e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(2); 1157-1161

Original Research Article

Adverse Drug Reaction Profile of Liposomal Amphotericin B Used For Postcovid Mucormycosis in a Tertiary Care Hospital - A Prospective, Observational Study

VishnuPriya R[1*], Ramachandra Bhat C[2], Sudha K M[3], Abiramasundari[4], Sharon Snehaa Jeyakumar[5], Devipriya[6]

[1]Department of Pharmacology, Government Medical College Krishnagiri, Krishnagiri-115
[2,3,4,5,6]Institute of Pharmacology, Madras Medical College, Chennai-3

Received: 25-11-2023 / Revised: 23-12-2023 / Accepted: 26-01-2024
Corresponding Author: Dr. R. VishnuPriya
Conflict of interest: Nil

Abstract:

Liposomal Amphotericin B (LAMB) 3-5 mg/kg/day were the management of choice for Post covid Mucormycosis which caused various adverse drug reactions (ADR). Hence this study was undertaken to assess & classify ADRs in patients on LAMB used for Post covid Mucormycosis. This was a prospective, Observational study conducted in the Departments of ENT and Internal medicine, Madras Medical College between June 2021 to November 2021. All suspected ADRs were analyzed, classified & reported by pharmacologist to Regional Pharmacovigilance centre, Madras Medical College. Around 1118 patients of postcovid mucormycosis were present in the ward. Among them, 906(81%) were known diabetes mellitus patients who presented with Mucormycosis following Covid 19 infection. 447(40%) known Diabetes Mellitus(DM) patients with the history of Corticosteroid usage during covid 19 infection presented with Mucormycosis . Among them, 268 patients (24%) presented with one or more ADRs following the use of LAMB for mucormycosis. Following were the incidence of various ADRs- Infusion related reactions (28%), Anemia (64%), Hypokalemia (56%), Hyponatremia (63%), increased blood urea & serum creatinine levels (11%), Increased Alkaline Phosphate levels (28%) and Increased alanine transferase and aspartate transferase levels (11%). Causality was assessed using WHO-UMC causality assessment scale and 28% reports were assessed as certain and 72% reports were classified as possible. Preventability was assessed using Schumock and Thornton criteria and 28% ADRs were found to be definitely preventable and 72% ADRs were classified as not preventable. Severity was assessed by Modified Hartwig Siegel severity assessment scale and all the ADRs were found to be of moderate severity. This study would strengthen Pharmacovigilance monitoring and create awareness on importance of reporting by healthcare professionals.

Keywords: ADRs, LAMB, DM

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) caused Coronavirus disease 2019 (Covid-19) worldwide. Since the first case was detected in December 2019, there have been various turns and twists in terms of its pathophysiology, diagnosis, management, sequelae and complications [1]. Mucormycosis is an invasive fungal infection which seems to be on rise after 4-6 weeks of covid infection.

Critically ill patients, especially those admitted to intensive care unit and those who required mechanical ventilation, or who had a longer duration of hospital stays, even as long as 50 days, are more likely to develop Mucormycosis [2]. Extensive use of steroids in Covid-19 management can also suppress immunity, allowing opportunistic fungal infections to colonise [3]. The rate of incidence of mucormycosis varies from 0.005 to 1.7 per million populations globally [4]. Whereas, in Indian population its prevalence is 0.14 per 1000, which is about 80 times higher than developed countries [5]. The fatality rate of mucormycosis globally is 46% [6]. However, factors like intracranial or orbital involvement, irreversible immune suppression increases fatality to as high as 50% to 80% [7].

There was a sudden surge in the cases of mucormycosis after the second wave of Covid 19. Intravenous administration of amphotericin B remains the treatment of choice for invasive mucormycosis. Four formulations of Amphotericin B namely Conventional Amphotericin B, Amphotericin B colloidal dispersion, Liposomal Amphotericin B and Amphotericin B -Lipid complex are available for the management of

Mucormycosis. Patients on these formulations of Amphotericin B exhibit a spectrum of various adverse drug reactions ranging from infusion related reactions, gastro intestinal reactions, anemia, nephrotoxicity to hepatotoxicity [8]. Liposomal Amphotericin B (LAMB) is preferred over other formulations in our wards because of its better tolerability profile compared to other formulations.

