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QT Prolongation with Antimicrobial Agents

Understanding the Significance

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Abstract

Cardiac toxicity has been relatively uncommon within the antimicrobial class of drugs, but well described for antiarrhythmic agents and certain antihistamines. Macrolides, pentamidine and certain antimalarials were traditionally known to cause QT-interval prolongation, and now azole antifungals, fluoroquinolones and ketolides can be added to the list. Over time, advances in preclinical testing methods for QT-interval prolongation and a better understanding of its sequelae, most notably torsades de pointes (TdP), have occurred. This, combined with the fact that five drugs have been removed from the market over the last several years, in part because of QT-interval prolongation-related toxicity, has elevated the urgency surrounding early detection and characterisation methods for evaluating non-antiarrhythmic drug classes. With technological advances and accumulating literature regarding QT prolongation, it is currently difficult or overwhelming for the practising clinician to interpret these data for purposes of formulary review or for individual patient treatment decisions.

Certain patients are susceptible to the effects of QT-prolonging drugs. For example, co-variates such as gender, age, electrolyte derangements, structural heart disease, end organ impairment and, perhaps most important, genetic predisposition, underlie most if not all cases of TdP. Between and within classes of drugs there are important differences that contribute to delayed repolarisation (e.g. intrinsic potency to inhibit certain cardiac ion currents or channels, and pharmacokinetics). To this end, a risk stratification scheme may be useful to rank and compare the potential for cardiotoxicity of each drug. It appears that in most published cases of antimicrobial-associated TdP, multiple risk factors are present. Macrolides in general are associated with a greater potential than other antimicrobials for causing TdP from both a pharmacodynamic and pharmacokinetic perspective. The azole antifungal agents also can be viewed as drugs that must be weighed carefully before use since they also have both pharmacodynamic and pharmacokinetic characteristics that may trigger TdP. The fluoroquinolones appear less likely to be associated with TdP from a pharmacokinetic perspective since they do not rely on cytochrome P450 (CYP) metabolism nor do they inhibit CYP enzyme isoforms, with the exception of grepafloxacin and ciprofloxacin. Nonetheless, patient selection must be carefully made for all of these drugs.

For clinicians, certain responsibilities are assumed when prescribing antimicrobial therapy: (i) appropriate use to minimise resistance; and (ii) appropriate patient and drug selection to minimise adverse event potential. Incorporating information learned regarding QT interval-related adverse effects into the drug selection process may serve to minimise collateral iatrogenic toxicity.

The discovery of the germ theory of disease ended the reign of infectious diseases as the leading cause of mortality in the US in the mid-20th century.[1] This important discovery led to human responses such as the advent of public health, sanitation, vaccination, antimicrobial agents and antisepsis.[1] Along with the important discovery of antimicrobial agents came uncommon but important adverse effects. Until recently, cardiac adverse effects were limited to macrolides and less frequently used antiparasitics, such as pentamidine. Cardiac toxicity can occur as an unintended consequence of drug therapy and is considered to be an increasingly important adverse drug reaction (ADR). In the US alone, between 300 000 and 400 000 people die annually of sudden cardiac death.[2] Torsades de

Table I. Risk factors for QT prolongation and torsades de pointes, resulting in reduced repolarisation reserve[15]

Drug-related risk factors	Host-related risk factors
Intrinsic QT-prolonging potential (e.g. I_{Kr} antagonism)	Electrolyte derangements (hypokalaemia, hypomagnesaemia, hypocalcaemia)
Effects on cardiac ion currents other than the I_{Kr}	Increased age
Co-medications associated with significant QT prolongation: class IA antiarrhythmics (quinidine, disopyramide, procainamide) and class III antiarrhythmics (sotalol, amiodarone, ibutilide, dofetilide, almokalant)	Gender (female > male)
	Structural heart disease (congestive heart failure, myocardial ischaemia)
Metabolic drug interactions (e.g. inhibition of CYP isoenzymes, especially CYP3A4, which results in supratherapeutic concentrations of a second coadministered drug known to cause QT prolongation)	Bradycardia
	Organ dysfunction with failure to adjust dosage accordingly for drugs known to prolong the QT interval
	Hypothyroidism
High dose of drug	CNS infection or tumour
Route of drug (IV vs PO) [e.g. erythromycin IV and PO]	Obesity
Arsenic, organophosphates	Genetics (known and unknown gene variants encoding mutations in cardiac ion currents)
Alcoholism, cocaine use	
Potassium-wasting diuretics (e.g. furosemide [frusemide]), resulting in depletion of potassium	

CYP = cytochrome P450; **I_{Kr}** = rapid component of the delayed rectifier potassium current; **IV** = intravenous; **PO** = oral.

pointes (TdP), a potentially fatal polymorphic ventricular tachyarrhythmia, has been linked to genetic predisposition, which may even underlie many drug-induced cases.[3-5] In addition to genetic susceptibility, drugs associated with QT-interval prolongation have been demonstrated to play a role in TdP. The Institute of Medicine[6] issued a report in 2000 stating that from 44 000 to 98 000 deaths occur annually from medical errors and that, of these deaths, approximately 7000 are attributable to ADRs.[6,7] Polypharmacy undoubtedly contributes to the occurrence of ADRs. For instance, a study showed that 64% of all visits to the physician result in a prescription.[8] As a result, 2.8 billion prescriptions were issued in the US in 2000, indicating a rate of ten prescriptions per person.[9] Ultimately, studies have shown that the rate of ADRs is significantly increased when a patient is on four or more prescriptions.[10] Prolongation of the QT interval underlies most reported cases of TdP, and is a characteristic feature of an increasing number of noncardiac drugs such as certain psychotropics, non-sedating antihistamines and antimicrobial agents.[11,12]

QT prolongation has traditionally been separated into two general categories: (i) inherited long QT syndrome (LQTS); and (ii) acquired LQTS. The most common cause of the latter is drug therapy. The number of drugs that are associated with QT-interval prolongation has grown considerably over the last few years, which is at least in part a function of the introduction of systematic preclinical screening. It is not uncommon for patients to receive drugs that cause QT-interval prolongation.[13] However, it is unusual for QT-interval prolongation in and of itself to result in TdP. Nonetheless, the extent of QT-interval prolongation is governed by multiple factors that can be divided into those that are host- and drug-related (table I). In most cases of non-antiarrhythmic drug-induced TdP, multiple risk factors are often, but not always, apparent.[12,14] These risk factors are important for clinicians to be familiar with in order to select 'safe' antimicrobial regimens.

Factors contributing to TdP include the intrinsic QT prolongation potential for a drug, its pharmacokinetic characteristics and the various host-related dynamics that determine a patient's susceptibility to drug-induced TdP. The background incidence for TdP in the general population has been reported to be 8.6 cases per 10 million people.[16] The incidence for the population receiving (any) drug therapy is estimated to be 40 cases per 10 million people (antibacterials were responsible for only a small number of cases).[16] Antimicrobial consumption in the community is dynamic. Over the last decade, it

has become more popular to use newer macrolides (e.g. azithromycin, clarithromycin) and newer generation quinolones.[13,17] This is important since the mentioned antibacterials can be associated with QT prolongation. This review covers basic electrophysiological information, predisposing risk factors, information required to interpret cardiac safety studies, and offers recommendations regarding the use of antimicrobials associated with QT prolongation.

1. QT-Interval Prolongation

1.1 The Cardiac Action Potential

The cardiac action potential is the fundamental unit of electrical activity in the heart (figure 1).[18] The voltage contour of the action potential is formed by the number and type of specific ion channels and ion transporters in the surface membrane of each myocyte.[19] The type and density of ion channels is in turn regulated genetically (which can be influenced by inherited diseases) or by transcriptional factors (which can be effected by mechanical overload).[20] Since the complement of channels and transporters varies in different regions of the heart, the shape of the action potential is different in atrial, ventricular and nodal tissue, as shown in figure 1. For more detailed discussion, the reader is referred to specific reviews of general electrophysiological principles[4,21] and antimicrobial-related electrophysiology.[12]

The standard surface ECG represents a temporal and spatial summation of individual action potentials across the entire heart (figure 1). The QRS complex corresponds to the depolarisation phase of the action potential. The width of the QRS complex roughly correlates with the time required for the wave of depolarisation to spread from ventricular myocyte to ventricular myocyte and to activate both left and right ventricles. The QT interval encompasses both the depolarisation phase and the repolarisation phase of the action potential. In the ab-

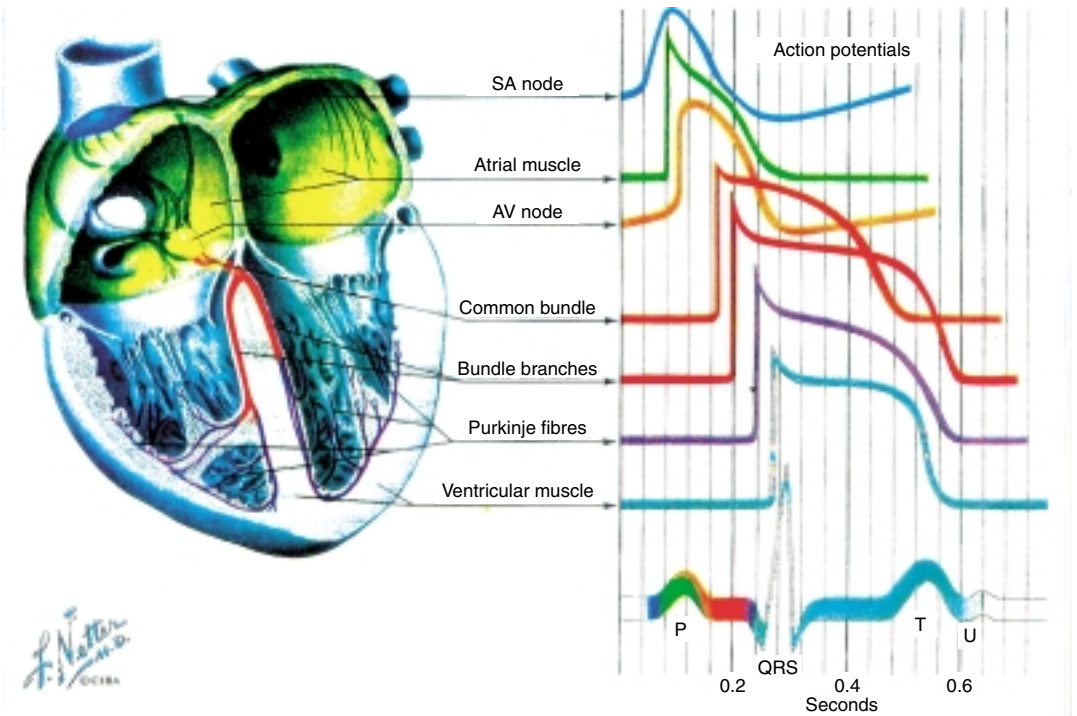

Fig. 1. The cardiac action potential (© 1969. Icon Learning Systems, LLC, a subsidiary of MediMedia USA Inc. Reprinted with permission from ICON Learning Systems, LLC, illustrated by Frank H. Netter, MD. All rights reserved.).[18] **AV** = atrioventricular; **SA** = sinoatrial.

sence of intermittent intraventricular conduction delays (e.g. intermittent or variable bundle branch block), changes in the QT interval reflect changes in cardiac repolarisation. Factors that impede membrane repolarisation and lengthen the duration of the action potential in individual myocytes may cause the QT interval to be prolonged. The QT interval is also modulated by heart rate, autonomic tone, gender and age.[12] The QT interval is dynamic with variability that exists from beat to beat, on a diurnal basis and from day to day.[22-24] Fluctuations in autonomic tone are the predominant factors that modulate QT variability. Other factors that contribute to QT variability include, for example, concomitant medications, electrolyte levels and myocardial ischaemia.[25,26]

The fundamental concern of a prolonged QT interval is the establishment of an electrophysiological milieu that predisposes to the occurrence of a polymorphic ventricular tachyarrhythmia termed 'torsades de pointes' (twisting of the points) as noted by the French cardiologist Dessertenne.[27] The drug-related mechanism thought to be responsible for drug-induced QT prolongation is the blockade of the human ether-à-go-go-related gene (HERG) that encodes the rapid component of the delayed rectifier potassium current or channel (I_{kr}).[28] The blockade of the HERG-encoded I_{kr} current results in the accumulation of potassium within the myocyte, which, in return, delays cardiac repolarisation. Electrical instability that occurs during the repolarisation phase may abruptly reverse its course and depolarise to produce an early after-depolarisation (EAD) that in turn may trigger a second action potential. If the second action potential excites the rest of the ventricle, a premature ventricular complex (PVC) will appear on the ECG. This pathophysiological process may be repetitive and self-sustaining, thereby giving rise to a series of after-depolarisations that result in a polymorphic ventricular arrhythmia referred to as TdP. If sustained and rapid, TdP can be life threatening.

