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Original Article

Comparative Interventional Clinical Approach to Study the Safety and Efficacy of Solithromycin with Azithromycin in the Treatment of Community Acquired Pneumonia

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ABSTRACT

Pneumonia is an acute infection of the lung parenchyma distal to the terminal bronchiole, most commonly bacterial in nature, and associated with clinical and/or radiological evidence of consolidation of part or parts of one or both lungs. It remains a cause of considerable morbidity and mortality throughout the world. Mortality is improved by early initiation of antibiotics to which the causative organism(s) are susceptible, and adversely affected by delayed or inappropriate initial therapy. To evaluate the safety and efficacy of solithromycin in subjects suffering with pneumonia. To evaluate the occurrence of relapse.To evaluate the occurrence of superinfection. The trial was a randomized, active-controlled comparative study which was intended to evaluate the efficacy and safety of Solithromycin in comparison with Zithromax in pneumonia (HAP) caused by β - lactamase (extended spectrum beta lactamase and metallo-beta lactamase) producing gram negative bacteria. Totally 90 evaluable ESBL producing gram negative infection cases were included in the study. Although thiswas a retrospective cohort study, the strict inclusion and exclusion criteria used in this study resulted in two groups thatwere extremely well balanced at baseline. Drawing the study groups from the same time period mitigated any temporalbiases introduced by improvements in clinical care standards. The safety of both drugs were compared and the subjects with azithromycin have experienced more adverse effects. From our study the results suggest that the test drug is greater and safer than the Azithromycin therapy in subjects suffering with pneumonia condition.this is the first study, to the best of our knowledge that has specifically examined the outcomes of empirical Solithromycin versus Azithromycin for patients with severe CAP. The results strongly suggest that Solithromycin therapy increases survival for this severely ill patient group and is safer than the azithromycin. Further study of Solithromycin empirical therapy versus Azithromycin for patients with severe CAP in a prospective, randomized clinical trial with optimal dosages of Solithromycin is warranted based on these results.

Keywords: Solithromycin, Pneumonia, Lung.

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1. INTRODUCTION

Pneumonia is a common illness affecting approximately 450 million people a year and occurring in all parts of the world[1].

It is a major cause of death among all age groups resulting in 4 million deaths (7% of the worlds yearly total). The annual incidence of pneumonia diagnosed in the community is estimatedto be between 5 and 11 per 1000 adult population.4 Incidence varies by agefrom about 6 per 1000 population in the 18-39 age-group to 34 per 1000population in those aged 75 years and above[2].Risk factors for pneumoniainclude increasing age, male sex,co morbidities, cigarette smoking, preexisting chronic obstructive pulmonary disease, heart disease andoccupational dust exposure[3].

Our aim is to evaluate the safety and efficacy of solithromycinin subjects suffering with pneumonia .To compare the clinical response of IP with reference drug.

DRUG PROFILE:

SOLITHROMYCIN -

Solithromycin is a ketolide antibiotic undergoing clinical development for the treatment of community-acquired pneumonia (CAP) and other infections. It is expected to be the first macrolideantibiotic available in intravenous, oral, and pediatric suspension formulations in over 20 years.Solithromycin is a highly potent next-generation macrolide, the first fluoroketolide, which has potent activity against most macrolide-resistant strains. In vitro and in vivo studies have shown potent activity against S. pneumoniae as well as an extended spectrum of activity against CA-MRSA, streptococci, Haemophilus, enterococci, Mycobacterium aviumand in animal models of malaria. It is also active against atypical bacteria, such as legionella, chlamydia, mycoplasma and ureaplasma, and against gonococci and other organisms that cause genitourinary tract infections. It is 8-16 times more potent than azithromycin and is active against azithromycin-resistant strains[4]. Solithromycin's activity against resistant strains is driven by its ability to interact with three sites on the bacterial ribosome, compared to one for current macrolides. The binding to three ribosomal sites is expected to limit resistance development.

The highly potent fluoroketolide candidate, solithromycin, is not likely to exhibit similar toxicities as it lacks the pyridine side-chain and does not show significant inhibition of these receptors.In addition, solithromycin has three binding sites on the bacterial ribosome compared to either one or two sites with other macrolides[5]. This additional binding site is believed to strengthen ribosomal binding interactions and, thereby, minimize the potential for resistance development when compared with other macrolides.8 to 16 times more potent than azithromycin and is active against organisms that have become resistant to azithromycinPotent in vitro activity against all important respiratory pathogens, including pneumococci, β-hemolytic streptococci, staphylococci, Hemophilus, Legionella, Mycoplasma, Moraxella and Chlamydophila. Potent in vitro activity against other medically significant pathogens including CA-MRSA, M. avium, malaria, enterococci and gonococci.

