Journal of Pharmacovigilance and Drug Research

October- December 2020
JPADR, 2020; 1(2); 1-5

DOI: 10.53411/jpadr.2020.1.2.1



REVIEW ARTICLE

Journal home page: www.jpadr.com

Risk-benefit associated with azithromycin: A brief review

Anil Kumar Pradhan [a,] *, Ajit Nahak [b], Gyanendra Narayan Mohapatra [a]

[a] Department of Pharmacology, Roland Institute of Pharmaceutical Sciences Brahmapur, Odisha India- 760004

[b] Department of Pharmacology, Royal College of Pharmacy and Health Sciences, Brahmapur, Odisha India- 760002

A R T I C L E I N F O

Received 25 September 2020;
Revised 07 November 2020;
Accepted 23 November 2020.

Keywords:
Macrolide antibiotics, ductopenia, leukopenia, conjunctivitis, non-occupational allergic contact dermatitis, ototoxicity

A B S T R A C T

Introductions: Azithromycin is the most popular prescribed antimicrobial agent around the world. It comes under the class of macrolide antibiotics. Because of its higher efficacy, tolerance, and broad-spectrum activity, it is primarily used in upper and lower respiratory tract infections, some sexually transmitted infections, and major bacterial infections.

Methods: Pieces of literature were reviewed to access the risk and benefits associated with azithromycin.

Results: Generally, this is commercially available in solids, liquids, and ophthalmic formulations due to its minimal adverse events. It is also used in the case of COVID-19 drug therapy due to its pharmacological and therapeutic properties.

Conclusions: The review of literature presented that it may increase the risk of cardiac death, hepatic injury, ototoxicity, hypersensitivity reactions.

An official publication of Global Pharmacovigilance Society.

Introduction

Azithromycin is a semisynthetic macrolide class of antibiotics derived from erythromycin. It is a highly potent and well-tolerable oral antibiotic. This class of antibiotics is most frequently prescribed by the physician (Martinez *et al.*, 2015). It is frequently prescribed for upper respiratory tract infection, pneumonia, sinusitis, bronchitis, and also currently uses in the coronavirus infection world widely (Maggioli *et al.*, 2011) though there is a risk of some adverse event.

The risk associated with hepatic System

Wide clinical trials have been reported that the drug produces acute, transient, and asymptomatic increases in serum aminotransferase levels with a dose of 250 mg or 500 mg in 1% or 2% of patients and few cases of cholestatic hepatitis with jaundice (Chandrupatla *et al.*, 2002).

It also causes hepatocellular injury and induces jaundice. In these cases, the latency is short and it maybe 1-3 days. Serum aminotransferase (ALT) levels are markedly increased, and alkaline phosphatase (ALP) values are typically less than twice the normal upper limit, although they may increase over time to higher levels. Azithromycin hepatocellular forms of liver injury may be serious and lead to acute liver failure and death or liver transplant emergency. Recovery happens within 4 to 8 weeks in most cases. In some patients of liver biopsy shows markedly cholestasis and reduction in the number of ducts in an organ (ductopenia). Some patient ultimately recovers of jaundice and with their symptoms, although it frequently increases

* Corresponding Author
Anil Kumar Pradhan
E-mail: anilkumarpradhan562@gmail.com
Contact: +916371266932

* Copyright: 2582-7235 // © 2020 The Author(s).
Published by Global Pharmacovigilance Society.
This is an open-access article under the CC BY-NC-ND license.

Available online 1 December 2020

the serum of enzyme and liver biopsy found in ductopenia. Azithromycin induces the absence of the bile duct in other patients and produces serious ductopenia which biliary cirrhosis which eventually needs liver transplantation due to liver dysfunction (Martinez *et al*., 2015).

