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Azithromycin, cardiovascular risks, QTc interval prolongation, *torsade de pointes*, and regulatory issues: A narrative review based on the study of case reports

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***Abstract*:** Over the past year, three articles have appeared in the *New England Journal of Medicine* describing conflicting findings about azithromycin and cardiac safety, particular azithromycin-induced QTc interval prolongation and *torsade de pointes*. The FDA wants healthcare providers to consider azithromycin-induced fatal cardiac arrhythmias for patients already at risk for cardiac death and other potentially arrhythmogenic cardiovascular conditions. In a systematic review of case reports we sought to determine factors that link to azithromycin-induced/associated QTc interval prolongation and *torsade de pointes*. We found 12 cases: seven female and five male. Of the nine adults with reported azithromycin doses, concurrent QTc interval measurement, and without congenital long QT syndrome, we found no significant relationship between dose and QTc interval duration. Additional risk factors were female sex, older age, heart disease, QTc interval prolonging drugs and metabolic inhibitors, hypokalemia, and bradycardia. All 12 subjects had at least two additional risk factors. Elderly women with heart disease appear to be at particularly risk for drug-related QTc interval prolongation and *torsade de pointes*.

***Keywords*:** azithromycin, cardiovascular death, drug-induced QTc interval prolongation, risk factors, torsade de pointes

Introduction

Azithromycin has a broad range of indications and is among the most commonly prescribed macrolide antibiotics in ambulatory care settings [Grijalva *et al.* 2009]. Safer alternatives may not be available. All macrolides are associated with QTc interval prolongation with risk apparently greater with erythromycin and clarithromycin than with azithromycin [Guo *et al.* 2010].

A series of studies over the past year have led to more restrictive product labeling so that now healthcare providers must be cognizant of azithromycin-induced fatal cardiac arrhythmias when prescribing this antibiotic for patients already at risk for sudden cardiac death and other potentially serious cardiovascular conditions. Azithromycin may induce QTc interval prolongation setting the stage for *torsade de pointes*. Clinicians should consider this adverse effect when selecting among antibiotics with the understanding that macrolide and non-macrolide antibiotics, especially fluoroquinolones, also may induce QTc interval prolongation and *torsade de pointes* [Food and Drug Administration, 2013].

In this paper, we will review the interplay of relevant studies and progressively restrictive product labeling followed by a new study suggesting that younger patients are much less likely to experience adverse cardiovascular effects while taking azithromycin creating a somewhat conflicted portrait of the cardiovascular risk profile of this drug. We then embark on a careful study of case reports linking azithromycin, QTc interval prolongation, and *torsade de pointes*. We believe the study of such case reports will diminish the confusion

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currently surrounding the cardiovascular risks associated with azithromycin administration.

Azithromycin and the risk of cardiovascular death

In 2012, Ray and colleagues [Ray *et al.* 2012] sought to detect increased risk of death due to short-term medication-ascribed cardiac effects in a cohort of patients who received azithromycin (347,795 prescriptions), propensity-score-matched patients free of antibiotics (1,391,180 control periods), and patients who received amoxicillin (1,348,672 prescriptions), ciprofloxacin (264,626 prescriptions), or levofloxacin (193,906 prescriptions). Specifically, the study cohort comprised patients in the Tennessee Medicaid program who were between the ages of 30 and 74 years, had no life-threatening noncardiovascular condition, had no diagnosis of drug abuse, had not lived in a nursing home in the previous year, and had not been hospitalized during the preceding month. Exclusionary criteria included patients at high risk for death from conditions not related to short-term effect of proarrhythmic drugs and patients with serious noncardiovascular illness.

They reported an increased risk of cardiovascular death and death from any cause among patients taking azithromycin compared with controls and patients taking amoxicillin and ciprofloxacin. The risk of cardiovascular death was not significantly different between patients who took azithromycin *versus* levofloxacin. Among the azithromycin patients, increased cardiovascular deaths were greatest among those patients with high baseline risk of cardiovascular disease.

