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ORIGINAL ARTICLE

A STUDY OF EFFICACY AND ADVERSE DRUG REACTIONS OF CONVENTIONAL AMPHOTERICIN 'B' IN THE TREATMENT OF KALA-AZAR

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ABSTRACT: INTRODUCTION: Kala-azar is a chronic infection of the reticulo-endothelial system, caused by the organism leishmania donovani and transmitted by the bite of sand fly vector, Phlebotomus argentipes. Amphotericin B has long been recognized as a powerful anti-kala-azar drug and still remains to be the only safer and effective parenteral therapy for kala-azar. **MATERIALS AND METHODS:** The present study was conducted among 100 new or untreated randomly selected patients of kala-azar for the treatment with conventional ampho B (Am BD) in the dose of 0.75 mg/kg body weight on alternate day for a total of 14-20 doses. All the cases were followed up for the occurrence of adverse drug reactions and the results were analyzed statistically. **RESULTS:** Our study showed that most of the cases (76%) were below 30 yrs. of age and were male (58%). Response of ampho B on fever was maximum between 6 to 10 days and there was a reduction in spleen size at the end of therapy. All the patients uniformly showed rise in haemoglobin concentration. It is also found that there was a significant ($P<0.05$) rise in mean blood urea nitrogen (BUN) during treatment although it did not cross the normal limit. There was no significant ($P>0.05$) rise in mean serum creatinine level during treatment. **CONCLUSION:** Present study observed no significant toxicity to warrant withdrawal of the drug and in the dose of 0.75 mg/kg body weight is also responsive at the dose of 0.5 mg/kg body weight resistant case. No resistant cases has been found at this dose of ampho B in Kala-azar.

KEYWORDS: Efficacy, Kala-azar, Amphotericin 'B'.

INTRODUCTION: Kala-azar is a chronic infection of the reticulo-endothelial system, characterized by fever (Continuous or remittent in nature), with loss of bodyweight, spleenomegaly, hepatomegaly, anemia and dark pigmentation of skin and hence the name. It is caused by the organism leishmania donovani and transmitted by the bite of sand fly vector, phlebotomus argentipes. Kala-azar occurs in more than 80 countries in Asia, Africa, Southern Europe and South America, with a total of 200 million people at risk (Murray HW, 2001,[1] Guerin P et al, 2002[2]). About 90% of the estimated new symptomatic cases per year occur in just five countries- India, Sudan, Bangladesh, Nepal and Brazil (Arias JR et al, 1996).[3] India contributes to about 40-50% of the world's total cases. Among the total cases of Kala-azar which occurs in India, 90% are reported from Bihar state alone. Particularly northern districts of Bihar such as Darbhanga, Sitamarhi, Samastipur, Vaishali and Muzaffarpur are more affected. It has major medical, psychological and financial implications and remains a serious public health problem in Bihar (Ranjan A et al, 2005).[4]

Amphotericin B has long been recognized as a powerful anti kala-azar drug and still remains to be the only safer and effective parenteral therapy for kala-azar. In India, 98% of long term cure has been obtained in both antimonial unresponsive and previously untreated patients with conventional Ampho B desoxycholate (AmBD). However, primary adverse effects i.e., infusion related side effects

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(fever, chill, bone-pain) and renal toxicities (renal tubular acidosis, hypokalemia, nephrocalcinosis, acute renal failure etc.,) are major problems faced during the treatment of Kala-azar with conventional ampho B. Though lipid formulations of amphotericin B (i.e., Ampho. B Lipid Complex-ABLC, Ampho B Colloidal Dispersion- ABCD and Liposomal Ampho B- L amph B) have been proved to limit the toxicity of conventional Ampho. B. But unfortunately, their practical utility has been challenged in spite of their increased efficacy, due to much higher cost and lack of suitably designed prospective pharmacoeconomic (Cost-effective) trials.

OBJECTIVES: Objectives of this study are:

1. Early detection of unknown adverse reactions and interactions.
2. Detection of increase in frequency of unknown adverse reactions.
3. Identification of risk factors underlying adverse reactions.
4. Estimation of quantitative aspects of beneficial risk analysis and dissemination of information on the need to improve drug prescription and regulation.

