A Case-Based Approach to Evaluating Azithromycin Use and Cardiovascular Risks

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Azithromycin is a commonly prescribed macrolide antibiotic for the management of community-acquired pneumonia in the outpatient setting. Recent data have led to a growing concern of abnormal changes in cardiac electrophysiology and arrhythmias associated with its use. As azithromycin continues to be prescribed, clinicians should be aware of the new safety data and how it may affect concomitant medications or comorbid conditions in a patient. This article utilizes a case-based approach to assess azithromycin use and the risk of QT-prolongation and cardiac arrhythmias.

KEY WORDS: Arrhythmias, Azithromycin, Community-acquired pneumonia, Macrolides, Methadone, QT-prolongation, Risperidone, Torsade de pointes.

ABBREVIATIONS: CAP = Community-acquired pneumonia, ICU = Intensive care unit, IDSA = Infectious Diseases Society of America.

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Introduction

Community-acquired pneumonia (CAP) is an infection of the lungs that occurs in the outpatient setting or within 48 hours of hospitalization.[1] Common CAP pathogens include: *Streptococcus pneumoniae, Mycoplasma pneumoniae, Haemophilus influenzae, Chlamydophila pneumoniae, Legionella* species, and respiratory viruses.[2] As a concern worldwide, it has also been associated with serious morbidity and mortality, especially in patients of advanced age with comorbidities.[1,3] Appropriate and timely management of CAP is, therefore, of utmost importance.

According to the Infectious Diseases Society of America (IDSA) and American Thoracic Society, treatment is dependent on the setting a patient is managed in (outpatient, inpatient, or inpatient-intensive care unit [ICU]). Both the site of care and initial severity of illness can be assessed by the CURB-65 criteria: **C**onfusion, **U**remia (BUN > 20 mg/dL), **R**espiratory rate (≥ 30 breaths/minute), low **B**lood pressure (systolic < 90 mm Hg or diastolic ≤ 60 mm Hg), and age (**65** years of age and older). Patients with a score of 0 to 1 would be treated as an outpatient, a score of 2 would be treated as an inpatient or closely supervised outpatient, and a score of 3 or higher would be hospitalized and possibly treated in the ICU. For outpatient management, patients who are otherwise healthy with no use of antimicrobials in the last three months should receive a macrolide or doxycycline. Alternatively, if patients have comorbidities (e.g., diabetes mellitus, alcoholism, asplenia), a respiratory fluoroquinolone or combination beta-lactam plus a macrolide is recommended. For inpatient management (non-ICU or ICU), a respiratory fluoroquinolone, or combination beta-lactam plus a macrolide is recommended.[3]

Since its release in the early 1990s, azithromycin has become a commonly prescribed macrolide antibiotic for the management of CAP in the outpatient setting.[4-6] However, recent data have led to a growing concern for abnormal changes in cardiac electrophysiology and arrhythmias associated with its use.[5,6] As azithromycin continues to be available, clinicians should be aware of the new safety data and how they may affect concomitant medications or comorbid conditions in a patient. This article utilizes a case-based approach to assess azithromycin use and the risk of QT-prolongation and cardiac arrhythmias.

Patient Case

A 67-year-old male (weight = 90 kg, height = 5'10") presents to his primary care physician's office with complaints of productive cough and shortness of breath. He has a past medical history significant for heroin abuse and schizophrenia. He has no known drug allergies. His home medications include: methadone 100 mg by mouth daily, risperidone 4 mg by mouth twice daily, and multivitamin by mouth daily. Upon physical exam:

- The patient is a well-nourished Caucasian male in mild-to-moderate respiratory distress.
- Vital signs: blood pressure = 155/85 mmHg, pulse = 85 beats per minute, respiratory rate = 22 breaths per minute, temperature = 100° F.
- Lungs: tachypneic, labored breathing, decreased breath sounds in right lower lung fields.
- Cardiovascular (CV): audible S1 and S2; tachycardic with a regular rate and rhythm.
- Neurologic: alert and oriented to time and place.
- Laboratory data: elevated white blood count = 14 x 10^3/mm^3; all other laboratory data were within normal limits.

