COMMENTARY

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Azithromycin and risk of sudden cardiac death: Guilty as charged or falsely accused?

A MARCH 2013 WARNING by the US Food and Drug Administration that azithromycin (Zithromax, Zmax, Z-pak) may increase the risk of sudden cardiac death does not mean we must abandon using it. We should, however, try to determine if our patients have cardiovascular risk factors for this extreme side effect and take appropriate precautions.

AZITHROMYCIN: THE SAFEST OF THE MACROLIDES?

Azithromycin, a broad-spectrum macrolide antibiotic, is used to treat or prevent a range of common bacterial infections, including upper and lower respiratory tract infections and certain sexually transmitted diseases.

In terms of overall toxicity, azithromycin has been considered the safest of the macrolides, as it neither undergoes CYP3A4 metabolism nor inhibits CYP3A4 to any clinically meaningful degree, and therefore does not interfere with the array of commonly used medications that undergo CYP3A4 metabolism.

Also, in vitro, azithromycin shows only limited blockade of the potassium channel hERG. This channel is critically involved in cardiomyocyte repolarization, and if it is blocked or otherwise malfunctioning, the result can be a prolonged QT interval, ventricular arrhythmias, and even sudden cardiac death.[1–4] Therefore, lack of blockade, as reflected by a high inhibitory concentration (TABLE 1), boded well for the safety of azithromycin in terms of QT liability. However, we should be cautious in interpreting in vitro data.

With 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 the IMS Institute for Healthcare Informatics.

THE FDA RECEIVES 203 REPORTS OF ADVERSE EVENTS IN 8 YEARS

However, beginning with a report of azithromycin-triggered torsades de pointes in 2001,[5] a growing body of evidence, derived from postmarketing surveillance, has linked azithromycin to cardiac arrhythmias such as pronounced QT interval prolongation and associated torsades de pointes (which can progress to life-threatening ventricular fibrillation). Other, closely related macrolides such as clarithromycin and erythromycin are also linked to these effects.

Furthermore, in the 8-year period from 2004 to 2011, the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) received a total of 203 reports of azithromycin-associated QT prolongation, torsades de pointes, ventricular ar-

Compelling evidence exists that azithromycin is not free of the QT-prolonging and torsadogenic effects long associated with other macrolides

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TABLE 1

Comparison of commonly prescribed macrolide antibiotics

Macrolide antibiotic	hERG IC_{50} (μM)[a]	CYP3A4 substrate	CYP3A4 inhibitor	Adverse events in FAERS[b]	Fatal events in FAERS
Azithromycin[3–5]	1,091	No	No	203	65
Clarithromycin[4,5]	45.7	Yes	Yes	246	66
Erythromycin[4,5]	38.9	Yes	Yes	50	17
Telithromycin[4,5]	42.5	Yes	Yes	107	29

CYP3A4 = cytochrome P450 3A4; FAERS = Food and Drug Administration Adverse Event Reporting System; hERG = human ether à-go-go-related gene (a potassium channel involved in myocyte repolarization) ; IC_{50} = half maximal inhibitory concentration

[a]These represent experimental values obtained under dissimilar experimental conditions. As such, use of these values to directly compare the propensity of each drug to prolong the QT interval and cause torsades de pointes should be avoided.

[b]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.

rhythmia, or, in 65 cases, sudden cardiac death (TABLE 1).[6]

At face value, the number of FAERS reports appears to be similar between the various macrolide antibiotics. However, it is important to remember that these drugs differ substantially in the number of prescriptions written for them, with azithromycin being prescribed more often. Also, the FAERS numbers are subject to a number of well-known limitations such as confounding variables, uneven quality and completeness of reports, duplication, and underreporting. These limitations preclude the use of such adverse reporting databases in calculating and thereby comparing the true incidence of adverse events associated with the various macrolide antibiotics.[6–9]

All physicians should consider risk factors for QT prolongation and torsades de pointes when prescribing azithromycin

RAY ET AL FIND A HIGHER RISK OF CARDIOVASCULAR DEATH

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[10] to assess its safety in an observational, nonrandomized study of people enrolled in the Tennessee Medicaid program.

They found that, over the typical 5 days of therapy, people taking azithromycin had a rate of cardiovascular death 2.88 times higher than in people taking no antibiotic, and 2.49 times higher than in people taking amoxicillin (TABLE 2).

However, the absolute excess risk compared with amoxicillin varied considerably according to baseline risk score for cardiovascular disease, with 1 excess cardiovascular death per 4,100 in the highest-risk decile compared with 1 excess cardiovascular death per 100,000 in the lowest-risk decile.[10,11]

Moreover, the increase in deaths did not persist after the 5 days of therapy. This time-limited pattern directly correlated with expected peak azithromycin plasma levels during a standard 5-day course.