Earlier FDA concerns and FDA response to the paper from Ray and colleagues

In 2011, the FDA reviewed azithromycin product labeling information with an emphasis on drug-related QTc interval prolongation and *torsade de pointes* [Food and Drug Administration, 2012]. On 17 May 2012 coincident with the publication of the paper from Ray and colleagues [Ray *et al.* 2012], the FDA noted a small increase in cardiovascular deaths and deaths from any cause among patients taking a 5-day course of azithromycin compared with patients receiving amoxicillin, ciprofloxacin, or no drug [Food and Drug Administration, 2012].

On 12 March 2013, the FDA issued a Drug Safety Communication discussing azithromycin's risk of potentially fatal heart rhythms [Food and Drug Administration, 2013]. According to the FDA, healthcare providers must be cognizant of azithromycin-induced fatal cardiac arrhythmias when prescribing this antibiotic for patients *already* at risk for sudden cardiac death and other potentially serious cardiovascular conditions. Azithromycin may induce QTc interval prolongation setting the stage for *torsade de pointes*. Clinicians should consider this adverse effect when selecting among antibiotics with the understanding that macrolide and nonmacrolide antibiotics, especially fluoroquinolones, also may induce QTc interval prolongation and *torsade de pointes* [Food and Drug Administration, 2013].

Co-administration of azithromycin and chloroquine

In the January 2013 product labeling for Zithromax [Pfizer Labs, 2013] appears a randomized, placebo-controlled parallel trial in 116 healthy controls receiving 1000 mg of chloroquine alone or in combination with increasing doses of azithromycin (500, 1000, and 1500 mg daily). Co-administration of azithromycin increased QTc interval (Fridericia) 5 (10), 7 (12), and 9 (14) ms, respectively [Pfizer Labs, 2013]. There was a perfect correlation between azithromycin dose and QTc interval increase (Pearson $r = 1$, $p = 0.01$) in the dose range 500 mg (10 ms) to 1500 mg (14 ms). The age and sex of these healthy controls were not identified. One rationale for using these drugs together is the formation of combination therapy to protect against malaria and sexually transmitted infections in pregnancy [Chico and Chandramohan, 2011].

In 2007, Fossa and colleagues [Fossa *et al.* 2007] pointed out that current preclinical regulatory assays may poorly determine the arrhythmia liability of drugs associated with QTc interval prolongation. This results in some drugs that link to QTc interval prolongation being dropped prematurely from further development. Alterations in cardiac action potential duration constitute one measure of cardiac instability associated with new-onset ventricular fibrillation. These authors assessed action potential duration alterations (alternans) in anesthetized guinea pigs following azithromycin or chloroquine administration alone or in combination at clinically appropriate plasma concentrations used to manage malaria. Chloroquine alone but not azithromycin produced a marked increase in action potential duration while minimally

affecting alternans (−10 ms). Azithromycin alone or when combined with chloroquine did not increase alternans beyond vehicle baseline responses consistent with no additional arrhythmia liability.

Azithromycin and death from cardiovascular causes

Recently, Svanström and colleagues [Svanström *et al.* 2013] published findings from a nationwide historical cohort study in which they linked filled prescription registry data, causes of death, and patient characteristics. The Danish Civil Registration System was used to select patients aged 18–64 years between the years 1997 and 2010. Personal identifiers linked information including prescription drug use, cause of death, and potential confounders. After adjusting for propensity scores, the authors found that current azithromycin use was not linked to increased cardiovascular death risk compared with penicillin V. Svanström and colleagues [Svanström *et al.* 2013] concluded that, in a general population of young and middle-aged adults, azithromycin was not associated with death from cardiovascular causes.

