Divergent Proarrhythmic Potential of Macrolide Antibiotics Despite Similar QT Prolongation: Fast Phase 3 Repolarization Prevents Early Afterdepolarizations and Torsade de Pointes

PETER MILBERG, LARS ECKARDT, HANS-JÜRGEN BRUNS, JULIA BIERZ, SHAHRAM RAMTIN, NICO REINSCH, DIRK FLEISCHER, PAULUS KIRCHHOFF, LARISSA FABRITZ, GÜNTER BREITHARDT, and WILHELM HAVERKAMP

Hospital of the Westfälische Wilhelms-University, Department of Cardiology and Angiology and Institute for Arteriosclerosis Research, Münster, Germany

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ABSTRACT

Macrolide antibiotics are known to have a different proarrhythmic potential in the presence of comparable QT prolongation in the surface ECG. Because the extent of QT prolongation has been used as a surrogate marker for cardiotoxicity, we aimed to study the different electrophysiological effects of the macrolide antibiotics erythromycin, clarithromycin, and azithromycin in a previously developed experimental model of proarrhythmia. In 37 Langendorff-perfused rabbit hearts, erythromycin (150–300 μM, n = 13) clarithromycin (150–300 μM, n = 13), and azithromycin (150–300 μM, n = 11) led to similar increases in QT interval and monophasic action potential (MAP) duration. In bradyventricular (atrophicventricular-blocked) hearts, eight simultaneously recorded epicardial and endocardial MAPs demonstrated increased dispersion of repolarization in the presence of all three antibiotics. Erythromycin and clarithromycin led to early afterdepolarizations (EADs) and torsade de pointes (TdP) after lowering of potassium concentration. In the presence of azithromycin, no EAD or TdP occurred. Erythromycin and clarithromycin changed the MAP configuration to a triangular pattern, whereas azithromycin caused a rectangular pattern of MAP prolongation. In 13 additional hearts, 150 μM azithromycin was administered after previous treatment with 300 μM erythromycin and suppressed TdP provoked by erythromycin. In conclusion, macrolide antibiotics lead to similar prolongation of repolarization but show a different proarrhythmic potential (erythromycin > clarithromycin > azithromycin). In the presence of azithromycin, neither EAD nor TdP occur. This effect may be related to a rectangular pattern of action potential prolongation, whereas erythromycin and clarithromycin cause triangular action potential prolongation and induce TdP.

QT interval prolongation is a risk factor in a number of cardiovascular as well as noncardiovascular diseases. In the congenital long QT syndrome, prolongation of the QT interval is associated with recurrent syncope and sudden cardiac death. Both result from potentially life-threatening polymorphic tachycardias of the torsade de pointes (TdP) type. TdP are not only observed in long QT syndrome but also in clinical conditions such as bradycardia (Kurita et al., 1994) or hypokalemia (Shimizu et al., 1991), especially if occurring in the presence of various drugs, which prolong repolarization (Haverkamp et al., 2000).

The most commonly known cause of TdP is the administration of antiarrhythmic drugs (Eckardt et al., 1998a; Haverkamp et al., 2000). These drugs have in common that they prolong repolarization via block of the rapid component of the delayed rectifier potassium current, I_{Kr} (Haverkamp et al., 2000). In drug-induced TdP, antiarrhythmic agents still play an important role, but the number of noncardiovascular drugs that is associated with QT prolongation and may have a possible proarrhythmic potential has been rising continuously. Estimation of the true incidence of TdP during treatment with these drugs is difficult. For several noncardiovascular drugs, which have been involved in the generation of TdP, only a few case reports are available (Haverkamp et al., 2000).

