REVIEW

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The cardiotoxicity of macrolides: a systematic review

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Objectives: We aimed to evaluate the cardiac safety of macrolides either used alone or co-administered with other agents. *Methods:* Pubmed and Embase databases were searched for the cardiac safety of macrolides in the treatment of infected patients. Identified studies were evaluated by two independent reviewers. Case reports, case series, controlled trials and randomly controlled trials were included. *Results:* A total of 48 reports (18 clinical studies and 30 case reports) were included in the present study. Among these reports, 25 were about macrolides used alone, and 23 about combination therapy. Based on the available data, we found that erythromycin carries the greatest risk of QT prolongation and Tdp from all macrolides in clinical practice (21/48), followed by clarithromycin (12/48) and azithromycin (6/48). Old age, high dosage, rapid administration and cardiac related diseases are additional risk factors. *Conclusions:* Macrolides may induce cardiotoxicity themselves when used alone. When co-administered, they may also increase the risk of other drugs that potentially prolong the QTc interval or induce Tdp. Therefore, early and correct adjustment of the dosage, close daily ECG monitoring and the avoidance of co-administration of other known QT-prolonging agents should be used in order to prevent the development of adverse effects.

1. Introduction

Macrolides are one of the most effective antibiotics for the treatment of mild-to-moderate infections, and they are largely considered free of serious toxicity. Common adverse effects associated with macrolides (such as nausea and diarrhea) are usually mild and require no discontinuation of therapy. However, QT prolongation has been reported in macrolide-treated patients. The QT interval is a measure of the time from the earliest activation of the ventricular myocardium to the latest ventricular repolarization. QT prolongation is caused by blocking the rapid component (IKr) on the delayed rectifier potassium current on cell membrane of the cardiac myocytes. It is associated with the risk of triggering a particular arrhythmia. This major cardiac adverse effect may lead to malignant polymorphic ventricular tachycardias, termed Torsades De Pointes (Tdp), which may degenerate into ventricular fibrillation and cause sudden death.

Some macrolides (e.g., erythromycin, clarithromycin, azithromycin, and telithromycin) sometimes induce QT prolongation when used alone. Another common mechanism of macrolide-induced QT prolongation is the potential effects of macrolides that decreases the metabolism of other QTc-prolonging drugs at high concentrations (e.g., terfenadine) as a result of inhibition of cytochrome P450 enzymes. Although there are some reports about prolonged QT intervals and Tdp among patients concurrently receiving macrolides and other QTc-prolonging drugs, the clinical importance of this possible drug-drug interaction remains unclear.

Thus, we systematically reviewed the available data on human studies, regarding the cardiac safety of macrolides for various infections either used alone or in combination with other agents.

2. Methods

2.1. Data sources

Data were obtained through literature search from PubMed and EMBASE from January 1990 to March 2009. A literature search was performed by terms including 'proarrhythmia', 'QT prolongation', 'Torsades De. Pointes' or 'Tdp', 'erythromycin', 'azithromycin', 'clarithromycin', 'roxithromycin', 'telithromycin', 'spiramycin' and 'dirithromycin' as well as the combinations of these terms. Relevant publications in English as well as references from relevant studies and reviews were identified.

2.2. Study selection and data extraction

First, studies reporting clinical adverse effects of macrolides on cardiac conduction system were considered potentially eligible for our systematic review. Second, the reviews or studies using experimental animal models were excluded. Third, studies without providing exact data were also excluded. Thus, our study only included only the clinical trials and case reports that mainly discussed the adverse effects of macrolides.

3. Results and discussion

Using the above-mentioned method, we found 780 potentially relevant articles. The Fig. shows that with our inclusion criteria 18 clinical studies and 30 case reports were identified for further evaluation. In particular, most of the controlled studies were designed for studying the drug interactions between macrolides and other antimicrobial agents, which may induce QT prolongation. Furthermore, Table 1 shows the available data from published studies, including the randomly controlled studies and case studies reporting the incidence of cardiac toxicity (such as QT prolongation, arrhythmia and Tdp). Moreover, studies about the interactions between macrolides and other QTc-prolonging drugs were also included (Table 2).

