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Original Research Article

Prevalence of hypokalemia in a patients of post COVID-19 mucormycosis receiving injection liposomal-amphotericin B at tertiary care hospital

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ABSTRACT

Background: Hypokalemia is one of the most common electrolyte disturbances seen in clinical practice and in patients receiving liposomal-amphotericin B (L-AMB). The aim of this retrospective study was to examine the prevalence of hypokalemia in patients of post COVID-19 mucormycosis receiving L-AMB and to evaluate common presenting symptoms of hypokalemia in them.
Methods: The present study was conducted as a retrospective study on 100 patients of post COVID-19 mucormycosis who received L-AMB for 1st time between May 2021 and August 2021 at department of otorhinolaryngology and head and neck surgery, Netaji Subhash Chandra Bose medical college and hospital, Jabalpur, Madhya Pradesh, India.
Results: In the present study, hypokalemia of varying grades occurred in 23% of the patients, making it an adverse event that requires attention and correction. Hypokalemia is reported in middle aged adults, more in males compared to females and at doses less than 2 gm of L-AMB. Majority (91.30%) of the patients of mucormycosis who developed hypokalemia presented with generalized weakness, anorexia and muscle cramps followed by nausea which is seen in 82.60% patients. Constipation, bloating and abdominal pain being other presenting symptoms in them seen in 56.50%, 56.50% and 52.20% patients respectively.
Conclusions: Hypokalemia is a common electrolyte disorder occurring in patients receiving L-AMB which if undetected can be life threatening. Adequate medical management of these patients not only requires proper antifungal administration but also management of electrolyte imbalances related to the administration. L-AMB is a life-saving drug provided it is used judicially and with utmost care.

Keywords: Post COVID-19 mucormycosis, L-AMB, Hypokalemia, Hypomagnesemia

INTRODUCTION

Mucormycosis (previously called zygomycosis) is a rare but serious angio-invasive infection caused by a group of fungi called mucormycetes. Spores of these ubiquitous fungi (commonly found in soil, fallen leaves, compost, animal dung and air) can be inhaled and then infect the lungs, sinuses, and extend into the brain and eyes. Less often, infection may develop when the spores enter the body through a cut or an open wound. Mucormycosis is not a contagious disease, it cannot be spread from one person to another. Mucormycosis mainly affects people who are immunocompromised, or patients already infected with other diseases. High risk groups include people with diabetes (especially diabetic ketoacidosis), solid organ transplantation, neutropenia (low neutrophils, a type of white blood cells), long-term systemic corticosteroid use, and iron overload (hemochromatosis). The risk is high for those using immunomodulating drugs and anti-fungal drug voriconazole in some high-risk

groups. Clinical presentation is classified according to the organ involvement. It can be rhino-orbital cerebral, pulmonary, cutaneous, gastrointestinal, or disseminated and rhino-orbital cerebral is the commonest form in adults.[1]

COVID-19 associated mucormycosis

Fungal infections, including mucormycosis, aspergillosis and invasive candidiasis, have been reported in patients with severe COVID-19 or those recovering from the disease and have been associated with severe illness and death.[1] The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen (hypoxia), high glucose (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]), high iron levels (increased ferritins) and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators.[2]

The early diagnosis of mucormycosis requires the availability of imaging techniques, trained personnel to do endoscopic evaluation, and mycological culture and histological evaluation. Patients with suspected rhino-orbital cerebral mucormycosis presenting with discoloration of face, facial pain and numbness, blood-stained nasal discharge, periorbital or retroorbital pain and partial or complete loss of vision should be referred immediately to a facility equipped with proper patient care set up where proper treatment can be done.[3]

The guidelines for treatment of mucormycosis strongly supports an early complete surgical treatment for mucormycosis whenever possible, in addition to adequate systemic antifungal treatment. Debridement should be as radical as possible. There may be requirement of revision surgery in some patients. The antifungal drug of choice is L-AMB as it is better tolerated and can be given in larger doses to combat the fungus.

