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RISK-BENEFIT PROFILE OF AZITHROMYCIN: A BRIEF REVIEW

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Abstract:

Introduction: *The most commonly given antibacterial drug worldwide is azithromycin. It belongs to the group of antibiotics known as macrolides. It is typically utilized in upper and lower respiratory tract infections,some sexually transmitted diseases,and severe bacterial infections due to its increased efficacy,tolerance,and broad-spectrum activity.****Methods****:Articles from the literature were examined to learn more about the risks and advantages of azithromycin.* ***Results*** *: Due to its low incidence of side effects, this is often marketed in solid, liquid, and ophthalmic formulations.Owing to its pharmacological and therapeutic qualities,it is also employed in the medication therapy for COVID-19.* ***Conclusions****: According to a review of the literature,there may be a higher risk of cardiac mortality, liver damage, ototoxicity, and hypersensitivity reactions.*

Keywords*: Macrolides, Antibiotics, Azithromycin,QT prolongation,Ototoxicity*

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INTRODUCTION:

An antibiotic in the semi-synthetic macrolide class that is developed from erythromycin is azithromycin. It is an oral antibiotic that is very effective and well-tolerated. The doctor most commonly recommends this class of antibiotics (Martinez *et al*., 2015). Although there is a chance of an adverse event, it is regularly prescribed for upper respiratory tract infections, pneumonia, sinusitis, bronchitis, and coronavirus infections globally (Maggioli *et al*., 2011).

THE RISK ASSOCIATED WITH HEPATIC SYSTEM

According to numerous clinical trials, the medication causes just a few occurrences of cholestatic hepatitis with jaundice and acute,temporary,and asymptomatic elevations in serum aminotransferase levels when given in doses of 250 mg or 500 mg to patients, respectively (Chandrupatla *et al*., 2002). Jaundice and hepatocellular damage are additional side effects. In these situations, the latency is brief and may only last a few days. Alkaline phosphatase (ALP) values are typically less than twice the normal upper limit, though they may rise over time to higher levels. Serum aminotransferase (ALT) levels are markedly elevated.

Hepatocellular liver injury caused by azithromycin can be fatal, result in abrupt liver failure and death, or necessitate a liver transplant. In most situations, recovery takes place between 4 to 8 weeks. A liver biopsy in certain patients reveals cholestasis and a substantial decrease in the number of ducts in the organ (ductopenia). While it frequently raises the serum of enzyme and liver biopsy detected in ductopenia, some patients eventually recover from jaundice and their symptoms. Azithromycin causes significant ductopenia that leads to biliary cirrhosis and eventually necessitates liver transplantation in other patients by making their bile ducts disappear (Martinez *et al*., 2015).

THE RISK ASSOCIATED WITH CARDIOVASCULAR SYSTEM

According to reports, taking azithromycin causes an increase in Q-T prolongation in older people (Russo *et al*., 2006). The evidence therefore revealed that azithromycin may cause cardiac arrhythmia-related side effects at first, such as polymorphic ventricular tachycardia without Q-T intervals (Kim *et al*., 2005) torsades de pointers (Huang *et al*., 2007) Several investigations also revealed that azithromycin raises the risk of cardiovascular mortality. According to the research conducted in the years 2012 and 2013, taking azithromycin increases cardiac death risk similarly to taking amoxicillin (hazard ratio, 2.49; 95% CI, 1.38 to 4.50; P=0.002), followed by Tennessee Medicaid cohort design (Ray *et al*., 2012). A cohort study including 1.1 million Danish individuals taking azithromycin showed no increased risk of cardiac death compared to penicillin V (rate ratio, 2.85; 95% confidence interval, 1.13 to 7.24) (Svanstrom *et al*., 2013). The FDA also states that using azithromycin has a risk of causing torsades de pointes, QRS complex, and other irregular cardiac rhythms (Poluzzi *et al*., 2009).

THE RISK ASSOCIATED WITH BLOOD CIRCULATORY SYSTEM

Compared to other antibiotics, azithromycin is preferred as the first-line treatment for bacterial infections because of its better bioavailability and fewer side effects, but in a clinical trial study conducted in Japan, it was found that 11 patients developed leukopenia (0.88%) and 2 patients developed neutropenia (0.22%) after receiving azithromycin therapy (Higa & Saito, 2000). These adverse effects, in particular the abnormal neutrophil count, are found to be too moderate and temporary (1.5% in adults and 1.9% in children) (Treadway & Pontani, 1996).

THE RISK ASSOCIATED WITH TOPICAL USE

Azithromycin topical use prior to 2011 was not associated with any cases of an adverse event (Flavia Monteagudo Paz *et al*., 2011). In 2011, an 85-year-old woman with a history of bilateral phacoemulsification, allergic rhinoconjunctivitis, and chronic dacryocystitis was reported as the first case. Azyter eye drop administration causes an adverse incident the second time after a one-year break. After that, her eyelid eczema got better the following second week after she stopped taking Azyter.