The risk associated with cardiovascular System

It was reported, that there is an increase in the Q-T prolongation in elderly patients by taking azithromycin (Russo *et al.*, 2006). So, the evidence suggested that azithromycin may have an initial stage of cardiac arrhythmia related adverse effects including polymorphic ventricular tachycardia with the absence of Q-T intervals (Kim *et al.*, 2005) torsades de pointers(Huang *et al.*, 2007) and various studies showed that azithromycin increases risks of cardiovascular death. In the years 2012 and 2013 the study found that an increase in the risk of cardiac death by taking azithromycin is similar to 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 with 1.1million Danish adults with azithromycin showed that no cardiac death risk as compared with penicillin V(rate ratio,2.85;95%CI,1.13 to 7.24)(Svanstrom *et al.*, 2013). The FDA also concludes the adverse event of azithromycin use, it can potentially cause irregular heart rhythms, QRS complex, torsades de pointes (Poluzzi *et al.*, 2009).

The risk associated with blood circulatory System

Azithromycin is preferred as the first-choice drug in bacterial infections as compared to other antibiotics because of their better bioavailability and lower side effects but in a clinical trial study in Japan it was observed that 11 patient showed leukopenia (0.88%), 2 patients showed neutropenia (0.22%) after talking azithromycin therapy (Higa & Saito, 2000). These adverse events are reported too mild and transient especially abnormal neutrophil count is observed in adults is 1.5% and more in children (1.9%) (Treadway & Pontani, 1996).

The risk associated with topical use

No case of adverse event was reported due to the topical use of azithromycin earlier to the year 2011 (Flavia Monteagudo Paz *et al.*, 2011). The first case was reported in 2011 of an 85-year-old lady with a history of bilateral phacoemulsification, allergic rhinoconjunctivitis, and chronic dacryocystitis. After a 1-year interval, the second time application of Azyter eye drop causes an adverse event. Then when she stopped Azyter, on the next second-week eyelid eczema was improved.

Department of Dermatology, Hospital General Universitario de Alicante also found an adverse event of Azithromycin. A 76-year-old lady, who had to have acute eczema and acute conjunctivitis affecting the eyelids and cheeks, was reported. Three months before the event, she underwent pseudophakia surgery. Due to that, she prescribed tabradex and azydrop single-dose container. As it was suspected that allergic contact dermatitis was caused by this two ophthalmic preparation the application of these eye drops was stopped. Then after two weeks, later the patient had improved (Milkovic-Kraus & Kanceljak-Macan, 2001).

Occupational allergic contact is generally common and was observed in the case of pharmaceutical workers who were involved in azithromycin synthesis or formulation. This shows air-bone contact dermatitis. The Spanish baseline series patch testing D2 and D4 showed a positive reaction to azydrop. But this was the first case of non-occupational allergic contact dermatitis reported ever but no positive reactions were observed by erythromycin and clarithromycin so it could be possibly be explained. Erythromycin and clarithromycin containing 14 carbon atoms but azithromycin contain 15 carbon atom cycles (Milkovic-Kraus *et al.*, 2007).

The risk associated with the auditory system

Azithromycin rarely causes ototoxicity (Wallace *et al.*, 1994; Tseng *et al.*, 1997). Most of the people had a problem with reversible SNHL during prolonged high-dose therapy related to AIDS. But a rare case of irreversible SNHL was found in a 39-year-old woman when exposing to low dose azithromycin. Who just started taking azithromycin for urinary tract infection. She was advised to take two tablets of 250 mg per day but she stopped after the second dose due to worsening tinnitus and subjective bilateral hearing loss. She did not have any past medical and family histories. She also denied vertigo, imbalance, or other vestibular symptoms. But Still auditory symptoms did not improve after she stopped the medication. Azithromycin comes under macrolide antibiotics. Which causes Macrolide ototoxicity from the early 1970s (Mintz *et al.*, 1973).

The risk associated with GIT

Most of the antimicrobial agents having the major risk factor of clostridium difficult infections (CDI). In some articles, it was found that the risk of CDI infection was different with different classes of antibiotics followed by the meta-analysis method. Macrolide antibiotics are a lesser risk of CDI as compared to clindamycin and fluoroquinolones antibiotics. Azithromycin is coming under macrolide antibiotics so that the risk of clostridium difficult infections is low (Deshpande *et al.*, 2013; Brown *et al.*, 2013).