Ray et al used appropriate analytic methods to attempt to correct for any confounding bias intrinsic to the observational, nonrandomized study design. Nevertheless, the patients were Medicaid beneficiaries, who have a higher prevalence of comorbid conditions and higher mortality rates than the general population. Therefore, legitimate questions were raised about whether the results of the study could be generalized to populations with substantially lower baseline risk of cardiovascular disease and if differences in the baseline characteristics of the treatment groups were adequately controlled.[12,13]

THE FDA REVISES AZITHROMYCIN'S WARNINGS AND PRECAUTIONS

The striking observations by Ray et al,[10] coupled with the concerns raised by postmarketing surveillance reports, compelled the FDA

TABLE 2

Risk of cardiovascular death in Tennessee Medicaid patients and young to middle-aged Danish adults taking a 5-day course of azithromycin

Population	Azithromycin vs no antibiotic use		Azithromycin vs beta-lactam use[a]		Overall cardiovascular mortality rate (per 1 million azithromycin courses)
	Risk ratio	95% CI	Risk ratio	95% CI	
Tennessee[10]	2.88	1.25–2.75	2.49	1.38–4.50	85.2[b]
Denmark[14]	2.85	1.13–7.24	0.93	0.56–1.55	15.4

[a]Amoxicillin was used for comparison in the Tennessee Medicaid population, whereas penicillin V was used for comparison in the Danish population.
[b]Increases to 245 deaths per 1 million azithromycin courses for those patients with the highest decile cardiovascular risk scores.

to review the labels of azithromycin and other macrolide antibiotics.

Ultimately, 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 torsades de pointes. In a March 2013 safety announcement, it also urged health care professionals to use caution when prescribing azithromycin to patients known to have risk factors for drug-related arrhythmias, including congenital long QT syndrome, acquired QT interval prolongation, hypokalemia, hypomagnesia, bradycardia, and concurrent use of other medications known to prolong the QT interval, specifically the class IA (eg, quinidine and procainamide) and class III (eg, amiodarone, sotalol, and dofetilide) antiarrhythmics.

SVANSTRÖM ET AL FIND NO INCREASED RISK

However, just when the medical community appeared ready to accept that azithromycin may not be as safe as we thought it was, a large prospective study by Svanström et al, published in early May 2013, found no increased risk of cardiovascular death associated with azithromycin (TABLE 2).[14]

The patients were a representative population of young to middle-aged Danish adults at low baseline risk of underlying cardiovascular disease.

Interestingly, Svanström et al were careful to point out that their study was only powered to rule out a moderate-to-high (> 55%) increase in the relative risk of cardiovascular death. Furthermore, profound differences existed in the baseline risk of death and cardiovascular risk factors between their patients and the Tennessee Medicaid patients studied by Ray et al.[14] Therefore, the authors suggested that their study complements rather than contradicts the study by Ray et al. They attributed the differences in the findings to treatment-effect heterogeneity, in which the risk of azithromycin-associated cardiovascular mortality is largely limited to high-risk patients, namely those with multiple preexisting cardiovascular risk factors.[14]

ACC/AHA RECOMMENDATION: IDENTIFY THOSE AT RISK

Collectively, the data reviewed above provide compelling evidence that azithromycin is not completely free of the QT-prolonging and torsadogenic effects that have long been associated with other macrolide antibiotics. However, the findings from both the study by Ray et al and that of Svanström et al suggest that preexisting cardiovascular risk factors play a prominent role in determining the incidence of azithromycin-associated cardiovascular death in a given population (TABLE 2).[10,14]

These findings should prompt physicians to carefully reassess the risks and benefits of azithromycin use in their clinical practices. They also reinforce a recent call by the American Heart Association (AHA) and American College of Cardiology (ACC) to better identify, early on, patients at risk of drug-induced

Although azithromycin may increase the relative risk of a cardiovascular event, for most otherwise-healthy patients the absolute risk is miniscule

TABLE 3

Risk factors for QT prolongation and torsades de pointes

Modifiable risk factors

Electrolyte disturbances
- Hypocalcemia (calcium < 4.65 mg/dL)
- Hypokalemia (potassium < 3.4 mmol/L)
- Hypomagnesemia (magnesium < 1.7 mg/dL)

QT-prolonging medication polypharmacy
- Concurrent use of ≥ 1 QT-prolonging medication (see www.azcert.org)

Nonmodifiable risk factors

Common diagnoses
- Acute coronary syndrome
- Anorexia nervosa or starvation
- Bradyarrhythmias < 45 bpm
- Cardiac heart failure (ejection fraction < 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)

Personal or family history of QT interval prolongation or sudden unexplained death in the absence of a clinical or genetic diagnosis

Elderly (> 65 years of age)

Female

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.

ventricular arrhythmias and sudden death and to subsequently improve how these patients are monitored when the use of QT-prolonging and torsadogenic drugs is medically necessary.[15]

AN ELECTRONIC MEDICAL RECORD FLAGS QTc ≥ 500 MS

On the heels of these AHA/ACC suggestions, our hospital has adopted an institution-wide QT alert system. Here, the electronic medical record system (Centricity EMR; GE Healthcare) uses a proprietary algorithm to detect and electronically alert ordering physicians when a patient has a prolonged QT interval, and gives information about the potential clinical significance of this electrocardiographic finding.[16] Physicians also receive a warning when ordering QT-prolonging drugs in patients at risk.