However data regarding ADRs of LAMB seem to be limited. Hence the current study was undertaken to monitor, assess & classify the Adverse Drug Reactions (ADRs) in patients on Liposomal Amphotericin B for Post covid Mucormycosis.

Aim: To monitor, assess & classify the ADRs in patients on LAMB for Post Covid Mucormycosis

Objectives:

Primary Objective: To assess the frequency of ADRs in patients on LAMB for Post covid Mucormycosis

Secondary Objective: To evaluate & classify the ADRs based on Causality, Preventability & Severity scales to strengthen Pharmacovigilance monitoring and reporting.

Study Methodology:

Study Design: Prospective, Observational study

Study Centre: Institute of Pharmacology in collaboration with Institute of ENT & Institute of Internal Medicine, RGGGH, Chennai-3

Study Period: June 2021 to November 2021(6 months)

Sample Size: Consecutive cases

Study Population: In patients with Post Covid Mucormycosis in ENT ward & Internal medicine ward, RGGGH

Eligibility Criteria:

Inclusion Criteria:

1. Patients in all age groups diagnosed with Mucormycosis irrespective of their Diabetic status.
2. Patient must have tested RTPCR positive for COVID-19, 2-6 weeks prior to the study

Exclusion Criteria:

1. Patients with hepatic/ renal disease
2. Patients on immunosuppressive drugs like Steriods, Tacrolimus, Antiproliferative agents like Azathioprine
3. Patients on nephrotoxic drugs like aminoglycosides, Cyclosporin
4. Pregnant patients

Study Procedure:

Study was commenced after obtaining approval from Institutional Ethics Committee, Madras Medical College, Chennai and was conducted in accordance with Good Clinical Practice guidelines. Patients fulfilling the inclusion & exclusion criteria were included in the study.
Formulations used: Liposomal Amphotericin B -5 mg/kg/day. All suspected ADRs following the use of LAMB were initially assessed, managed & reported by ENT surgeon using the case record form (Attached in Annexure).

ADR details were reported to the Regional Pharmacovigilance centre; Madras Medical College in a format specified by Pharmacovigilance Program of India and the pharmacologist, then analyzed and classified the ADRs. Causality was assessed using WHO-UMC causality assessment scale [9]. Preventability was assessed using Schumock and Thornton criteria [10]. Severity of ADRs was assessed by Modified Hartwig Siegel severity assessment scale [11].

Statistical Analysis: Data obtained was analyzed by Descriptive statistics viz frequency.

Results:

Around 1118 patients of postcovid mucormycosis were present in the wards. Among them, 906(81%) were known diabetes mellitus patients who presented with Mucormycosis following Covid 19 infection. 447(40%) known Diabetes Mellitus(DM) patients with the history of Corticosteroid usage during covid 19 infection presented with Mucormycosis.
Among them, 268 patients (24%) presented with one or more ADRs following the use of LAMB for mucormycosis. (Fig 1)

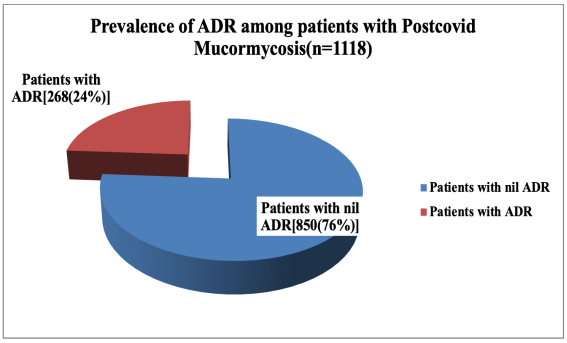

Fig 1: Prevalence of ADR among patients with Post covid Mucormycosis

With respect to the frequency of ADRs occurring in patients, around 172(64%) patients presented with Anemia. 170 patients (63%) presented with hyponatremia, 150 patients (56%), presented with hypokalemia. Infusion related reactions reported in 74 patients (28%), Increased Alkaline phosphatase levels noted in 74 patients (28%), Increased alanine transferase and aspartate transferase levels noted in 30 patients (11%) and increased blood urea & serum creatinine levels observed in 30 patients (11%).(Fig 2)