Risk of drug-interaction

Azithromycin is a macrolide class of antibiotics it contains bacteriostatic effects of both gram +ve and gram -ve microorganisms (McMullan & Mostaghim, 2015). The Macrolide class of antibiotics also affects the other drugs of the metabolism process. Except Azithromycin and clarithromycin do not significantly interfere with the metabolism process. Many of the drugs are metabolized by microsomal isoenzyme CYP3A4. This macrolide class of drugs interacts with other drugs and it inhibited the CYP450

so it prevents the activation of other enzymes responsible for metabolism it can lead to increases in the drug concentration and produce toxic effects (Franklin, 1977). Various compounds are available over the counter (OTC) so, physicians are generally aware of this type of interaction and cautious for antibiotics prescribing.

Use of azithromycin in combination with theophylline

It is widely used in bronchodilation for the treatment of asthma patients. These drugs are generally metabolized in isoenzyme CYP3A4 in the liver. Coadministration of other drugs in the same pathway can competitively inhibit the Theophylline clearance. The macrolide class of Erythromycin and Theophylin are also be metabolized in the CYP450 enzyme (Ludden, 1985). So Theophylline metabolism inhibited and increases the plasma concentration and produced toxic symptoms include dizziness, headache, tachycardia, palpitation, etc. Some studies suggest that the combination of Azithromycin and Theophylline no significant increases the plasma concentration of Theophylline. Azithromycin contains a lack of effect on CYP450 interaction. As a result, these studies suggest that Azithromycin can administer Theophylline use of asthmatic patients (Debruyne *et al.*, 1986).

Use of azithromycin in combination with cyclosporine

Cyclosporine is an immunosuppressant drug commonly used in graft rejection of organ transplantation and also used in an autoimmune disorder. This cyclosporin is also metabolized in liver isoenzyme CYP3A4. Antibiotics like macrolide class also are metabolized in this isoenzyme so cyclosporine not metabolized it and increases the cyclosporine concentration (Kronbach *et al.*, 1988). Increases plasma concentration causes renal dysfunction, hepatotoxicity, abdominal pain, psychosis, etc (Jensen *et al.*, 1987). In a study 3995 patients administer Azithromycin, no case has been found in Azithromycin-Cyclosporine interaction (Vernillet *et al.*, 1989). As a result of no interaction occurs between Azithromycin-Cyclosporine.

Use of azithromycin in combination with carbamazepine

Carbamazepine is an anticonvulsant drug used to treat patients with epilepsy. These drugs also interact with antibiotics. To suggest the physician appropriately choose the medication and prescribe it. Signs of toxicity include confusion, vertigo, ataxia, and vomiting, etc (Nahata, 1996). In the case of Azithromycin are not able to find any interaction with Carbamazepine (Rapeport *et al.*, 1991). In clinical studies more than 600 patients receive a combination of medication, to find no clinical evidence combination with Azithromycin (Hopkins & S, 1994).

Use of azithromycin in combination with warfarin

Warfarin is generally used in anticoagulant to prevent the clotting factors. Erythromycin also inhibits Warfarin metabolism as a result increases the serum concentration to causes an increase in prothrombin time and hemorrhage (Bartle, 1980). A case of 23 healthy volunteers in the combination of Azithromycin and Warfarin to show an absence of interaction between them. As a result, Azithromycin is not to be affected in prothrombin time while administrating the warfarin (Sato *et al.*, 1984).

Use of azithromycin in combination with hormonal contraceptives

This contraceptive pill available in either progesterone-estrogen combination or only progesterone preparation. It is also effective for birth control. These contraceptive pills are also an interaction between broad-spectrum antibiotics (Orme *et al.*, 1991). In a clinical review of 6655 patients, not any interaction between azithromycin and Oral contraceptive(Nahata, 1996).

Use of azithromycin in combination with zidovudine

Zidovudine is widely used in AIDS treatment to inhibit the reverse transcriptase enzyme. In a study, azithromycin also administers HIV patients not able to affect zidovudine metabolism. As a result, azithromycin also is used in HIV-affected patients used in zidovudine (Chave *et al.*, 1992).

