

The cardiotoxicity of macrolides: the role of interactions

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Drug-induced long QT syndrome (LQTS) is characterized by prolongation of the QT interval and the risk of syncope and sudden cardiac death due to torsades de pointes (TdP) ventricular tachycardia upon exposure to certain antiarrhythmic and non-cardiovascular drug therapy. Most of the drugs responsible for LQTS can also block the rapid delayed rectifier K⁺ current, I_{Kr}, in ventricular cardiomyocytes. The present review addresses the intrinsic proarrhythmogenic effect of macrolides and the role of interactions in their cardiotoxicity. Among macrolides, erythromycin and clarithromycin have the greatest potential for causing QT interval prolongation and TdP. Furthermore, macrolides can potentiate cardiotoxicity of other proarrhythmic agents applied concomitantly due to drug interactions. Pharmacodynamic interactions occur when macrolides are coadministered with other drugs with I_{Kr} blocking potential. On the other hand, pharmacokinetic interactions of macrolides arising from inhibition of cytochrome P450 3A4 (CYP3A4) isoenzyme and/or P-glycoprotein transport system may also increase the risk of cardiotoxicity. The awareness of this potentially lethal side effect of macrolide antibiotics is fundamental for health professionals. Simultaneous therapy with macrolides and other QT interval prolonging drugs, especially those metabolized by CYP3A4, should be avoided.

Keywords macrolides; proarrhythmia

1. Introduction

Proarrhythmia, the development of new or aggravation of pre-existing arrhythmias precipitated by drug therapy constitutes a major clinical problem. A drug-induced or drug-aggravated cardiac arrhythmia may evolve as a dreadful side effect related to the administration of some antiarrhythmic drugs, as well as drugs for other indications. The most common and problematic form of proarrhythmia is drug-induced long QT syndrome (LQTS) and as a consequence, a malignant polymorphic ventricular dysrhythmia called torsades de pointes (TdP) [1]. The QT interval represents the duration of ventricular depolarization and repolarization. It is measured from the beginning of the QRS complex to the end of the T wave in the surface ECG. The QT interval is heart rate dependent, therefore correction to heart rate is needed. There are a number of different correction methods, the most widely used is Bazett's formula: $QTc = QT / \sqrt{RR}$, where QTc is the corrected QT interval and RR is the time in seconds between two R waves [2]. A corrected QT interval (QTc) of ≥ 440 ms is considered prolonged but TdP usually occurs at values of 500 ms or more [3]. TdP is a polymorphic form of ventricular tachycardia characterized by progressively and more or less regularly waxing and waning amplitude during attacks and QT interval prolongation between attacks (Figure 1). Mechanisms associated with TdP are heterogeneous prolongation of repolarization, leading to early afterdepolarizations mainly in M (midmyocardial) cells and Purkinje cells, and initiation or maintenance of ventricular tachyarrhythmias due to intramural reentry pathways [4]. Well-known features of LQTS are dragging ventricular repolarization, which reveals itself as a prolonged QT interval on the surface ECG, and high risk of TdP or ventricular fibrillation.

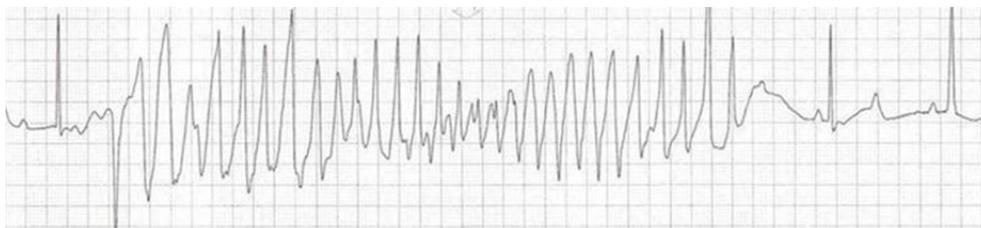


Fig. 1 Torsades de pointes associated with third degree atrioventricular block.

