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Original Article

A Comparative Study of Caspofungin and Micafungin in Treating Candidiasis Patients in Indian Population

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ABSTRACT

The study was conducted in different hospitals at Hyderabad on 86 patients, who satisfied the eligibility criteria, were accrued during the study period. These patients were randomized into 2-Arms, and were then evaluated according to the treatment protocol and the study was conducted for 8 months. A Total 86 subjects were enrolled into the study. Out of them 44 were randomized into test group and 42 were randomized into reference group. Caspofungin 70 mg daily once was given to test group, micafungin 150 mg daily once was the reference drug given to reference or control group. Drug treatment is given for 2 weeks the dosage form is IV infusion for one hour. The treatment can be exceeded if the condition If a subject does not respond for two weeks therapy. All the subjects were given treatment for 2 weeks and the response was taken in case repot forms. Candidiasis infections reported, there were esophageal candidiasis subjects 19 from test group and 19 from the reference group, invasive candidiasis 19 from test and 16 from the reference group. Vaginal candidiasis 5 from test and 7 from reference group. There were 5 subjects with vaginal candidiasis in the test and 7 subjects in the reference group, 4 subjects of test had reduction in the vaginal discharge, and 3/7 in reference group had reduction. 4/5 had reduction in the c. culture in blood in test group and 3/7 from the reference group. Vaginal P^H had exceeded to 6 in all the subjects. In the test 5/5 had showed reduction in the P^H 6/7 from the reference group. Fever, chills, nausea, vomiting, rash etc were reported by subjects, in the study the reference group had showed more number of subjects experienced adverse events. Thus, from the results of our study, caspofungin showed greater efficacy and safety than reference group.

Key Words: Capsofungin, micafungin, invasive candida, vaginal candida, esophageal candida.

1. INTRODUCTION

Candidiasis is infection by Candidiasis sp (most often C. albicans), manifested by mucocutaneous lesions, fungaemia, and sometimes focal infection of multiple sites [1]. Symptoms depend on the site of infection and include dysphagia, skin and mucosal

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lesions, blindness, vaginal symptoms (itching, burning, and discharge), fever, shock, oliguria, renal shutdown, and disseminated intravascular coagulation [2]. Diagnosis is confirmed by histopathology and cultures from normally sterile sites. Treatment is with amphotericin B, fluconazole, echinocandins, voriconazole, or posaconazole.

Candidiasis involving the mouth and esophagus is a defining opportunistic infection in AIDS. Although mucocutaneous candidiasis is frequently present in HIV-infected patients, hematogenous dissemination [3] is unusual unless other specific risk factors are present (see below). Neutropenic patients (e.g., those receiving cancer chemotherapy) are at high risk of developing life-threatening disseminated candidiasis.

Candidemia may occur in non neutropenic patients during (4) prolonged hospitalization. This bloodstream infection is often related to one or more of the following:

- Central venous catheters
- Major surgery
- Broad-spectrum antibacterial therapy
- IV hyperalimentation

The aim of the study is to evaluate the safety and efficacy of Caspofungin and Micafungin for the management of Candidiasis and the objective of the study is to compare the difference in the proportion of patients who develop significant drug-related adverse events(s) between the caspofungin and micafungin groups and to evaluate the difference in the overall response by each of esophageal candidiasis, invasive candidiasis and record the adverse events and the efficacy and safety of the two study groups.

Drug profile:

Caspofungin:

Caspofungin is an antifungal drug; the first of a new class termed the echinocandins from Merck & Co., Inc. It shows activity against infections with Aspergillus and Candidiasis, and works by inhibiting β(1,3)-D-Glucan of the fungal cell wall [5]. Caspofungin is administered intravenously. This compound belongs to the cyclic peptides. These are compounds containing a cyclic moiety bearing a peptide backbone. For the treatment of esophageal candidiasis and invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

Mechanism of action:

Caspofungin inhibits the synthesis of beta-(1,3)-D-glucan, an essential component of the cell wall of *Aspergillus* species and *Candidiasis* species. beta-(1,3)-D-glucan is not present in mammalian cells(6). The primary target is beta-(1,3)-glucan synthase.

Pharmacodynamics:

Caspofungin is an antifungal drug, and belongs to a new class termed the echinocandins. It is used to treat *Aspergillus* and *Candidiasis* infection, and works by inhibiting cell wall synthesis. Antifungals in the echinocandin class inhibit the synthesis of glucan in the cell wall, probably via the enzyme 1,3-beta glucan synthase [7]. There is a potential for resistance development to occur, however *in vitro* resistance development to Caspofungin by Aspergillus species has not been studied.