FDA concerns about cardiovascular risks with azithromycin

In a *Perspective* [Mosholder *et al.* 2013] appearing in the same issue of the *New England Journal of Medicine* containing the article by Svanström and colleagues [Svanström *et al.* 2013], the FDA noted that during 2011 about one eighth of the US population received an outpatient prescription for azithromycin. The FDA explained why they approved revisions to the azithromycin product labels regarding drug-induced QTc interval prolongation and *torsade de pointes*. The revised product labeling advised against using azithromycin when known risk factors such as QTc-interval prolongation, hypokalemia, hypomagnesemia, bradycardia, or co-administration with such antiarrhythmic drugs as quinidine, procainamide, dofetilide, amiodarone, and sotalol (drugs associated with QTc interval prolongation) are present.

The FDA noted that such studies as those conducted by Ray and colleagues [Ray *et al.* 2012] have limitations intrinsic to observational, nonrandomized, clinical trials. However, these limitations did not prevent the FDA from promoting more restrictive product labeling as a consequence of the study from Ray and colleagues [Ray *et al.* 2012]. Furthermore, the FDA noted that Svanström and colleagues [Svanström *et al.* 2013] asserted that their findings did not differ from those of Ray and colleagues [Ray *et al.* 2012].

Preclinical data including classical hERG channel studies on pro-arrhythmic potential of azithromycin

It is widely recognized that there is a strong correlation between drug-induced QTc interval prolongation and pharmacological inhibition of the cardiac hERG potassium channel [Finlayson *et al.* 2004; Hancox *et al.* 2008]. For example, the macrolide antibiotic erythromycin has been linked to QT interval prolongation [Mishra *et al.* 1999] and inhibits hERG current (I_{hERG}) with an IC_{50} of ~39–72 μM [Volberg *et al.* 2002; Stanat *et al.* 2003; Duncan *et al.* 2006]. Other macrolides including clarithromycin and roxithromycin also inhibit hERG channel current [Stanat *et al.* 2003]. However, azithromycin appears to have rather low affinity for the hERG channel: at a high concentration of 300 μM, ~22.5% inhibition of hERG current has been reported, with an IC_{50} value of 1091 μM estimated in the same study [Thomsen *et al.* 2006]. In an investigation of the utility of canine Purkinje fiber action potentials as an assay for acquired long QT syndrome, azithromycin was included in a group of drugs producing <15% prolongation of action potential duration [Gintant *et al.* 2001]. In a separate study, intravenous administration of the drug failed to produce significant QTc interval prolongation in anaesthetized dogs with chronic atrioventricular block and was found not to increase short-term (beat-to-beat) variability in monophasic action potential repolarization, whilst dofetilide (a class III antiarrhythmic, used as a positive control) caused QTc interval prolongation and *torsade de pointes* [Thomsen *et al.* 2006]. Perhaps particularly striking are results from a study comparing the pro-arrhythmic potential of different macrolide antibiotics using Langendorff-perfused rabbit heart preparations [Milberg *et al.* 2002]. In this study, erythromycin, clarithromycin, and azithromycin were found to produce similar QTc interval and monophasic action potential prolongation and to affect endo-epicardial dispersion of repolarization [Milberg *et al.* 2002]. However, whilst both erythromycin and clarithromycin elicited early after-depolarizations and *torsade de pointes* in the presence of lowered extracellular potassium, this was not the case for azithromycin [Milberg *et al.* 2002]. Both erythromycin and clarithromycin induced monophasic action potential triangulation, whilst monophasic action potential