Use of azithromycin in combination with Antacid

Antacids are generally used to neutralize the acid in the stomach and are used in the treatment of gastritis, Zollinger Ellison syndrome, and ulcer. In the case of Azithromycin administer with Antacid to decreases the absorption of Azithromycin concentration in the body. To avoid this type of interaction to take after 3hr. administration of Azithromycin. Physicians provide information about the interaction between those drugs (Foulds *et al.*, 1991).

Use of azithromycin in combination with hydroxychloroquine

HCQ is a popular drug widely used in the treatment of Malaria, Rheumatoid arthritis, currently used in Coronavirus infections. Together with use in HCQ and Azithromycin to causes increases the risk of irregular heart rhythm and QT prolongations. This type of interaction has harmful effects on our body system. Clinicians are finding out the history of any heart risk of patients and to avoid this type of combination.

Risk in SARS Cov-2

COVID-19 or SARS Cov-2 is known as a severe acute respiratory syndrome. There are four types of coronavirus such as alpha, beta, gamma, and delta. The genomic structure of the Coronavirus is a single standard RNA virus (+SSRNA) and the diameter is 80-120 nm. The mechanism of the Coronavirus is bound to the ACE2 receptor of the human lungs. Various types of medicinal agents are used to treatment of Coronavirus such as hydroxychloroquine,

azithromycin, favipiravir, and remdesivir, etc (Wrapp *et al.*, 2020).

Azithromycin is widely used for covid-19 treatment. It is a macrolide class of antibiotics derived from erythromycin. This drug is highly potent and increases the penetration of tissue and it inhibits the 50s ribosomal subunit to halt the protein synthesis (Parra-Lara *et al.*, 2020). Fatal cardiac arrhythmias are caused by azithromycin in coronavirus treatment. Azithromycin may also be induced QTc prolonged and increased torsed de points (Tdp) (Kezerashvili *et al.*, 2007) studied that, a 55-year-old patient to show the QT extension and Tdp associated use in Azithromycin. Observed that, a 90-year-old man with high blood pressure after taking Azithromycin within few hours to increase QT extension and Tdp. The Macrolide class of Azithromycin also inhibited CYP3A4 metabolism so increases the risk of Tdp(Guo *et al.*, 2010). Those patients are associated with a high-risk cardiovascular disease it increases the chance of death of the patients. In some case reports studies observe that middle-aged adult patients are not associated with cardiac death but some age patients between 60-70 age patients are at high risk of cardiovascular diseases (Hancox *et al.*, 2013). Azithromycin-related adverse effects mainly nausea, vomiting, abdominal pain, and diarrhea are seen in only 10% of cases. The mechanism of EAD and QT interval is prolonging due to blocking the efflux of potassium ions. The combination of HCQ and Azithromycin causes increases in the risk of mortality rate. Alone HCQ uses to decrease the mortality rate. Among those patients having a high risk of coronary artery disease to take azithromycin to increases cardiac death (Lighter & Raabe, 2020). In the above studies, caution is if Azithromycin is used with Hydroxychloroquine or alone to treat Coronavirus both are risk of torsed de points (Sultana *et al.*, 2020).

Conclusions

Safety and efficacy both are important factors. From the study of the above research articles, we conclude that no doubt azithromycin is a highly potent and well-tolerable oral antibiotic, most frequently prescribed by the physician but it may also show some adverse effects. So due safety point of view more this type of study should be done and a comparison test also should be done with other antibiotics to detect the problem.

Conflict of Interest

There is no conflict of interest between the authors.

References

Bartle W. R. (1980). Possible warfarin-erythromycin interaction. *Archives of internal medicine*, *140*(7), 985–987.

Brown, K. A., Khanafer, N., Daneman, N., & Fisman, D. N. (2013). Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. *Antimicrobial agents and chemotherapy*, *57*(5), 2326–2332.

Chandrupatla, S., Demetris, A. J., & Rabinovitz, M. (2002). Azithromycin-induced intrahepatic cholestasis. *Digestive diseases and sciences*, *47*(10), 2186–2188.

