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Case Review

CASE REVIEW ON EFFECTS OF AZITHROMYCIN AND ERYTHROMYCIN ON LOWER RESPIRATORY INFECTION

E. M. Varshini Goud*, Roshan Ali, V. V. Rajesham, T. Rama Rao
Department of Pharmacology, CMR College of Pharmacy, Kandlakoya (V), Medchal (RD), Hyderabad, Telangana, India
**Corresponding author: varshinigoud245@gmail.com*

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ABSTRACT
Lower respiratory infections are generally caused by viral or bacterial agents. The majority of bronchitis and bronchiolitis cases are caused by viruses. *Streptococcus pneumoniae* is the most common bacterial agent in community-acquired pneumonias. An open, randomized study of the efficacy and safety of the prototype antibiotics azithromycin, and erythromycin in the treatment of lower respiratory infection were compared. Azithromycin and Erythromycin doses were administered and studied on various cases, in the treatment of lower respiratory infections, azithromycin seems to be as effective as erythromycin and better tolerated with lower side effects and effective therapeutic effects.

Keywords: Lower respiratory infection, Azithromycin, Erythromycin, Pneumonia, Coronavirus.

1. INTRODUCTION
Respiration is defined as the release of energy from the breakdown of food molecules in the presence of oxygen, also a process by which carbon dioxide and oxygen are exchange between blood, cells, and air present in lungs. The respiratory system contains important components that help it function. Apart from the mouth, the nose is one of the first parts of the body to be involved in the process of respiration. It allows you to breathe in air that contains 21% oxygen and 0.4% carbon dioxide and directs it to your lungs. The pharynx is the space between the throat and the windpipe. "It acts as a channel for both air and food" [1].

The lower respiratory tract extends from the trachea to the lungs. The tract enters the lungs before splitting into the bronchi. The bronchi then divide further into smaller air pipes known as bronchioles. Bronchioles develop from secondary and tertiary bronchi. These bronchioles terminate in small air sacs known as alveoli. The alveolar sac is formed by a grouping of many alveoli. Blood capillaries emerge from these alveoli. Every alveolus exchange air, and the capillaries that emerge from these alveolar sacs and spread throughout the body transport the blood that entered from veins located throughout the body [2].

2. LOWER RESPIRATORY TRACT INFECTION
Lower respiratory tract infection is the term used by doctors to describe an infection that occurs in the human body's lower respiratory tract. Infections begin in the lower larynx and can spread to the bronchi and even the entire lungs. Bronchiolitis, pneumonia, bronchitis, and flu are the most common illnesses. The various viruses that attack our system are the primary cause of lower respiratory tract infection. Viruses that enter our bodies frequently take the form of structural proteins and thus go undetected by our immune system [2]. Common lower respiratory tract infections are discussed below.

2.1. Acute Bronchitis (AB)
It is an acute illness that occurs in a patient who does not have chronic lung disease and has symptoms such as coughing that may or may not be productive, as well as other symptoms or clinical signs that suggest LRTI and no other explanation (*e.g.,* sinusitis or asthma) [4].

2.2. Influenza
An acute illness characterised by fever and one or more of the following symptoms: headache, myalgia, cough, or sore throat [4].

2.3. Community-acquired pneumonia (CAP)
Acute illness characterised by a cough and at least one of the following new focal chest signs: fever lasting more than four days, dyspnoea/tachypnoea, and no other obvious cause [4].

2.4. Definite community-acquired pneumonia (CAP)

As previously stated, but supported by new chest radiograph findings of lung shadowing. The presence of chest radiograph shadowing in the elderly accompanied by acute clinical illness (unspecified) with no other obvious cause.

2.5. Acute exacerbation of bronchiectasis (AEBX)

An event in the natural course of the disease characterised by a worsening of the patient's baseline dyspnoea, cough, and/or sputum beyond day-to-day variability sufficient to warrant a change in management in a patient with bronchiectasis. If there is shadowing on the chest radiograph that is consistent with infection, the patient is diagnosed with CAP.

2.6. Pneumonia

Pneumonia is another infection of the lower respiratory tract. The virus *Streptococcus pneumoniae* causes it. The virus causes severe lung damage and has a 25% mortality rate among patients infected with it. If a child under the age of five is affected, he or she may not survive at all. Though this is not generally contagious, if your immunity is low, direct contact with the cough discharges may pass the virus on to you [2].

2.7. Few others

Bacterial meningitis caused by the virus *Neisseria meningitides* can cause infection of the lower respiratory tract and Group a strep cause's scarlet fever [2].

