Proarrhythmic Potential of Antimicrobial Agents

J. Simkó, A. Csilek, J. Karászi, I. Lőrincz

Abstract
Several antiarrhythmic and non-cardiovascular drug therapies including antimicrobial agents have been implicated as the causes for QT interval prolongation, torsades de pointes (TdP) ventricular tachycardia and sudden cardiac death. Most of the drugs that have been associated with the lengthening of the QT interval or development of TdP can also block the rapidly activating component of the delayed rectifier potassium current (IKr) in the ventricular cardiomyocytes. This article presents a review of the current literature on the QT interval prolonging effect of antimicrobials based on the results of the *in vitro*, *in vivo* studies and case reports. Our observations were derived from currently available Medline database. As we found, the most frequently QT interval prolonging antimicrobials are erythromycin, clarithromycin, fluoroquinolones, halofantrine, and pentamidine. Almost every antimicrobial-associated QT interval prolongation occurs in patients with multiple risk factors of the following: drug interactions, female gender, advanced age, structural heart disease, genetic predisposition, and electrolyte abnormalities. In conclusion, physicians should avoid prescribing antimicrobials having QT-prolonging potential for patients with multiple risk factors. Recognition and appropriate treatment of TdP are also indispensable.

Infection 2008; 36: 194–206
DOI 10.1007/s15010-007-7211-8

Introduction

The term torsades de pointes (TdP) refers to a ventricular tachycardia characterized by alternating QRS axis of 180° during attacks and QT interval prolongation between attacks (Figure 1). The attacks may stop spontaneously, but sometimes they persist long enough to provoke syncope, or even sudden cardiac death if ventricular fibrillation evolves [1]. The long QT syndrome (LQTS) is characterized by dragging ventricular repolarization (Figure 2) and high risk of TdP or ventricular fibrillation. LQTS can be either idiopathic (congenital) or acquired. The acquired form is a potentially fatal side effect of class I and class III antiarrhythmic agents and several other drugs (antihistamines, antipsychotics, antimicrobials, etc.).

The QT interval is the time from the beginning of the QRS complex to the end of the T wave in the surface ECG. It represents the duration of ventricular depolarization and repolarization. Describing the QT interval should always include the assessment of T wave morphology and appearance of abnormal TU patterns. The analysis of all 12 leads and multiple measurements in each ECG is necessary. Since the duration of the QT interval is heart-rate dependent, correction to heart rate is needed. There are several methods for adjusting the QT interval to heart rate, the most widely used is Bazett's formula: $QT_c = QT/\sqrt{RR}$, where QT_c is the corrected QT interval and RR is the time in seconds between two R waves. The adequacy of Bazett's formula has been questioned; it overcorrects QT interval at fast heart rates and undercorrects it at low heart rates. A corrected QT interval (QT_c) of ≥ 440 ms is defined as abnormal [2]. During phase I/II studies a drug-related increase in mean QT_c as small as 6 ms between baseline and maximal drug effect should be taken seriously. Moreover, a single outlier with drug-induced QT prolongation > 500 ms or an increase by 60 ms from baseline may be more important [3].

QT dispersion, defined as the difference between the longest and shortest QT intervals on a 12-lead ECG, seems to be an approximate and imprecise expression of repolarization abnormalities and should not be taken as a gold standard for a non-invasive measure of repolarization heterogeneity [3].

The prolongation of the ventricular myocyte repolarization is caused either by a reduction of outward current or an increase of inward current [3]. While congenital LQTS can be caused by mutations that produce the loss of function of different K^+ currents or gain of function of Na^+ currents, virtually all drugs with QT interval prolonging potential block the rapidly activating component of cardiac delayed rectifier K^+ current (IKr) [4]. IKr is rapidly activated by depolarization during the action potential and thereafter participates in repolarization. IKr is carried by HERG (human ether-a-go-go re-

J. Simkó *(corresponding author)*
First Department of Internal Medicine, Semmelweis Hospital, Csabai kapu 9-11, Miskolc 3529, Hungary; Phone: (+36/46) 555666; Fax: -562592
e-mail: sjozs74@hotmail.com
A. Csilek, J. Karászi
Dept. of Infectology, Semmelweis Hospital, Miskolc, Hungary
I. Lőrincz
First Department of Internal Medicine, Medical and Health Science Center, University of Debrecen, Debrecen, Hungary

Received: May 10, 2007 · Revision accepted: October 24, 2007
Published online: May 3, 2008

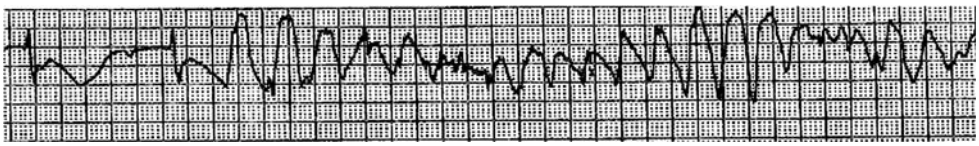

Figure 1. Initiation of torsades de pointes. Note the prolonged QT interval of the last preceding beat, the twisting polarity and the changing amplitude of the QRS complexes during the arrhythmia.

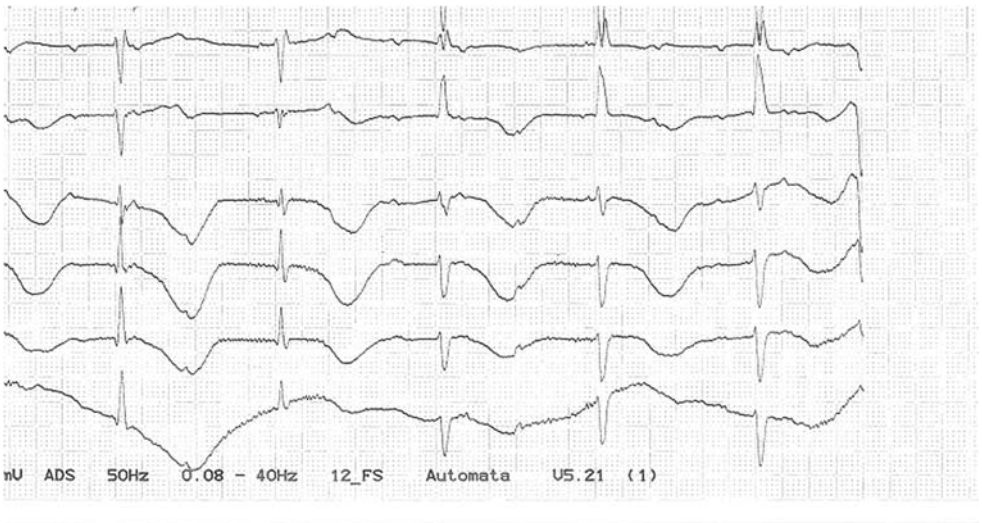

Figure 2. Precordial ECG leads of a patient between epizodes of torsades de pointes. Note the third degree atrioventricular block, the prolonged QT interval, and the large negative T waves.

lated gene) K^+ channel proteins coded by KCNH2 gene. Drugs blocking the HERG with high affinity interact primarily with the aromatic side groups of the channel, Tyr (Y652) and Phe (F656) [5]. Prolongation of the repolarization can facilitate the development of early afterdepolarizations mainly in M (midmyocardial) cells and Purkinje cells. Early depolarization-induced premature ventricular beats can trigger reentry and TdP if increased dispersion of repolarization is present.

This paper presents a review on the QT interval prolonging effect of antimicrobials. The authors wish to call the health professionals' attention to this potentially lethal side effect of certain antibiotics, antifungal, antimalarial, and antiviral agents, and discuss the facilities of prevention and therapy. Our observations were derived from Medline database until April 2007 using the key words ''QT interval'', ''torsades de pointes'', ''macrolides'', ''fluoroquinolones'', ''antifungals'', ''antimalarials'', ''antivirals'', and ''acquired long QT syndrome''. We then reviewed the references of the original articles for additional publications.

Several antimicrobial agents have been associated with QT prolongation and/or TdP in clinical reports. Most of them have a well-documented IKr-blocking effect (erythromycin, clarithromycin, grepafloxacin, gatifloxacin, sparfloxacin, moxifloxacin, and halofantrine). Trimethoprim-sulfamethoxazole, amantadine, clindamycin, HIV proteases, and metronidazole have also been associated with TdP but the mechanism of the QT-prolonging effect is less clear. The European Society of Cardiology considers erythromycine, clarithromycine, grepafloxacin, sparfloxacin, cotrimoxazole, spiramycin (from antibiotics), amantadine (from antiviral drugs), ketoconazole, itraconazole (from antifungal drugs), pentamidine, chloroquine, halofantrine and quinine (from antiprotozoal and antimalarial drugs), as drugs that can generate TdP [3]. However, in most of the publications there were only anecdotal reports on arrhythmia during antimicrobal treatment, without demonstrating a clear-cut connection. In the macrolide group, erythromycin and clarithromycin have the greatest potential for causing QT interval prolongation and TdP [6]. Cardiotoxicity is a class effect of fluoroquinolones but there are great differences between the various members of this group in their proarrhythmic potential [2]. The cardiotoxic risk of imidazole antifungals is in great part due to their ability to inhibit the metabolization of several drugs with QT-prolonging effect [7]. In the group of antimalarials, halofantrine, chloroquine, and quinine may cause QT interval prolongation and TdP [8, 9]. Intravenous pentamidine therapy has been reported to provoke TdP in several case reports, whereas inhalatory pentamidine is considered to be relatively safe [10].