Table 1: Data from published studies including RCTS and case studies examining the cardiac adverse effects of different macrolides

Medication	Reference	study design	No.	Year/sex	Basic disease	Dosage	Control	Effect on QTc and Episodes of Tdp	control
Erythromycin	Mishra et al. (1999)	Prospective, comparative drug study	19	21–86y 6M, 13F	CAP	Erythromycin: IV500 mg,	cefuroxime, iV 750 mg	QTc pro and heart rate increased. Then stopped 5 min. after the infusion	no effects
	Kneen et al. (1998)	Randomized, open-label study	90	Vietnamese children/ N. A.	diphtheria	Erythromycin 50mg/[kg·d]	benzylpenicillin, 50, 000 U/[kg·d] for 5d then oral penicillin, 50 mg/[kg ·d] for 5d	N. S.	no effects
	Kdesh (1999)	Clinical study	63	21–92 28M, 35F	CAP	Cumulative dose: 3. 2 +/- 0. 2 g	N. C.	QTc pro 68%	N. C.
	Brixius et al. (1999)	Case report	1	newborn	congenital complete av-block	N. A.	N. C.	QTc pro and developed Tdp	N. C.
	Lengyel et al. (1997)	Case report	1	N. A.	N. A.	Erythromycin: orally 1. 5 g/day	N. C.	QTc pro and developed Tdp	N. C.
	Oberg et al. (1995)	Cases analyse	49		N. A. All received intravenous erythromycin lactobionate during a 1-year period	Erythromycin: 18-83(42+/–18) mg/kg/day	N. C.	QTc pro	N. C.
	Rezkalla and Pochop (1994)	Case report	1	82/F	Bilateral pneumonia	N. A.	N. C.	QTc pro and developed Tdp	N. C.
	Orban et al. (1995)	Case report	1	32/F	Systemiclupus erythematosus, insulindependent diabetes mcllitus, and renaal transplant with chronic rejection presented with ritght lower lobepneumonia	Erythromycin: 1g administered intravenously every 6 hours in normal saline solution as an infusion entended to last 30 to 60 minutes	N. C.	QTc pro and developed Tdp	N. C.
	Brandriss et al. (1994)	Case report	1	N. A.	N. A.	N. A.	N. C.	QTc pro and developed Tdp	N. C.
	Benoit et al. (1991)	Case report	1	8 day-old newborn	N. A.	Erythromycin: 5 injections	N. C.	QTc pro and developed Tdp and an atrioventricular block	N. C.
	Schoenenbergerr (1990)	Case report	1	61/F	fever, pneumonia, and severe respiratory distress	Erythromycin: 1g three times daily infused in saline over 90 minutes	N. C.	QTc pro and developed Tdp	N. C.

Clarithromycin	Germanakis et al. (2006)	Clinical trial	28	Children/ N. A.	respiratory tract infections	Clarithromycin 15 mg/kg/d	N. C.	QTc pro but no Tdp	N. C.
	Hensey and Keane (2008)	Case report	1	79/F	hypertension and a congenitally long QT	N. A.	N. C.	Developed complete heart block and the episodes of Tdp	N. C.
	Kamochi et al. (1999)	Cases report	2	(1)78/F (2) 62/M	1. Respiratory disease 2. Idiopathic interstitial pneumonia and chronic hepatitis C	Clarithromycin 400 mg/d	N. C.	QT prolongation and Tdp	N. C.
Azithromycin	Strle and Maraspin (2002)	A prospective study	47	19–77y, 31M, 16F	typical solitary erythema	Azithromycin: 600 mg/d for 5d	N. C.	N. S.	N. C.
	Kezerashvili et al. (2007)	Case report	1	55/F	Staphylococcus aureus infection	Azithromycin: 500 mg/d for 7d	N. C.	QTc pro and developed Tdp	N. C.
	Huang et al. (2007)	Case report	1	90/F	hypertension and an old cerebrovascular accident	Azithromycin: 500 mg/d for 1d	N. C.	QTc pro and developed Tdp	N. C.
	Russo et al. (2006)	Case report	1	65/M	CAP	Azithromycin: 0. 5g followed by oral 0. 25 g daily	N. C.	QTc pro but no Tdp	N. C.
	Tilelli et al. (2006)	Case report	1	9-month infant	Weighted 9. 2 Kg	Azithromycin 50 mg/Kg	N. C.	QTc pro, Started a widecomplex bradycardia and complete heart block	N. C.
Telithromycin	Demolis et al. (2003)	Double-blind randomized crossover place-controlled study	34	20–34, 17M, 17F	healthy	1. Teilithromycin: 800mg twice daily 2. Teilithromycin 800mg/1600mg/2400mg	placebo	1. N. S. 2. N. S.	no effects
Roxithromycin	Justo et al. (2003)	Case report	1	N. A.		N. A.	N. C.	QTc pro and developed Tdp	N. C.
	Promphan et al. (2003)	Case report	1	6/girl	congenital complete hear block and cyanotic heart disease	Roxithromycin 10 mg/kg/d	N. C.	QTc pro and developed Tdp	
	Keskin et al. (2005)	Case report	1	N. A.		N. A.	N. C.	QTc pro and developed Tdp	N. C.
	Woywodt et al. (2000)	Case report		72/ M	three vessel coronary heart disease with moderately impaired left ventricular function	Roxithromycin 150 mg twice a day	N. C.	QTc pro and congestive heart failure caused by ischaemic heart disease	N. C.
Spiramycin	Stramba-Badiale et al. (1997)	Controlled clinical study	16	1. 8 newborn infants 2. Control: 8 newborn infants	1. Toxoplasmosis 2. Control:healthy	Spiramycin: 350, 000 i. U. /kg/ day	no drugs	QTc pro, QTc dispersion increased, cardiac arrest;thickening of the left ventricular posterior wall	no effects