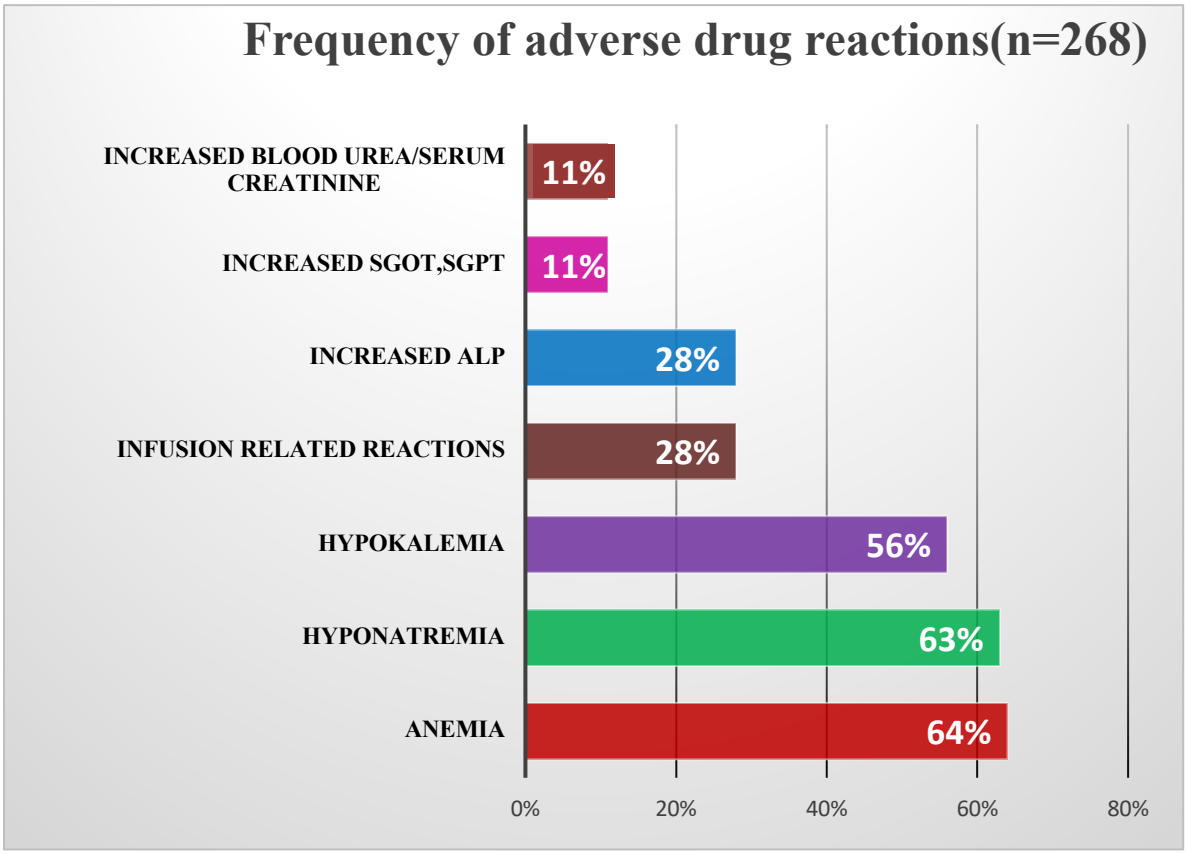

Fig 2: Frequency of Adverse Drug Reactions

Causality was assessed using WHO-UMC causality assessment scale and 28% reports were assessed as Certain and 72% reports were classified as possible. Preventability was assessed using Schumock and Thornton criteria and 28% ADRs were found to be definitely preventable and 72% ADRs were classified as not preventable. Severity was assessed by Modified Hartwig Siegel severity assessment scale and all the ADRs were found to be of moderate severity. (Table 1)

