Macrolide Antibiotics and the Risk of Cardiac Arrhythmias

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Abstract

Randomized, controlled trials have demonstrated that chronic therapy with macrolide antibiotics reduces the morbidity of patients with cystic fibrosis, non–cystic fibrosis bronchiectasis, chronic obstructive pulmonary disease, and nontuberculous mycobacterial infections. Lower levels of evidence indicate that chronic macrolides are also effective in treating patients with panbronchiolitis, bronchiolitis obliterans, and rejection after lung transplant. Macrolides are known to cause torsade des pointes and other ventricular arrhythmias, and a recent observational study prompted the FDA to strengthen the Warnings and Precautions section of azithromycin drug labels. This summary describes the electrophysiological effects of macrolides, reviews literature indicating that the large majority of subjects experiencing cardiac arrhythmias from macrolides have coexisting risk factors and that the incidence of arrhythmias in absence of coexisting risk factors is very low, examines recently published studies describing the relative risk of arrhythmias from macrolides, and concludes that this risk has been overestimated and suggests an approach to patient evaluation that should reduce the relative risk and the incidence of arrhythmias to the point that chronic macrolides can be used safely in the majority of subjects for whom they are recommended.

Keywords: arrhythmias; QT prolongation; azithromycin

Pulmonary physicians frequently encounter patients for whom chronic macrolide therapy should be considered based on the results of high-quality randomized trials (i.e., cystic fibrosis, non–cystic fibrosis bronchiectasis, chronic obstructive pulmonary disease [COPD] and nontuberculous mycobacterial infections). Lower levels of evidence suggest that chronic macrolides are also effective in treating subjects with panbronchiolitis and those with bronchiolitis obliterans and rejection after lung transplantation.

In response to a recently published observational study (1), the FDA warned that azithromycin can change the electrical activity of the heart and reiterated a 2011 product label revision stating that patients with risk factors were at particular risk and strengthened the Warnings and Precautions section of azithromycin drug labels. Accordingly, physicians have to weigh the relative risk (RR) of arrhythmias developing versus the reduction in morbidity that could be achieved by prescribing chronic macrolides.

This review describes the electrophysiological effects of macrolides, explains the genetic mechanisms of these effects, summarizes the importance of coexisting risk factors in the development of arrhythmias, critically reviews recently published studies estimating the increased RR of macrolide-associated arrhythmias, and suggests an approach by which these risks can be reduced.

Definitions

The QT interval of the electrocardiogram (ECG) varies from beat-to-beat, from day-to-day, and diurnally and is affected by numerous factors, including gender, age, autonomic tone, and heart rate (Table 1). The QT interval is expressed as the QTc interval after adjusting for heart rate using any of several of correction formulas. QT prolongation itself does not adversely affect cardiac function (2), but prolongation portends the possibility of more serious arrhythmias.

Normal values for the QT interval and the RR of torsade des pointes (TdP) have been estimated from population-based studies (Table 2) (3). Roden (4) suggested that QT prolongation beyond 500 milliseconds, or by >50 milliseconds from the baseline, as a result of a medication should prompt a search for potential predisposing or contributing factors, and if these cannot be identified and corrected the benefit of continuing the associated medication should

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Table 1: Factors Prolonging the QT Interval and Possibly or Probably Increasing the Risk of Cardiac Arrhythmias Developing after Macrolide Administration

Risk Factor Category	Examples
Genetic	Long QT syndrome Unidentified channelopathies Female gender
Underlying cardiac disease	Bradycardia Congestive heart failure Baseline QT prolongation Myocardial ischemia and infarction Cardiomyopathies Atrial fibrillation
Metabolic abnormalities	Hypokalemia Hypomagnesemia Hypocalcemia Acute hypercarbia and/or hypoxia
Taking other medications with risk of QT prolongation without dose adjustment when metabolism or clearance of these medications is impaired	Renal or hepatic insufficiency Genetic polymorphisms Concurrent cytochrome P450 inhibitors
Administration of multiple drugs with QT liability	As summarized in Reference 8

Summary of References 6, 7, and 65 with additions.

be reconsidered. Several groups, however, suggest that QT prolongation is an insensitive and nonspecific predictor of adverse cardiac events because the majority of patients with medication-induced QT prolongation do not develop TdP, and many patients who develop TdP have a normal QT interval (5–7).

