

Drug Induced Anaphylactic Reaction and Electrolyte Imbalance by Amphotericin B Emulsion: A Case Report

Comment [AF1]: Suggest removing.

ABSTRACT

Amphotericin B, a polyene antifungal antibiotic derived from a strain of *Streptomyces nodosus*. It acts by binding to sterols in the cell membrane of susceptible fungi, with a resultant change in the permeability of the membrane. Amphotericin B can cause allergic reactions, electrolyte imbalance and severe side effects, such as chest discomfort accompanied by dyspnea, flushing, agitation, tachypnea, tachycardia, hypoxemia, hypotension, or hypertension, are likely to develop following the injection of amphotericin B. Anaphylaxis, cardiac toxicity and respiratory failure have also been associated to different formulations of amphotericin B as life-threatening acute events. This case report is on a 57-year-old male patient who was admitted with a condition of left diabetic foot with non-healing medial supra heel ulcer and fungal infection on the site of wound. The patient was given amphotericin B in emulsion form due to the high priority of fungal infection and the need for antifungal medicine, which led to anaphylactic reaction and electrolyte imbalance, which were treated immediately and the same preparation was continued with a low infusion rate. When the infusion is discontinued, antihistamines can assist to alleviate the symptoms. In this case, it is recommended that the patient's condition and clinical parameters should be closely followed after the medicine has been administered.

Comment [AF2]: Perform correction.

Keywords: Amphotericin , Antifungal, Electrolyte Imbalance, Hypersensitivity

Comment [AF3]: Use words that are not part of the manuscript title.

1. INTRODUCTION

Amphotericin B is a polyene macrolide antibiotic produced from *Streptomyces nodosus*, a type of actinomycete. Of the 200 known polyene agents, amphotericin B is the only one with toxicities that are sufficiently limited to permit intravenous administration [1]. Amphotericin B is one of the oldest, yet most efficient antimycotic agents. However, its usefulness is limited due to dose-dependent side-effects, notably nephrotoxicity [2]. Newer formulations of amphotericin B (AmB) complexed with liposomes or lipid emulsions have been developed. AmB in Intralipid (IL) has been shown in preliminary studies to be as effective as conventional AmB formulations while being less toxic, but there are few data on its stability, compatibility, or in vitro antifungal activity [3]. Amphotericin B has a broad spectrum and has remained the drug of choice for life-threatening invasive fungal infections[4]. The mechanism of action of the binding of the AmB molecule to the ergosterol in the fungal cell membrane, forming an aggregation that generates a transmembrane channel, enabling cytoplasmic contents to flow out, resulting in cell death[5]. It causes oxidative stress in the cells. Moreover, amphotericin B modulates the immune system,

Comment [AF4]: Reduce paragraphs size.

Comment [AF5]: I suggest replacing the "." per ","

Comment [AF6]: Perform correction.

Comment [AF7]: I suggest this is a new paragraph.

Comment [AF8]: I suggest replacing the "." per ","

and this activity has been related to the protective effect of the molecule, but also to its toxicity in the host[6]. Antifungal treatment with amphotericin B is the gold standard for the most severe mycoses. However, side effects are widespread, with nephrotoxicity being the most dangerous, appearing early in treatment and usually reversible in the majority of individuals. Acute renal failure is the most significant complication of amphotericin B therapy. Tubular damage is a well-known concern related with the drug[7]. Male gender, greater average daily dose of AmB (35 mg/day), diuretic use, body weight 90 kg, simultaneous use of nephrotoxic medications, and impaired baseline renal function are all risk factors for AmB nephrotoxicity.

Comment [AF9]: I suggest this is a new paragraph.