LQTS can be either idiopathic (congenital) or acquired. To date, more than ten different types of congenital LQTS associated with gene mutations of pore forming (α) or regulatory (β) subunits of cardiac ion channels or channel interacting proteins, have been identified. As a consequence, the duration of repolarization is prolonged due to increasing inward currents or decreasing outward currents. Though many different clinical conditions (including electrolyte disturbances, subarachnoid hemorrhage, complete heart block, and acute myocardial infarction) may be associated with acquired LQTS, it occurs most frequently as a potentially fatal side effect of type IA and type III

antiarrhythmic agents and several other drugs (antihistamines, antipsychotics, antimicrobials etc.) as presented in Table 1. While congenital LQTS can be associated with mutations of different cardiac ion channels, virtually all drugs responsible for acquired LQTS block the rapid delayed rectifier K^+ current, I_{Kr} . I_{Kr} is carried by $K_v11.1$ (sometimes simply denoted as HERG) channel protein coded by the human ether-a-go-go-related gene HERG (now termed $KCNH2$) [5].

Table 1 Drugs that prolong the QT interval and have a risk of TdP [1-3].

Antiarrhythmic agents	Type IA	quinidine, disopyramide, procainamide, ajmaline
	Type IC	flecainide, encainide
	Type III	sotalol, amiodarone, dronedarone, dofetilide, ibutilide, bretylium, almokalant, azimilide, tedisamil
Calcium channel inhibitors		prenylamine (withdrawn), terodiline (withdrawn), bepridil (withdrawn)
Neuroleptics	conventional antipsychotics	haloperidol, droperidol, thioridazine, chlorpromazine, pimozide
	atypical antipsychotics	sertindole (withdrawn), ziprasidone, quetiapine, risperidone
Antidepressants	tri- and tetracyclic antidepressants	amitryptiline, nortryptiline, imipramine, desipramine, clomipramine, maprotiline, doxepin
	selective serotonin reuptake inhibitors	citalopram, fluoxetine, paroxetine
Opioid agonists		methadone, levomethadyl
Antihistamines		terfenadine (withdrawn), astemizole (withdrawn), loratadine
Antimicrobials	macrolides	erythromycin, clarithromycin, azithromycin, telithromycin, roxithromycin
	fluoroquinolones	sparfloxacin, grepafloxacin (withdrawn), levofloxacin, gatifloxacin, moxifloxacin, ciprofloxacin
	other antibiotics	sulfamethoxazole
	antimalarial drugs	quinine, halofantrine, chloroquine
	antiprotozoals	pentamidine
	antivirals	amantadine, atazanavir, foscarnet
	antifungals	voriconazole, fluconazole, ketoconazole, itraconazole
Promotility medications		cisapride (withdrawn), domperidone
Miscellaneous drugs		arsenic trioxide, vandetanib, tacrolimus, probucol (withdrawn), indapamide, ondansetron, felbamate, suxamethonium, vasopressin, organophosphates

Drug-induced LQTS is a rare idiosyncratic adverse reaction. However, at least one of the well-known risk factors including female gender, structural heart disease, bradycardia, genetic predisposition (“forme fruste” of congenital LQTS or alterations of genes encoding drug metabolizing enzymes), electrolyte abnormalities, drug interactions, recent conversion from atrial fibrillation, advanced age, and liver or renal failure is nearly always present when TdP evolves [6]. All of these above mentioned conditions may increase the susceptibility for TdP, syncope, and sudden cardiac death reducing the patient’s physiological repolarization reserve [7].

2. The intrinsic proarrhythmic potential of macrolides

Macrolide antibiotics are widely used to treat respiratory tract infections, though they also have some other clinical uses including soft-tissue infections, *Chlamydia* urethritis, toxoplasmosis, and *Helicobacter pylori* infection associated active gastric ulcer disease.

