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A Clinical Pharmacist Intervention in a Case of COVID-Associated Mucormycosis

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ABSTRACT

Background: India has reported an increasing number of COVID-19 infections and subsequently has brought along a variety of fungal and bacterial infections. We report a diabetic COVID-19 patient who developed mucormycosis and required clinical pharmacist interventions to optimize the medications. **Case Presentation:** A 54-year-old diabetic male patient previously diagnosed with COVID-19 and treated with methylprednisolone and other supportive medications due to severe lung involvement was re-admitted to the hospital, due to right maxillofacial swelling and blurring of vision, a week after discharge. **Diagnosis:** COVID-associated Mucormycosis. **Investigations and Treatment:** Debridement and nasal biopsy showed broad septate hyphae. He was prescribed Inj. Amphotericin Liposomal 150 mg/day, Tab. Posaconazole 300 mg/day to manage his condition post-surgery. **Interventions:** On the suggestions of a clinical pharmacist, the patient was administered liposomal Amphotericin 150 mg as the nurse was giving him 150 mg of conventional Amphotericin without light protection. Delayed release tab. posaconazole was replaced with injectable posaconazole as the patient was on nasogastric tube. Posaconazole was combined with atorvastatin, and this interaction potentiates the effect of atorvastatin. So atorvastatin was switched to rosuvastatin. The HCPs were trained, the dosing guide for Amphotericin B was prepared and the prescription was audited daily. **Conclusion:** Our report highlights the importance of a structured and collaborative patient care process involving a clinical pharmacist to enhance medication therapy management.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has invited a wide range of opportunistic bacterial and fungal infections. An unwelcome triad of diabetes, rampant use of corticosteroids with COVID-19 as a backdrop have contributed to a surge in cases of mucormycosis. The prime reason that makes the germination of Mucorales possible in people with COVID-19 is favorable conditions of hypoxia, hyperglycemia, acidosis, increased ferritins levels, and decreased phagocytic activity of WBCs due to immunosuppression combined with other risk factors, including extended hospitalizations with or without mechanical ventilators.[1] India ranks second as the largest population with Diabetes Mellitus (DM) and incidentally also emerged with the highest cases of mucormycosis in the world.[2] DM has been the popular risk factor associated with mucormycosis in India and worldwide, with a global mortality rate of 46% DM-associated mucormycosis.[3] While prolonged corticosteroid therapy has been linked to opportunistic fungal infections, including aspergillosis and mucormycosis, even a short course of corticosteroids has lately been linked to mucormycosis, particularly in people with diabetes.

The management of mucormycosis includes a multimodal approach: treating the offending conditions, aggressive surgical debridement of involved tissues, and antifungal therapy.[4]

The initial choice of an antifungal is 5mg/kg/day of liposomal amphotericin B and is strongly recommended, with clinicians also increasing the dose up to 10mg/kg/day in an attempt to control the infection. Whereas intravenous or oral, Posaconazole (300 mg every 12 hr on the first day followed by 300 mg every 24 hr) or Isavuconazole (200 mg every 8 hr for 2 days followed by 200 mg every 24 hr) are considered salvage therapy or step down therapy depending on the response of amphotericin B by the patient.[5] The dose of 1-1.5mg/kg Amphotericin B deoxycholate is advised against, in light of significant toxicity, but it may be the only choice with limited-resource settings.[6]

The treatment of mucormycosis can be challenging, and a slight lapse in inpatient care can appear to be fatal in an already terrifying disease. Elimination of underlying risk factors, antifungal therapy, and treatment of any new additional symptoms can subject patients to drug interactions, dosage errors, and wrong administration techniques. Even though there are adequate case reports on COVID associated mucormycosis, there are none from a clinical

pharmacist's perspective. This raises the need to encourage active reporting of medication errors and include clinical pharmacists in the management of the disease in critical and noncritical settings. Medication errors that go unnoticed or missed or committed out of lack of knowledge can impede recovery, and prove deadly leaving us all second-guessing the nature of the disease. The following case study is of a 54-year-old Asian male diagnosed with mucormycosis and it illustrates the pharmacotherapeutic interventions by clinical pharmacists on potential drug-drug interactions, drug and dosage errors, and also suggests long-term resolutions to combat these errors.