prolongation with azithromycin was described as 'rectangular' [Milberg *et al.* 2002]. Action potential prolongation without instability or triangulation has been suggested to be antiarrhythmic, whilst prolongation with these features is proarrhythmic [Hondeghem *et al.* 2001]. It is notable, therefore, that when azithromycin was applied to rabbit hearts following erythromycin, it suppressed erythromycin-associated *torsade de pointes* [Milberg *et al.* 2002]. Considered collectively, the findings of these preclinical studies indicate that azithromycin is a weak hERG blocker and even under conditions where it has been seen to delay repolarization, it did not share proarrhythmic features with other macrolides. In healthy volunteers receiving short-term azithromycin (500 mg daily for 3 days), peak plasma levels close to 400 ng/ml (~0.5 μM) have been reported [Matzneller *et al.* 2013] that are ~2000-fold less than the estimated hERG IC_{50} of >1000 μM [Thomsen *et al.* 2006]. Although it has been reported that tissue concentrations of azithromycin can significantly exceed those in plasma (with muscle concentrations of ~1 mg/kg, in excess of 1 μM), it is not clear that these are indicative of possible cardiac levels commensurate with significant hERG block [Foulds *et al.* 1990]. In anesthetized rats (a species that, unlike humans, does not rely on hERG for ventricular repolarization), azithromycin has been reported to induce QTc interval prolongation at concentrations exceeding the clinical range [Ohtani *et al.* 2000]. Considered collectively, the preclinical data appear to argue against a strong pro-arrhythmic potential of the drug, at least in the experimental preparations described.

Methods

We employed several strategies to conduct a systematic review (up to and including 18 March 2013) of case reports. Initially, we entering the following MeSH terms: 'azithromycin and qtc prolongation' (5) and 'azithromycin and torsade' (8) into Medline. We searched CredibleMeds (http://www.azcert.org/) for case reports of azithromycin, QTc interval prolongation, and *torsade de pointes* This search was initiated via AZCERT: ("Azithromycin"[MeSH] AND ("Long QT Syndrome"[MeSH] OR "Torsades de Pointes"[MeSH])) OR (((torsade[ti] OR torsadegenic[ti] OR torsades[ti] OR torsadogenesis[ti] OR torsadogenic[ti] OR torsadogenicity[ti]) OR qt[ti]) AND azithromycin[ti]). Please see the Website for more detailed instructions on using CredibleMeds that accesses PubMed. We searched EMBASE (19) and Cochrane (0) only for case reports. There were no language limits and only human studies were included. We also reviewed reports from our files and reference lists yielding a total of 12 cases as shown in Table 1 and Appendix A (available online: it provides a more detailed case report narrative). Titles and abstracts were independently reviewed by two investigators (WVRV and AB). Disagreement was resolved by consensus.

SPSS was used to derive parametric and nonparametric statistical analysis of data appearing in Table 1.

Results

We found six women, one female infant, and five men (Table 1 and online Appendix A). Among the nine adults with reported azithromycin doses, concurrent QTc interval measurement, and without congenital long QT syndrome, we found no statistically significant relationship between azithromycin dose and QTc interval duration (Pearson $r = 0.334$, $p = 0.379$; Kendall's tau_b $r = 0.331$, $p = 0.291$; Spearman's $\rho = 0.389$, $p = 0.301$). Among the adults, the traditional risk factors independent of azithromycin administration were: female sex ($n = 6$); older age ($n = 4$); heart disease ($n = 6$); acute medical condition ($n = 11$); drugs associated with QTc interval prolongation and *torsade de pointes* ($n = 6$); hypokalemia ($n = 4$); and bradycardia ($n = 3$). All subjects had at least two risk factors besides azithromycin.

Discussion

The studies discussed in the introduction [Ray *et al.* 2012; Pfizer Labs, 2013; Svanström *et al.* 2013] employed statistics based on a normal (Gaussian) distribution. The FDA *Perspective* [Mosholder *et al.* 2013] supported those principles of statistical analysis and the observations that azithromycin administration leaves the patient vulnerable to QTc interval prolongation and *torsade de pointes*. Large numbers of patients were employed and large bodies of data were analyzed to reach these conclusions. Unfortunately after reading this material, the clinician is provided little information upon which to base a future decision to prescribe or not prescribe azithromycin.

In our study (Table 1 and online Appendix A), there was neither a parametric nor a nonparametric statistically significant relationship between azithromycin dose and QTc interval

Table 1. Risk factors for QTc interval prolongation and *torsade de pointes* by case reports among patients receiving azithromycin (AZM).