The clinical presentation of TdP is important and its recognition can be elusive. TdP may present clinically as syncope, fainting, dizziness, palpitations, ventricular tachycardia or sudden death, or not at all (asymptomatic) if the duration of TdP is relatively short. In the cardiac adverse event description section of studies, it is uncommon to see TdP listed. However, the aforementioned manifestations should be scrutinised since they may be important surrogate markers for TdP.

1.2 QT Interval Measurement and Interpretation

The length of the QT interval varies inversely with heart rate and therefore shortens as the heart rate increases. To compare QT intervals over time for an individual or across a population, it is necessary to normalise the measured QT interval for heart rate effects. Several correction formulas exist. Bazett's formula (square root) generates a corrected QT interval (QTc) according to: $QTc = QT/(RR)^{0.5}$, where RR is the average interval in seconds between QRS complexes.[29] The Fridericia formula (cubic root) is calculated as follows: $QTc = QT/(RR)^{0.33}$.[30] The Framingham linear regression formula is a third correction factor. This formula is the only one to be derived from a large patient population and has been termed the most rigorous formula from an epidemiological perspective.[31,32] Bazett's formula is the most commonly used correction calculation and has been criticised because it overcorrects at high heart rates and it undercorrects at low heart rates.[33,34] The Fridericia formula may reflect a more accurate correction factor in patients with infection, particularly since fever is often associated with tachycardia. Experts have agreed that the optimal approach to correcting for heart rate remains to be validated.[35,36]

1.3 Inherited and Acquired Long QT Syndromes

As mentioned previously, LQTS has been categorised based on its suspected source or cause (i.e. inherited or acquired LQTS). It has been suggested that inherited LQTS may play a role in most forms of QT-interval-related cardiac toxicity.[15] Evidence for this is based on the findings from pharmacogenetic studies that have described clinically silent

forms of inherited LQTS, in which QT-interval measurements are usually normal, despite apparent genetic defects in cardiac ion channels.[37-39] In some cases, a diagnosis of congenital LQTS has been made only after an I_{Kr} antagonist was administered. The inherited forms of LQTS are caused by mutations in genes that modulate cardiac repolarisation. Seven genotypes have been identified (LQT1–LQT7) and there appear to be distinct symptoms, triggers for cardiac events, risks for mortality and treatment for each.[40] Diagnosis of inherited forms cannot reliably be established in as many as 50% of cases because of limitations in genetic analyses or the presence of gene mutations not yet identified. The principal clinical manifestations include recurrent syncope, vertigo, QT-interval prolongation and T- and U-wave abnormalities on the ECG, TdP and sudden cardiac death.[41,42] The frequencies of syncope and sudden cardiac death vary by family, gene and mutation, reflecting a complex set of environmental factors and other modifier genes that contribute to the risk. Importantly, some forms will remain clinically silent until a pharmacological or other stimulus surfaces, thus unmasking the cardiac ion mutation resulting in symptomatic arrhythmias.[15]

A variety of drug- and host-related factors contribute to acquired forms of LQTS (table I)[15] and, although discussed as separate entities, it must be acknowledged that genetic predisposition influences the outcome of many so-called acquired forms of LQTS. In most of these cases, reversal of the associated risk or disorder leads to normalisation of the QT interval. The administration of a drug that minimally prolongs the QT interval, such as an antimicrobial agent, may unmask clinically silent genetic cardiac channel anomalies.[15,43] An increasingly long list of drugs is now known to prolong the QT interval to varying degrees and clinical significance.[15,44] Some of these drugs are used intentionally to prolong cardiac repolarisation resulting in profound effects on the QT interval (e.g. class Ia and III antiarrhythmics), while for most other drugs QT prolongation is an untoward collateral effect. Importantly, not all drugs associated with QT prolongation cause proarrhythmic effects. For instance, the class III antiarrhythmic agent amiodarone and the calcium channel antagonist verapamil cause QT prolongation, but are not usually associated with arrhythmias; in fact, the former is actually used in the treatment of TdP.[33] One possible explanation for this is that amiodarone is associated with additional electrophysiological characteristics (e.g. noncompetitive β-blocking, and calcium and sodium current blocking effects) that influence the electrophysiological milieu, favouring stability as opposed to a torsadogenic environment.[45] This being stated, amiodarone has been associated with TdP and may play a role in causing TdP when concurrently administered with other QT-prolonging drugs. On the other hand, other antiarrhythmic agents such as quinidine, sotalol, dofetilide and ibutilide cause significant dose-dependent QT prolongation and, in effect, cause a relatively high incidence of TdP. Quinidine and sotalol, for example, have been associated with an incidence of TdP ranging from 2.0% to 8.8% and 1.8% to 4.8%, respectively.[33,46-52] Newer generation quinolones by comparison are associated with an incidence far less than 1%.[53,54]

2. General Risk Assessment for QT Interval-Related Toxicity

Relatively small changes in the QT interval (e.g. <10 msec) attributable to a drug have generated much attention.[55,56] In an effort to ascertain the potential a drug has to cause TdP, a single *in vitro* or *in vivo* test that would characterise the risk in preclinical testing would be ideal. Unfortunately, this test has not yet been discovered. In early 2002, regulatory guidance for QT-interval prolongation was provided, in draft form, by the US FDA's International Conference on Harmonisation S7B.[57] The draft document recommends three tests be performed on new pharmaceuticals in preclinical programmes: (i) HERG current studies to ascertain the impact of the drug on the I_{Kr} current; (ii) action potential duration assay using canine Purkinje fibres; and (iii) *in vivo* testing of the ECG in the rodent model. In addition to these proposed standards, the US FDA has begun to require the sponsor to submit

raw ECG data to the US FDA for the purposes of independent analyses of cardiac safety.[32]

2.1 Nonclinical *In Vitro* and *In Vivo* Assays

In general, several categories of *in vitro* and *in vivo* models have been used to determine drug-related cardiac toxicity. Experts have previously reviewed this elsewhere, and a recapitulation of the methods, animal or cell types used, benefits and limitations is presented in tabular form (see table II).[33,55] Drugs cause TdP by blocking the HERG-encoded potassium currents or by impacting the metabolism of other QT-prolonging drugs.[33] Thus, HERG-transfected cell studies seem logical to predict drug effects. These HERG studies measure the concentration of drug required to produce 50% inhibition (IC_{50}) of the I_{Kr} channel. Clinicians need to be cognisant of certain information to properly evaluate HERG studies. Potent I_{Kr} antagonists (i.e. IC_{50} <1.0 μmol/L) include dofetilide, sotalol, terfenadine and cisapride. Other less potent drugs (i.e. with higher IC_{50} values) may also pose a risk for QT prolongation, depending on a variety of factors, including their therapeutic free plasma concentrations and degree of accumulation in cardiac tissues. Thus, for most drugs within these classes, their respective IC_{50} values will be in excess of that achievable in human serum.[12,58] For HERG studies, testing limitations exist. Firstly, human drug exposures for many drugs are usually far below IC_{50} values reported. This is important in order to correlate a drug's potential to inhibit the HERG currents at clinically achievable concentrations. Secondly, QT prolongation has been recognised for drugs at concentrations causing <20% inhibition of HERG.[59] Drugs including cisapride, terfenadine, dofetilide and risperidone cause QT prolongation at clinical concentrations appreciably lower than IC_{50} values reported to inhibit HERG currents.[59] Thirdly, plasma concentrations may not always be the best surrogate marker for drug exposure to cardiac ion currents that reside in tissues. This is predominantly true for drugs exhibiting rapid uptake from systemic circulation by monocytes resulting in accumulation in tissue (e.g. most macrolides). Fourthly, it is unlikely that protein-bound drug is available to interact with cardiac ion channels. The degree of protein binding may be protective to a degree in that the drug is not able to penetrate into tissues and interact with ion channels when in bound form. The extent of protein binding may differ significantly, depending on the antimicrobial studied (e.g. gatifloxacin ~20% compared with gemifloxacin ~60%). Lastly, *in vitro* studies of a single cardiac ion current may oversimplify the complex physiological relationship between the various ion currents, and ignores other known factors that influence electrical instability. Nonetheless, HERG studies have emerged as a useful tool to assess a drug's I_{Kr}-antagonistic potential.

2.2 Clinical Measures of Risk

2.2.1 The Corrected QT Interval as a Surrogate Marker

In product labelling and clinical studies, QT-interval prolongation is often reported in terms of mean increase (± standard deviation [SD]). These values can be misleading and difficult to interpret since the mean values often have wide and overlapping standard deviations. For instance, mean QT prolongation might be calculated using 12 healthy volunteers or 200 hospitalised patients enrolled in a clinical trial. Importantly, a mean increase in the QT interval from a population does not predict the TdP risk for an individual. In addition, two drugs can be associated with the same degree of QT interval prolongation but have different risks for TdP.[43] On the other hand, evaluating an adequate sample size of potential recipients of the drug individually for so-called outlier values does in fact allow for risk assessment to be generally predicted. The Committee for Proprietary Medicinal Products (CPMP), one of the two main scientific bodies of the European Agency for the Evaluation of Medicinal Products,[16] published a document suggesting ranges for normal, borderline, and prolonged QTc intervals. For an individual patient taking a new drug, this document proposes that: (i) a drug-associated increase in the QTc of 30–60 msec may represent a drug effect and therefore "raises concern about the potential risk";

Table II. Nonclinical assays used to determine drug-related cardiac toxicity[33,55]

