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Immediate hypersensitivity reaction following liposomal amphotericin-B (AmBisome) infusion

Progganda Nath[1], Ariful Basher[2], Michiyo Harada[3], Santana Sarkar[4], Shahjada Selim[5], Richard J Maude[6,7], Eisei Noiri[8] and Abul Faiz[9]

Abstract

Liposomal amphotericin-B (AmBisome) is now becoming first choice for the treatment of visceral leishmaniasis (kala-azar) patients due to high efficacy and less toxicity. The reported incidence of hypersensitivity reactions to liposomal amphotericin-B (AmBisome), especially during therapy, is very rare. We report two patients with kala-azar: one developed breathing difficulties and hypotension followed by shock and the other had facial angioedema with chest tightness during treatment. Both patients were managed with immediate action of injection: adrenaline, diphenhydramine and hydrocortisone. In our experience, AmBisome can cause severe hypersensitivity reactions that warrant proper support and close supervision.

Keywords

Leishmaniasis, AmBisome

Introduction

Kala-azar is one of the major public health problems in Bangladesh and affects largely the socially marginalised community. The current Bangladesh National Guideline for Kala-azar Management (2013), recommends liposomal amphotericin (AmBisome) as first-line treatment[1] and it is likely that AmBisome may shortly become the mainstay of treatment, either used alone or in combination with miltefosine or paromomycin, for all patients worldwide.[2] Fever and chills are common infusion-related reactions during treatment with AmBisome and cardiopulmonary events, including chest pain, dyspnoea, flushing and hypotension, occur less frequently.[3] Here we describe two cases who experienced potentially life-threatening sequelae during AmBisome infusion and discuss possible strategies for preventing such events.

Case report 1

A 43-year-old man was referred to the Surya Kanta Kala-azar Research Centre (SKKRC), Mymensingh, Bangladesh with prolonged fever, anorexia and progressive weight loss. He was moderately anaemic with an enlarged spleen of 7 cm below the costal margin. Kala-azar was confirmed by positive Rk-39 test and 3+ LD bodies on splenic aspirate. He was administered intravenous AmBisome infusion at a dose of 5 mg/kg daily for 3 days. His initial blood pressure was 130/90 mmHg, with pulse 90/min and respiratory rate 20/min. The test dose of 1 mg of AmBisome in 500 mL 5% dextrose and subsequent first treatment dose were infused uneventfully over 4 h. During the second treatment dose, 10 min after commencing the infusion, the patient suddenly

[1]Medical Officer, Surya Kanta Kala-azar Research Centre, Mymensingh Medical College Hospital, Bangladesh
[2]Registrar & Incharge, Department of Infectious and Tropical Diseases, Mymensingh Medical College Hospital, Bangladesh
[3]Research Fellow, Department of Hemodialysis & Apheresis, The University of Tokyo Hospital, Japan
[4]Medical Officer, Surya Kanta Kala-azar Research Centre, Mymensingh Medical College Hospital, Bangladesh
[5]Registrar, Department of Medicine, Shaheed Suhrawardy Medical College Hospital, Bangladesh
[6]Senior Clinical Research Fellow, Mahidol-Oxford Tropical Medicine Research Unit, Thailand
[7]Senior Clinical Research Fellow and Honorary Consultant Physician, Centre for Tropical Medicine, Nuffield Department of Medicine, University of Oxford, UK
[8]Associate Professor, Department of Hemodialysis & Apheresis, The University of Tokyo Hospital, Japan
[9]Professor and Director General of Health Services (Retired), Bangladesh

Corresponding author:
Ariful Basher, Infectious and Tropical Diseases Department, Mymensingh Medical College Hospital, Mymensingh, Bangladesh.
Email: arifulbasher@yahoo.com

became restless, developed shortness of breath with clear lungs, a rapid fall in blood pressure to 60/20 mmHg and tachycardia.. The AmBisome was stopped immediately and the patient given 0.5 mL intramuscular adrenaline with intravenous diphenhydramine and hydrocortisone. The patient's symptoms gradually resolved over the following 20 min. The rest of the AmBisome dose was discarded and administration of another dose was attempted on the succeeding day following prophylaxis with diphenhydramine (10 mg) and hydrocortisone (100 mg). The patient developed a similar reaction to the previous day. His leishmaniasis was then successfully treated with oral miltefosine over 28 days.

Case report 2

An 11-year-old girl was admitted to SKKRC in June 2013 with a 3-month history of fever, anorexia and weight loss. On admission, she was pyrexial with a temperature of 38°C. Her spleen was palpable at 4 cm below the costal margin. Investigations revealed anaemia with haemoglobin of 4.8 g/dl. The diagnosis of kala-azar was confirmed by the finding of positive LD bodies in a splenic aspirate. She had no history of allergic reaction to any drug. Three units of whole blood were transfused and her haemoglobin increased to 7.8 g/dl. The patient's initial blood pressure was low at 90/70 mmHg with heart rate 90/min and respiratory rate 20/min. Treatment was commenced with intravenous AmBisome. During the test dose; she experienced chills and rigors, facial flushing, puffiness, chest tightness and respiratory distress. The patient was quickly managed with intravenous antihistamine and hydrocortisone.

Discussion

Amphotericin B is available as the plain drug, a cholesteryl sulfate complex, a lipid complex and as a liposomal preparation. The latter three formulations were developed to improve tolerability for the patient.[2] The immune effects of liposomal carrying agents (therapeutic liposomes) have not been well studied despite an interaction of phospholipid bilayers with the immune system having been described.[3,4] Patients who experience hypersensitivity reactions to liposomal amphotericin have usually not received it previously and thus could not have been sensitised to it. This suggests that mechanisms other than a type I hypersensitivity reaction are involved in these cases.[4,5] Liposomes and lipid excipient-based drugs are generally recognised by the immune system as foreign, resulting in a variety of adverse immune phenomena. One of them is complement activation, the cause, or major contributing factor to, a hypersensitivity syndrome.[6] Some authors postulate that the lipid component, and not AmBisome itself, is responsible for causing these reactions.[3] It is suggested that AmBisome causes massive complement activation in normal human serum.[6] Few studies have examined the efficacy of strategies to reduce the risk of severe adverse reactions to AmBisome.[8] The effects on a patient's tolerance to AmBisome of treatment with progressively increasing doses, reduction of the infusion rate and use of premedication to minimize the risk of severe adverse reactions are not clear. The first patient described above, who tolerated the first dose of AmBisome, developed a serious allergic reaction during the second and third doses.

The occurrence of allergic reactions to AmBisome during treatment of kala-azar warrants close supervision of patients, particularly since AmBisome is currently first-line treatment for visceral leishmaniasis in endemic areas. However, in many patients these reactions seem to be related to complement production on first exposure to the drug, rather than on second exposure as for type 1 hypersensitivity, and therefore the routine use of an initial test dose might not be necessary. AmBisome should be administered under close observation. The use of prophylactic premedication requires further study and should be considered. The optimal means of administration should be clarified to allow the safe continuation of treatment with this essential drug.

Declaration of conflicting interests

None declared.

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