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AZITHROMYCIN'S FUNCTION AMONG PATIENTS

Qail Ibraimi[1], Nadir Ajruli[2], Diturim Xheladini[2]

[1] Faculty of Medical Sciences, Department of Pharmacology - University of Tetovo
[2] Clinical Hospital – Tetovo, Department of Internal Disease
[2] Clinical Hospital – Tetovo, Department of Pediatrics

Corresponding author: qail.ibraimi@unite.edu.mk

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Abstract

The total rate of adverse events to Azithromycin is 0.7%. Only diarrhea, nausea, and abdominal pain were experienced by more than 1% of individuals. Palpitation, angina, dyspepsia, flatus, vomiting, melena, jaundice, vaginal candidiasis, vaginitis, nephritis, dizziness, headache, vertigo, somnolence, and weariness were also recorded in adult clinical studies. After low-dose use, Azithromycin has also been linked to angioedema and photosensitivity, intrahepatic cholestasis, hypersensitivity syndrome, toxic pustuloderma, and irreversible deafness. When given to patients with infectious mononucleosis, it can cause a maculopapular eruption. It is also capable of causing contact dermatitis. The study included 87 patients at the Clinical Hospital in Tetovo, as well as some children in the Pediatric department. The tolerability of Azithromycin oral suspension, 10 mg/kg once daily for 3 days, was evaluated in children at the Pediatric department of a clinical hospital in Tetovo. The incidence of treatment-related adverse events was considerably lower in the 87 individuals who took Azithromycin, whereas withdrawal rates were comparable. With Azithromycin, there were much fewer gastrointestinal problems and their duration was significantly shorter.

Keywords: Acute generalized exanthematous pustulosis (AGEP), melena, jaundice, and flatus.

Method

This was an observational study conducted on 87 patients who were recently admitted to Tetovo Clinical Hospital. Included in this analysis were all clinical trials of Azithromycin for the treatment of patients of both pediatric and adult ages. After screening the included studies for inclusion/exclusion criteria and conducting a bias risk assessment, the data were extracted from the studies that were included. In order to obtain forest and funnel plots, we made use of statistical analysis as well as the medical histories of patients that were stored in the archives of the department of Internal Disease and Pediatric at the Clinical Hospital in Tetovo.

Results

11.9% of the 87 patients who were treated with Azithromycin for Urethritis/Cervicitis and received either 1.5 g in divided doses over a period of 6 days or 1 g as a single dose experienced adverse events. Patients over the age of 63 had a 10.7% incidence rate, while children under the age of 13 had a 5.4% incidence rate.

The adverse effects that were experienced most frequently were those of the gastrointestinal variety (15.8%), followed by those of the central nervous system and the peripheral nervous system (0.9% each). In total, 51% of the adverse events were deemed to be mild, 29% were deemed to be moderate, and only 4.8% were deemed to be severe, with the majority of the adverse events involving the gastrointestinal tract.

Indications

Physicians in the United States often prescribe Azithromycin, an antimicrobial macrolide that exhibits a wide range of effectiveness. This is a modified form of erythromycin that exhibits enhanced effectiveness against gram-negative bacteria (including Enterobacteriaceae) and provides broad spectrum coverage against numerous gram-positive organisms.

- Azithromycin is effective against various "atypical" bacteria, such as Chlamydiae (e.g., Chlamydiae trachomatis and Chlamydophila psittaci), legionella (e.g., Legionella pneumophila), mycoplasma (e.g., Mycoplasma pneumoniae), and mycobacteria (e.g., Mycobacterium avium). It achieves this by inhibiting bacterial protein synthesis, rather than functioning as a peptidoglycan cell-wall inhibitor like beta-lactam agents.

- Azithromycin, an antibiotic, is not only effective against Streptococcus pneumoniae, Hemophilus influenzae, and Moraxella catarrhalis, but it is also recommended by the FDA for the treatment of community-acquired pneumonia (CAP).

- Azithromycin is authorized for the treatment of various infectious conditions affecting the upper respiratory tract, such as acute Otitis media (AOM) and acute exacerbation of chronic obstructive pulmonary disease (COPD), among others.

