e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(6); 2346-2355

Original Research Article

Analysis Efficacy and Safety Between Naringenin and Azithromycin in Bronchial Pneumonia Among Children

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Received: 20-03-2023 / Revised: 11-04-2023 / Accepted: 05-05-2023
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Conflict of interest: Nil

Abstract:

Introduction: Pneumonia has several causes and symptoms. The American Thoracic Society classifies CAP, HAP, and VAP. Bacterial, viral, or fungal infections cause bronchial pneumonia, which is frequent in children. Long-term antibiotic use can cause resistance and adverse effects. Anti-inflammatory and antibacterial flavonoid naringenin may treat respiratory disorders. Mycoplasma resists the macrolide antibiotic azithromycin. For respiratory infections, it is broad-spectrum action and tissue penetration are appealing.

Aims and Objectives: This study has compared the efficacy and safety of naringenin and azithromycin in pediatric bronchial pneumonia.

Methods: 106 hospitalised children with bronchial pneumonia were included in a randomised controlled experiment. They were separated into two groups, AZI and NAR. For 5 days, those in the NAR group took oral naringenin (5 mg/kg/day), while those in the AZI group took oral azithromycin (10 mg/kg/day). The levels of IL-6, IL-8, IL-10, and TNF-a in the blood were evaluated using ELISA at four different time points.

Results: Table 1 shows that the two groups had similar baseline characteristics in age, gender ratio, and concurrent diseases. ELISA compared clinical indicators and cytokines. Pro-inflammatory cytokines decreased from T0 to T3 in both groups. The NAR group experienced faster antipyretic, lung rale, and cough disappearance than the AZI group. Naringenin reduced lung bullae, gastrointestinal haemorrhage, and proteinuria. Naringenin for paediatric bronchial pneumonia was safe since the NAR group had fewer side effects.

Conclusion: The study has concluded that naringenin may be an effective anti-inflammatory treatment for paediatric bronchial pneumonia, although more research is needed.

Keywords: naringenin, azithromycin, bronchial pneumonia, pneumonia, macrolide.

Introduction

The term "pneumonia" refers to an infection that affects the lung parenchyma. Instead of seeing pneumonia as a singular disease, healthcare professionals must remember that it is an umbrella term for a series of syndromes created by a variety of organisms, leading to a diversity in both results and presentations. A number of attempts have been made to classify pneumonia based on its aetiology, the clinical setting in which the patient caught the infection, the nature of lung parenchyma involvement, as well as additional characteristics. The classification method used in this article by the American Thoracic Society to analyse pneumonia [1]. Pneumonia acquired from the community (CAP) is any case of

pneumonia outside of a hospital. Pneumonia acquired in a hospital (HAP). HAP refers to any pneumonia that appeared 48 hours after being admitted to an inpatient facility, like a hospital but did not exist at the time of admission. The words "hospital-acquired pneumonia" and "pneumonia associated with healthcare" are now better defined due to this classification. All pneumonia currently falls under the heading of community-acquired pneumonia, and only cases that take place in hospitals are designated as HAP. This includes pneumonia contracted while residing in assisted living facilities, rehab facilities, and other healthcare facilities [2].

Pneumonia Associated with Ventilators

Any pneumonia that appears 48 hours after a VAP is considered endotracheal intubation.

These categories have facilitated the identification of the usual microorganisms responsible for each kind if pneumonia and the development of successful treatment procedures for both in-patient and out-patient care [3].