Table 2: Data from published studies including RCTS and case studies examining the pharmacodynamic interactions between macrolides and other QTc-prolonging drugs (co-administration)

Medication	Reference	study design	NO	Year/sex/Basic disease	Dosage	Coadministration dosage	Control	Pharmacodynamic interactions		QTc and Episodes of Tdp	
								Macrolides	Control	Macrolides	Control
Erythromycin	Banfield et al. (2002)	Prospective, comparative Drug study	24	19–46/12M,12F healthy,	Erythromycin: 500mg/8h for 10 d	Desloratadine 7.5mg daily for 10d	Placebo+ Desloratadine	Increased in the Cmax of desloratadine	no effects	N. S.	no effects
	Pesco-Koplowitz et al. (1999)	Randomized, open-label study	38	18–45/M. healthy	Erythromycin: 333mg	Levocabasine two sprays per nostril(0. 05 mg/spray)	Placebo+ Levocabasine	N. S.	no effects	N. S.	no effects
	Katoh et al. (2003)	Clinical trial	10	N.A./M healthy	Erythromycin: 1200 mg/d for 7d	Mosapride: 15mg/d for7 d	N. C.	Increased in the Cmax of mosapride	N. C.	N. S.	N. C
	Honig et al. (1992)	Clinical trial	9	N. A.	Erythromycin: 500 mg /8 h for 7d	Terfenadine: 60 mg/12 h for 7d	N. C.	Increased in the Cmax and metabolite area under the concentration-time curve of Terfenadine	N. C.	QT prolongation but no Tdp	N. C.
	Kyrmizakis et al. (2002)	Case report	1	47/M	Erythromycin: 500 mg	Cisapride	N. C.	N. A.	N. C.	QT prolongation, and develop Tdp	N. C.
	Koh (2001)	Case report	1	75/F mild mitral stenosis	Erythromycin: 250 mg 4times/d for 7 d	Carbimazole on long-term	N. C.	Increased in Serum magnesium Was	N. C.	QT prolongation and develop Tdp	N. C.
	Goldschmidt et al. (2001)	Case report	1	79/F	Erythromycin: 2000mg/d	Verapamil 480 mg/d	N. C.	Both increased in the Cmax of erythromycin and Verapamil	N. C.	left ventricular hypertrophy, and possibly ischemic heart disease	N. C.
	Lin and Quasny (1997)	Case report	1	95/ M atrial fibrillation and CAP	N. A.	Quinidine	N. C.	N. A.	N. C.	Developed Tdp and subsequently cardiac arrest	N. C.
	Chennareddy (1997)	Case report	1	12/ Boy	N. A.	Terfenadine	N. C.	N. A.	N. C.	QT prolongation, and developed Tdp	N. C.
	Hsieh et al. (1996)	Case report	1	30/F congenital Prolongation of QTc interval	Erythromycin: 250mg/12h for 3 d	Astemizole 10mg/12h for 3 d	N. C.	Analysis of urine astemizole showed continuously positive for 10	N. C.	QT prolongation, and develop Tdp	N. C.