MATERIALS & METHODS: The present study was conducted among 100 new (untreated) randomly selected patients of Kala-azar for the treatment with conventional ampho B (AmBD) in the dose of 0.75 mg/kg bodyweight on alternate day for a total of 14-20 doses. The study was conducted in the department of pharmacology, in collaboration with the department of medicine, DMCH, Laheriasarai, from Oct-2014 to Dec-2014. All the 100 patients were selected from the pool of patient of splenic smear positive symptomatic cases of kala-azar, admitted in the hospital. The study was approved by the local institutional ethical committee and informed written consent was obtained prior to start of the study from patients selected for the study. All the cases were followed-up for the occurrence of adverse-drug reactions. The possible treatment and outcomes of adverse drug reaction was noted. All the investigations, carried to confirm on suspected adverse drug reaction was done by standard biochemical, histopathological or other methods. The results obtained were analyzed statistically.

METHODOLOGY: Conventional Ampho B is available by brand name of “Fungizone”, which contains 50 mg of lyophilized powder and 41mg of deoxycholate bile salt. Addition of bile salt is to make the drug water dispersible. Powder formulation was mixed with 10 mg of sterile water for injection resulting in 10ml of solution. So, the solution contains 5mg of Ampho B per ml. Both form of drug, either powdered or solution was stored in refrigerator. On the first day of treatment, 1ml of drug in 5% Dextrose (500ml) water was given slowly at test dose. Next, increment dose intermediate between full dose as 0.75 mg/kg body weight, infused in the same manner. Third infusion was considered of first full dose. All infusion were given through intravenous cather. Patients were keenly observed for infusion related side effects during infusion and till four hours after completion of infusion. Acute febrile reactions were controlled with paracetamol tablets. Chills and rigors responded to intravenous injection of pheniramine maleate. Test dose and increment dose was excluded while calculating total dose of the drug.

RESULTS: 100 new cases of Kala-azar admitted in the DMCH, Laheriasarai were randomly selected for the study. Diagnosis was confirmed by L.D. body demonstration in splenic smear.

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Age group in years	Number of cases with percentages					
	Male		Female		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
10-20	18	18	10	10	28	28
21-30	28	28	20	20	48	48
31-40	06	06	06	06	12	12
41-50	04	04	06	06	10	10
51-60	02	02	0	0	02	02
Total	**58**	**58**	**42**	**42**	**100**	**100**

TABLE 1: DETAILS OF AGE AND SEX INCIDENCE

The above table shows that most of the cases (76%) were below the age of 30 years. Out of 100 cases, 58% were male and 42% were female. Most of the cases belonged to low socio-economic group. The main symptoms were irregular fever, abdominal distention, pain in left hypochondrium.

No. of days of Ampho-B in dose of 0.75 mg/kg body weight for cases to become afebrile	No. of cases	Percentage	Total percentage of afebrile cases
1-5	16	16	16
6-10	80	80	96
11-15	04	04	100

TABLE 2: EFFECT OF AMPHO-B IN THE DOSE OF 0.75 MG/KG BODY WEIGHT ON FEVER IN VL.

Above table shows that response of Ampho-B on fever in Kala-azar cases was maximum between 6 to 10 days and minimum days required for the Ampho- B in dose of 0.75 mg/kg body weight to make a patient afebrile was four days and maximum no. of days was 14 days. By the 15th days, 100% of the cases were afebrile.

	No. of cases	Splenic size			
		Range (cm)	Mean (cm)	+SD	+ SEM
Before Therapy					
Palpable spleen	100	1-12	7.4	+2.87	+0.39
Non-palpable spleen	0				
At the end of therapy					
Palpable spleen	20	1-6	0.5	+1.30	+0.176
Non-palpable spleen	80				
Reduction in splenic size	100	4-12	6.9	+2.609	+0.358
P<0.001 (Highly significant)					

TABLE 3: Reduction in Splenic size during Ampho-B therapy in dose of 0.75 mg/kg body weight

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Initial size of spleen at the beginning of therapy was 7.4 + 2.87 cm (splenic axis from left coastal margin in cm). At the end of therapy, spleen was non-palpable in 80 cases and palpable in just 20 cases. Reduction during therapy is shown in table no. 3. All patients witnessed dramatic reduction in splenic size and the mean dropped to 0.5 + 1.3 cm.