- Azithromycin is approved for treating infections caused by Streptococcus pyogenes. It can be used instead of beta-lactam antibiotics to treat skin infections caused by S. pyogenes, Staphylococcus aureus, or Streptococcus agalactiae. It is also used to prevent and treat Mycobacterium avium complex (MAC) infections in patients with advanced acquired immunodeficiency syndrome (AIDS). Additionally, it is effective against sexually transmitted infections such as Chlamydia, gonococcal disease, chancroid (caused by Hemophilus ducreyi), and Mycoplasma genitalium. Infections caused by Mycobacterium avium complex (MAC) in individuals with advanced acquired immunodeficiency syndrome (AIDS).

- Additionally, Azithromycin demonstrates efficacy against a diverse range of protozoan organisms, such as Plasmodium species (the causative agent of malaria), Babesia sp., Toxoplasma gondii, and the bacteria responsible for B. microti. Occasionally, it is utilized off-label alongside antiprotozoal medications, such as atovaquone, for the treatment of parasitic diseases. However, the FDA does not endorse this practice.

- The utilization of Azithromycin in the treatment of viral infections like SARS-CoV-2 and respiratory syncytial virus (RSV) is currently uncertain.

- Last but not least, individuals who have undergone lung transplantation may utilize Azithromycin off-label as a prolonged preventive measure against bronchiolitis obliterans (BO). This action is contraindicated by the manufacturer.

The mechanism behind the action

Azithromycin is primarily a bacteriostatic agent, which means that it inhibits the growth of bacteria. This characteristic sets Azithromycin apart from other antibiotics within its category. Azithromycin, an antibiotic, has demonstrated bactericidal effects against various bacteria, such as streptococci and H. pylori. It is particularly effective against influenzae, especially when administered in higher doses. Azithromycin is pharmacokinetically effective against intracellular pathogens due to its rapid tissue penetration from the bloodstream and its ability to easily cross cellular membranes. This is due to the fact that it enters tissues quickly from the bloodstream. In non-bacterial organisms, such as apicomplexan parasites like Toxoplasma sp., Plasmodium sp., and Babesia sp., Azithromycin inhibits the 50S ribosome present in the parasite apicoplast. The apicoplast is an organelle derived from endosymbiosis that performs important metabolic tasks and contains protein-synthesizing machinery similar to that of bacteria.

Aside from its antibacterial properties, Azithromycin possesses potent immunomodulatory properties. These properties have been shown to significantly reduce the levels of C-reactive protein, IL-8 gene expression, and airway neutrophilia in lung transplant recipients. Experimentally treating SARS-CoV-2 with Azithromycin has garnered some interest because of the antibiotic's antiviral properties when tested in vitro. Azithromycin enhanced the production of interferons in vitro by inducing the expression of RIG-I-like helicases in cultured cells from patients with COPD, in response to rhinovirus infection. However, this effect was not observed in the cultured cells of healthy COPD patients.

Administration

- Azithromycin is available in both oral and intravenous formulations for administration. Production of the extended-release formulation of Azithromycin has ceased. The suggested dosage is either 250 mg or 500 mg, to be taken once daily for a duration of three to five days. However, higher dosages may be required in cases of severe infections. Adults with Chlamydia are occasionally administered a single dose of 1 gram, while 30 milligrams per kilogram is used to treat Otitis media.

- The oral formulations consist of packets (1 gram dissolved in 14 cup or 60 ml of water), tablets (250 mg, 500 mg), and suspensions with concentrations of 100 mg/5 ml and 200 mg/5 ml. Food may be consumed even while the medication is being administered in its full dose.

- An IV solution of Azithromycin, with a dosage of 500 milligrams and no preservatives, is available for reconstitution. Administering Azithromycin via infusion for a minimum duration of one hour is preferable to delivering it through intramuscular injection or intravenous bolus.

- An ophthalmic solution (1%) is accessible in a 2.5 milliliter bottle for the treatment of bacterial conjunctivitis.

Azithromycin demonstrates both remarkable tissue penetration and accumulation within the cells of the body. There is some hepatic metabolism, but Biliary excretion does most of the work. Azithromycin has a longer half-life when compared to other antimicrobials, and it only needs to be taken once daily to be effective. This allows the treatment to be completed in a shorter amount of time. For instance, the treatment of a Chlamydia infection calls for the administration of 1 gram of Azithromycin rather than 100 milligrams of doxycycline twice a day for a period of seven days. The creatinine clearance level of a patient is inconsequential in determining the prescription of Azithromycin for individuals with renal failure or illness. In most cases, there is no need to alter the prescribed dosage.