Severe adverse reactions such as chest discomfort accompanied by dyspnea, flushing, agitation, tachypnea, tachycardia, hypoxemia, hypotension, or hypertension likely to occur after the administration of amphotericin B[8]. Currently, three lipid liposomal amphotericin B (AmBisome, NeXstar Pharmaceuticals/Fujisawa, San Dimas, CA), amphotericin B colloidal dispersion (ABCD, Amphocil, Sequus Pharmaceuticals, Menlo Park, CA), and amphotericin B lipid complex are commercially available formulations (ABLC, Abelcet, Liposome Company, Princeton, NJ). Although these novel formulations are safer than the parent medicine amphotericin B deoxycholate, they are quite expensive, and data on their enhanced efficacy in treating systemic fungal infections is still lacking[9]. Other reported life-threatening acute reactions associated with the different formulations of B are anaphylaxis, cardiac toxicity, respiratory failure and electrolyte imbalance[10]. The antihistamines can help to relieve the symptoms that occur quickly after the infusion is stopped. In this case, anaphylactic reactions and electrolyte imbalance were induced by the drug and which is corrected immediately and resumed with the same preparation with a slow infusion rate. Here report a clinical observation of amphotericin B induced anaphylactic reaction and electrolyte imbalance.

Comment [AF10]: Perform correction.

Comment [AF11]: case report

2. CASE PRESENTATION

A 57-year-old male patient was admitted with a condition of sustained accidental burning wood had fallen on his left foot about a month ago and developed a bleb in the area that he had poked with a safety pin, he had been working in a farm, and subsequently developed an infection and was taken to a local hospital. Tab. linezolid and Tab. Clindamycin was given and debridement was performed. On 06/09/2021, the patient was transferred here with a swelling and blackish discoloration after being treated at another hospital with injections of piperacillin and tazobactam and injection metronidazole. His medical history revealed that he had Type 2 diabetes for the previous 15 years, had diabetic foot care, and had recently been diagnosed with systemic hypertension. On local examination, a 4x3cm non-healing lesion was discovered, and an x-ray of the left foot was performed. On 7th September 21, the left foot was debrided once more. A high risk of fungal infection exists, as well as the possibility of a fungal infection. On the left medial supra heel region, fungal-like elements were seen on the surface of the wound. Despite the fact that the culture report of the tissue specimen revealed no fungal elements, injections of amphotericin B were started after consultation with the hospital's clinical pharmacist.

Comment [AF12]: Repetition

Comment [AF13]: Was there any photographic record of this observation that could be added to the study to support this statement and the indication for the use of amphotericin B, since the laboratory tests were negative?

Comment [AF14]: Were other tests performed before starting treatment?

Comment [AF15]: Isn't this table 1?

Potassium level	Day 1	Day 2	Day 3	Day 4	Day 5

Serum K ⁺ [3.5-5.1mmol/L]	4.79	3.42	4.29	4.29	4.44
--------------------------------------	------	------	------	------	------

On 07/09/21 (day 1) ,administered 200mg of amphotericin B in 250 ml of 5% dextrose and infused for 3-4 hours (60mg/h).On the next day, drug-induced hypokalemia was discovered, with the patient's serum K⁺ level dropping from 4.79mmol to 3.42 mmol/L (3.5-5.1mmol/L), which was conservatively controlled with inj.KCL (Potassium chloride) 20mmol and syrup KCL 10ml, TDS. On the 3rd day, the serum K⁺ level returned to normal, at 4.29 mmol/L, and remained stable.

Comment [AF16]: Or B?

Despite the fact that his clinical condition did not improve, his non-healing foot persisted, and his condition worsened, left above the knee was amputated on 09/09/21. As surgical prophylaxis inj. piperacillin tazobactam 4.5 g IV was given and empirically continued for 5 more days. On 10/09/21 (4th day), the same doses of inj.amphotericin B was given, infused over 3-5 hours (70mg/hr) and the next day (5th day), the same dose was given, but the patient developed anaphylactic reactions, including breathing difficulties, shivering, and a fever spike of 100.8°F, which lasted 30 minutes. Inj. hydrocortisone 100mg IV Stat and inj. paracetamol 1g, as well as nebulization with Budesonide, has been given and managed conservatively. On the same day, catheterized urine was sent for a fungal stain, but no fungal materials were found. On September 12 and 13 (6th and 7th day) inj. amphotericin B 200mg mixed with 250ml of 5% dextrose was given infusions over 3-4 hours (50mg/hr). The patient was stable, and he was checked on every hour.

