Published in final edited form as:

Cleve Clin J Med. 2013 September ; 80(9): 539–544. doi:10.3949/ccjm.80a.13077.

Azithromycin and Risk of Sudden Cardiac Death: Guilty as Charged or Falsely Accused?

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Azithromycin is a broad-spectrum macrolide antibiotic, marketed in the United States under the trade name Zithromax or Zmax/Z-pak, used to treat or prevent a range of common bacterial infections including upper and lower respiratory tract infections and certain sexually transmitted diseases. From a cardiac toxicity perspective, azithromycin has been considered the safest of the macrolide derivatives due to divergent pharmacokinetic properties (e.g. minimal CYP3A4 metabolism/inhibition) and limited *in vitro* blockade of the rapid delayed rectifier potassium current (I_{Kr}) conducted by human ether-à-go-go-related gene (hERG)-encoded Kv11.1 potassium channel at therapeutic concentrations (Table 1).^{1–4} As a result of its broad antibiotic spectrum and perceived favorable safety profile, azithromycin has become one of the top 15 most prescribed drugs and the best-selling antibiotic in the United States accounting for 55.4 million prescriptions in 2012, according to recent IMS Institute for Health Informatics market data.

However, beginning with the first report of azithromycin-triggered *torsades de pointes* (TdP) in 2001⁵, a growing body of evidence, derived from postmarketing surveillance, has linked azithromycin, like the closely related macrolides clarithromycin and erythromycin, to arrhythmia-related adverse cardiac events including pronounced QT interval prolongation and associated TdP that provide the substrate for potentially life-threatening arrhythmias such as ventricular fibrillation (VF). Furthermore, a recent analysis of the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) over an eight-year period extending from 2004 to 2011 revealed a total of 203 reports of azithromycin-associated QT prolongation, TdP, ventricular arrhythmia, and or sudden cardiac death resulting in a total of 65 fatalities (Table 1).⁶ At face value, the number of FAERS reports appears to be relatively similar between the various macrolide antibiotics. However, it is important to remember that FAERS, and the study cited above, fail to account for substantial differences in prescription volume and are subjected to number of well-known biases (e.g. confounding variables, quality and completeness of reports, duplication, underreporting, etc) that preclude the use of such adverse reporting databases in the calculation, and thereby comparison, of the true incidence of adverse arrhythmia-related cardiac events associated with the various macrolide antibiotics.^{6–9}

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Disclosures: MJA is a consultant for Transgenomic. Intellectual property derived from MJA's research program resulted in license agreements in 2004 between Mayo Clinic Health Solutions (formerly Mayo Medical Ventures) and PGxHealth (formerly Genaissance Pharmaceuticals and now Transgenomic).

Despite these inherent flaws, initial postmarketing surveillance reports cast enough doubt on the long standing notion that azithromycin is the safest macrolide antibiotic to prompt Ray et al to directly assess the safety of azithromycin in an observational, nonrandomized study of individuals enrolled in the Tennessee Medicaid program.¹⁰ In this study, the use of azithromycin was associated with a 2 to 3 fold increased risk of cardiovascular (CV) death compared to both nonuse and amoxicillin use (Table 2).¹⁰ However, the absolute excess risk over amoxicillin varied considerably according to baseline risk score for cardiovascular disease, with one excess CV death per 4100 amongst the highest risk decile compared to one excess CV death per 100,000 amongst the lowest risk decile.^{10, 11} While Ray et al used appropriate analytic methodologies to attempt to correct for any confounding bias intrinsic to the observational, nonrandomized nature of the study design, due to a higher prevalence of comorbid/co-existing conditions and increased mortality rates associated with Medicaid beneficiaries in the United States, legitimate questions were raised about whether the results of the study could be generalized to populations with substantially lower baseline CV disease risk and if differences in the baseline characteristics of the treatment groups were adequately controlled.^{12, 13}

Regardless, the striking observations by Ray et al, particularly the time-limited pattern of excess sudden cardiac death risk that directly correlated with expected peak azithromycin plasma levels during a standard 5-day course and preferentially affected those with underlying CV disease, coupled with the significant concerns raised by postmarketing surveillance reports compelled the FDA to review the labels of azithromycin and other macrolide antibiotics.¹⁰ Ultimately, on the basis of these reviews the FDA opted to revise the “warning and precautions” section of the azithromycin drug label to include a warning about the potential risk of fatal arrhythmias, specifically QT interval prolongation and TdP associated with azithromycin. In a March 2013 safety announcement, health care professionals were also urged to use caution when prescribing azithromycin to patients with known risk factors for drug-related arrhythmias including congenital long QT syndrome (LQTS), acquired QT interval prolongation, hypokalemia, hypomagnesia, bradycardia, and/or concurrent use of azithromycin with other medications known to prolong the QT interval, specifically the class IA (e.g. quinidine and procainamide) and class III (e.g. amiodarone, sotalol, and dofetilide) antiarrhythmics..