	No. of cases	Hb concentration in gm/dl				't' value	'P' Value
		Range	Mean	+ SD	+ SEM		
Before therapy	100	4.3 – 11.7 = 7.4	7.5	+ 1.5	+ 0.2		
After therapy	100	7.8-13.2	10.5	+ 1.3	+ 0.18		
			X=2.9	+ 1.09	0.15	19.33	< 0.001(Highly significant)

TABLE 4: Effect of Ampho-B on Hb concentration in dose of 0.75 mg/kg body weight

Table no. 4 shows that the mean haemoglobin concentration at the beginning oftherapy was 7.5 + 1.5 gm/dl which significantly raised following the therapy to 10.5 + 1.3 gm/dl. All the patients uniformly showed rise in haemoglobin concentration.

Days of observation	Blood urea Nitrogen level (in mol/l)	Serum creatinine level (in micro mol/l)
	Mean + S.D	Mean + S.D
1st	3.71 + 0.56	74.6 + 71.25
8th	3.98 + 0.69	94.58 + 32.7
15th	4.14 + 0.59	95.47 + 33.59
22nd	4.26 + 0.53	108.73 + 34.47
30th	5.99 + 0.21	114.03 + 35.36

TABLE 5: Effect of Ampho B on Blood urea Nitrogen & serum creatinine in dose of 0.75 mg/kg body weight

Table no. 5 shows that there was significant (P<0.05) rise in mean blood urea nitrogen level during treatment, although it did not cross the normal level. In one case, there was great rise in blood urea after 22nd day of treatment, which did not normalized and ultimately died due to uremia.

Table no. 5 also shows that there was not significant (P>0.05) rise in mean serum creatinine level during treatment, except in one case who died during treatment.

However, it was also shown in our study that during treatment there was no significant (P>0.05) rise in mean serum SGPT level and mean serum bilirubin level. Also, it was observed that there was no significant (P>0.05) fall in mean serum potassium level during the treatment.

DISCUSSION: In the present study, 100 diagnosed cases of kala-azar including one with stibonate failure and two with primary unresponsiveness to pantamidine isethionate and five cases primarily resistant to Miltefosine were selected randomly and given the ampho-B in dose of 0.75 mg/kg body weight.

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Table no.1 shows the age and sex distribution of the patients. Most cases (76%) were below the age of 30 years. It was only because VL is common in this age group. 58% of the cases were male and 42% were female. The male preponderance may be attributed to the fact that in kala-azar endemic region, female sleeps inside the house, whereas the male members sleep outside, in the cattle shed (Bathan), which makes them were susceptible to sand fly bite. Kala-azar was more common in low socio-economic group.

Table no. 2 shows that response of ampho B on fever in 80% (80 out of 100) cases was maximum between 6 to 10 days and minimum days required for the ampho B in the dose of 0.75 mg/kg body weight to make a patient afebrile was 4 days and maximum no. of days was 14 days. By the 15th day, 100% of the cases were afebrile.

Table no. 3 shows that initial size of spleen at the beginning of the therapy was 7.4+2.87 cm (Splenic axis from left costal margin in cm). At the end of therapy spleen was non-palpable in 80 cases and palpable in just 20 cases. There was significant (P<0.001) reduction in spleen size during second week of therapy. None of the patient reported increase in splenic size during follow up.

Table no. 4 shows the mean Hb concentration at the beginning of therapy was 7.5+1.5 gm/dl, which significantly raised following the therapy to 10.5+1.3 gm/dl, which were highly significant (P<0.001) and all the patients uniformly showed rise in Hb concentration.

Table no. 5 showing mean blood area nitrogen (BUN) level of patients during treatment and follow-up on the day 1st, 8th, 15th, 22nd and 30th as 3.71 + 0.56, 3.98 + 0.69, 4.14+0.59, 4.26+0.53 and 5.99+0.21 respectively. There was significant (P<0.05) rise in BUN level during treatment, although it did not cross normal limit, except in one case, where there was a great rise in blood urea after 22 days of treatment which did not normalized and the patient died ultimately due to uremia.

