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Azithromycin and the Risk of Cardiovascular Complications

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Abstract

The purpose of this review was to evaluate the literature to assess the incidence and true clinical relevance of recent Food and Drug Administration warnings regarding QT prolongation with azithromycin, given its widespread use, with over 40 million US outpatient prescriptions written in 2011. A literature search of MEDLINE (1946 to May 2013) and International Pharmaceutical Abstracts (1970 to May 2013) was conducted using the terms azithromycin, QT prolongation, torsades de pointes, arrhythmia, and cardiovascular death. A bibliographic search was also performed. Several relevant studies and case reports were identified and reviewed. One cohort study revealed an increased risk of cardiovascular death with azithromycin compared to no antibiotic, especially in those with higher cardiovascular risk. Another cohort study comparing azithromycin, penicillin V, and no antibiotic in a younger Danish population with less cardiac risk found no increased cardiovascular death associated with azithromycin use. The majority of case reports involved ill and/or elderly patients with multiple comorbidities and concomitant medications who were already at a higher risk of cardiovascular events. Although there is evidence that azithromycin may induce QT prolongation and adverse cardiac events, the incidence is fairly limited to patients with high baseline risk, including those with preexisting cardiovascular conditions and concomitant use of other QT-prolonging drugs.

Keywords

arrhythmia, azithromycin, cardiovascular death, torsades de pointes, QT prolongation

Question

Are patients at an increased risk of cardiovascular events with the use of azithromycin?

Background

Azithromycin is a commonly prescribed antibiotic and is considered a first-line agent for multiple bacterial infections due to its efficacy and favorable safety profile. In 2011, 40.3 million outpatients received a prescription for azithromycin.[1-3] In May 2012, the Food and Drug Administration (FDA) released a statement cautioning prescribers of a possible link between azithromycin and increased cardiovascular death, based on an article published by Ray et al, until a formal review could be completed.[1,4] After analyzing the study and an unpublished manufacturer-conducted trial, the FDA issued a Drug Safety Communication in March 2013 regarding the use of azithromycin and the risk of potentially fatal heart rhythms, including QT prolongation.[2-4] This communication and subsequent labeling changes have caused increased concern among clinicians regarding the potential risks of azithromycin. Azithromycin's label now emphasizes these cardiovascular warnings, including information regarding QT prolongation, life-threatening torsades de pointes, and other abnormal heart rhythms. Patients with the following characteristics are thought to be at greatest risk[2-5]:

- proarrhythmic electrolyte abnormalities (eg, hypokalemia and/or hypomagnesemia)
- a documented history of bradyarrhythmias, QT prolongation, torsades de pointes, uncompensated congestive heart failure, or congenital long QT syndrome
- use of antiarrhythmic drugs: class IA (quinidine, procainamide, or disopyramide), class III (amiodarone, ibutilide, sotalol, dofetilide, or dronedarone), or other medications known to prolong the QT interval (terfenadine, chloroquine, droperidol, haloperidol, methadone, chlorpromazine, ciprofloxacin, etc)
- elderly patients, as they may be more susceptible to azithromycin's QT-prolonging effects.

Drug-induced QT prolongation is primarily associated with inhibition of the human ether-à-go-go-related gene (*hERG*) that

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encodes the rapid component of the delayed rectifier potassium current (I_{KR}). The I_{KR} regulates outward flow of potassium from ventricular myocytes and is the predominant current responsible for ventricular repolarization. Inhibition of *hERG* leads to impaired functioning of I_{KR}, resulting in intracellular accumulation of potassium and delayed ventricular repolarization, hence QT prolongation.[6] A normal QT interval for males is less than 430 milliseconds and less than 450 milliseconds for females.[5] According to the FDA's regulatory guidance, drug-induced QT prolongation greater than 10 milliseconds above baseline suggests the potential for clinical significance, while a QT prolongation greater than 20 milliseconds above baseline has a substantially increased likelihood of being proarrhythmic. Discontinuation of a drug is often recommended with a QT interval greater than 500 milliseconds or a QT prolongation greater than 60 milliseconds above baseline.[7]

Literature Review

A literature search was performed using MEDLINE (1946 to May 2013) and International Pharmaceutical Abstracts (1970 to May 2013) with terms including azithromycin, QT prolongation, QT, long QT syndrome, torsades de pointes, torsade, torsades, torsadegenic, torsadogenesis, torsadogenic, torsadogenicity, arrhythmia, cardiovascular death, and cardiovascular risk. This search yielded 2 retrospective cohort studies, 1 manufacturer-funded randomized clinical trial, 2 prospective studies, 1 published analysis from the FDA Adverse Event Reporting System (FAERS), and 9 case reports, along with multiple editorials and reviews. All references were reviewed for quality and relevance. A bibliographic search was also performed for additional sources.