Among noncardiovascular drugs that prolong repolarization, macrolide antibiotics are widely prescribed. Apart from their antibiotic effects, macrolide antibiotics were found to prolong action potential duration (Ohtani et al., 2000). It was demonstrated that erythromycin prolongs repolarization by a block of I_{Kr} (Daleau et al., 1995). In several case reports, TdP was reported after oral (Freedman et al., 1987) and in-pa-
ticular after intravenous administration (Nattel et al., 1990). In the early nineties, erythromycin was the most commonly used macrolide antibiotic in the United States. Since 1998, azithromycin has taken the place of erythromycin with more than 30 million prescriptions in the year 2000 (Shaffer and Singer, 2001). Given the widespread use of erythromycin, it should be noted that erythromycin-related arrhythmias are rare in spite of its QT-prolonging potential (Katapadi et al., 1997; Eckardt et al., 1998b). Clarithromycin has a macrolide structure similar to erythromycin and may thus share similar electrophysiological properties and proarrhythmic potential. It is, therefore, not surprising that several cases of clarithromycin-related TdP were reported (Lee et al., 1998; Wasmcr et al., 1999). However, for azithromycin case reports have been extremely rare (Samarendra et al., 2001). Apart from a different prescription behavior this may also reflect different electrophysiological properties of the various macrolide antibiotics. We therefore investigated the electrophysiological effects of erythromycin, clarithromycin, and azithromycin in a previously developed model of TdP (Eckardt et al., 1998b, 2002).

Materials and Methods

Preparation of Hearts for Perfusion. The method has been described previously (Eckardt et al., 1998b, 2002). In summary, male New Zealand White rabbits (n = 37) weighing 2.5 to 3.0 kg were anesthetized with sodium thiopental (200–300 mg i.v.). After mid-sternal incision and opening of the pericardium, the hearts were anesthetized with sodium thiopental (200–300 mg i.v.). After mid-sternal incision and opening of the pericardium, the hearts were removed and immediately placed in an ice-cold Krebs-Henseleit solution (1.80 mM CaCl2, 4.70 mM KCl, 1.18 mM KH2PO4, 0.83 mM MgSO4, 118 mM NaCl, 24.88 mM NaHCO3, 2.0 mM Na-pyruvate, and 5.55 mM d-glucose). The aorta was cannulated, the pulmonary artery was incised, and the spontaneously beating hearts were retrogradely perfused at constant flow (52 ml/min) with warm (36.8–37.2°C) Krebs-Henseleit solution. Perfusion pressure was kept stable at 100 mm Hg. The hearts were placed in a heated, solution-filled tissue bath. After cannulation the hearts were given 10 min to stabilize. The perfusate was equilibrated with 95% O2 and 5% CO2 at 100 mm Hg. The hearts were placed in a heated, solution-filled latex balloon was inserted into the left ventricle and connected to a pressure transducer to control hemodynamic stability. The atrio-ventricular (AV) node was ablated by a surgical tweezers under ECG control to slow the intrinsic heart rate. This resulted in complete AV block and subsequently stored on a removable hard disk (BARD Laboratory, Murray Hill, MA).

Experimental Protocol. After placing the MAP catheters and achieving complete AV block, cycle length dependence was first investigated under baseline conditions. Thereafter, erythromycin, clarithromycin, or azithromycin (150, 200, and 300 μM) were infused. The concentrations for all three macrolides were several multiples higher than the expected free plasma concentrations in patients to create a maximal proarrhythmic milieu and to better study the underlying mechanisms of proarrhythmia. The experimental setup was designed to reproduce conditions and circumstances that are clinically known to be associated with an increased propensity to the development of TdP (Zabel et al., 1997; Eckardt et al., 1998a). Pacing, MAP recording, and measurement of ECG parameters were repeated after drug infusion. Thereafter, the potassium concentration was lowered to 1.5 mM/l to provoke EAD and TdP. Low potassium concentration has been demonstrated to exert additional block of If(Kr), even in the presence of maximal drug-related Ik block (Yang and Roden, 1996). Five minutes later, the potassium concentration was increased to 5.8 mM/l, the drug concentration of the macrolide was thereafter increased to the next dosage, and pacing was repeated. Again, this was followed by lowering the potassium concentration for 5 min. The latter two steps were repeated for each drug concentration.