Adverse effects

Only a small percentage of patients stop taking Azithromycin because of its side effects, and the medication is generally considered to be safe. Additionally, when compared to other Macrolides (such as erythromycin and clarithromycin), it is believed to be safer and cause less damage to the heart than the other Macrolides.

- Azithromycin, like other Macrolides, has been associated with an increased risk of developing polymorphic ventricular tachycardia and torsades de pointes. Additionally, it can result in a prolonged QTc. When compared to amoxicillin, the use of Azithromycin was found to be associated with an increased risk of cardiovascular death as well as a slight but significant absolute increase in the number of cardiovascular deaths. Patients

who already had the highest baseline cardiovascular risk were the ones who felt the effects of these findings the most strongly. However, a significant supplementary longitudinal study conducted on a group of young and middle-aged individuals failed to detect an elevated mortality risk associated with cardiovascular-related causes.

- Hepatotoxicity is another rare side effect of Azithromycin, and it typically presents itself as damage to hepatocellular tissue one to three weeks after treatment with the medication has begun. There are two clinical signs of hepatotoxicity, and they are elevated transaminase levels and cholestatic jaundice.

- Azithromycin, similar to other Macrolides, is recognized for inducing gastrointestinal adverse effects, including nausea and diarrhea, in a substantial proportion of patients. All Macrolides stimulate gastric motility by activating the intestinal motilin receptors in a dose-dependent manner, which results in increased intestinal motility. (Because of this mechanism, gastroparesis treatment with erythromycin is frequently recommended by medical professionals.)

- Severe allergic reactions to Azithromycin that have the potential to cause death are exceptionally uncommon. Some examples of these reactions include anaphylaxis and Stevens-Johnson syndrome (SJS).

- The use of Macrolides is also associated with the development of a Clostridium difficile infection; although to a lesser degree compared to other commonly used antibiotics like clindamycin, fluoroquinolones, and Cephalosporins.

Contraindications

Individuals with a documented record of intense hypersensitivity reactions to Azithromycin or any other macrolide antibiotic (such as anaphylaxis or SJS) are not suitable candidates for Azithromycin treatment. Furthermore, healthcare practitioners must exercise caution when prescribing Azithromycin alongside other medications that have the potential to prolong the QTc interval, such as antipsychotics.

Patients who are taking pimozide, an antipsychotic medication of the first generation, should not take Azithromycin. When macrolide antimicrobials like Azithromycin and pimozide are used together, the enzyme known as cytochrome CYP3A4, which is responsible for the metabolism of pimozide, is inhibited. This can lead to dangerous plasma concentrations of pimozide, which can cause QTc prolongation and other arrhythmias that could potentially be fatal. Even though Azithromycin does not inhibit CYP3A4 as effectively as other Macrolides do, avoiding this interaction is still strongly advised.

Furthermore, Azithromycin inhibits the glycoprotein transporter in cell membranes known as p-glycoprotein/ABCB1, which is responsible for transporting glycoproteins. A relative contraindication to the use of Azithromycin could be the presence of a drug that is a substrate of the P-glycoprotein, particularly one that is also a substrate of the CYP3A4 enzyme. Two examples of this would be the drug colchicine as well as small-molecule antagonists of the calcitonin gene-related peptide (CGRP).

A decrease in bronchiolitis obliterans-free and overall survival was found in a study that compared Azithromycin to a placebo for the prevention of bronchiolitis obliterans (BO) in recipients of hematopoietic stem cell transplant (HSCT). Azithromycin, on the other hand, effectively maintains FEV and improves bronchiolitis obliterans (BO), but it has no impact on the patient's overall survival rate after lung transplantation. Therefore, long-term prophylaxis with Azithromycin is not recommended for hemodialysis patients as a preventative measure.