A retrospective cohort study by Ray et al, comparing azithromycin, amoxicillin, ciprofloxacin, levofloxacin, and no antibiotic, enrolled patients in the Tennessee Medicaid program who were prescribed a standard 5-day course of azithromycin between 1992 and 2006. The 3 active comparators and propensity score matching were utilized to control for confounding factors. The study participants were between 30 and 74 years of age without life-threatening noncardiovascular illnesses (eg, certain cancers, HIV, end-stage renal disease, multiple sclerosis, recent stroke, congenital cardiovascular anomalies, cystic fibrosis, etc) or diagnosis of drug abuse. Patients who had resided in a nursing home in the previous year or who were hospitalized in the 30 days prior to filling the prescription were excluded. The final azithromycin cohort included 347 795 prescriptions. The primary study end points were cardiovascular death (a cumulative end point involving sudden cardiac death as well as other cardiovascular events) and death from any cause. When compared to matched periods of no antibiotic, a 5-day course of azithromycin was associated with an increase in all-cause mortality, primarily due to cardiovascular death, as there was no association between azithromycin and noncardiovascular death (hazard ratio [HR] = 1.85, 95% confidence interval [CI] = 1.25-2.75, $P = .002$; HR = 2.88, 95% CI = 1.79-4.63, $P < .001$; and HR = 0.74, 95% CI = 0.33-1.67, $P = .47$, respectively). In addition, a 5-day course of azithromycin was associated with significantly increased incidence of cardiovascular death when compared to amoxicillin and ciprofloxacin but not levofloxacin (HR = 2.49, 95% CI = 1.38-4.50, $P = .002$; HR = 3.49, 95% CI = 1.32-9.26, $P = .01$; and HR = 1.27, 95% CI = 0.66-2.47, $P = .48$, respectively). Increased cardiovascular death was not seen on days 6 to 10 when compared to matched periods of either no antibiotic or amoxicillin (HR = 0.88, 95% CI = 0.43-1.80, $P = .72$; and HR = 0.95, 95% CI = 0.44-2.06, $P = .89$, respectively). The absolute risk of any death per 1 million courses with a 5-day course of azithromycin was 85.2 deaths, when compared to 31.5 deaths with amoxicillin and 29.8 deaths with no antibiotic. Compared to amoxicillin, the investigators calculated an additional 9 cardiovascular deaths with azithromycin per 1 million courses (1 death per 111 111 courses) in patients with the lowest cardiovascular risk scores, an additional 47 cardiovascular deaths per 1 million courses (1 death per 21 277 courses) in those with moderate risk scores, and an additional 245 cardiovascular deaths per 1 million courses (1 death per 4082 courses) in those with the highest risk scores. In this cohort, the risk of cardiovascular death with azithromycin was greatest in those with the highest cardiovascular risk.[4]

Another retrospective cohort study performed in Denmark by Svanström et al compared the risk of cardiac death in a cohort of patients receiving azithromycin between 1997 and 2010 to those receiving no antibiotic and with penicillin V. The patient population was between 18 and 64 years old and had not been hospitalized or used another antibiotic within the past 30 days. To adjust for potential confounders, an active comparator and propensity score matching were used. In addition, the investigators limited their study sample to young and middle-aged adults to account for the increased risk of cardiovascular death that naturally occurs with aging and adjusted for 61 potential confounding variables. The final azithromycin cohort consisted of 1 102 050 subjects. The study end points and end point definitions were intentionally matched to Ray et al's study, with cardiovascular death as the primary end point and noncardiovascular death as the secondary end point. The deaths were stratified based on current use (1-5 days), recent use (6-10 days), and past use (10-35 days) of azithromycin. Current use of azithromycin was associated with a significant increase in the risk of cardiovascular death compared to no antibiotic; however, this was not observed with recent or past use of azithromycin (risk ratio [RR] = 2.85, 95% CI = 1.13-7.24; RR = 1.44, 95% CI = 0.46-4.54; and RR = 0.69, 95% CI = 0.41-1.17, respectively). Adjusting for propensity scores resulted in no association with the risk of cardiovascular death for any users of azithromycin compared to penicillin V (RR = 0.93, 95% CI = 0.56-1.55; RR = 0.75, 95% CI = 0.34-1.62; and RR = 0.92, 95% CI = 0.60-1.42, respectively). As a patient taking antibiotics for an acute infection is inherently sicker and more prone to complications than a healthy person with no need for antibiotics, the authors specifically included penicillin V as a comparator group to prevent the confounding factor of infection. Thus, the increased risk of death in the azithromycin cohort compared to no antibiotic could not be solely attributed to azithromycin's cardiac effects since the risk of death was similar between the azithromycin and penicillin V cohorts. Instead,

