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Comparative Study of Miltefosine in Two Different Doses in Treatment of Visceral Leishmaniasis in Children

KEYWORDS: visceral leishmaniasis, Miltefosine, Kala-azar

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ABSTRACT *Objective : To compare the efficacy and side effects of miltefosine in 2 different doses in treatment of V. leishmaniasis in children. Method : 40 patients alternately assigned to 2.5 & 2mg/kg/day of miltefosine & outcome were analysed for efficacy and side effects. Conclussion : efficacy of miltefosine was 90% & there was no any significant differences in efficacy was found between two different doses of Miltefosine whereas decrease in gastro intestinal side effects was noted with lower doses of Miltefosine.*

Introduction :-
Visceral lieshmaniasis is the protozoal infection of reticuloendothelial system caused by parasite of genus Leishmania. In India visceral leishmaniasis is transmitted by female sand fly phlebotomus. Leishmania are able to survive and multiply in macrophages of reticuloendothelial organs like spleen, liver & bone marrow Visceral lieshmaniasis classically manifest as fever, spleenohepatomegaly and pancytopenia. The most common symptoms are intermittent fever and discomfort beneath the left costal margin due to enlarged spleen.

Dark pigmentation of skin is a consistent finding in Indian visceral leishmaniasis and this given the name kala-azar of this disease. In India, Visceral leishmaniasis has its home in plain of Gangas and Brahamputra. It has known to occur epidemically and endemically in well defined area of Eastern India viz, Bihar, W.Bengal, Assam and occasionally in other areas of India.In Bihar Kala-azar is a big health problem for districts situated north to Ganga.

Available treatment are Pentavalent antimony, Pentamidine, and Amphotericin-B. However due to toxicity and increasing resistance to antimony and pentamidine, Amphotericin-B has been emerged as a first line drug for treatment of Visceral leishmaniasis. But, all conventional drugs are parenteral and administerd under medical supervision to the hospitalized patient. Hospitalization increases treatment cost and it makes burden over limited hospital beds.So, quest for an orally active, efficacious, cost effective and safe drug is on.

Miltefosine is the first orally effective drug for treatment of visceral leishmaniasis.Miltefosine initially developed as an antineoplastic agent found to be effective against leishmaniasis. In past few year various studies of efficacy and toleratibility of miltefosine in treatment of visceral leishmaniasis have been undertaken. But most of studies are in adult patient and only few are in pediatrics age group. In view of above mentioned fact this study was undertaken to help further our knowledge regarding optimal dose which achieve high cure rate on one hand and does not cause adverse effect on other.

Aim & Objective
- To study the efficacy of Miltefosine in 2 different dose, in the treatment of Visceral leishmaniasis in children.
- To study the side effects & its relation to 2 different does of Miltefosine in treatment of Visceral leishmaniasis in children.

Material & method
This study was carried out in upgraded department of pediatrics, Patna Medical College and Hospital, Patna. And this was conducted on 40 selected cases of visceral leishmaniasis admitted in department of pediatrics from Aug. 2004 to Aug. 2006. Patient for study were 2-18 year of age with either sex and had visceral leishmaniasis suspected on the basis of clinical presentation and confirmed by demonstration of L.D. body in splenic or bone marrow smear.Since in this study comparison of two different doses of Miltefosine on treatment of visceral leishmaniasis was done, so patient with near same base line SGPT,S. cretinine and spleen size were included in this study.

Exclusion criteria:
Patient with following feature were not included in this study

- HIV positive patient
- Pregnant or lactating patient
- Severe liver and renal disease
- platelets count <50,000/cum
- Patient with total Leukocyte count <1000/cum.

After confirmation of diagnosis, first patient was given 2.5 mg/kg/day of miltefosine for 28 days and this patient was labeled as first case of Group A. When next case of visceral leishmaniasis came to department, it was given 2.0 mg/kg/day of Miltefosine for 28 days and it was labeled as first case of group B. And this way alternate patient was included in group A and group B respectively. Finally each group having 20 patient and total patient for study was 40.

After start of treatment with miltefosine each patient was examined everyday during treatment period for vitals including temperature and splenic size.Patient also looked for any unwanted effect of miltefosine. Patient also asked for adverse event like nausea, vomiting and loose stool during treatment period. During treatment period at weekly interval, investigation like CBC, R/E of urine, SGOT, SGPT and S. creatinine was done.

At the end of treatment i.e., 28 days besides above mentioned investigation splenic aspiration was done to exclude

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LD body presence and if spleen not palpable bone marrow aspiration was done for same purpose. An initial parasitological cure was indicated by absence LD body in splenic/ bone aspirate after 28 days of treatment. Patient were classified as having initial cure if initial parasitological cure was accompanied by marked clinical improvement after 28 days of treatment. Patient with initial cure was sent back to home and asked for follow up visit after 1 month and then monthly for total 6 months.