Table 2: (*Continued*)

Medication	Reference	study design	NO	Year/sex/Basic disease	Dosage	Coadministration dosage	Control	Pharmacodynamic interactions		QTc and Episodes of Tdp	
								Macrolides	Control	Macrolides	Control
Clarithromycin	Shi et al. (2005)	Randomized, open-label clinical trial	32	≥60/ N. A. renal impairment who were medically stable and CLCR > 30 ml/Min.	Clarithromycin: 500 mg twice daily for 5 d	Ketoconazole 400 mg once daily for 5 d	Placebo+ Ketoconazole	Increased in the Cmax, ss and AUC(0-24h)ss of clarithromycin	no effects	QT prolongation, but no Tdp	no effects
	Desta et al. (1999)	Double-blind, randomised placebo-controlled crossover study	12	22–47/7M 5F Healthy	Clarithromycin: 500 mg twice daily for 5 d	Pimozide a single 6-mg orally after clarithromycin	Placebo+ Pimozide	Increased in the Cmax and decrease in the clearance of pimozide	no effects	QT prolongation: 23. 8 +/- 12. 2 ms	QT prolonga-tion: 16. 8 +/- 6 ms
	VanHaarst et al. (1998)	Randomized, open-label two-treament period Crossover study	12	19–31/ N. A. healthy	Clarithromycin: 500 mg twice a day from day 6 through 10	Cisapride 10 mg 4 times/d for 10 d	Cisapride alone	Increased in the Cmax of cisapride	no effects	QT prolongation of 25 ms,	QT pro-longation of 6 ms
	Carr et al. (1998)	Randomized crossover design	24	23–40 healthy	Clarithromycin: 500 mg orally every 12h for 10 d	Loratadine 10 mg orally every 24h for 10d	Loratadine alone	Increased in the steady-state Cmax: and AUC0-24 central values of loratadine	no effects	N. S.	N. S.
	Choudhury et al. (1999)	Case report	1	76/F chronic bronchitis	Clarithromycin: 250 mg twice daily for 5d	Disopyramide for long-term150 mg twice daily since 1980	N. C.	Increased in the concentration of disopyramid	N. C.	QT prolongation, and develop Tdp	N. C.
	Piquette (1999)	Case report	1	77/F pneumonia and exacerbation of congestive heart failure	Clarithromycin: 500 mg/d	Cisapride 10mg/d	N. C.	increase in the Cmax of Cisapride	N. C.	symptomatic Tdp, arrhythmia	N. C.
	Iida et al. (1999)	Case report	1	59/ M	Clarithromycin: 600 mg/d	Disopyramide: 50 mg/d since 1987	N. C.	Increase in the serum concentration of disopyramide	N. C.	QT prolongation and no Tdp	N. C.
	Hayashi et al. (1999)	Case report	1	76/F had a history of myocardial infarction 5 years earlier	Clarithromycin: 200 mg twice one day	Disopyramide 100 mg three times a day for 5 years	N. C.	Increase in plasma concentration of disopyramid	N. C.	QT prolongation, and develop Tdp	N. C.

Table 2: (*Continued*)