these deaths may have been due to acute infection alone. A subgroup analysis of those with a history of cardiovascular disease revealed a trend toward an increased risk of cardiovascular death with current use of azithromycin compared to penicillin V. This did not reach statistical significance, possibly due to lack of power for this outcome (RR = 1.35, 95% CI = 0.69-2.64, $P = .16$). In a post hoc analysis, azithromycin was not associated with a significant increase in cardiovascular death when compared to amoxicillin use (RR = 0.60, 95% CI = 0.29-1.23).[8]

An unpublished, in-house, randomized, placebo-controlled clinical trial conducted by Pfizer included 116 healthy subjects who received either chloroquine 1000 mg alone or chloroquine in combination with azithromycin (500 mg, 1000 mg, or 1500 mg). A dose-dependent prolongation of the corrected QT interval (QTc) was found with the coadministration of azithromycin when compared to chloroquine alone. The maximal mean prolongation (95% upper CI) was 5 (10) milliseconds, 7 (12) milliseconds, and 9 (14) milliseconds with the coadministration of azithromycin 500 mg, 1000 mg, and 1500 mg, respectively.[3] According to the FDA definitions, this was considered to be potentially clinically significant and therefore was included in the prescribing information.[3,7]

A prospective study, published in 2002 by Strle et al, was performed in 47 patients in Slovenia, who had typical erythema migrans skin lesions to examine the QT intervals associated with previous azithromycin use within the past 7 or 14 days. The study did not assess the risk of QT prolongation with current users of azithromycin. The participants included 31 females and 16 males, aged 19 to 77, with no history of chronic heart or lung disease and had not received any other medication prior to treatment with azithromycin. They were given azithromycin 1 g on day 1, followed by 500 mg daily on days 2 through 5. Electrocardiogram (ECG) readings were performed on each patient at baseline, day 7, and day 14 for a total of 141 ECG readings. Evaluation of the ECGs was blinded. There was no difference in the mean QTc interval when compared to baseline (mean $\pm$ standard deviation: baseline, 413 $\pm$ 28.0 milliseconds; day 7, 415 $\pm$ 30.7 milliseconds; day 14, 416 $\pm$ 30.0 milliseconds; $P =$ not reported). Only 2 cases of a QTc prolongation from normal to greater than 440 milliseconds were noted.[9]

In 2011, Albert et al published a prospective, parallel-group, placebo-controlled clinical trial studying the chronic use of azithromycin for the prevention of chronic obstructive pulmonary disease (COPD) exacerbations. Although prolongation of the QTc interval was not measured as either a primary or a secondary outcome, the investigators were cautious of the potential cardiac effects of azithromycin, as they excluded patients who had resting tachycardia, heart failure, hypokalemia, family history of long QT syndrome, a baseline QTc interval of greater than 450 milliseconds, or patients who were taking medications known to prolong the QTc interval or cause torsades de pointes (excluding amiodarone, for reasons unspecified). Of the 1142 participants who received azithromycin 250 mg daily for a 1-year duration, the following cardiac events were reported: 1 case of cardiovascular death ($P = 1.00$), 1 case of a severe QTc prolongation ($P = .57$), and 6 cases of QTc prolongation leading to drug discontinuation ($P = .55$).[10]

Between January 2004 and December 2007, a total of 20 cases of azithromycin-induced torsades de pointes were spontaneously reported to the FDA. The reported odds ratio (OR) was based on cases of azithromycin-induced torsades compared to noncases, defined as all other nontorsades azithromycin events reported (OR = 6.5, 95% CI = 4.1-10.4). The crude OR was then adjusted for the concomitant use of antiarrhythmic drugs (OR = 7.8, 95% CI = 4.9-12.5). As the information was gathered from the FAERS, patient-specific factors surrounding the events were not included. Thus, whether there was a true causal relationship between azithromycin and torsades de pointes cannot be established.[11] Additional case reports are summarized in Table 1.[12-20]

Discussion

Azithromycin is a commonly prescribed macrolide antibiotic often used for infections such as bacterial sinusitis, community-acquired pneumonia, and pharynigits.[3] After the first retrospective cohort study was published, the FDA warned health care professionals of the accumulating evidence from studies and case reports that azithromycin, previously thought to be safe and relatively void of major side effects, could cause cardiovascular death.