Case/arrhythmia/ time to arrhythmia onset	QTc (ms)	AZM daily dose [mg]	Female sex	Elderly	Heart disease	Hypo-K^+	Hypo-Mg^{++}	Brady-cardia	CYP3A4 blockers	QTc prolonging drugs	Additional risk factors
(1) [Samarendra *et al.* 2001] 68-year-old woman *torsade de pointes* presumed Time to onset: 3 days	660	250	Yes	Yes	Yes	No	No	Yes	No	Amiodarone	Acute medical condition
(2) [Arellano-Rodrigo *et al.* 2001] 68-year-old woman *torsade de pointes* occurred Time to onset: 2 days	809	1500	Yes	Yes	Yes	No	No	No	No	No	Chronic liver disease, acute medical condition, previously unrecognized congenital long QT syndrome
(3) [Matsunaga *et al.* 2003] 51-year-old man No arrhythmia	680	750	No	No	Yes	No	No	No	No	No	Acute medical condition
(4) [Kim *et al.* 2005] 51-year-old woman *torsade de pointes* occurred Time to onset: 2 hours	430	500	Yes	No	No	Yes	No	No	No	No	Acute medical condition, chronic medical conditions
(5) [Tilelli *et al.* 2006] 9-month-old infant girl Cardiopulmonary collapse was accompanied by wide-complex bradycardia with third-degree atrioventricular block interpreted as *torsade de pointes* Time to onset: 20 minutes (after IV administration)	620	500	Yes	No	No	Yes	No	Yes	No	No	Overdose, acute medical condition
(6) [Russo *et al.* 2006] 65-year-old man No arrhythmia	660	750	No	Yes	Yes	No	No	No	No	No	Acute medical condition
(7) [Huang *et al.* 2007] 90-year-old woman *torsade de pointes* occurred Time to onset: 4 hours	740	500	Yes	Yes	Yes	No	No	No	No	No	Acute medical condition, S/P stroke

(continued)

Table 1. Continued.

Case/arrhythmia/ time to arrhythmia onset	QTc (ms)	AZM daily dose [mg]	Female sex	Elderly	Heart disease	Hypo-K^{+}	Hypo-Mg^{++}	Brady-cardia	CYP3A4 blockers	QTc prolonging drugs	Additional risk factors
(8) [Kezerashvili *et al.* 2007] 55-year-old woman *torsade de pointes* occurred Time to onset: 7 days	610	500	Yes	No	Yes	No	No	Yes	No	Moxifloxacin, ciprofloxacin	Acute renal failure, acute medical condition
(9) [Santos *et al.* 2010] 41-year-old man Bradycardia Time to onset: unknown	520	500	No	No	No	No	No	Yes	No	Cotrimoxazole	Acute medical condition, chronic medical condition
(10) [Del Rosario *et al.* 2010] 27-year-old woman *torsade de pointes* occurred Time to onset: unknown	459	Un-known	Yes	No	No	Yes	No	No	No	Tizanidine	Acute medical condition, chronic medical condition
(11) [Yazdan-Ashoori *et al.* 2012] 22-year-old man *torsade de pointes* occurred Time to onset: 2 days	602	500	No	No	No	Yes	Yes	No	No	Moxifloxacin	Acute medical condition
(12) [Winton and Twilla, 2013] 47-year-old man Cardiac arrest Time to onset 3 days	490	250	No	No	No	No	No	No	No	Methadone	Acute medical condition with Glasgow Coma Score of 10, chronic opioid addiction

measurement in a sample of patients with QTc interval prolongation linking to *torsade de pointes*. Our findings contrasted with those of Pfizer [Pfizer Labs, 2013] in a sample of healthy controls where co-administration of azithromycin increased QTc interval (Fridericia) 5 (10), 7 (12), and 9 (14) ms, respectively. In the Pfizer study, there was a perfect correlation between azithromycin dose and QTc interval increase (Pearson $r = 1$, $p = 0.01$) in the dose range 500 mg (10 ms) to 1500 mg (14 ms). That is, when risk factors are absent, azithromycin dose links perfectly to the subsequent QTc interval changes; and when risk factors are present, conventional statistics no longer explain the relationship between azithromycin dose and drug-related QTc interval changes. In a larger set of drug doses *versus* QTc interval measurements involving methadone, QTc interval prolongation, and *torsade de pointes* [Vieweg *et al.* 2013], failure of statistically significant findings were similar to our present case report study. We believe we are largely left with case report analysis to guide azithromycin prescribing practices.

