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REVIEW ARTICLE OPEN ACCESS

A Review on Drug-Drug Interactions in Mucormycosis-Affected Patients Using Amphotericin B

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Abstract

Drug-drug interaction is a public health problem that constitutes one of the leading causes of morbidity and mortality worldwide. In India, only a few studies reported drug-drug interactions occurring while using Amphotericin-B in patients with mucormycosis-induced drug interactions. The objectives of the present study were to assess the drug interactions occurring due to polytherapy and the frequency, severity, and preventability of the ADRs occurring because of drug-drug interactions. Drug-drug interaction checking, a multimodal approach for the treatment of mucor patients, involves highly complex regimens and hence accounts for a high susceptibility towards adverse drug reactions (ADRs). The present study aims to determine the prevalence of adverse events in patients treated with amphotericin-b. Drug interaction-related ADRs among mucor patients are worrisome. It has a worse impact on patient quality of life and, in addition, increases the cost of therapy along with the loss of lives or body organs. It is found that timely reporting of drug interaction-related ADRs and having an effective ADR monitoring system in place ensure the preventability of drug-related ADRs in many cases. Surgeons should be actively involved in ADR reporting (PV) and exchange constructive information, update each other, and educate each other about the appropriate use of anti-fungal drugs. Pharmacovigilance is the need of the hour and could be of immense value in reducing morbidity and mortality if practiced with all its might.

KEY WORDS: ADR (adverse drug reaction), mucormycosis, amphotericin B, drug interaction etc.

1. INTRODUCTION

'WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem[1]. Pharmacovigilance is a practice whose aim is to monitor drug safety in real-life conditions and to observe post-marketing adverse events related to the drugs[2].

The concerns of pharmacovigilance have been broadened to include herbals, traditional and complementary medicines, blood products, biologicals, vaccines, and medical devices[3].

There are some specific purposes of pharmacovigilance that are to improve patients care and safety in relation to the use of medicines and all medical interventions, including paramedical interventions. Contribute to the assessment of benefit and harm including risk and effectiveness of medicine. It also aims to promote education, understanding and clinical training. Responding to the needs of a particular and WHO personnel strength running the programme, pharmacovigilance has developed and will continue to be develope together with the encouraging souls[4,5].

ages extracts of *Ziziphus spina-christi* have been used as inflammatory treat toothache, analgesic, pectoral, astringent (LF), anti-rheumatic, purgative (FR), for stomach pain, anti-helminthic[6,7]. Some species, like *Ziziphus mauritiana* Lam. and *Ziziphus spina-christi* (L.) wild occur on nearly every continent.

2. Drug-Drug Interaction

Drug-drug interactions (DDIs) are one of the commonest causes of medication errors[3]. A drug interaction occurs when a patient's response to a drug is modified by food, nutritional supplements, formulation excipients, environmental factors, other drugs, or disease. Interactions between drugs (drug-drug interactions) may be beneficial or harmful[4]. It can be defined as the pharmacological or clinical responses arising due to the combination of drugs that have been administered for the prevention and management of any disease. It frequently conjures images of a sudden catastrophic and even fatal outcome. Drug interaction occurs when the outcome of one drug is modified

by some other drug(s). It may arise either from alteration of the pharmacokinetic and pharmacodynamic pathways or from the combination of their actions or effects[5-7]. Drug interactions can be a consequence of various situations that reflect the growing number of drugs available on the market, the increasing complexity of polytherapy, and the very widespread practice of self-medication, making the situation more severe and difficult. Most of the studies evaluated, analysed, and estimated that drug interactions may affect up to 63% of all hospitalised patients.