Medication	Reference	study design	NO	Year/sex/Basic disease	Dosage	Coadministration dosage	Control	Pharmacodynamic interactions		QTc and Episodes of Tdp	
								Macrolides	Control	Macrolides	Control
clarithromycin	Sekkarie (1997)	Case report	2	52/ F chronic renal failure	Clarithromycin: 500 mg twice daily for 4 d	Cisapride 10 mg three times daily for long-term	N. C.	Increase in plasma concentration of cisaprode	N. C.	QT prolongation and develop Tdp	N. C.
				83/M chronic renal failure	Clarithromycin: 500 mg twice daily for 9 d	Cisapride 10 mg twice daily for long-term					
Azithromycin	Gupta et al. (2001)	Third part-blind, randomised placebo-controlled parallel-Group trial	18	19–46/ N. A. healthy subjects	Azithromycin: (day3): two 250-mg capsule (day4-7): 250-mg once daily	1Desloratadin 2Fexofenadine 5 mg/d for 7 d	Placebo+ desloratadine Or fexofenadine	1. N. S. 2. Increased in the Cmax and the AUC of desloratadine	no effects	1. N. S. 2. N. S.	no effects
Telithromycin	Shi et al. (2005)	Randomized, open-label,clinical trial	32	≥60/ N. A. renal impairment who were medically stable and CLCR > 30 ml/Min.	Telithromycin: 800 mg once daily for 5 d	Ketoconazole 400 mg once daily for 5 d	Placebo+ telithromycin	Increases in the Cmax, ss and AUC0-24, ss of telithromycin	no effects	N. S.	no effects
	Demolis et al. (2005)	Double-blind, randomized, two period, crossover place-controlled study	24	19–36/F healthy subjects	Telithromycin: a single does: 800mg	Sotalol a single does: 169 mg	Placebo+ sotalol	Decreased in the Cmax, aUC0-24 and AUC0-inf: of sotalol 34%, 27%, 20%, respectively	no effects	The QTc max interval mean difference, -15. 5 ms	
Spiramycin	Verdun et al. (1997)	Case report	1	21/F congenital long QT syndrome	N. A.	Mequitazine	N. C.	N. A.	N. C.	QT prolongation, and develop Tdp	N. C.
Dirithromycin	Bachmann et al. (1997)	Randomized two-way crossover placebo-controlled study	18	21–36/ N. A. healthy subjects	Dirithromycin: 500 mg every morning for 10 d	Astemizole 30mg on day 4	Placeo+ Astemizole (oral)	Astemizole CL: slower, volume of distribu-tion:larger and half-life: longer	no effects	N. S.	no effects

IT, intrathecal; IV, intravenous; IU, international units; N. A., not available date; N. C., no control; N. S., no significant effects; F, female; M, male; QT pro, QT prolongation; Tdp, Torsade de pointes; CAP, community-acquired pneumonia;

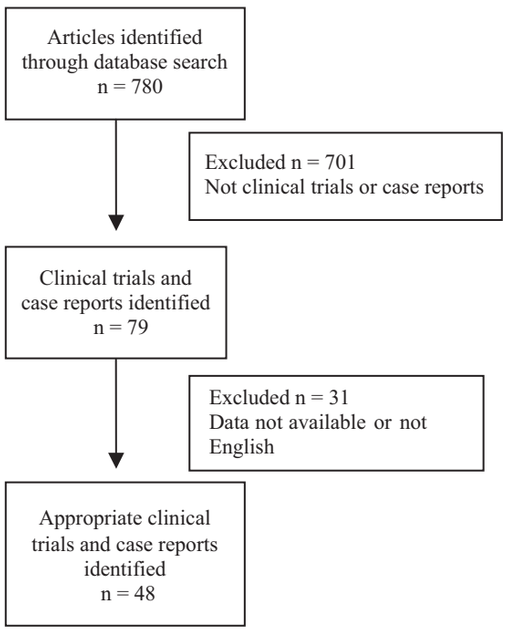

Fig.: Retrieval and selection of clinical studies and case reports included in the systematic review

The QTc interval is one of the normal cardiac cycles that have clinical significance in a surface ECG. The upper limit of a normal QTc interval is 470 ms in females and 480 ms in males, respectively. The length of the QTc interval is inversely correlated with the heart rate. The surface 12 lead ECG represents the electrical summation of the currents in all cell membrane of the cardiac myocytes. The cell membrane of myocytes is polarized with a resting electrical potential of −90 mV, and the repolarization comes from the outward movement of potassium ions from the cytosol of myocyte to the extracellular fluid. This movement is accomplished through specific potassium ion channels in the cell membrane. Each of these potassium channels is strictly regulated, and mutations in these channels are responsible for congenital long QTc syndromes (Iannini 2002). Macrolides prolong the QTc interval by blocking the rapid component (IKr) on the delayed rectifier potassium current. IKr is encoded by human ether-a-go-go-related gene (hERG), and inhibition of this gene delays cardiac repolarization by blocking the outward flow of potassium ions from myocytes. At the final phase of repolarization, early-after-depolarization (EAD) often occurs as a result of QTc interval prolongation. Subsequently, it induces a ventricular arrhythmia, called 'Tdp', which may cause ventricular fibrillation, cardiac arrest and even sudden death. Therefore, in order to reduce the risk of death during treatments, predicting the potential of QT prolongation is important for clinical physician. Our data from published studies, including RCTS and case reports, suggest that erythromycin has the greatest cardiac risk of the macrolide class, followed by clarithromycin, azithromycin and telithromycin. Meanwhile, roxithromycin, spriramycin and dirithromycin are also reported to be associated with cardiac adverse effects, although with a lower risk of QT prolongation.