According to the usual pattern in involvement, pneumonia has additionally been investigated historically as

- One lung lobe is affected by focal non-segmental and lobar pneumonia.
- lobular pneumonia or multifocal bronchopneumonia
- A specific or widespread interstitial pneumonia [4]

Children frequently contract lobular pneumonia, additionally referred to as bronchial pneumonia, which constitutes a common infectious condition, particularly in young children and newborns. Children frequently develop bronchial pneumonia in the winter & spring when the climate is chilly and unreliable [5]. In children, pathogenic infections such as those caused by bacteria, viruses, moulds, mycoplasma pneumoniae, and even superinfections of viruses and bacteria often cause bronchial pneumonia. The main clinical signs are high-grade fever, cough, shortness of breath, persistent medium to fine, moist rales in the lungs, and severe respiratory failure. antibiotics such as lactams, macrolides, aminoglycosides, and neuraminidase inhibitors are some of the therapeutic medications now available for the management of pneumonia of the lungs. However, prolonged use of inhibitors and antibiotics may lead to medication resistance and undesirable side effects, including an imbalance in the flora of the digestive tract. Additionally, using ultrasonic nebulisation for an adjuvant therapy might produce symptoms in infants and toddlers, such as coughing and bronchospasm, and it is challenging to utilise due to young children's lack of cooperation. Therefore, it is essential to create a new medication that treats children's bronchial pneumonia and has fewer negative effects [6].

The glycogen part of naringin, naringenin, is a sort of flavourless and colourless flavonoid. Free radical scavenging, antioxidant, anti-inflammatory, anti-atherosclerotic, and cellular protective capabilities of naringenin have been demonstrated, in addition to pharmacological actions such as anti-microbial, inflammation-resolving, and anti-cancer effects. Naringin-containing oral liquid containing the appropriate Chinese patent medication injectable has previously been preserved in the pharmacopoeia in China. Additionally, many studies on animals have previously shown that naringenin is effective in treating inflammatory illnesses of the airways, such as asthma or chronic obstructive pulmonary disease. However, naringin has not been used as a drug to treat paediatric bronchial pneumonia [7]. Children with pneumonia frequently receive antibiotics, & depending on how bad their condition is, some could need hospitalisation and extra oxygen. A macrolide antibiotic called azithromycin

efficiently treats pneumonia by preventing the normal metabolism of the mycoplasma and inhibiting the creation of mycoplasma protein. Due to the extensive usage of azithromycin, azithromycin resistance was frequent and has advanced to the point where it affects clinical effectiveness. Other side effects include gastrointestinal problems and liver function impairment. The adrenal cortex secretes the steroid hormone glucocorticoid, which can control fat metabolism, protein biology, and associated metabolites. It has anti-inflammatory and antitoxic properties and may be used to treat paediatric pneumonia in the clinic [8].

Macrolide antibiotics, which were initially identified from Streptomyces species, consist of various sugar substituents attached to an inner macrocyclic lactone ring of 14, 15, and 16 carbon atoms connected. The first macrolide to be made commercially accessible was the 14-membered ring molecule erythromycin. Semi-synthetic molecules, including The macrolide ring of azithromycin (AZM), which distinguishes it from erythromycin by having a nitrogen methyl-substituted, have subsequently been produced to expand the spectrum of action of erythromycin and to enhance its pharmacokinetic and tolerance profiles [9]. In fact, This 15-membered ring macrolide has broad-spectrum antimicrobial activity against a variety of bacteria, including Gram-positive ones like Haemophilus influenzae, Campylobacter spp., Neisseria gonorrhoeae, and Legionella pneumophila, as well as some unusual ones like Mycoplasma spp. or Chlamydia spp [10]. Because of a poor diffusion through the outer membrane and an aggressive efflux, Pseudomonas aeruginosa (PA) along with other bacteria of the Enterobacteriaceae family, typically develop AZM resistance. However, this molecule is recommended as a replacement for other methods of treating certain Enterobacteriaceae that cause diarrhoea, indicating that it has superior in vivo action than anticipated [11]. By reducing bacterial protein synthesis, macrolides restrict bacterial growth and so have bacteriostatic effects. Macrolides prevent bacterial protein translation by blocking the 50S ribosomal subunit's peptide escape channel through their reversible interaction with 23S rRNA. By doing this, they stop the nascent chain from developing, leading to the premature separation of truncated peptide chains. The "peptidyl-tRNA drop-off" phenomenon causes the pools of aminoacyl-tRNA available for protein production inside cells to deplete [12].