2.8. Coronaviruses (covid 19)

Coronaviruses are enveloped positive sense RNA viruses with spike-like projections on their surface that give them a crown-like appearance under an electron microscope, hence the name coronavirus. Four corona viruses, HKU1, NL63, 229E, and OC43, have been found in humans and cause mild respiratory disease. COVID-19 clinical features range from asymptomatic to acute respiratory distress syndrome and multi organ dysfunction. Fever (not always), cough, sore throat, headache, fatigue, headache, myalgia, and shortness of breath are common clinical features. Conjunctivitis is also mentioned. As a result, they are difficult to distinguish from other respiratory infections. In a subset of patients, the disease can progress to pneumonia, respiratory failure, and death by the end of the first week. All types of respiratory viral infections (influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, human metapneumovirus, non COVID-19 coronavirus), atypical organisms (mycoplasma, chlamydia), and bacterial infections are included in the differential diagnosis. COVID-19 cannot be distinguished from these infections clinically or through routine lab tests. As a result, travel history is important. However, as the epidemic spreads, the travel history will be rendered obsolete [5].

3. ERYTHROMYCIN

Erythromycin is an antibiotic produced by the actinomycete *Streptomyces erythreus*, which was discovered in a soil sample from the city of 110-110 on the Philippine archipelago's Panay Island. McGuire and his colleagues developed, purified, tested, and reported the antibiotic for the first time in 1952 [6].

3.1. Mechanism of action

Erythromycin is a bacteriostatic antibiotic, which means it inhibits bacterial growth rather than directly killing it. This is accomplished by inhibiting protein synthesis. Erythromycin binds to the 23S ribosomal RNA molecule in the bacterial ribosome's 50S subunit, causing a blockage in peptide chain synthesis and, ultimately, inhibiting protein synthesis. Because humans only have the 40S and 60S subunits and no 50S subunits, erythromycin has no effect on protein synthesis in human tissues. Erythromycin is effective against gram-positive and gram-negative bacteria, as well as a variety of other organisms. *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Listeria monocytogenes*, Coryne-bacterium minutissimum, and *Corynebacterium diphtheria* are among the gram-positive bacteria. *Legionella pneumophila, Neisseria gonorrhoeae, Haemophilus influenzae*, and *Bordetella pertussis* are among the gram-negative bacteria. Erythromycin also kills *Chlamydia trachomatis, Entamoeba histolytica, Mycoplasma pneumoniae, Treponema pallidum*, and *Ureaplasmaurealyticum*. Resistance to erythromycin can develop through modification of the 23S rRNA found in the 50S rRNA. Erythromycin is unable to bind to the ribosome, allowing the bacteria to continue protein synthesis. Erythromycin is a pro-motility drug in addition to being a bacteriostatic macrolide antibiotic. It is a motilin agonist, which increases motility in the gut [7].

3.2. Adverse Effect

It may also increase the risk of new born pyloric stenosis. All antibiotics have a high risk of causing nausea,

vomiting, abdominal pain, and diarrhoea. Erythromycin is a motilin agonist, so it is more likely to cause gastrointestinal side effects than other antibiotics. There is also the possibility of a rash, an allergic reaction, and reversible deafness. Stevens-Johnson syndrome and toxic epidermal necrolysis are uncommon side effects [7].

3.3. Uses

Streptococcal throat infections ("strep throat") and skin infections Lung infections, such as pneumonia caused by *Streptococcal pneumoniae, Mycoplasma pneumoniae*, and *Legionella pneumophila* (legionnaires disease), Inflammation of the cervix, Erythrasma, whooping cough, Listeriosis, Amebiasis of the intestine. It is used to treat staphylococcal skin infections and as an alternative antibiotic to treat syphilis, gonorrhoea, and chlamydia.
Erythromycin is used to prevent recurrent rheumatic fever and infections of the heart's valves (endocarditis) in patients with valvular abnormalities of the heart before dental treatments in patients who are allergic to penicillin [8].

4. AZITHROMYCIN

Azithromycin is anantibiotic that has been structurally modified from erythromycin. It has a broader spectrum of activity and better tissue pharmacokinetics than erythromycin. The drug is known for its activity against some gram-negative organisms linked to respiratory tract infections, specifically H. *influenzae*. Azithromycin is active against atypical pathogens such as *Legionella pneumophilae* (*L. pneumophilae*), *C. pneumoniae* and *M. pneumoniae*, and has similar properties to other macrolides against *S. pneumoniae* and *Moraxella catarrhalis* [9].