3.1. Erythromycin

Erythromycin has the greatest cardiac risk among the macrolides. It prolongs cardiac re-polarization, and its effect resembles that of a class III antiarrhythmic drug. Erythromycin can affect ECG and produce arrhythmia through various direct and indirect actions. Here we found three clinical studies and seven case reports about the QT prolongation induced by erythromycin. A prospective study (Mishra 1999) demonstrates that a single dose of IV erythromycin, which is used on 19 patients with community-acquired pneumonia, prolongs the rate-normalized QTc interval. The prolongation of QTc interval becomes significant at 15 min. after erythromycin treatment, from the mean value of base line: 411 ± 7 ms to 431 ± 8 ms, and it is no longer evident 5 min. after infusion termination. Although the changes are small, they are statistically significant. In a randomized clinical trial, Kneen et al. (1998) examined the effects of erythromycin and showed that only one of 42 erythromycin-treated patients develops prolonged QTc (> 0.44 s) during the treatment. However, they found that the QTc of all patients during treatment and convalescent period is longer than that at the beginning of admission, the median QTc is 0.42 s, 0.42 s and 0.39 s, respectively. Another clinical study by Kdesh et al. (1999) shows abnormal electrocardiograms and QT prolongation. In 27 patients who received erythromycin for 3 days intravenously, the QTc increases from 427 ± 5 ms to 461 ± 8 ms during 24 h, but the QTc shows no further increase by day 3 (457 ± 10 ms). None of patients in these three studies developed Tdp. Oberg et al. (1995) retrospectively studied 278 erythromycin-treated patients. For 49 patients electrocardiograms were available, which allowed comparing QTc before and during erythromycin therapy. The mean QTc was significantly increased after erythromycin therapy (489 ms *vs.* 432 ms). In addition, this tendency is significantly greater in patients with preexisting heart disease.

These data show that prolongation of the QTc interval commonly occurs in patients who intravenously received erythromycin, while Tdp rarely occurs. However, seven case reports show that Tdp is associated with erythromycin even when erythromycin is administered alone and at high doses (Benoit et al. 1991; Brandriss et al. 1994; Brixius et al. 1999; Lengyel et al. 1997; Orban et al. 1995; Rezkalla et al. 1994; Schoenenberger et al. 1990), or co-administered with other agents, suggesting that it increases the risk of sudden death from cardiac causes (Chennareddy et al. 1996; Goldschmidt et al. 2001; Honig et al. 1992; Hsieh et al. 1996; Koh et al. 2001; Kyrmizakis et al. 2002; Lin et al. 1997). Notably, the prolonged QTc interval attributed to erythromycin is typically associated with rapid infusion rates in excess of 10 mg/min. (Haefeli et al. 1992). Another clinical study indicates that the extent of QT prolongation is significantly correlated with the infusion rate (mg/min, $r = 0.765$, $p = 0.05$) in critically ill patients (Camilleri et al. 1989). In conclusion, rapid intravenous injection of erythromycin is a possible cause of QT prolongation, which potentially induces life-threatening ventricular arrhythmia. In order to avoid this, a low infusion rate and close cardiac rhythm monitoring should be used in erythromycin treatment.

3.2. Clarithromycin

Clarithromycin is a macrolide antibiotic, which possesses an improved antimicrobial spectrum and side-effect profile compared with erythromycin. A clinical trial by Germanakis et al. (2006) shows the effect of clarithromycin on the QTc interval in a group of 28 children treated for respiratory tract infections. QTc was measured before and during 24 h of treatment. They observed a modest (average 22 ms, 95% CI 14–30 ms) but significant QT prolongation ($p < 0.001$), and seven cases with a QTc > 440 ms during treatment (including a single case with QTc > 460 ms).