CASE REPORT

A 54-year-old Asian man with, a known case of DM, Hypertension (HTN), and Ischaemic Heart Disease (IHD), admitted to a tertiary care hospital in Pune, presented with right maxillofacial swelling, redness, swelling, lacrimation, and blurring of vision in the right eye for the past five days associated with frontal headache. He further complained of intermittent fever spikes and dysphagia. His past medical history included admission to another rural hospital for severe COVID-19 pneumonia and uncontrolled DM. A week after discharge, he developed right eye swelling and facial swelling on his right cheek. His routine medications consisted of aspirin 150 mg once daily, clopidogrel 75 mg once daily, atorvastatin 40 mg once daily, chlorthalidone/metoprolol 6.25mg/50 mg, deflazacort 6 mg, glimepiride/ metformin 1 mg/500 mg twice daily, vildagliptin 50 mg once daily, zinc 50 mg twice daily, Vit C 500 mg thrice daily, forecourt 200 mg thrice daily and deriphylline 150 mg once daily.

On arrival at the emergency department, his visual acuity was 6/6, and was vitally stable with right eye ophthalmoplegia and lesions on his palate. A baseline workup, along with blood culture and nose samples for fungal smear and culture, was sent. Computed Tomography (CT) of the chest for COVID-19 screening and CT of the facial region with contrast were ordered. Ear, nose, and throat examinations were done, and a infectious disease specialist was consulted a decision was made to start amphotericin B and discontinue deflazacort. Magnetic Resonance Imaging (MRI) of the head was advised after neurology and ophthalmology inputs.

Investigations

Baseline results showed normal creatinine, normal electrolyte count, increased total lymphocyte count (12000/mm3) with neutrophils of 77.4/mm3, and elevated C-reactive

protein of 123 mg/L. He had glycated hemoglobin (HbA1C) of 11.9%. Blood and urine cultures showed negative growth, cytological smear of the nasal cavity showed broad septate hyphae suggestive of mucormycosis.

CT Chest was suggestive of past COVID-19 infection. CT facial region with contrast and MRI (head) revealed inflammatory/infective processes suggestive of mucormycosis.

Treatment

Emergency Septoplasty/ Right Turbinectomy/ Right Functional Endoscopic Sinus Surgery (FESS)/ Debridement/ Right partial Maxillectomy/ Alveolectomy was performed on the second day of hospitalization, and the patient was shifted from the surgery ward to the male ward. HTN and DM medications were optimized, and a feeding Nasogastric (NG) tube was placed. The patient was on Inj. cefuroxime 1.5 g every 12 hr for 5 days and was also prescribed intravenous Liposomal Amphotericin B 150 mg/day and Tab Posaconazole 300 mg twice a day on day 1, followed by 300 mg daily during his hospital stay and continued his past medications.

Clinical Pharmacist Interventions

During the routine ward round, the clinical pharmacist observed the following medication errors:

1. **Administration Error (Wrong Formulation):** To treat the mucor infection, doctors prescribed liposomal amphotericin B 150 mg/day, but the nursing staff indented and administered conventional amphotericin B deoxycholate 150 mg. The standard dose of liposomal amphotericin B is 3-6 mg/kg/day while the dose of conventional amphotericin deoxycholate is 0.5-1.5mg/kg/day and needs to be administered over 24 hr with light protection to avoid drug degradation.

The clinical pharmacist noticed the error after the first conventional Amphotericin dose was administered, corrected to liposomal amphotericin B 150mg/day with dextrose 5% water over 2-6 hr.

2. **Prescription and Administration Error (Wrong Route):** After undergoing FESS, the patient was put on a feeding tube. As part of the mucor therapy, tab. posaconazole was prescribed and the nurse administered the drug by crushing the tablet. As the posaconazole

tablet comes in delayed release and gastro-resistant formulation, crushing it makes the drug less potent. Upon noticing the error, the clinical pharmacist informed the doctor and advised him to change it to either syrup or an injectable formulation of posaconazole to gain the desired clinical effect.

3. Drug-Drug Interaction: Tab. Atorvastatin which was a part of the patient's routine medication for his treatment of IHD was concomitantly administered with posaconazole and that can lead to a severe type of drug-drug interaction. However, after discussing the severity of the interaction, the patient's condition, and the future implications of the interaction with the physician, a decision was made to switch to tab. rosuvastatin.

Patient Outcomes

The patient suffered no adverse events or reactions during his entire hospital stay, and a close watch was kept over his lab results and symptoms. He was discharged with Liposomal Amphotericin B 150 mg/day and Tab. Posaconazole 300 mg/day after 12 days of hospital stay.

Also, the consent of the patient was taken for the case report.