Toxicity

A prolonged QTc interval is linked to the administration of Azithromycin, as well as other Macrolides. Patients with a prior occurrence of QTc interval disturbance, cardiac arrhythmia, or those currently using other medications linked to QTc prolongation should exercise particular caution when using Azithromycin. This antibiotic has the potential to induce life-threatening arrhythmias, such as torsades de pointes. Animal studies have shown that Azithromycin causes similar QTc prolongation as other Macrolides. However, Azithromycin seems to have a lesser effect on arrhythmia.

While Azithromycin rarely leads to significant liver damage, Macrolides are widely recognized as a cause of drug-induced liver injury characterized by a combination of hepatocellular and cholestatic effects. Discontinuing Azithromycin treatment typically allows for the possibility of reversing liver damage with minimal long-term consequences. Patients who experience hepatotoxicity as a result of Azithromycin use often exhibit immunoallergic symptoms, including fever, rash, and eosinophilia. Certain severe manifestations of immune-mediated allergic reactions, such as anaphylaxis, Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS), are uncommon occurrences.

Most patients adhere to the complete regimen of Azithromycin treatment as prescribed, and although gastrointestinal toxicity is prevalent, it is generally of a mild nature. The main factor contributing to this toxicity is the stimulation of pro-motility receptors in the gastrointestinal tract, which happens when Azithromycin is administered.

Study

When treating Urethritis and Cervicitis, 87 patients were given Azithromycin either as a single dose of 1 g or as divided doses of 1.5 g spread out over the course of 6 days. In 11.9% of these patients, adverse events occurred. This rate was found in 10.7% of patients older than 63 years old and in 5.4% of patients younger than 13 years old. The adverse effect that was reported most frequently was on the gastrointestinal system (15.8%), while adverse effects on the central nervous system and the peripheral nervous system were reported in 0.9% of cases. The gastrointestinal tract was responsible for an overall 51% of the mild adverse events, 29% of the moderate adverse events, but only 4.8% of the severe adverse events.

Only 0.9% of patients discontinued treatment as a result of adverse events; this percentage is lower than what is seen with other Macrolides. Rare side effects of treatment included Leukopenia (1.3–1.8%) and treatment-related increases in liver enzymes (under 3%). Infections such as Acute Otitis Media (AOM) (n = 1150) and streptococcal pharyngitis (n = 754) were treated with Azithromycin in phase II/III clinical trials that were carried out at the Clinical Hospital in Tetovo. The participants' ages ranged from 6 months to 15 years. Azithromycin was administered to the majority of them between 5 and 12 milligrams per kilogram per day. Thirty patients, or 10.9%, experienced one or more of the following adverse reactions as a result of taking the medication: loose stools (1%), vomiting (7.8%), diarrhea (4.1%), abdominal pain (2.9%), and rash (2%). Both the overall incidence of adverse effects caused by Azithromycin (7.7% versus 31%) and the withdrawal rates caused by Azithromycin (0.3% versus 3.6%) were significantly lower than those caused by co-amoxiclav in three different comparisons.

However, the incidence of side effects was significantly higher with Azithromycin in patients who had streptococcal pharyngitis when compared to patients who were given penicillin V. The difference was 13% versus 6.7%. In a nutshell, it would appear that Azithromycin is completely risk-free and well tolerated by both adults and children. Children who participated in an open study and were given Azithromycin for a prolonged period of time had chronic airflow limitation or end-stage lung disease that was not improving despite conventional treatment. Seven children, with a mean age of 12 years, participated in the study. All of the participants had taken Azithromycin for longer than two months, and they were all colonized with Pseudomonas aeruginosa. Both the FEV1 and the FVC showed significant signs of improvement. Although the precise mechanism of action of Azithromycin is not known, there is a possibility that it does not kill bacteria.

It has been hypothesized that the effect could be caused by the Upregulation of a P-glycoprotein, which is a member of the family of multidrug resistant proteins. This hypothesis is based on the fact that erythromycin induces an Upregulation of P-gp expression in a monkey model. However, there is a paucity of direct evidence that

supports this theory at the moment. Twenty-eight of the nine adult patients with confirmed or suspected acute toxoplasmic encephalitis who were given Azithromycin at doses of 900, 1200, or 1500 mg/day in conjunction with pyrimethamine responded to treatment during the induction phase. Six patients withdrew from the study because of potentially reversible adverse effects during the induction phase; three of them had elevated liver enzymes, two of them had hearing loss, and one of them had neutropenia.