Amphotericin B is a polyene antifungal agent with a broad range of activity against yeasts and molds, as well as the protozoan parasite *Leishmania* spp. L-AMB binds to ergosterol in the fungal cell membrane leading to ion leakage and cell death. The initial formulation was amphotericin B deoxycholate (DAmB), which was developed in the 1950s. For many decades DAmB was the only antifungal agent available for the treatment of invasive fungal diseases. However, the significant dose-limiting toxicity of DAmB (most notably nephrotoxicity and infusion-related reactions) provided the impetus to develop new less toxic formulations. Liposomal amphotericin B (AmBisome®; L-AMB) is a unique lipid formulation of amphotericin B that has been used for nearly 20 years to treat a broad range of fungal infections. While the antifungal activity of amphotericin B is retained following its incorporation into a liposome bilayer, its toxicity is significantly reduced.[4]

In several case series, the use of L-AMB successfully treated mucormycosis with various organ involvement patterns. Daily dose ranges from 1 mg/kg per day to 10 mg/kg per day. Recipients of increased doses tends to have increased response rates. Patients receiving 10 mg/kg per day had substantial serum creatinine increase that were mostly reversible. However, doses higher than 10 mg/kg per day did not result in higher blood concentrations of drug. In CNS involvement, L-AMB at 10 mg/kg per day can be started. In the absence of CNS involvement, amphotericin B lipid complex 5 mg/kg per day can be used successfully. Amphotericin B deoxycholate has been the drug of choice for decades. It is effective, but its use is limited by its substantial nephrotoxicity, specifically in the doses and treatment durations needed for mucormycosis. Use of amphotericin B deoxycholate should be restricted as it is having nephrotoxic effects and adequate doses cannot be given.

Treatment should be continued till the adequate doses for clinical condition is achieved that is for intracranial form cumulative dose should be 10 gm and for a limited form it should be 5-7 gm. It should be supplemented by clinical response and follow up imaging along with decline in indirect inflammatory markers like C-reactive Protein (CRP). Isavuconazole or posaconazole may be administered in patients allergic to L-AMB, unable to tolerate L-AMB or as a maintenance therapy.[3]

L-AMB has the potential to cause two major adverse events, renal dysfunction and serum potassium abnormality (hypokalemia); however, appropriate clinical response to treatment remains unpredictable and response may vary from patients to patients.[5]

Hypokalemia is an electrolyte imbalance characterized by low serum potassium concentrations (normal range: 3.5-5.0 meq/l). Severe and life-threatening hypokalemia is defined when potassium levels are <2.5 meq/l. In outpatient population undergoing laboratory testing, mild hypokalemia can be found in almost 14%. Furthermore, as many as 20% of hospitalized patients are found to have hypokalemia but only in 4-5% this is clinically significant. Severe hypokalemia is relatively uncommon. Approximately 80% of patients who are receiving diuretics become hypokalemic, while many of patients with hypokalemia could also have an associated systemic disease. There are no significant differences in its prevalence between males and females.[6]

The severity of clinical manifestations of hypokalemia tends to be proportionate to the degree and duration of serum potassium reduction. Symptoms generally do not become obvious until serum potassium is below 3.0 meq/l, unless it falls rapidly or the patient has a potentiating factor, such as the use of digitalis, in which

patients have a predisposition to arrhythmias. According to the severity of hypokalemia, symptoms can vary from absent to lethal heart arrhythmias. Symptoms usually resolve with correction of the hypokalemia.

More specifically, we could categorize the manifestations according to the affected system. The effects of hypokalemia regarding the renal function can be metabolic acidosis, rhabdomyolysis (in severe hypokalemia) and, rarely, impairment of tubular transport, chronic tubulointerstitial disease and cyst formation. Nervous system is affected, the patient can suffer from leg cramps, weakness, paresis or ascending paralysis. Constipation or intestinal paralysis and respiratory failure often present as signs of severe hypokalemia. Last but not least, hypokalemia can have detrimental effects on the cardiovascular system, leading to electrocardiographic (ECG) changes (U waves, T wave flattening and ST-segment changes), cardiac arrhythmias (sometimes lethal) and heart failure.[6]

The treatment of hypokalemia has four aims: (a) reduction of potassium losses, (b) replenishment of potassium stores, (c) evaluation for potential toxicities and (d) determination of the cause, in order to prevent future episodes, if possible. Major goal of treatment should be the 1) management of the underlying disease which can be because of drug induced (L-AMB induced or diuretic induced) or non-response to potassium supplementation in cases with hypomagnesemia or 2) elimination of the causative factor.

