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RESEARCH ARTICLE

Liposomal Amphotericin-B Infusion-related Reactions and Rate of Infusions: A Single Center Cohort Study

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ABSTRACT

Objectives: Liposomal amphotericin B is a broad-spectrum antifungal treatment used for life-threatening infections, but it commonly induces infusion-related adverse events that may prevent treatment completion. Based on anecdotal evidence, a slow infusion guideline at treatment initiation has been suggested to reduce these reactions. This study aimed to determine if slowing down the infusion rate on treatment initiation would reduce the rate of infusion-related adverse events.

Methods: A retrospective cohort study was conducted examining the primary outcome of adverse event rates between patients who received slow and standard (2-hour or faster) infusions at a major hospital in Australia. Secondary outcomes were risk factors associated with infusion reactions. The rates of adverse events were analyzed using Fisher's exact test.

Results: An 8-year audit identified 47 patients who were administered liposomal amphotericin-B. The average age of the study population was 61.7 years and 28 (59.6%) were male patients. Slower than standard infusions were given to 5 (10.6%) patients on treatment initiation. Infusion-related adverse events occurred in 2 (40.0%) patients with reduced rates and 5 (11.9%) patients with standard infusion rates (p=0.154). Typical reactions were myalgia, dyspnoea, and flushing. Four patients with adverse events had been rechallenged after further rate reductions and prophylactic medications with the completion of treatment. No risk factors for adverse events were identified among demographics, comorbidities, or co-prescribed medications.

Conclusion: Slowing the infusion rate of liposomal amphotericin-B administration does not appear to reduce the likelihood of infusion-related reactions, however, it can be trialed for adverse-event management. *J Microbiol Infect Dis 2022; 12(4): 148-153.*

Keywords: *Liposomal Amphotericin B, Adverse events, Intravenous infusions, Treatment*

INTRODUCTION

Liposomal amphotericin-B is a board spectrum antifungal agent used for various fungal infections [1]. Despite being an effective therapy, it is associated with infusion-related reactions in up to 20-40% of patients [2,3]. Typical reactions include dyspnoea, flushing, urticaria, and musculoskeletal pain [1-4]. These reactions can cause significant distress and preclude the use of this life-saving therapy.

The pathophysiology of these reactions is considered to be related to the activation of the immune system via Toll-like Receptor 2 and the transmembrane signaling protein CD14, with consequential production of inflammatory cytokines such as Tumour Necrosis Factor α and interleukin-6 [4]. However, this cytokine stimulation and its production takes hours and does not fit with the timeline of infusion reactions.

Currently, there is a lack of evidence on appropriate preventative strategies to minimize

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the occurrence of liposomal amphotericin-B infusion-related reactions. Previous studies of prophylactic antihistamines have not demonstrated a benefit in reducing the incidence of adverse events (AEs) and are not routinely used [2-4]. Similarly, there was no difference in slower infusions of the original amphotericin-B formulation when infusion rates were slowed from 2 to 4 hours [5].

Based on the experience of the local Infectious Disease team, slower infusion rates with gradual rate escalation have been used for the initial liposomal amphotericin-B infusions. As a result, they anecdotally have been suggested to have a lower rate of AEs.

Aim

This study evaluated the relationship between liposomal amphotericin-B infusion rates and the incidence of AEs.

Ethics approval

The local Human Research Ethics Committee approved this study with reference number QA/61207/PH-2020-220678(v1).

METHODS

Method

A retrospective cohort study of all patients who were prescribed and administered intravenous liposomal Amphotericin-B (Ambisome®) at a major hospital in Victoria, Australia, was conducted. Patients were identified via dispensing records from the Pharmacy Department at the study site between 2012 and 2020. Exclusion criteria were limited to patients who had unavailable medication charts in scanned, digitized medical records or lacked administration documentation in the electronic health record.

Data collected included patient demographics, length of stay, comorbidities, amphotericin-B doses, administration rates recorded by nursing, medical and pharmacy staff, duration of treatment, AEs, premedication, and AEs treatments, and patient mortality. Primary diagnosis and microbiological isolates were also collected.

The primary outcome was the rate of infusion-related AEs occurring during the infusions in patients who have had slower than standard infusions compared to those administered at standard infusion guideline rates over 2 hours or less, as per local hospital guidelines. Liposomal amphotericin-B infusions were prepared at 0.4-1.8 mg per milliliter concentrations. Slower than standard infusions were commenced at a low infusion rate, which was increased at 15-minute increments if there was an absence of AEs. Most of the slow infusions were commenced at 4 milliliters per hour and then increased to 10, 40, and 80 milliliters per hour every 15 minutes until the standard infusion rate was reached.

Secondary endpoints were rates of AEs based on risk factors such as age, gender, immunosuppressive therapy use, inflammatory markers, and co-administration of drugs such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II Receptor 1 blockers (ARBs), corticosteroids and immunosuppressants (including chemotherapy).