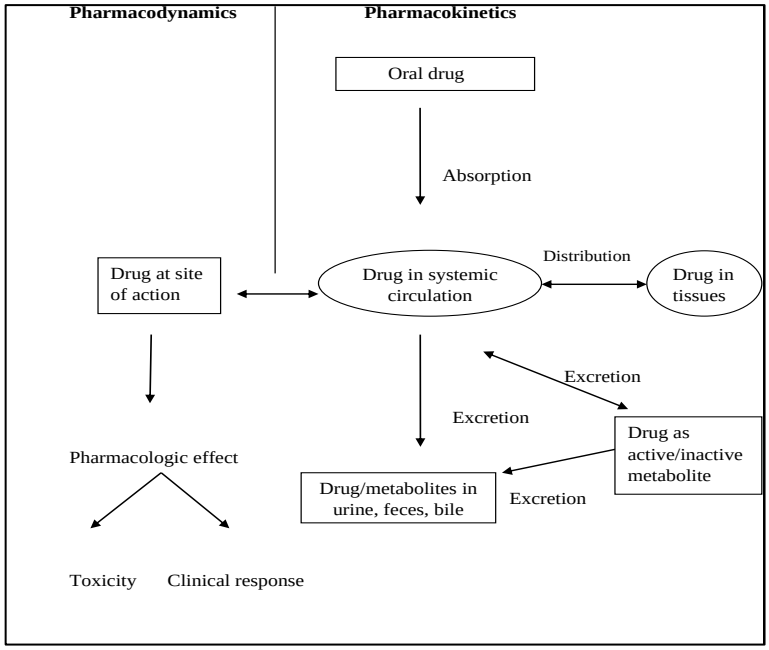

Figure 1. Pharmodynamic and Pharmacokinetic activity of drug

Pharmaceutical drug-drug interactions occur outside the body when the formulation of a drug is disturbed by another before it is administered. For example, precipitation of sodium thiopentone and vecuronium within an intravenous dose[4] Pharmaceutical drug interactions can be classified into two parts: chemical and physical drug interactions. An example of chemical drug-drug interaction can be seen among potassium phosphate and calcium chloride in total parental nutrition preparations, also known as TPNs or hyperalimentation. These two drugs may result in the formation of calcium phosphate, which will form a precipitate in the IV fluid bag. Physical alterations may occur in many different ways. For example, if a sustained-release medicine is crushed, it will release its API more quickly as per its actual release rate. Other examples of physical alteration are changes in environmental conditions such as the presence of light, which may affect the drug's chemical nature due to which many drugs are protected in amber-coloured glass containers or opaque containers; humidity, which may affect the medicines; and temperature too.

2.1 Causes of unwanted drug effects and interactions

Unwanted drug effects and drug interactions may arise due to a number of reasons and natural clamors. For example, when the drug given to the patient has expired and is taken in emergency conditions by their own, when the drug is being judged incorrectly, which can be because of similar names or pronunciation and possibly the same visualisation, when no prior kidney function test (KFT) is being done before prescribing the drugs to the patient, when the wrong dosage is administered by the patient, that is, overdose if taken of any medicine, if the route of drug administration is not according to the nature of the drug, when errors occur in consuming the drugs, transmission errors, etc.

Adverse drug reactions, known as ADRs, may be defined as an unexpected response of drugs to animals or human beings and are regarded as one of the most prevalent causes of morbidity and mortality in hospitalised patients. ADRs are of two types: Type-A (these reactions are common, predictable, and may occur in any individual) and Type-B (these are uncommon and unpredictable and only occur in susceptible individuals)[10].

According to the WHO, coronaviruses are a group of viruses belonging to the family of Coronaviridae that infect both animals and humans. Human coronaviruses can cause mild disease similar to a common cold, while others cause more severe disease (such as MERS, Middle East Respiratory Syndrome, and SARS, Severe Acute Respiratory Syndrome). A new coronavirus that previously had not been identified in humans emerged in Wuhan, China, in December 2019. The disease indication may include respiratory symptoms, including fever, cough, and shortness of breath. In more severe cases, infection can cause pneumonia, respiratory syndromes, which may be severe to acute, and sometimes death[11].