Whether oral or intravenous potassium will be administered, this should be decided according the severity of the hypokalemia. It is important to remember that every 1 meq/l decrease in serum potassium, represents a potassium deficit of approximately 200–400 meq. However, this calculation could either overestimate or underestimate the true potassium deficit. Patients with potassium levels of 2.5-3.5 meq/l (representing mild to moderate hypokalemia), may need only oral potassium replacement. If potassium levels are less than 2.5 meq/l, intravenous (IV) potassium should be given, with close follow-up, continuous ECG monitoring, and serial potassium levels measurements. The IV route should be also our choice in patients with severe nausea, vomiting or abdominal distress.

In patients with renal impairment, potassium should be very cautiously replaced and the nephrologist should be also contacted, if the patient is on dialysis or has severe renal impairment. Administration of oral potassium should be accompanied with plenty of fluid (between 100 and 250 ml of water, depending on the form of the tablet of potassium) and is better to be given with or after meals. Regarding IV therapy, 0.9% sodium chloride is the preferred infusion fluid, as 5% glucose may cause transcellular shift of potassium into cells. We should prefer pre/mixed IV infusions. It is critical also to correct the levels of serum magnesium, in order to achieve an adequate treatment of hypokalemia.[6]

METHODS

The present study was conducted as a retrospective study on 100 patients of post COVID-19 mucormycosis who received L-AMB for the first time between May 2021 and August 2021 at Department of ENT, Netaji Subhash Chandra Bose Medical College and Hospital, Jabalpur (M.P.). The objectives of our study were as follows: 1) To evaluate the prevalence of hypokalemia in patients of Post COVID-19 Mucormycosis receiving injection L-AMB. 2) To evaluate the common presenting symptoms of hypokalemia.

Inclusion and exclusion criteria

All the patients who were diagnosed with COVID-19 associated mucormycosis who were treated at Department of ENT, Netaji Subhash Chandra Bose Medical College and Hospital, Jabalpur (M.P.) were included in the study.

Patients with allergic rhinosinusitis, hysterical symptoms were kept apart from the study.

Data collection method

The data of 100 patients from IPD records were reviewed for the following parameters: Demographic data, dose of L-AMB at which patients developed initial symptoms of hypokalemia and presenting symptoms of hypokalemia. All the records were recorded by using structured schedule and entered in Microsoft excel sheet.

Ethical approval

Ethical approval was not needed as this was an observational study.

Statistical analysis

Data of the present study was recorded/fed into the computers and after its proper validation, check for error, decoding, it was compiled and analysed with the help of SPSS software for windows. Findings and patterns have been noticed and presented in the form of pie and bar charts here.

RESULTS

Prevalence of hypokalemia

Out of the 100 patients of mucormycosis who had received L-AMB, 23 patients developed hypokalemia of varying severity. The 21 patients manifested with symptoms of hypokalemia while rest being asymptomatic.

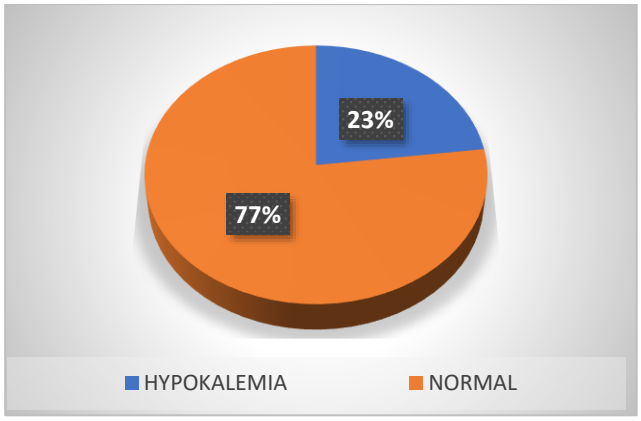

Figure 1: Prevalence of hypokalemia.