The predisposing factors to be emphasized are female gender, organic heart disease, taking another QT interval

prolonging medication at the same time, reduced drug elimination (due to drug interaction, renal or hepatic dysfunction), hypokalaemia or hypomagnesaemia, bradycardia, prolonged heart rate corrected QT interval (more than 450 ms) interval before therapy and genetic predisposition. Congenital LQTS is assumed to occur sometimes in ''forme fruste'' with only drug-induced QT interval prolongation and only drug-induced development of TdP in spite of the underlying cardiac ion channel mutation [11]. *Justo* and *Zeltser* [4] studied 61 reports on 78 patients with antibiotics-induced TdP. Most of the patients were women (66.7%); patients with advanced heart disease and patients who used concomitantly another QT-prolonging agent or an inhibitor of liver drug metabolism were also present mostly (59 and 48.7%, respectively). *Zeltser* et al. [12] reported that 96% of 249 patients in previously published cases of TdP associated with non-cardiac drugs had at least 1 concomitant risk factor for TdP and that 71% had at least 2 predisposing factors.

Although the incidence of drug-induced acquired LQTS is very low, the number of patients treated with these drugs is high and the risk/benefit ratio is unacceptable for those few patients presenting with TdP. Even a minor risk of a life-threatening arrhythmia is unacceptable during the treatment of a benign, well-tolerable condition, such as gastroesophageal reflux or uncomplicated upper respiratory tract infection.

Macrolides

Similar to class III antiarrhythmics, macrolide antibiotics prolong the repolarization period of the action potential by blocking the HERG potassium channels [13]. Erythromycin, clarithromycin, azithromycin, spiramycin, and dirithromycin have been reported to prolong the QT interval and to provoke TdP in the clinical setting. Nevertheless, they have different torsadogenic potentials [14]. In a retrospective analysis of 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, there was a difference in proarrhythmic potential of macrolide antibiotics in a total number of 156 patients; 53% was associated with erythromycin, 36% with clarithromycin, and 11% occured in azithromycin-treated patients. Seventy percent were women, at least one cardiac abnormality was reported in 42% of the cases and either hypokalemia or hypomagnesemia was present in 17% of the reports. Fifty percent of the reports mentioned coadministration of other drug prolonging the QT interval. These data are influenced by well-known biases including underreporting and various prescription rates. Nevertheless, this analysis also emphasizes the importance of risk factors [6].

Several reports on the *in vitro* and *in vivo* studies give an account of the repolarization lengthening effect of erythromycin [15]. Erythromycin was shown to prolong the QT interval and action potential duration in isolated heart preparations from guinea pigs and dogs [16, 17]. It also increased the QT interval in isolated perfused rabbit hearts. The overall drug-effect relationship was significantly different in males and females, former requiring more than ten times the concentration of erythromycin to produce the same QT interval prolongation [18].

In the majority of the reported cases on the association of erythromycin and arrhythmia intravenous use of the drug is involved. Rapid injections of erythromycin and large fluctuations in serum concentration should be avoided [19]. However, in a retrospective study by *Ray* et al. [20], the rate of sudden cardiac death was twice as high among current users of oral erythromycin as in those who had not used any of the study antibiotics (erythromycin or amoxicillin).

Erythromycin is a weak IKr blocker that is metabolized by cytochrome P450 3A4. Recent data suggest that the concomitant use of oral erythromycin with CYP 450 3A4 inhibitors (nitroimidazole antifungal agents, diltiazem, verapamil, troleandomycin) increases sudden death rate compared to a control antibiotic (ampicillin) or when used alone [20]. Cimetidine, grapefruit juice, some antidepressant drugs, ciprofloxacin, norfloxacin, protease inhibitors are also inhibitors of cytochrome P450 3A4.

The experimental findings by *Milberg* et al. [14] prove the relative safety of azithromycin treatment. In Langendorff-perfused rabbit hearts they found that erythromycin and clarithromycin had a comparable proarrhythmic potential, whereas azithromycin showed no proarrhythmic effect although QT interval, monophasic action potential duration and dispersion of repolarization were markedly prolonged. Erythromycin and clarithromycin changed the monophasic action potential configuration to a triangular pattern by phase 3 prolongation, whereas azithromycin caused a rectangular pattern of monophasic action potential prolongation by phase 2 prolongation. Moreover, when azithromycin was administered to rabbit hearts that had already been treated with erythromycin demonstrating TdP, it suppressed TdP in seven out of ten hearts showing an antiarrhythmic potential.

Toxoplasmosis prophylaxis with spiramycin in neonates may induce QT interval prolongation, leading to electric instability, even in the absence of additional risk factors. Sex-related differences in QT_c observed in the adult population are not present at birth [21]. Roxithromycin has been reported to cause TdP in a girl with congenital complete A-V block [22] and in an old patient receiving amiodarone and paroxetine (which may also prolong the QT interval) [23].

All the macrolide antibiotics (except azithromycin) are also potent inhibitors of cytochrome P450 3A4, elevating the serum levels of some drugs metabolized on the same pathway. Drug interaction between macrolides and other QT interval prolonging drugs metabolized via

Table 1
QT interval prolonging drugs metabolized by CYP 3A4, which may possibly interact both pharmacokinetically and phamacodinamically with macrolides and imidazole antifungals.

Antiarrhythmics	Amiodarone (with roxithromycin [23]), quinidine (with erythromycin [116]), disopyramide (with clarithromycin [117, 118])
Antifungals	Fluconazole, ketoconazole, itraconazole, miconazole
Prokinetics	Cisapride (with clarithromycin, [119, 120], with erythromycin [121])
Antihistamines	Terfenadine (with erythromycin [122, 123], with troleandomycin [124]), astemizole (with erythromycin [125]), loratidine
Antipsychotics	Pimozide (with clarithromycin [126, 127]), chlorpromazine, haloperidol, ziprasidone, risperidone, clozapine, quetiapine
Immunsuppressive drugs	Tacrolimus
Opioid agonists	Methadone
Antimalarials	Quinine, chloroquine, halofantrine

Case reports on torsades de pointes or QT prolongation during coadministration of macrolide agents and other repolarization prolonging drugs are in brackets

cytochrome P450 3A4 may lead to serious consequences [24]. Indeed, vast majority of drugs that may cause cardiac arrhythmias by prolonging the QT interval are metabolized by cytochrome P450 3A (Table 1). Both dangerous effects (intrinsic HERG channel blocking effect and inhibition of metabolism of other QT prolonging drugs) are particularly associated with erythromycin and clarithromycin [6].

Recent reports have shown that macrolides can alter the function of drug transporters such as P-glycoprotein which may mediate some drug–drug interactions, including those involving antihistamines [25].

Fluoroquinolones

Fluoroquinolones are among the drugs of choice for the treatment of common bacterial infections due to their wide spectrum against respiratory, gastrointestinal, and genitourinary pathogens. *In vitro* studies demonstrated that sparfloxacin, grepafloxacin, moxifloxacin, and gatifloxacin blocked the HERG channel currents with clinically relevant IC_{50} (half-maximal inhibitory concentration) values, while levofloxacin, ciprofloxacin, and ofloxacin required much higher concentrations to create blockade [26]. The proarrhythmic side effect of these antimicrobial agents is receiving more and more attention since the withdrawal from market of grepafloxacin and sparfloxacin due to adverse cardiac events [27]. QT interval prolongation and TdP were also reported in case presentations associated with other fluoroquinolones (gatifloxacin and levofloxacin). In the United States 25 cases of TdP associated with other quinolones (ciprofloxacin 2, ofloxacin 2, levofloxacin 13, gatifloxacin 8, moxifloxacin 0) have been reported to the Spontaneous Reporting System and the Adverse Events Reporting System of the FDA from January 1, 1996 to May 2, 2001. Ciprofloxacin was associated with a significantly lower rate of TdP (0.3 cases/10 million prescriptions, 95% confidence interval [CI] 0.0–1.1) than levofloxacin (5.4/10 million, 95% CI 2.9–9.3, $p < 0.001$) or gatifloxacin (27/10 million, 95% CI 12–53, $p < 0.001$ for comparison with ciprofloxacin or levofloxacin) [28]. These data are influenced by well-known biases of spontaneous reporting systems including various prescription rates and willingness of professionals to report. Moreover, this analysis only captures adverse event reports for the first full year gatifloxacin and moxifloxacin were widely available in the Unites States [29]. In virtually all cases of TdP associated with fluoroquinolones, patients had at least one concomitant risk factor for TdP [30].