A list of medications that prolong the QT interval and cause TdP, categorized into four groups of presumed risk, is available on the internet (8). Erythromycin, azithromycin, and clarithromycin are all listed in risk category 1 ("Substantial evidence… that these drugs…can prolong the QT interval and can have a risk of torsades de pointes"). Forty-one other medications are included in this category, including haloperidol and droperidol, ondansetron, moxifloxacin, and methadone.

Electrophysiology and Genetics

In their resting state, cardiac myocytes have a transmembrane electrical potential of approximately −90 mV. When the cells depolarize (represented by the QRS complex), the potential increases to approximately +20 mV. Repolarization (represented by the T wave and the QT interval) occurs in three phases. The early repolarization and plateau phases (phase 1 and 2, respectively) are largely the result of potassium and calcium currents. Phase 3 repolarization occurs when potassium channels open and the cell returns to its resting negative state (phase 4). QT prolongation can result in early after-depolarizations (EADs) in the third phase. If EADs reach the threshold electrical potential, they can induce TdP, which can result in ventricular fibrillation. Accumulation of potassium within the myocytes delays repolarization. The rapidly activating delayed rectifier potassium channel (I_{Kr}) controls movement of potassium out of the myocyte, is responsible for phase 3 repolarization, is encoded by the human ether-a-go-go-related gene (hERG), and is affected by macrolides and many other medications in a concentration-dependent fashion (9–12).

Mutations in hERG are responsible for the congenital Type 2 Long QT syndrome and for the prolonged QT intervals acquired as a result of Type Ia and Type III antiarrhythmic agents. Almost all medications that prolong the QT interval and cause TdP block I_{Kr}, but many medications that do not cause TdP also block I_{Kr} (e.g., verapamil and amiodarone) (7, 13). The observation that not all patients prolong their QT interval after taking macrolides and that even fewer patients experience potentially lethal arrhythmias suggests that additional patient-specific variables are important (see below).

From 5 to 20% of patients who develop TdP after taking QT-prolonging medications have subclinical congenital QT prolongation. Incomplete penetrance of hERG mutations may be present despite near-normal QT intervals, representing a second mechanism by which macrolides may prolong the QT interval (14–18). In addition, several I_{Kr}-specific genes have been identified that do not independently cause QT prolongation but that block I_{Kr}, prolong the QT interval, and cause TdP in the presence of medications (5, 14, 19–23).

The effect of macrolides on repolarization is only observed in the His-Purkinje tissue and the M cells in the ventricular myocardium (i.e., there is little or no drug effect in the endocardium and epicardium). This disparity leads to dispersion of repolarization across the myocardium, a third mechanism by which the risk of arrhythmias and TdP can develop.

The QT interval before receiving an at-risk medication is longer in patients who develop TdP after receiving the medication than in those who do not (23–25). This observation led to the concept of "repolarization reserve" (23), suggesting that anything that impairs repolarization (as summarized in Table 1) makes TdP more likely when an I_{Kr}-blocking medication is prescribed.

Table 2: QT Interval Prolongation and Risk of Sudden Cardiac Death in Patients > 55 yr of Age

	Male Patients		Female Patients	
	QT Interval (*ms*)	Hazard Ratio for Sudden Cardiac Death	QT Interval (*ms*)	Hazard Ratio for Sudden Cardiac Death
Normal	<430	1.0	<450	1.0
Borderline	431–450	1.3	451–470	1.8
Prolonged	>450	2.5	>470	2.6

Data from Reference 3.

Dose–Response Issues

Ponsonnaille and colleagues (26) first assessed the electrophysiological effects of intravenous erythromycin and found that the effect on the QTc interval was directly related to the rate of infusion because the QTc interval increased an average of 42 and 33 milliseconds in subjects who received a 500-mg dose of the medication over 1 or 20 minutes, respectively. Atrial and ventricular refractory periods were also prolonged by the rapid, but not the slower, infusion. Similar results were reported by others (27, 28).

In vitro studies find no effect of erythromycin on repolarization at a concentration of 10 mg/L (29), prolonged repolarization at 20 to 50 mg/L, further prolongation at 100 mg/L, and EADs at 50 to 200 mg/L (9–11, 29). Intravenous administration of erythromycin (500 mg) over 15 minutes produces peak serum concentrations of approximately 45 mg/L 3 minutes after the injection (30). Slower administration produces lower levels (31), whereas oral administration results in a peak concentration of ~2 to 4 mg/L (32). Accordingly, arrhythmias should not occur after oral dosing in the absence of other confounding issues.