Upon a more detailed evaluation, it appears the risk of cardiovascular death associated with azithromycin is higher in patients with baseline risk factors for abnormal heart rhythms. The study by Ray et al and the majority of case report subjects represented an older population with multiple comorbidities such as hypertension, heart failure, COPD, and diabetes using multiple medications.[4,12,15,17] There is evidence of azithromycin-induced QT prolongation and cardiac events noted in patients with hypokalemia,[14,18] concomitantly taking other QT-prolonging drugs such as chloroquine,[3] trazodone,[18] and methadone,[20] previous history of cardiac abnormalities,[13,15,16] and HIV.[19] Inclusion of these populations with an increased baseline risk of cardiac death may have resulted in the increased number of adverse azithromycin-associated cardiovascular outcomes, thus affecting the external validity of these findings. The study by Svanström et al, however, studied a younger population with fewer comorbidities and medications. Overall, they had better cardiovascular health and thus, a lower baseline risk.[8] Likewise, the study by Strle et al also featured a healthier population with no history of heart disease. The prospective study showed no statistically significant increase in the QTc even when using a higher dosing regimen than is commonly prescribed (a cumulative 3g vs 1.5 g). However, Strle et al's data must be considered with caution because there was no comparator group.[9] The study by Albert et al excluded populations deemed to be at high risk of QT prolongation.[10] Despite chronic, daily use of azithromycin, their results showed no statistically significant increase in the risk of QT prolongation in a population without major cardiac risk factors, complementing the findings of Svanström et al.[8,10]

Although the absolute risk of azithromycin (85.2 deaths per 1 million courses) as observed by Ray et al may seem low, approximately 40.3 million patients received an outpatient

Table 1. Case Reports Involving Azithromycin-Induced Cardiovascular Complications.