Iannini et al. [31] found QT prolongation > 30 ms in four patients, > 60 ms in two, and an absolute prologation of the uncorrected QT interval to > 500 ms in four (one of these developed TdP but was also taking amiodarone) in a group of 23 patients on levofloxacin 500 mg/day. *Bertino* et al. [32] reported four cases of TdP in patients receiving gatifloxacin (two of them died). All patients had a history of heart disease, three patients were receiving concomitant therapy with QT interval prolonging potential (amiodarone, amitriptyline, imipramine) and three patients had elevated serum creatinine levels without dose correction of gatifloxacin. Gatifloxacin and levofloxacin undergo renal elimination and require dose adjustment in patients with renal failure [30].

Ciprofloxacin is believed to be safer than other quinolones but in some patients with reduced ''repolarization reserve'' (presence of several risk factors) it also provoked QT interval prolongation and TdP [33]. Ciprofloxacin has been shown to prolong cardiac repolarization by blocking IKr current in a dose-dependent manner [34]. Moxifloxacin produces an average QT interval prolongation between 6 and 10 ms at a dose 400 mg and approximately double the increase at a dose of 800 mg [2]. It was considered to be safe but an update of the above-mentioned report on adverse drug events identified 20 moxifloxacin associated TdP events in the FDA database from November 1997 to September 2003 [35]. Moxifloxacin undergoes both hepatic metabolism and renal elimination, thus dose adjustment in renal impairment or mild hepatic dysfunction is not necessary [30].

In addition, fluoroquinolones have the potential to interact with other drugs that prolong the QT interval. In human and rat hepatic microsomes, ciprofloxacin and norfloxacin decreased CYP 3A- and CYP 1A-mediated biotransformation by competitive inhibition showing that

they may elevate the serum levels of agents metabolized by these enzymes [36]. Drugs with a QT interval lengthening effect metabolized by cytochrome P450 3A4 are shown in table 1. Some tricyclic antidepressants and antipsychotics are metabolized by cytochrome P450 1A2 (at least partly).

Antifungals

Imidazole and triazole antifungal agents inhibit the growth of fungi by blocking ergosterol synthesis via inhibition of a specific cytochrome P450 enzyme. Ketoconazole, itraconazole, miconazole and fluconazole inhibit the metabolism of certain drugs through the hepatic cytochrome P450 3A4 enzyme (see Table 1). Ketoconazole and fluconazole also inhibit 2C19 and 2C9, respectively, which take part in the metabolism of antidepressants. The combination of azole agents and other QT prolonging drugs which metabolization is inhibited by antifungals (antihistamines, tricyclic antidepressants) can lead to serious consequences. Several episodes of syncope were associated with concomitant amitriptyline and fluconazole therapy in a patient, confirmed by readministration [37]. The same combination caused TdP in a patient suffering from cryptococcal pneumonia [38]. The coadministration of astemizole and ketoconazole caused TdP in a 63-year-old woman [39]. Symptomatic TdP occurred as a consequence of the interaction between itraconazole [40] or ketoconazole [41] and terfenadine. In a prospective cohort study of six healthy volunteers, the administration of terfenadine (60 mg every 12 h for 7 days) led to QT_c interval prolongation from 408 ± 8 to 416 ± 6 ms, which lengthened further to 490 ± 16 ms ($p = 0.0001$) after the coadministration of ketoconazole (200 mg every 12 h) with the accumulation of unmetabolized terfenadine [7].

While the consequencies of pharmacokinetic interactions of azole agents with other QT-prolonging agents are investigated thoroughly, much less data are available on the per se IKr blocking and QT interval prolonging effect of these antifungals. Ketoconazole reportedly blocks IKr in Xenopus oocytes [42] and causes QT interval prolongation. Miconazole and ketoconazole have been shown to bind preferentially to activated HERG channels and to a receptor site involving the F656 residue [43, 44].

Fluconazole-associated TdP was reported in a patient with acute myeloblastic leukemia on consolidation chemotherapy [45]. Fluconazole caused TdP in a 25-year-old woman with baseline QT interval prolongation, hypokalemia and hypomagnesemia (she was also receiving amiodarone) [46]. In a 59-year-old woman with peritonitis from cirrhotic liver disease, TdP developed shortly after iv fluconazole 400–800 mg/day was switched to 150 mg/day intraperitoneally [47]. In a fourth report, a 68-year-old woman with ovarian cancer experienced TdP after 8 days of treatment with oral fluconazole in the presence of a normal potassium level, absence of other drug therapy, no cardiac ischemia, and normal findings on her baseline ECG. Her QT_c interval returned to normal after discontinuation of fluconazole [48]. A 15-year-old patient with acute lymphoblastic leukemia and fusarium infection was treated with a newer azole agent, voriconazole. She developed asymptomatic bradycardia, QT interval prolongation, and non-sustained, polymorphic ventricular tachycardia, which recurred upon rechallenge with the drug [49].

Antimalarials

Malaria is one of the most important infectious diseases in the world that is endemic in over 100 countries, with a mortality estimated more than a million people worldwide annually. The side effects of antimalarials are viewed differently if the drug is given for malaria treatment or prophylaxis [50]. The risk of drug toxicity must not exceed an acceptable measure, particularly when used for prophylaxis.

Quinine is the mainstay for treating severe malaria in many countries. Cardiovascular toxicity is less frequent than that of its optical isomer, quinidine, but conduction disturbances, arrhythmias, hypotension may occur in case of overdose. Hypotension or cardiac arrest may result from rapid intravenous injections; intravenous administration should be only performed through infusion and cardiac monitoring is recommended. Quinine may lengthen the QT interval by approximately 10%, which mainly result from a slight QRS widening. The effect on repolarization is much less than that with quinidine [51]. Combination with halofantrine or coadminstration with other QT interval prolonging drugs should be avoided. *Martin* et al. [52] presented a case of an episode of TdP after a single dose of quinine while taking astemizole. Since quinine is extensively metabolized via CYP 3A4, concomitant treatment with CYP 3A4 inhibitors may be hazardous. Excessive amounts of grapefruit juice and quinine-containing tonic water caused QT interval prolongation and frequent attacks of TdP in a patient with a previously asymptomatic congenital LQTS and diabetic polydipsia [53].

Although the widespread resistence of *Plasmodium falciparum* decreased the use of chloroquine, it still maintains considerable efficacy against other *Plasmodium* species. Chloroquine has been shown to prolong action potential duration and refractory period in sheep Purkinje fibers [54] and to inhibit IKr in feline ventricular myocytes [55]. Mild and transient QT_c prolongation occured in healthy subjects at therapeutic doses [56]. Chloroquine-associated TdP was reported in a case of accidental chloroquine poisoning [9]. Recently, a patient with polymorphic ventricular tachycardia, QT interval prolongation, and conduction disorders due to long-term treatment with chloroquine was reported [57].

Halofantrine is widely used for the treatment of uncomplicated chloroquine-resistant *Plasmodium falciparum* malaria. Cardiac adverse effects (including sudden

death) of halofantrine were discovered in 1993, during a clinical study involving 400 patients on the Thai–Burmese border. There have also been some spontaneous reports of sudden deaths of patients treated with halofantrine [58, 59]. QT interval prolongation was noted in several studies of patients on halofantrine therapy, especially using higher doses than recommended [60–62]. QT prolongation and TdP were also more frequent when mefloquine was administered previously; the QT interval was prolonged before halofantrine therapy or the patient had a thiamine deficiency [63]. QT_c interval prolongation and episodes of TdP occurred in a mother and her son with a mutation of the SCN5A sodium channel after receiving halofantrine, suggesting the role of dual ion channel block (ion channel mutation with gain-of-function in a sodium channel and drug-induced loss of function in a potassium channel) [64].

The cardiac adverse effects of halofantrine have been investigated thoroughly in cell lines overexpressing IKr channels, in isolated heart and *in vivo* animal models. In the Chinese hamster ovary (CHO-K1) cells, halofantrine blocked HERG tail currents elicited on repolarization to –60 mV from +30 mV with an IC_{50} of 196.9 nM. The therapeutic plasma concentration range for halofantrine is 1.67–2.98 μM [65]. Halofantrine preferentially blocked open and inactivated HERG channels heterologously expressed in *Xenopus laevis* oocytes. The potency of halofantrine was reduced by mutation to Ala of aromatic residues (Y652, F656) located in the S6 domain, or a Val (V625) located in the pore helix [66]. In anaesthetized guinea-pigs iv.-administered consecutive bolus doses of halofantrine caused dose-dependent prolongation of the QT_c interval and bradycardia. The change in heart rate became significant after administration of 10 mg/kg halofantrine, whereas the increase in QT_c was significant with only 1 mg/kg halofantrine [67]. In anaesthetized rabbits increasing iv doses of halofantrine caused dose-dependent prolongation of the QT_c interval with progressive bradycardia. TdP occurred in four out of six in halofantrine-treated rabbits [68].