However, just when the medical community at large appeared ready to accept the unfortunate fate of azithromycin, a large prospective study by Svanström et al published in early May 2013 found no increased risk of CV death associated with azithromycin in a large, representative population of young to middle-aged Danish adults with low baseline risk for underlying CV disease (Table 2).¹⁴ Interestingly, Svanström et al were careful to point out that 1) their study was only powered to rule out a moderate-to-high (> 55%) increase in the relative risk of CV death associated and 2) profound differences in the baseline risk of death and CV risk factors existed between Danish patients and the Tennessee Medicaid patients studied by Ray et al.¹⁴ As such, Svanström et al suggest that their study serves as a complement to the study by Ray et al, rather than a contradiction, attributing the observed differences between the two studies to treatment-effect heterogeneity, whereby the increased the risk of azithromycin-associated CV mortality is largely limited to high-risk patients, namely those with multiple preexisting CV risk factors.¹⁴

Collectively, the pharmacologic and epidemiologic data reviewed above provides compelling evidence to suggest that azithromycin is not completely free of the QT-prolonging/torsadogenic effects that have long been associated with other macrolide antibiotics. However, data from both the Ray et al and Svanström et al studies suggest that pre-existing CV risk factors play a prominent role in determining the overall incidence of

azithromycin-associated CV death in a given population (Table 2).^{10, 14} As a result, these findings should prompt prescribing physicians to not only carefully reassess the risks and benefits of azithromycin use in their respective clinical practices, but also reinforce a recent call by the American Heart Association (AHA) and American College of Cardiology (ACC) on the pressing need to enhance the early detection of individuals at-risk for drug-induced ventricular arrhythmias/sudden death and subsequently improve how these individuals are monitored when the use of QT-prolonging/torsadogenic medications is a medical necessity.¹⁵

On the heels of these AHA/ACC suggestions, an institution-wide QT alert system was developed and implemented recently at the Mayo Clinic in Rochester, MN that seamlessly integrates commercial rules management technology into a Centricity-based electronic medical record (EMR) to identify and electronically alert ordering physicians to the presence of a patient with a prolonged QT interval and the potential clinical significance of this electrocardiographic finding.¹⁶ While this system is still in its early infancy, it has already confirmed that a prolonged QT interval (QTc > 500 ms) serves as a potent predictor of all-cause mortality and demonstrated that mortality in those with prolonged QT intervals increases in a dose-dependent fashion as the number of modifiable (e.g. electrolyte disturbances or QT-prolonging medications) and non-modifiable (e.g. genetic disposition, female sex, structural heart disease, or diabetes mellitus) risk factors increases.¹⁶ Furthermore, this study also provides evidence that modifiable risk factors may have a more pronounced effect on mortality than non-modifiable risk factors.¹⁶ As such, this study suggests that the continued development and implementation of information technology-based QT alert systems may one day provide physicians with an important tool to efficiently identify and possibly even modify the risk of CV death in high-risk individuals by correcting electrolyte abnormalities and/or reducing the burden of QT-prolonging medications.

While the implementation of such electronic QT alert systems in the vast majority of institutions and clinical practices is still years if not decades away, in light of the ever-growing list of otherwise clinically useful medications known to prolong the QT interval the studies by Ray, Svanström, and Haugaa as well as the recent FDA drug safety communication on azithromycin described above, all physicians should begin considering risk factors for QT-prolongation/TdP (summarized in Table 3) when weighing the risks and benefits of prescribing azithromycin over alternative antibiotics with minimal QT liability. This is a relatively simple safety exercise that can and should be done with the understanding that although there may be a small increased relative risk of an untoward CV event, for the vast majority of otherwise healthy hosts, their personal, absolute risk is miniscule. However, if the use of azithromycin and other QT-prolonging antibiotics (e.g. macrolides and fluoroquinolones) in an increasingly at-risk host (e.g. an individual with baseline QT prolongation and/or multiple QTc inciting risk factors) becomes a medical necessity due to preferential bacterial susceptibility and/or patient allergies, every effort should be made to correct modifiable risk factors (e.g. electrolyte abnormalities) and avoid if possible polypharmacy with multiple QT prolonging drugs. Further, for the patient with multiple QTc inciting factors where treatment with a known QT prolonging medication is still deemed in the patient's best interest, strong consideration should be given for inpatient administration and monitoring until their treatment with such a QT-prolonging medication has been completed. With careful consideration of modifiable and non-modifiable risk factors as well as a little extra caution when prescribing potential QT-prolonging medications such as azithromycin, the clinical benefit of these often-advantageous medications can be maximized and the incidence of these tragic albeit rare drug-induced sudden cardiac deaths can be reduced.