Azithromycin side effects were also discovered at the Dermatology Department of the Hospital General Universitario de Alicante. It was stated that a 76-year-old woman had severe conjunctivitis and acute eczema on her cheeks and eyelids. She had surgery to correct her pseudophakia three months earlier. She recommended Tabradex and Azydrop single-dose containers as a result. As it was believed that these two ophthalmic preparations were the root of allergic contact dermatitis, the usage of these eye drops was discontinued. The patient then improved two weeks later (Milkovic-Kraus & KanceljakMacan, 2001).

It has been noted that pharmaceutical personnel who

were engaged in the manufacture or formulation of azithromycin frequently experience occupational allergic contact. This demonstrates air-bone contact dermatitis. Patch tests D2 and D4 from the Spanish baseline series revealed an azydrop-positive response. But despite the fact that erythromycin and clarithromycin did not cause any positive reactions, this was the first case of non-occupational allergic contact dermatitis ever reported, thus it may be explained. While azithromycin has 15 carbon atom cycles, erythromycin and clarithromycin only have 14 carbon atom cycles (Milkovic-Kraus *et al*., 2007).

THE RISK ASSOCIATED WITH AUDITORY SYSTEM

Rarely does azithromycin induce ototoxicity (Wallace *et al*., 1994; Tseng *et al*., 1997). The majority of patients experiencing extended high-dose therapy for AIDS experienced reversible SNHL issues. But a rare case of irreversible SNHL was observed in a 39-year-old woman while exposing to low dose azithromycin who recently began taking azithromycin for a urethral infection. She was instructed to take two 250 mg tablets daily, but she quit after the first dose because of her perceived bilateral hearing loss and worsening tinnitus. She lacked any prior medical or familial history. But even after she stopped taking the drug, her hearing issues persisted. Macrolide antibiotics include azithromycin. It started in the early 1970s and produces Macrolide ototoxicity (Mintz *et al*., 1973).

THE RISK ASSOCIATED WITH GIT

Clostridium difficile infections are a substantial risk factor for most antimicrobial medications (CDI). According to the meta-analysis method used in several papers, the risk of CDI infection varied with different antibiotic classes. Compared to clindamycin and fluoroquinolone antibiotics, macrolide drugs carry a lower risk of CDI. In order to reduce the risk of clostridium difficile infections, azithromycin is being added to the category of macrolide antibiotics (Deshpande *et al*., 2013; Brown *et al*., 2013).

RISK OF DRUG INTERACTION

The antibiotic azithromycin belongs to the macrolide class and has bacteriostatic properties against both gram +ve and gram -ve pathogens (McMullan & Mostaghim, 2015). Other medications involved in the metabolic process are likewise impacted by the antibiotics in the macrolide class. The microsomal isoenzyme CYP3A4 metabolises a number of the medications. This class of drugs, known as macrolides, interacts with other medications and inhibits the CYP450 enzyme, which prevents the activation of other enzymes involved in metabolism. As a result, the drug's concentration may rise and it may have toxic effects (Franklin, 1977). Due to the wide variety of over-the-counter (OTC) medications, doctors are often aware of this type of interaction and cautious when giving antibiotics.

USE OF AITHROMYCIN IN COMBINATION WITH THEOPHYLLINE

It is frequently used to treat asthma sufferers through bronchodilation. The isoenzyme CYP3A4 in the liver is usually where these medications are processed. When many medications in the same route are taken together, theophylline clearance may be competitively inhibited. Erythromycin and Theophylline, both members of the macrolide class, are also metabolised by the CYP450 enzyme (Ludden, 1985). Therefore, theophylline metabolism was slowed, increasing plasma levels, and producing hazardous symptoms as tachycardia, palpitations, headaches, and dizziness. According to several research, the plasma content of theophylline does not significantly rise when azithromycin and the drug are combined.As a result, these trials imply that Azithromycin can be used to treat asthmatic patients who are taking theophylline (Debruyne *et al*., 1986).

USE OF AZITHROMYCIN IN COMBINATION WITH CYCLOSPORINE

An immunosuppressive medication called cyclosporine is frequently used in the treatment of autoimmune disorders as well as graft rejection after organ transplantation. This cyclosporin is also metabolized in liver isoenzyme CYP3A4. Since this isoenzyme also breaks down antibiotics from the macrolide class, cyclosporine isn't metabolised, which raises the concentration of cyclosporine (Kronbach *et al*., 1988). Increased plasma concentration results in hepatotoxicity, stomach discomfort, insanity, and other conditions (Jensen *et al*., 1987). No instances of an interaction between azithromycin and cyclosporine have been reported in a research involving 3995 patients who received azithromycin (Vernillet *et al*., 1989). Azithromycin and Cyclosporine do not interact because of this.

USE OF AZITHROMYCIN IN COMBINATION WITH CARBAMAZEPINE

Anticonvulsant medication carbamazepine is prescribed for epileptic patients. Confusion, dizziness, ataxia, and vomiting are a few symptoms of poisoning (Nahata, 1996). No interactions between Carbamazepine and azithromycin have been discovered in this case (Rapeport *et al*., 1991). Despite administering a combination of medications

to more than 600 people in clinical investigations, no clinical evidence was discovered.