AZITHROMYCIN:

Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is C38H72N2O12, and its molecular weight is 749.00. Azithromycin has the following structural formula:

- Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of C38H72N2O12• 2H2O and a molecular weight of 785.0.
- ZITHROMAX (azithromycin for injection) consists of azithromycin dihydrate and the following inactive ingredients: citric acid and sodium hydroxide. ZITHROMAX (azithromycin for injection) is supplied in lyophilized form in a 10-mL vial equivalent to 500 mg of azithromycin for intravenous administration. Reconstitution, according to label directions, results in approximately 5 mL of ZITHROMAX for intravenous injection with each mL containing azithromycin dihydrate equivalent to 100 mg of azithromycin.

Pharmacokinetics

In patients hospitalized with community-acquired pneumonia receiving single daily one-hour intravenous infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/mL, the mean Cmax± S.D. achieved was 3.63 ± 1.60 µg/mL, while the 24-hour trough level was 0.20 ± 0.15 µg/mL, and the AUC24 was 9.60 ± 4.80 µg·h/mL.

Metabolism

In vitro and in vivo studies to assess the metabolism of azithromycin have not been performed.

Elimination

Plasma concentrations of azithromycin following single 500 mg oral and i.v. doses declined in a polyphasic pattern with a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hours[6]. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues.

Drug-Drug Interactions

- Drug interaction studies were performed with oral azithromycin and other drugs likely to be co-administered. The effects of co-administration of azithromycin on the pharmacokinetics of other drugs are shown in Table 1 and the effect of other drugs on the pharmacokinetics of azithromycin are shown in Table 2.
- Co-administration of azithromycin at therapeutic doses had a modest effect on the pharmacokinetics of the drugs listed in Table 1. No dosage adjustment of drugs listed in Table 1 is recommended when co-administered with azithromycin[9].
- Co-administration of azithromycin with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin.

INDICATIONS AND USAGE

- azithromycin for injection is indicated for the treatment of patients with infections caused by susceptible strains of the designated microorganisms in the conditions listed below. As recommended dosages, durations of therapy, and applicable patient populations vary among these infections.
- Community-acquired pneumonia due to Chlamydia pneumoniae, Haemophilusinfluenzae, Legionella pneumophila, Moraxella catarrhalis, Mycoplasma pneumoniae, Staphylococcus aureus, or Streptococcus pneumoniae in patients who require initial intravenous therapy[7].
- Pelvic inflammatory disease due to Chlamydia trachomatis, Neisseria gonorrhoeae, or Mycoplasma hominis in patients who require initial intravenous therapy. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with ZITHROMAX.
- ZITHROMAX (azithromycin for injection) should be followed by ZITHROMAX by the oral route as required.
- Appropriate culture and susceptibility tests should be performed before treatment to determine the causative microorganism and its susceptibility to azithromycin. Therapy with ZITHROMAX may be initiated before results of these tests are known; once the results become available[8], antimicrobial therapy should be adjusted accordingly.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZITHROMAX (azithromycin) and other antibacterial drugs, ZITHROMAX (azithromycin) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria[10]. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2. MATERIALS AND METHODS

- The trial was a randomized, active-controlled comparative study which was intended to evaluate the efficacy and safety of SOLITHROMYCIN in comparison with Zithromax in pneumonia (HAP) caused by β - lactamase (extended spectrum beta lactamase and metallo-beta lactamase) producing gram negative bacteria.
- Totally 90 evaluable ESBL producing gram negative infection cases were included in the study.
- Subjects who were MBL positive and show sensitivity to study drugs were enrolled in the study and analyzed separately.