Acute and chronic lung infections are frequently brought on by the Gram-negative opportunistic bacterium Pseudomonas aeruginosa, especially in individuals with weakened mucosal immunity or pneumonia brought on by a “ventilator (VAP)” with “cystic fibrosis (CF)”. PA can acquire resistance to various kinds of antibiotics and is inherently resistant to a wide array of antibiotics, creating significant treatment problems [13]. Although this species possesses elevated antibiotics must have “minimum inhibitory concentrations (MICs)” of at least 512 mg/L. AZM has been proposed to be a fresh therapeutic adjuvant for the treatment of PA. Low-dose AZM therapy was found to be effective in having a beneficial effect on clinical results in individuals with long-term PA infections, including diffuse panbronchiolitis and cystic fibrosis, indicating that AZM has anti-PA properties. Additionally, viral respiratory diseases caused by the influenza virus, the respiratory syncytial virus, etc., have been shown to benefit from using AZM. suggesting immune system impacts. The positive profile of AZM has also been highlighted by pharmacokinetic studies, which show that it has Excellent tissue penetration was seen, notably in the lungs, along with increased intracellular accumulation, especially in white blood cells and alveolar macrophages. This makes

using AZM as an alternative to treating respiratory infections particularly intriguing [14].

Methods

Study design

A randomised controlled trial was used to perform the current investigation to reduce the likelihood of confounding variables. In this trial, a total of 106 hospitalised kids with bronchial pneumonia were enrolled. 106 individuals were divided into the AZI & NAR groups at random.

The AZI group was used as a good control. Naringenin pills, at a daily dosage of 5 mg/kg, were given orally to patients in the NAR group for 5 days. For five days, oral azithromycin pills containing 10 mg/kg/day were administered to patients in the AZI group. The two medication pills were broken up into powder and eaten with water for better absorption.

At 4 different time intervals, comprising T0, the day before pharmacological intervention, T1, the day after therapy, the third day following treatment (T2), and the fifth day following treatment (T3), two millilitres of blood were drawn from the left radial artery of each patient. Centrifugation was used to separate the serum, then kept at 20°C. By using an ELISA, the supernatant concentrations of IL-6, IL-8, IL-10, and TNF-a were determined.

Inclusion and exclusion criteria

Children had been eligible to participate in the clinical study provided they met each of the following six criteria: (a) they needed to be between the ages of 1.5 and 6 years; (b) their clinical signs had to match the diagnostic requirements for paediatric bronchial pneumonia; (c) they had to have a normal digestive function; (d) they couldn't have taken an antibiotic within the previous three months; (e) they couldn't have a history or naringenin allergies; & (f) informed consent is given by the patients' guardians as well.

Children who fit one of the following five criteria for disqualification were not taken part in the study: (a) those with serious illnesses of their hearts, brains, kidneys, liver, or endocrine system, or those with tumours or tuberculosis; (b) those with atelectasis, pulmonary abscess, bronchiectasis, or broncho-pulmonary dysplasia; and (c) those with mental disorders who weren't willing to participate during the trial.

Statistical analysis

Appropriate statistical analysis was performed on the study using SPSS 25. Although discrete data is represented as frequencies and their corresponding percentage terms, continuous data is reported as mean, and standard deviations. The study used ANOVA as a statistical analysis tool. The threshold for significance was set at $P< 0.05$.

Ethical approval

Each patient was informed of the study's methodology, and their agreement was subsequently acquired. The Ethical Committee of the relevant hospital has approved the study's methodology.

Results

Table 1 provides an overview of the fundamental data for the participants in the two groups. Age, gender ratio, and concurrent diseases significantly did not differ among the groups' baseline characteristics. Additionally, it was discovered that clinical markers, such as body temperature, WBC counts, neutrophil numbers, and heart rates (96 ± 9 [number/min] in the AZI group vs NAR group), were compared among the groups.