Because of the different proarrhythmic potential found with erythromycin and clarithromycin compared with azithromycin (see Results), we also tested the effects of azithromycin in hearts (n = 13) that were pretreated with erythromycin. In the presence of erythromycin and azithromycin, the above-described steps of lowering the potassium concentration were repeated.

Dispersion was expressed as the difference between the minimum and the maximum of MAP90 and MAP90 (Zabel et al., 1997). EADs were defined as a positive voltage deflection that interrupted the smooth contour of phase 2 or 3 repolarization of the action potential (Eckardt et al., 1998b, 2002). TdP was defined as a polymorphic ventricular tachyarrhythmia of more than five beats with a changing ventricular axis and spontaneous termination (Dessertenne, 1966).

Data Acquisition and Statistical Analysis. ECG, pressure, volume, and MAPs were recorded on a multichannel recorder. Data were digitized on line at a rate of 1 kHz with 12-bit resolution and stored on a disk. All data are presented as mean ± S.D. The influence of each drug on ECG parameters, and MAP duration, as well as dispersion of repolarization was assessed using Friedmann test. Wilcoxon test was used to investigate cycle length dependence. To compare the three drugs we used the Kruskal-Wallis test and the nonparametric Mann-Whitney U test. To compare the incidence of EAD and TdP, the χ2 test was used.

Results

Dose-Dependent Effects of Macrolide Antibiotics on QT Interval and Action Potential Duration. All electrocardiographic parameters reached equilibrium within 10 min. MAP recordings and pacing thresholds (mean threshold 1.6 ± 1.4 mA) remained highly reproducible throughout the experimental protocol. After an initial stabilization period of approximately 5 to 10 min, the MAP amplitude did not change by more than 20% for the subsequent investigation period. The macrolide antibiotics led to a dose-dependent prolongation of QT interval and MAP duration (p < 0.001)
When azithromycin was administered in the presence of erythromycin, an additional increase in QT interval was observed. Figures 1 and 2 illustrate the dose-dependent effects of macrolide antibiotics on MAP$_{50}$ and MAP$_{90}$. In the presence of 300 μM erythromycin, the increase in MAP$_{90}$ ranged between 14% at a cycle length of 300 ms and 46% at a cycle length of 900 ms. This marked reverse use dependence was also observed with clarithromycin and azithromycin. In the presence of 300 μM clarithromycin, the increase in MAP prolongation ranged between 28% at 300 ms and 45% at 900 ms. With azithromycin, it measured 21% at 300 ms and 46% at 900 ms. For the three drugs, the increase in MAP$_{90}$ was paralleled by a dose-dependent increase in MAP$_{50}$ and QT interval. In accordance to MAP$_{90}$, the increase in MAP$_{50}$ and QT interval was also cycle length-dependent. When azithromycin was administered in the presence of erythromycin, the prolongation of MAP$_{90}$ ranged between 14% at a cycle length of 300 ms and 46% at 900 ms. This marked reverse use dependence was also observed with clarithromycin and azithromycin. In the presence of 300 μM clarithromycin, the increase in MAP prolongation ranged between 28% at 300 ms and 45% at 900 ms. With azithromycin, it measured 21% at 300 ms and 46% at 900 ms. For the three drugs, the increase in MAP$_{90}$ was paralleled by a dose-dependent increase in MAP$_{50}$ and QT interval. In accordance to MAP$_{90}$, the increase in MAP$_{50}$ and QT interval was also cycle length-dependent. When azithromycin was administered in the presence of erythromycin, the prolongation of MAP$_{90}$ ranged between 37% at 300-ms cycle length and 77% at 900-ms cycle length.