3. RESULTS

Efficacy Evaluation

Table 1: Baseline Demographic Characters

DEMOGRAPHIC BASELINE CHARACTERS	REFERENCE GROUP (n=39)	TEST GROUP (n=33)	P Value
AGE (YEARS)	50.9(11.4)	48.5(11.4)	0.485
MALES	25	21	0.327
FEMALES	14	12	0.245
BMI (kg/m$^{2)}$	26.6(5.2)	25.1(4.2)	0.326
PRIOR EPISODES OF PNEUMONIA	7	2	0.005
PRIOR ANTIBIOTIC THERAPY	33	29	0.145

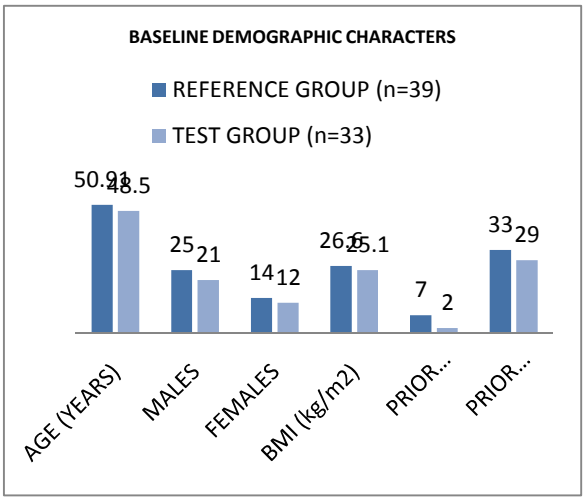

Fig 1: Baseline Demographic Character

Charecterstic (Causative pathogen)	**No. (%) of patients with the indicated characteristic**			
	Baseline		**Follow-up**	
	SOL (n = 33)	**AZT (n = 39)**	**SOL (n = 33)**	**AZT (n = 39)**
Streptococcus pneumoniae	33	35	30/33	29/35
Haemophilusinfluenzae	18	20	17/18	15/20
Haemophilus spp.	21	28	21/21	21/28
Staphylococcus aureus	13	17	13/13	17/17
Klebsiellapneumoniae	31	37	31/31	34/37
Pseudomonas aeruginosa	25	30	25/25	36/30
Escherichia coli	21	28	20/21	22/28
MRSA	30	36	29/30	34/36

Table 2: Causative Pathogens Before and Eot

PSI Score	Baseline PSI		PSI at EOT (after 5 days)	
	TEST (n=33)	REFERENCE (n=39)	TEST (n=33)	REFERENCE (n=39)
Class I	0	0	7	2
Class II	0	0	15	18
Class III	0	0	11	17
Class IV	10	19	0	2
Class V	23	20	0	0

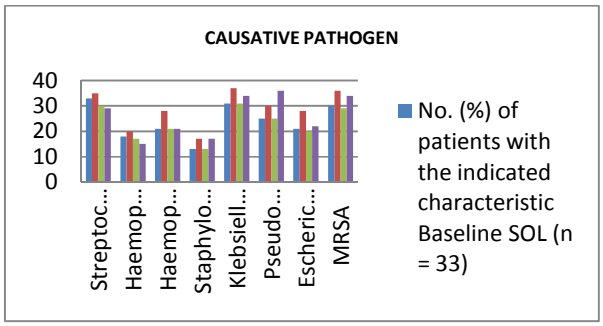

Fig 2: Causative Pathogens Before And Eot

Table 3: efficacy assessment by psi score at baseline and Eot

APACHE SCORE	APACHE Baseline		APACHE SCORE at EOT (after 5 days)	
	TEST (n=33)	REFERENCE (n=39)	TEST (n=33)	REFERENCE (n=39)
0-5	0	0	0	0
6-10	0	0	0	0
11-15	0	0	0	0
16-20	0	0	0	0
21-25	0	0	5	9
26-30	0	0	28	30
> 30	33	39	0	0