Macrolide therapy has been associated with QT prolongation and/or TdP in clinical reports. Prolongation of cardiac repolarization may be a class effect of macrolides due to inhibition of I_{Kr} [8]. Among macrolide antibiotics, erythromycin and clarithromycin induced QT interval prolongation at clinically relevant concentrations, while roxithromycin and azithromycin evoked QT prolongation only at higher concentrations in rats [9]. *Shaffer et al.*

retrospectively evaluated case reports that appeared in the United States Food and Drug Administration (FDA) Adverse Event Reporting System from 1987 to 2000 on macrolide antibiotics and TdP. Their analysis of 156 cases confirmed that macrolides have different proarrhythmic potential. 53% of the cases was associated with erythromycin, 36% with clarithromycin, and 11% occurred during azithromycin therapy. This analysis also emphasizes the importance of risk factors, such as 70% of all patients were women, at least one cardiac abnormality and hypokalemia or hypomagnesemia were also frequently present (42% and 17%, respectively). Half of the reports mentioned concomitant use of another drug believed to prolong the QT interval [10].

2.1. Erythromycin

Several reports on in vitro and in vivo studies demonstrated the proarrhythmic potential of erythromycin. Erythromycin was shown to prolong the QT interval and action potential duration in isolated heart preparations from guinea pigs and dogs and in isolated rabbit hearts [11]. In the clinical setting, prospective studies demonstrated QTc prolongation during erythromycin therapy without development of TdP [12]. These effects were usually observed during intravenous infusions of erythromycin but have also occurred during oral therapy. Torsades de pointes was associated with rapid intravenous injection of erythromycin in the majority of the case reports [13]. However, the rate of sudden cardiac death was higher among current users of oral erythromycin in a retrospective study [14].

2.2. Clarithromycin

Clarithromycin also blocked I_{Kr} potassium current in HEK 293 cells at clinically relevant concentrations [15]. In a prospective study clarithromycin therapy was associated with a modest but significant QT interval prolongation in children treated for respiratory tract infections [16]. Although QT prolongation and TdP were not frequently reported during clarithromycin therapy in the absence of other drugs with proarrhythmic potential, physicians should be aware of this potentially lethal side effect when prescribing clarithromycin, especially for the elderly [17].

2.3. Azithromycin

Azithromycin is considered relatively safe having less effect on the QT interval than other macrolides [9]. Azithromycin showed remarkably lower proarrhythmic effect than clarithromycin and erythromycin in Langendorff-perfused rabbit hearts although QT interval, monophasic action potential duration and dispersion of repolarization were markedly prolonged [18]. Differences in the proarrhythmic potential may result from different drug-induced changes of action potential morphology. Erythromycin and clarithromycin changed the ventricular action potential morphology to a triangular pattern by phase 3 prolongation, whereas azithromycin caused a rectangular pattern of action potential prolongation due to phase 2 prolongation [18]. Moreover, in vitro studies suggest that azithromycin is a weak I_{Kr} inhibitor compared to other macrolides. In a prospective study involving previously healthy persons, a modest statistically insignificant prolongation of the QTc interval was observed after completion of a course of 3 g of azithromycin administered over a period of 5 days [19]. QT prolongation and/or TdP occurs rarely during azithromycin therapy, usually in case of additional risk factors or massive overdose [20]. However, during treatment with azithromycin, a 55-year-old woman developed prolonged QT interval and TdP in the absence of known risk factors [21]. Tdp was also reported in a 90-year-old woman with hypertension and an old cerebrovascular accident within a few hours after taking azithromycin [22]. In a retrospective study on a Tennessee Medicaid cohort, Ray et al. found that patients taking a 5-day-course of azithromycin had an increased risk of cardiovascular death compared to those who took no antimicrobials or who were on amoxicillin treatment (hazard ratio 2.88 and 2.49, respectively). The risk of cardiovascular death with azithromycin did not differ significantly from that with levofloxacin, a fluoroquinolone with recognized proarrhythmic potential [23].

2.4. Other macrolides

Other macrolides are also reported to be associated with QT interval prolongation, although the proarrhythmic risk is low. Roxithromycin has been reported to cause QT-related adverse effects, especially in patients with other risk factors, such as complete atrioventricular block [24] or in case of coadministration with other cardiotoxic drugs [25]. Roxithromycin has been rarely reported to cause QT prolongation or TdP so far, although it is a relatively potent HERG blocker. Toxoplasmosis prophylaxis with spiramycin in neonates may induce QT interval prolongation, leading to electric instability, even without any additional risk factors [26]. In healthy subjects, the ketolide telithromycin did not increase the QT interval compared to placebo [27].