Acknowledgments

Funding sources: This work was supported by the Windland Smith Rice Sudden Comprehensive Sudden Cardiac Death Program. Mr. Giudicessi is supported by a National Heart, Lung, and Blood Institute Kirchstein NRSA Individual Predoctoral MD/PhD Fellowship (F30-HL106993).

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Table 1

Comparison of the Potency of hERG/Kv11.1 (I_{Kr}) Blockade, Metabolic Liability, and Number of Postmarketing Surveillance Adverse Events for Commonly Prescribed Macrolide Antibiotics.

Macrolide Antibiotic	hERG IC ₅₀ (μM) *	Cytochrome P450 Substrate	Cytochrome P450 Inhibitor	Adverse Events in FAERS (Fatal Events) #	Reference
Azithromycin	1091	No	No	203 (65)	3, 4, 5
Clarithromycin	45.7	CYP3A4	CYP3A4	246 (66)	4, 5
Erythromycin	38.9	CYP3A4	CYP3A4	50 (17)	4, 5
Telithromycin	42.5	CYP3A4	CYP3A4	107 (29)	4, 5

Abbreviations: CYP3A4, cytochrome P450 3A4; FAERS, Food and Drug Administration Adverse Event Reporting System; hERG, human-ether-a-go-go-related gene; and IC₅₀, half maximal inhibitory concentration.

* hERG IC₅₀ represent experimental values obtained under dissimilar experimental conditions. As such, use of these values to directly compare the QT/TP liability of each drug should be avoided.

Adverse event reporting from postmarketing surveillance does not account for prescription volume and is often subjected to significant bias from confounding variables, quality of reported data, duplication, and underreporting of events.

Table 2

Comparison of the Risk of Cardiovascular Mortality between Tennessee Medicaid Patients and Young to Middle-Aged Danish Adults Taking a 5-Day Course of Azithromycin

Population	Risk Ratios for Azithromycin Compared to Nonuse	Risk Ratios for Azithromycin Compared to β -Lactam Use [*]	Overall Cardiovascular Mortality Rate
Tennessee	2.88; 95% CI, 1.25 to 2.75	2.49; 95% CI, 1.38 to 4.50	85.2 deaths per 1 million azithromycin courses [#]
Denmark	2.85; 95% CI, 1.13 to 7.24	0.93; 95% CI, 0.56 to 1.55	15.4 deaths per 1 million azithromycin courses

Abbreviations: CI; confidence interval

^{*} Amoxicillin was used for comparison in the Tennessee Medicaid population, whereas penicillin V was used for comparison in the Danish population.

[#] Increases to 245 deaths per 1 million azithromycin courses for those patients with the highest decile cardiovascular risk scores.

Table 3

Modifiable and Non-Modifiable Risk Factors for QT-Prolongation and Torsades de Pointes*

Modifiable Risk Factors
<u>Electrolyte disturbances</u>
Hypocalcemia (< 4.65 mg/dL)
Hypokalemia (< 3.4 mmol/L)
Hypomagnesemia (< 1.7 mg/dL)
<u>QT-prolonging medication polypharmacy</u>
Concurrent use of ≥ 1 medication from www.azcert.com
Non-Modifiable Risk Factors
<u>Common Diagnoses</u>
Acute coronary syndrome
Anorexia nervosa or starvation
Bradyarrhythmias < 45 bpm
Cardiac heart failure (EF < 40%; uncompensated)
Congenital long QT syndrome or other genetic susceptibility
Chronic renal failure requiring dialysis
Diabetes mellitus (Type 1 and 2)
Hypertrophic cardiomyopathy
Hypoglycemia (documented and in absence of diabetes)
Pheochromocytoma
Status post cardiac arrest (within 24 hours)
Status post syncope or seizure (within 24 hours)
Stroke, subarachnoid hemorrhage, or other head trauma (within 7 days)
<u>Clinical History</u>
Personal or family history of QT interval prolongation or sudden unexplained death in the absence of a clinical or genetic diagnosis
<u>Demographic</u>
Elderly (> 65 years of age)
Female gender

* While no formal risk scorecard for drug-induced QT-prolongation exists, a “pro-QTc” score ≥ 4 based on risk factors similar to those listed above was an independent predictor of mortality in patients with QT interval prolongation.¹⁶ Unfortunately, the predictive value of these risk factors in patients with normal or borderline QT intervals has not been assessed.