This system is still in its infancy, but it has already confirmed that a prolonged QT interval (QTc ≥ 500 ms) is a powerful predictor of death from any cause and has demonstrated that mortality rates in those with prolonged QT intervals increase in a dose-dependent fashion with the patient's number of modifiable risk factors (eg, electrolyte disturbances or QT-prolonging medications) and nonmodifiable risk factors (eg, genetic disposition, female sex, structural heart disease, diabetes mellitus).[16] We have also found evidence that modifiable risk factors may have a more pronounced effect on mortality risk than nonmodifiable risk factors.[16]

These findings suggest that 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 cardiovascular death in patients at high risk, for example, by correcting electrolyte abnormalities or reducing the burden of QT-prolonging medications.

CONSIDER RISK OF QT PROLONGATION WHEN PRESCRIBING AZITHROMYCIN

For most institutions and clinical practices, such electronic QT alert systems are still years if not decades away. However, in light of the information summarized above, all physicians should begin considering risk factors for QT prolongation and torsades de pointes (summarized in TABLE 3) and weighing the risks and benefits of prescribing azithromycin vs alternative antibiotics with minimal QT liability. This should be relatively simple to do. Things to keep in mind:

- Although azithromycin may increase the relative risk of a cardiovascular event, for most otherwise-healthy patients, the absolute risk is miniscule.

- In a patient at risk (eg, with baseline QT prolongation or multiple risk factors for it), if azithromycin or another QT-prolonging antibiotic such as a macrolide or fluoroquinolone is medically necessary due to preferential bacterial susceptibility or patient allergies, every effort should be made to correct modifiable risk factors (eg, electrolyte abnormalities) and, if possible, to avoid polypharmacy with multiple QT-prolonging drugs.
- For patients who have multiple risk factors for QT prolongation in whom treatment with a known QT-prolonging medication is still deemed in the patient's best interest, strong consideration should be given to inpatient administration and monitoring until the treatment has been completed.

With careful consideration of modifiable and nonmodifiable 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 but rare drug-induced sudden cardiac deaths can be reduced.

REFERENCES

1. **Hopkins S**. Clinical toleration and safety of azithromycin. Am J Med 1991; 91:40S–45S.
2. **Milberg P, Eckardt L, Bruns HJ, et al**. Divergent proarrhythmic potential of macrolide antibiotics despite similar QT prolongation: fast phase 3 repolarization prevents early afterdepolarizations and torsade de pointes. J Pharmacol Exp Ther 2002; 303:218–225.
3. **Ioannidis JP, Contopoulos-Ioannidis DG, Chew P, Lau J**. Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for upper respiratory tract infections. J Antimicrob Chemother 2001; 48:677–689.
4. **Owens RC Jr, Nolin TD**. Antimicrobial-associated QT interval prolongation: pointes of interest. Clin Infect Dis 2006; 43:1603–1611.
5. **Arellano-Rodrigo E, García A, Mont L, Roqué M**. Torsade de pointes and cardiorespiratory arrest induced by azithromycin in a patient with congenital long QT syndrome. (Article in Spanish.) Med Clin (Barc) 2001; 117:118–119.
6. **Raschi E, Poluzzi E, Koci A, Moretti U, Sturkenboom M, De Ponti F**. Macrolides and torsadogenic risk: emerging issues from the fda pharmacovigilance database. J Pharmacovigilance 2013; 1:104.
7. **Shaffer D, Singer S, Korvick J, Honig P**. Concomitant risk factors in reports of torsades de pointes associated with macrolide use: review of the United States Food and Drug Administration Adverse Event Reporting System. Clin Infect Dis 2002; 35:197–200.
8. **Stephenson WP, Hauben M**. Data mining for signals in spontaneous reporting databases: proceed with caution. Pharmacoepidemiol Drug Saf 2007; 16:359–365.
9. **Bate A, Evans SJ**. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf 2009; 18:427–436.
10. **Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM**. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012; 366:1881–1890.
11. **Mosholder AD, Mathew J, Alexander JJ, Smith H, Nambiar S**. Cardiovascular risks with azithromycin and other antibacterial drugs. N Engl J Med 2013; 368:1665–1668.
12. **Louie R**. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012; 367:774–775.
13. **Koga T, Imaoka H**. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012; 367:774–775.
14. **Svanström H, Pasternak B, Hviid A**. Use of azithromycin and death from cardiovascular causes. N Engl J Med 2013; 368:1704–1712.
15. **Drew BJ, Ackerman MJ, Funk M, et al; American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, the Council on Cardiovascular Nursing, and the American College of Cardiology Foundation**. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation 2010; 121:1047–1060.
16. **Haugaa KH, Bos JM, Tarrell RF, Morlan BW, Caraballo PJ, Ackerman MJ**. Institution-wide QT alert system identifies patients with a high risk of mortality. Mayo Clin Proc 2013; 88:315–325.

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