Age distribution of patients with hypokalemia

Out of 23 patients who developed hypokalemia, majority belonged to middle age group.4 patients were between age group 31-40, 8 between age group 41-50, 7 between age group 51-60 while 4 patients belonged to old age group.

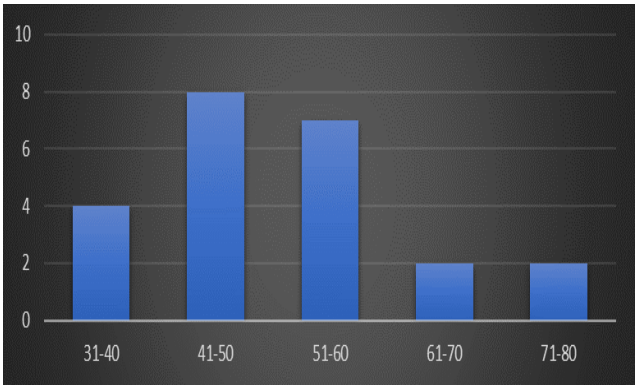

Figure 2: Age distribution of patients with hypokalemia.

Sex distribution of patients with hypokalemia

Among the 23 patients with hypokalemia, 17 patients were males and rest were females.

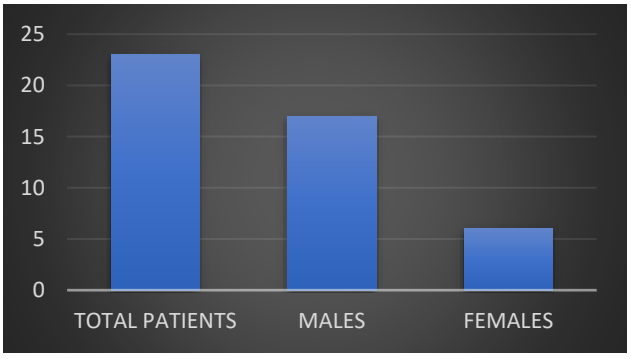

Figure 3: Sex distribution of patients with hypokalemia.

Severity of hypokalemia

The 11 patients out of 23 developed mild hypokalemia (3-3.4 meq/l), 11 patients developed moderate hypokalemia (2.5-2.9 meq/l) while only 1 patient manifested with severe hypokalemia (<2.5 meq/l).

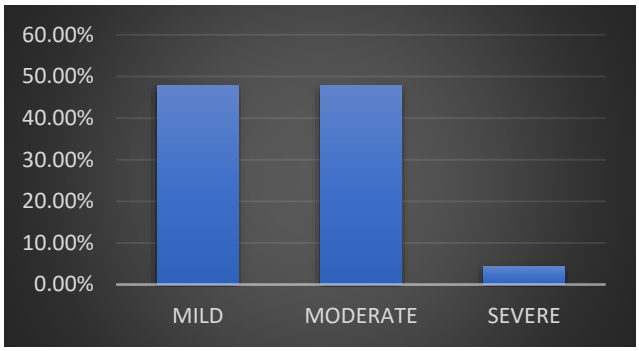

Figure 4: Severity of hypokalemia.

Dose at which hpokalemia manifested

Most (82.60%) of the mucormycosis patients developed symptoms of hypokalemia in less than 2 gm of L-AMB while in the rest hypokalemia occurred after administration of more than 2 gm of L-AMB. The 30.40% patients developed hypokalemia within 50-500 mg of L-AMB, 17.40% within 550-1000 mg of L-AMB, 26.10% within 1050-1500 mg of L-AMB, 8.60% within 1550-2000 mg of L-AMB, 4.30% within 2050-2500 mg of L-AMB, 8.60% within 2550-3000 mg of L-AMB and 4.30% within 4050-4500 mg of L-AMB.