Patients who were taking 1500 mg per day had the highest incidence of adverse events that caused treatment to be discontinued. In an open and prospective study, thirty out of thirty-five patients who had gingival hyperplasia caused by cyclosporin responded favorably to treatment with Azithromycin at a dosage of 250 milligrams per day for five days. The patients reported that they were satisfied with the anesthetic, and that their bleeding and pain had stopped. After taking Azithromycin, there was no discernible change in either the concentration of cyclosporin or renal function.

Azithromycin

Azithromycin is frequently prescribed in an inappropriate manner, particularly in primary care settings, despite the fact that it is an effective antimicrobial agent with a number of clinical indications and a profile that is, for the most part, well tolerated. Azithromycin was identified as the most commonly misused medication in several important retrospective cohort studies that demonstrated elevated rates of inappropriate antimicrobial prescribing.

It is customary to prescribe Azithromycin even when there is no clinical indication for antimicrobial use, and in many cases (such as acute Otitis media), Azithromycin is not the first choice of treatment.

Antibiotic Azithromycin is frequently recommended as a first-line treatment for Acute Otitis media (AOM), one of the conditions for which a narrow-spectrum beta-lactam, such as amoxicillin, is the recommended initial course of treatment. The percentage of bacteria that are resistant to Azithromycin is increasing, particularly in S. pneumoniae isolates, which gives rise to significant concerns regarding the widespread use of this medication for upper respiratory infections. When it comes to treating upper respiratory infections, the use of broad-spectrum antimicrobials is associated with higher rates of side effects. This is in contrast to the use of narrow-spectrum agents.

There is a potential correlation between patients who claim to have an allergy to penicillin and the frequent prescription of Azithromycin. The use of Macrolides, specifically Azithromycin, is favored over the use of beta-lactam medications for a wide variety of clinical indications. Researchers were surprised to find that 12.8% of patients in one sizable cohort of an electronic medical records database had penicillin

sensitivities listed on their profiles. Patients with a documented penicillin allergy are at a heightened risk of being prescribed a macrolide antibiotic, with up to a fourfold increase compared to patients without a history of penicillin allergy. However, a comprehensive history of the patient's adverse reaction(s) to penicillin is often sufficient to clarify a listing of penicillin allergy, and it may even be sufficient to remove the listing altogether. This includes paying close attention to symptoms that might point to IgE-mediated hypersensitivity, such as Urticaria (hives) (hives) and anaphylaxis. Patients who have medical histories that are more cause for concern may be recommended to undergo allergy testing or be referred to an allergy specialistLastly, it is crucial for medical practitioners to recognize the minimal occurrence of cross-reactivity between penicillin allergy and Cephalosporins, particularly those belonging to the third and subsequent generations.

A broad range of clinical applications are appropriate for the utilization of Azithromycin and other antimicrobial agents, which can be carried out by proficient medical practitioners. When prescribing Azithromycin, healthcare professionals such as medical doctors, osteopaths, nurse practitioners, and physician assistants should adhere to the guidelines provided by the society and consider the existing evidence. It is imperative for clinicians who work with or supervise non-physician prescribers to ensure that all prescriptions adhere to evidence and guideline-based practice. This responsibility falls to clinicians who collaborate with non-physician prescribers. Patients who reveal concerns about their allergies to medications or who request antimicrobial treatment when it is not required should also be provided with education and the appropriate follow-up care. It is possible for nurses to be of great assistance in responding to questions posed by patients and ensuring that they receive consistent care. Pharmacists are highly valuable in assisting medical professionals in choosing the most efficient antimicrobial agent, dosage, and treatment plan for their patients. In addition, they can assist medical professionals and patients in avoiding interactions between Azithromycin and other medications that change the QTc interval. Although Azithromycin is a powerful and safe antibiotic, doctors must exercise caution when prescribing it. By meticulously selecting antimicrobial therapy, patients are protected from unnecessary side effects, leading to improved patient outcomes, enhanced public health, and increased patient safety.

Conclusion

Azithromycin exhibits a relatively high degree of clinical safety in comparison to other antibiotics. Nevertheless, it is prudent to exercise caution when administering high doses for the treatment of specific conditions. The reason for this is that Azithromycin can induce severe adverse reactions.

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