During follow up any patient with sign and symptoms suggesting visceral leishmaniasis relapse was admitted. Relapse was defined as presence of parasite in splenic/bone marrow aspirate after initial parasitological cure. Patient with relapse or patient who did not respnded initially (i.e. during treatment period) treated with Amphotericin- B.

Patients who experienced initial cure were designated as final cure if they did not experienced relapse during 6 month follow up.

Observation:
Following observations are made during study :

- Maximum number of cases were observed in 6-10 year age.
- Fever was presenting complain in all cases of leishmaniasis and fever was usually intermittent in type.
- In present study spleen was palpable in all cases of visceral leishmaniasis whereas hepatomegaly was recorded in 87.5% case.
- Anaemia was observed as constant feature of leishmaniasis.
- In the present study only 95% of patient became afebrile after 4 week of miltefosine treatment in both dose group of patient i.e, fever in 5% of patient did not subsided with miltefosine treatment.
- Maximum patient were afebrile between 6-10 days of treatment and all cases who responded to treatment became afebrile by 15th days of treatment.
- During treatment period mean splenic size of all cases decreased dramatically from 6 to 1 cm.
- Vomiting was observed as a common side effect of miltefosine. It was observed in 45% patient of group A whereas in patient of group B it was observed in only 35% . vomiting was mild in severity and it lasted for only 1 to 3 days.
- Diarrhoea was second common side effect seen during miltefosine treatment but it was mild and lasted for 1 to 3 days.
- SGPT were increased in 50 and 45% patient of group A and B respectively during first week of treatment and it came down to within normal range in next one week in both groups of cases.
- One patient (5%) of both group A and B were not LD body negative after completion of 28 days of treatment. These are the same patients who did not became afebrile with miltefosine treatment and were term as "Initial failure".
- During 6 months follow up visit one patient (5%) of both group A and B had relapse of visceral leishmaniasis.
- In this study efficacy of miltefosine to cure visceral leishmaniasis is 90% and there was no difference in efficacy when dose of miltefosine decreased from 2.5 to 2.0 mg/kg/day.

Discussion
In this study 95% of patient became afebrile after 4 weeks of miltefosine treatment in both group A and B (i.e. fever in 5% of patient did not subside with miltefosine treatment).Sunder et al. observed 100% of patient becoming afebrile after 4 week of miltefosine treatment, where as in the present study 5% of patient of both group failed to respond to the treatment i.e. they remained febrile with miltefosine treatment. This could be due to the emergence of cases of visceral leishmaniasis resistant to many antileishmanial drug including miltefosine.

In present study spleen size gradually decreased from 6 cm to 1cm during Miltefosine treatment and there was no difference in rate of regression and final spleen size when dose of Miltefosine decreased from 2.5mg/kg/day to 2.0 mg/kg/day .Sunder et al. had found dramatic decrease in spleen size from 6.9cm to 1 cm after 4 weeks of treatment. Bhattacharya et al. noted mean spleen size decreased steadily from 6.8cm to 4cm after 2 weeks of treatment and 1.5 cm at the end of treatment. The observation of present study is similar to their observation.

In the present study 90% of patient were cured with miltefosine treatment and there was no difference in efficacy when dose of miltefosine was decreased from 2.5mg to 2.0mg/kg/day.Bhattacharya et al. found 94% efficacy of miltefosine to cure visceral leishmaniasis. Sunder et al. in his dose ranging study had found 88% and 90% efficacy of 2.5mg and 1.5mg/kg/day of miltefosine respectively to cure visceral leishmaniasis patient.

In our study 45 and 35% patient of group A and group B respectively had vomiting during miltefosine treatment, that means vomiting is a common side effect during miltefosine treatment and incidence of vomiting decreased to 45 to 35% when dose of miltefosine was decreased from 2.5 to 2.0 mg/kg/day.Sunder et al. in his study found 38 & 30% of patient with miltefosine 2.5 mg and 1.5 mg/kg/day respectively experienced vomiting during miltefosine treatment. And their study favours present study observation.

Conclusion:
Miltefosine is effective and safe therapeutic option for visceral leishmaniasis in children. Miltefosine may be particularly advantageous as it can be administered orally. It is concluded in this study that 2.0 mg/kg/d of miltefosine for 28 days is as efficacious as 2.5 mg/kg/d. There is less incidence of G.I.T. side effect like vomiting and diarrhea with miltefosine dose of 2.0 mg/kg/day compared to the dose of 2.5 mg/kg/day.

However, this is a small study, so larger studies are required to knowing the full efficacy and profile of toxicity of miltefosine and its relation to dose of miltefosine.

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