Type of model	Brief description	Animals/cells used	Utility	Limitations
***In vitro* models**				
Heterologous expression systems	Microinjection of ion channel (e.g. HERG) RNA into cells resulting in a functional recombinant expression system	Human embryonic kidney cells (HEK 293) Mouse fibroblasts (C-cells) Chinese hamster ovary cells Amphibian oocytes (*Xenopus laevis*)	Ideal method to study effect on I_{Kr} current Allows assessment of channel blockade over a wide range of drug concentrations If mammalian cells used, allows the use of physiological temperatures (e.g. 37°C)	Does not allow ion channel assessment other than I_{Kr} Impact of drug metabolites is not accounted for, unless specifically isolated and studied separately Full physiological effect cannot be appreciated (e.g. heart rate, changing drug concentrations) Cannot correlate dynamics of human pharmacokinetics into fixed drug concentration exposure *in vitro* Lack of standardisation among laboratories can result in different IC_{50} values If drug is insoluble in water, concentrations used may be restricted Amphibian oocyte model may overestimate the IC_{50} because of large amounts of lipophilic material in oocyte Studies must be conducted at room temperature
Isolated tissue studies	Tissues studied include Purkinje fibres, papillary muscles, specific myocytes, transmural wedge preparation of the left ventricle	Dog Rabbit Guinea pig Sheep Cat	Large numbers of compounds can be screened in conditions that favour I_{Kr} blockade (e.g. low K^+) Full effect on panel of ion channels can been appreciated Animal tissues selected demonstrate some similarity with human myocardium	Variability of ventricular myocytes exists, so endocardial, epicardial and M-cell muscle regions must be studied Differences between species in the type and number of ion currents exists (e.g. guinea pig, sheep, dog, both I_{Kr} and I_{Ks} are present; whereas in cat, rabbit and humans, I_{Kr} predominates) Rat and mouse not ideal models because of excessive variation in ion current type and distribution The type and number of ion currents may differ by gender Cannot correlate dynamics of human pharmacokinetics into fixed drug concentration exposure *in vitro*
Isolated intact hearts	Allows ECG and monophasic action potential measurement for intact hearts during drug exposure. Typical measurements include the concentration of a drug (mg/L) required to produce a certain percentage of prolongation of Purkinje fibres	Langendorff perfused guinea pig heart Langendorff perfused rabbit heart	Allows for ECG and monophasic action potential recordings to be evaluated Good for screening large numbers of compounds for I_{Kr} effects under expanded physiological conditions compared with other *in vitro* tests Provides consistent effects to be observed between I_{Kr}-blocking agents and nonblocking agents Possible to induce experimental TdP	Lacks precision Correlation between humans and animals and different animal species is questioned Does not account for effect of metabolites Results of comparative studies testing fluoroquinolones demonstrate consistent effects at the extremes (e.g. sparfloxacin at the high frequency end and ciprofloxacin at the low potential end), but has trouble distinguishing those in the middle (e.g. moxifloxacin and grepafloxacin); whereas HERG studies can distinguish all four agents tested For compounds insoluble in water, testing high concentrations may be limited

Continued next page

Table II. Contd

Type of model	Brief description	Animals/cells used	Utility	Limitations
***In vivo* (animal) models**				
ECG recordings in conscious or anaesthetised animals	Measurement of serial drug-induced changes in repolarisation	Dogs Pigs Monkeys	Ideal for dose-response evaluation	Establishment of baseline stability in model difficult to achieve (e.g. T-wave morphology is highly variable in dogs)
		Species with high baseline heart rates: rabbits rat guinea pigs mice	Provides complementary data to *in vitro* tests (by factoring in pharmacokinetics, including the effect of metabolites, dynamic drug concentrations, measurement of drug concentration and volume of distribution) Multilead ECGs can be performed to characterise a drug's effect on the QT interval in an *in vivo* system with the benefit of physiological assessment	Drugs that effect heart rate in addition to QT changes are challenging since human heart rate correction factors are not applicable to animals Interspecies drug metabolism may differ, and also may be different than in humans Limitations lead to difficulty in generalising results to humans

HERG = human ether-à-go-go–related gene; **IC_{50}** = concentration which produces 50% inhibition; **I_{Kr}** = rapid component of the delayed rectifier potassium current; **I_{Ks}** = slow component of the delayed rectifier potassium current; **TdP** = torsades de pointes.

and (ii) a QTc >500 msec or a QTc increase of >60 msec "raises clear concern about the potential risk".[16] These parameters have been termed 'outliers', and are of value in determining a drug's potential to cause TdP.

The data are derived from risk assessment for TdP in patients receiving sotalol. In a high-risk group of patients with clinically significant cardiac arrhythmias treated with sotalol, those with a drug-induced QTc >500 msec or an increase in QTc of >65 msec had a >3% incidence of TdP.[60] These recommendations may be revised in the future; however, they currently provide the metrics for considering ECG parameters and are fundamental to proarrhythmia risk assessment. Data regarding outlier values obtained from clinical trials, where available, are presented in section 4 under the individual antimicrobial agents.

2.2.2 Pharmacokinetic/Pharmacodynamic Risk Factors

In addition to the intrinsic ability of the individual drug to prolong the QT interval by interfering with the I_{Kr} current, presence of bradycardia, electrolyte imbalances and structural heart disease (e.g. pharmacodynamics), the pharmacokinetics of a drug (particularly the absorption, metabolism and elimination) may amplify the risk for TdP under specific conditions. Because the degree of QT prolongation appears to be related to drug concentration, alterations in pharmacokinetics may amplify the risk for TdP. The generally poor absorption of macrolides, for instance, probably plays a role in the observed difference in TdP incidence between intravenous and orally administered erythromycin (absolute bioavailability <50%). In fact, in 16 of 23 published cases of TdP, patients received intravenous high-dosage erythromycin 3–4 g/day, whereas only 3 of 23 cases occurred following administration of the usual dosage of oral erythromycin (1.5–2 g/day).[61-63] Typical peak erythromycin serum concentrations after 900mg administered intravenously are approximately 30 μg/mL versus 2–4 μg/mL following 500mg given orally.[64] The relatively poor bioavailability of erythromycin is not unique among

the macrolides and their derivatives (e.g. azithromycin and telithromycin).[65,66]

In terms of metabolism, being a substrate or inhibitor of cytochrome P450 (CYP) isoforms may significantly influence drug exposure under certain conditions and potentially lead to TdP (for drugs associated with QT prolongation). For example, the concurrent administration of CYP3A4-inhibiting azoles or macrolides with cisapride or terfenadine leads to exaggerated exposures to the latter two drugs.[67] CYP3A4 is currently the most important isoform for serious drug interactions (e.g. TdP, rhabdomyolysis) since it is responsible for metabolism of nearly 60% of all oxidised drugs.[67] Historical examples of this scenario involve terfenadine, cisapride and coadministration with drugs such as erythromycin, clarithromycin and ketoconazole. Malik and Camm[33] reviewed 14 terfenadine studies that demonstrated relatively minimal effects on the QT interval when no CYP3A4-inhibiting drugs were concurrently administered. However, a study investigating the effect of the antifungal agent ketoconazole on the elimination of terfenadine demonstrated a substantial 82 msec increase in the QT interval.[68] Likewise, initial investigations of cisapride revealed QT prolongation between 6 and 18 msec when no co-medications known to inhibit CYP3A4 isoenzymes were given; conversely, when CYP3A4 inhibitors were coadministered, a 3-fold increase in cisapride plasma concentrations was observed, corresponding with a mean increase in the QT interval of 25 msec.[69] The QT-prolonging substrates of CYP2C9, CYP2C19 and CYP2D6 may pose a risk for another reason, genetic polymorphism. Unlike the unimodal population distribution of CYP3A4, the quantity or functionality of the aforementioned isoforms is dependent on genetics.[67,70] For example, an estimated 15–30% of the Asian population and 3–5% of Caucasians are poor metabolisers of CYP2C19 substrates because of genetic polymorphism; approximately 1% of Asians show reduced CYP2C9 activity.[71] When administered, substrates of these isoforms may result in significantly elevated drug exposure because of the failure to metabolise them. The undesirable result is supratherapeutic concentrations of intrinsic QT-prolonging drugs or their metabolites.

Another pharmacokinetic variable that may result in exaggerated drug concentrations is renal insufficiency, as in the case of chronic or acute renal failure or age-related decreases in glomerular filtration rates.[72] Because QT prolongation is proportional to drug concentration, failure to dose adjust for organ dysfunction may contribute to establishing a milieu ideal for TdP to occur. Antimicrobials that prolong the QT interval and require dosage adjustments for renal impairment include clarithromycin, gatifloxacin, gemifloxacin, levofloxacin, cotrimoxazole (trimethoprim-sulfamethoxazole) and fluconazole.

2.2.3 Individual Host Susceptibility

Knowledge of host- and drug-related variables should be integrated to form a multidimensional understanding and assessment of antimicrobial-related TdP. Arrhythmias do not occur in the vast majority of patients who receive QT-prolonging drugs. In fact, most drug-induced TdP cases appear to occur in a so-called 'susceptible' population. Although not definitive, this hypothesis is supported by the discovery that a mutation in *KCNE2*, a potassium channel regulatory gene that combined with HERG forms the I_{Kr} channel, correlates with susceptibility to drug-induced QT prolongation.[73] Studies of a patient diagnosed with clarithromycin-induced TdP actually identified that they carried a sporadic missense mutation in *KCNE2* which made subunits of the I_{Kr} channel 3-fold more susceptible to clarithromycin than wild-type channels.[73] Studies of sulfamethoxazole-induced TdP have resulted in similar findings.[39] The frequency of this mutation in the general population is approximately 1.6%.[39]

The term 'repolarisation reserve' was introduced by Roden[74] to describe repolarisation adaptation to a variety of insults. This concept is central to the idea that the accumulation of multiple risk factors predisposes to TdP. In the normal ventricle, there exists virtually no potential for TdP to develop; this is principally a result of the purpose of the repolarising currents, in particular the I_{Kr} and the slow com-

ponent of the delayed rectifier potassium current (I_{Ks}), in maintaining a large repolarisation reserve that encourages electrical stability. However, when multiple TdP risk factors (table I) accumulate, the repolarisation reserve becomes exhausted, resulting in electrical instability within the ventricle. Figure 2 illustrates the multiple risk factors that can accumulate in an individual and result in TdP.