3. Pharmacodynamic interactions

Pharmacodynamic interactions may occur in case of coadministration of drugs having the same (or opposing) pharmacologic actions. Concomitant administration of a macrolide and another drug with I_{Kr} blocking potential may

lead to the summation of the proarrhythmic effects with remarkable QT interval prolongation and the risk TdP. Class IA and class III antiarrhythmics, several antipsychotics, antihistamines, other antimicrobials (fluoroquinolones, antimalarials, pentamidine), prokinetics, and some other drugs (tacrolimus, methadone, arsenic trioxide) show synergistic proarrhythmic effects when coadministered with macrolides. Several cases of QT interval prolongation and TdP due to the interaction of macrolides and antiarrhythmics (quinidine [28], disopyramide [29], amiodarone [25]) were reported. In a canine model of complete atrioventricular block, *Watanabe* et al. demonstrated the additive proarrhythmic effect of erythromycin and a class IA antiarrhythmic agent, disopyramide [30]. In Purkinje fibres telithromycin and a class III antiarrhythmic, sotalol showed a synergistic effect on action potential prolongation [31]. However in a double-blind, randomized study of healthy subjects, in presence of telithromycin, sotalol-induced QTc prolongation was less pronounced since sotalol plasma concentrations decreased [31]. The risk of clinically significant drug interactions is enhanced in elderly patients, in case of polypharmacy, renal or hepatic insufficiency or genetic susceptibility.

4. Pharmacokinetic interactions

4.1. CYP3A4-mediated interactions

Pharmacokinetic interactions occur when one medication increases or decreases the serum concentration of another via altering absorption, distribution, metabolism or excretion (ADME). Several enzymes are responsible for the two phases of drug metabolism also called biotransformation. The cytochrome P (CYP) 450 family of heme monooxygenases is responsible for the Phase I metabolism of a large number of structurally diverse drugs. CYP enzymes are located mostly in the endoplasmic reticuli of hepatocytes and enterocytes. Several clinically significant pharmacokinetic interactions can occur due to the concomitant administration of medications which are substrates, inhibitors or inducers of the same CYP isoenzyme. CYP-mediated biotransformation can be inhibited by two distinct mechanisms: reversible inhibition (due to competition of drugs) and mechanism-based inhibition including quasi-irreversible and irreversible inhibition [32]. The clinical relevance of the consequential increased serum concentrations and/or elimination half-life of the substrate depends on the degree of accumulation, the therapeutic window of the substrate and the presence or absence of alternative pathways of elimination. Mechanism-based inhibition involves the inactivation of the CYP enzyme by the formation of metabolic intermediates that bind tightly and irreversibly to the enzyme. Catalytic activity can be reconstructed only through de novo enzyme synthesis. As a consequence, the inhibitory effect may last long even after the withdrawal of the inhibitor.

Erythromycin and clarithromycin are metabolized by CYP3A4. Data from a retrospective study by *Ray* et al. suggest that concomitant use of oral erythromycin with CYP3A4 inhibitors (nitroimidazole antifungal agents, diltiazem, verapamil, troleandomycin) increases sudden death rate compared to a control antibiotic (ampicillin) or when used alone [14]. Cimetidine, grapefruit juice, amiodarone, some antidepressant drugs, ciprofloxacin, norfloxacin, quinupristin, chloramphenicol, isoniazid, cyclosporine, imatinib, delavirdin, efavirenz, omeprazole, mifepristone, tamoxifen, aprepitant, zafirlukast, protease inhibitors are also inhibitors of CYP3A4 [32]. Telithromycin is metabolized via CYP3A4 and non-CYP-dependent elimination pathways. *Shi* et al. reported a 1.9-fold increase in the area under the concentration-time curve (AUC) of telithromycin during concomitant administration of a potent CYP3A4 inhibitor, ketoconazole. This relatively small increase in telithromycin exposure results from the alternative pathways of elimination [33]. Azithromycin is not a substrate for CYP3A4. Azithromycin is principally eliminated via biliary excretion, predominantly as unchanged drug. Unlike erythromycin or clarithromycin, azithromycin does not interfere with the metabolism of other drugs via CYP3A4 interactions [34].