3. Mucormycosis

Mucormycosis is a difficult-to-diagnose rare disease with high mortality and morbidity. Mucormycosis-associated mortality is unacceptable, and recently developed treatment approaches are required. Due to delayed diagnosis, diseases tend to progress rapidly. Urgent surgical and medical intervention is lifesaving because of the often rapidly progressive and destructive nature of the infection. Delayed initiation of therapy is associated with increased mortality. Maximising survival rates requires rapid diagnostic and therapeutic intervention, including the immediate

involvement of a multidisciplinary medical, surgical, radiological, and laboratory-based team. Small focal lesions should be surgically resected before they progress to involve critical structures or distal organs. It is considered a therapeutic challenge since mucorales are resistant to most antifungals[12]. Only two systemic antifungals are currently available with good Mucorales activity: amphotericin B (including the lipid formulations) and the triazole posaconazole[13]. Dissemination of infection to a few sites is not so common, like the skin, brain, and some other sites. But if patients do not receive aggressive surgical and medical therapy, then direct extension of the infection can occur at the contiguous site[14].

3.1. Mucormycosis treatment using Amphotericin B

Amphotericin B deoxycholate is a polyene anti-fungal agent available since the 1960s. Amphotericin B has been formulated in three different forms: lipid complex, cholesteryl sulphate, and liposomal Amphotericin [16].

Amphotericin B (AmB) is a critical component of the treatment of serious systemic fungal infections[61], whereas specific dosage guidelines for paediatric use are still lacking. Amphotericin B has provocative track records, but in spite of this, it has serious toxic side effects due to which discontinuation of therapy may be required despite a life-threatening fungal infection. The principal chronic side effect of amphotericin B is nephrotoxicity. It may cause a renal tear due to a variety of mechanisms, mostly seen in men, and unusual baseline renal function. Clinical manifestations of amphotericin B nephrotoxicity include renal insufficiency, hypokalemia, hypomagnesemia, metabolic apathy, and polyuria due to nephrogenic diabetes insipidus. Based on a human study, it was discovered that consuming sodium in a good amount may reduce the incidence and severity of AmB[17]. Immunosuppressed patients are more susceptible to invasive fungal infections, such as those caused by tumours or transplantation, which result in morbidity and mortality. Amphotericin B is the oldest anitmycotic agent, but its use is limited due to its dose-dependent toxicity, especially nephrotoxicity. Amphotericin B has been designed in different pharmaceutical formulations in order to increase its safety margin, especially for its detrimental effects on the kidneys[18]. Amphotericin B has a broad spectrum of action[19]. Amphotericin B has been available since 1960 and remains the choice of treatment for most serious systemic fungal infections[20].

4. COVID-19

COVID-19 is a respiratory system-attacking disease recognised in December 2019, elaborately called coronavirus December 2019. COVID-19 is structurally similar to the virus causing severe acute respiratory syndrome (SARS). In comparison to SARS (2002 and 2003) and MERS (Middle East Respiratory Syndrome, 2012 and till present), COVID-19 put public health, research, and communities into a great challenge[21]. COVID-19 is epicenter-center in Hubei Province of the People's Republic of China and has spread initially in many countries and then throughout the world. After seeing the critical condition of many countries, the WHO emergency committee declared this a global health emergency at Chinese and international locations. The coronavirus was described first in 1966 by Tyrell and Bynoe, who cultivated the viruses from patients who were suffering from the common cold. These are enveloped, positive single-stranded large RNA viruses that cause infections in human beings, but they also affect a wide range of animals[22]. COVID-19-infected patients are prone to developing pneumonia with severe symptoms related to acute respiratory distress syndrome (ARDS) and multiple-level organ failure. SARS-infected patients show decreased peripheral T-cell subsets, and a rapid restoration in peripheral T-cell subsets was seen in those who were recovering from the infection. The recent novel coronavirus (COVID-19) disease outbreak caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is seeing a rapid increase in infected patients worldwide. SARS-CoV-19 activates anti-viral immune responses with a rise in uncontrolled inflammatory responses characterised by marked pro-inflammatory cytokine release in patients with severe COVID-19, leading to lymphopenia, lymphocyte dysfunction, and granulocyte and monocyte abnormalities. Rational management of SARS-CoV-19, including enhancing anti-viral immunity while inhibiting systemic inflammation, may be key to successful treatment[23]. Coronavirus is positive-stranded RNA (+ssRNA) that belongs to the subfamily Orthocoronavirinae of the Coronaviridae family (order Nidovirale) and is classified into four genera of CoVs: Alphacoronavirous, Betacoronavirous, Deltacoronavirous, and Gammacoronavirous. SARS-CoV-2 is prone to genetic mutations just like other RNAs while chasing new hosts, which results in variant mutants having different characteristics in comparison with the ancestoral strains. According to WHO, ‘’only a few variants of SARS-CoV-19-2 had effects on global public health and are considered variants of concern (VOCs), that is, the Alpha-first variant of concern described in the United Kingdom (UK) in late December 2020, the Beta-first reported in South Africa in December 2020, the Gamma-first reported in Brazil in early January 2021, and the Delta-first reported in India in December 2020. The origin of SARS-CoV-19 is not recognised, and it is estimated that it originated from some animal implicating zoonotic transmission. whereas genomic analysis suggests that SARS-CoV-19 has possibly evolved from a strain found in bats[24]. COVID-19 is a deadly infection and has no particular treatment at present, for which reason it has been managed by heavy utilisation of steroids and supportive care equipment such as oxygen cylinders and ventilators in emergencies. In the midst of this pandemic, people who got treatment for COVID-19 developed secondary infections such as mucormycosis, commonly known as black fungus[25].