Branch R A (1988)[5] had used ampho B in 81 cases of systemic fungal infection and had documented that 93% cases showed rise in blood urea level. Mc Curdy et al (1968)[6] and Hamilton Miller JMT (1974)[7] reported renal impairment in 85% of the cases treated with ampho B for fungal infection. Christiansen K.J et al (1985)[8] have reported azotemia in 80% cases treated with ampho B for mycosis. They found the toxicity to be dose related and transient. The above mentioned studies are based on treatment of fungal infection where high dose and prolonged duration of therapy is the rule. The difference regarding extent of renal impairment observed during present study appears to be done to comparatively small total dose and short duration of therapy. Goodman – Gilman (2001)[9] reported that permanent renal impairment was noted only when the total dose exceeds 3-4 grams.

Table no. 5 also shows mean serum creatinine level in patients during treatment on day 1st, 8th, 15th, 22nd, 30th as 74.6 + 72.25, 94.58 + 32.7, 95.47 + 33.59, 108 + 34.47 and 114.03 + 35.36 respectively. There was no significant (P>0.05) rise in mean serum creatinine level during treatment except in one case in which there was a great rise in serum creatinine after 22 days of treatment which did not normalized and the patient ultimately died due to uremia, recorded a serum creatinine above 124.76 umol/L. As the serum creatinine is considered to be a better indicator of renal function in comparison to blood urea, it is evident that the dose of ampho B in 0.75 mg/kg body weight is less nephrotoxic, than the dose of 1mg/kg body weight on alternate day regimens.

J. Berman et al (1999),[10] in their multivariate model study observed that risk of nephrotixicity increases 3.7 fold for each 50 mg increase in total dose of ampho B for fixed duration of therapy and weight of the patient. The risk decreases by a factor of 0.4 for each extra day of therapy for a fixed total dose of drug and weight of the patient. They suggested that a day off in therapy might be

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hypothesized priority to decreases the risk of ampho B related nephrotoxicity. In their opinion a day "off" might allow restoration of glomerular filteration rate (GFR) with beneficial effect on renal function. Maddur M.S et al (1980),[11] have also suggested to follow alternate day dose schedule to prevent renal toxicity.

CONCLUSION: After the confirmation of diagnosis of kala-azar the treatment with ampho B in dose of 0.75 mg/kg body weight in alternate day dose schedule in 5% Dextrose (500ml) for 14-20 doses. Pulse, B. P, weight and systematic examination were done routinely. Baseline investigations, CBC with Hb%, SGPT, blood urea, S. Creatinine were repeated every 7th day during the therapy. Splenic aspirate smear examination for L. D bodies was repeated at the completion of therapy and at the 6th month from the end of therapy. Most of the cases (76%) were below the age of 30 years. It was observed that VL was more common in male than female. Kala-azar is also more common in low socio-economic group of people. The following observations were made in our study:

1. 76% of the patients were below 30 years of age.
2. It is more common in male than female.
3. 80% of the patients became afebrile between 6-10 days and all the patients became afebrile by 15th day.
4. BUN and serum creatinine also markedly increased initially, but eventually decreases.
5. All the patients registered marked decrease in splenic size.
6. All the patients showed marked improvement in Hb% and leucopenia.
7. The efficacy of ampho B in this study was 99%.
8. One case was dead due to nephrotoxicity who was also suffering from TB and taken anti TB drug along with ampho B.

Present study observed no sufficient toxicity to warrant withdrawal of the drug and in the dose of 0.75 mg/kg body weight is also responsive at the dose of 0.5 mg/kg body weight resistant case. During the 6 month of follow up period of cases, no any resistant or relapse of kala-azar has been observed. As dose of 1 mg/kg body weight ampho B causes more toxicity, other effect and also at 0.5mg/kg body weight, more resistant cases are developed, so the safest and efficient dose of ampho B for the treatment of kala-azar is 0.75 mg/kg body weight, in alternate dose schedule in Darbhanga and its neighbouring areas. No resistant case has been found at this dose of ampho B for kala-azar. Results have been statistically analyzed. Thakur C.P et al (1999),[12] has reported that alternate day regimen and infusion of ampho B over an extended period leads to reduction in the incidence of nephrotoxicity in patients of VL.

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