Pharmacokinetics:

92% tissue distribution within 36-48 hours after intravenous infusion Metabolized slowly by hydrolysis and N-acetylation. After single intravenous administration of [3H] caspofungin acetate, excretion of caspofungin and its metabolites in humans was 35% of dose in feces and 41% of dose in urine [8].

Uses :

Caspofungin is used to treat a variety of serious fungal infections. It is often used in patients who cannot use or do not respond to other antifungal medications

Micafungin

Mechanism of action:

Micafungin inhibits the synthesis of beta-1, 3-D-glucan, an essential component of fungal cell walls which is not present in mammalian cells [9]. It does this by inhibiting beta-1, 3-D-glucan synthase.

Pharmacodynamics:

Formerly known as FK463, micafungin is a semisynthetic lipopeptide synthesized from a fermentation product of *Coleophoma empetri* that works as an antifungal agent. It is a glucan synthesis inhibitor of the echinocandin structural class [10]. The U.S. Food and Drug Administration approved micafungin in March 2005. Micafungin inhibits an enzyme essential for fungal cell-wall synthesis.

Uses:

This medication is used to treat a variety of fungal infections (such as candidemia, esophageal candidiasis). It is also used to prevent fungal infections if you are having a bone marrow or stem cell transplant [11, 13], since people with weak immune systems have a higher risk of fungal infections.

Side effects:

Nausea, vomiting, diarrhea, headache, trouble sleeping, or irritation at the site of injection may occur(12). If any of these effects persist or worsen, notify your doctor or pharmacist promptly. A very serious allergic reaction to this drug is unlikely, but get medical help right away if it occurs. Symptoms of a serious allergic reaction may include: rash,itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

2. MATERIALS AND METHODS

The study was conducted in different hospitals at Hyderabad.

- 86 patients, who satisfied the eligibility criteria, were accrued during the study period.
- These patients were randomized into 2-Arms, and were then evaluated according to the treatment protocol and the study was conducted for 8 months.

Inclusion criteria:

Esophageal candidiasis: patients with clinical symptoms of esophageal candidiasis (i.e., odynophagia, dysphagia,and heartburn) and plaque observed on the esophageal mucosa by endoscopy. Patients with fever >38 °C observed, or fever of ≥37.5 °C that continues for 1 h or more despite the use of antibiotic therapy and positive results for the (1,3)-β-D-glucan test.Invasive candidiasis (except candidemia):fungal infection strongly suspected at screening based on the clinical course and symptoms, typical radiographic imaging findings on X-ray and computed tomography(CT) (based on infection site), and positive results for the (1,3)-β-D-glucan test.

Exclusion criteria:

Patients with mycoses due to causes other than Candidiasis spp. and Aspergillus species patients who had already received caspofungin or micafungin for the current fungal infection within the 7 days prior to initiation of the study. International Normalized Ratio (INR) (prothrombintime) of >2 × ULN (upper limit of normal) for patients not receiving anticoagulants; INR >4 × ULN for patients receiving anticoagulants total bilirubin of >5 ×ULN; aspartate aminotransferase (AST), alanine amino transferase (ALT), or alkaline phosphatase (ALP) of >5 × ULN. Patients with a history of serious drug-related allergy or sensitivity. Patients with moderate or severe hepatic insufficiency (acute hepatitis, hepatic cirrhosis, etc.). Patients who received another investigational drug within 1 month prior to study entry; Patients who are pregnant, intend to become pregnant during the period up to 2 weeks after study completion, or are lactating.

3. RESULTS

Table 1: baseline demographic characters

BASELINE DEMOGRAPHIC CHARACTERS	TEST DRUG (n=44)	REFERENCE DRUG (n=42)
Males (%)	36 (82.0)	32 (76.7)
Females (%)	8 (18.0)	10 (23.3)
Age in years (mean)	68.9	63.3
Weight in kgs (mean)	47.24	41.03
Diabetes mellitus	8 (18.0)	12(28.3)
Pulmonary disorder	9 (21.3)	6 (15.0)
TB	9 (14.8)	8 (18.3)
Use of immunosuppressive drugs	1 (1.6)	3 (6.7)
Use of steroids	1 (3.3)	2 (5.0)

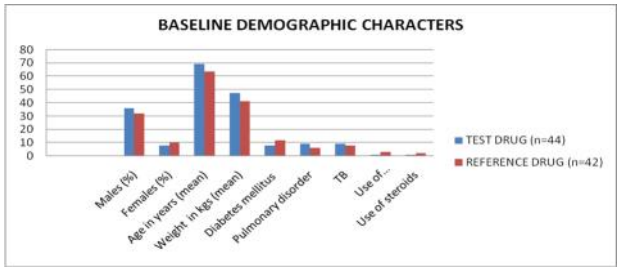

Fig 1: Baseline Demographic Character

Table 2: Types of Infection

Types of infection	Test group (n=44)	Reference group (n=42)
Esophageal candidiasis	19	19
Invasive candidiasis	19	16
Vaginal candidiasis	5	7