On the other hand, some macrolide antibiotics are also potent inhibitors of CYP3A4, interacting with the biotransformation of other compounds metabolized on the same pathway. Macrolides can be classified in three different groups on the basis of their abilities to interfere with CYP3A4.

1. Macrolides such as erythromycin, troleandomycin can induce their own biotransformation into nitrosoalkanes. These reactive metabolites interact with CYP3A4 to form a stable cytochrome P-450-Fe(II)-metabolite complex resulting in irreversible inhibition of enzyme activity [35].
2. The second group (e.g. clarithromycin, roxithromycin, josamycin) form cytochrome P-450-metabolite complexes to a lesser extent [34]. Telithromycin is a CYP3A4 inhibitor with a similar potency to clarithromycin in vivo [33].
3. The third group (azithromycin, spiramycin, rokitamycin, dirithromycin) do not interfere with CYP3A4 and are unable to inhibit the metabolism of other drugs [36].

Interactions between macrolides and pharmacologic agents metabolized by CYP3A4 with narrow therapeutic window and no alternative pathway of elimination can lead to drug toxicity. The vast majority of drugs that may cause cardiac arrhythmias by prolonging the QT interval are also metabolized by CYP3A4. Certain macrolides (e.g. erythromycin, clarithromycin) block the I_{Kr} potassium current and inhibit the biotransformation of coadministered agents with proarrhythmic potential performing pharmacodynamic and pharmacokinetic interactions at the same time.

Several antiarrhythmic agents with I_{Kr} blocking potential including quinidine, disopyramide, amiodarone, dronedarone, dofetilide undergo CYP3A4-mediated biotransformation. In healthy volunteers, erythromycin reduced the

total clearance of quinidine by 34% and maximum serum concentration (C_{max}) increased by 39% [37]. Troleandomycin potently inhibited the metabolism of both R(-)- and S(+) disopyramide enantiomers in human liver microsomes [38]. Coadministration of disopyramide and macrolides was associated with serious cases of ventricular dysrhythmia [39]. Though amiodarone possesses minimal proarrhythmic effects, it can cause serious QT-related adverse effects during cotreatment with macrolides [25]. On the other hand, some QT interval prolonging antiarrhythmic agents including procainamide and sotalol are not substrates of CYP3A4 and their serum concentrations do not increase in case of concomitant therapy with macrolides. On the contrary, coadministration of sotalol with telithromycin decreased C_{max} and AUC of sotalol due to decreased absorption [33].

Terfenadine is a nonsedating H_1 -receptor antagonist that can cause prolongation of the QT interval and TdP in susceptible patients in case of drug accumulation. Given that terfenadine is a substrate of CYP3A4, coadministration of CYP3A4 inhibitors including erythromycin and clarithromycin may reduce the metabolic clearance of terfenadine. Terfenadine was removed from the market due to cardiotoxicity [35]. Astemizole, another H_1 -receptor antagonist is extensively metabolized by CYP3A4-mediated first-pass biotransformation to form active metabolites. Astemizole is also known to cause QT prolongation and TdP, particularly in case of accumulation. During dirithromycin treatment astemizole clearance was 34% slower, volume of distribution was 24% larger, and half-life was 84% longer in healthy subjects. QT interval prolongation was not observed [40]. However, these older antihistamines (terfenadine, astemizole) are associated with similar proarrhythmic risk when their plasma concentrations are increased [41]. Loratadine undergoes biotransformation mediated by CYP3A4 and CYP2D6. Erythromycin and clarithromycin altered the pharmacokinetics of loratadine in healthy individuals [42]. Nevertheless, no electrocardiographic changes were observed due to the wide safety margin of loratadine [35]. Newer antihistamines including cetirizine, and fexofenadine are not associated with QT prolongation or TdP. Peak fexofenadine concentrations were increased by 69% and the AUC was increased by 67% in the presence of azithromycin. However, QT intervals did not appear to be affected by azithromycin in patients receiving fexofenadine [41].