2.3 Post-Marketing Data

The lack of a single case of TdP in clinical development does not guarantee against cardiac toxicity.[33] Thus, post-marketing surveillance studies can offer clinicians some assurance once a drug has obtained significant exposures under more realistic conditions provided by the clinic. Label changes based on post-marketing safety analyses for cisapride provides a model for the value of such studies. In June 1998, after several changes in the labelling of cisapride and 38 related deaths between 1993 and 1998, the US FDA mailed a 'Dear Doctor' letter advising clinicians to avoid combinations with antibacterials, antifungals, protease inhibitors, antidepressants and a list of underlying medical conditions.[75] In January 2000, the US FDA advised obtaining ECG data before prescribing cisapride and expanded the precautionary section of the product labelling following 270 related adverse events that included 70 fatalities; 85% of reported events occurred in patients with recognisable risk factors.[75] The manufacturer voluntarily withdrew the product from the US market in July 2000 citing over 300 arrhythmias resulting in 80 deaths.[75]

Post-marketing safety surveillance for QT-interval-related adverse events has become part of drug product approvals by the US FDA, as evidenced by phase IV commitments required by the manufacturers of gatifloxacin, moxifloxacin, levofloxacin, gemifloxacin and telithromycin. The US FDA's Adverse Event Reporting System (AERS) database is a valuable source of safety information.[54] Independent of regulatory requirements, investigators have also launched post-marketing studies to ascertain TdP risk factors for certain fluoroquinolones and macrolides.[76,77] It is worthwhile to mention that, while these studies are very useful, there are some limitations inherent to them. Firstly, causality cannot be established between the specific drug in question and the adverse event reported. One reason for this is that critical information to link

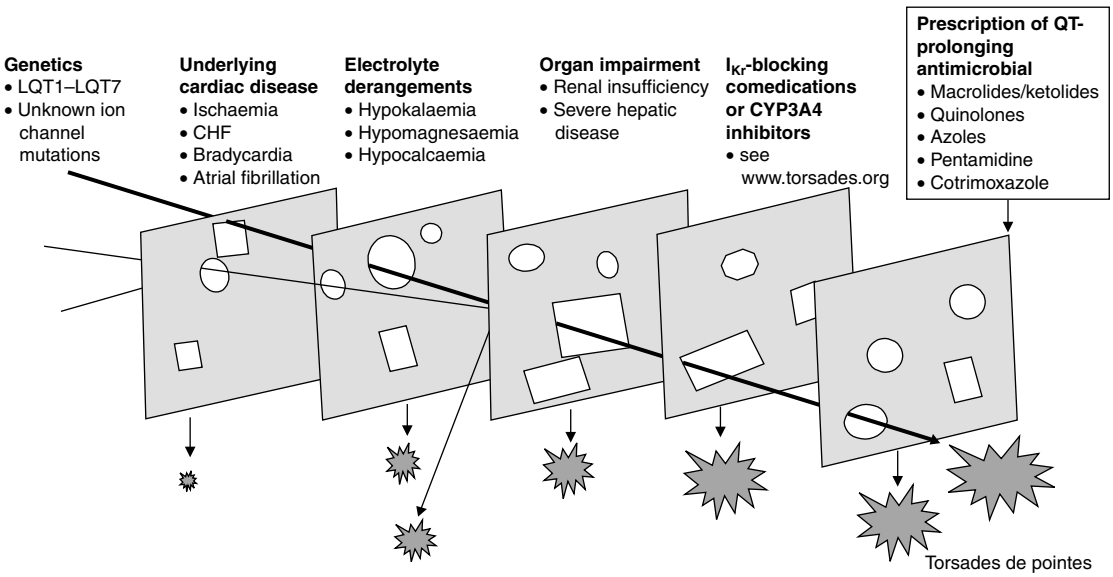

Fig. 2. Multiple risk model for antimicrobial-associated torsades de pointes. **CHF** = congestive heart failure; **CYP** = cytochrome P450; I_{Kr} = rapid component of the delayed rectifier potassium current; **LQT1–LQT7** = long QT genotypes.

cause and effect is often missing in the database. For example, in an evaluation of the AERS database, actual ECG data were available in only 24–36% of patients who were identified to have TdP.[56,76] One reason for this is that these databases are at the mercy of the reporting individuals and completing a spontaneous report form is left to the submitter, who is probably not knowledgeable about all aspects of the case and does not have adequate time to investigate all necessary information to provide enough data to the recipient of the form. In fact, up to 11% of the reports were missing vital demographic information such as age and gender.[56,76] Secondly, it is not uncommon for multiple reports of the same adverse event to exist in the database; one or more clinicians may report the event, the pharmaceutical industry is obligated to report an event if they are made aware of it and, sometimes, the patient will even report the event. Thus, duplicate reports must be separated and dismissed. Also, adverse event reports can be miscoded. Almost 40% of the macrolide and quinolone TdP cases originally identified in the AERS database had to be excluded.[56,76] Finally, integrating utilisation data with the number of spontaneous adverse event reports to establish the incidence of a particular event is flawed at best. Shaffer et al.[76] stated: "Such reporting rates and comparisons should be interpreted with caution, because drug use is based on a surrogate analytical population and because numerators are based on possibly biased spontaneous reports. Rates of prevalence or incidence cannot be determined.".

In summation, spontaneous reporting database evaluations provide valuable data that improve our understanding of a drug's safety profile and establish risk factors for a particular drug-related adverse event. Additional data should be considered and used to supplement post-marketing results in order to establish the credibility of the data collectively.

2.4 Antimicrobial Structure-Toxicity Relationships

An apparent structure-toxicity relationship exists among class III antiarrhythmic drugs (i.e. a para-substituted phenyl ring attached to a basic nitrogen).[4,78] Interestingly, this pharmacophore is evident in non-antiarrhythmic agents such as terfenadine, astemizole, cisapride and haloperidol. These compounds have increased affinity toward the HERG-encoded I_{Kr} channel, resulting in prolongation of the QT interval. In terms of anti-infectives, structural congruity exists between two drugs known to prolong the QT interval, procainamide and pentamidine. While a specific structural characteristic may explain the proclivity of these compounds to block the HERG-encoded I_{Kr} channel, several reviews have recently reported mixed opinion regarding any obvious structural relationship present in macrolides and fluoroquinolones.[79-82] It has been suggested that a methyl (grepafloxacin) or amino (sparfloxacin) substituent located at the 5 position on the quinolone nucleus is associated with greater prolongation of the QT interval than hydrogen atoms at the same position (ciprofloxacin, gatifloxacin, moxifloxacin, levofloxacin).[83] If an established association could be confirmed, certain pharmacophores could be flagged in the discovery phase of drug development to assist researchers and investors in decision making.

3. Risk Stratification

In an effort to ascertain and characterise the potential risk factors associated with QT-interval prolongation for antimicrobial agents, a variety of data were compiled. The results of this evaluation are presented in figure 3 and the data can be viewed in table III. Others have categorised QT interval-prolonging drugs in broad therapeutic categories. For instance, the Center for Education Research and Therapeutics from the University of Arizona (Tucson, AZ, USA)[84] has formulated risk categories for those drugs known to have an association with TdP. Groups based on TdP risk (1–4) were devised by the websites authors' assessments. Group 1: "drugs with risk for TdP are those generally accepted by authorities to cause TdP"; non-antimicrobials (for reference purposes here) include amiodarone, sotalol and dofetilide, for example, whereas antimicrobial agents include clarithromycin, erythromycin, sparfloxacin and pentamidine. Group 2 comprises

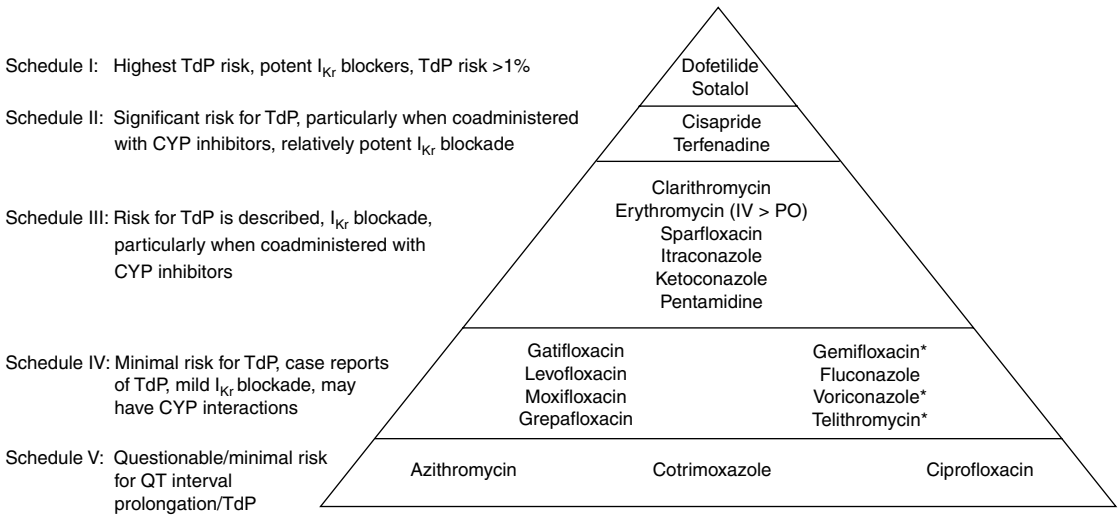

Fig. 3. Torsades de pointes (TdP) risk stratification schedules for antimicrobial agents. * New antimicrobials to the market or still investigational, minimal to no post-marketing data; based on additional data, the drug may be re-categorised in a higher or lower schedule. **CYP** = cytochrome P450; **I_{Kr}** = rapid component of the delayed rectifier potassium current.

"drugs with some reports associating them with TdP but at this time, lack substantial evidence for causing TdP": azithromycin, gatifloxacin, levofloxacin, moxifloxacin, telithromycin and voriconazole. Group 3 contains drugs "that should be avoided in patients diagnosed with LQTS", which includes those drugs listed in groups 1 and 2. Group 4 contains drugs "that, in some reports, have been weakly associated with TdP but that, when used in usual dosages, are unlikely to be a risk for TdP", and includes ampicillin, ciprofloxacin, itraconazole, ketoconazole and cotrimoxazole.

In general, these stratified groups make sense. However, limitations, in fact, exist. Selected drugs identified in group 4 are actually dual TdP threats (e.g. they are CYP-mediated substrates or inhibitors and possess intrinsic I_{Kr}-blocking potency), the azole antifungals are split between two distinct risk groups (e.g. voriconazole is in group 2 while ketoconazole and itraconazole are in group 4, despite voriconazole having less potent HERG-blocking capabilities and less potent CYP3A4-inhibitory qualities compared with ketoconazole),[143] and fluconazole was not assigned a risk group.

Figure 3 represents a risk stratification schedule for antimicrobial agents, integrating some information from the previous risk assessment scheme with nonclinical models, clinical studies, case reports, post-marketing safety studies and pharmacokinetics.

Risk Schedule I contains known potent I_{Kr} antagonists that may cause a high incidence of TdP (>1%) with minimal or no concurrent risk factors. This schedule is included for reference purposes and includes such agents as sotalol and dofetilide. Risk Schedule II contains no antimicrobial agents, but does include potent I_{Kr} antagonists that are usually torsadogenic only when coadministered with CYP-inhibiting drugs (e.g. cisapride, terfenadine). Risk Schedule III includes antimicrobials with well documented associations with TdP, which include multiple-threat agents (CYP-interacting drugs, unpredictable pharmacokinetics and/or known potent antagonists of I_{Kr} channels), such as erythromycin (intravenous more so than oral), clarithromycin, ketoconazole, itraconazole, pentamidine and sparfloxacin. Risk Schedule IV antimicrobials include those whose TdP risk is less well established, and the drugs have some safety features including predictable pharmacokinetics (gatifloxacin, levofloxacin, moxifloxacin) or multiple compensatory elimination pathways (telithromycin, moxifloxacin, gemifloxacin), or weaker CYP (particularly 3A4)-

Table III. Summary of risk factors from torsades de pointes (TdP) case reports and HERG inhibitory concentrations[a,b]