Dispersion of Repolarization and Early Afterdepolarizations. All antibiotics led to an increase in MAP$_{50}$ and MAP$_{90}$ dispersion (p < 0.001) with increasing drug concentration (Table 1). In the presence of 300 μM erythromycin, there was a significant 70% increase in interventricular dispersion of MAP$_{90}$. For 300 μM clarithromycin, an increase in dispersion of 145% was observed, whereas 300 μM azithromycin led to an increase of 161% (p < 0.05). In the presence of clarithromycin and especially in erythromycin-treated hearts, EADs and triggered activity were a frequent finding. With erythromycin, all hearts showed MAP recordings with EADs after lowering potassium at a concentration of 300 μM. In the presence of azithromycin, no EAD occurred. In the presence of clarithromycin and erythromycin, TdP was always associated with EADs.

Induction of TdP. After complete AV block and increasing the drug concentration to 300 μM as well as lowering potassium concentration from 5.88 to 1.5 mM/l, TdP occurred in 10 of 13 erythromycin- and clarithromycin-treated rabbit hearts, respectively (Fig. 3). Erythromycin and clarithromycin were found to have a similar proarrhythmic potential (Fig. 3). However, with regard to the number of events of TdP episodes, more episodes were observed in the presence of erythromycin (270) compared with clarithromycin (192) (Fig. 4). Noteworthy, no TdP occurred in the presence of azithromycin despite showing the largest increase in QT interval. Furthermore, azithromycin was found to have an antiarrhythmic potential. When it was administered to 13 hearts that were already treated with erythromycin and had demonstrated TdP, azithromycin suppressed TdP in 7 of 10 hearts.

### Triangular versus Rectangular MAP Configuration.

Azithromycin had a similar effect on MAP$_{50}$ (55 ms mean maximal prolongation) and MAP$_{90}$ (67 ms mean maximal prolongation), which resulted in a ΔMAP$_{90}$/MAP$_{50}$ ratio of 1.22. In contrast, erythromycin showed an MAP$_{50}$ of 29 ms (mean maximal prolongation) and MAP$_{90}$ of 44 ms, which resulted in a ΔMAP$_{90}$/MAP$_{50}$ ratio of 1.52. In the presence of clarithromycin, we observed an MAP$_{50}$ of 33 ms and an MAP$_{90}$ of 73 ms, which resulted in a ΔMAP$_{90}$/MAP$_{50}$ ratio of 2.21 (Table 1). Thus, in erythromycin and clarithromycin, MAP$_{90}$ is markedly lengthened, whereas MAP$_{50}$ is prolonged only moderately, rendering the action potential prolongation triangular. In contrast, azithromycin led to similar prolongation of MAP$_{50}$ and MAP$_{90}$, resulting in a rectangular action potential (Figs. 5 and 6). This is illustrated by significantly different ΔMAP$_{90}$/MAP$_{50}$ ratios (Fig. 7).

### Discussion

The main finding in the present study is that the three macrolide antibiotics erythromycin, clarithromycin, and azithromycin have a different proarrhythmic potential despite similar QT prolongation. The action potential configuration in the presence of the three drugs but not the extent of QT prolongation, nor the increase in dispersion of repolarization, nor different use dependence explained the occurrence of EADs and the different torsadogenic potential. A triangular MAP shape was related to proarrhythmia, whereas a rectangular MAP configuration was not associated with TdP. Moreover, adding azithromycin, which caused a rectangular pattern, to erythromycin, which caused a triangular MAP shape, inhibited previously induced TdP.