Clinical implications

Based on case reports, all three commonly used macrolides (azithromycin, clarithromycin, and erythromycin) carry the risk of QTc interval prolongation and/or *torsade de pointes*. Current literature does not allow ranking of the risk with individual agents with any precision. The number of case reports cannot be used to estimate incidence rates even after adjusting for overall exposure rates because of inconsistent reporting and publication bias. Based on the FDA Adverse Event Reporting System (AERS) database, erythromycin was the most commonly reported torsadogenic macrolide between 1987 and 2000 [Shaffer *et al.* 2002]. However between 2004 and 2011, *torsade de pointes* and QT/QTc interval abnormalities were most commonly reported with clarithromycin followed by azithromycin [Raschi *et al.* 2013]. These variations reflect differences between exposure rates to these agents over these two periods and exemplify the limitations in drawing conclusions from case reports.

As we have discussed throughout our paper, data consistently support the notion that *torsade de pointes* associated with macrolides (and other drugs) occurs most commonly when one or more risk factors besides the drug itself are present. It is important to be mindful of these risk factors and monitor them closely when indicated.

The recent publication by Raschi and colleagues [Raschi *et al.* 2013] suggests differences in the prevalence of concomitant risk factors for *torsade de pointes* (and other arrhythmias) associated with individual macrolide drugs. While the noted differences may be simply an artifact resulting from prescribing preferences and trends, it still is concerning that a majority (73%) of cases of azithromycin-associated *torsade de pointes*/QT/QTc interval abnormalities occurred in patients less than 65 years old. Differences in concomitant use of drugs associated with QTc interval prolongation or metabolic interaction (59% with azithromycin, 45% with clarithromycin, and 89% with erythromycin) or concomitant drugs with cardiovascular indication implying cardiac disease (22% for azithromycin cases, 21% for clarithromycin cases, and 10% for erythromycin cases) could not explain this finding. The authors concluded that considering azithromycin a safer option among macrolides in healthy patients appeared unjustified.

All macrolides cause varying degrees of CYP3A4 inhibition and their co-administration with drugs depending upon this enzyme for metabolism can have potentially serious consequences. For example, one-half of the reports of macrolide-associated *torsade de pointes* between 1987 and 2000 mentioned use of drugs believed to prolong the QT interval [Shaffer *et al.* 2002]. Azithromycin is a less potent inhibitor of CYP3A4 than clarithromycin and erythromycin but clinical implications of this advantage with regards to the torsadogenic potential of azithromycin are not clear. Theoretically, azithromycin would be a safer alternative than clarithromycin or erythromycin in the settings when CYP3A4 interactions are a concern.

In patients with multiple risk factors for QTc interval prolongation/*torsade de pointes*, it would be desirable to consider alternatives to macrolides keeping in mind that several other antibiotics are also associated with this potential complication. Poluzzi and colleagues [Poluzzi *et al.* 2010] retrieved 374 reports of *torsade de pointes* associated with antimicrobial therapy between 2004 and 2008. Among antibacterials, the most represented classes were macrolides and fluoroquinolones. All macrolides showed a significant disproportionality (with regards to reporting). Among fluoroquinolones, significant disproportionality was obtained for moxifloxacin, levofloxacin, ciprofloxacin, and gatifloxacin.

Readers are invited to this publication for a complete list and to the publication by Owens [Owens, 2004] for a comprehensive review of the subject.

