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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ARTICLE INFO

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 \( \beta \)-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 this was a retrospective cohort study, the strict inclusion and exclusion criteria used in this study resulted in two groups that were extremely well balanced at baseline. Drawing the study groups from the same time period mitigated any temporal biases 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.

1. INTRODUCTION

Pneumonia is a common illness affecting approximately 450 million people a year and occurring in all parts of the world\(^1\).
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. 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.
- 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, Haemophilus influenzae, 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, 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 empirical 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Reference Group (n=39)</th>
<th>Test Group (n=33)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE (YEARS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALES</td>
<td>25</td>
<td>21</td>
<td>0.327</td>
</tr>
<tr>
<td>FEMALES</td>
<td>14</td>
<td>12</td>
<td>0.245</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.6(5.2)</td>
<td>25.1(4.2)</td>
<td>0.326</td>
</tr>
<tr>
<td><strong>PRIOR EPISODES OF PNEUMONIA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>2</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>PRIOR ANTIBIOTIC THERAPY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>29</td>
<td>0.145</td>
</tr>
</tbody>
</table>

Fig 1: Baseline Demographic Character

Table 2: Causative Pathogens Before and Eot

<table>
<thead>
<tr>
<th>Characteristic (Causative pathogen)</th>
<th>No. (%) of patients with the indicated characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline SOL (n = 33)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>33/35</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>38/20</td>
</tr>
<tr>
<td>Haemophilus spp.</td>
<td>21/28</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>13/17</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>31/37</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>25/30</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>21/28</td>
</tr>
<tr>
<td>MRSA</td>
<td>30/36</td>
</tr>
</tbody>
</table>
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-β-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, and laboratory 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 comparing treatment regimens is a randomized, controlled trial, such a study would be prohibitively costly and difficult to execute for a variety of reasons (strict inclusion criteria, difficulty in obtaining consent from critically ill patients, etc.).

Although this was a retrospective cohort study, the strict inclusion and exclusion criteria used in this study resulted in two groups that were extremely well balanced at baseline. Drawing the study groups from the same time period mitigated any temporal biases 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 of Solithromycin with 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 that Solithromycintreatment increases survival for this severely ill patient group and is safer than the azithromycin. Further study of Solithromycinempirical 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.

6. REFERENCES

Conflict of Interest: None
Source of Funding: Nil