Halofantrine is metabolized into *N*-desbutyl-halofantrine by cytochrome P450 3A4. The inhibition of CYP 3A4 activity by grapefruit juice increases halofantrine area under the plasma concentration vs time curve (AUC) and peak plasma concentration (C_{max}), and decreases *N*-desbutyl-halofantrine AUC. Grapefruit juice increases halofantrine-induced QT interval prolongation. QT_c interval prolongation correlated better with halofantrine than with *N*-desbutyl-halofantrine concentration. Grapefruit juice should be contraindicated during administration of halofantrine [69]. Although not investigated, such pharmacokinetic interaction is likely to occur with other inhibitors of CYP 3A4. However, in human embryonic kidney (HEK 293) cells, not only halofantrine but also *N*-desbutylhalofantrine blocked HERG K^+ channels in a concentration-dependent manner with an IC_{50} of 21.6 and 71.7 nM, respectively, showing that the metabolite may be also responsible for cardiotoxicity [70]. In an anesthetized rabbit model, iv-administered *N*-desbutylhalofantrine caused dose-dependent prolongation of the QT_c interval [71]. This corresponds to a report by *Gundersen* et al. [72] on halofantrine-associated ventricular fibrillation in a patient with higher serum levels of *N*-desbutylhalofantrine (324 μg/l) than halofantrine (53 μg/l). However, in 34 male patients with uncomplicated falciparum malaria, the QT_c interval significantly correlated with the plasma halofantrine level, but not with the plasma *N*-desbutyl-halofantrine level [73].

Mefloquine, which is widely used in both the treatment and prophylaxis of *P. falciparum* malaria, has been shown to augment the proarrhythmic effect of halofantrine. The *per se* QT interval prolonging effect of mefloquine is controversial. Using the patch-clamp electrophysiology technique, *Kang* et al. [74] found that mefloquine inhibited KvLQT1/minK channel currents (which underlie the slow delayed rectifier–IKs–components of repolarization in the human myocardium) with an IC_{50} value of approximately 1 μM. HERG channel currents were less sensitive to block by mefloquine (IC_{50} = 5.6 μM). Concomitant therapy with mefloquine (which inhibits KvLQT1/minK) and halofantrine (which blocks HERG) may lead to excessive prolongation of the QT interval. In anaesthetized rabbits halofantrine dose-dependently prolonged the QT_c interval, while similar doses of mefloquine did not alter QT_c intervals significantly. The highest dose of mefloquine (30 mg/kg) caused cardiac contractile failure. Pretreatment with mefloquine before the first dose of halofantrine potentiated the effects of halofantrine on QT_c intervals. The blood concentrations of halofantrine were two to six times higher in the group pretreated with mefloquine compared to the halofantrine-alone group [75].

QTc interval prolongation was a mild and transient side effect of mefloquine ($p < 0.01$) in healthy adults [76]. In a prospective study of uncomplicated falciparum malaria patients, mefloquine (25 mg/kg) had no cardiac effects, but halofantrine (72 mg/kg) caused dose-dependent prolongation of the PR and QT intervals. The probability of significant QT_c interval lengthening was greater after halofantrine as secondary treatment (following treatment failure with mefloquine) than as primary medication [77]. Mefloquine and halofantrine are structurally similar and may compete for tissue-binding sites. In another study of 102 acute uncomplicated falciparum malarial patients treated with mefloquine (750 and 1,250 mg regimens) no significant changes in QT_c interval were found. Sinus bradycardia and sinus arrhythmia were frequent. Bradycardia was thought to be the result of autonomic control modulation after resolution of high fever [78]. There is no evidence of clinically significant pharmacodynamic interaction between quinine and mefloquine [79].

Lumefantrine belongs to the aryl aminoalcohol group of antimalarials, like quinine, halofantrine and mefloquine. In spite of similarities to halofantrine, lumefantrine does not have a significant effect on the QT interval [80].

Artemether, an artemisin derivative, caused QT_c interval prolongation after high-dose intramuscular administration in rats and dogs [81] and in a clinical study in patients with severe malaria [82]. However, to date, no QT_c prolongation has been reported after oral administration.

Co-artemether is an oral tablet of artemether (20 mg) and lumefantrine (120 mg) for the treatment of *P. falciparum* malaria. Artemether-lumefantrine did not alter the QT_c interval in a study of 13 healthy subjects [83]. Co-artemether may be used following failure of antimalarial prophylaxis or treatment with mefloquine. In a study of healthy males no clinically relevant QT_c interval prolongation was observed after the sequential administration of mefloquine and co-artemether or when either treatment was given alone [84]. In another study of 42 healthy Caucasian subjects, artemether–lumefantrine alone had no effect on the QT_c interval, while the infusion of quinine alone caused a transient prolongation of QT_c interval and this effect was slightly but significantly greater when quinine was infused after co-artemether. However, these occasional QT_c prolongations were not considered to be clinically relevant [85]. The concurrent administration of ketoconazole with co-artemether caused modest increases in AUC and C_{max} of artemether, its active metabolite dihydroartemisin, and lumefantrine in the healthy subjects. These increases in exposure to the antimalarial combination were much smaller than those observed with food intake [86]. However, the manufacturer of co-artemether advises the avoidance of concomitant therapy with potent CYP3A4 inhibitors and some potentially QT interval prolonging drugs [80].

In a study of four groups of patients (15 subjects in each group) with uncomplicated *P. falciparum* malaria the effects of quinine, halofantrine, mefloquine and artemether were compared. Mefloquine and artemether had no effect on the QT_c interval or QT dispersion. Quinine administration led to a slight lengthening of the QT_c interval and a modest, not significant increase in QT_c dispersion. Halofantrine caused significant QT_c interval prolongation and increase in QT_c dispersion, both significantly correlating with plasma halofantrine concentration but not with *N*-desbutylhalofantrine concentration. The QT_c dispersion was greater than 100 ms in five patients treated with halofantrine, a value similar to those observed in the congenital long QT syndrome [8].

Pentamidine

Pentamidine isethionate is an antiprotozoal agent used for leishmaniasis, trypanosomiasis and *Pneumocystis carinii* pneumonia. The use of pentamidine has become much more frequent during the last decades since *P. carinii* pneumonia is a common opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS) and during immunosuppressive therapy. Intravenous pentamidine therapy has been reported to provoke TdP in several recently published case reports [87–89]. In a prospective study by *Eisenhauer* et al. [90], three out of 14 patients (21%) were reported to develop TdP during intravenous pentamidine therapy, and five out of 14 (36%) developed QT_c prolongation of > 480 ms. However, in 16 consecutive HIV-infected patients treated with pentamidine, *Girgis* et al. [91] found neither a significant increase in incidence or complexity of ventricular arrhythmias nor a relevant increase in the QT_c interval as compared to premedication data or therapy with trimethoprim–sulfamethoxazole. Inhalatory pentamidine therapy does not seem to induce QT interval prolongation or to increase the risk of TdP [92]. *Taylor* et al. [10] have reported the safe and successful completion of therapy with pentamidine in aerosol form in a patient with TdP associated with the administration of intravenous pentamidine. On the other hand, *Engrav* et al. [93] reported multiple episodes of TdP in a HIV-infected patient treated with inhalatory pentamidine.

The proarrhythmic effects of pentamidine were thought to be related to its structural similarity with procainamide [88]. Hypomagnesemia, partly caused by pentamidine-induced tubular toxicity [94], malnutrition and human immunodeficiency virus-mediated myocarditis [95–97] may contribute to the pathogenesis of cardiotoxicity in patients with AIDS and *P. carinii* pneumonia. The arrhythmia usually appears relatively late and lasts longer after discontinuation, which can partly be explained by the tissue-binding charasteristics of the drug. In a review of the reported cases, *Mani* et al. [98] demonstrated that the average duration of intravenous pentamidine therapy before the onset of TdP was 12.5 days with a range of 6–20 days.

Katchman et al. [99] found that pentamidine had no acute blocking effect on HERG channels in stably transfected HEK 293 cells and no significant effect on QT intervals in the isolated perfused rabbit heart model, even at relatively high (micromolar) concentrations. *Kuryshev* et al. [100] also demonstrated that pentamidine had no significant acute inhibiting effect on HERG or other major cardiac membrane currents (KvLQT1/minK, Kv4.3, SCN5A Na^+ channels, and L-type Ca^{2+} channels). However, prolonged exposure to pentamidine caused a reduction in HERG currents in stably transfected HEK/HERG cells. Western blot and a chemiluminescence assay revealed that the reduction in HERG current density was associated with a decrease in the mature, fully glycosylated cell surface form of the HERG protein. The authors conclude that the delayed onset of the cardiac effect may be related to a pentamidine-induced inhibition of the HERG protein processing in the endoplasmic reticule with a consequential decrease in the expression of func-

tional HERG channels in the heart, rather than a direct blocking effect of the drug.

Other Antimicrobial Agents

Only isolated reports exist on the QT interval lengthening effect of the some other antimicrobal agents. The association of the following drugs with TdP is questionable.

Gabel et al. [101] reported a case of QT interval prolongation induced by clindamycin with subsequent repeated ventricular fibrillation and resuscitation. QT interval prolongation was found in a patient receiving methadone (which is known to block HERG potassium channel) and clindamycin [102].