Azithromycin may be the macrolide that is least likely to cause cardiac arrhythmias. Ohtani and colleagues (33) found the rank order of concentration-dependent QT prolongation in rats was erythromycin > clarithromycin > roxithromycin > azithromycin. Milberg and colleagues (34) found that erythromycin, clarithromycin, and azithromycin all prolonged the QT interval, but after decreasing potassium concentrations erythromycin and clarithromycin led to EADs and TdP, whereas azithromycin did not.

Cardiac Events after Macrolides and the Relationship to other Risk Factors

The patients who are described in the literature as developing arrhythmias after receiving macrolide antibiotics have a strikingly high prevalence of other factors that could cause or contribute to the arrhythmias.

Erythromycin

Of the first 13 reports of patients with arrhythmias occurring in conjunction with erythromycin (all after intravenous administration), 12 had one or more the conditions summarized in Table 1, and 4 or 5 of 11 reports with sufficient information to assess had acute hypoxemia or hypercarbia (35–45). The only patient with no apparent risk factors was an 8-day-old baby who received multiple intravenous injections of the macrolide. Bandriss and colleagues (46) concluded that intravenous erythromycin could induce TdP when given alone but that TdP occurred more commonly when the QTc interval was prolonged by other conditions.

Tschida and colleagues (47) performed a comprehensive review of 23 patients described in 17 case reports in which TdP and/or ventricular tachycardia were reported in association with erythromycin. Fourteen (61%) had known cardiac disease. Of the nine subjects without cardiac disease, five received the erythromycin as a rapid intravenous bolus, two were receiving other medications known to prolong repolarization, and one had active liver disease.

The first report of oral erythromycin causing arrhythmias was in a patient with congenital long QT syndrome (38). The next report occurred in a patient who was also taking disopyramide, a class Ia antiarrhythmic that prolongs the QT interval (48), and the third was in a patient with sinus bradycardia who received 4 g of erythromycin orally over 6 hours for a preoperative bowel preparation and became symptomatic directly after intravenous administration of ranitidine (49).

Clarithromycin

The first case report of arrhythmias developing after clarithromycin was in a patient with pulmonary hypertension, cor pulmonale, hypoalbuminemia, and transaminitis, and the second was in a patient with hepatitic C and heart failure who was on dialysis (50). The next four reports occurred in patients who were taking multiple QT-prolonging medications (one of whom also had hypokalemia) or had congenital QT prolongation (51–53).

Azithromycin

In 2013, over 57 million outpatient prescriptions were written for macrolide antibiotics in the United States, and 51.5 million of these (90%) were for azithromycin (54). The first patient reported to have arrhythmias in association with azithromycin was also receiving disopyramide (55). The second patient had congenital long QT syndrome, and the third, fourth, and fifth all had congestive heart failure (56–59). Kim and colleagues (60) and Kezerashvili and colleagues (61) published what they believed to be the first reports of TdP occurring in patients with no apparent predisposing comorbidities, but the first of these patients had taken pseudoephedrine in conjunction with the azithromycin and also had hypokalemia, and the second had a pacemaker for intermittent symptomatic bradycardia, had developed acute renal failure requiring dialysis, and was taking moxifloxacin and ciprofloxacin at the time the TdP was observed.

Raschi and colleagues (62) investigated cases of drug-induced arrhythmias submitted to the FDA Adverse Event Reporting System from 2004 through 2011. Over the 8-year study period, only 63 and 84 cases of TdP or QT prolongation, respectively, were reported in association with macrolides, and 59 and 45% of these, respectively, occurred in conjunction with the subjects taking other medications known to have a definite or probable risk of causing QT prolongation.

Justo and Zeltser (63) examined subjects reported in Pubmed citations to 2005 and identified by direct inquiry of pharmaceutical companies and found 78 patients who developed TdP. Macrolides were considered to be responsible for 50 (64%) of these cases, and 37 (74%) patients had two or more risk factors for TdP that could be determined from the subjects' history or ECG.