4.1. Mucormycosis due to COVID-19

Mucormycosis has been reported worldwide, mostly in patients who had COVID-19 previously. Aspergillus and candida have both been reported as the main fungal pathogens causing co-infection in people with COVID-19. Most of the cases of mucormycosis had especially described in India which may be possibly because of the ideal environment setup in patients of COVID-19 helping mucorales to germinate freely inside the COVID-19 infected patients that is , low oxygen amount (hypoxia), high glucose level (diabetes, new onset hyperglycemia, steroid induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis DKA), presence of increased amount of iron (

increased ferritin), decreased phagocytic activity of white blood cells (WBC) due to suppressed immune system (SARS CoV-2 mediated, steroid mediated or background comorbidities) coupled with several other risk factors which may cause prolonged hospitalisation[26]. Phagocytes have the main activity against mucormycosis and show defense mechanism for the protection of the host. Patients who have been infected with COVID-19 are highly susceptible to mucormycosis as a result of the barrier's deterioration, dysfunction of lymphocytes and phagocytes, and the use of medications such as steroids, an immunosuppressive agent that decreases the body's ability to fight with the foreign particles[27]. Mucormycosis in COVID-19-infected patients can occur due to less glycemic control, more and inappropriate use of corticosteroids, and the use of broad-spectrum antibiotics[28].

5. Management of Drug Interactions

Drug-drug interactions can be managed in different ways. By avoiding administering the combination of drugs. It precludes the concomitant medicine administration risk for patients. Combinations must be avoided unless it is determined that the benefit of coadministration of the drugs outweighs the risk to the patient. The addition of another drug to one of the interacting drugs is recommended when appropriate. Patients should be monitored carefully if the drugs are co-administered. Several potential management options are available: use of an alternative agent, change in drug regimen (dose, interval), or route of administration to minimise the interaction, or monitoring the patient if drugs are co-administered. The potential for harm is low, and no specific action is required other than to be aware of the possibility of the drug interaction. Available evidence suggests no interaction[29]. Any interactions between existing drugs in a given patient have already occurred. Hence, they are part of a differential diagnosis. Knowledge of the pharmacological effects of drugs and of patient physiology together allows recognition of potential pharmacodynamic drug-drug interactions. Drugs with a narrow therapeutic index are particularly susceptible to pharmacokinetic drug-drug interactions. A small number of drugs are important 'perpetrators' of pharmacokinetic drug-drug interactions. Starting or stopping a drug is a prescribing decision that may cause a drug interaction[30]. Drug interactions are manageable only if they are dependent on the time of administration and by separately administering the drugs and avoiding co-administering the two interacting drugs[31].

Different ways for avoiding drug-drug interaction in clinical practices

There are some rules to manage drug-drug interactions in clinical practices.

1. If existing drugs had any interactions among them previously in a particular patient that have now occurred, this will become part of the differential diagnosis.