Cisapride, a prokinetic agent used for gastro-oesophageal reflux, undergoes extensive CYP3A4-mediated first-pass metabolism. The proarrhythmic effects of cisapride (QT interval prolongation, TdP, death) occurred due to interactions with CYP3A4 inhibitors in more than 50% of the reported cases. Several cases of QT prolongation or polymorphic ventricular tachycardia due to simultaneous cisapride-macrolide therapy were reported [43]. AUC of cisapride was increased by 3.0- and 2.4-fold, respectively, when coadministered with clarithromycin and telithromycin, resulting in significant increases in QTc interval [33, 44]. In many countries, cisapride has been either withdrawn or had its indications limited due to serious cardiac dysrhythmias.

Several antidepressants and antipsychotics associated with ventricular arrhythmias are metabolized via CYP3A4. Clarithromycin coadministration inhibited the CYP3A4-mediated clearance of pimozide, a diphenylbutylpiperidine neuroleptic agent, resulting in elevation of plasma concentrations and significant QT prolongation in healthy subjects [45]. Two fatal cases of ventricular arrhythmia have been reported in which clarithromycin was coprescribed with pimozide [46]. CYP3A4 is involved in the metabolism of haloperidol but interactions with CYP3A4 inhibitors have little clinical significance [47]. The most cardiotoxic conventional antipsychotic drug, thioridazine, is not a CYP3A4 substrate [48]. However, coadministration of thioridazine with macrolides is contraindicated due to pharmacodynamic interactions.

Among atypical antipsychotics, sertindole and ziprasidone are the compounds associated with the highest risk of TdP. CYP3A4 is implicated in the biotransformation of both drugs, but the likelihood of serious CYP3A4-mediated pharmacokinetic interactions is low due to alternative metabolic pathways [49]. In healthy volunteers, erythromycin coadministration caused a slight, non-significant increase in plasma AUC of sertindole [50]. Nevertheless, sertindole doses should be halved for concomitant administration with strong CYP2D6 or CYP3A4 inhibitors [49]. Quetiapine is usually well tolerated and possesses minimal proarrhythmic effects. Quetiapine therapy was associated with only mild QTc prolongation in clinical studies. However, QTc prolongation was reported with quetiapine overdose [51] and sinus node dysfunction was also observed during quetiapine treatment [52]. CYP3A4-mediated interactions may occur when coadministered with macrolides due to the absence of alternative pathways of quetiapine elimination [53]. Moderate QTc prolongation may be observed during risperidone therapy in clinical practice. The risk of serious risperidone-macrolide interactions is low due to the dual metabolic pathways (CYP2D6 and CYP3A4) of risperidone [54].

Most tricyclic antidepressants (TCAs) can markedly prolong the QT interval. Moreover, evidence from cellular studies suggest that, similar to class Ic drugs, TCAs can induce cardiac sodium channel blockade [3]. Their complex biotransformation includes CYP2D6-mediated hydroxylation and demethylation mediated by CYP3A4 or other isoforms. The concurrent use of erythromycin did not influence the metabolism and steady-state plasma concentrations of tricyclic antidepressants [55]. However, altered trazodone clearance has been demonstrated following clarithromycin coadministration in healthy individuals [56].

Selective serotonin reuptake inhibitors (SSRIs), particularly citalopram, fluoxetine, and paroxetine have been implicated in causing TdP especially when other risk factors are present or in case of intoxication. Since citalopram and fluoxetine have multiple elimination pathways, CYP3A4 inhibition can result in a minimal increase in exposure [57]. CYP2D6 and to a lesser extent, CYP3A4 are involved in the metabolism of paroxetine [58]. As a consequence,

macrolides usually do not reduce the metabolic clearance of SSRIs. On the other hand, fluvoxamine and the active metabolite of fluoxetine are moderate inhibitors of CYP3A4 and can elevate the serum levels of macrolides [58].

Methadone, a strong opioid agonist used to treat heroin dependence can prolong the QTc in dose-dependent manner. Methadone therapy has been implicated in causing TdP in the presence of other risk factors for proarrhythmia. Inhibition of CYP3A4, responsible for N-demethylation of methadone, can lead to QT prolongation and TdP [59].