4.1. Mechanism of action

Azithromycin inhibits bacterial protein synthesis by binding to and interfering with the assembly of the 50S large ribosomal subunit and the growth of the nascent polypeptide chain. In contrast to larger macrocyclic antibiotics, it binds at the polypeptide exit tunnel, close to the peptidyl transferase centre (PTC) on the 23S rRNA, but does not inhibit PT activity. Because of azithromycin's basicity, it penetrates the outer membranes faster and enters the bacteria more effectively, increasing its activity against Gram-negative bacteria. Binding sites on the bacterial ribosome for the structurally distinct macrolides, lincosamines, streptogramin B, and ketolides (MLSbK) overlap significantly, so changes in a single ribosomal region alter susceptibility to multiple MLSbK antibiotics at the same time. Although azithromycin is ineffective as a bactericidal agent against *Pseudomonas aeruginosa* at clinically relevant concentrations, it inhibits the production of growth-stimulating, quorum-sensing, and alginate biofilm, which protects the microorganism from antibiotic action. Efficacy against *P. aeruginosa* virulence factor production and biofilm formation, as well as the ability to reduce the minimum inhibitory concentration (MIC) of anti-pseudomonas agents are all related to inhibition of ribosomal protein synthesis [10].

4.2. Adverse Effects

Hives, difficulty breathing, swelling in your face or throat, or a severe skin reaction are all symptoms of an allergic reaction to azithromycin (fever, sore throat, burning in your eyes, skin pain, red or purple skin rash that spreads and causes blistering and peeling). Seek medical attention if you have a severe drug reaction that affects multiple parts of your body. Skin rashes, fever, swollen glands, flu-like symptoms, muscle aches, severe weakness, unusual bruising, or yellowing of your skin or eyes are all possible symptoms. This reaction could happen several weeks after you started taking azithromycin. [11].

4.3. Uses

It is widely used for the treatment of chest infections such as pneumonia. In this pharmacokinetic feature mostly compressed between the extensive tissue distribution and high drug concentration is such diseases condition as fibroblasts, neutrophils, macrophages. It does not undergo metabolism and has prolonged half-life.

5. CASE REVIEWS

5.1. Comparison of azithromycin and erythromycin in the treatment of atypical pneumonias

Inpatients and outpatients of either sex having a clinical picture and chest X-rays compatible with atypical pneumonia were included in an open randomised multicentre trial. Patients with marked liver or kidney dysfunction, patients with any kind of gastrointestinal disease that could alter drug absorption, pregnant or lactating women, children under the age of 12, history and a physical examination. Before starting therapy, blood was taken for serological tests, and then again 15 to 21 days later. Before being into the study, participants had laboratory tests (haematology, blood biochemistry, urine analysis), as well as chest X-rays.

Outpatients had their clinical signs and symptoms of infection checked every 48 hours, on the sixth and eleventh days, and in the period from the fifteenth to the twenty-first day after starting therapy; inpatients were monitored daily. On the sixth and eleventh days after starting medication, haematological and other laboratory tests were redone. On the eleventh day after starting therapy, chest X-rays were taken again.

Azithromycin was administered at a dosage of 250 mg on day 1 and 250 mg once daily on days 2-5. Erythromycin was given for ten days at 500 mg qid. Only patients with known causative pathogens (four-fold rise of specific antibody titre) were included in the evaluation of clinical efficacy [12].

5.1.1. Result

Total 101 patients were included in the study; 57 patients were administered with azithromycin in which 31 were identified with *M. pneumoniae* and 8 patients were identified with *Chlamydia psittaci* and 8 were identified with other disease. Total 44 patients were administered with erythromycin, in which 24 was identified with *M. Pneumoniae* and 8 patients with *C. psittaci*, side effects observed in azithromycin and erythromycin respectively: Nausea (1 and 2), Vomiting (0 and 1), Epigastric pain (0 and 1), Diarrhoea (0 and 1), Urticarial rash (0 and 1) [12].