Risk factors for QTc interval prolongation and torsade de pointes

In the 2013 Zithromax product labeling [Pfizer Labs, 2013], at-risk groups included: (1) subjects with known QTc interval prolongation, history of *torsade de pointes*, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure; (2) subjects taking drugs known to prolong the QTc interval; and (3) subjects with ongoing proarrhythmic conditions such as hypokalemia, hypomagnesemia, bradycardia, or taking class 1A (quinidine, procainamide) or class III (dofetilide, amiodarone, sotalol) antiarrhythmic drugs.

In our study, adult risk factors excluding azithromycin administration were: female sex (6); older age (4); heart disease (6); acute medical condition (11); drugs associated with QTc interval prolongation and *torsade de pointes* (6); hypokalemia (4); and bradycardia (3). All subjects had at least two risk factors besides azithromycin.

Several other studies have observed the same. Shaffer and colleagues [Shaffer *et al.* 2002] retrospectively evaluated case reports that appeared in the FDA AERS to examine risk factors mentioned in reports of *torsade de pointes* associated with macrolides. A total of 156 nonduplicate reports of *torsade de pointes* from 1987 through 2000 were identified. A total of 53% of all reports involved use of erythromycin, 36% involved clarithromycin, and 18% involved azithromycin. The patients described in these reports were primarily older women. Drugs believed to prolong the QTc interval were mentioned in 78 reports (50%). At least one cardiac abnormality was noted in 42% and hypokalemia or hypomagnesemia was noted in 17% of all reports. The authors identified intravenous administration of the drug as an independent risk factor (28% of all reports and 41% for the reports in which a macrolide was the only QTc interval prolonging drug involved).

Raschi and colleagues [Raschi *et al.* 2013] provided a more recent data from FDA AERS. For 8 years between 2004 and 2011, they identified 183 cases of macrolide-associated *torsade de pointes* or QT abnormalities (*TdP*/QT abnormalities group) and 419 cases of ventricular arrhythmia or sudden cardiac death (VA/SCD group). Clarithromycin was the most frequently reported drug (84 and 162 cases), followed by azithromycin (63 and 140) and erythromycin (19 and 31), respectively. Most of the cases occurred in women. For *TdP*/QT abnormalities, 63% of cases receiving clarithromycin, 47% of cases receiving erythromycin, and 27% of cases receiving azithromycin were 65 years of age or older. Concomitant use of drugs associated with QTc prolongation or metabolic interaction was recorded in 59% of cases of *TdP*/QT abnormalities associated with azithromycin, 45% with clarithromycin, and 89% with erythromycin. Concomitant drugs with cardiovascular indication were reported in 22% of cases with azithromycin, 21% of cases with clarithromycin, and 10% of cases with erythromycin. While these data highlight the importance of concomitant risk factors in macrolide-induced *torsade de pointes*, they may also signify potential differences between individual drugs.

Presence of risk factors for QTc interval prolongation and/or *torsade de pointes* is common even when antibiotics besides macrolides are implicated. Justo and colleagues [Justo and Zeltser, 2006] searched PubMed for all published reports (until September 2005) on *torsade de pointes* induced by antibiotics and found 61 reports on 78 patients. A total of 66.7% of all patients were women and vast majority of them were of middle or older age. Advanced heart disease and concomitant use of a QT interval-prolonging agent or a metabolic inhibitor were also frequently present (59% and 48.7%, respectively). Most patients had at least one and 74.3% of all patients had two or more risk factors for *torsade de pointes* before initiation of antibiotic therapy. Following female sex (33/50, 66%), the use of another QT interval-prolonging agent or a metabolic inhibitor and the presence of advanced heart disease were the second and third most common risk factors for *torsade de pointes* among patients receiving macrolide antibiotics (54% and 50%, respectively). Advanced heart disease and female sex were the two most common risk factors for *torsade de pointes* among patients receiving quinolones (76% and 68%, respectively).