Two cases of QT prolongation and TdP have been reported in association with trimethoprim-sulfamethoxazole [103, 104]. A single-nucleotide polymorphism was found in the KCNE2 gene encoding MinK-related peptide 1 (MiRP1), a subunit of the potassium channel HERG, in a patient with trimethoprim-sulfamethoxazole induced QT interval prolongation. This T8A-MiRP1 polymorphism was found in 1.6% of the general population [105].

Amantadine is an antiviral agent also used for treating Parkinson's disease. Amantadine intoxication with suicidal intention caused repeated episodes of TdP in a 37-year-old woman [106].

Some HIV protease inhibitors were reported to prolong the QT interval or provoke TdP. Lopinavir, nelfinavir, ritonavir and saquinavir blocked HERG channels heterologously expressed in HEK 293 cells in a dose-dependent manner [107]. Recently, TdP was also reported in association with atazanavir therapy [108]. In addition, amprenavir, indinavir, nelfinavir, ritonavir and saquinavir inhibit CYP3A4, potentially elevating the plasma levels of other QT interval prolonging drugs.

Two patients were reported to develop TdP during ganciclovir infusion, which recurred upon rechallenge with the drug [109].

Another antiviral agent, foscarnet caused hypocalcemia and as a consequence, QT interval lengthening in one patient [110].

Metronidazole is an azole derivative with antibacterial and antiprotozoal properties structurally related to azole type antifungals. No evidence is available on the *per se* QT interval prolonging effect of metronidazole. However, TdP occurred in a patient receiving amiodarone and metronidazole. Metronidazole is a potent inhibitor of cytochrome 3A4 and 2C9 isoenzymes, amiodarone is mainly metabolized by CYP 3A4 [111]. Metronidazole can also elevate the serum concentration of quinidine [112].

Discussion

The overall risk of TdP associated with non-cardiac medication is very low but it is enhanced in patients with risk factors. The risk of sudden cardiac death was almost three times higher among people currently using non-cardiac QT interval lengthening agents in a population-based study elaborating a database with complete medical records from more than 500,000 persons in The Netherlands. The authors drew the conclusion that 320 cases of sudden cardiac death could be attributed to the use of non-cardiac QT prolonging drugs in The Netherlands on a yearly basis [113]. Among antimicrobial agents, macrolides have the greatest potential for causing QT interval prolongation and TdP. However, risk evaluation for a single substance has several difficulties. *In vitro* studies provide valuable data on IC_{50} values and cardiac safety indices calculated by dividing the IC_{50} values by the respective therapeutic free plasma concentrations [114] (Table 2). However, these studies were carried out on various cell lines, which make the data poorly comparable. Experiments were carried out on various species of animals with probably various HERG channel densities on cardiomyocytes. Data from clinical experience have even more limitations. Due to the low incidence of drug-induced long QT syndrome and perhaps marketing trends, only pilot studies are available for several drugs with low subject numbers. During Phase I/II studies of the recently developed drugs, thorough observation of QT interval prolongation is necessary. However, the number of subjects may not be sufficient, the selection of subjects may not be representative in these studies. Moreover, it is difficult to decide if minimal QT interval prolongation during antimicrobial therapy has clinical significance. The reason is, difficulties of measuring the QT interval and the

Table 2
Overview of the IC_{50} values for the block of IKr of antimicrobials, their peak-free plasma concentrations, and the calculated cardiac safety indices.

Drug	Free C_{max} (μM)	HERG IC_{50} (μM)	Cardiac safety index
Erythromycin [13]	1.34	72.2	54
Clarithromycin [13]	1.04	32.9	32
Roxithromycin [13]	2.39	36.5	15
Sparfloxacin [26]	1.8	18	10
Grepafloxacin [26]	3.1	50	16
Gatifloxacin 400 mg iv [26]	9.8	130	13
Gatifloxacin 400 mg p.o. [26]	9.0	130	14
Levofloxacin 500 mg iv [26]	13	915	70
Levofloxacin 500 mg p.o. [26]	12	915	76
Ciprofloxacin 400 mg iv [26]	11	966	88
Ciprofloxacin 750 mg p.o. [26]	10	966	97
Ofloxacin 400 mg iv [26]	14	1,420	101
Ofloxacin 400 mg p.o. [26]	8.7	1,420	163
Lumefantrine [114]	0.17	8.13	48
Halofantrine [114]	0.57	0.04	0.07
Chloroquine [114]	0.41	2.5	6.1
Mefloquine [114]	0.05	2.64	53

lack of correction to heart rate in several studies and the lack of a widely accepted correction formula make the judgement of QT interval prolongation difficult. Post-marketing surveillance is influenced by the underreporting of adverse events.

Macrolides, azole antifungals, some quinolones and HIV proteases can potentiate cardiotoxicity of some other torsadogenic agents in two ways: by a direct effect on IKr (pharmakodynamic interaction) and by an indirect effect on the metabolization of the other agents (pharmacokinetic interaction).

The onset of TdP varies. It may appear either in the first hours or days after initiation of the culprit drug or after several months or years of therapy. This delayed onset of the cardiac adverse effect may be related to a change in drug dose, a drug interaction, or the introduction of other risk factors (such as electrolyte abnormalities or bradycardia) [115]. The role of drug metabolites in drug-induced QT interval prolongation is important and should be thoroughly investigated, because some metabolites have HERG-blocking potential while other metabolites are safe and may be target molecules for the pharmaceutical industry.

Some patients with acquired LQTS are genetically susceptible to torsadogenic drugs. Mutation carriers of LQTS can have normal ECGs and remain symptom-free until initiation of QT interval prolonging agents. Mutations affecting genes encoding potassium and sodium channels or subunits (KCNQ1, KCNH2, KCNE1, KCNE2, SCN5A) have been identified in a minority of patients with acquired LQTS. Genetic testing of patients with drug-induced TdP is not done routinely in the clinical practice. Patients with LQTS (congenital or acquired) and their relatives should be informed on the increased risk from QT interval prolonging agents [115].

The risk of TdP can easily be reduced by the recognition of risk factors, amelioration of correctable abnormalities (for example hypokalemia), the avoiding of QT interval prolonging drugs in patients with multiple risk factors and appropriate QT interval monitoring during treatment in susceptible patients [30]. Physicians should prescribe potentially QT-prolonging antimicrobials only after cautious clinical evaluation of risk factors for TdP. Obtaining a pre-treatment ECG is also advisable. When drugs that inhibit CYP3A4 are coadministered, the plasma levels of the parent drug may rise considerably, thus leading to further lengthening the QT interval and increasing risk of TdP. The concomitant use of these drugs should be avoided.

The management of patients with drug-induced TdP includes identification of the arrhythmia, withdrawal of any QT interval prolonging drugs (and all non-essential drugs) and correction of predisposing factors (high normal serum potassium is desired). Emergency therapy includes defibrillation with unsynchronized DC shock (200–360 J) to terminate sustained episodes, intravenous magnesium sulfate (2 g over 1–2 min, repeat once or twice at 5 to 15-min intervals) and acceleration of heart rate to 100/min with temporary cardiac pacing or isoproterenol. Isoproterenol should be considered only in the presence of bradycardia if cardiac pacing cannot be started immediately in patients without hypertension or coronary artery disease. The use of class Ia, Ic and III antiarrhythmic drugs must be avoided. In resistant cases intravenous administration of lidocain (1 mg/kg over 2 min, repeat once, if a response is observed continue 1–4 mg/min) might be useful [115].

References

1. Yap YG, Camm AJ: Drug induced QT prolongation and torsades de pointes. Heart 2003; 89: 1363–1372.
2. Camm AJ: Clinical trial design to evaluate the effect of drugs on cardiac repolarization: current state of the art. Heart Rhythm 2005; 2: S23–S29.
3. Haverkamp W, Breithardt G, Camm AJ, Janse MJ, Rosen MR, Antzelevitch C, Escande D, Franz M, Malik M, Moss A, Shah R: The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications. Eur Heart J 2000; 21: 1216–1231.
4. Justo D, Zeltser D: Torsades de pointes induced by antibiotics. Eur J Intern Med 2006; 17: 254–259.
5. Sanchez-Chapula JA, Ferrer T, Navarro-Polanco RA, Sanguinetti MC: Voltage-dependent profile of human ether-a-go-go-related gene channel block is influenced by a single residue in the S6 transmembrane domain. Mol Pharmacol 2003; 63: 1051–1058.
6. Schaffer D, Singer S, Korvick J, Honig P: Concomitant risk factors in reports of torsades de pointes associated with macrolide use: review of the United States Food and Drug Administration Adverse Event Reporting System. Clin Infect Dis 2002; 35: 197–200.
7. Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC, Cantilena LR: Terfenadine-ketoconazole interaction: pharmacokinetic and electrocardiographic consequences. JAMA 1993; 269: 1513–1518.
8. Touze JE, Heno P, Fourcade L, Deharo JC, Thomas G, Bohan S, Paule P, Riviere P, Kouassi E, Buguet A: The effects of antimalarial drugs on ventricular repolarization. Am J Trop Med Hyg 2002; 67: 54–60.
9. Demaziere J, Fourcade JM, Busseuil CT, Adeleine P, Meyer SM, Saissy JM: The hazards of chloroquine self prescription in west Africa. J Toxicol Clin Toxicol 1995; 33: 369–370.
10. Taylor AJ, Hull RW, Coyne PE, Woosley RL, Eliasson AH: Pentamidine-induced torsades de pointes: safe completion of therapy with inhaled pentamidine. Clin Pharmacol Ther 1991; 49: 698–700.
11. Priori SG, Napolitano C, Schwartz PJ: Low penetrance in the long-QT syndrome: clinical impact. Circulation 1999; 99: 529–533.
12. Zeltser D, Justo D, Halkin A, Prokhorov V, Heller K, Viskin S: Torsade de pointes due to noncardiac drugs: most patients have easily identifiable risk factors. Medicine 2003; 82: 282–290.
13. Volberg WA, Koci BJ, Su W, Lin J, Zhou J: Blockade of human cardiac potassium channel human ether-a-go-go-related gene (HERG) by macrolide antibiotics. J Pharmacol Exp Ther 2002; 302: 320–327.