Table 1: Baseline characteristics of patients in each group

Groups	NAR group (n=53)	AZI group (n=53)	p-value
Age (years)	3.1 ± 2.1	3.0 ± 2.2	0.57
Gender n (%)			
Female	28 (52.9)	31 (58.4)	0.26
Male	25 (47.3)	26 (49.0)	0.29
Coexisting diseases			
Allergic rhinitis	17	20	0.35
Bronchial asthma	11	13	0.77
Diarrhea	7	8	0.17
Anemia	13	14	0.59
Indicators			
WBC counts	6.5 ± 1.5	6.8 ± 1.7	0.58
Neutrophils	9.2 ± 1.9	9.0 ± 1.5	0.30
Heart rate, number/min	95 ± 7	96 ± 9	0.65
Temperature	38.6 ± 2.7	38.7 ± 2.6	0.82

Using an ELISA technique, the serum concentrations of TNF-α, IL-8, IL-6, and IL-10 were measured. The results are presented in Table 2. It was discovered that at T0, the IL-6, IL-8, and TNF- serum concentrations in the NAR group and AZI group were essentially identical. Fortunately, both groups showed persistent downregulation in the three pro-inflammatory cytokines' levels in the blood following medication delivery from T0 to T3. Additionally, αcompared to Serum levels , IL-6, IL-8, or TNF- substantially dropped at T1 in the AZI group and the NAR group T2, and T3 (p .05), particularly at T2 and T3.

Table 2: comparing TNF-α, IL-8, IL-6, and IL-10 values between two groups

Index	Time points	NAR group (n=103)	AZI group (n=103)	p-value
IL-6 (ng/ml)	T0	79.8 ± 13.6	79.2 ± 12.9	0.88
	T1	65.2 ± 12.9*	73.4 ± 10.4	0.15
	T2	46.7 ± 10.5**	69.5 ± 9.8	0.05
	T3	35.2 ± 9.5***	54.8 ± 7.9*	0.04
IL-8 (ng/ml)	T0	63.7 ± 11.6	62.0 ± 10.5	0.70
	T1	43.2 ± 9.4*	58.4 ± 11.9	0.29
	T2	18.9 ± 4.6**	51.8 ± 11.2*	0.03
	T3	15.6 ± 2.9***	32.9 ± 11.2**	0.05
IL-10 (ng/ml)	T0	14.4 ± 2.1	13.4 ± 3.7	0.34
	T1	32.3 ± 4.8*	24.9 ± 8.9*	0.06
	T2	43.9 ± 9.3**	27.9 ± 9.3*	0.05
	T3	51.4 ± 15.8***	32.7 ± 6.9**	0.04
TNF-α (ng/ml)	T0	74.9 ± 16.7	74.3 ± 11.9	0.74
	T1	43.2 ± 8.9*	67.6 ± 12.6	0.05
	T2	36.1 ± 5.4**	55.9 ± 9.2*	0.03
	T3	26.7 ± 3.9***	52.0 ± 10.5	0.02

The NAR group has 1.7 ± 0.4 days of antipyretic time, which was significantly less than AZI group which has 4.0 ± 0.5 days; the The NAR group's lung rale disappearing time, 4.6 1.5 days, was likewise considerably shorter than the AZI group's 6.8 1.7 days, and both groups' cough disappearance times, 3.9 0.7 days against 5.8 0.7 days. The above results of the study suggested that naringenin could quicken the process of recovery from coughing, and fever and improve the results of therapy for the patient.

Table 3: comparing the values of antipyretic, lung rale, and cough disappearance time between both the groups

	NAR group (n=103)	AZI group (n=103)	p-value
Antipyretic time (day)	2.7 ± 0.5	4.0 ± 0.5	0.03
disappearance of cough time (day)	3.9 ± 0.7	5.8 ± 0.7	0.04
disappearance time of lung rale (day)	4.6 ± 1.6	6.8 ± 1.7	0.05

10% of patients on the AZI group exhibit lung bullae, compared to a significantly lower frequency of those with NAR had lung bullae. Furthermore, the NAR group had a markedly reduced incidence rate of gastrointestinal haemorrhage than the AZI group. Additionally, just three patients in the NAR group have proteinuria, compared to 15 patients in the AZI group who have the condition. When seen together, fewer patients experienced complications following naringenin therapy, indicating that the drug was able to lower the frequency and severity incidence of bronchial pneumonia complications.