Antimicrobial (no. of cases)	No. of cases with risk factors identified/no. of cases for which data were provided for that risk factor									References for risk factors	HERG inhibition (IC_{50}) in μmol/L	References for HERG inhibition
	none[c]	concurrent (non-CYP-interacting) QT-prolonging drugs	CYP-mediated drug interaction	electrolyte derangement (↓K^+, ↓Mg^{2+})	organ impairment without dosage adjustment	underlying cardio-vascular disease	inherited LQTS identified[d]	age >65 years	female			
Macrolides												
Azithromycin (2)	0/2	1/1	0/1	0/1	0/1	1/1	1/1	1/1	1/1	85,86	NA	NA
Clarithromycin (13)	2/13	1/13	6/11	1/9	4/10	6/12	0/13	5/12	8/12	87-97	32.9	59
Erythromycin (25)	0/25	0/23	7/23	2/19	3/7	16/21	1/1	12/21	17/25	61-63,98	72.2[e] 147.1[f]	59
Roxithromycin (1)[g]	0/1	0/1	1/1	0/1	0/1	1/1	NA	1/1	0/1	99,100	36.5	59
Spiramycin (1)	0/1	1/1	0/1	0/1	0/1	0/1	1/1	0/1	1/1	101	NA	NA
Telithromycin (2)	1/2	0/1	0/1	0/1	0/0	1/2	0/2	0/2	0/2	102	42.5	103
Troleandomycin (1)	0/1	0/1	1/1	NA	NA	NA	NA	NA	NA	104	339.6	59
Quinolones												
Ciprofloxacin (1)	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	105	966	28
Gatifloxacin (7)	0/7	6/7	0/7	3/7	2/7	7/7	0	4/7	3/5	12,14,106	130–329	28,107
Gemifloxacin	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	260	107
Levofloxacin (17)	1/17	6/17	0/8	6/16	4/13	12/15	0	10/15	9/15	108-114	827–915	28,107
Moxifloxacin (2)	0/2	0/2	0/2	2/2	0/2	2/2	0/2	2/2	2/2	12,115	129–354	28,107
Sparfloxacin (7)	0/7	3/7	0/7	NA	NA	7/7	1/7	5/7	6/7	116	18–37	28,107
Azoles												
Fluconazole (5)	0/5	3/5	2/5	2/5	3/5	2/5	1/5	1/5	4/5	113,117-120	NA	NA

Continued next page

Table III. Contd

Antimicrobial (no. of cases)	No. of cases with risk factors identified/no. of cases for which data were provided for that risk factor									References for risk factors	HERG inhibition (IC_{50}) in μmol/L	References for HERG inhibition
	none[c]	concurrent (non-CYP-interacting) QT-prolonging drugs	CYP-mediated drug interaction	electrolyte derangement ($\downarrow K^+$, $\downarrow Mg^{2+}$)	organ impairment without dosage adjustment	underlying cardio-vascular disease	inherited LQTS identified[d]	age >65 years	female			
Itraconazole (4)	0/4	0/2	4/4	0/2	0/2	0/2	NA	0/2	2/2	121-124	NA	NA
Ketoconazole (3)	0/3	0/3	3/3	0/2	0/3	0/3	0/3	0/3	3/3	125-127	49[h]	128
Voriconazole (1)	0/1	1/1	0/1	1/1	NA	1/1	NA	0/1	1/1	129	NA	NA
Miscellaneous												
Cotrimoxazole [trimethoprim-sulfamethoxazole] (4)	0/4	0/4	0/4	0/4	0/4	2/4	0/4	2/2	1/2	130,131	NA	NA
Pentamidine (13)	5/13	1/13	3/13	4/13	0/3	0/13	0/13	0/13	2/13	132-142	NA	NA

a In most cases, TdP was the identified ventricular arrhythmia; one case of significant QTc prolongation was included (roxithromycin).

b For each individual risk category, the total number (n) of each associated risk may not add up to the total number of arrhythmia cases since for each case, information on the risk factor may not have been reported. Totals across each risk factor may not all add up to the number of total cases reported since some data were missing from the case reports.

c No identified obvious risk factors other than the antibacterial administered.

d Inherited forms of LQTS were not actively tested for in most cases.

e Erythromycin.

f Des-methyl erythromycin.

g Patient had severe QTc prolongation but did not develop TdP, drug was discontinued and QTc prolongation resolved.

h Ketoconazole was studied in HERG-transfected *Xenopus* oocytes, and thus may result in a higher IC_{50} value than if expressed in mammalian cells.

CYP = cytochrome P450; **HERG** = human ether-á-go-go-related gene; **IC_{50}** = concentration which produces 50% inhibition; **LQTS** = long QT syndrome; **NA** = not available; **QTc** = corrected QT interval; ↓ indicates decrease.

inhibitory potential compared within other drugs in the same class (fluconazole, voriconazole). Risk Schedule V includes drugs with weak or questionable associations with TdP that may or may not be related to the drug or may only be considered potentially harmful in patients diagnosed with specific genetic LQTS variants, including cotrimoxazole, ciprofloxacin and azithromycin.

Drug evaluation technology and genetic diagnostics are evolving rapidly. In addition, recognising that some investigational and newly licensed drugs have been evaluated to provide a sense of general risk assessment, antimicrobial agents assigned to one schedule may warrant movement to another schedule based on the best marker for risk, a long-standing record of clinical safety in diverse populations.

4. Evaluating QT Prolongation and Torsades de Pointes by Antimicrobial Class

In an effort to characterise and compare risk factors from individual case reports of TdP, a Medline search was used to identify TdP case reports and case series. The query, conducted from 1966 through March 2004, was performed using search terms that included the name of each identified antimicrobial agent, and the following: 'arrhythmia(s)', 'QT(c)', 'torsade(s)', 'extrasystole' and 'prolongation'. In addition, references were extracted from the bibliographies of identified citations. Each case report was examined for concurrent TdP risk factors. Table III also includes, where available, the IC_{50} results from HERG studies.

4.1 Macrolides, Azalides, Ketolides

Of the currently available antimicrobial classes, the macrolides appear to be associated with the greatest degree of QT-interval prolongation and risk for TdP. This is, in part, because of their dual risk mechanisms (e.g. pharmacodynamic and pharmacokinetic). Although for the purposes of discussion pharmacokinetic and pharmacodynamic risks can be separated, both are likely to be intertwined clinically, resulting in a composite risk potential. Risk factors include the CYP3A4 inhibition, drug exposure (dose and route of administration), and intrinsic I_{Kr}-antagonistic potencies. Macrolides (and derivatives) with at least one identified published case report of TdP include azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin, troleandomycin and telithromycin (see table III).[99-101,104] Variation exists within the macrolide family of compounds in terms of both I_{Kr}-antagonistic potency and CYP3A4-inhibition potential and, therefore, the risk of TdP for each drug is different.

4.1.1 Pharmacokinetic Risk Factors

Metabolic drug interactions and exposures following different dosage regimens can be associated with an increased risk for TdP, depending on the macrolide and clinical situation. From a drug interaction standpoint, increased risk of TdP may occur when macrolides are administered concomitantly with drugs that prolong the QT interval (e.g. class IA or III antiarrhythmics), certain QT-prolonging drugs whose metabolism rely upon CYP3A4 (e.g. terfenadine, cisapride, pimozide) or drugs that may alter the delicate electrolyte balance (e.g. potassium-depleting diuretics).[144-146] The CYP3A4-inhibitory potency for the studied macrolides (no comparative data are available for telithromycin) in descending order is as follows: erythromycin, troleandomycin > clarithromycin, roxithromycin > azithromycin, dirithromycin, spiramycin.[147] An example of the potent inhibition of CYP3A4 by clarithromycin can be best described by its concurrent administration with cisapride.[148] While each drug administered individually prolonged the QTc interval in healthy volunteers by a mean of 6 msec, concurrent administration of both drugs led to a 25 msec prolongation of the QTc interval. It is not surprising that most TdP cases reported for clarithromycin have been in patients concurrently receiving contraindicated drugs such as cisapride, terfenadine and pimozide.[87-96,148,149] However, TdP has been reported in patients with organ impairment.[87] One patient had significantly elevated hepatic enzymes and the other had biopsy-proven hepatitis C and was undergoing haemodialysis.[87] Since clarithromycin and its active 14-hydroxy metabolite are eliminated by hepat-

ic and renal mechanisms, their accumulation resulting in supratherapeutic concentrations may have been responsible for the excessive QT prolongation. Similarly, two cases of TdP were reported in patients taking clarithromycin 400 mg/day in Japan for the treatment of respiratory tract infections.[97] As in the previous cases, no underlying drug interactions could explain the development of arrhythmias during therapy.

Azithromycin, an azalide that is chemically dissimilar to the other macrolides, minimally inhibits CYP3A4, resulting in the lack of an appreciable interaction with CYP3A4 substrates such as terfenadine.[150] Two case reports exist in the published literature describing TdP with azithromycin.[85,86] In both cases the patients appeared to have a low repolarisation reserve, as indicated by the presence of significant risk factors. In one case, inherited LQTS was documented. The second case involved a 68-year-old female who had been receiving amiodarone for paroxysmal atrial fibrillation for more than a year and had stable congestive heart failure (CHF). Three days after initiating the conventional dosage of azithromycin (500mg orally on day 1, followed by 250 mg/day orally for 5 days total), she experienced intermittent dizziness. At that time, an ECG showed a QTc of 660 msec and QT dispersion.

Although erythromycin is torsadogenic when administered with contraindicated drugs, it appears that the administration of high-dose intravenous erythromycin in the absence of interacting drugs contributes to TdP. This is surmised because of the number of TdP cases reported for erythromycin in patients receiving 4 g/day intravenously.[61-63,98] Peak serum concentrations following high-dosage intravenous erythromycin are 7–15 times larger than those following usual dosages given orally (e.g. 500mg every 6 hours).[64,151,152] Additional data to support this arise from the Purkinje fibre model that assess the duration of the action potential. Erythromycin, at concentrations of 10, 50 and 100 mg/L, was associated with a concentration-dependent effect on action potential duration.[153] Other conditions leading to increased erythromycin serum concentrations and, thus, enhanced probability of TdP, include intravenous administration over a short infusion period (<1 hour) and the presence of severe hepatic disease (the primary route of metabolism of erythromycin).[98]

4.1.2 Pharmacodynamic Risk Factors

With regard to pharmacodynamic differences among the macrolides, the I_{Kr}-antagonistic potential for several macrolides via HERG expression in human embryonic kidney-293 cells has been studied.[59] A rank order of I_{Kr}-inhibitory potential in descending order is as follows: clarithromycin > roxithromycin > erythromycin > josamycin > desmethyl erythromycin > erythromycylamine > oleandomycin. It is interesting to note that a metabolite of erythromycin (des-methyl erythromycin) also inhibits the I_{Kr} current, albeit at a higher concentration than the parent compound. Some preclinical data for telithromycin are available (table III).[103]

Erythromycin is the most widely studied macrolide because it is a known torsadogenic drug and has been available for use for over 40 years. The anaesthetised dog model demonstrated that QT prolongation associated with erythromycin occurred as a result of its action on the I_{Kr} current, which resulted in EADs leading to TdP.[64] A comparative pharmacodynamic study conducted in the rat model approximating exposures similar to human concentrations established that erythromycin and clarithromycin were more likely than azithromycin to cause TdP.[154] Concentrations (150–300 μmol/L), of erythromycin, clarithromycin and azithromycin were compared in the Langendorff-perfused rabbit heart proarrhythmia model.[155] While all three drugs prolonged the action potential, both erythromycin and clarithromycin led to EADs and TdP. Interestingly, while azithromycin prolonged the action potential similarly to the other two macrolides, no EADs or TdP were observed. It was noted that for azithromycin, monophasic action potentials (MAPs) were rectangular as opposed to the traditional triangular pattern as seen with both erythromycin and clarithromycin; these rectangular MAPs led to late but fast repolarisation. All three agents resulted in similar electrophysiological effects, yet additional

channel interactions or pharmacological effects may explain the failure of clear QT prolongation to deteriorate to EADs or TdP for azithromycin. This finding adds to the complexity of predicting TdP and emphasises that the use of a single surrogate marker for predicting human proarrhythmia is unrealistic.

