Update on azithromycin and cardiac side effects

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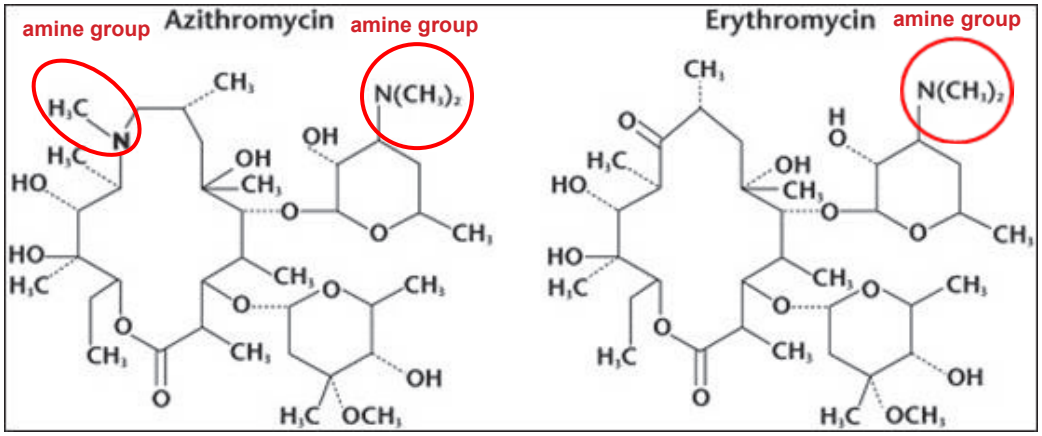
1. Mechanism of action of azithromycin

Azithromycin is a macrolide antibiotic and the sole member of the azalide subclass. Derived from erythromycin, it has an aza-methyl substitution (insertion of a nitrogen atom) in the macrolide ring. This addition increases the stability of its structure but does not change the mechanism of action(Figure 1). The addition of the second amine group resulted in important advantages over erythromycin, including greater tissue penetration and an extended half-life.[1] Azithromycin binds to the 50S ribosome subunit and blocks protein synthesis by inhibiting the transpeptidation/translocation step. This prevents mRNA translation and ultimately inhibits bacterial growth. Macrolides typically have bacteriostatic activity but can be bactericidal at high enough concentrations and with very susceptible organisms.

Azithromycin has broad antimicrobial activity against both anaerobic and aerobic Gram-positive and Gram-negative bacteria.[3] However, azithromycin may have greater activity against Gram-negative organisms, especially *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Neisseria gonorrhea*, *Ureaplasma urealyticum*, and *Borrelia burgdorferi*.[4] Like other macrolides azithromycin is also highly effective against atypical intracellularorganisms, such as *Legionella pneumophila*, *Chlamydia spp*, and *Mycoplasma spp*.[5]

Figure1. Chemical structures of Azithromycin and Erythromycin[2]



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2. Pharmacokinetics

Following oral administration, azithromycin exhibits rapid intracellular uptake from blood to tissue compartments, resulting in tissue concentrations higher than the minimum inhibitory concentration for many

pathogens. This explains its efficacy against intracellular organisms in particular.[5] It is subsequently slowly released back into circulation due to its long terminal phase elimination half-life of ~60 hours.[4] Azithromycin is predominately eliminated through biliary excretion, and approximately 6% of the administered dose is excreted through the urine as unchanged drug. Due to the elimination profile of azithromycin, there is no need for dosage adjustment in patients with renal or hepatic dysfunction. However, it is recommended to use caution in patients with a glomerular filtration rate (GFR) <10 milliliters/minute as the area under the curve is increased by 35% compared to patients with normal renal function. Furthermore, although there is no dose adjustment recommended for hepatic dysfunction, in rare cases azithromycin has the potential for hepatotoxicity, and clinicians should discontinue the drug immediately if signs or symptoms of hepatic toxicity develop. This pharmacokinetic profile of azithromycin allows for once-daily dosing and consequently promotes patient compliance.