Chave, J. P., Munafo, A., Chatton, J. Y., Dayer, P., Glauser, M. P., & Biollaz, J. (1992). Once-a-week azithromycin in AIDS patients: tolerability, kinetics, and effects on zidovudine disposition. *Antimicrobial agents and chemotherapy*, *36*(5), 1013–1018.

Debruyne, D., Jehan, A., Bigot, M.C. *et al.* (1986). Spiramycin has no effect on serum theophylline in asthmatic patients. *European journal of clinical pharmacology*, 30, 505–507.

Deshpande, A., Pasupuleti, V., Thota, P., Pant, C., Rolston, D. D., Sferra, T. J., Hernandez, A. V., & Donskey, C. J. (2013). Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. *The Journal of antimicrobial chemotherapy*, *68*(9), 1951–1961.

Dylewski J. (1988). Irreversible sensorineural hearing loss due to erythromycin. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne*, *139*(3), 230–231.

Foulds, G., Hilligoss, D. M., Henry, E. B., & Gerber, N. (1991). The effects of an antacid or cimetidine on the serum concentrations of azithromycin. *Journal of clinical pharmacology*, *31*(2), 164–167.

Gedar Totuk, O. M., & Yukselen, A. (2019). Acute allergic reaction caused by topical azithromycin eye drops: A report of two cases. *Saudi journal of ophthalmology : official journal of the Saudi Ophthalmological Society*, *33*(2), 180–182.

Guo, D., Cai, Y., Chai, D., Liang, B., Bai, N., & Wang, R. (2010). The cardiotoxicity of macrolides: a systematic review. *Die Pharmazie*, *65*(9), 631–640.

Hancox, J. C., Hasnain, M., Vieweg, W. V., Crouse, E. L., & Baranchuk, A. (2013). Azithromycin, cardiovascular risks, QTc interval prolongation, torsade de pointes, and regulatory issues: A narrative review based on the study of case reports. *Therapeutic advances in infectious disease*, *1*(5), 155–165.

Higa, F., & Saito, A. (2000). *The Japanese journal of antibiotics*, *53 Suppl B*, 125–135.

Hopkins S. (1991). Clinical toleration and safety of azithromycin. *The American journal of medicine*, *91*(3A), 40S–45S.

Huang, B. H., Wu, C. H., Hsia, C. P., & Yin Chen, C. (2007). Azithromycin-induced torsade de pointes. *Pacing and clinical electrophysiology : PACE*, *30*(12), 1579–1582.

Jensen, C. W., Flechner, S. M., Van Buren, C. T., Frazier, O. H., Cooley, D. A., Lorber, M. I., & Kahan, B. D. (1987). Exacerbation of cyclosporine toxicity by concomitant administration of erythromycin. *Transplantation*, *43*(2), 263–270.

Kim, M. H., Berkowitz, C., & Trohman, R. G. (2005). Polymorphic ventricular tachycardia with a normal QT interval following azithromycin. *Pacing and clinical electrophysiology: PACE*, *28*(11), 1221–1222.

Kronbach, T., Fischer, V., & Meyer, U. A. (1988). Cyclosporine metabolism in human liver: identification of a cytochrome P-450III gene family as the major cyclosporine-metabolizing enzyme explains interactions of cyclosporine with other drugs. *Clinical pharmacology and therapeutics*, *43*(6), 630–635.

Lighter, J., & Raabe, V. (2020). Azithromycin Should Not Be Used to Treat COVID-19. *Open forum infectious diseases*, *7*(6), ofaa207.

López-Lerma, I., Romaguera, C., & Vilaplana, J. (2009). Occupational airborne contact dermatitis from azithromycin. *Clinical and experimental dermatology*, *34*(7), e358–e359.

Ludden T. M. (1985). Pharmacokinetic interactions of the macrolide antibiotics. *Clinical pharmacokinetics*, *10*(1), 63–79.