Table 4: comparing the complications in both groups

Groups	NAR group (n=53)	AZI group (n=53)	p-value
Bullae of lung	2 (3.7)	6 (11.3)	0.05
Gastrointestinal bleed	1 (1.8)	7 (13.2)	0.04
Proteinuria	2 (3.7)	9 (16.9)	0.02

In the NAR group, the frequency and severity rates of adverse events—including nausea, vomiting, increased urine protein, leukopenia, and neutropenia—were significantly lower than those in the AZI group. Furthermore, naringenin-treated subjects showed no signs of diarrhoea or dermatitis. These results demonstrated that naringenin was a safe option for treating paediatric bronchial pneumonia.

Table 5: comparing adverse reactions between both groups

Groups	NAR group (n=53)	AZI group (n=53)	p-value
Diarrhoea	0 (0)	9 (16.9)	NA
Rash	0 (0)	11 (20.7)	NA
Vomiting	1 (1.8)	10 (18.9)	0.03
Nausea	1 (1.8)	6 (11.3)	0.01
Elevated alanine aminotransferase	2 (3.7)	11 (20.7)	0.02
Leukopenia	1 (1.8)	9 (16.9)	0.03
Elevated urine protein	2 (3.7)	6 (11.3)	0.04
Neutropenia	2 (3.7)	13 (24.5)	0.02

Discussion

Children frequently get bronchial pneumonia, an infectious condition that can result in hyperthermia, lung moist rales, and possibly respiratory failure. Conventional treatments for paediatric bronchial pneumonia frequently bring on drug resistance and adverse effects. Owing to its inflammatory- and microbial-fighting capabilities, naringenin has recently been mentioned as a possible therapy for several inflammatory illnesses of the airways [15]. A current clinical trial sought to evaluate naringenin's effectiveness and security in treating paediatric bronchial pneumonia. 180 eligible patients in total were divided into the "Azithromycin (AZI)" and "naringenin (NAR)" groups were randomly chosen. Every participant was told to follow the five-day oral regimen, including during the clinical intervention, and their blood cytokine levels were assessed [16]. Following therapy, the timing of clinical symptom elimination as well as the occurrences Comparisons among the two groups were made in terms of complications and negative outcomes. Naringenin was effective at controlling inflammation, reducing the frequency of bronchial pneumonia problems along with unpleasant responses, minimising the time it took for clinical symptoms to go away, and enhancing the patient's health. The study's findings showed that naringenin is safe and helpful for kids with bronchial pneumonia, offering fresh information on the drug's therapeutic use [17].

An anti-inflammatory and immunomodulatory flavonoid is naringenin. The study investigated whether naringenin may lessen allergen-induced airway inflammation and its putative mechanism in a mouse model of asthma. Ovalbumin was used to challenge and sensitise mice. Before the ovalbumin challenge, naringenin was given to certain mice. We looked at the occurrence of airway inflammation & reactivity [18]. By using an ELISA, interleukin (IL)4, IL13, chemokine (C-C motif) ligand (CCL)5, as well as CCL11 levels in serum total IgE and bronchoalveolar lavage fluid were measured. Using a Western blot, the lungs' levels of "inducible nitric oxide synthase (iNOS)" and kappa alpha degradation were assessed. By using an electrophoretic mobility shift assay, we also evaluated the binding activity of NF-kappaB. Real-time PCR was used to find the iNOS, CCL5, & CCL11 mRNA levels [19]. In experimental mice, naringenin reduced the inflammation and responsiveness of the airways brought on by ovalbumin. All bronchoalveolar lavage fluid had less IL4 and IL13 in the naringenin-treated animals and less serum total IgE. Naringenin also prevented the degradation of pulmonary Ikappa Balpha and the ability of NF-kappaB to bind DNA. CCL5, CCL11, & iNOS levels were all considerably decreased. The findings suggested that naringenin could have preventive functions in the development of asthma. These phenomena observed effects could be explained by the suppression of NF-kappaB and the lowered levels of its target genes [20].