Tdp is known to be related to erythromycin. However, its association with clarithromycin has not frequently been reported, and the precise mechanism of clarithromycin-induced TdP remains unclear. It may be similar to erythromycin-induced TdP as

previously described. Here we found two reports including three cases of clarithromycin-associated TdP in the absence of other drugs, which are known to produce QT prolongation. Hensey and Keane (2008) reported about a 79-year-old lady with frequent episodes of Tdp following commencement of clarithromycin. The QT interval was markedly increased (usually to 600 ms or greater). Kamochi et al. (1999) demonstrated two cases of clarithromycin-induced Tdp. One is about a 78-year-old female, taking 400 mg/d of clarithromycin for respiratory infection. A 12-lead electrocardiogram at the time of admission showed a marked QT prolongation (0.52 s) and a mean heart rate of 95 bpm; 1 h later, the patient became unconscious with the development of Tdp. Another case was a 62-year-old male with idiopathic interstitial pneumonia, who was treated with 400 mg/d of clarithromycin. The heart monitor shows that he had non-sustained episodes of TdP, and an ECG showed a normal sinus rhythm with QT interval prolongation (0.56 s). After clarithromycin treatment was terminated, the ECG became normal.

Taken together, although Tdp is rarely reported in clarithromycin therapy, one should be cautious when prescribing it, especially for the elderly. ECGs mornitoring is also important in the follow-up of patients.

3.3. Azithromycin

Azithromycin is a macrolide antibiotic derived from erythromycin. It is an effective agent against pneumonia and has a better safety profile than other macrolides. Reports of azithromycin-induced QT prolongation are limited.

We found four reports plus one study of QT prolongation induced by azithromycin alone. In a prospective study, Strle and Maraspin (2002) described a modest QTc interval prolongation after a course of azithromycin administered for 47 subjects with typical solitary erythema. Comparison with the QTc interval before azithromycin administration, 7 days and 14 days after the azithromycin treatment revealed a mild but not significant prolongation (median values 406, 412.5 and 419 ms with ranges of 339–488, 352–510, and 346–505 ms, respectively). Kezerashvili et al. (2007) studied the incidence of Tdp followed by QT prolongation, and reported a case of QT prolongation and Tdp associated with the use of azithromycin in a 55-year-old woman without any other known factors. Two ECGs on the day before and after the episode were recorded with heart rates of 55 and 53 bpm and QT/QTc intervals of 620/580 and 640/610 ms, respectively. There were no further episodes of Tdp when azithromycin was discontinued. Huang et al. (2007) report that a 90-year-old woman with hypertension and an old cerebrovascular accident had a significant typical QT prolongation and Tdp within a few hours after taking azithromycin. However Russo et al. (2006) described a case of significant QT prolongation without Tdp associated with the use of azithromycin in the absence of other QTc-prolonging drugs, which occurs in a patient with pre-existing dilated cardiomyopathy. Moreover, a study by Tilelli et al. (2006) reports that overdose and rapid infusion of azithromycin was followed by a life-threatening arrhythmia in a 9-month infant.

In conclusion, although high serum levels of azithromycin induce QT prolongation, azithromycin has less proarrhythmic potential than erythromycin or clarithromycin. According to Milberg et al. (2002), azithromycin exhibits different interference mechanisms with the repolarization and has a different incidence of Tdp, though it has a similar increase in the QTc interval and monophasic action potential duration in Langendoff-perfused rabbit heats. Erythromycin and clarithromycin lead to EAD and TdP after lowering the potassium concentration. However, EAD or TdP occurs rarely in the presence of azithromycin.

3.4. Telithromycin

Telithromycin belongs to the class of ketolides, which represent a novel drug in addition to the macrolide lincosamide-streptogramin B class of antimicrobials. Demolis et al. (2003) examined the effect of oral doses of telithromycin on the duration of QTc intervals in healthy subjects at the time of expected maximal plasma concentration, and they also assessed the safety and tolerability of different doses of telithromycin and the relationship between the possible QT interval prolongation and its plasma concentration. The results show that telithromycin administered as repeated doses of 800 mg (recommended doses) or as single dose up to three times of this recommended dose does not increase the QTc interval at any heart rate. Telithromycin does not prolong the QT-interval when administered to healthy young male and female subjects. Moreover, we found no case report showing significant QT prolongation and Tdp after telithromycin administration. Therefore, telithromycin is considered to be at a lower risk on cardiac effect compared with other common macrolides.