14. Milberg P, Eckardt L, Bruns H-J, Biertz J, Ramtin S, Reinsch N, Fleischer D, Kirchoof P, Fabritz L, Breithardt G, Haverkamp W: Divergent proarrhythmic potential of macrolide antibiotics despite similar QT prolongation: fast phase 3 repolarization prevents early afterdepolarizations and torsade de pointes. J Pharmacol Exp Ther 2002; 303: 218–225.
15. West PD, Martin DK, Bursill JA, Wyse KR, Campbell TJ: Comparative study of the effects of erythromycin and roxithromycin on action potential duration and potassium currents in canine purkinje fibers and rabbit myocardium. J Cardiovasc Pharmacol Ther 1998; 3: 29–36.
16. Daleau P, Lessard E, Groleau M-F, Turgeon J: Erythromycin blocks the rapid component of the delayed rectifier potassium current and lenghtens repolarization of guinea pig ventricular myocytes. Circulation 1995; 91: 3010–3016.
17. Antzelevitch C, Sun A-Q, Zhang Z-Q, Yan G-X: Cellular and ionic mechanisms underlying erythromycin-induced long QT intervals and torsade de pointes. J Am Coll Cardiol 1996; 28: 1836–1848.
18. Drici M-D, Knollmann BC, Wang W-X, Woosley RL: Cardiac actions of erythromycin. Influence of female sex. JAMA 1998; 280: 1774–1776.
19. Schoenenberger RA, Haefeli WE, Weiss P, Ritz RF: Association of intravenous erythromycin and potentially fatal ventricular tachycardia with *Q-T* prolongation (torsades de pointes). BMJ 1990; 300: 1375–1376.
20. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM: Oral erythromycin and the risk of sudden death from cardiac causes. N Engl J Med 2004; 351: 1089–1096.
21. Stramba-Badiale M, Nador F, Porta N, Guffanti S, Frediani M, Colnaghi C, Grancini F, Motta G, Carnelli V, Schwartz PJ: QT interval prolongation and risk of life-threatening arrhythmias during toxoplasmosis prophylaxis with spiramycin in neonates. Am Heart J 1997; 133: 108–111.
22. Promphan W, Khongphatthanayothin A, Horchaiprasit K, Benjacholamas V: Roxithromycin induced torsade de pointes in a patient with complex congenital heart disease and complete atrioventricular block. Pacing Clin Electrophysiol 2003; 26: 1424–1426.
23. Justo D, Mardi T, Zeltser D: Roxithromycin-induced torsades de pointes. Eur J Intern Med 2004; 15: 326–327.
24. Honig PK, Woosley RL, Zamani K, Conner DP, Cantilena LR Jr: Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. Clin Pharmacol Ther 1992; 52: 231–238.
25. Gupta S, Banfield C, Kantesaria B, Marino M, Clement R, Affrime M, Batra V: Pharmacokinetic and safety profile of desloratadine and fexofenadine when coadministered with azithromycin: a randomized, placebo-controlled, parallel-group study. Clin Ther 2001; 23: 451–466.
26. Kang J, Wang L, Chen XL, Triggle DJ, Rampe D: Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K^+ channel HERG. Mol Pharmacol 2001; 59: 122–126.
27. Dupont H, Timsit JF, Souweine B, Gachot B, Wolff M, Regnier B: Torsades de pointe probably related to sparfloxacin. Eur J Clin Microbiol Infect Dis 1996; 15: 350–351.
28. Frotingham R: Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. Pharmacotherapy 2001; 21: 1468–1472.
29. Bellomo S: Quinolone safety and efficacy. Emerg Infect Dis 2005; 11: 985–986.
30. Amankwa K, Krishnan SC, Tisdale JE: Torsades de pointes associated with fluoroquinolones: importance of concomitant risk factors. Clin Pharmacol Ther 2004; 75: 242–247.
31. Iannini PB, Doddamani S, Byazrova E, Curciumaru I, Kramer H: Risk of torsades de pointes with non-cardiac drugs. Prolongation of QT interval is probably a class effect of fluoroquinolones. BMJ 2001; 322: 46–47.
32. Bertino JS, Owens RC Jr, Carnes TD, Iannini PB: Gatifloxacin-associated corrected QT interval prolongation, torsades de pointes, and ventricular fibrillation in patients with known risk factors. Clin Infect Dis 2002; 34: 861–863.
33. Prabhakar M, Krahn AD: Ciprofloxacin-induced acquired long QT syndrome. Heart Rythm 2004; 1: 624–626.
34. Katritsis D, Camm AJ: Quinolones: cardioprotective or cardiotoxic? Pacing Clin Electrophysiol 2003; 26: 2317–2320.
35. Frotingham R: Quinolone safety and efficacy. Emerg Infect Dis 2005; 11: 986–987.
36. McLellan RA, Drobitch RK, Monshouwer M, Renton KW: Fluoroquinolone antibiotics inhibit cytochrome P450-mediated microsomal drug metabolism in rat and human. Drug Metab Dispos 1996; 24: 1134–1138.
37. Robinson RF, Nahata MC, Olshefski RS: Syncope associated with concurrent amitriptyline and fluconazole therapy. Ann Pharmacother 2000; 34: 1406–1409.
38. Dorsey ST, Biblo LA: Prolonged QT interval and torsades de pointes caused by the combination of fluconazole and amitryptiline. Am J Emerg Med 2000; 18: 227–229.
39. Tsai WC, Tsai LM, Chen JH: Combined use of astemizole and ketoconazole resulting in torsade de pointes. J Formos Med Assoc 1997; 96: 144–146.
40. Pohjola-Sintonen S, Toivonen L, Neuvonen P: Itraconazole prevents terfenadine metabolism and increases risk of torsades de pointes ventricular tachycardia. Eur J Clin Pharmacol 1993; 45: 191–193.
41. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR Jr: Torsades de pointes occurring in association with terfenadine use. JAMA 1990; 264: 2788–2790.
42. Dumaine R, Roy ML, Brown AM: Blockade of HERG and Kv1.5 by ketoconazole. J Pharmacol Exp Ther 1998; 286: 727–735.
43. Kikuchi K, Nagatomo T, Abe H, Kawakami K, Duff HJ, Makielski JC, January T, Nakashima Y: Blockade of HERG cardiac K+ current by antifungal drug miconazole. Br J Pharmacol 2005; 144: 840–848.
44. Ridley JM, Milnes JT, Duncan RS, McPate MJ, James AF, Witchel HJ, Hancox JC: Inhibition of the HERG K^+ channel by the antifungal drug ketoconazole depends on channel gating and involves the S6 residue F656. FEBS Lett 2006; 580: 1999–2005.
45. Tatetsu H, Asou N, Nakamura M, Hanaoka N, Matsuno F, Horikawa K, Mitsuya H: Torsades de pointes upon fluconazole administration in a patient with acute myeloblastic leukaemia. Am J Hematol 2006; 81: 366–369.
46. Khazan M, Mathis AS: Probable case of torsades de pointes induced by fluconazole. Pharmacotherapy 2002; 22: 1632–1637.
47. Wassmann S, Nickenig G, Bohm M: Long QT syndrome and torsades de pointes in a patient receiving fluconazole. Ann Intern Med 1999; 131: 797.
48. Tholakanahalli VN, Potti A, Hanley JF, Merliss AD: Fluconazole-induced torsade de pointes. Ann Pharmacother 2001; 35: 432–434.
49. Alkan Y, Haefeli WE, Burhenne J, Stein J, Yaniv I, Shalit I: Voriconazole-induced QT interval prolongation and ventricular tachycardia: a non-concentration-dependent adverse effect. Clin Infect Dis 2004; 39: e49–e52.
50. Taylor WR, White NJ: Antimalarial drug toxicity: a review. Drug Saf 2004; 27: 25–61.