Despite a viral origin in many cases, lower respiratory tract infections tend to be treated with antibiotics. Low procalcitonin concentrations may be able to identify people with lower respiratory tract infections who won't likely respond well to drugs, however, this is still uncertain. To treat lower respiratory tract infections among people with low procalcitonin, the study compared the effectiveness and safety of using azithromycin to a placebo [21]. When it came to clinical recovery on day five in those who had fewer respiratory tract infections with low procalcitonin concentrations, the placebo was not superior to azithromycin. It is uncertain if antibiotics are recommended for individuals with an infection of the respiratory tract of a low procalcitonin level

after considering the percentages of reported adverse events and clinical improvement on day five [22].

Describing the clinical efficacy treatment of respiratory tract infections with azithromycin in children up to the age of 12; examining the persistence monitoring symptoms following the start of treatment; noting any negative reactions that could have been brought on by the azithromycin treatment [23]. According to the study's findings, azithromycin has a good clinical efficacy and a low incidence of side effects when used to treat paediatric respiratory tract infections. However, the study's Observational, postmarketing, non-comparative research design and the fact that the cause of infections was not established are two of its key weaknesses. However, it can still be argued that azithromycin is a reliable antibiotic. that effectively treats paediatric respiratory tract infections, resulting in rapid symptom relief and few side effects in those with bacterial infections [24].

The study examined the in vitro susceptibilities of nine antimicrobial drugs in Taiwan against "methicillin-resistant Staphylococcus aureus (MRSA)". 20 hospitals in Taiwan collected an aggregate of 1,725 isolates between 2006 and 2010. The lowest inhibitory concentrations (MICs) for all nine drugs were identified using the agar dilution technique. There were no intra-hospital or inter-hospital transmissions among the nine MRSA isolates that did not respond with vancomycin, teicoplanin, daptomycin, and tigecycline. Each of these isolates had a unique pulsotype.

The prevalence of MRSA isolates in Taiwan with high MICs (2 g/ml) or MIC creep with daptomycin may alert doctors to the need to treat severe MRSA infections [25].The purpose of the study conducted previously was to report azithromycin's clinical efficacy in the treatment of infections of the lower respiratory tract within routine clinical practice, to look at how long symptoms persisted after the start of therapy, and to document any potential side effects of azithromycin use. The investigation of azithromycin's efficacy involved 153 patients in total, 94 of whom had "community-acquired pneumonia (CAP)" & 59 of whom had "acute exacerbations chronic bronchitis (AECB)". As a result of a three-day course of azithromycin therapy, clinical success was evaluated as improvement, cure, or failure. Abdominal discomfort, diarrhoea, and vomiting were the most frequently reported adverse effects, each occurring in four (2.6%) individuals. As a result, azithromycin was discovered to have a high level of clinical efficacy and few side effects while treating infections of the lower respiratory tract.[26]

Conclusion

In conclusion, the randomised controlled study showed that providing naringenin orally to children with bronchial pneumonia significantly decreased pro-inflammatory cytokine levels, such as IL-6, IL-8, and TNF-. These results show that naringenin may have anti-inflammatory effects and be a possible treatment for paediatric bronchial pneumonia. More research is needed to determine how effective and safe it is for a bigger group of patients. There are, however, a few limitations to this study that must be addressed. First, the sample size was low, which could restrict the validity of the results. Furthermore, additional routes of administration of naringenin were not investigated, with the focus instead being placed on oral administration. The duration of the trial was also short, and it is yet unclear what kind of long-term impact naringenin has on paediatric bronchial pneumonia. Finally, the study did not evaluate possible adverse effects or drug interactions. More research is needed to better understand the possible benefits and limitations of naringenin for treating paediatric bronchial pneumonia, ideally with bigger sample sizes, longer follow-up

periods, and more thorough safety assessments and other administration routes.

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