5.2. Simplified treatment of acute lower respiratory tract infection with azithromycin: A comparison with erythromycin and amoxicillin

Male or female patients aged 18 years or more were recruited for the study. Patients were required to have an acute bacterial infection of the lower respiratory tract. Patients with acute bronchitis, with or without underlying pulmonary disease, and acute exacerbations of chronic bronchitis were also included but patients with chronic pulmonary disease without an acute infective exacerbation were excluded. Patients with life-threatening conditions, cystic fibrosis, or known hypersensitivity to macrolides were excluded from the study. Other patients excluded were those who had received antibiotics in the 48hr preceding the start of the study, those with any past or present factor which may have affected drug absorption, those with evidence of drug or alcohol abuse, or women of child-bearing potential. If patients were receiving concomitant treatment with warfarin, carbamazepine and/or ergotamine, they were excluded.

Table 1: Dosing of Azithromycin and Erythromycin

Dose administered in mg	Azithromycin	Erythromycin
Day 1	Two 250 doses with 12hrs interval	500mg 4 times daily 7 to 10 days
Day 2-5	250 mg / day	

5.2.1. Study Design

Patient was instructed to return to efficacy assessment with in 48hr of the last dose of study medication and again 7-10 days after the last dose. Efficacy was calculated from data obtained at the latest examination in period 10-15 days after the start of treatment. Clinical response was categorized by changes, compared to pre-treatment in the following parameter as appropriate total and differential leucocyte counts body temperature frequency and severity of abnormal chest sounds or auscultation. Haematology, biochemistry and urine analysis safety parameters were recorded at each visit and 28 days.

5.2.2. Result

In the randomized studies azithromycin treatment (1.5g in 5 or 6 doses over 5 days) was compared with erythromycin treatment (14 or 20 grams in 28 doses over 7 days) in patient with acute respiratory tract infection. In these studies azithromycin gave a complete clinical cure in 70 % of the patients whereas erythromycin gave a cure in 60% of patient's acute respiratory tract infection [13].

5.3. Prospective Open Randomized Study Comparing Efficacies and Safeties of a 3-Day Course of Azithromycin and a 10-Day Course of Erythromycin in Children with Community-Acquired Acute Lower Respiratory Tract Infections

In these studies, children from 2-16 years age with acute LRTI were enrolled and studied. Patient excluded are inability to take oral medication and hypersensitive to erythromycin and azithromycin. Orally dosage of azithromycin suspension 10 mg / kg body weight at 3 doses for 3 days similarly erythromycin suspension 40mg / kg/ day at 3 doses for 10 days was administered.

5.3.1. Study design

Patients were divided in to two groups. Each child was examined clinically before and on days of 4-6, 10-14, 25-30 during treatment. Serum chemistry and haematology test along with urine analysis were performed before treatment and at 2nd interval. If any clinically relevant abnormalities were shown, a controlled chest X-ray was done at 25-30 days. During the examination at 3 intervals all possible side effects where included. Azithromycin 10 mg/kg once daily for 3 days and erythromycin 50mg/kg/day in 3 doses for 14 days to both the groups was subjected.

5.3.2. Result

The two treatment groups did not differ with respect to gender, age and initial diagnosis. 95 % of the patients from 85 members had initial abnormal chest X-ray. 85% have proven pneumonia and 17 patients were diagnosed with acute bronchitis. 45 patients are treated with azithromycin and 40 patients are treated with erythromycin. At second follow up visit after 10-14 days, 31 versus 27 patients in the azithromycin and erythromycin groups respectively were cured, 12 versus 9 were improved and 1 versus 4 treatment were considered to failure. At the third follow up visit (after 25 to 30 days), 41 vs 33 patients were cured in the azithromycin v/s erythromycin group respectively, 1 v/s 3 were improved and 2 patients in azithromycin group developed a new or recurrent LRTI with in the steady period. Treatment success defined as cure or major improvement was achieved in 42 of 45 (93%) azithromycin recipients' v/s 36 of 40(90%) erythromycin recipients. Adverse events were reported in 12 0f 45 and 6 of 40 of the patients treated with azithromycin and erythromycin respectively, a difference which was not statistically significant [14].

5.4. Comparative randomized trial of azithromycin versus erythromycin and amoxicillin for treatment of community-acquired pneumonia in children

5.4.1. Patient and specimen

The children considered were from 1 month to 14years old with clinical diagnosis of bacterial community acquired pneumonia eligible for treatment with oral antibiotics. The investigators divided the study population into two groups according to the clinical and radiological patterns *'Group 1'*; the children who presented with signs of classic bacterial pneumonia, crackles and chest X - ray with segmental, alveolar or lobar consolidation. *'Group2';* the patients included are with atypical pneumonia with prominent and frequently paroxysmal cough with clinical signs of consolidation, crackles, wheezing and chest X-ray with mixed alveolar - interstitial pattern. Both the groups are treated with same drugs.