51. White NJ, Looareesuwan S, Warrell DA: Quinine and quinidine: a comparison of EKG effects during the treatment of malaria. J Cardiovasc Pharmacol 1983; 5: 173–175.
52. Martin ES, Rogalski K, Black JN: Quinine may trigger torsades de pointes during astemizole therapy. Pacing Clin Electrophysiol 1997; 20: 2024–2025.
53. Hermans K, Stockman D, Van den Branden F: Grapefruit and tonic: a deadly combination in a patient with the long QT syndrome. Am J Med 2003; 114: 511–512.
54. Harris L, Downar E, Shaikh NA, Chen T: Antiarrhythmic potential of chloroquine: new use for an old drug. Can J Cardiol 1988; 4: 295–300.
55. Sanchez-Chapula JA, Salinas-Stefanon E, Torres-Jacome J, Benavides-Haro DE, Navarro-Polanco RA: Blockade of currents by the antimalarial drug chloroquine in feline ventricular myocytes. J Pharmacol Exp Ther 2001; 297: 437–445.
56. Bustos MD, Gay F, Diquet B, Thomare P, Warot D: The pharmacokinetics and electrocardiographic effects of chloroquine in healthy subjects. Trop Med Parasitol 1994; 45: 83–86.
57. Stas P, Faes D, Noyens P: Conduction disorder and QT prolongation secondary to long-term treatment with chloroquine. Int J Cardiol 2007. doi: 10.1016/j.ijcard.2007.04.055.
58. Akhtar T, Imran M: Sudden deaths while on halofantrine treatments: a report of two cases from Peshawar. J Pak Med Assoc 1994; 44: 120–121.
59. Malvy D, Receveur MC, Ozon P, Djossou F, Le Metayer P, Touze JE, Longy-Boursier M, Le Bras M: Fatal cardiac incident after use of halofantrine. J Travel Med 2000; 7: 215–216.
60. Karbwang J, Na Bangchang K: Clinical pharmacokinetics of halofantrine. Clin Pharmacokinet 1994; 27: 104–119.
61. Lavallee I, Marc E, Moulin F, Treluyer JM, Imbert P, Gendrel D: Cardiac rhythm disturbances and prolonged QT interval with halofantrine. Arch Pediatr 2001; 8: 795–800.
62. Monlun E, Le Metayer P, Szwandt S, Neau D, Longy-Boursier M, Horton J, Le Bras M: Cardiac complications of halofantrine: a prospective study of 20 patients. Trans R Soc Trop Med Hyg 1995; 89: 430–433.
63. Wesche DL, Schuster BG, Wang W-X, Woosley RL: Mechanism of cardiotoxicity of halofantrine. Clin Pharmacol Ther 2000; 67: 521–529.
64. Piippo K, Holmström S, Swan H, Viitasalo M, Raatikka M, Toivonen L, Kontula K: Effect of the antimalarial drug halofantrine in the long QT syndrome due to a mutation of the cardiac sodium channel gene SCN5A. Am J Cardiol 2001; 87: 909–911.
65. Tie H, Walker BD, Singleton CB, Valenzuela SM, Bursill JA, Wyse KR, Breit SN, Campbell TJ: Inhibition of HERG potassium channels by the antimalarial agent halofantrine. Br J Pharmacol 2000; 130: 1967–1975.
66. Sanchez-Chapula JA, Navarro-Polanco RA, Sanguinetti MC: Block of wild-type and inactivation-deficient human ether-a-go-go-related gene K^+ channels by halofantrine. Naunyn Schmiedebergs Arch Pharmacol 2004; 370: 484–491.
67. Batey AJ, Lightbown ID, Lambert JP, Edwards G, Coker SJ: Comparison of the acute cardiotoxicity of the antimalarial drug halofantrine *in vitro* and *in vivo* in anaesthetized guinea-pigs. Br J Pharmacol 1997; 122: 563–569.
68. Batey AJ, Coker SJ: Proarrhythmic potential of halofantrine, terfenadine and clofilium in a modified *in vivo* model of torsade de pointes. Br J Pharmacol 2002; 135: 1003–1012.
69. Charbit B, Becquemont L, Lepere B, Peytavin G, Funck-Brentano C: Pharmacokinetic and pharmacodynamic interaction between grapefruit juice and halofantrine. Clin Pharmacol Ther 2002; 72: 514–523.
70. Mbai M, Rajamani S, January CT: The antimalarial drug halofantrine and its metabolite N-desbutylhalofantrine block HERG potassium channels. Cardiovasc Res 2002; 55: 799–805.
71. McIntosh MP, Batey AJ, Porter CJ, Charman WN, Coker SJ: Desbutylhalofantrine: evaluation of QT prolongation and other cardiovascular effects after intravenous administration *in vivo*. J Cardiovasc Pharmacol 2003; 41: 406–413.
72. Gundersen SG, Rostrup M, von der Lippe E, Platou ES, Myrvang B, Edwards G: Halofantrine-associated ventricular fibrillation in a young woman with no predisposing QT_c prolongation. Scand J Infect Dis 1997; 29: 207–208.
73. Touze JE, Bernard J, Keundjian A, Imbert P, Viguier A, Chaudet H, Doury JC: Electrocardiographic changes and halofantrine plasma level during acute falciparum malaria. Am J Trop Med Hyg 1996; 54: 225–228.
74. Kang J, Chen X-L, Wang L, Rampe D: Interactions of the antimalarial drug mefloquine with the human cardiac potassium channels KvLQT1/minK and HERG. J Pharmacol Exp Ther 2001; 299: 290–296.
75. Lightbown ID, Lambert JP, Edwards G, Coker SJ: Potentiation of halofantrine-induced QT_c prolongation by mefloquine: correlation with blood concentrations of halofantrine. Br J Pharmacol 2001; 132: 197–204.
76. Davis TM, Dembo LG, Kaye-Eddie SA, Hewitt BJ, Hislop RG, Batty KT: Neurological, cardiovascular and metabolic effects of mefloquine in healthy volunteers: a double-blind, placebo-controlled trial. Br J Clin Pharmacol 1996; 42: 415–421.
77. Nosten F, ter Kuile FO, Luxemburger C, Woodrow C, Kyle DE, Chongsuphajaisiddhi T, White NJ: Cardiac effects of antimalarial treatment with halofantrine. Lancet 1993; 341: 1054–1056.
78. Laothavorn P, Karbwang J, Na Bangchang K, Bunnag D, Harinasuta T: Effect of mefloquine on electrocardiographic changes in uncomplicated falciparum malaria patients. Southeast Asian J Trop Med Public Health 1992; 23: 51–54.
79. Supanaranond W, Suputtamongkol Y, Davis TM, Pukrittayakamee S, Teja-Isavadharm P, Webster HK, White NJ: Lack of a significant adverse cardiovascular effect of combined quinine and mefloquine therapy for uncomplicated malaria. Trans R Soc Trop Med Hyg 1997; 91: 694–696.
80. Members of the Technical Guidelines Development Group: Pharmacology of antimalarial drugs. In: WHO guidelines for the treatment of malaria. WHO Press Geneva, Switzerland, 2006, pp 87–129, ISBN 92 4 154694 8.
81. Brewer TG, Grate SJ, Peggins JO, Weina PJ, Petras JM, Levine BS, Heiffer MH, Schuster BG: Fatal neurotoxicity of arteether and artemether. Am J Trop Med Hyg 1994; 51: 251–259.
82. Hien TT, Day NPJ, Phu NH, Mai NTH, Chau TTH, Loc PP, Sinh DX, Chuong LV, Vinh H, Waller D, Peto TEA, White NJ: A controlled trial of artemether or quinine in Vietnamese adults with severe Falciparum Malaria. N Eng J Med 1996; 335: 76–83.
83. Bindschedler M, Lefevre G, Degen P, Sioufi A: Comparison of the cardiac effects of the antimalarials co-artemether and halofantrine in healthy participants. Am J Trop Med Hyg 2002; 66: 293–298.
84. Bindschedler M, Lefevre G, Ezzet F, Schaeffer N, Meyer I, Thomsen MS: Cardiac effects of co-artemether (artemether/lumefantrine) and mefloquine given alone or in combination to healthy volunteers. Eur J Clin Pharmacol 2000; 56: 375–381.
85. Lefevre G, Carpenter P, Souppart C, Schmidli H, Martin JM, Lane A, Ward C, Amakye D: Interaction trial between artemether-lumefantrine (Riamet) and quinine in healthy subjects. J Clin Pharmacol 2002; 42: 1147–1158.