Data were analyzed using SPSS 25 with comparisons of patient characteristics between patients who experienced infusion-related reactions and those who did not. Analysis for bivariate outcomes was performed using Fisher's exact test. In addition, normally distributed variables were analyzed using the Student's t-test, and non-normally distributed variables using the Mann-Whitney U test.

RESULTS

Over the study period, 47 patients met the inclusion criteria, and one patient was excluded due to a lack of medical record documentation of liposomal amphotericin-B administration. The average age of the study population was 61.7 years and 28 (59.6%) were male patients. The most common patient comorbidities were cancer, hypertension, chronic obstructive pulmonary disease, and hyperlipidemia (Table 1). Pneumonia and sepsis were the most common primary diagnoses; however, 7 (14.9%) patients had no identified pathogen, 3 (6.4%) had viral pathogens, 12 (25.5%) had bacterial infections, 22 (46.8%) had fungal pathogens and 3 (6.4%) had mixed bacterial and fungal infections identified during their admission. Due to the severity of the illness and additional comorbidities, 20 (42.6%) patients died during admission.

Documented slower-than-standard infusions were given to five (10.6%) patients on treatment initiation and, as per hospital guidelines, to 16 (34.0%) patients. In

comparison, the other 26 (55.3%) patients had no specified rate recorded in the medical records. They were considered to have been administered the treatment per hospital guidelines at the standard infusion rate over 2 hours or less.

Table 1. Patient characteristics.

Variables	Values
Age years (range)	61.7 (18-93)
Males	28 (59.6%)
LOS (days)	26.1
Congestive Cardiac Failure	7 (14.9%)
Ischaemic Heart Disease	7 (14.9%)
Hypertension	20 (42.6%)
Cerebrovascular accident	3 (6.4%)
GEFD	7 (14.9%)
COPD	10 (21.3%)
Chronic Kidney Disease	5 (10.6%)
Asthma	5 (10.6%)
Inflammatory Bowel Disease	1 (2.1%)
Smoker	9 (19.1%)
Ex-smoker	10 (21.3%)
Cancer	24 (51.1%)
Atrial Fibrillation	5 (10.6%)
Hyperlipidaemia	10 (21.3%)
Diabetes	7 (14.9%)
Leukecytes count $x10^9$/mL	12.2 (0.2-42.4)
Creatinine mcmol/L	83.1 (18-513)
C reactive protein mg/L	122.3 (1-389)
Dose mg (range)	282.2 (100-450)
Number of dose (range)	8.4 (1-46)
Rate of administration	
Not specified	26 (55.3%)
As per guideline over 2 hours	11 (23.4%)
As per guideline ≤1 hour	5 (10.6%)
Reduced rate	5 (10.6%)
Premedication use	2 (4.3%)

COPD= Chronic Obstructive Pulmonary Disease, GERD= Gastroesophageal reflux disease

The primary outcome of infusion-related AEs occurred in 7 (14.9%) patients and 2 (40.0%) among those with reduced rates, and 5 (11.9%) among those with standard infusion rates (p=0.154). The most common AEs recorded by clinical staff during infusions were: flushing or diaphoresis 3 (6.4%), dyspnoea 3 (6.4%), palpitations 2 (4.3%), and rash or itch 2 (4.3%) (Table 2). One patient experienced non-infusion-related reactions of acute renal failure. Four (8.5%) of the patients who experienced AEs had their infusions restarted at a slower rate, with two patients receiving an antihistamine and 1 of these patients also receiving hydrocortisone for prophylaxis. Only one patient had further reactions on a 50% reduced infusion rate but tolerated it when it was reduced to 12.5% of the standard infusion rate.

Table 2 Infusion-related adverse events due to liposomal amphotericin B, treatment and infusion management.

Total Adverse Events	N=7 (14.9%)
Gastrointestinal	0 (0.0%)
Cardiovascular	
Chest tightness	1 (2.1%)
Palpitations	2 (4.3%)
Dizziness	1 (2.1%)
Fever	1 (2.1%)
Flushing/diaphoresis	3 (6.4%)
Respiratory	
Dyspnoea	3 (6.4%)
Neurological	
Dizziness	1 (2.1%)
Dermatological	
Rash/itch	2 (4.3%)
Musculoskeletal	
Myalgia/arthralgia	4 (8.5%)
Adverse event treatments	6 (12.8%)
Hydrocortisone	1 (2.1%)
Loratidine	1 (2.1%)
Promethazine	2 (4.3%)
Fexofenadine	1 (2.1%)
Oxycodone	1 (2.1%)
Diazepam	1 (2.1%)
Oxygen	1 (2.1%)
Rate reduced	3 (6.4%)
Infusion ceased	7 (14.9%)
Infusion restarted	4 (8.5%)

None of the pre-specified risk factors for AEs for secondary outcomes were statistically significant between patients who experienced AEs and those who did not (Table 3). Patients who experienced AEs were younger and less likely to use immunosuppressive treatments than those without AEs, and there were no dose differences between the groups (282.9 mg versus 278.6 mg, p=0.903).

Table 3. Risk factor analysis.