Regulatory agency concerns

Ray and colleagues [Ray *et al.* 2012] assessed Tennessee Medicaid records to reach their conclusion that 'during 5 days of azithromycin

therapy, there was a small absolute increase in cardiovascular deaths' particularly among subjects with an increased risk of cardiovascular disease. Risk factors for cardiovascular disease (not a risk factor for QTc interval prolongation) and *torsade de pointes* appeared among their references rather than in the published text. A summary risk score was derived from 30 cardiovascular risk factors.

Ray and colleagues [Ray *et al.* 2012] referred to the paper by Poluzzi and colleagues [Poluzzi *et al.* 2009] ('Drug-induced *torsade de pointes*: data mining of the public version of the FDA Adverse Event Reporting System [AERS]') in their introduction and discussed it no further in their text. Ray and colleagues [Ray *et al.* 2012] referenced cases 1–4 and 6–8 in our Table 1 but did not refer to any narrative material contained in those cases.

Svanström and colleagues [Svanström *et al.* 2013] concluded that azithromycin administration did not link to increased risk of cardiovascular death in a general population of young and middle-aged adults. Their study population was healthier and younger than the population studied by Ray and colleagues [Ray *et al.* 2012]. Ray and colleagues reported that during 5-day treatment with azithromycin, there was a small absolute increase in deaths from cardiovascular causes and this increase was more pronounced in the subset of patients with high baseline increase in cardiovascular disease risk. Based on our assessment of risk factors (Table 1), these seemingly disparate findings are explained by the difference in health and age of the patients studied. That is, Ray and colleagues' study subjects were older and less healthy and, therefore, more likely to experience adverse events than the younger and healthier study subjects in the Svanström and colleagues [Svanström *et al.* 2013] study.

We continue to believe that drugs such as azithromycin linked to QTc interval prolongation and/or *torsade de pointes* are only one of the likely factors explaining these electrocardiographic changes [Vieweg *et al.* 2012, 2013; Hasnain *et al.* 2013]. We continue to urge regulatory agencies and pharmaceutical manufacturers to make available to the public case report material (narrative medicine) [Vieweg *et al.* 2012, 2013; Hasnain *et al.* 2013]. Specifically, elderly women with heart disease are at greatest risk for azithromycin-related QTc interval prolongation and *torsade de pointes* and we propose identifying this triad as major risk factors. Lesser risk is operative when less than three of these major risk factors are present. There are numerous minor risk factors.

Limitations

One potential limitation with case reports is that, as fatalities are not always reported, this approach can involve selection bias. In addition, as *torsade de pointes* is relatively rare, the numbers of case reports with particular drugs tend to be limited, as is the case here for azithromycin (12 cases: seven females and five males, with 11 of 12 being adults). Nevertheless, the case report approach confers some advantages. In particular, case reports give information obtained in a clinical setting and, in those cases where *torsade de pointes* is reported, they provide direct information regarding arrhythmia occurrence. This contrasts with 'thorough QT' investigations that are typically performed on healthy volunteers and use QT (QTc) interval changes as a surrogate marker of arrhythmic risk [Darpo, 2010; Stockbridge *et al.* 2012]. Owing to the fact that there are comparatively few case reports on azithromycin-linked *torsade de pointes*, conclusions from case report analysis need to be extrapolated to larger populations with caution. However, considered together with the results of larger-scale studies [Ray *et al.* 2012; Mosholder *et al.* 2013; Svanström *et al.* 2013], they provide a valuable resource.

Conclusion

Azithromycin has recently come under regulatory scrutiny because of its purported link to life-threatening cardiac tachyarrhythmias and cardiac death. This appears to be less of an issue for younger and healthier patients. Both epidemiologic studies and individual reports suggest this link derives from aspects of the drug itself. Conventional statistics have not better defined this link. Using search conditions that allow a systematic review of relevant case reports (narrative medicine) lead us to conclude that accompanying risk factors offer a more complete understanding of any link between azithromycin and untoward outcomes derived from cardiac arrhythmias. We urge that regulatory agencies and pharmaceutical manufacturers make available to prescribing physicians detailed case reports of drug-induced/related QTc interval prolongation and/or *torsade de pointes*.

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