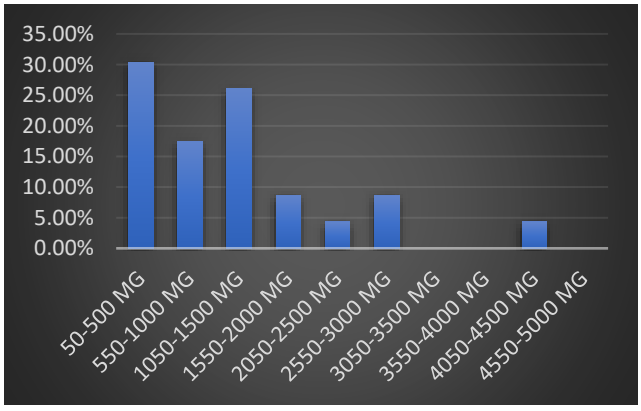

Figure 5: Dose at which hpokalemia manifested.

Presenting symptoms of hypokalemia

Majority (91.30%) of the patients of mucormycosis who developed hypokalemia presented with generalized weakness, anorexia and muscle cramps followed by nausea which is seen in 82.60% patients. Constipation, bloating and abdominal pain being other presenting symptoms in them seen in 56.50%, 56.50% and 52.20% patients respectively. Two patients (8.70%) were asymptomatic with mild hypokalemia.

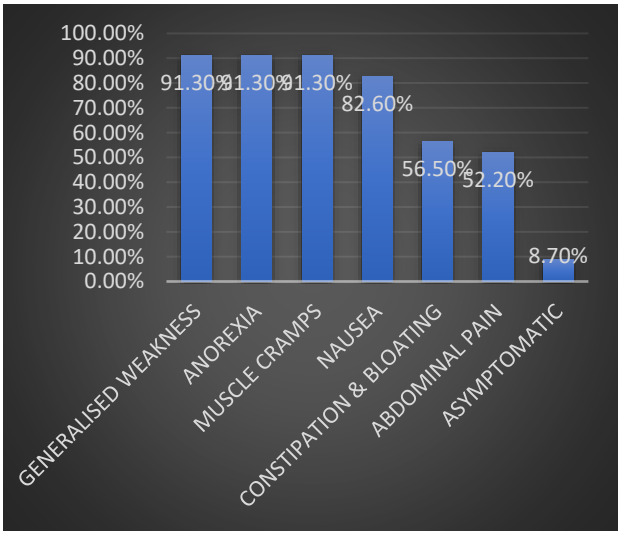

Figure 6: Presenting symptoms of hypokalemia.

DISCUSSION

L-AMB possesses broad-spectrum antifungal activity and is a first-line indication against unconfirmed fungal infections in empirical therapy.[7] Competitive studies with other antifungal drugs have demonstrated the efficacy of L-AMB.[8,9]

L-AMB may reduce the levels of blood potassium by damaging the renal tubules.[10,11] Based on the findings of AMB deoxycholate nephrotoxicity, it was suggested that the two major mechanisms that might contribute to L-AMB induced renal dysfunction and serum potassium abnormalities were direct renal vasoconstriction, which results in a profound reduction in renal blood flow Sabra et al and direct damage to the distal tubule cell membranes, which results in hypokalemia, hypomagnesemia, and bicarbonate and amino acid loss Sawaya et al and Steinmetz and Lawson.[12-14] Therefore, renal dysfunction and serum potassium abnormality appear to result from a combination of glomerular ischemia and tubular toxicity Sawaya et al.[13] In particular, glomerular ischemia could contribute to elevation of serum creatinine and hyperkalemia whereas tubular injury could cause hypokalemia.[15]

The incidence of hypokalemia in patients treated with L-AMB was reported as 36% by Ringden in 1994 and as 51.3% by Sunakawa et al in 2012.[16,17]

In the present study, hypokalemia of varying grades occurred in 23% of the patients, making it an adverse event that requires attention.