4.1.3 Post-Marketing Data

In 1999, a US FDA presentation stated the number of spontaneous reports of QT-interval-related toxicity to their MedWatch reporting system.[156] In this report, the estimated incidence of cardiac toxicity (defined under the coding terms 'ventricular arrhythmias' and 'cardiac arrest') based on outpatient prescription data (estimated from IMS Health National Prescription Audit) was given for several antimicrobials. Because adverse effects of a drug are more likely to be reported within the first 2 years on the market, only these years for each drug were included. Of the macrolides reported, adjusted rates per 10 million prescriptions were 30 for clarithromycin and ten for azithromycin.[156] A sensitivity analysis was conducted using the same search terms and the first 2 years of availability for cisapride and omeprazole. Crude incidences were reported as 63 for cisapride and 13 for omeprazole per 10 million prescriptions.

Following the heightened attention surrounding antimicrobial-associated TdP, Shaffer and colleagues[56,76] conducted a descriptive evaluation of the US FDA's AERS database. TdP-associated cases involving macrolides (erythromycin, clarithromycin, dirithromycin and azithromycin) as well as ten fluoroquinolones were evaluated. Not unexpectedly, macrolides accounted for the majority of reported TdP cases (77%). Among the macrolides, TdP was reported more frequently for erythromycin (erythromycin > clarithromycin > azithromycin), while no cases were reported for dirithromycin. When an estimated number of outpatient prescriptions is factored into the number of cases reported, the crude incidence in descending order is: clarithromycin > erythromycin > azithromycin.[157] In 50% of the TdP cases, a QT-prolonging drug (19%) or contraindicated drug (31%) was given concurrently with the macrolide.[157] The contraindicated drugs included cisapride (78%), terfenadine (14%) and astemizole (8%). This emphasises the fact that 'Dear Doctor' letters and product label revisions continue to be ignored by prescribers.[158] Other risk factors noted included advanced age, underlying cardiac disease, organ dysfunction (impairing the route of drug elimination), and electrolyte derangements. Large changes in the QT interval from baseline were noted in the TdP cases, with a mean (± SD) increase in QTc of 172 (± 67) msec. This was a pioneering study of post-marketing safety reports. These data, combined with the information assimilated in table III, indicate that a significant number of identifiable risk co-factors exist that contributed to TdP.

Large administrative claims databases used by national pharmacy benefit managers in the US can be searched for patients receiving concurrent QT-prolonging prescriptions. One such analysis revealed that 22.8% of almost 5 million patients filled prescriptions for QT-prolonging drugs and, of these, 9.4% filled overlapping prescriptions for at least two QT-prolonging drugs. The database query also indicated that among those receiving QT-prolonging medications, 22% of patients were ≥65 years and 74% were women. The most commonly prescribed QT-prolonging drugs were antibacterials, namely clarithromycin (26.7%), erythromycin (20.7%) and levofloxacin (13.8%). Unfortunately, patient outcomes cannot be determined from such databases.

In the largest comparative, randomised, post-marketing antimicrobial safety study conducted to date (n = 24 000), telithromycin 800 mg/day for 5 days was compared with amoxicillin/clavulanic acid 875/125mg every 12 hours for 7–10 days for the treatment of outpatient respiratory tract infections.[159] A goal of the study was to further characterise the safety profile of telithromycin under conditions similar to usual practice, thus exclusion criteria were intentionally minimised and included only the presence of inherited LQTS, pregnancy/breast-feeding, hypersensitivity to either drug and/or concurrent use of ergot alkaloids. In terms of defining the telithromycin population in all patients that received the drug, the following risk categories were evident: concurrent use of CYP3A4 inhibitors

(29.7%), concurrent use of CYP3A4 substrates (48%), history of cardiovascular disease (24.4%) and age ≥65 years (18.7%). Overall, adverse events were reported in 23% of telithromycin recipients versus 23% of amoxicillin/clavulanic acid recipients. No positively adjudicated cardiac adverse events were reported for telithromycin, and a single case was reported for amoxicillin/clavulanic acid. Post-marketing data available from countries where telithromycin is approved for use have indicated two cases of TdP as of March 2004.[102]

Despite the apparent lack of drug interaction potential for azithromycin, the US FDA's database has reported ten cases of QTc-related cardiac events per 10 million prescriptions of azithromycin.[156] This may represent background noise associated with spontaneous adverse event reporting systems, the overall background incidence of TdP in the general population,[16] or may demonstrate some minimal effect on the QT interval.

4.1.4 Investigational Ketolides

Telithromycin, chemically derived from clarithromycin, is the first member of the ketolide family. Telithromycin is available in an oral formulation in several countries outside the US and is administered at a dosage of 800mg (2 × 400mg tablets) once daily regardless of renal function. Similar to clarithromycin, telithromycin is an inhibitor of CYP3A4; hence, larger than expected exposures of CYP3A4 substrates are anticipated if concurrently administered.[103] The pharmacokinetics of telithromycin are also non-linear as a result of saturable metabolism. Pharmacokinetic studies in the elderly also revealed higher exposures in this population after administration of a standard dose.[103] Because of the potential for unpredictable pharmacokinetics in certain patients receiving telithromycin, multiple scenarios have been studied (e.g. patients receiving CYP3A4 inhibitors with renal or hepatic impairment). Results from these investigations indicate increased exposure ratios, as measured by area under the concentration-time curves (AUCs), occur when telithromycin is coadministered with ketoconazole (1.9) or itraconazole (1.5), or when administered to patients with significant renal impairment (creatinine clearance <30 mL/min) [2.0].[102]

The effects on the QTc interval for telithromycin were compared with an active control (clarithromycin) and placebo in young healthy men and women (17 each) in double-blind, crossover studies.[160] One arm compared QTc intervals at rest and following submaximal exercise after receiving single and multiple oral dosages of telithromycin 800 mg/day, clarithromycin 500mg twice daily and placebo. The second arm evaluated QTc intervals following single-dose telithromycin 800, 1600 and 2400mg versus placebo. ECGs were not obtained by holter monitoring; rather, they were measured at the anticipated time of peak serum concentration for the parent compound. Bazett's formula was used to correct for heart rate. Significant QTc prolongation was not noted in either arm of the protocol for telithromycin. Interestingly, concentrations in the dose-escalating study were remarkably low (e.g. those observed following the 2400mg dose were similar to that usually observed following 800mg). This confirms the large variability observed with telithromycin pharmacokinetics, which are more apparent when smaller numbers of patients are studied. Outlier values for the first protocol were reported (QTc interval increase of >60 msec from baseline) as: placebo (n = 0), telithromycin (n = 2) and clarithromycin (n = 6). Outlier values for the second protocol (QTc interval increase of >60 msec from baseline) were: placebo (n = 1), telithromycin 800mg (n = 2), telithromycin 1600mg (n = 3) and telithromycin 2400mg (n = 1). Interestingly, when Fridericia's correction formula was applied, no outliers >60 msec existed, demonstrating the fact that heart rate influenced, to some degree, the changes observed. According to the authors, telithromycin appeared to be similar to clarithromycin in terms of QT-interval prolongation.[160]

Drug interaction studies evaluating the impact of ketoconazole on the disposition and resulting QTc prolongation of telithromycin were performed in humans. Coadministration of ketoconazole 400 mg/day with telithromycin 800 mg/day resulted in increased telithromycin exposures (95% increase in

the AUC from time 0 to 24 hours [AUC_{24}]), and a mean increase in QTc of 10.49 msec ($p = 0.004$).[103] Telithromycin and ketoconazole were administered alone at the same dose and duration and were associated with mean increases in QTc (compared with placebo) of 3.3 and 6.4 msec, respectively.[103]

4.2 Quinolones

Before the increased intensity of regulatory agencies and the subsequent introduction of a more systematic approach to drug testing for QT prolongation, the quinolones, with minor exceptions, were not perceived as drugs that were associated with cardiac toxicity. Even with this attention, actual cases of reported QT-interval-related adverse events are rare. Like sparfloxacin, the discovery of the tendency of moxifloxacin to prolong the QTc interval was detected in early clinical development and most patients at risk for QTc prolongation were excluded from trial participation.[161,162] In fact, because of the early signal in development, according to the US FDA's *Pink Sheet*, an acclaimed preclinical and clinical cardiac safety package was presented to the FDA.[156] QT prolongation is presumably a class effect, yet there appears to be considerable variability within this class in the potential to cause TdP.[163] Furthermore, it is difficult to make comparisons with any certainty, since the quinolones are rarely associated with dysrhythmias. Sections 4.2.1 to 4.2.5 review the current literature regarding quinolones and TdP.

4.2.1 Pharmacokinetic Risk Factors

The currently available quinolones are devoid of known CYP-mediated drug interactions, with the historical exception of grepafloxacin and the current exception of ciprofloxacin, both of which inhibit CYP1A2.[164,165] This interaction is perhaps inconsequential from a QT-interval prolongation perspective because of the type of drugs that are affected by CYP1A2. All of the currently available quinolones, regardless of intravenous or oral administration, produce similar exposures (e.g. peak concentrations, AUC values). Thus, unlike the macrolides, the route of administration is an unlikely contributor to the development of TdP, unless the intravenous formulation is administered too rapidly. Moxifloxacin, sparfloxacin and ciprofloxacin are so-called dual-elimination quinolones. Among the currently marketed quinolones, only gatifloxacin and levofloxacin rely primarily on renal elimination. Failure to adjust doses in patients with renal impairment may thus amplify the risk for these drugs to cause QT prolongation.[14,54]

4.2.2 Pharmacodynamic Risk Factors

The I_{Kr}-inhibitory potential for many quinolones has been evaluated through HERG studies, and the results are presented in table III.[107,166] Most HERG IC_{50} values are far in excess of typically achievable plasma concentrations for quinolones in humans. However, as alluded to previously, IC values in the lower range (e.g. IC_{20}) can be significant enough to cause TdP. Unfortunately, few studies report the entire IC distribution. One particular study reported the I_{Kr}-inhibitory values for fluoroquinolones (using HERG-transfected cells) at the lower end of the distribution range.[166] The IC percentages at the lowest concentration tested (10 μmol/L) were reported, allowing comparisons to be made at near physiological concentrations in humans: sparfloxacin (16.9%), grepafloxacin (15.2%), moxifloxacin (10.3%), gatifloxacin (3.3%) and ciprofloxacin (5.1%). Another study used Chinese hamster ovary cells expressing HERG channels, and a range of drug concentrations (3, 10, 30 and 100 μg/mL) were tested for their inhibitory potential, resulting in HERG IC_{50} values of 37.5 μg/mL for grepafloxacin, 41.2 μg/mL for moxifloxacin, 13.5 μg/mL for sparfloxacin; ciprofloxacin did not inhibit HERG in this model.[167] To translate laboratory concentrations to human concentrations, a standardised 400mg dose was used for all drugs tested and, furthermore, all drug exposures were corrected for protein binding based on estimates obtained from the literature. The percentage of HERG current reduction occurring after attainable human exposures revealed that moxifloxacin, sparfloxacin and grepafloxacin resulted in a 4.2%, 2.4% and 0.2% reduction, respectively. A few conclusions can be drawn from these HERG studies. Firstly, all quinolones are capable of inhibiting HERG potassium channels and, similar to

other drugs that cause QT prolongation, it is the likely mechanism by which they cause QT prolongation. Secondly, even at the high end of clinically achievable concentrations, most of the currently marketed quinolones only minimally inhibit HERG potassium channels relative to drugs whose mechanism of action depends on HERG inhibition (e.g. class Ia and III antiarrhythmic agents). Because of this, concurrent drug- or host-related factors are likely to be important contributors to the majority of reported TdP cases.