4.2. P-glycoprotein-mediated interactions

In addition to the enzymes involved in biotransformation, transporters play an important role in the pharmacokinetics of medications. P-gp, the most important drug transporter is a widely distributed efflux pump expressed in many barrier tissues including kidney, liver, intestine, and blood-tissue barriers. In the gastrointestinal tract, it is located in the apical brush border of the enterocytes, transporting xenobiotics from the cells back into the intestinal lumen [60]. In the liver and in renal tubular cells, P-gp functions to remove toxic compounds from the circulation into bile and urine. In the enterocytes, CYP3A4 and P-gp are co-localized and, as suggested by some evidence, coordinately regulated in order to maximize the effectiveness of elimination of xenobiotics [60]. The functional interaction between CYP3A4 and P-gp should be considered an important part of overall first-pass effect. Numerous medications inhibit P-gp activity (including macrolides, verapamil, amiodarone, quinidine, cyclosporine, atorvastatin, itraconazole, etc.) conferring the potential for serious drug interactions in case of coadministration with P-gp substrates.

P-gp appears to play a key role in the pharmacokinetics of digoxin. Due to digoxin's narrow therapeutic index, P-gp inhibition can cause digoxin toxicity. On Caco-2 cells with high P-gp expression, telithromycin, roxithromycin and clarithromycin inhibited P-gp efflux for digoxin and its derivatives. On the hand, azithromycin showed no inhibitory activity in spite of being a P-gp substrate [61, 62]. Erythromycin demonstrated only partial P-gp inhibitory capacity, which suggested that its role in drug interactions derived from CYP3A4 inhibition predominantly [62]. In a 15-year, population-based, nested case-control study that evaluated the association between hospitalization for digoxin toxicity and simultaneous therapy with macrolides, clarithromycin was associated with the highest risk of digoxin toxicity, whereas erythromycin and azithromycin were associated with much lower risk [63]. Several cases of digoxin toxicity after concomitant administration with macrolides were reported [64, 65]. Digoxin toxicity can be associated with a multitude of arrhythmias including atrial tachycardia, ventricular bigeminy, sinus bradycardia, atrioventricular block, and polymorphic or bidirectional ventricular tachycardia. QT prolongation is unlikely to occur in cardiac glycoside toxicity.

The role of P-gp in pharmacokinetic drug interactions is an emerging issue. *Goldschmidt* et al. reported complete atrioventricular block and QTc prolongation due to simultaneous verapamil and erythromycin therapy. Both drugs are potent inhibitors of CYP3A4 and of P-glycoprotein [66]. Alterations of P-gp function due to macrolide coadministration may have a role in the altered pharmacokinetics of antihistamines. Roxithromycin significantly enhanced the bioavailability of loratadine by reducing first-pass metabolism mediated by CYP3A4 and/or P-gp in rats [67]. Among antipsychotics, amisulpride, aripiprazole, risperidone and paliperidone are substrates for P-gp in therapeutic concentrations. There is limited information regarding sertindole and ziprasidone [68].

5. Discussion

Macrolide antibiotics are widely used as effective antimicrobials against Gram-positive bacteria. Although usually well tolerable, macrolide therapy can be associated with common side effects including nausea, abdominal discomfort, diarrhoea, and changes in taste. These side effects are temporary and rarely lead to treatment discontinuation. On the other hand, macrolides have the greatest potential for causing QT interval prolongation and TdP among antimicrobial agents. The incidence of macrolide-induced acquired LQTS is very low. However, it should be taken into account that this life-threatening side effect may occur during the treatment of well-tolerable conditions, such as uncomplicated upper respiratory tract infection. Moreover, the risk of macrolide-induced proarrhythmia can be minimized by identification of the patient's risk factors and careful selection of the antimicrobial agent. Patients receiving macrolides should be promptly treated for correctable abnormalities including electrolyte disturbances such as hypokalaemia.