Prolongation of action potential duration is considered a

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<th>QT-Interval (ms)</th>
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<th>Disp APD$_{50}$</th>
<th>APD$_{90}$ (ms)</th>
<th>Disp APD$_{90}$</th>
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Disp, dispersion.

| Table 1 Effect of azithromycin, clarithromycin, erythromycin, and the combination of erythromycin and azithromycin on QT-interval, MAP duration, and dispersion of refractoriness
| Data in milliseconds. |
major antiarrhythmic mechanism but paradoxically, it frequently is also proarrhythmic and may induce TdP (Haverkamp et al., 2000). This represents the dilemma in the use of class III antiarrhythmic agents but also a great number of noncardiovascular drugs. The macrolide antibiotics erythromycin, clarithromycin, and azithromycin prolong MAP duration and QT interval. Nevertheless, they have a different torsadogenic potential. In a postmarketing analysis on macrolide antibiotics and TdP, the Food and Drug Administration reported a difference in proarrhythmic potential of macrolide antibiotics in a total number of 156 reported patients. Fifty-three percent of reported TdP occurred in the presence of erythromycin, 36% with clarithromycin-, and only 11% in azithromycin-treated patients (Shaffer and Singer, 2001). Our experimental findings are in agreement with this report. We used a setup that does reproducibly induce TdP in isolated rabbit hearts if \( I_{Kr}\)-blocking drugs such as sotalol are administered (Eckardt et al., 1998b). Using this setup, only two of three macrolides induced TdP. Erythromycin and clarithromycin had a comparable proarrhythmic potential, whereas azithromycin showed no proarrhythmic effects although the QT interval, MAP duration, and dispersion of repolarization were markedly prolonged. Our findings are also in agreement with a study by Ohtani et al. (2000) on the in vivo effects of macrolide antibiotics in rats. They also reported that the arrhythmogenic risk of macrolide antibiotics should be ranked as follows: erythromycin greater than clarithromycin greater than azithromycin.

Our data present evidence that in the presence of noncardiovascular drugs that prolong QT interval, the extent of QT prolongation does not necessarily increase the risk for TdP. Moreover, we demonstrated for the first time that azithromycin suppressed TdP induced by erythromycin. Therefore, QT prolongation alone may not serve as a surrogate marker of cardiotoxicity. Although erythromycin resulted in the smallest increase in MAP duration, it was associated with the highest incidence of TdP. No TdP occurred in the absence of EADs, which have earlier been acknowledged as the most important mechanism underlying TdP in experimental models of TdP (Eckardt et al., 1998a). In the present setting, there was a high incidence of EADs in erythromycin- and clarithromycin-treated rabbit hearts at low levels of extracellular potassium and at slow heart rates, but no EADs occurred in hearts after administration of azithromycin, which resulted in the largest increase in QT and MAP durations. Thus, the occurrence of EADs was not directly related to the degree of QT prolongation. However, EADs were directly linked to the occurrence of proarrhythmia and the lack of EADs with azithromycin corresponded to the lack of TdP with this macrolide antibiotic. EADs are likely to provide the trigger (i.e., premature ectopic beats) that induces proarrhythmia in the presence of the appropriate substrate (i.e., increased dispersion of repolarization, resulting in electrical heterogeneity with nonuniform repolarization and refractoriness) for the initiation and perpetuation of TdP. Triggered activity seems to be the most
probable cause for the appearance of ectopic beats preceding TdP, at least for the first beat in a run of TdP, when EADs reach the critical threshold for activation of a depolarizing current. The subsequent beats may then result from circus movement reentry due to dispersion of repolarization (Habab and el-Sherif, 1990). The manifestation of EADs is usually associated with a critical prolongation of the repolarization phase due to a reduction in net outward current (Antzelevitch and Sicouri, 1994). We demonstrated that different use dependence, or a different increase in dispersion of...
repolarization could not explain the observed different torsadogenic potential. Erythromycin was reported to cause prominent dispersion of repolarization in the canine ventricular wall (Antzelevitch et al., 1996; Fazekas et al., 1998). In addition, Verduyn et al. (1997) found an increased bradycardia-dependent interventricular dispersion in dogs with chronic AV block after adding the \( I_{Kr} \) blocker sotalol, and they proposed that dispersion of repolarization should be added to the relevant factors for the initiation of TdP. In the present study, the increase in dispersion may be associated with TdP but was not sufficient enough to explain the occurrence of TdP.

