American Journal of Virology 2 (1): 20-24, 2013
ISSN: 1949-0097

doi:10.3844/ajvsp.2013.20.24 Published Online 2 (1) 2013 (http://www.thescipub.com/ajv.toc)

Adverse Effects of Amphotericin B in Patients of Visceral Leishmaniasis: A Short Survey at Research Hospital Patna

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Received 2013-06-20, Revised 2013-07-14; Accepted 2013-07-20

ABSTRACT

Leishmaniasis is a disease caused by *Leishmania* parasite. *Leishmania* currently affects 12 million people in 98 countries, with an annual incidence of approximately two million new cases. Leishmaniasis is a devastating disease impairing economic productivity and impeding socioeconomic development. The objective of this article was to study the adverse effects of amphotericin B in patients of visceral leishmaniasis which was carried out at Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), Patna, India. The numbers of patients included were 19. Subjects of age groups 10-30 years (73.68%) were found to be more susceptible to visceral leishmaniasis. In this short survey we observed that the common adverse effects of amphotericin B among these patients were loss of appetite and nephrotoxicity.

Keywords: Visceral Leishmaniasis, Amphotericin B, Adverse Effects

1. INTRODUCTION

Leishmaniasis is a group of diseases caused by trypanosomatids from the genus Lieshmania (Freitas-Junior *et al*., 2012).

Leishmaniasis is caused by unicellular obligatory intracellular protozoa of the genus *Leishmania* and primarily affects the host's reticuloendothelial system (Longo *et al*., 2011). The disease affects 12 million people in 98 countries most commonly South Asia, Sudan, America, North and East Africa, Ethiopia, Kenya. In India, it is estimated that 2 lakh new cases occur annually, of which 90% are in Bihar. Other states are Eastern Uttar Pradesh, West Bengal, Assam and Tamil Nadu. In north Bihar it is a serious problem. The rise of Leishmaniasis is due to multiple factors including the AIDS epidemic, increase of international travel, lack of effective vaccines, difficulties in controlling vectors, international conflicts and the development of resistance to chemotherapy (Gupta and Nishi, 2011).

Leishmania donovani is the most common species of *Leishmania* responsible for the disease in humans and the most common vector is *Phlebotomus argentipes*. The transmission may be of two types-anthroponotic (the vector transmits the infections from infected human to healthy human) or zoonotic (the vector transmits the infections from an animal reservoir to humans). Leishmaniasis is of three types-cutaneous leishmaniasis caused by *L. major*, *L.tropica*, visceral leishmaniasis caused by *L. Donovani* and mucocutaneous leishmaniasis caused by *L. Brazilensis*. Visceral leishmaniasis is also known as "Kala-Azar". Symptoms of cutaneous leishmaniasis are difficulty in breathing, skin sores, nose bleeding, difficulty in swallowing.

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Symptoms of visceral leishmaniasis (kala-azar) are fever (moderate to high), the spleen may be palpable by the second week of illness and, depending on the duration of illness, may become hugely enlarged[2], hepatomegaly, fatigue, weakness, loss of appetite, scaly grey dark skin. Secondary infections such as measles, pneumonia and tuberculosis are common. The drugs used in the treatment of leishmaniasis are sodium stibogluconate, amphotericin B, pentamidin, miltefosine, paromomycin. Amphotericin B is a macrolide polyene antifungal antibiotic obtained from a bacterium *Streptomyces nodosus* (Monzote, 2009). Amphotericin B in the form of amphotericin B deoxycholate (Fungizone) is the drug of choice for visceral leishmaniasis when antimonial therapy fails. In Bihar, the commonly used drug for the treatment of leishmaniasis is amphotericin B. The serious adverse reactions associated with amphotericin B are fever with chills, severe hypokalemia, nephrotoxicity. Nephrotoxicity is the most common side-effect of Amphotericin B. Therapeutic doses of Amphotericin B deoxycholate of 0.5 to 1 mg kg^{-1} by endovenous bolus daily for 20 days can be administered or alternate days and with a total dosage between 1.5 to 2.0 g (Monzote, 2009). Some recent research has examined new medications for the treatment of leishmaniasis. Wang studied the use of arylimidamides, DB 745 and DB 746, as the potential oral treatment for *L. donovani*. Axenic amastigote and intracellular leishmaniasis (Clem, 2010). It was also noted that pyrazinamide produced collateral immunostimulation and may be a potential antileishmanial therapy (Mendez *et al*., 2009).

2. MATERIALS AND METHODS

2.1. Study Design and Setting

The survey was conducted at Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), Patna, India which is a branch institute of Indian Council of Medical Research (ICMR), New Delhi, India. This was a prospective study including case series analysis of patients with visceral leishmaniasis. The survey was conducted for a given period of time (November 2012 to March 2013) at RMRIMS. During clinical ward rounds various procedures were being followed such as patient counseling, assessment of laboratory reports, medication therapy and discussion with the doctors.