3.5. Others

Roxithromycin is a macrolide, which is also widely used. Roxithromycin-induced QTc interval prolongation without TdP has been reported (Malcolm 2000). However, it also has the potential to cause Tdp (Justo et al. 2004; Promphan et al. 2003), especially in patients with other risk factors, such as complete AV block and complex heart disease, which may prolong QTc interval and cause TdP. In addition, some other macrolides, such as spiramycin (Stramba-Badiale et al. 1997), also prolong the QTc interval.

3.6. Drug interactions

As shown in Table 2, about half of the 48 reports show that macrolide use is correlated with concomitant administration of drugs that prolong the QTc interval. The propensity of macrolides to inhibit the metabolism of other drugs may prolong the QTc interval at high concentrations, which may be due to the inhibition of cytochrome P450 enzymes. A study by Ray et al. (2004) shows that in the presence of some macrolides, an inactive cytochrome P450 complex is formed. Therefore, macrolides can increase the steady-state concentration of drugs, and this effect is primarily dependent upon CYP3A metabolism. This result can be clinically significant for drugs with a narrow therapeutic index. Notably, antihistamine, arrhythmia agents and agents for gastrointestinal system disorders account for the majority of contraindicated drug interactions. Moreover, 18 of 24 studies show that the concomitant use of these three types of drugs prolong the QTc interval. Table 2 and Table 3 show the main outcome.

Erythromycin use is mentioned in 41.7% of all reports, and the cases and studies (Banfield et al. 2002; Chennareddy et al. 1996; Goldschmidt et al. 2001; Honig et al. 1992; Hsieh et al. 1996; Katoh et al. 2003; Koh 2001; Kyrmizakis et al. 2002; Lin and Quasny 1997; Pesco-Koplowitz et al. 1999) have highlighted a previously undescribed drug interaction and emphasized the importance of predisposing factors in Tdp induced by drug co-administration.

Table 3: Concomitant administration of drugs that induce QTc interval prolongation and Tdp

Concomitant drug	Reports	Ratio
Antihistamine agents	7	29. 2%
Arrhythmia agents	6	25%
Agents for gastrointestinal system	5	20. 8%
Antipsychotic agents	1	4. 2%
Others	5	20. 8%
Total	24	100%

Clarithromycin use is mentioned in 37.5% of all the reports. Several cases describe the co-administration between clarithromycin and ketoconazole (Shi et al. 2005), pimozide (Desta et al. 1999), cisapride (Piquette 1999; van Haarst et al. 1998), loratadine (Carr et al. 1998) and disopyramide (Choudhury et al. 1999; Hayashi et al. 1999; Iida et al. 1999). Additionally, TdP associated with azithromycin use is rarely reported. Gupta et al. (2001) accessed the effects of co-administration of desloratadine or fexofenadine with azithromycin. However, no significant cardiac effects were observed, because azithromycin is not often believed to inhibit hepatic metabolism (Rubinstein 2001).
In addition, potent inhibitors of CYP3A (e.g., omeprazole) may also alter the metabolism of erythromycin and clarithromycin, because they are extensively metabolized by cytochrome P-450 3A isozymes. Commonly used medications, which inhibit the effects of CYP3A, may increase plasma erythromycin/clarithromycin concentration, thereby increasing the risk of ventricular arrhythmias and sudden death. However, we found no report.

4. Conclusion

Data from recent literature suggest that the incidence of QT prolongation and Tdp resulting from the use of macrolides is mainly due to two factors: (1) the cardiac side effects induced by macrolides themselves when used alone; (2) co-administration of macrolides with other drugs that has the potential to prolong the QTc interval or induce Tdp. Old age, high dosage, fast administration and cardiac related diseases are also risk factors. Alarmed by this life-threatening adverse effect of macrolides use, prescription should be made with great caution, especially for patients with multiple risk factors for arrhythmia. To help prevent the development of adverse effects, several steps should be considered: early and correct adjustment of the macrolides dosage in the presence of impaired cardiac function, close daily ECG monitoring, and the avoidance of concurrent administration of other known QT-prolonging agents. If possible, less cardiac toxicity macrolides (e.g., azithromycin) are recommended. However, most of our data come from cases reports. In order to assess the safety profile of macrolides and to clarify drug-drug interactions more accurately, further large-scale studies are required.

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