To date, three retrospective, univariate, or multivariate analyses demonstrated that older age by Patel et al, Rocha et al higher dose by Cornely et al, Patel et al, diuretics by Rocha et al, vasopressors, and concomitant nephrotoxins Patel et al, Rocha et al, Ueda et al (i.e., IV contrast, antibiotics, and angiotensinconverting enzyme inhibitors) were risk factors for L-AMB induced nephrotoxicity and electrolyte imbalance.[3,15,18-21]

In the present study is hypokalemia is reported in middle aged adults, more in males compared to females and at doses less than 2 gm of L-AMB.

The consequences of acute and chronic hypokalemia include muscle weakness, palpitations and cardiac dysrhythmias, as well as worsening diabetic control (a result of impaired insulin release and reduced tissue sensitivity to insulin). In addition, polyuria commonly occurs, through an impaired ability to concentrate urine. Cardiovascular risks and adverse effects of anesthesia in patients with hypokalemia have always been a particular clinical concern. In contrast to the response of skeletal muscle, hypokalemia induced hyperpolarization increases excitability in cardiac muscle (although why is unclear) and delays repolarization, causing atrial and ventricular dysrhythmias. Changes observed in the electocardiogram of patients with hypokalemia are characterized by an early T wave flattening followed by an ST-Tdepression and a U wave that can sometimes be difficult to distinguish from the T wave, with prolongation of the QU or QT interval.[22]

In present study majority (91.30%) of the patients of mucormycosis who developed hypokalemia presented with generalized weakness, anorexia and muscle cramps followed by nausea which is seen in 82.60% patients. Constipation and abdominal pain being other presenting symptoms in them seen in 56.50% and 52.20% patients respectively.

Management of hypokalemia[23]

Potassium deficit

If the hypokalemia is due to potassium depletion, a potassium deficit of 10% of the total body potassium stores is expected for every 1 meq/l decrease in the serum potassium. The correlation between potassium deficits and the severity of hypokalemia is shown in Table 1. These estimates do not consider any contribution from transcellular potassium shifts, and thus they are meant only as rough guidelines for gauging the severity of potassium depletion.

Table 1: Potassium deficits in hypokalemia.

Serum potassium (meq/l)	meq %	Potassium deficit
		Total body K
3.0	175	5
2.5	350	10
2.0	470	15
1.5	700	20
1.0	875	25

*Estimated deficits for a 70 kg adult with a total body potassium content of 50 meq/kg.

Potassium replacement solutions

The usual replacement fluid is potassium chloride, which is available as a concentrated solution (from 1 and 2 meq/ml) in ampules containing 10, 20, 30, and 40 meq of potassium. These solutions are extremely hyperosmotic (the 2 meq/l solution has an osmolality of 4000 mosm/l H_2O) and must be diluted. A potassium phosphate solution is also available (contains 4.5 meq potassium and 3 µm phosphate per ml) and is preferred by some for-potassium replacement in diabetic ketoacidosis (because of the phosphate depletion that accompanies ketoacidosis).

Infusion rate

The standard method of intravenous potassium replacement is to add 20 meq of potassium to 100 ml of isotonic saline and infuse this mixture over 1 hour. The maximum rate of intravenous potassium replacement is usually set at 20 meq/hour, but dose rates up to 40 meq/hour occasionally may be necessary (e.g., with serum K+ below 1.5 meq/l or serious arrhythmias), and dose rates as high as 100 meq/hour have been used safely. A large central vein should be used for infusion because of the irritating properties of the hyperosmotic potassium solutions. However, if the desired replacement rate is greater than 20 meq/hour, the infusion should not be given through a central venous catheter because of the theoretical risk of transient hyperkalemia in the right heart chambers, which can predispose to cardiac standstill. In this situation, the potassium dose can be split and administered via two peripheral veins.

Response

The serum potassium may be slow to rise at first, Full replacement usually takes a few days, particularly if potassium losses are ongoing. If the hypokalemia seems refractory to replacement therapy, the serum magnesium level should be checked. Magnesium depletion promotes urinary potassium losses and can cause refractory hypokalemia.