86. Lefevre G, Carpenter P, Souppart C, Schmidli H, McClean M, Stypinski D: Pharmacokinetics and electrocardiographic pharmacodynamics of artemether-lumefantrine (Riamet) with concomitant administration of ketoconazole in healthy subjects. Br J Clin Pharmacol 2002; 54: 485–492.
87. Mitchell P, Dodek P, Lawson L, Kiess M, Russell J: Torsades de pointes during intravenous pentamidine isethionate therapy. CMAJ 1989; 140: 173–174.
88. Wharton JM, Demopulos PA, Goldschlager N: Torsade de pointes during administration of pentamidine isethionate. Am J Med 1987; 83: 571–576.
89. Otsuka M, Kanamori H, Sasaki S, Taguchi J, Harano H, Ogawa K, Matsuzaki M, Mohri H, Okubo T, Sumita S, Ochiai H: Torsades de pointes complicating pentamidine therapy of Pneumocystis carinii pneumonia in acute myelogenous leukemia. Intern Med 1997; 36: 705–708.
90. Eisenhauer MD, Eliasson AH, Taylor AJ, Coyne PE Jr, Wortham DC: Incidence of cardiac arrhythmias during intravenous pentamidine therapy in HIV-infected patients. Chest 1994; 105: 389–395.
91. Girgis I, Gualberti J, Langan L, Malek S, Mustaciuolo V, Costantino T, McGinn G: A prospective study of the effect of I.V. pentamidine therapy on ventricular arrhythmias and QT_c prolongation in HIV-infected patients. Chest 1997; 112: 646–653.
92. Cardoso JS, Mota-Miranda A, Conde C, Moura B, Rocha-Goncalves F, Lecour H: Inhalatory pentamidine and the duration of the QT interval in HIV-infected patients. Int J Cardiol 1997; 59: 285–289.
93. Engrav MB, Coodley G, Magnusson AR: Torsade de pointes after inhaled pentamidine. Ann Emerg Med 1992; 21: 1403–1405.
94. Gradon JD, Fricchione L, Sepkowitz D: Severe hypomagnesemia associated with pentamidine therapy. Rev Infect Dis 1991; 13: 511–512.
95. Stein KM, Haronian H, Mensah GA, Acosta A, Jacobs J, Kligfield P: Ventricular tachycardia and torsades de pointes complicating pentamidine therapy of Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. Am J Cardiol 1990; 66: 888–889.
96. Stein KM, Fenton C, Lehany AM, Okin PM, Kligfield P: Incidence of QT interval prolongation during pentamidine therapy of Pneumocystis carinii pneumonia. Am J Cardiol 1991; 68: 1091–1094.
97. Cohen IS, Anderson DW, Virmani R, Reen BM, Macher AM, Sennesh J, DiLorenzo P, Redfield RR: Congestive cardiomyopathy in association with the acquired immunodeficiency syndrome. N Engl J Med 1986; 315: 628–30.
98. Mani S, Kocheril AG, Andriole VT: Case report: pentamidine and polymorphic ventricular tachycardia revisited. Am J Med Sci 1993; 305: 236–240.
99. Katchman AN, Koerner J, Tosaka T, Woosley RL, Ebert SN: Comparative evaluation of HERG currents and QT intervals following challenge with suspected torsadogenic and nontorsadogenic drugs. J Pharmacol Exp Ther 2006; 316: 1098–1106.
100. Kuryshev YA, Ficker E, Wang L, Hawryluk P, Dennis AT, Wible BA, Brown AM, Kang J, Chen XL, Sawamura K, Reynolds W, Rampe D: Pentamidine-induced long QT syndrome and block of hERG trafficking. J Pharmacol Exp Ther 2005; 312: 316–323.
101. Gabel A, Schymik G, Mehmel HC: Ventricular fibrillation due to long QT syndrome probably caused by clindamycin. Am J Cardiol 1999; 83: 813–815.
102. Srivatsa U, Hoppe B, Lu J, Feld GK: Sequential appearance of both Brugada and long QT patterns in a single patient receiving methadone. Heart Rythm 2005; 2: S50.
103. Wiener I, Rubin DA, Martinez E, Postman J, Herman MV: QT prolongation and paroxysmal ventricular tachycardia occurring during fever following trimethoprim-sulfamethoxazole administration. Mt Sinai J Med 1981; 48: 53–55.
104. Lopez JA, Harold JG, Rosenthal MC, Oseran DS, Schapira N, Peter T: QT prolongation and torsades de pointes after administration of trimethoprim-sulfamethoxazole. Am J Cardiol 1987; 59: 376–377.
105. Sesti F, Abbott GW, Wei J, Murray KT, Saksena S, Schwartz PJ, Priori SG, Roden DM, George AL Jr, Goldstein SA: A common polymorphism associated with antibiotic-induced cardiac arrhythmia. Proc Natl Acad Sci 2000; 97: 10613–10618.
106. Sartori M, Pratt CM, Young JB: Torsade de Pointe: malignant cardiac arrhythmia induced by amantadine poisoning. Am J Med 1984; 77: 388–391.
107. Anson BD, Weaver JG, Ackerman MJ, Akinsete O, Henry K, January CT, Badley AD: Blockade of HERG channels by HIV protease inhibitors. Lancet 2005; 365: 682–686.
108. Ly T, Ruiz ME: Prolonged QT interval and torsades de pointes associated with atazanavir therapy. Clin Infect Dis 2007; 44: e67–e68.
109. Cohen AJ, Weiser B, Afzal Q, Fuhrer J: Ventricular tachycardia in two patients with AIDS receiving ganciclovir (DHPG). AIDS 1990; 4: 807–809.
110. Balfour HH Jr, Fletcher CV, Erice A, Henry WK, Acosta EP, Smith SA, Holm MA, Boivin G, Shepp DH, Crumpacker CS, Eaton CA, Martin-Munley SS: Effect of foscarnet on quantities of cytomegalovirus and human immunodeficiency virus in blood of persons with AIDS. Antimicrob Agents Chemother 1996; 40: 2721–2726.
111. Kounas SP, Letsas KP, Sideris A, Efraimidis M, Kardaras F: QT interval prolongation and torsades de pointes due to a coadministration of metronidazole and amiodarone. Pacing Clin Electrophysiol 2005; 28: 472–473.
112. Cooke CE, Sklar GE, Nappi JM: Possible pharmacokinetic interaction with quinidine: ciprofloxacin or metronidazole? Ann Pharmacother 1996; 30: 364–366.
113. Straus SMJM, Sturkenboom MCJM, Bleumink GS, Dieleman JP, van der Lei J, de Graeff PA, Kingma JH, Stricker BHC: Non-cardiac QT_c-prolonging drugs and the risk of sudden cardiac death. Eur Heart J 2005; 26: 2007–2012.
114. Traebert M, Dumotier B, Meister L, Hoffmann P, Dominguez-Estevez M, Suter W: Inhibition of hERG K+ currents by antimalarial drugs in stably transfected HEK293 cells. Eur J Pharmacol 2004; 484: 41–48.
115. Tong KL, Lau YS, Teo WS: A case series of drug-induced long QT syndrome and torsade de pointes. Singapore Med J 2001; 42: 566–570.
116. Lin JC, Quasny HA: QT prolongation and development of torsades de pointes with the concomitant administration of oral erythromycin base and quinidine. Pharmacotherapy 1997; 17: 626–630.
117. Choudhury L, Grais IM, Passman RS: Torsades de pointes due to drug interaction between disopyramide and clarithromycin. Heart Dis 1999; 1: 206–207.
118. Hayashi Y, Ikeda U, Hashimoto T, Watanabe T, Mitsuhashi T, Shimada K: Torsades de pointes ventricular tachycardia induced by clarithromycin and disopyramide in the presence of hypokalemia. Pacing Clin Electrophysiol 1999; 22: 672–674.
119. Sekkarie MA: Torsades de pointes in two chronic renal failure patients treated with cisapride and clarithromycin. Am J Kidney Dis 1997; 30: 437–439.
120. Piquette RK: Torsade de pointes induced by cisapride/clarithromycin interaction. Ann Phamacother 1999; 33: 22–26.

121. Kyrmizakis DE, Chimona TS, Kanoupakis EM, Papadakis CE, Velegrakis GA, Helidonis ES: QT prolongation and torsades de pointes associated with concurrent use of cisapride and erythromycin. Am J Otolaryngol 2002; 23: 303–307.
122. Paris DG, Parente TF, Bruschetta HR, Guzman E, Niarchos AP: Torsades de pointes induced by erythromycin and terfenadine. Am J Emerg Med 1994; 12: 636–638.
123. Biglin KE, Faraon MS, Constance TD, Lieh-Lai M: Drug-induced torsades de pointes: a possible interaction of terfenadine and erythromycin. Ann Pharmacother 1994; 28: 282.
124. Fournier P, Pacouret G, Charbonnier B: A new cause of torsades de pointes: combination of terfenadine and troleandomycin. Ann Cardiol Angeiol 1993; 42: 249–252.
125. Hsieh MH, Chen SA, Chiang CE, Tai CT, Lee SH, Wen ZC, Chang MS: Drug-induced torsades de pointes in one patient with congenital long QT syndrome. Int J Cardiol 1996; 54: 85–88.
126. Desta Z, Kerbusch T, Flockhart DA: Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and extensive metabolizers of cytochrome P450 2D6 (CYP2D6). Clin Pharmacol Ther 1999; 65: 10–20.
127. Flockhart DA, Drici MD, Kerbusch T, Soukhova N, Richard E, Pearle PL, Mahal SK, Babb VJ: Studies on the mechanism of a fatal clarithromycin-pimozide interaction in a patient with Tourette syndrome. J Clin Psychopharmacol 2000; 20: 317–324.