Ray and colleagues (64) reported that the RR of sudden death from cardiac causes was higher in patients currently using erythromycin compared with subjects who were taking no antibiotics (Table 3). The effect of taking CYP3A inhibitors was striking in this study. Subjects taking erythromycin in addition to CYP3A inhibitors had a 3-fold greater incidence of sudden cardiac death than those taking erythromycin alone, and the incidence of sudden cardiac death in subjects taking erythromycin without CYP3A inhibitors was within the 95% confidence interval (CI) of the incidence

Table 3: Incidence of Sudden Cardiac Death in Subjects Taking Oral Antibiotics with or without CYP3A Inhibitors

Medication(s)	Deaths	Person-Years of Follow-up	Incidence Ratio (95% CI)
Erythromycin with or without CYP3A inhibitor	10	5,305	20.1 (1.08–3.75)
Amoxicillin with or without CYP3A inhibitors	8	6,846	1.18 (0.59–2.36)
No antibiotic with or without CYP3A inhibitors	1,358	1,126,013	1.00
Erythromycin with CYP3A inhibitor	3	194	5.35 (1.72–16.64)
Erythromycin without CYP3A inhibitor	7	4,874	1.79 (0.85–3.76)
Amoxicillin with CYP3A inhibitor	0	254	0
Amoxicillin without CYP3A inhibitor	8	6,304	1.48 (0.74–2.97)
No antibiotic with CYP3A inhibitors	116	36,518	0.93 (0.76–1.13)
No antibiotic without CYP3A inhibitors	1,235	1,163,087	1.00

Definition of abbreviation: CI = confidence interval.
Data from Reference 64.

in subjects taking amoxicillin alone (Table 3).

In sum, it is difficult to find reports of patients experiencing arrhythmias in response to macrolides who do not have one or more additional risk factors for developing arrhythmias. Mosholder and colleagues (65) concluded that having a risk factor for QT prolongation increases the likelihood of azithromycin-associated cardiovascular death by more than 24-fold.

RR and Incidence of Arrhythmias

In 2001, the FDA Pink Sheet reported 10 cases of QTc-related cardiac events out of 10 million prescriptions of azithromycin (66).

The article resulting in the reemergence of concern for macrolide-associated arrhythmias was published by Ray and colleagues (1). They examined 14 years of data collected from a Medicaid database in Tennessee and found an increased risk of cardiovascular deaths and death from any cause during the first 5 days after patients were prescribed azithromycin compared with when they were prescribed no antibiotics or amoxicillin (Table 4). Several issues complicate interpretation of their data.

First, the paper focused on the RR of arrhythmias and did not present the number of patients included in the three treatment groups. Accordingly, the incidence of arrhythmias could not be determined. Based on the data provided, the incidence could vary at least 10-fold.

Second, because of the large number of antibiotic courses studied, the low number of deaths observed (i.e., 29 in the azithromycin arm over 14 yr), and the observational design of the study, even small differences in any of numerous comorbidities could account for some or all of the difference in the RRs of cardiovascular deaths reported. For example, current or past use of antipsychotic medications was reported in 11.5% of the patients during periods when they were receiving no antibiotics and in 11.8% of the patients during periods when azithromycin was taken. Given the large number of periods studied, this 0.3% difference could equate to as many as 1,043 more courses of azithromycin being taken while patients were receiving antipsychotics. If even a few of the deaths observed in the azithromycin arm were the result of concurrent antipsychotic use, it could alter the RRs reported for azithromycin to a considerable extent. A similar concern would pertain to many other medications that could contribute to QT prolongation.

Third, the history obtained regarding other medications grouped the responses as "current or past use." This blurs the matching process because the effect that other medications might have on the development of arrhythmias obviously depends on whether these medication were being taken at the time the patient was assessed. In reviewing the results of this study, Mosholder and colleagues (65) pointed out that it was not possible to know for certain whether the propensity scores successfully adjusted the data.

Fourth, women made up 78% of the cohort. QTc intervals are longer and TdP occurs more commonly in women than in men, possibly because of the effects of sex hormones on myocardial tissue (67–74). Lehmann and colleagues (74) suggest that

Table 4: Summary of the Results of Ray and Colleagues (1)

Variable	No Antibiotics	Amoxicillin	Azithromycin
Treatment courses	1,391,180	1,348,672	347,795
Cardiovascular deaths	41	42	29
Cardiovascular deaths/million courses	29.8	31.5	85.2
HR (95% CI)	1	0.95 (0.55–1.63)	2.88 (1.79–4.63)
P value		0.85	<0.001
Sudden cardiac death	33	29	22
Sudden cardiac deaths/million courses	24.0	21.8	64.6
HR (95% CI)	1	0.85 (0.45–1.60)	2.71 (1.58–4.64)
P value		0.62	<0.001

Definition of abbreviations: CI = confidence interval; HR = hazard ratio.

TdP occurs three times more commonly in women than in men. Using the FDA Medwatch data, Drici and colleagues (69) found that 67% of the macrolide-related deaths occurred in women despite there being no gender differences in prescribing patterns. If both of these estimates are correct, Ray and colleagues (1) could have overestimated the RR of azithromycin causing cardiac deaths by nearly 30% because of the imbalance of women in the cohort.