Article	Characteristics of patient	Evidence of QT prolongation and/or arrhythmia	Resolution
Samarendra (2001)[12]	68-Year-old female History: stable CHF, aneurysm of the posterior communicating artery Medications: long-term amiodarone 200mg/day Patient placed on po Z-pak Electrolytes WNL	Patient experienced short durations of intermittent dizziness on day 3 of Z-pak administration. ECG showed sinus bradycardia at 53 bpm and QT/QTc 676/660 ms	4 Days after azithromycin discontinuation, ECG results returned to baseline: QT/QTc 541/523 ms and QT dispersion 60 ms. Prolongation likely due to azithromycin/amiodarone combination
Matsunaga (2003)[13]	51-Year-old male History: dilated cardiomyopathy secondary to alcohol abuse Patient started on ceftriaxone 1 g IV daily, azithromycin 500 mg IV once then 250 mg po daily Electrolytes WNL	6 Hours after second dose of antibiotics, patient developed mild palpitations, which resolved in seconds. ECG showed normal sinus rhythm, heart rate 60 bpm, and QT/QTc 720/680 ms with deep, inverted T waves	3 days after discontinuing azithromycin, QT/QTc returned to 470/464 ms with no recurrence of QT prolongation
Kim (2005)[14]	51-Year-old female History: hypothyroidism, bladder cancer Patient prescribed azithromycin 500 mg Hypokalemia	2 Hours after taking azithromycin dose, presented to the ED after experiencing loss of consciousness twice. Telemetry revealed polymorphic ventricular tachycardia (PMVT) with normal QT/QTc. Defibrillation restored normal sinus rhythm; however, recurrent episodes required defibrillation	10 Hours after discontinuation of azithromycin, the ventricular arrhythmias ceased. Patient was monitored for 7 days and was arrhythmia free without further evidence of QT prolongation
Russo (2006)[15]	65-Year-old male History: idiopathic dilated cardiomyopathy Patient started on ceftriaxone 1 g IV daily, azithromycin 500 mg IV once then 250 mg po daily	6 Hours after the second dose of antibiotics, the patient developed a mild palpitation, resolving in seconds. ECG showed normal sinus rhythm, heart rate 60 bpm, QT/QTc 680/660 ms.	3 Days after the discontinuation of azithromycin, QT/QTc returned to 460/430 ms.
Kezerashvili (2007)[16]	55-Year-old female History: pacemaker placement for intermittent bradycardia, QT/QTc interval 1 week PTA = 520/420 ms Started azithromycin 500 mg po daily Baseline on azithromycin: heart rate = 55 bpm and QT/QTc interval = 620/580 ms Electrolytes WNL	After the seventh dose of azithromycin, telemetry showed 2 brief episodes of torsades de pointes. The day after the first episode, heart rate = 53 bpm and QT/QTc = 640/610 ms. The second episode showed heart rate = 58 bpm and QT/QTc interval = 680/670 ms	Azithromycin was discontinued and there were no further episodes of torsades de pointes
Huang (2007)[17]	90-Year-old female History: hypertension, stroke Patient placed on penicillin/sulbactam and azithromycin 500 mg electrolytes WNL	4 Hours after the administration of azithromycin, ECG showed a QTc of 740 ms and repetitive PMVT. The diagnosis of torsades de pointes was confirmed	After stopping azithromycin for 1 day, the QT interval returned to normal with no further episodes of PMVT/torsades de pointes
Del Rosario (2010)[18]	27-Year-old female History: fibromyalgia, depression, anxiety, chronic lower back pain, "*possibly*" had congenital long QT syndrome Medications: bupropion, trazodone, zolpidem, tizanidine, fexofenadine, tramadol PRN, ibuprofen PRN, and sumatriptan PRN. Patient started on azithromycin Potassium = 3.1 mEq/L	Patient lost consciousness at home and found in cardiac arrest, probably due to ventricular fibrillation, and successfully defibrillated. Further brief episodes of self-limiting PMVTs were seen in the hospital. ECG revealed a QTc of 459 ms	The patient became comatose due to anoxic brain injury and was declared brain dead
Santos (2010)[19]	41-Year-old male History: immunosuppressed HIV-positive Medications: current antiretroviral regimen not specified Patient given cefotaxime, sulfamethoxazole/trimethoprim, and azithromycin Electrolytes WNL	On the second day of treatment (after a single dose of 500 mg azithromycin), the patient developed profuse sweating with 3 separate ECGs showing sinus bradycardia at average heart rate 41 bpm and QT/QTc 613/507 ms	36 Hours after discontinuing azithromycin, the patient's heart rate rose to 68 bpm and the QT/QTc interval returned to 420/440 ms
Winton (2013)[20]	47-Year-old male History: hypertension, prescription opioid addiction Medications: methadone Patient prescribed azithromycin	Presented to the ED on day 3 of azithromycin with sudden cardiac arrest. ECG showed sinus tachycardia and QTc of 490 ms. Extended toxicology screening showed the arrest was not due to opioid overdose	Patient's status gradually improved with no further arrhythmias. The providers concluded the addition of azithromycin to chronic methadone, which has a block box warning for QT interval prolongation, precipitated the episode

Abbreviations: CHF, congestive heart failure; ECG, electrocardiogram; ED, emergency department; IV, intravenous; po, orally; PMVT, polymorphic ventricular tachycardia; PRN, as required; WNL, within normal limits

azithromycin prescription in 2011.[4,21] With such high use, the overall incidence becomes more apparent.

Physicians should not be deterred from prescribing azithromycin in the general population based solely on the new FDA warning. Other antibiotics with similar indications (erythromycin, clarithromycin, ciprofloxacin, levofloxacin, and moxifloxacin) have been well-known inducers of QT prolongation yet are commonly prescribed.[22,23] Caution is truly warranted in high-risk populations, as outlined in the studies, case reports, prescribing information, and by the FDA.

Summary

Although the FDA has recently issued warnings on increased cardiovascular events with the use of azithromycin, the data are still conflicting. As with every drug, clinicians should weigh the risk versus benefit profile of azithromycin in each specific case. When it comes to antibiotic selection, clinicians should assess the risks of QT prolongation and cardiovascular events, including patient-specific factors, comorbid conditions, and concomitant medications. When it is put into perspective, azithromycin is still considered first line for many bacterial infections and is still considered safe in the general population. Caution is warranted in those with known QT prolongation or congenital long QT syndrome, history of torsades de pointes, bradyarrhythmias, electrolyte abnormalities, the elderly, concomitantly taking drugs known to prolong the QT interval, and patients with other cardiovascular diseases. It is important to note that other macrolides (clarithromycin and erythromycin) and fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin) have been shown to induce QT prolongation as well.

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