The patient was treated for CAP and prescribed a Z-Pak (azithromycin 500 mg by mouth daily for one day, then 250 mg by mouth daily for four days), acetaminophen 500 mg by mouth four times daily as needed, and his prior home medications, as scheduled.

Medication-Related Issues

- Azithromycin, methadone, and/or risperidone
  - All three medications are associated with QT-prolongation[7]
  - Coadministration may result in an increased risk for QT-prolongation and cardiac arrhythmias[7]
- Azithromycin and methadone
  - Methadone can inhibit the metabolism of azithromycin, resulting in increased serum concentrations of azithromycin[7]

Discussion

This is a 67-year-old patient with a past medical history significant for schizophrenia and heroin abuse. He is diagnosed with CAP based on his clinical presentation and has a calculated CURB-65 score of 1 (older than 65 years of age). According to the IDSA empiric treatment recommendations, the patient can be managed in the outpatient setting with either a macrolide or doxycycline.[2] Moreover, this patient was prescribed a five-day course of azithromycin therapy.

Azithromycin is a widely used macrolide antibiotic in the community setting and, in 2011, accounted for more than 50 million prescriptions.[4] It is approved by the Food and Drug Administration (FDA) for the management of CAP, among other infections (e.g., bacterial sinusitis, pharyngitis/tonsillitis, uncomplicated skin and skin structure infections). Commonly reported adverse effects are gastrointestinal in nature, including abdominal pain, diarrhea, flatulence, nausea, vomiting.[5,7] Despite case reports of cardiotoxicity, azithromycin appeared to be the safest macrolide in the class with minimal interaction with the CYP3A4 substrates.[8]

With recent postmarketing data, it is important to highlight the risk of fatal arrhythmias with azithromycin use.[5-7] A cohort study conducted by Ray et al. assessed the risk of CV death in patients taking prescriptions for azithromycin, amoxicillin, ciprofloxacin, levofloxacin, or no antibiotic. Patients were identified through the Tennessee Medicaid program between 1992 and 2006. When compared with those who did not take the antibiotics during a five-day course of therapy, azithromycin resulted in an increased risk of CV death (hazard ratio [HR] = 2.88, 95% confidence interval [CI] 1.79-4.63; $P < 0.001$). Similarly, azithromycin resulted in an increased risk of death from any cause (HR = 1.85, 95% CI 1.25-2.75; $P = 0.002$). When compared with amoxicillin or ciprofloxacin, azithromycin was shown to significantly increase the risk of CV mortality. However, CV mortality as compared with levofloxacin did not significantly differ.[6]

In May 2012, FDA released a statement advising health care professionals to be aware of the potential for fatal cardiac arrhythmias secondary to azithromycin use.[9] Notably, the azithromycin drug labels under the "warnings and precautions" section have also been updated for this medication.[9,10] Although macrolides (e.g., erythromycin, clarithromycin) within the class and alternative nonmacrolide antibiotics such as fluoroquinolones share this warning and risk for QT-prolongation, it is important to consider patient-specific risk factors for developing this condition. This includes the presence of structural heart disease, hepatic impairment, electrolyte disturbances (hypomagnesemia, hypokalemia), concomitant use of medications that can prolong QT, bradycardia, or existing QT-interval prolongation (≥ 450 milliseconds) (Tables 1, 2).[10-12]

Table 1. Risk Factors for QT-Prolongation and/or Torsade de Pointes

Drugs interactions
Coadministration with drugs that inhibit the metabolism of drugs that prolong QT-interval
Coadministration with drugs that are known to prolong QT-interval
Cardiac abnormalities
Atrioventricular block
Bradycardia
Prolonged baseline QT-interval ≥ 450 milliseconds
Sinoatrial block
Electrolyte imbalances
Hypokalemia
Hypomagnesemia
Family history
Female gender
Hepatic impairment
Structural heart disease
Cardiomyopathy
Heart failure
Myocardial infarction
Valvular disease

Source: References 11, 12.