2. Knowing the patient's psychology with the prescribing drug plays a vital role in further improvements and knowing the pharmacodynamic potential of upcoming drug-drug interactions.

3. Drugs are susceptible to pharmacokinetic drug-drug interactions if they have a narrow therapeutic index.

4. Drug interactions may also result from decisions made when prescribing or stopping a drug[32].

6. Conclusion

The group of patients targeted in the study for pharmacovigilance was those who got diagnosed with the infection of mucormycosis following COVID-19 infection. The group of patients was observed for a period of six months, from June 2021 to October 2021. All mucormycosis patients were receiving treatment with either the liposomal formulation or the conventional formulation of Amphotericin B.

During this observation period of six months, adverse drug reactions occurring as a result of drug-drug interactions were tabulated and reported to the ADR Monitoring Centre (AMC), All India Institute of Medical Sciences. The Amphotericin B-related ADRs were uploaded on VIGIFLOW and sent to the National Coordinating Centre at Ghaziabad.

After analysing the reported ADRs related to the drug interactions, it was observed that the male population was more infected in accordance with the female population with mucormycosis. It was recorded that hypokalemia is the most common ADR recorded, followed by hypocalcemia, increased serum creatinine, hypomagnesia, diarrhoea, and chills.

Targeted pharmacovigilance added considerable information regarding adverse drug reactions that were observed in patients with mucormycosis.

References

[1]. Kumar MR, Bodhanapu S, Mani TT, Phaneendra P, Rahiman OF. Pharmacovigilance and its importance in drug regulation: An Overview. Der Pharmacia Lettre. 2011;3(2):165-9.

[2]. Mulchandani R, Kakkar AK. Reporting of adverse drug reactions in India: A review of the current scenario, obstacles and possible solutions. International Journal of Risk & Safety in Medicine. 2019 Jan 1;30(1):33-44.

[3]. Remington JS, Wilson CB, Nizet V, Klein JO, Maldonado Y. Infectious diseases of the fetus and newborn E-book. Elsevier Health Sciences; 2010 Aug 27.

[4]. Shekar HS, Chandrashekhar HR, Bhagawan BC. Study of identification and assessment of drug-drug interactions. Journal of Evolution of Medical and Dental Sciences. 2014 Feb 10;3(6):1373-9.

[5]. Sheldon H, Preskorn, and David F. Guide to Psychiatric Drug Interactions. April; 2006; 13(4):3564.

[6]. Shekar HS, Chandrashekhar HR, Bhagawan BC. Study of identification and assessment of drug-drug interactions. Journal of Evolution of Medical and Dental Sciences. 2014 Feb 10;3(6):1373-9.

[7]. Grönroos PE, Irjala K M, Huupponen R K, Scheinin H, Forsström J, Forsström JJ. A medication database-a tool for detecting drug interactions in hospital. Eur J ClinPharmacol 1997; 53(1):13– 17.

[8]. Katon W, Cantrell C, Sokol MC, Chiao E, Gdovin JM. Impact of antidepressant drug adherence on comorbid medication use and resource utilization. Arch Intern Med 2005;165:2497-503.