DISCUSSION

The patient's prescription necessitated therapy modification to achieve safe and optimum use of medications. Too much or too little of the correct drug, wrong drug or administration techniques, and drug-drug interactions were the problems identified by the clinical pharmacist in this case.

Because of the extent of the patient's drug-related errors, the focus was first on administering the correct drug. Amphotericin B Deoxycholate and Liposomal Amphotericin differ in their doses, toxicity profiles, cost, and administration techniques. Excessive amounts of the former drug and inadequate amounts of the latter drug can cause nephrotoxicity and subtherapeutic dosing, respectively. The antifungal activity of Amphotericin B deoxycholate reduces within 24 to 96 hr of light exposure, as suggested by data.[7] A case report by Groeneveld *et al.*, describes two pediatric patients who received an overdose of conventional Amphotericin B instead of the liposomal formulation and suffered severe adverse effects resulting in renal insufficiency and cardiac dysfunction, respectively.[8] *Nagel and Nguyen* in their report

identified a 42-year-old woman who received a 5-fold overdose of conventional Amphotericin and developed acute kidney injury.[9] Also, a case report by Mohr *et al.*, describes a fatal amphotericin B overdose to a patient due to the administration of Amphotericin B deoxycholate 5mg/kg instead of liposomal amphotericin B 5mg/kg.[10] There are very limited case reports or analyses of the errors that are caused by Amphotericin B. Hence it is imperative to publish such articles to create awareness and to practice optimum medication management.

The root of confusion was easy to understand as both of these drugs were Amphotericin with similarities in their brand name and only a change in their formulations. It seemed likely that the first brand that popped up on the system while indenting was the one selected and administered. On further routine audits, we found multiple observations of the same kind, and tackling this repetitive pattern of error required the creation of a dosing guide of Amphotericin B for nurses and doctors alike (Annexure 1). The dosing guide was uploaded to every system of the hospital, which provided easy access to all healthcare professionals, and they were also educated periodically. Specific to Amphotericin, an alert could be created in the system, and at any point of the wrong indent by the nurse or dispensation by the pharmacist, the computer produces an incessant low-tone ringing sound to signal an error.

The next target of therapy modification was administering the appropriate dosage form. Not all oral solid products can be tampered with if a patient is unable to swallow the medication orally. Sustained-release, extended-release, and gastro-resistant formulations are a few of these examples which should be refrained from crushing as the pharmacokinetic profile of such drugs may turn erratic. Subtherapeutic serum Posaconazole concentrations are observed in patients with normally functioning Gastrointestinal (GI) tracts.[11] Yi *et al.* studied posaconazole therapeutic drug monitoring in 100 patients given different posaconazole formulations. Of the 100 patients, subtherapeutic levels (≤0.7 μg/ml) were seen in 3.4% (29/100) and 18.2% (33/100) receiving intravenous and delayed-release tablets, respectively.[12] Tverdek *et al*. also reported subtherapeutic serum levels (<0.7 μg/ml) in 18% (14/76) of patients receiving delayed-release posaconazole tablets for invasive fungal infection prophylaxis.[13]

Therefore, to provide a deeper understanding of the subject, nurses and resident doctors were trained on the different dosage forms. Permanently blocking out this error was the aim, so along with implementing a ‘Do not Crush’ list with our hospital’s brands and generics,

routine bedside medication audits were also initiated to detect errors of this variety. Special identification markers could also be put on the strips before dispensing to completely cancel out such errors.

The final intervention was eliminating the drug-drug interaction, involving atorvastatin and posaconazole. Concomitant use of posaconazole with HMG-CoA reductase inhibitors that are largely metabolized by CYP3A4 (e.g. atorvastatin) is prohibited since elevated plasma concentrations of these drugs might cause rhabdomyolysis. It is presumed that posaconazole inhibits CYP3A4, an enzyme responsible for atorvastatin metabolism.[14] There are no clinical reports on posaconazole and atorvastatin interaction, but Dybro *et al.* reported a case of rhabdomyolysis caused by a drug interaction between simvastatin and itraconazole. Owing to the risk of rhabdomyolysis, including myalgia, CYP3A4 inhibitors (voriconazole, fluconazole, clarithromycin) are contraindicated with CYP3A4 metabolizers (simvastatin, atorvastatin, lovastatin).[15]

After the drug was changed to rosuvastatin, the patient was counseled on the therapy modification, medication education on rosuvastatin was provided to the patient and patient queries were answered. Common drug interactions in the future can be prevented with hospitals developing software listing out the frequently consumed drugs, ranging from cardiovascular to dermatologic drugs. So, when two contraindicated drugs are prescribed, the computer generates an alert system, minimizing the error at the primary level.