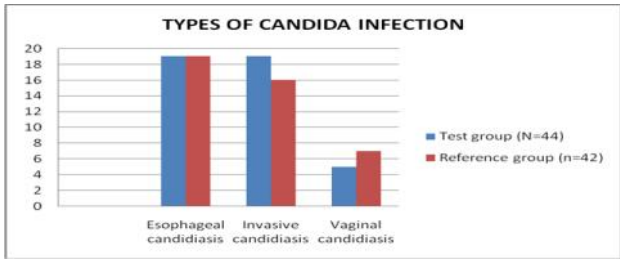

Fig 2: Types of Candida Infection

Table 3: base line infection of candida species micbrobiology

BASELINE INFECTION OF CANDIDA SPECIES	TEST GROUP (n=44)	REFERENCE GROUP (n=60)
c. albicans	18	15
c. glabrata	11	14
c. tropicalis	8	8
c. parapsilos	7	9
Other candida species	3	2

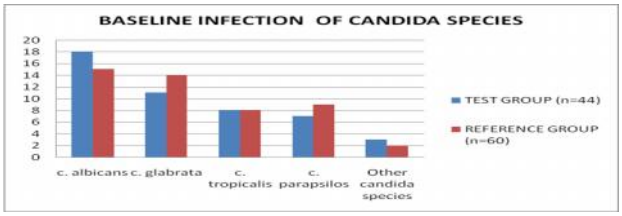

Fig 3: baseline Infection of Candida Species

Table 4: Eot Candida Species Microbioilgy

EOT INFECTION OF CANDIDA SPECIES	TEST GROUP (n=61)	REFERENCE GROUP (n=60)
c. albicans	16/18	11/15
c. glabrata	8/11	10/14
c. tropicalis	6/8	6/8
c. parapsilos	7/7	5/9
Other candida species	1/3	2/2

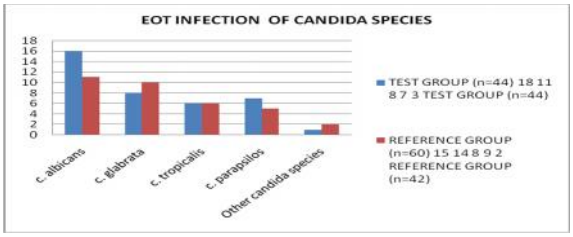

Fig 4 : EOT of c. Speceies microbiology

Table 5: Esophageal Candidiasis Baseline Endoscopic Analysis

ESOPHAGEAL CANDIDIASIS BASELINE ENDOSCOPIC ANALYSIS	TEST GROUP (n)	REFERENCE GROUP (n)
Grade- 4	**16**	**14**
Grade -3	**2**	**6**
Grade- 2	**3**	**2**
Grade-1	**1**	**2**
Grade – 0.5	**0**	**0**
Grade-0	**0**	**0**

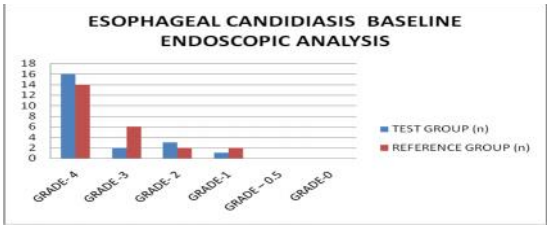

Fig 5: Esophgeal Candidiasis Baseline and EOT

Evaluation of invasive candida:

Table 6: Apache Ii Score Baseline

APACHE II SCORE FOR INVASIVE CANDIDA	TEST GROUP	REFERENCE GROUP
0-5	0	0
6-10	2	1
11-15	4	1
16-20	6	8
21-25	9	8
26-30	5	3
> 30	1	2

Table 7: Apache Ii Score EOT

APACHE II SCORE FOR INVASIVE CANDIDA	TEST GROUP	REFERENCE GROUP
0-5	**7**	**2**
6-10	**12**	**8**
11-15	**2**	**3**
16-20	**1**	**3**
21-25	**5**	**6**
26-30	**1**	**1**
> 30	**0**	**0**

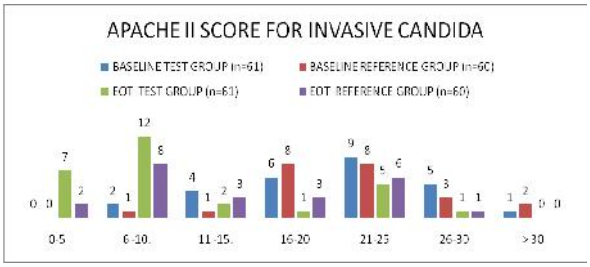

Fig 6: Baseline And Eot Apache Score

Evaluation of vaginal candidiasis:

Table 8: Vaginal Candida Clinical Response

MEASUREMENT VAGINAL CANDIDA.	TEST GROUP	REFERNCE GROUP
Vaginal discharge	4/5	6/7
Reduction in c.culture microbilogy	4/5	3/7
Vaginal p^{h} less than 4.5	5/5	6/7

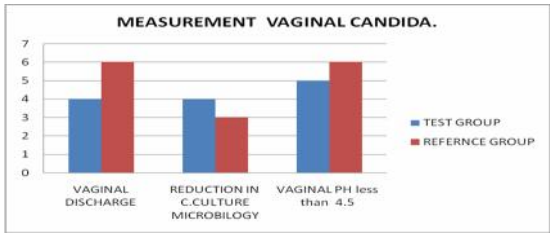

Fig 7: Vaginal Candida Clinical Response

Safety evaluation:

Table 9: Adverse Events Reported

Adverse events reported	Test group (n=44)	Reference group (n=42)
Fever	9	10
Chills	4	6
Nausea	4	7
Vomiting	1	2
Diarrhea	1	2
Headache	6	9
Rash	1	1
Phlebitis	1	3

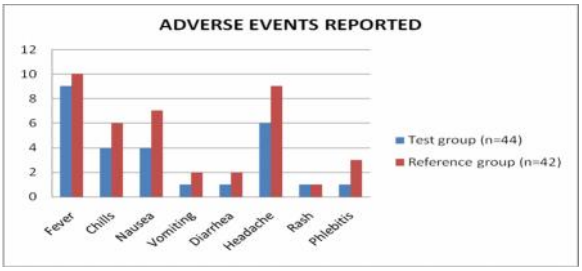

Fig 8: Adverse Events Reported

4. DISCUSSION

A Total 86 subjects were enrolled into the study. Out of them 44 were randomized into test group and 42 were randomized into reference group. Study was conducted under the supervision of the investigator. The subjects were explained about the risks and benefits of the study. Subjects were selected according to the protocol. All subjects were asked to sign the informed consent form. The study was conducted at prime hospital. Caspofungin 70 mg daily once was given to test group, micafungin 150 mg daily once was the reference drug given to reference or control group. Drug treatment is given for 2 weeks the dosage form is IV infusion for one hour. The treatment can be exceeded if the condition if a subject does not respond to two weeks therapy. All the subjects were given treatment for 2 weeks and the response was taken in case repot forms, the baseline demographic characters were recorded in the CRF, age, weight, and height, sex distribution were collected and are represented in the table 1, and presented graphically in graph no 1 and 2,

the presence of TB, DM, pulmonary disorders and any use of drugs and steroids were all taken at baseline. The 2nd table represents the types of candidiasis infections reported, there were esophageal candidiasis subjects 19 from test group and19 from the reference group, invasive candidiasis 19 from test and 16 from the reference group. Vaginal candidiasis 5 from test and 7 from reference group.Table 3 and 4 represents the baseline and clinical response before and after the drug treatment the present of infection the candidiasis species in the blood. The clinical response is presented in the graph no4.Table 5 and 6 represent the change in endoscopic grade score for esophageal candidiasis before and after the treatment, there is significant change in the test group compared with reference group. More subjects responded to the test group. The difference between test and reference group is presented in graph no 5.Table no 6 and 7 represents the change in the baseline and EOT of invasive candidiasis with drug treatment, the test group have responded significantly than the reference group after the treatment. This is represented in the graph no 6.Table no 8 represents the measurement of vaginal candidiasis there were 5 subjects with vaginal candidiasis in the test and 7 subjects in the reference group, 4 subjects of test had reduction in the vaginal discharge, and 3/7 in reference group had reduction.4/5 had reduction in the c. culture in blood in test group and 3/7 from the reference group. Vaginal P^H had exceeded to 6 in all the subjects. In the test 5/5 had showed reduction in the P^H 6/7 from the reference group. Over all the test group have showed greater clinical response in the reduction of vaginal candidiasis. Table no-9 presents the overall adverse events reported from the subjects during the study. Fever, chills, nausea, vomiting, rash etc were reported by subjects, in the study the reference group had showed more number of subjects experienced adverse events.

5. CONCLUSION

Candida species are the most common cause of opportunistic fungal infection worldwide. *Candida*is the major fungal pathogeno fhumans causing diseases ranging from super ficial mucosal infections to disseminated, systemic infections that are often life threatening. The study was conducted in different hospitals at Hyderabad on the finished populations for 8 months. The safety and efficacy of capsofungin and micafungin was studied for invasive candida, esophageal candida, and vaginal candida. Thus, from the results of our study, capsofungin showed greater efficacy and safety than reference group. .

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