Risk factors	Patients without adverse events (n=40)	Patients with adverse events (N=7)	*p*-value
Gender (female)	34 (68.0%)	3 (42.9%)	0.226
Age (years)	63.5	52.0	0.080
Rate of administration			
As per guideline	37 (92.5%)	5 (71.4%)	0.154
Reduced rate	3 (7.5%)	2 (28.6%)	
Angiotensin Converting Enzyme Inhibitors	4 (10.0%)	1 (14.3%)	0.571
Angiotensin II Receptor I Blockers	2 (5.0%)	0 (0.0%)	1.000
Corticosteroids	16 (40.0%)	2 (28.6%)	0.692
Immunosuppressants	12 (30.0%)	0 (0.0%)	0.166
C-reactive protein (mg/L)	132.0	60.8	0.112
Mean dose (mg)	282.9	278.6	0.903
Asthma	3 (7.5%)	2 (28.6%)	0.154
Congestive Cardiac Failure	7 (17.5%)	0 (0.0%)	0.573
Chronic Kidney Disease	5 (12.5%)	0 (0.0%)	1.000
Hypertension	18 (45.0%)	2 (28.6%)	0.682
Smoker	6 (15.0%)	3 (42.9%)	0.117
Ex-smoker	10 (25.0%)	0 (0.0%)	0.318
Ischaemic heart disease	7 (17.5%)	0 (0.0%)	0.573
Cerebrovascular accident	3 (7.5%)	0 (0.0%)	1.000
Gastro-oesophageal reflux disease	6 (15.0%)	1 (14.3%)	1.000
Chronic Obstructive Pulmonary Disease	9 (22.5%)	1 (14.3%)	1.000
Cancer	22 (55.0%)	2 (28.6%)	0.245
Atrial Fibrillation	5 (12.5%)	0 (0.0%)	1.000
Diabetes Mellitus	6 (15.0%)	1 (14.3%)	1.000
Hyperlipidaemia	9 (22.5%)	1 (14.3%)	1.000
Inflammatory Bowel Disease	1 (2.5%)	0 (0.0%)	1.000

DISCUSSION

The results of this cohort study indicate that infusion-related AEs to liposomal amphotericin-B infusions are very common, but lower in our cohort (14.9%) compared to the 20%-40% identified from previous studies [2-7]. The types of AEs observed in our cohort were comparable to those previously reported with common dyspnoea, fever, and diaphoresis [6]. Variability was observed in AEs frequency for events such as myalgia and urticaria in our patients compared to previous studies, where either none of these reactions

were reported [6,7] or up to 8.8% in other studies [8]. Only 2 (4.2%) patients had their infusions discontinued without re-initiation, which is lower than the previously reported rates of 8.0% [7].

However, none of the previous studies used slower infusions routinely for AEs reduction strategies. Additionally, there was no routine premedication used, and given that many of the reactions do not reflect typical histamine release patterns, there is limited usefulness from antihistamine or corticosteroid premedication for liposomal amphotericin-B infusions [9,10].

Other research into strategies and pathophysiology of infusion-related AEs suggests that unlike the original formulation of amphotericin-B, the lipid-based formulations induce a different pattern of reactions due to the liposome and not amphotericin-B [9]. However, an Amphotericin B Cholesteryl-Sulfate Complex study found that corticosteroid premedications significantly reduced infusion reactions [11]. In our cohort of patients, corticosteroids did not reduce the rate of reactions significantly, 40.0% versus 28.6% (p=0.692), while immunosuppressant use was trending towards a lower rate of AEs during the infusions.

Similar to previous a study [2], a high proportion of patients who experienced AEs were rechallenged (4 out of 7 patients). All four rechallenged patients tolerated the remainder of treatments, with some receiving antihistamines and or corticosteroids, with reduced infusion rates. This is comparable to a previous study that reported 93% of patients could tolerate infusions after receipt of diphenhydramine with the same infusion rate [2]. The role of antihistamines in preventing infusion reactions remains uncertain as it is evident from our cohort and a previous study [2] that some patients can be successfully rechallenged with liposomal amphotericin-B without the use of antihistamine. Simply slowing down the infusion rate has been successfully trialed on rechallenge in our study and in previous case reports to prevent further AEs [12,13]. Only one patient in our cohort had further reactions on a 50% reduced infusion rate but tolerated the infusion when it was reduced to 12.5%, suggesting a very slow infusion rate may be necessary for some patients. The primary AEs that contributed to infusions cessation and rate reduction were myalgia and arthralgia. Some patients require reassurance that a reduced rate may prevent reactions and assist with treatment completion.

The main limitations of our study are the single-center design, small size, and high patient comorbidity level with significant in-hospital mortality, which was higher than in other studies [7,10]. Additionally, the study was limited by a lack of clear documentation regarding the infusions rates for 55.3% of patients. We assumed that the nursing and medical staff had followed the local guideline or the product information and infused the antifungal treatment over 2 hours or less.

Conclusion

Based on the results of our small cohort study, rates of infusion-related AEs to liposomal amphotericin-B were not reduced by slowing down the infusion rate on therapy initiation. However, it can be considered a management strategy for those who experience AEs to complete their therapy.

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