The patient does not have any underlying cardiac conditions or electrolyte disturbances. However, he is taking other medications that can increase the risk of QT-prolongation when coadministered with azithromycin. The first medication of concern is methadone, an opioid-agonist used for pain management and opioid addiction. Since its release, additional boxed warnings have been issued because of observed cases of QT-prolongation and serious arrhythmias such as torsade de pointes.[7,13] A retrospective case series by Krantz et al. identified 17 methadone-treated patients with torsade de pointes. The mean age was 49 ± 9 years, and the mean daily methadone dose was 397 ± 283 mg. The average QTc (corrected QT) interval was reportedly 615 ± 77 milliseconds. Of note, there were underlying risk factors for QT-prolongation in some patients: one patient received nelfinavir, an inhibitor of methadone metabolism; nine patients received concomitant therapy that can also prolong QT-interval; three patients had underlying structural heart disease; and seven patients had hypokalemia.[14] This case series reaffirms the risk factors for QT-prolongation mentioned previously. Considering the average dose administered in this case series, there is also a concern for a dose-dependent effect of methadone on a patient's QT-interval, whereby higher doses may increase the risk of arrhythmias.[14,15] It is advised to use the lowest effective dose of methadone to manage patients.[16]

Similarly, another medication of concern in the patient case is risperidone, an atypical antipsychotic used for the management of bipolar disorder or schizophrenia. Postmarketing data have described case reports of QT-prolongation with its use.[7,17] Although both methadone and risperidone are associated with QT-prolongation, it is also important to recognize that methadone inhibits

Table 2. Examples of Drugs That Can Induce QT-Prolongation and/or Torsade de Pointes

Antiarrhythmic Drugs	Amiodarone Flecainide Ibutilide Procainamide Quinidine Sotalol
Antimicrobial Drugs	Azithromycin Chloroquine Clarithromycin Erythromycin Ketoconazole Levofloxacin Moxifloxacin Pentamidine Quinine
Psychiatric Drugs	Amitriptyline Clomipramine Haloperidol Lithium Nortriptyline Risperidone Thioridazine Ziprasidone
Promotility Drugs	Cisapride
Miscellaneous	Cocaine Methadone

Source: References 7, 8, 11, 12.

the CYP3A4 isoenzyme. Azithromycin is metabolized by this substrate. Concurrent use with methadone may result in elevated concentrations of azithromycin and an increased risk of QT-prolongation and/or arrhythmias.[7]

Furthermore, with the patient case and safety concerns reviewed, the addition of azithromycin to the current home regimen may result in an increased risk for QT-prolongation and/or life-threatening arrhythmias such as torsade de pointes. According to the American Heart Association, in rare cases, drugs that potentiate the risk of torsade de pointes in a patient with a history of QT-prolongation may be initiated in the hospital setting, with appropriate cardiac monitoring.[18,19] Despite continuing azithromycin on the outpatient setting for this patient,

Clinical Pearls

- Azithromycin is linked to QT-prolongation and/or cardiac arrhythmias.
- Prior to initiating azithromycin, risk factors that may potentiate QT-prolongation (e.g., medications, electrolyte disturbances, cardiac abnormalities) should be assessed.
- For patients with risk factors for QT-prolongation, consider alternative CAP management when possible or perform additional monitoring and patient education if azithromycin was to be continued.

there was no adverse outcome. However, a baseline electrocardiogram prior to its initiation may not have been unreasonable in this case. If the measured QT-interval is ≥ 450 milliseconds, it may have been best to pursue an alternative therapy for the management of CAP. This includes switching to doxycycline, which seemingly does not share the same arrhythmogenic potential compared with azithromycin.[7] The patient should be educated on reporting any signs and symptoms of dizziness, palpitations, or syncope. Finally, a complete medication history should be performed to ensure that there were no other medications that would have influenced this patient's QT-interval.[16]

Conclusion

Azithromycin is a common macrolide antibiotic prescribed for the outpatient management of CAP as a five-day course of therapy.[4] There have been recent safety concerns prompted by postmarketing data regarding the potential for life-threatening arrhythmias. It is vital for clinicians to recognize risk factors (e.g., medications, electrolyte disturbances, cardiac abnormalities) that can potentiate this phenomenon to ensure safe and appropriate use of azithromycin.

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