Fifth, the increased risk of cardiovascular deaths observed with azithromycin in comparison to periods when no antibiotics were taken could have resulted from the adverse effects of the infection for which the antibiotic was prescribed (i.e., confounding by indication) rather than to azithromycin-induced arrhythmias *per se*. Ray and colleagues (1) address this limitation by reporting no increase in deaths during periods when patients took amoxicillin compared with when no antibiotics were being taken (Table 4). Although patients who took azithromycin were carefully matched with those taking no antibiotics, no matching was done for those taking amoxicillin "because matching would have substantially decreased the sample size" (1). Compared with patients receiving no antibiotics, those receiving azithromycin were nearly identically matched with respect to nearly every variable assessed, but a lower percentage of those receiving amoxicillin were taking every medication recorded with the exceptions of digoxin and insulin (and with strikingly lower use of statins and β agonists), and the amoxicillin group had a lower prevalence of every major comorbid condition recorded (including heart failure) and fewer hospital and urgent care visits. Accordingly, fewer deaths could have occurred in those receiving amoxicillin because they were healthier than those receiving no antibiotics.

Because of the high prevalence of coexisting conditions and the high mortality in the cohort reported by Ray and colleagues (1), Svanstrom and colleagues (75) asked whether the increased risks of cardiovascular death with azithromycin would generalize to patients seen in routine clinical practice. In their study, the number of cardiovascular deaths within the first 5 days of receiving a prescription for azithromycin was small but greater than what was observed in subjects with no antibiotic use (17/1,102,050 prescriptions of azithromycin vs. 6/1,102,050 episodes of no antibiotics [RR, 2.85; 95% CI, 1.13–7.24) but was the same as that seen within 5 days of receiving a prescription for penicillin V (RR, 0.93; 95% CI, 0.56–1.55). They interpreted their data as indicating that the increased death rate observed with azithromycin relative to no antibiotic use "was entirely attributable to the risk of death associated with acute infection…rather than with its treatment." Svanstrom and colleagues (75) found a cardiovascular mortality of 5.4 deaths/million periods of observation when no antibiotics were being taken, compared with 29.8/million periods of observation reported by Ray and colleagues (1). Although the 5.5-fold difference suggests that there were major differences in the cohorts studied, an additional explanation could be the widely recognized limitations of observational studies (76).

Two studies have reported that treatment with macrolides was associated with an increased risk of cardiovascular events occurring well beyond the period when the macrolide was taken (77, 78). Both studies were designed to test the hypothesis that macrolides decreased the inflammation associated with cardiovascular disease, thereby decreasing adverse cardiac events. In the first study, Jespersen and colleagues (77) studied the effect of 2 weeks of clarithromycin (500 mg daily) versus placebo in 4,373 patients with stable coronary artery disease. No difference between the two groups was seen with respect to the primary outcome (i.e., composite of all-cause mortality, myocardial infarction, or unstable angina at 3 yr) or secondary outcome (i.e., composite of cardiovascular mortality myocardial infarction or unstable angina at 3 yr), and none of the prespecified outcomes was significantly different by multivariate analysis. However, when the primary and secondary endpoints were analyzed separately (which the authors identified as being tertiary outcomes), all-cause mortality was higher in the subjects receiving clarithromycin as a result of cardiovascular mortality. Jespersen and colleagues (77) pointed out two potential weaknesses in their study: (*1*) the study groups might not have been balanced with respect to cardiac function because they had no information pertaining to New York Heart Association class or ejection fraction at randomization, and (*2*) they had no knowledge of what treatments the patients in either group received during the 3-year follow-up. An additional observation from this study is that, as opposed to the striking difference in cardiovascular deaths within 5 days of starting azithromycin reported by Ray and colleagues (1), Jespersen and colleagues (77) found two early cardiovascular deaths in patients receiving clarithromycin and four in those receiving placebo.

