cumm, S.creatinine o.70mg/dl, Blood urea 33.16 mg/dl at the time of enrollment and the mean value of hemoglobin level 9.81gm/dl, Total count of WBC 4927/ cumm, Platelet count 2,04,522/cumm, S.creatinine 0.79 mg/dl, Blood urea 34.29 mg/dl after end of therapy (Table no-3).

Regarding the adverse effects of Miltefosin, some gastrointestinal side effects like nausea in 29.5% patients, vomiting in 22.7% patients and diarrhea in 18.2% patients were observed (Figure no-3). All the adverse effects last for 2-3 days. Patients with diarrhea were given oral rehydration solution and patients with vomiting were treated with only anti emetic drugs. No adverse effects lead to discontinuation of therapy for any patient. Bhattacharya et al (2004) in their study had shown that, 26% patients had vomiting and 25% patients had diarrhea after initiations of Miltefosin therapy and no patient had to discontinue treatment due to adverse effects[15].

Sunder et al (2006) had shown in their study that, transient rise of serum transaminases occurred in 15% patients in the first two weeks of treatment with Miltefosin[17]. The present study closely resembles with the above study, where AST and ALT level is elevated in 11.4% patients (Figure no-3). Reversible elevation of transaminase level occurred in first two weeks of treatment. But it started to decrease gradually after two weeks and came to normal level in the 4th week of treatment. This transient elevation of transaminase level neither led to discontinuation of therapy nor led to serious liver disease.

Conclusion

Miltefosin is an effective and well tolerable antileshmanial drug. The dose is 2.5 mg/kg/day for 28 days.The drug has few gastrointestinal side effects like nausea, vomiting, diarrhea that usually persists for 2-3 days. But it was not needed to stop treatment for these adverse effects.

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