Prior to HERG studies being conducted for quinolones, animal studies in dogs demonstrated that sparfloxacin was capable of prolonging the QTc interval following oral administration, leading to proactive monitoring in human phase I and certain phase III trials.[116] The anaesthetised rabbit model revealed grepafloxacin's propensity to cause dose-dependent transient arrhythmias.[168,169] Grepafloxacin caused dose-related transient arrhythmias in all animals that received doses of 30 mg/kg, one of which developed ventricular tachycardia. At these doses, ciprofloxacin was not associated with arrhythmias; however, at ten times the dose (300 mg/kg) ventricular tachycardia was noted. The rabbit Purkinje fibre model demonstrated that concentrations up to 100 μmol/L did not appear to be associated with altered action potentials for ofloxacin and levofloxacin, while sparfloxacin demonstrated a concentration-dependent increase in action potential duration at concentrations as low as 10 μmol/L.[170]

Anderson and colleagues[171] employed both *in vitro* and *in vivo* techniques to evaluate the I_{Kr}-antagonistic properties and impact on the action potential duration for sparfloxacin, grepafloxacin, moxifloxacin and gatifloxacin. I_{Kr}-inhibitory potential was studied using mouse atrial tumour cells rather than cells transfected with HERG. Inhibitory results were proportionally similar to studies using HERG methodologies, with some exceptions, and were reported as I_{Kr} IC_{50} values (mean ± SEM): sparfloxacin (0.23 ± 0.07 μmol/L), moxifloxacin (0.75 ± 0.31 μmol/L), gatifloxacin (26.5 ± 13.4 μmol/L) and grepafloxacin (27.2 ± 11.6 μmol/L). On the surface, the I_{Kr}-antagonistic properties of the quinolones differ in this mouse cardiac cell model from HERG studies for grepafloxacin (less inhibitory) and moxifloxacin (more inhibitory). For grepafloxacin, the standard error ranges were very large and overlapped at the mean value for gatifloxacin. The same quinolones were then studied to determine their impact on the QT and QTc interval in the methoxamine pre-treated rabbit arrhythmia model.[171] The results were reported as maximum QT interval observed (mean ± SEM) from baseline (241 ± 10 msec): sparfloxacin (370 ± 30 msec), grepafloxacin (280 ± 25 msec), moxifloxacin (270 ± 30 msec) and gatifloxacin (255 ± 23 msec). Among the tested quinolones, only sparfloxacin was associated with significant QTc-interval prolongation and TdP. Despite the good correlation observed between the degree of I_{Kr} blockade and QT prolongation for sparfloxacin and moxifloxacin, uniform correlation did not exist, particularly for grepafloxacin. These discrepant results raise several questions regarding the limitations of nonclinical models, including the influence of other cardiac ion channels (other than the I_{Kr} channel), effect of gender, dosage and pharmacokinetics (clinically achievable concentrations in humans and differences in drug elimination). Thus, clinicians and formulary committees must be careful when evaluating nonclinical studies comparing drugs for potential to cause QT prolongation.

A human, placebo-controlled, pharmacodynamic study was conducted using sparfloxacin in three dosage regimens (loading dose/daily dose [mg]: 200/100, 400/200 and 800/400) in 90 healthy male volunteers without risk factors for QTc-interval prolongation.[172] The placebo-adjusted increases in QTc on day 1 were 9, 16 and 28 msec after receipt of the 200/100mg, 400/200mg and 800/400mg regimens, respectively. Approximately 10% of patients had QTc intervals exceeding the *a priori* normal cut-off of 460 msec.

4.2.3 Post-Marketing Data

The first quinolone-related post-marketing TdP data were published for sparfloxacin after its release to the market in France.[116] Although a safety board concluded that the frequency and severity of the

adverse events reported in patients receiving sparfloxacin did not differ significantly from that of the comparator groups, spontaneous reports of adverse events over an 8-month period revealed seven cases of serious cardiac-related adverse events.[116] Of these, three cases of reversible ventricular tachycardia and two fatalities attributed to sudden death were reported in patients. Further analysis of the cases revealed multiple risk factors for TdP were present, including the use of amiodarone in some cases. Additional cases of post-marketing TdP associated with sparfloxacin have been reported.[173,174] Sparfloxacin was voluntarily removed from the market in 2001, but has provided us with a historical perspective and a journey through development for quinolone-related cardiotoxicity.

In the US FDA presentation at the moxifloxacin Anti-Infective Advisory Committee[156] meeting, post-marketing data from the US FDA indicated the number of spontaneous reports of QT interval-related toxicity. For sparfloxacin, 145 reports of QT-related cardiac events per 49 000 prescriptions topped the listed agents.[156] The remaining antimicrobials are presented in crude reporting rates (cases per estimated 10 million prescriptions) in ascending order: cefuroxime axetil (3), ciprofloxacin (9), azithromycin (10), levofloxacin (15), ofloxacin (18), norfloxacin (22) and clarithromycin (30).[156] As mentioned previously in section 4.1.3 for comparative purposes, crude incidences for an active and negative control were reported per 10 million prescriptions for cisapride (n = 63) and omeprazole (n = 13), respectively.

Frothingham[53] published the crude rates of TdP associated with select quinolones based on reports queried from two databases, the Spontaneous Reporting System (1969–97) and the AERS database (from 1997 to May 2001) and estimated outpatient prescription data (based on US prescriptions from 1996 to 2000).[53] Reporting rates for TdP are represented as cases per 10 million prescriptions, and listed in ascending order: moxifloxacin (0), ciprofloxacin (0.3), ofloxacin (2.1), levofloxacin (5.4) and gatifloxacin (27). These numbers are different from those presented by the US FDA at an advisory hearing in 1999,[156] in part because different definitions of cardiac toxicity were used, with Frothingham's definition being more specific to TdP.

Leone et al.[77] evaluated ADRs identified by spontaneous reports for antibacterials from three Italian regions. The purpose of their study was to characterise and compare ADR reports for fluoroquinolones in relation to other commonly used antibacterials. An estimation of incidence for each type of reaction was calculated by using IMS Health data (measure of antimicrobial consumption). The fluoroquinolones available in Italy included ciprofloxacin, pefloxacin, moxifloxacin, levofloxacin, norfloxacin and rufloxacin. Over a 3-year period, 422 fluoroquinolone-associated ADRs were reported. Overall, cardiovascular-related ADRs were uncommon and serious rhythm disorders specifically were very rare: levofloxacin (n = 3), moxifloxacin (n = 1) and pefloxacin (n = 1).

Shaffer et al.[56] evaluated the AERS database for cases of TdP for four macrolides (discussed previously in section 4.1.3) and ten quinolones. Specific quinolones were not mentioned in the abstract. In 24% of TdP cases, a concurrent QT-prolonging drug was coadministered with a quinolone, underlying cardiac disease was present in 62% of patients, renal impairment in 7%, hypokalaemia or hypomagnesaemia in 17%, female gender in 67%, and mean age was 72 ± 15 years. The type and frequency of TdP risk factors are similar to those observed in the cases reported in the published literature and presented in table III.

The manufacturers of gatifloxacin and moxifloxacin were required to conduct post-marketing safety evaluations as a requisite for US FDA approval. Spontaneous reports from 1.2 million patients who received moxifloxacin were reported.[12] One case of moxifloxacin-associated TdP was reported in a patient harbouring a number of TdP amplifiers, including hypokalaemia, coronary heart disease and bradycardia requiring an implanted pacemaker. As a part of collecting important safety information and in an attempt to characterise the post-marketing gatifloxacin experience, a surveillance study was designed.[175] More than 15 000 patients were

enrolled in an open-label, multicentre, noncomparative phase IV trial in an attempt to evaluate both the safety and efficacy of gatifloxacin in patients with respiratory tract infections. With respect to the overall cardiac safety profile, no arrhythmias were reported to have occurred. Safety data regarding gatifloxacin in patients with cardiovascular disease were presented.[176] Of the 15 752 patients who received gatifloxacin at standard dosages in this outpatient-based treatment study, 4906 were identified to have underlying cardiovascular disease or to be receiving cardiovascular medications. In this patient population, cardiovascular adverse events that were reported included one case each of myocardial infarction, CHF and chest pain, and none were determined to be related to the administration of gatifloxacin. Importantly, no arrhythmias were reported.

A study was conducted to determine post-marketing labelling compliance with warnings in the moxifloxacin product labelling against the concurrent use of QT-prolonging agents (e.g. sotalol, amiodarone, quinidine and procainamide).[177] A longitudinal pharmacy claims database containing healthcare data for more than 100 million patients, processing almost one-fifth of all US retail prescriptions was used. The search identified 107 062 patients who received moxifloxacin and, of them, 111 patients concurrently received amiodarone (0.11%). No moxifloxacin-treated patients concurrently received any of the other identified antiarrhythmic agents. Overall, the current labelling for moxifloxacin in the US appears to be adhered to with minor exceptions.

Hospitals have evaluated the effects of levofloxacin on QTc prolongation, and individual case reports of levofloxacin-associated TdP exist.[108-111,113,114] Iannini and colleagues[111] characterised the effects of levofloxacin on the QT interval in 37 hospitalised patients. Patients were evenly balanced with respect to gender, and the mean age was 70 (range 29–86) years. In this study, the mean increase in the QTc interval attributed to levofloxacin, compared with baseline, was reported to be 4.6 msec, with a range of −47 to +92 msec. Risk factors for QTc prolongation existed in eight patients with electrolyte disturbances and in six patients who were receiving one of the following medications: cotrimoxazole, amiodarone, cisapride or fluoxetine. Of the 37 patients, the incidence of outliers, defined as QTc >60 msec from baseline and QTc >500 msec overall, was reported to be 3% (1 of 37) and 11% (4 of 37), respectively. One of four patients exhibiting a QT interval >500 msec developed TdP and was also concurrently receiving amiodarone. Similarly, Fedutes et al.[110] evaluated the impact of levofloxacin on the QT interval in patients admitted to a large teaching hospital system. Over a 1.5-year time period, 81 patients (including 38 women) met inclusion and exclusion criteria that essentially amounted to patients having some form of pre- and post-ECG monitoring in addition to receiving levofloxacin. Results were stratified for CPMP clinical risk significance. In terms of outliers, eight patients (10%) were reported to have a QTc interval increase of >60 msec from baseline (raising clear concerns) [mean increase ± SD: 102.5 ± 38.1 msec], and 12 patients experienced clinical arrhythmias during levofloxacin treatment. In the 12 patients who developed arrhythmias, the following amplifiers existed: age >65 years (n = 9), female (n = 6), hypokalaemia (n = 2), hypomagnesaemia (n = 2), bradycardia (n = 2), history of cardiac disease (n = 7), renal disease (n = 3) and co-medications known to prolong the QT interval (n = 4). Similar to other quinolone-associated cardiac toxicity reports, multiple amplifiers were evident in these patients. One limitation in the study was the timing of the ECGs, as the pre-treatment ECG could be obtained within 90 days prior to therapy, and the post-treatment ECG was able to be obtained any time during treatment and up to 24 hours afterwards if the creatinine clearance (CL_{CR}) was >50 mL/min or up to 48 hours afterwards if the CL_{CR} was ≤50 mL/min. Nonetheless, the association of levofloxacin could not be ruled out in any of the proarrhythmic events.