2.2. Patient Counseling

The study group consisted of patients admitted in RMRIMS, Patna. The age group of patients were 10 to 20, 20 to 30 and 45 to 55 years. Both male and female patients were included in the survey. During the survey we counsel the patient. During the counseling we observed that most of the patient has past history of tuberculosis or any other infectious disease. Some patients were co-infected with HIV.

2.3. Laboratory Data Reports

During the survey, the various pathological reports were being observed and recorded for haematological profile, kidney and liver function test and electrolyte imbalance. The data were collected from patient case records, which include clinical laboratory test forms and pathological report forms.

2.4. Medication

During the survey we observed that initially, most of the patients were prescribed similar medications such as Vitamin ac tablet (once daily), Ribozyme syrup (1 tablespoon twice daily) and OTC drugs (paracetamol). Along with these medications, intravenous infusion of Fungizone (Amphotericin B) 1 mg kg^{-1} in 5% dextrose alternate days for 15 days were also prescribed to all the patients diagnosed with visceral leishmaniasis. Oral Rehydration Solution (ORS) was prescribed to some patients who were suffering from loose motion. For dry cough, Gemifloxacin and Telekast (monteleukast) were prescribed. For gastric acidity, Omez capsule (omeprazole) was prescribed.

2.5. Discussion with the Doctors

During the survey, we discussed with the doctors regarding the common adverse effects of amphotericin B, their drug interactions with the other prescribed drugs and their administration profile.

2.6. Statistical Analysis

The data collected during the survey were evaluated for demography and common adverse effects of amphotericin B. The data considered were age and gender based. Both clinical and pathological profiles were evaluated. For putting results in its significant range various statistics were being performed. The data were presented as percentage (%) for categorical variables. The variable considered were age group,

gender, serum creatinine for kidney, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT) for liver and total WBC, eosinophil count and haemoglobin for haematological profile respectively.

3. RESULTS

The data collected during the survey were evaluated for demography and common adverse effects of amphotericin B in patients of visceral lieshmaniasis. During the survey period 19 patients were lodged, among them 15 were male and 4 were female. Among males, 6 were from age group of 10-20 years, 4 were from age group of 20-30 years and 5 were from age group of 45-55 years. Among females, all 4 were from the age group of 20-30 years. Out of 15 male patients, 5 were with increased SGOT and increased eosinophil level, 6 were with decreased WBC, 11 were with decreased haemoglobin, 4 were with increased serum creatinine, 2 were with increased SGPT and 2 were with decreased RBC. Out of 4 female patients, 3 were with decreased RBC, 1 was with decreased WBC, 1 was with increased eosinophil and serum creatinine, respectively and all 4 were with decreased haemoglobin.

The various parameters during the survey were found to be as follows:

3.1. Demography

AGE

The patients were divided into three groups ranging from >10 to <55 years. On the basis of the survey, visceral leishmaniasis was found to be more prevalent in the age group of 10-30 and it was found to be 73.68%. The age-wise distribution of patients with visceral leishmaniasis is summarized in **Fig. 1**.

GENDER

Gender-wise distribution is summarized in **Fig. 2**. During the survey, visceral leishmaniasis was found to be more prevalent in male:

- Total no. Of patients = 19
- % of patients male = 78.94%
- % of patients female = 21.05%

3.2. Abnormal Laboratory Findings Associated with Amphotericin B Infusion

A total of 19 patients with visceral leishmniasis were evaluated for the abnormal laboratory findings.

It was found that the SGOT and SGPT levels were increased in males, total RBC was decreased more in females than males and haemoglobin was decreased in both male and female. The abnormal laboratory findings are summarized in **Table 1**.