Table 1: Analysis of ADR

Parameter		**Number of ADRs (%)**
Causality	Certain	**74(28%)**
	Probable	Nil
	Possible	**194(72%)**
	Unassessable	Nil
	Unclassifiable	Nil
Severity	Mild	Nil
	Moderate	**268(100%)**
	Severe	Nil
Preventability	Definitely preventable	**74(28%)**
	Not preventable	**194(72%)**

Discussion:

81% of patients who presented with Mucormycosis following Covid 19 infection were known diabetes mellitus patients. This was due to the alteration in innate & cell mediated immunity, phagocyte dysfunction, reduction of natural killer activity and the presence of more pro-inflammatory M1 macrophages in diabetic patients, which predisposed to immunosuppressive state that lead to mucormycosis [12]. 40% of known Diabetes

Mellitus (DM) patients with the history of Corticosteroid usage during covid 19 infection presented with Mucormycosis in our study. Study by Ponniah et al concludes that the participants with Diabetes mellitus were five times more likely to have Mucormycosis and steroid use irrespective of cumulative dose was also significantly associated with mucormycosis [13]. Also it is substantiated that the occurrence of mucormycosis in patients using steroid is mediated through hyperglycemia and neutrophil/macrophage dysfunction [14].

Infusion related reactions (IRRs) are reported in 28% patients in our study. However in a study by Walsh et al, 21% of patients presented with infusion reactions, when LAMB was infused to 3622 patients [15]. Acute infusion related reactions usually occur alone or in combination with one of the three symptom complexes a) flushing and urticaria, b) severe flank, leg or abdominal pain c) dyspnoea, chest pain and hypoxia. The mechanism of these infusion related reactions are thought to be due to liposomal activation of complement cascade leading to release of anaphylotoxins(C3a and C5a) [16]. These IRRs were managed with cessation of LAMB infusion followed by the administration of Acetaminophen, Diphenhydramine and Hydrocortisone in our hospital. 64% of patients with ADR, reported with anaemia in our study. Rafael et al states that around 75% of patients treated with Amphotericin B presented with anaemia in their study and it is mainly because of the erythropoiesis suppression caused by the drug [17]. Hypokalemia occured in 56% of patients with ADR in our study. Renal injury due to Amphotericin B is attributed to renal vasoconstriction of afferent arteriole, specifically due to renal tubular injury which induces renal potassium wasting leading to hypokalemia. Hence potassium amd magnesium levels must be monitored regularly during LAMB therapy as depletion of these electrolytes can result in generalized weakness, ascending paralysis, neurological dysfunction and life threatening arrhythmias [18].

11% of patients in our study presented with increased serum creatinine levels. This could have been prevented with pre loading with Normal saline in patients on LAMB. A Study by Anderson CM states that initiation of intravenous infusion of 150 mEQ of sodium chloride as bolus or continuous infusion in low risk patients at least one day prior to AMB regimen prevents rise in serum creatinine levels but had no effect on development of tubular defects including diminished acidification, potassium wasting and decreased concentrating ability [19]. Renal toxicity is less with LAMB when compared to liver toxicity. This has been attributed to the preferential distribution of LAMB to the liver and spleen as compared to the renal tract [20] and also to the absence of glomerulofiltration due to the size of the liposomes [20].

Increased alkaline phosphatase levels and increased alanine & aspartate transaminase levels were observed in 28% and 11% patients respectively in our study. Increased rate of hepatotoxicity occur with LAMB. This is attributed to the higher delivery of this formulation to liver and it results in liver injury at high doses [21]. With the causality assessment been done for this study using WHO-UMC causality assessment scale, 28% reactions had certain causal association with the drug and 72% reactions had possible causal association with the drug. Preventability was assessed using Schumock and Thornton criteria and 28% ADRs were found to be definitely preventable and 72% ADRs were classified as not preventable. Severity was assessed by Modified Hartwig Siegel severity assessment scale and all the ADRs were found to be of moderate severity.

Conclusion: ADRs are preventable. Hence there is an urgent need in reinforcing ADR monitoring of adverse drug reactions to drugs, public education regarding ADRs, introduction of drug safety awareness and reporting of ADRs by medical students in the undergraduate medical curriculum as well as periodic sensitisation of health care professionals regarding ADR reporting.