Comment [AF17]: Previously, the exam was negative for fungi, again the exam was negative for fungi; what is the basis for the continued use of amphotericin B?

Table 1: The laboratory examination revealed abnormalities:

Parameters	Observed value	Normal value
C-reactive protein	27.78 mg/L	Upto 5.0mg/L
WBC	15100 cells/mm ³	4000-10000 cells/mm ³
Platelets	438000 cells/mm ³	150000-410000 cells/mm ³
Eosinophils	7.0%	1-6%
Basophils	0.4%	1-2%
Lymphocytes	16%	20-40%
HCT	21.1%	40-50%
Hb	6.9g/dl	13-17g/dl
Total RBC	2.45mil/mm ³	4.5-5.50mil/mm ³
Serum alkaline phosphatase	186.6 U/L	30-120U/L
Serum GGT	158 U/L	11-50U/L
Serum protein	5.50g/dl	6-8g/dl
S.Albumin,	2.66g/dl	3.5-5.0g/dl
Blood urea	46.79 mg/dl	10-40mg/dl
S .creatinine	2.30mg/dl	0.5-1.2mg/d

Comment [AF18]: ??

In the nephrologist's opinion, the patient was having nonoliguric AKI, From the ophthalmologist's opinion required to roll out diabetic retinopathy. The patient got symptomatically better and was discharged with advised to monitor their blood glucose periodically and advised to do OCT scan. On the Naranjo's causality assessment scale the adverse event was 4 indicating a possible reaction to Amphotericin B.

Comment [AF19]: Confusing and meaningless phrase.

Comment [AF20]: Optical Coherence Tomography?

3. DISCUSSION

Amphotericin B, antifungal activity is based on its hydrophobic moiety binding to the ergosterol moiety of the fungal cell membrane, causing depolarization of the membrane and influx of protons and monovalent cations by increasing membrane permeability, destroying activity and allowing the cytoplasmic contents to leak out, resulting in cell death [11] [14]. Treatment of fungal infection in diabetic patients may be complicated due to the various disease-related changes to the pharmacokinetics and pharmacodynamics (PK/PD) of a drug [12]. As a result, in individuals who are resistant to long-term antibiotic therapy, fungal pathogens should be investigated. In high-risk people, early identification of fungal infections is crucial for avoiding serious outcomes such as amputation of the foot [13]. Hyperkalemia, hypokalemia, hypocalcemia, hyperphosphatemia, hypophosphatemia, hypomagnesemia are some electrolyte imbalances induced by Amphotericin B. In this patient, after the wound debridement on the left ankle region, fungal like elements seen on the surface of wound, even the fungal stain culture report shows no growth, based on clinical experience of the physician, high probability of fungal infection, antifungal medication, inj. amphotericin B have been started. Later developed hypokalemia induced by inj. amphotericin B, which then managed conservatively with inj. KCL (Potassium chloride) 20mmol and syrup KCL 10ml, TDS. Apparently the condition was not improving they have done left knee amputation and resumed the antifungal treatment with amphotericin B without dose alteration. Later, breathing difficulty, shivering, and fever were induced by inj. amphotericin B emulsion, which lasted for 30 minutes, and oxygen ventilation for breathing was provided immediately, as well as inj. hydrocortisone, inj. paracetamol, and budecort nebulisation. After lowering the infusion rate, the adverse effects were corrected, patient became comfortable, and a febrile. The same preparation was resumed for 2 more days with the slow infusion rate. This case study demonstrates the importance of meticulously planning patient care prior to, during, and after the injection of amphotericin B emulsion.

Clinical parameters should be monitored regularly, if any abnormalities have been found should be corrected immediately with appropriate treatment. Hyperkalemia, hypokalemia, hypocalcemia, hyperphosphatemia, hypophosphatemia, hypomagnesemia are some electrolyte imbalances induced by Amphotericin B.

4. CONCLUSIONS

In this scenario, it is suggested that after the drug administration, the patient's state and clinical parameters should be carefully monitored. Deep tissue infections could also be caused by invasive fungal infections. As a result, in individuals who are resistant to long-term antibiotic therapy, fungal pathogens should be investigated. Early identification of fungal infections in high-risk persons is crucial for avoiding serious outcomes like amputation of the foot.