The second study used an observational design to examine databases of 1,343 patients with COPD and 1,631 patients with community-acquired pneumonia who were hospitalized in the United Kingdom (78). Patients were considered to have used macrolides if they received at least one dose of clarithromycin during their index hospitalization, and the maximum duration of treatment studied was 14 days. During the 1-year follow-up, 268 patients with

Table 5: Frequency of Cardiovascular Events in Clarithromycin Users versus Nonusers

Events	COPD Cohort		CAP Cohort	
	Use (*n* = 281)	Nonuser (*n* = 1,062)	User (*n* = 980)	Nonuser (*n* = 651)
Myocardial infarction, n (%)	12 (4.3)	29 (2.7)	25 (2.6)	9 (1.4)
NSTEMI or ACS, n (%)	14 (5.0)	40 (3.8)	29 (3.0)	11 (1.7)
CHF or LVF, n (%)	32 (11.4)	56 (5.3)	32 (3.3)	21 (3.2)
Arrhythmia, n (%)	47 (16.7)	108 (10.2)	64 (6.5)	23 (3.5)
Cardiac arrest/sudden cardiac death, n (%)	2 (0.7)	3 (0.3)	14 (1.4)	6 (0.9)

Definition of abbreviations: ACS = acute coronary syndrome; CAP = community-acquired pneumonia; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; LVF = left ventricular failure; NSTEMI = non–ST elevation myocardial infarction.
Data from Reference 76.

COPD and 171 patients with community-acquired pneumonia were readmitted to a hospital as a result of a cardiovascular event, with hazard ratios of cardiovascular events for those who took clarithromycin of 1.48 (95% CI, 1.13–1.94) and 1.75 (95% CI, 1.25–2.45), respectively (Table 5). Again as opposed to the findings of Ray and colleagues (1), Schembri and colleagues (78) found no increased mortality for patients taking the macrolide for the first 6 days and found no association between the risk of cardiovascular events while patients were taking the clarithromycin compared with when they were not.

The increased cardiovascular mortality seen in these two studies conflict directly with at least 11 large, randomized trials testing the same hypothesis. The randomized studied reported either no increase or reductions in cardiac deaths in patients receiving various durations of macrolides to treat the inflammation associated with vascular disease (79–89).

Reducing the Risk of Arrhythmias

Al-Khatib and colleagues (5) suggest that ECGs should be obtained on all patients before and after starting medications known to prolong the QT interval. Shah (2) proposes a similar approach but limits ECGs to patients with additional risks of QT prolongation.

In our recently published study of azithromycin in patients with COPD (90), we screened patients by taking a history targeting evidence of heart failure, episodes of hypokalemia, a family history of long QT syndrome, or use of other medications known to prolong the QT interval and performed an ECG before starting treatment. This resulted in excluding 113 of 1,577 subjects (7.1%), 88 (5.6%) on the basis of history and 25 (1.6%) because of a prolonged QTc interval. We excluded another 10 subjects (0.8%) because they developed QTc prolongation on an ECG obtained 1 month after starting therapy (six [1.05%] were receiving azithromycin, and four [0.70%] were receiving placebo; $P = 0.55$). Using this approach, after 1 year of therapy we only encountered one cardiovascular death in each treatment group (0.18%), and all-cause mortality was 3.1% in subjects receiving azithromycin and 3.5% in those receiving placebo ($P = 0.87$) (88).

Although there are insufficient data available to know how much the above approach might decrease the incidence of macrolide-associated arrhythmias, the low cost and lack of risk associated with obtaining histories and ECGs suggest that it would be cost effective.

Conclusions

Macrolides can prolong the QT and QTc interval and cause cardiac arrhythmias, including TdP, ventricular tachycardia, and ventricular fibrillation, via their effect on the I_{Kr} potassium channel. Having conditions associated with QT prolongation or various other comorbidities increases the risk of developing arrhythmias in response to macrolides, perhaps by more than 24-fold (65). Studies documenting the RRs of subjects developing arrhythmias when taking macrolides compared with other classes of antibiotics or no antibiotics have reached conflicting conclusions (1, 64), perhaps because they examined different patient populations, but the study by Ray and colleagues (1) that reported increased RR of arrhythmias may have overestimated the RRs for the reasons discussed above.

The risk of arrhythmias in response to macrolides is related to the concentration of the medication in the blood and therefore to the dose, route, and rate of administration. Given the low concentrations resulting from oral dosing of macrolides, arrhythmias are unlikely to occur in the absence of additional issues that would reduce the "repolarization reserve." Consistent with this concept is the estimate that the incidence of arrhythmias in response to macrolides in absence of additional risk factors is very low, perhaps $<$ 1 in 100,000 subjects (65).

Regardless of what the RR and incidence of macrolide-associated arrhythmias might be, both can be reduced by not prescribing this class of medications to patients with comorbidities of concern, the majority of which can be discovered by taking a history, performing an ECG before initiating therapy, and repeating the ECG a short time thereafter. ■

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