Possible Mechanisms for Different Proarrhythmic Potential. Our study points out for the first time that the difference in MAP configuration may be the reason for the difference in the proarrhythmic potential of macrolide antibiotics. Erythromycin and clarithromycin mainly prolonged phase 3 of the action potential.

Hondeghem et al. (2001) recently speculated that prolonging phase 3 of the repolarization process can generate EADs by spending too much time in the window voltage for calcium channel reactivation. By prolonging action potential duration within the L-type \( \text{Ca}^{2+} \) "window" voltage range, which occurs in the presence of drugs that block \( I_{Kr} \), EADs and thereby TdP are likely to be generated (January et al., 2000). Thus, we may speculate that erythromycin and clarithromycin may allow enough time in this voltage window by slowing of phase 3 of repolarization. Thereby, one of the main charge carriers may be activated, which may then cause EADs (Volders et al., 2000). The effect of erythromycin to prolong QT interval due to inhibition of \( I_{Kr} \), thus leading to a triangulated MAP has been reported before (Antzelevitch et al., 1996). \( I_{Kr} \) is active in phase 3 of repolarization when \( I_{Ca,L} \) is reactivated. A reduction in \( I_{Kr} \) amplitude by erythromycin prolongs this critical time window so that more calcium can enter the cell and lead to EADs (Rubart et al., 1993). In contrast to erythromycin and clarithromycin, azithromycin produced a rectangular MAP configuration in the present study and therefore led to a late but fast repolarization that may not have allowed enough time for calcium channel reactivation. A possible explanation for the rectangle MAP configuration may be a different interaction of azithromycin with potassium channels compared with erythromycin or clarithromycin. When erythromycin and azithromycin were combined, the effects upon MAP\(_{50}\) and MAP\(_{90}\) seemed additive. The plateau and the repolarization phase were prolonged. However, the larger prolongation of action potential did not lead to more proarrhythmia. Noteworthy, the proarrhythmic effect of erythromycin was attenuated or even blocked by azithromycin. This represents a new and so far unexplainable antiarrhythmic potential of a QT-prolonging agent.

Conclusion

The macrolide antibiotics erythromycin, clarithromycin, and azithromycin prolong myocardial repolarization. Compared with erythromycin and clarithromycin, the torsadogenic potential of azithromycin seems to be remarkably low. In the Langendorff-perfused rabbit heart model of TdP, azithromycin did not display the proarrhythmic profile typical for blockers of \( I_{Kr} \), such as erythromycin or sotalol (Éckardt et al., 1998b). The mechanisms responsible for this behavior of azithromycin are probably multifactorial. Although we demonstrated that the three drugs have similar electrophysiological characteristics such as reverse use de-
pendence and dose-dependent increase in dispersion of repolarization, they presented with a significant different potential to induce EADs and TdP. It is possible that a different mode of interaction between azithromycin and the channel and/or additional pharmacological effects of azithromycin may play a role. Triangulation of the action potential observed in the presence of erythromycin and clarithromycin corresponded to the occurrence to TdP, whereas rectangulation of the action potential due to azithromycin had no proarrhythmic effects and suppressed TdP induced by erythromycin. Thus, azithromycin showed some of the characteristics of what may be considered an ideal antiarrhythmic agent with lengthening of action potential duration but with low risk of proarrhythmia. The present study clearly demonstrated that prolongation of the action potential and QT interval may not necessarily be proarrhythmic. In the absence of triangulation of the action potential it may be safe and not result in proarrhythmia. Further investigation in particular intracellular action potential recordings will be necessary to clarify whether drugs that lead to a rectangle action potential prolongation represent the antiarrhythmic agents of the future.

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References


**Address correspondence to:** Peter Milberg, Universitätsklinikum Münster, Medizinische Klinik und Poliklinik C-Kardiologie und Angiologie, D-48129 Münster, Germany. E-mail: milbergp@uni-muenster.de