USE OF AZITHROMYCIN IN COMBINATION WITH WARFARIN

Typically, warfarin is used as an anticoagulant to stop the clotting factors. Warfarin metabolism is also inhibited by erythromycin, which raises the serum levels and causes an increase in prothrombin time and bleeding (Bartle, 1980). 23 healthy individuals were given the drugs Warfarin and azithromycin to demonstrate that there was no interaction between them. As a result, while taking warfarin, azithromycin shouldn't have any effects on prothrombin time (Sato *et al*., 1984).

USE OF AZITHROMYCIN IN COMBINATION WITH HORMONAL CONTRACEPTIVES

This contraceptive pill is available as a progesterone-only formulation or a progesterone-estrogen combination. It works well for birth control as well. Additionally, there is a connection between broad-spectrum antibiotics and these contraceptives (Orme *et al*., 1991). There was no interaction between azithromycin and oral contraceptives in a clinical evaluation of 6655 patients (Nahata, 1996).

USE OF AZITHROMYCIN IN COMBINATION WITH ZIDOVUDINE

Zidovudine is frequently used to suppress the reverse transcriptase enzyme in AIDS treatment. Azithromycin is also given to HIV patients in a trial who cannot impact the metabolism of zidovudine. As a result, zidovudine patients who are HIV-positive also utilise azithromycin (Chave *et al*., 1992).

USE OF AZITHROMYCIN IN COMBINATION WITH ANTACIDS

In order to treat conditions including gastritis, Zollinger Ellison syndrome, and ulcers, antacids normally work by neutralising the stomach's acid. If you take azithromycin along with antacids, the amount of azithromycin your body absorbs will be reduced. Take this kind of medication three hours after giving the azithromycin. The interactions between those medications are disclosed by doctors (Foulds *et al*., 1991)

USE OF AZITHROMYCIN IN COMBINATION WITH HYDROXYCHLOROQUINE

HCQ is a well-known medication that is currently used to treat coronavirus infections in addition to treating rheumatoid arthritis and malaria. The risk of an irregular heartbeat and QT prolongations increases when used with HCQ and azithromycin. The repercussions of this kind of connection are detrimental to our biological systems. In order to avoid this kind of combo, clinicians are seeking out the patient's medical history for any heart risks.

A RISK IN SARS Cov-2

A severe acute respiratory syndrome is also referred to as COVID-19 or SARS Cov-2. Coronaviruses come in four different varieties: alpha, beta, gamma, and delta. The human lungs' ACE2 receptor is where the coronavirus's mechanism is bound. A variety of medications, including hydroxychloroquine, azithromycin, favipiravir, and remdesivir, among others, are used to treat coronavirus infections (Wrapp *et al*., 2020).

For the treatment of COVID-19, azithromycin is frequently utilized. It is an antibiotic in the macrolide class produced from erythromycin. The 50s ribosomal subunit is inhibited by this medication, which also improves tissue penetration and stops protein synthesis (Parra-Lara *et al*., 2020). When administered to treat coronavirus, azithromycin can result in fatal cardiac arrhythmias. Azithromycin may also cause QTc to be extended and torn de points (Tdp) A 55-year-old patient was evaluated by (Kezerashvili *et al*., 2007) to demonstrate the QT prolongation and Tdp-associated use of azithromycin. A 90-year-old man with high blood pressure was noted to have increased QT and Tdp after taking azithromycin a short time earlier. The risk of Tdp is increased by the Macrolide class drug azithromycin, which also inhibits CYP3A4 metabolism (Guo *et al*.,2010).

Because those patients have a high-risk cardiovascular condition, their danger of passing away is increased. However, some patients between the ages of 60 and 70 are at a high risk of cardiovascular diseases, according to some case reports studies. Middle-aged adult patients are not linked to cardiac death (Hancox *et al*., 2013). Only 10% of people experience side effects from azithromycin, the most common of which are nausea, vomiting, abdominal pain, and diarrhoea. The inhibition of potassium ion outflow is the cause of the EAD and QT interval mechanism. The risk of mortality increases when HCQ and azithromycin are combined. HCQ is used alone to lower death rates.

Azithromycin use among people at high risk for coronary artery disease raises the risk of cardiac death (Lighter & Raabe, 2020). In the studies mentioned above, there is a risk of torsed de points whether Azithromycin is administered with Hydroxychloroquine or alone to treat coronavirus (Sultana *et al*., 2020).

CONCLUSION:

Both effectiveness and safety are significant factors. The analysis of the above research articles leads us to the conclusion that azithromycin is undoubtedly a highly effective and well-tolerated oral antibiotic that is commonly recommended by doctors, but it may also manifest some negative effects. In order to find the issue, a comparison test with different antibiotics should also be conducted as part of this type of investigation, which is necessary from a safety standpoint.

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