Antimicrobial agents are usually coadministered with continuously taken drugs. Most studies of drug interactions are conducted in healthy volunteers. However, macrolides are frequently used in older patients, with liver or renal failure and polymorbidity controlled with several drugs. As a consequence, the results of these studies cannot be extrapolated directly to the clinical practice and the risk of serious interactions is increased in the elderly. This underlines the necessity of postmarketing surveillance. Nevertheless, postmarketing data are influenced by well-known biases such as underreporting and different prescription rates [69]. It has been suggested that the real incidence of serious adverse reactions is at least 10 times higher than it appears in spontaneous reports [3]. However, as far as possible, polypharmacy should be avoided to prevent dangerous interactions. Performing ECGs at baseline and after initiation of macrolide therapy is also advisable, at least in susceptible patients. Macrolide coadministration with other drugs that can prolong the QT interval should be preferably avoided. Nevertheless, in most cases the mechanism of increased risk of ventricular dysrhythmias is due to altered drug metabolism. Concomitant use of macrolides with agents that interfere

with their metabolism via CYP3A4 inhibition may cause significant QT prolongation and TdP. The greatest risk of TdP evolves when macrolides that have strong I_{Kr} blocking and CYP3A4 inhibitory potentials at the same time (e.g. erythromycin, clarithromycin) are coadministered with other QT prolonging pharmacologic agents metabolized by CYP3A4 with narrow therapeutic index and no alternative pathway of elimination. Physicians should be vigilant of this mechanism of drug-drug interaction, which can lead to a life-threatening arrhythmia. In this clinical setting, azithromycin with less effect on the repolarization and no effect on CYP3A4-mediated biotransformation could be a safer choice. Alternatively, an antibiotic from another group should be chosen. In certain cases, temporary discontinuation or at least, dose adjustment of the other CYP3A4-metabolized, QT interval prolonging drug should be taken into consideration during macrolide therapy.

Furthermore, variations of genes responsible for the normal repolarization of the myocardium have been identified in some patients with drug-induced TdP. “Forme fruste” mutations of cardiac ion channels can reduce the capacity of the cardiomyocytes to achieve rapid repolarization through normal mechanisms, the so-called “repolarization reserve” [7]. For example, individuals with subclinical mutations of KCNQ1, which encodes the α subunit of the slow delayed rectifier K^+ current, I_{Kr} , may display no manifest repolarization abnormalities. However, superimposition of drug-induced I_{Kr} block in these patients may lead to marked QT interval prolongation and TdP [70]. These “gene-drug interactions” are assumed to play a significant role in 10-15% of drug-induced LQTS [71]. Moreover, the metabolism of drugs with QT interval prolonging potential can be influenced by genetic factors [72]. For example, some cardiotoxic drugs undergo CYP3A4 and CYP2D6-mediated biotransformation. About 7% of Caucasians are CYP2D6 poor metabolizers, who are unable to use CYP2D6-dependent pathways for drug elimination [73]. In these patients, coadministration of the QT interval prolonging drug with CYP3A4 inhibitors including macrolides may lead to increased exposure to the cardiotoxic agent. These factors give some explanation for the interindividual variability in the extent of susceptibility to drug-induced LQTS.

Transport proteins including P-gp play a prominent role in the disposition of many xenobiotics. Increasing evidence suggests that some drug interactions result from alterations in P-gp activity. The available evidence clearly indicates that macrolide therapy can considerably influence the pharmacokinetics of digoxin that may lead to digoxin toxicity. Moreover, changes in P-gp function due to macrolide coadministration may alter the disposition of certain QT interval prolonging drugs, though there is limited information in this regard.

If a patient develops TdP, any QT interval prolonging drugs should be withdrawn, and the electrolyte abnormalities must be corrected (high normal serum potassium is desired). Though most of the TdP episodes are self-terminated, sustained episodes require defibrillation with unsynchronized DC shock (200–360 J) [69]. Prevention of recurrence includes administration of intravenous magnesium sulfate (2 g bolus over 1-2 min, repeat once or twice at 5 to 15-min intervals or followed by intravenous infusion at a rate of 2–4 mg per minute) [74]. Acceleration of heart rate to 100/min with temporary cardiac pacing is highly effective in preventing recurrences. Intravenous isoproterenol may be indicated if temporary pacing is unavailable in patients without hypertension or coronary artery disease. In resistant cases intravenous administration of lidocaine should be taken into consideration. However, only 50% of cases of torsades de pointes respond to lidocaine. In cases of sinus node dysfunction or atrioventricular block and bradycardia, permanent pacing should be considered [75].

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