Without a doubt, doctors, nurses, clinical pharmacists, and patients should be included in the implementation of resolution strategies and optimal disease management. An open mind by each healthcare professional and a multidisciplinary team approach in treating each patient would ensure the best for every patient.

CONCLUSION

Patient safety and accurate therapy management go hand in hand. Given the high-risk nature and possibilities of sub-therapeutic dosing of these drugs, it is imperative to identify and prevent errors in the prescribing, administering, and dispensing stages. In this case report, the authors describe inadvertent errors that were caused due to unawareness and oversight, and also discuss long-term solutions to tackle the redundancy of errors. The potential safety concerns and uncertainty that arise with using Amphotericin can be alleviated with

communication among healthcare professionals. It is critical to report such errors, through case reports, to promote patient safety.

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CONFLICT OF INTEREST

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A Quick Guide to Administration of Amphotericin B

(Annexure 1)

Types of Formulation	**Usual Daily Dose**	**Reconstitution/ Dilution**	**Administration IV**
Conventional/ Deoxycholate Formulation AMPHOTRET FUNGIZONE AMFOCAN NEOTERIC	0.5-1.5 mg/kg	Reconstitution: 50mg drug with 10ml Sterile Water for Injection (SWFI). Dilution: Dilute 50mg with 500ml of 5% Dextrose (D5W) (Conc. 0.1 mg/ml). Test Dose: Administer 1mg of Amphotericin B over 10 - 30 min without administration	Infuse over 6-24 hr. As rapid infusion can lead to hypotension, hypokalaemia, arrhythmia, and shock. Light Protection: Use Photo guard IV set / aluminium foil paper. Premedication: Paracetamol with Avil or

		of premedication.	Hydrocortisone.
Liposomal Formulation AMBISOME PHOSOME LAMBIN AMPOHNEX AMPHOGARD ABHOPE	3-6 mg/kg	Reconstitution: 50mg drug with 12ml SWFI (4mg/ml). Dilution: Dilute to the final concentration of 0.2-2mg/ml. Test Dose: Administer l mg of Liposomal Amphotericin over 10 min without administration of premedication.	Step 1: Reconstitute each vial and shake it vigorously to obtained yellow solution. Step2: Withdraw the final solution into a sterile syringe. Step3: Use 5 micron filter which is already provided with the Inj. and insert the the reconstituted solution into 5% dextrose (D5W). Step 4: Infuse over 2-6 hr. Light Protection is not required.
Emulsion AMPHOMUL	5mg/kg	Dilution: Dilute with 500ml D5W (Conc. 0.5-2mg/ml) Infusion rate- 2.5mg/kg/hr). Test Dose: Administer 1mg of Emulsion Amphotericin over 20 min without administration of premedication.	Step l: Shake the vial gently and withdraw the content from the vial syringes. Step 2: Remove the needle from each syringe filled with AMPHOMUL. Step3: Use 5 micron filter syringe filter provided with each vial pack and then fix the needle to the other

			end of the syringe filter. Step 4: Insert the needle into an I.V. bag containing 5% Dextrose and empty the contents into the bag. Step5: Infuse over 2-4 hr. Light Protection is not required.
Amp-B lipid complex Formulation (ABLC) AMPHOLIP	5 mg/kg	Dilution: Dilute with 500ml D5W 5 mg/kg (Conc. 1 mg/ml, Infusion Rate-2.5mg/kg/hr). Test Dose: Administer 1mg of ABLC Amphotericin over 10 min without administration of premedication.	Step l: Shake the vial gently and withdraw the content from the vial syringes. Step 2: Remove the needle from each syringe filled with AMPHOLIP. Step3: Use 5 micron filter syringe filter provided with each vial pack and then fix the needle to the other end of the syringe filter. Step 4: Insert the needle into an I.V. bag containing 5% Dextrose and empty the contents into the bag.

			Step 5: Infuse over 2 hr. Light Protection is not required.

IMPORTANT POINTS TO REMEMBER

1. Do flush the IV line with Dextrose 5% (D5W) before and after administration.
2. Dilute only in D5% (incompatible with NS, RL, and other salt-containing solutions).
3. Do not administer simultaneously (Y-site) with other drugs prepared with salt containing IV fluids.
4. Lipid-based and conventional formulations are not interchangeable and have different dosing recommendations.
5. INCOMPATIBILITIES: Amphotericin B should not be co-administered through the same I.V. catheter with blood or plasma.

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