CONSENT

The patient's informed consent was obtained before the case facts were published.

Comment [AF21]: Is there no other study in the literature that reports the occurrence of anaphylactic reactions in patients after using amphotericin B? If there is, I suggest that it be mentioned during the discussion.

Comment [AF22]: Another paragraph.

Comment [AF23]: L

Comment [AF24]: Is this repeated again? I believe it can be removed, as it was already reported at the beginning of the discussion.

Comment [AF25]: I suggest a reassessment of the conclusion, as the study did not present any data proving fungal infection and the title of the study is aimed at the occurrence of anaphylactic reaction to amphotericin B.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author.

REFERENCE

1. Ellis D. Amphotericin B: spectrum and resistance. *Journal of Antimicrobial Chemotherapy*. 2002 Jan1;49(suppl_1):7-10.
2. Lemke A, Kiderlen AF, Kayser O. Amphotericin b. *Applied microbiology and biotechnology*. 2005Aug;68(2):151-62.
3. Walker S, Tailor SA, Lee M, Louie L, Louie M, Simor AE. Amphotericin B in lipid emulsion: stability, compatibility, and in vitro antifungal activity. *Antimicrob Agents Chemother*. 1998 Apr;42(4):762-6. doi: 10.1128/AAC.42.4.762. PMID: 9559779; PMCID:PMC105538
4. Dupont B. Overview of the lipid formulations of amphotericin B. *Journal of Antimicrobial Chemotherapy*. 2002 Jan1;49(suppl_1):31-6.
5. Laniado-Laborín R, Cabrales-Vargas MN. Amphotericin B: side effects and toxicity. *Revista iberoamericana de micología*. 2009 Oct1;26(4):223-7.
6. Mesa-Arango AC, Scorzoni L, Zaragoza O. It only takes one to do many jobs: Amphotericin B as antifungal and immunomodulatory drug. *Frontiers in microbiology*. 2012 Aug 8;3:286.
7. Fanos V, Cataldi L. Amphotericin B-induced nephrotoxicity: a review. *Journal of chemotherapy*. 2000 Jan1;12(6):463-70.
8. Roden MM, Nelson LD, Knudsen TA, Jarosinski PF, Starling JM, Shiflett SE, Calis K, DeChristoforo R, Donowitz GR, Buell D, Walsh TJ. Triad of acute infusion-related reactions associated with liposomal amphotericin B: analysis of clinical and epidemiological characteristics. *Clinical infectious diseases*. 2003 May 15;36(10):1213-20.
9. Hiemenz JW, Walsh TJ. Lipid formulations of amphotericin B: recent progress and future directions. *Clinical infectious diseases*. 1996 May 1;22(Supplement_2):S133-44.
10. Bishara J, Weinberger M, Lin AY, Pitlik S. Amphotericin B—not so terrible. *Annals of Pharmacotherapy*. 2001 Mar;35(3):308-10.
11. Philip JM, Vijayan M. Liposomal Amphotericin B Induced Pancytopenia-A Rare Case Report. *Journal of Pharmaceutical Sciences and Research*. 2017 Jun 1;9(6):867.
12. Mohd Sazly Lim S, Sinnollareddy M, Sime FB. Challenges in antifungal therapy in diabetes mellitus.
13. Ozturk AM, Taşbakan M, Metin DY, Yener C, Uysal S, ŞİMŞİR İY, Ertam İL, Pullukçu HÜ, Arda B, Çetinkalp ŞE. A neglected causative agent in diabetic foot infection: a retrospective evaluation of 13 patients with fungal etiology. *Turkish journal of medical sciences*. 2019 Feb 1;49(1):81-6.
14. Vivekanandan Lalitha, Sheik Hajasherief, Singaravel Sengottuvelu, Thangavel Sivakumar, "Assessment of Efficacy and Safety of Clindamycin Against Methicillin-Resistant

Staphylococcus aureus (MRSA) Infected Subcutaneous Abscess Model", *Anti-Infective Agents* 2020; 18(2) .

UNDER PEER REVIEW