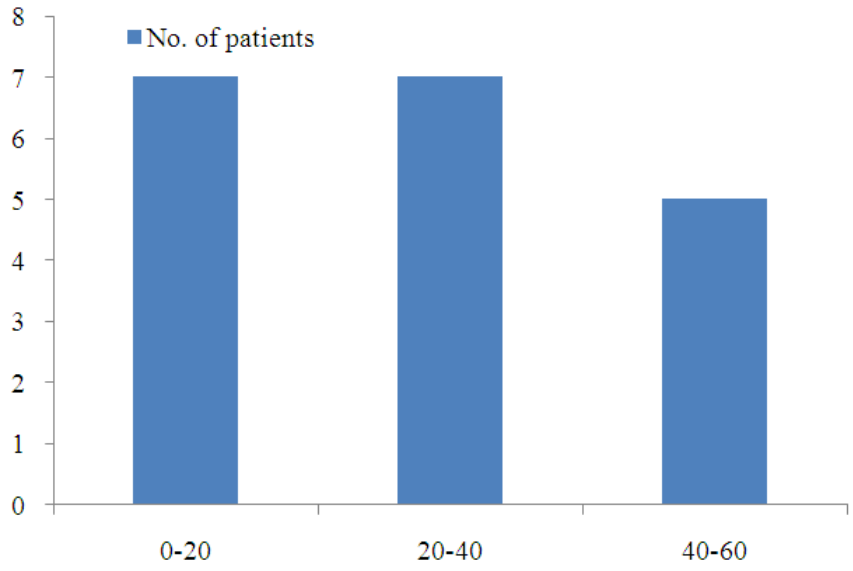

Fig. 1. Age-wise distribution of patients

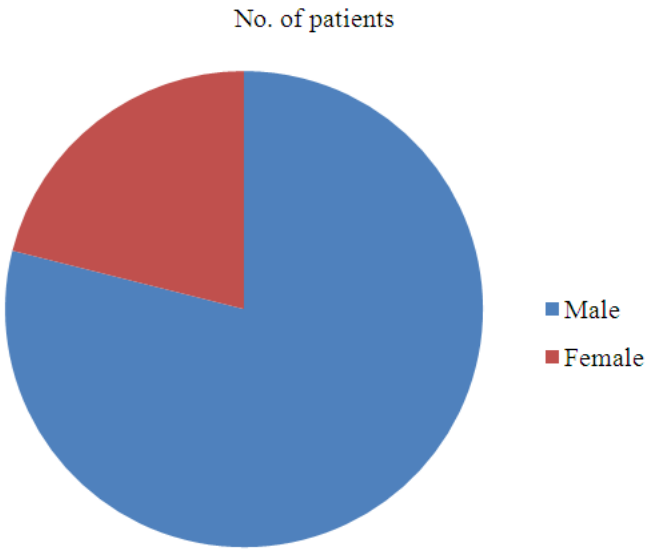

Fig. 2. Gender-wise distribution of patients

Table 1. Abnormal laboratory clinical reports

Abnormal Findings	Male n = 15 (78.94%)	Female n = 4 (21.05%)	Overall n = 19 (%)
SGOT (increase)	5 (33.33%)	0	5 (26.31%)
SGPT (increase)	2 (13.33%)	0	2 (10.52%)
Total RBC (decrease)	2 (13.33%)	3 (75%)	5 (26.31%)
Total WBC (decrease)	6 (40%)	1 (25%)	7 (36.84%)
Eosinophil (increase)	5 (33.33%)	1 (25%)	6 (31.57%)
Serum creatinine (increase)	4 (26.66%)	1 (25%)	5 (26.31%)
Heamoglobin (decrease)	11 (73.33%)	4 (100%)	14 (73.68%)

4. DISCUSSION

In India, amphotericin B is a key agent in the management of visceral leishmaniasis (kala-azar). The mechanism of action of amphotericin B is based on the binding of hydrophobic moiety of the amphotericin B molecule to the fungal cell membrane ergosterol moiety, producing an aggregate that forms transmembrane channels. These defects cause depolarization of the membrane and an increase in membrane permeability to protons and monovalent cations allowing leakage of intracellular components. Amphotericin B is fungistatic or fungicidal depending on the concentration obtained in body fluids and the susceptibility of the fungus.

Principle acute adverse effects of amphotericin B are nausea, vomiting, rigors, fever and hypoxia. Continuous infusion of amphotericin B deoxycholate causes neutropenic fever. Loss of apetite is mainly due to raised levels of SGOT and SGPT. Another serious chronic adverse effect of amphotericin B is azotemia. Azotemia was defined as an increase in serum creatinine to 2.5 mg dL^{-1} (Falci *et al*., 2010). Decreased renal blood flow and increased tubular membrane permeability are believed to be the causes of amphotericin B deoxycholate nephrotoxicity (Falci *et al*., 2010). Anemia is a very common adverse effect of amphotericin B and is due to suppression of erythropoietin production by amphotericin B. New drug delivery systems such as nanospheres and microspheres can result in higher concentrations of amphotericin B in the liver and spleen and lower concentrations in kidney and lungs, decreasing its toxicity.

Such adverse reactions (e.g., renal insufficiency, hypokalemia and/or decreased haemoglobin level) were typically associated with lengthy administration of amphotericin B deoxycholate. During the survey it was observed that, haemoglobin level were found to be

decreased in 73.68% of patients, increased serum creatinine in 26.31% of patients, increased SGOT in 26.31% of patients, decreased total WBC in 36.84% of patients and increased eosinophil in 31.57% of patients. It was observed that, some common adverse effects associated with the use of amphotericin B such as loss of appetite, fever, anemia, cough with expectoration and nephrotoxicity were due to alteration in these above mentioned variables. The present study observed that, in most of the patients these variables were altered after 7th infusion of amphotericin B deoxycholate.

5. CONCLUSION

In India (Bihar), the drug of choice for visceral leishmaniasis (kala-azar) is amphotericin B deoxycholate. During the survey it was found that the common adverse effects of amphoteircin B are fever, loss of appetite, anemia, nephrotoxicity and sometimes cough. In our study it was found that these above mentioned adverse effects are due to alteration in haemoglobin level, serum creatinine, total WBC, eosinophil and SGOT levels respectively. From the study, it can be concluded that the above mentioned adverse reactions in patients of visceral leishmaniasis were due to lengthy administration of amphotericin B deoxycholate.

6. ACKNOWLEDGEMENT

The researchers acknowledge the help and support of Doctors and other staff members at Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), Patna, India.

6.1. Conflict of Interest

The author has no conflicts of interest to disclose. This project was not funded.

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