Acknowledgement: I sincerely acknowledge the Regional Pharmacovigilance centre, Madras Medical College for their technical support.

References:

1. Wuhan City Health Committee. Wuhan Municipal Health and Health Commission's briefing on the current pneumonia epidemic situation in our city 2019. In: http:// wjw. wuhan.gov.cn/front/web/showDetail/2019123108989[14 January 2020]
2. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–81
3. Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Ralph ZJ. Invasive fungal diseases during COVID-19: we should be prepared. J Mycol Med 2020;30:100971
4. W. Jeong, C. Keighley, R. Wolfe, et al., The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports, Clin. Microbiol. Infect. 25 (2019) 26–34.
5. J. Chander, M. Kaur, N. Singla, R. Punia, S. Singhal, A. Attri, J. Guarro, Mucormycosis: battle with the deadly enemy over a five-year period in India, J. Fungi 4 (2) (2018) 46, https://doi.org/10.3390/jof4020046.

6. Werthman-Ehrenreich, Mucormycosis with orbital compartment syndrome in a patient with COVID-19, Am. J. Emerg. Med. 42 (2021) 264.e5–264.e8, https://doi. org/ 10. 1016/j.ajem.2020.09.032.
7. P.G. Deutsch, J. Whittaker, S. Prasad, Invasive and non-invasive fungal rhinosinusitis—a review and update of the evidence, Medicina 55 (2019) 1–14.
8. Laurence Brunton, Bjorn Knollmann, RandaHilal- Dandan- Goodman and Gilman's The Pharmacological Basis of Therapeutics: 2017; 13 the edition; Chapter 61, page 1090
9. The Use of the WHO-UMC System for Standardised Case Causality Assessment. Available from: http://www.whoumc. org/Graphics/ 24 734.pdf.
10. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm 1992; 27:538.
11. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992; 49:2229-32.
12. Revannavar SM, et al; COVID-19 triggering mucormycosis in a susceptible patient: a new phenomenon in the developing world?. BMJ Case Rep 2021; 14:e241663. doi:10.1136/bcr-2021-241663
13. Ponnaiah et al; Hyperglycemia and steroid use increase the risk of rhino-orbito-cerebral mucormycosis regardless of COVID-19 hospitalization: Case-control study, India.Plos one 2022; e0272042
14. Aditya et al; SARS-CoV-2, Uncontrolled Diabetes and Corticosterids- An unholy Trinity in Invasive fungal infections of the Maxillofacial region? A retrospective, Multicentric analysis. J. Maxillofac. Oral Surg. July-Sept 2021; 20(3): 418-425
15. 15.Walsh TJ, Finberg RW, Arndt C, Hiemenz J, Schwartz C, Bodensteiner D, et al. Liposomal amphotericin b for empirical therapy in patients with persistent fever and neutropenia. N Engl J Med. 1999; 340:764–71.
16. Groll et al; Clinical pharmacokinetics, Pharmacodynamics, safety and efficacy of Liposomal Amphotericin B. Clinical infectious Disease 2019; 68(S4):S260-74.
17. Rafael Laniado, Maria Noemi; Amphotericin B: Side effects and toxicity;Rev Iberoam Micol 2009;26(4):223-227
18. Bagnis CI, Deray G; Amphotericin B nephrotoxicity: Saudi J kidney Dis Transplant 2002; 13:481-91
19. Anderson CM; Sodium chloride treatment of Amphotericin B nephrotoxicity Standard of care?; West J Med 1995; 162: 313-7.
20. Loo AS, Muhsin SA, Walsh TJ. Toxicokinetic and mechanistic basis for the safety and tolerability of liposomal amphotericin B. Expert Opin Drug Saf. 2013 Nov; 12(6):881–95. [PubMed: 23931455]
21. 21. Bekersky I, Boswell GW, Hiles R, Fielding RM, Buell D, Walsh TJ. Safety, toxicokinetics and tissue distribution of long-term intravenous liposomal amphotericin B (AmBisome): a 91-day study in rats. Pharm Res. 2000 Dec; 17(12):1494–502. [PubMed: 11303959]