Routine laboratory test was done such as white blood cell and differential counts, erythrocyte sedimentation rate (ESR) and chest X-ray before the treatment. Nasopharyngeal aspirates were collected and divided into three equal parts. One part is mixed with the phosphate buffered solution for detection of virus by indirect immunofluorescence, second portion was mixed with the PBS for detection of bacillus pertussis by direct immunofluorescence and third portion was inoculated in 2ml of 0.2M sucrose phosphate transport medium for polymerase chain reactions. After treatment, children were evaluated at intervals of 3, 7, 14 days with all chest x-rays for response for the treatment with macrolides (azithromycin and erythromycin).

5.4.2. Result

On day 7, children with classic pneumonia who received azithromycin are normalized their chest x-ray more often than erythromycin and the same was true in case of atypical pneumonia, their chest x-rays were normalized by day 14(100% in those with azithromycin and 82% in those with erythromycin). Also, children treated with azithromycin had earlier cessation of cough than children treated with erythromycin [15].

5.5. Azithromycin in COVID-19 Patients: Pharmacological 2qa Mechanism, Clinical Evidence and Prescribing Guidelines

5.5.1. Clinical study of azithromycin on COVID-19

The main clinical evidence on use of azithromycin with or without hydroxychloroquine or chloroquine in COVID-19 infection. It was done in non-randomised clinical trial in France recruiting with 42 hospitalised persons of COVID-19 over 14 days.

In this trial, six patients were taken to prevent bacterial superinfection and they were treated with hydroxychloroquine 600 mg daily with the azithromycin (500 mg on day 1 followed by 250 mg per day for the next 4 days). The investigators found that on 6th day after the enrolment, of 100 % patients who were treated with hydroxychloroquine and azithromycin had no detectable viral load and compared with 57.1% in patients who were treated with only

hydroxychloroquine monotherapy and 12.5% of effect was showed in the control group. There are several methodological problems with this document that have been described in detail which includes poor reporting, missing PCR data and unjustified exclusion of patients with clinically important outcomes. These constraints have a significant impact on the study's quality, making the results' reliability suspect.

Recent modest French research on eleven COVID-19 patients treated with hydroxychloroquine with azithromycin at the same dosage used by Gautret *et al.* found contradictory results. One of the 11 patients died, two were moved to critical care, and one acquired a prolonged QT interval, which forced the treatment to be stopped. By the end of the study, eight patients (73%) were still positive for SARS-CoV-2, 5-6 days after the start of treatment a recent observational study has also raised concerns about the benefits of hydroxychloroquine/chloroquine, used alone or with a macrolide, in COVID-19 patients. In one research, 1438 hospitalised patients with COVID-19 were recruited. 735 (51.1 percent) were given hydroxychloroquine with azithromycin, 271 (18.8 percent) were given hydroxychloroquine alone, 211 (14.7 percent) were given azithromycin alone, and 221 (15.4%) were given other medicines.

Patients receiving hydroxychloroquine plus azithromycin, hydroxychloroquine alone, or azithromycin alone had no significant changes in in-hospital mortality as compared to patients receiving neither medication. To our knowledge, major scientific societies, drug regulatory agencies, and public health organisations have not advised azithromycin usage in COVID-19. The use of azithromycin, either alone or in combination with hydroxychloroquine/chloroquine, for the treatment of COVID-19 patients is not advised, according to the Italian Drug Agency (AIFA), unless bacterial superinfections develop. The benefit-risk profile of these medicines in COVID-19 patients, on the other hand, is still being uncovered. To date there are 20 ongoing clinical trials concerning the use of azithromycin, alone or in combination with other drugs, in COVID-19 registered in clinicaltrials.gov [16, 17].

6. CONCLUSION

The study was performed to compare effects of azithromycin and erythromycin on lower respiratory Infection. From the above comparative studies in the literature, it is concluded that azithromycin has more efficacy and less adverse effect when compared to the erythromycin. The administration of azithromycin drug is preferred more comparatively to the erythromycin. Azithromycin and erythromycin have been examined for their effectiveness and safety in treating acute lower respiratory tract infections in children. More azithromycin recipients than erythromycin recipients experienced treatment success, which is defined as a cure or a significant improvement. Results have revealed that the ingestion of azithromycin significantly showed decreased in the lower respiratory infection and the possible mechanism of action is more effective than erythromycin.

Conflict of interest

None declared

7. REFERENCES

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