3. Side effects

The most common treatment related side effects involve the gastrointestinal tract, including diarrhea, nausea, and abdominal cramping.[6] Less common side effects include clinically insignificant elevations in liver enzymes and even more infrequently cholestatic hepatitis, jaundice, and liver failure.[7] Some side effects that occur with a frequency of 1% or less include palpitations, chest pain, dyspepsia, vomiting, flatulence, dizziness, headache, fatigue, rash, pruritus, and photosensitivity.

4. Cardiac side effects

Until recently azithromycin was considered to have minimal cardiac effects compared to the other antibiotics in its class. Interestingly, in previous studies other members of the macrolide class, such as erythromycin and clarithromycin, had an increased risk for arrhythmias and had a greater risk for cardiac side effects.[8,9] However, several case studies have identified QT interval prolongation and torsade de pointes as possible side effects from azithromycin treatment.[10,11] A study in 2002 investigating only azithromycin and its cardiac side effects revealed a modest and insignificant prolongation of QT intervals; patients otherwise had no clinical side effects. Notably, these patients were healthy and not taking any medications prior to the study.[12] The cardiac side effects of azithromycin, namely QT prolongation, increase when concomitantly used with other QT prolonging medications. Amiodarone used in combination with azithromycin causes marked QT prolongation and QT dispersion.[13] In addition, azithromycin was suspected of precipitating sudden cardiac arrest in a patient using methadone, which also causes QT prolongation and arrhythmias.[14]

The cardiac side effects of azithromycin became a more prominent concern after the publication of a recent study in *the New England Journal of Medicine* comparing the risk of cardiovascular death in patients treated with azithromycin versus those treated with amoxicillin, ciprofloxacin, levofloxacin, or no antibiotics at all.[9] After five days of treatment, patients taking azithromycin had a greater risk for cardiovascular death and all cause death than those taking no antibiotics.The risk of cardiovascular death was significantly greater with azithromycin than with either amoxicillin or ciprofloxacin. When compared to amoxicillin, there were 47 additional cardiovascular deaths per 1 million courses. Furthermore, in patients with the highest risk for cardiovascular disease there were 245 additional cardiovascular deaths per 1 million courses.[9] However, a subsequent study from Denmark concluded that azithromycin was not associated with an increased risk of death from cardiovascular causes in young and middle-aged adults when compared to penicillin V.[15]

5. Clinical implications

In March of 2013, the Food and Drug Administration (FDA) announced that azithromycin labels had been revised to reflect the information that azithromycin can prolong the corrected QT interval and increase the risk of cardiac arrhythmias and torsades de pointes.[16] Additional risk factors for cardiac effects in patients treated with azithromycin include

increased age, high doses and rapid administration leading to higher serum concentrations, a prior history of cardiac disease, and risk factors for cardiovascular disease such as diabetes.[9,10] This increased mortality risk due to the cardiotoxicity with azithromycin should prompt clinicians to carefully review the indications for treatment and avoid concomitant use of other drugs known to prolong the QT interval.[9] However, the risk of cardiovascular death from the use of azithromycin is probably outweighed by the benefits of using this antibiotic for bacterial infections, especially in healthy patients with no cardiac disease or cardiovascular risk factors.

Addendum

The official FDA statement on the website section entitled Postmarket Drug Safety Information for Patients and Providers reads:

The U.S. Food and Drug Administration (FDA) is warning the public that azithromycin (Zithromax or Zmax) can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Patients at particular risk for developing this condition include those with known risk factors, such as existing QT interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, or use of certain drugs used to treat abnormal heart rhythms, or arrhythmias. (www.fda.gov/drugs/drugsafety; accessed 11/16/2013).

Keypoints

1. Azithromycin has very favorable pharmacological properties.
2. Azithromycin can prolong the QT interval and cause arrhythmias, especially when used with other drugs which prolong the QT interval.
3. Clinicians need to consider patient cardiac risk factors and drug interactions before using this medication, especially in hospitalized patients.

Key words: macrolide antibiotics, azithromycin, cardiac toxicity, QT prolongation

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