Maggioli, C., Santi, L., Zaccherini, G., Bevilacqua, V., Giunchi, F., Caraceni, P. (2011). A Case of Prolonged Cholestatic Hepatitis Induced by Azithromycin in a Young Woman. *Case reports in hepatology*, 2011, 1-4.

Martinez, M. A., Vuppalanchi, R., Fontana, R. J., Stolz, A., Kleiner, D. E., Hayashi, P. H., Gu, J., Hoofnagle, J. H., & Chalasani, N. (2015). Clinical and histologic features of azithromycin-induced liver injury. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association*, *13*(2), 369–376.e3.

McMullan, B. J., & Mostaghim, M. (2015). Prescribing azithromycin. *Australian prescriber*, *38*(3), 87–89.

Milković-Kraus, S., Macan, J., & Kanceljak-Macan, B. (2007). Occupational allergic contact dermatitis from azithromycin in pharmaceutical workers: a case series. *Contact dermatitis*, *56*(2), 99–102.

Nahata M. (1996). Drug interactions with azithromycin and the macrolides: an overview. *The Journal of antimicrobial chemotherapy*, *37 Suppl C*, 133–142.

Orme, M., Back, D., Tjia, J. (1991). The lack of interactions between azithromycin and oral contraceptive steroids. *British journal of Clinical pharmacology*, 3J, 229.

Parra-Lara, L. G., Martínez-Arboleda, J. J., & Rosso, F. (2020). Azithromycin and SARS-CoV-2 infection: Where we are now and where we are going. *Journal of global antimicrobial resistance*, *22*, 680–684.

Poluzzi, E., Raschi, E., Moretti, U., & De Ponti, F. (2009). Drug-induced torsades de pointes: data mining of the public version of the FDA Adverse Event Reporting System (AERS). *Pharmacoepidemiology and drug safety*, *18*(6), 512–518.

Rapeport, W. G., Dewland, P. M., Muirhead, D. C., Forster, P. L. (1991). Lack of interaction between azithromycin and carbamazepine. *In Proceedings of the British Pharmacological Society*, 1991; London.

Ray, W., Murray, K., Hall, K., Arbogast, P., Stein, C. (2012). Azithromycin, and the Risk of Cardiovascular Death. *New England Journal Of Medicine*, 366(20), 1881-1890.

Russo, V., Puzio, G., & Siniscalchi, N. (2006). Azithromycin-induced QT prolongation in elderly patient. *Acta bio-medica : Atenei Parmensis*, *77*(1), 30–32.

Sato, R. I., Gray, D. R., & Brown, S. E. (1984). Warfarin interaction with erythromycin. *Archives of internal medicine*, *144*(12), 2413–2414.

Sultana, J., Cutroneo, P. M., Crisafulli, S., Puglisi, G., Caramori, G., & Trifirò, G. (2020). Azithromycin in COVID-19 Patients: Pharmacological Mechanism, Clinical Evidence and Prescribing Guidelines. *Drug safety*, *43*(8), 691–698.

Svanstrom, H., Pasternak, B., Hviid, A. (2013). Use of Azithromycin and Death from Cardiovascular Causes. *New england journal ff medicine*, 368(18): 1704-1712.

Treadway, G., & Pontani, D. (1996). Paediatric safety of azithromycin: worldwide experience. *The Journal of antimicrobial chemotherapy*, *37 Suppl C*, 143–149.

Tseng, A. L., Dolovich, L., & Salit, I. E. (1997). Azithromycin-related ototoxicity in patients infected with human immunodeficiency virus. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *24*(1), 76–77.

Vernillet, L., Bertault-Peres, P., Berland, Y., Barradas, J., Durand, A., & Olmer, M. (1989). Lack of effect of spiramycin on cyclosporin pharmacokinetics. *British journal of clinical pharmacology*, *27*(6), 789–794.

Wallace, M. R., Miller, L. K., Nguyen, M. T., & Shields, A. R. (1994). Ototoxicity with azithromycin. *Lancet (London, England)*, *343*(8891), 241.

Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Hsieh, C. L., Abiona, O., Graham, B. S., & McLellan, J. S. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science (New York, N.Y.)*, *367*(6483), 1260–1263.