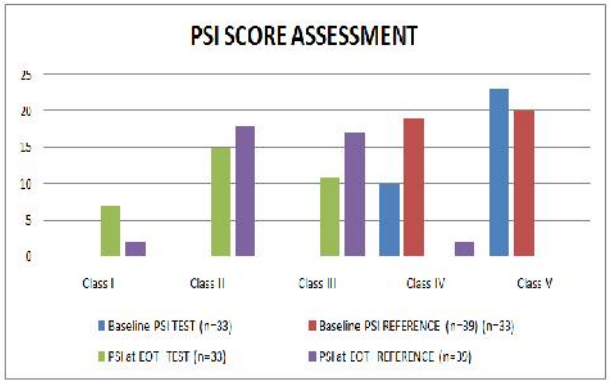

Fig 3: Efficacy Assessment By Psi Score At Baseline And Eot

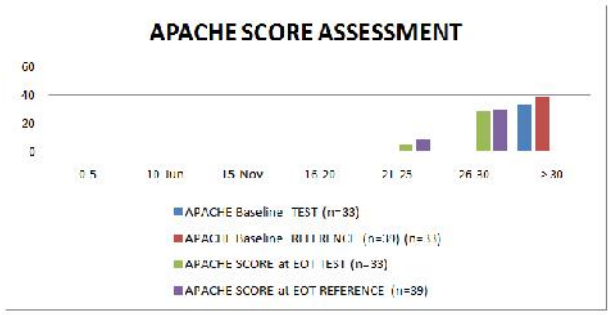

Fig 4: Efficacy Assessment By Apache At Baseline And Eot

Table 5: Adverse Reported By Both Test And Reference Group

ADVERSE EVENTS REPORTED	TEST GROUP(n=33)	REFERENCE GROUP (n=39)
DIARRHEA	9	11
NAUSEA	2	7
ABDOMINAL PAIN	8	11
VOMITING	7	15
INSOMNIA	5	12

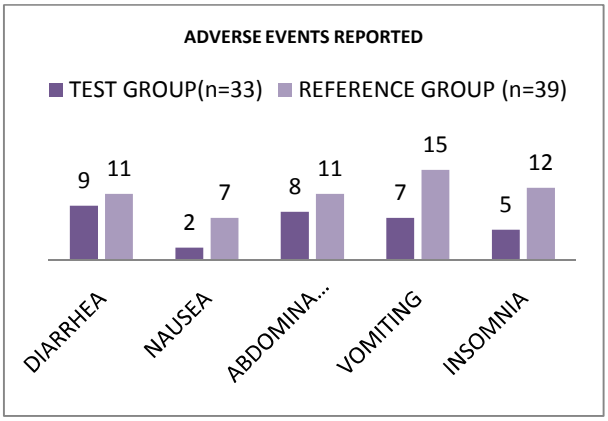

Fig 5: Adverse Reported By Both Test And Reference Group

4. DISCUSSION

A total of 75 LRTI patients were hospitalized with a diagnosis of CAP during the study period; of these patients satisfied the IDSA CAP definition, did not die within the first 24 h after presentation to the hospital, and had not been hospitalized or resided in a long-term care facility for >14 days in the 30 days prior to admission.

- Of the 100 CAP patients, 33 received test drug therapy and 39 received reference drug. The empirical antibiotic regimens provided to the other CAP patients are shown in Table
- All patients in the test received a β lactam–_-lactamase inhibitor combination antibiotic with azithromycin.
- Bivariate comparisons of baseline clinical and laboratory characteristics between treatment groups are shown in Table 1.

- The two groups were similar with respect to age, gender, andlaboratory findings, prior episodes of CAP, prior antibiotic use,and mean PSI and APACHE-II scores.
- Within PSI category V, the treatment groups were similar with respect to clinical and laboratory characteristics.
- Overall, there were differences test drug treatment compared with the reference Among patients with severe CAP.
- Currently available data suggest that test drug therapy for severe CAP confers a significant benefit on patients, particularly those with bacteremic pneumococcal disease .
- Almost all of the clinical studies comparing azithromycin with the standard therapeutic CAP regimen were designed to show non inferiority or bioequivalence in order to gain licensing approval; therefore, high-risk patients in PSI class IV or V were usually excluded or poorly represented in these clinical trials.
- While the optimal study design for comparingtreatment regimens is a randomized, controlled trial, such astudy would be prohibitively costly and difficult to execute fora variety of reasons (strict inclusion criteria, difficulty in obtainingconsent from critically ill patients, etc.).
- Although thiswas a retrospective cohort study, the strict inclusion and exclusioncriteria used in this study resulted in two groups thatwere extremely well balanced at baseline. Drawing the studygroups from the same time period mitigated any temporalbiases introduced by improvements in clinical care standards.
- The safety of both drugs were compared and the subjects with azithromycin have experienced more adverse effects.
- From our study the results suggest that the test drug is greater and safer than the Azithromycin therapy in subjects suffering with pneumonia condition.

5. CONCLUSION

The study was conducted at PRIME HOSPITALS, HYDERABAD on the finished population. The purpose of the study was to find out the efficacy and safety ofSolithromycinwith Azithromycin in severe PNEUMONIA patients. In conclusion, this is the first study, to the best of our knowledge that has specifically examined the outcomes of empirical Solithromycin versus Azithromycin for patients with severe CAP. The results strongly suggest thatSolithromycintherapy increases survival for this severely ill patient group and is safer than the azithromycin. Further study of Solithromycinempirical therapy versusAzithromycin for patients with severe CAP in a prospective, randomized clinical trial with optimal dosages of Solithromycin is warranted based on these results.

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