In present study, patients with mild hypokalemia were treated with oral potassium supplementation (Potassium chloride oral solution Potklor) while those with moderate and severe hypokalemia were treated with IV KCl.

Magnesium deficiency[23]

The antibiotics that causes magnesium depletion are the aminoglycosides, amphotericin and pentamidine.

Magnesium replacement therapy

Magnesium sulfate

The standard intravenous preparation is magnesium sulfate ($MgSO_4$). Each gram of magnesium sulfate has 8 meq (4 mmol) of elemental magnesium. A 50% magnesium sulfate solution (500 mg/ml) has an osmolarity of 4000 mosm/l, so it must be diluted to a 10% (100 mg/ml) or 20% (200 mg/ml) solution for intravenous use. Saline solutions should be used as the diluent for magnesium sulfate. Ringer's solutions should not be used because the calcium in Ringer's solutions will counteract the actions of the infused magnesium.

Mild, asymptomatic hypomagnesemia

The following guidelines can be used for patients with mild hypomagnesemia and no apparent complications: 1. Assume a total magnesium deficit of 1 to 2 meq/kg, 2. Because 50% of the infused magnesium can be lost in the urine, assume that the total magnesium requirement is twice the magnesium deficit. 3. Replace 1 meq/kg for the first 24 hours, and 0.5 meq/kg daily for the next 3 to 5 days and 4. If the serum magnesium is greater than 1 meq/l, oral magnesium can be used for replacement therapy.

Moderate hypomagnesemia

The following therapy is intended for patients with a serum magnesium level less than 1 meq/l or when hypomagnesemia is accompanied by other electrolyte abnormalities: 1. Add 6 g $MgSO_4$ (48 meq Mg) to 250- or 500-ml isotonic saline and infuse over 3 hours. 2. Follow with 5 g $MgSO_4$ (40 meq Mg) in 250- or 500-ml isotonic saline infused over the next 6 hours and 3. Continue with 5 g $MgSO_4$ every 12 hours (by continuous infusion) for the next 5 days.

Life-threatening hypomagnesemia

When hypomagnesemia is associated with serious cardiac arrhythmias (e.g., torsades de pointes) or generalized seizures, do the following: 1. Infuse 2 gm $MgSO_4$ (16 meq Mg) intravenously over 2-5 minutes. 2. Follow with 5 gm $MgSO_4$ (40 meq Mg) in 250- or 500-ml isotonic saline infused over the next 6 hours. 3. Continue with 5 g $MgSO_4$ every 12 hours (by continuous infusion) for the next 5 days. Serum magnesium levels will rise after the initial magnesium bolus but will begin to fall after 15 minutes. Therefore, it is important to follow the bolus dose with a continuous magnesium infusion. Serum magnesium levels may normalize after 1 to 2 days, but it will take several days to replenish the total body magnesium stores.

To summarize, in this retrospective analysis we came to a conclusion that 23% patients developed hypokalemia and in these patients in order to detect early hypokalemia regular monitoring of serum potassium should be done along with clinical correlation. Hypokalemia in these patients should be corrected by oral or intravenous potassium. In some patients L-AMB induced hypokalemia does not respond to treatment. So, a detailed evaluation of patient along with hematological work up

should be done to know the cause of resistant hypokalemia and the commonest cause being hypomagnesemia should be looked forward and serum magnesium levels should be evaluated and should be corrected accordingly. Also, in these patients a special eye should be kept on renal function and blood sugar management.

CONCLUSION

Hypokalemia is a common electrolyte disorder occurring in patients receiving L-AMB which if undetected can be life threatening. In all patients receiving L-AMB administration, serum potassium levels should be monitored right from day 1, so that preadministration hypokalemia can be corrected and hypokalemia at early stage can be detected and preventing it from becoming severe hypokalemia. Also, these patients can develop hypomagnesemia which should be monitored. Invasive opportunistic fungal infections are a serious cause of morbidity and mortality for immunocompromised patients. Therefore, adequate medical management of these patients not only requires proper antifungal administration but also management of electrolyte imbalances related to the administration. L-AMB is a lifesaving drug provided it is used judicially and with utmost care.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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