[9]. Gallicano K, Drusano G. Introduction to drug interactions. InDrug interactions in infectious diseases 2005 (pp. 1-11). Humana Press.
[10]. Shibbiru T, Tadesse F. Adverse drug reactions: An overview. History. 2016;1(0).
[11]. World Health Organization. Coronavirus disease (COVID-19) outbreak: rights, roles and responsibilities of health workers, including key considerations for occupational safety and health: interim guidance, 19 March 2020. World Health Organization; 2020.
[12]. Boucher HW, Groll AH, Chiou CC, Walsh TJ. Newer systemic antifungal agents: pharmacokinetics, safety and efficacy. Drugs. 2004 Sep;64:1997-2020.
[13]. Huang YQ, Tremblay JA, Chapdelaine H, Luong ML, Carrier FM. Pulmonary mucormycosis in a patient with acute liver failure: a case report and systematic review of the literature. Journal of critical care. 2020 Apr 1;56:89-93.
[14]. Sugar AM. Mucormycosis. Clinical infectious diseases. 1992 Mar 1;14(Supplement_1):S126-9.
[15]. Remington JS, Wilson CB, Nizet V, Klein JO, Maldonado Y. Infectious diseases of the fetus and newborn E-book. Elsevier Health Sciences; 2010 Aug 27.
[16]. Palleria C, Di Paolo A, Giofrè C, Caglioti C, Leuzzi G, Siniscalchi A, De Sarro G, Gallelli L. Pharmacokinetic drug-drug interaction and their implication in clinical management. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2013 Jul;18(7):601.
[17]. Benson JM, Nahata MC. Pharmacokinetics of amphotericin B in children. Antimicrobial agents and chemotherapy. 1989 Nov;33(11):1989-93.
[18]. Lemke A, Kiderlen AF, Kayser O. Amphotericin b. Applied microbiology and biotechnology. 2005 Aug;68(2):151-62.
[19]. Warnock DW. Amphotericin B: an introduction. Journal of antimicrobial chemotherapy. 1991 Jan 1;28(suppl_B):27-38.
[20]. Zhang C, Chen M, Wang G, Fang W, Ye C, Hu H, Fa Z, Yi J, Liao WQ. Pd@ Ag nanosheets in combination with Amphotericin B exert a potent anti-cryptococcal fungicidal effect. Plos one. 2016 Jun 7;11(6):e0157000.
[21]. Fauci AS, Lane HC, Redfield RR. Covid-19—navigating the uncharted. New England Journal of Medicine. 2020 Mar 26;382(13):1268-9.
[22]. Velavan TP, Meyer CG. The COVID-19 epidemic. Tropical medicine & international health. 2020 Mar;25(3):278.
[23]. Yang L, Liu S, Liu J, Zhang Z, Wan X, Huang B, Chen Y, Zhang Y. COVID-19: immunopathogenesis and Immunotherapeutics. Signal transduction and targeted therapy. 2020 Jul 25;5(1):1-8.
[24]. Cascella M, Rajnik M, Aleem A, Dulebohn S, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). StatPearls. 2021 Apr 20.
[25]. Mahalaxmi I, Jayaramayya K, Venkatesan D, Subramaniam MD, Renu K, Vijayakumar P, Narayanasamy A, Gopalakrishnan AV, Kumar NS, Sivaprakash P, Rao KR. Mucormycosis: An opportunistic pathogen during COVID-19. Environmental Research. 2021 Jul 6:111643.
[26]. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2021 Jul 1;15(4):102146.
[27]. Mishra N, Mutya VS, Thomas A, Rai G, Reddy B, Mohanan AA. A case series of invasive mucormycosis in patients with COVID-19 infection. Int J Otorhinolaryngol Head Neck Surg. 2021 May;7(5):867-70.
[28]. Selarka L, Sharma S, Saini D, Sharma S, Batra A, Waghmare VT, Dileep P, Patel S, Shah M, Parikh T, Darji P. Mucormycosis and COVID-19: an epidemic within a pandemic in India. Mycoses. 2021 Oct;64(10):1253-60.
[29]. Isaac T, Weissman JS, Davis RB, Massagli M, Cyrulik A, Sands DZ, et al. Overrides of medication alerts in ambulatory care. Arch Intern Med 2009;169:305-11.
[30]. Macedo D, Leonardelli F, Dudiuk C, Vitale RG, Del Valle E, Giusiano G, Gamarra S, Garcia-Effron G. In Vitro and in vivo evaluation of voriconazole-containing antifungal combinations against Mucorales using a Galleria mellonella model of mucormycosis. Journal of Fungi. 2019 Jan 8;5(1):5.
[31]. van der Sijs H, Lammers L, van den Tweel A, Aarts J, Berg M, Vulto A, van Gelder T. Time-dependent drug–drug interaction alerts in care provider order entry: software may inhibit medication error reductions. Journal of the American Medical Informatics Association. 2009 Nov 1;16(6):864-8.
[32]. Snyder BD, Polasek TM, Doogue MP. Drug interactions: principles and practice. Australian prescriber. 2012 Jun 1;35(3).