A small number of TdP cases have been reported for gatifloxacin.[14,53,106] In the identified cases, multiple risk factors that were likely to have reduced the repolarisation reserve were present, such as female gender (n = 2), age >65 years (n = 3), underlying

heart disease (n = 4) [specifically, congestive heart failure (n = 2)], QT interval-prolonging co-medications (including amiodarone) [n = 3], renal insufficiency and no dosage modifications (n = 3), and one patient had a prolonged QT interval prior to starting gatifloxacin.

4.2.4 Investigational/Newly Marketed Quinolones

Gemifloxacin is a fluoroquinolone that is only available in oral form that has received an approvable letter from the US FDA for the treatment of respiratory tract infections. Gemifloxacin is dually excreted but requires dosage adjustments for moderate to severe renal insufficiency. The effect of gemifloxacin, administered as both single and multiple doses, on the QTc interval compared with placebo was evaluated in 119 healthy volunteers.[178] The data were analysed by means of meta-analysis, as the patients were originally enrolled in a variety of early development studies and most patients received the standard therapeutic gemifloxacin 320 mg/day dosage. The point estimate of QTc prolongation after single-dose treatment was reported to be +3.71 msec (90% CI 0.04, 7.38). Data were made available from clinical trials involving 137 gemifloxacin-treated patients and 122 comparator-treated patients (comparators were β-lactams and macrolides).[178] The reported mean QTc prolongation in these patients (± SD) associated with gemifloxacin was 5.0 (± 25.6) msec. Small numbers of patients were reported to have outlier values: overall QTc intervals >500 msec for gemifloxacin (n = 2) and comparators (n = 2), and for increased QTc intervals from baseline of >60 msec for gemifloxacin (n = 4) and comparators (n = 1).

Garenoxacin is a novel des-F(6) quinolone with potent Gram-positive activity, anaerobic activity and modest Gram-negative activity. Garenoxacin is administered once daily and comes in both intravenous and oral formulations. Garenoxacin is a dual excretion quinolone that undergoes partial hepatic metabolism (non-CYP mediated) and will be unlikely to require dosage modifications for renal impairment. Grasela et al.[179] studied the pharmacokinetics and safety of multidose oral garenoxacin in 40 healthy adult volunteers.[179] Ranges of garenoxacin dosages studied included 200–1200 mg/day. A double-blind, placebo-controlled, dose-ranging (200–800mg) study was conducted that evaluated the effects of intravenous garenoxacin on the QTc interval in healthy male volunteers.[180] The use of serial ECGs recorded over 24 hours on each of the pre-dose administration days (days −3, −2 and −1), and on the dose administration days (days +1, +11 and +18) were manually interpreted and corrected for using Bazett's formula. This is one of the first studies to take advantage of continuous ECG monitoring, which eliminates the limitations of single ECG recording (e.g. the timing of the ECG in relation to the peak drug or metabolite concentration attainment, diurnal variation, adequate baseline evaluation). In the 30 volunteers, no outliers (>60 msec change from time-averaged baseline) were reported, but four volunteers (three garenoxacin, one placebo) had a QTc increase of >30 msec but <60 msec from baseline. Garenoxacin did not demonstrate outlier QTc values determined to be drug related over a wide range of doses. Of note, garenoxacin is no longer being developed by Bristol-Myers Squibb and was returned to Toyoma Pharmaceuticals for undisclosed reasons.

4.2.5 Current Status

In general, the quinolones lack certain pharmacokinetic risk factors that predispose other antimicrobials to TdP risk, such as CYP3A4, CYP2C9 and CYP2C19 inhibition, reliance on CYP isoforms for metabolism, and non-linear pharmacokinetics. The quinolones do interact with the I_{Kr} current to varying degrees and some require dose adjustments to avoid excessive concentrations. Thus far, the product labels have not been changed to reflect additional safety concerns with the currently available quinolones (e.g. ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin) in the US. Grepafloxacin was voluntarily removed by the manufacturer from the worldwide market in late 1999 amidst reports of seven cardiac-related fatalities and three cases of TdP, in addition to poor product sales.[156] The product withdrawal statement read "Glaxo Wellcome has recently concluded an extensive review of the safety of Raxar (grepafloxacin)

and determined that due to an effect of Raxar on cardiac repolarisation, manifested as QT interval prolongation on the ECG, some patients may be at risk of a very serious ventricular arrhythmia known as torsades de pointes when treated with the product"[1].[17] Sparfloxacin is also no longer marketed in the US as of 2001. Despite evidence suggesting that levofloxacin is similar to gatifloxacin and moxifloxacin in terms of having a minimal impact on the QT interval, and that QT-interval prolongation is a quinolone class effect, representatives of the manufacturer believe differently. In fact, a torrent of editorials have been published related to these or similar discussions, mostly between manufacturers.[112,115,181-183] All three drugs are rarely associated with QT interval-related toxicities, making comparisons exceptionally difficult and inconclusive. As such, they are considered interchangeable from a cardiac safety perspective. The most likely quinolone to cause TdP, sparfloxacin, is no longer marketed. Because of the relatively few numbers of patients treated with grepafloxacin, it is difficult to ascertain its overall risk, though it does appear to inhibit I_{Kr}, albeit to a lesser degree than sparfloxacin. Ciprofloxacin remains the safest quinolone to date in terms of TdP risk, as confirmed through *in vitro* and *in vivo* models and from post-marketing experience. A single case of TdP has been reported to occur in association with ciprofloxacin administration in India.[105] The newer/investigational agents (e.g. gemifloxacin and garenoxacin) will be better differentiated as data become available. For gemifloxacin, gatifloxacin, levofloxacin and moxifloxacin class Ia and III antiarrhythmic agents should be strictly avoided. Similar to other drugs discussed with even minimal impact on the QT interval, patients with diagnosed forms of LQTS should prudently avoid QT interval-prolonging drugs unless the benefits outweigh any risk.

4.3 Azoles

Unlike the macrolides and quinolones, the azole antifungal agents have not been scrutinised as thoroughly for cardiac toxicity, as evidenced by minimal published nonclinical studies and post-marketing safety studies. One possible reason for this is because of the risk/benefit analysis, which favours treatment options where few choices are available. Such is the case with invasive fungal disease and the azole antifungals. In contrast with the quinolones, only two oral azoles are indicated for the treatment of invasive aspergillosis, and both entities (i.e. voriconazole and itraconazole) have their limitations. Nevertheless, the fact remains that ketoconazole, itraconazole, fluconazole and voriconazole are capable of prolonging the QT interval.[117,184-186] The currently marketed azoles variably inhibit CYP3A4, thus increasing the risk for elevated exposures of interacting drugs. Also, studies have demonstrated that this class of drugs is capable of intrinsically prolonging the QT interval. For example, at dosages of 200mg every 12 hours for 4 days, ketoconazole resulted in a mean increase in the QT interval of 5.5 msec compared with placebo administration in volunteers ($p < 0.02$).[184] In the absence of interacting co-medications and other risk factors, the azoles appear to be associated with a low risk for TdP, though crude incidence studies have not been conducted.

4.3.1 Pharmacokinetic Risk Factors

Among the azoles, pharmacokinetic profiles differ significantly, ranging from relatively predictable dose-response relationships observed with linear profiles (fluconazole) to less predictable non-linear pharmacokinetics (voriconazole).[129] Only fluconazole is primarily renally eliminated, requiring dosage modifications for renal insufficiency. As mentioned in section 4.3, all of the azoles inhibit CYP3A4, albeit to different degrees. Thus, concurrently administered medications known to affect the QT interval that also serve as substrates for CYP3A4 must be carefully managed or avoided so as to circumvent potential toxicity. It has been noted that ketoconazole and itraconazole are more potent inhibitors of CYP3A4 than voriconazole, which is in turn more potent than fluconazole.[186] The historical

1 The use of trade names is for product identification purposes only and does not imply endorsement.

example of this potent interaction is between ketoconazole and terfenadine.[68] While negligible increases in the QT interval were noted following the administration of ketoconazole and terfenadine individually, the combination resulted in a considerable increase of 82 msec. Fluconazole, voriconazole, ravuconazole, itraconazole and ketoconazole (but not posaconazole) also inhibit CYP2C9 and CYP2C19, and substrates of these isoforms should be avoided if they are associated with QT prolongation unless specific studies state otherwise. Voriconazole is also a substrate of CYP2C19, CYP2C9 and CYP3A4. Drugs metabolised by CYP2C19 and CYP2C9 are, as mentioned, vulnerable to larger than expected exposures if administered to patients with genetic polymorphisms of these CYP isoforms. The product labelling of itraconazole includes a long list of contraindicated medications, primarily those metabolised via the CYP3A4 system.[187]

A number of TdP cases have been published, most as a result of combinations of either itraconazole or ketoconazole with terfenadine, astemizole, cisapride or quinidine derivatives.[68,121-126] Case reports exist of ketoconazole-associated TdP, usually when coadministered with the CYP3A4-metabolised terfenadine and cisapride.[125-127] Voriconazole is primarily metabolised, as mentioned previously in this section, with eight identified metabolites. Less than 2% of the active drug is renally eliminated.[186] Voriconazole exhibits non-linear pharmacokinetics because of saturable metabolism and, as a result, disproportionate concentrations may be encountered when recommended doses are exceeded. For example, an average 2.5-fold increase in exposure results from a 1.5-fold increase in dose (e.g. from 200 to 300mg).[143] Because of the drug interaction potential and resulting cardiac toxicity, voriconazole is contraindicated in patients receiving terfenadine, cisapride, astemizole or quinidine.[186]

4.3.2 Pharmacodynamic Risk Factors

Minimal data exist evaluating the I_{Kr}-antagonistic properties of the azoles. Table III contains HERG IC_{50} values, where available. The impact of ketoconazole on the HERG potassium channel was evaluated by Dumaine and colleagues,[128] demonstrating that it is, in fact, an I_{Kr} antagonist within physiological concentrations. In addition, higher concentrations of ketoconazole were also shown to inhibit another gene, *Kv1.5*, which is responsible for repolarisation of the atrium rather than the ventricle. As a part of the registration package for voriconazole, comparative HERG inhibition studies were conducted.[129] At the lowest concentration tested (0.01 μmol/L), ketoconazole demonstrated HERG inhibition (9.4%), which increased to 46.3% inhibition across the achievable concentration range. Voriconazole did not demonstrate HERG antagonism until drug concentrations reached 50 μmol/L, which resulted in 8.56% inhibition. Thus, voriconazole is only likely to block the I_{Kr} channel when unusually large exposures to it occur (coadministration with a CYP2C19, CYP2C9 or CYP3A4 substrate or inhibitor that also blocks the I_{Kr} current, voriconazole recommended dose is exceeded, or recipient exhibits genetic polymorphism among CYP2C19, CYP2C9 or CYP3A4). Some nonclinical and clinical cardiac safety evaluations were also presented at the US FDA advisory hearing for voriconazole.[129] It was noted that high doses of voriconazole administered to dogs resulted in arrhythmias, PVCs and prolonged QT intervals. In placebo-controlled phase I studies, the effect of voriconazole was measured in healthy volunteers following single and multiple doses. The Fridericia correction factor was used to calculate QTc. In terms of identified outliers, 39 of 138 (28%) of voriconazole-treated volunteers had increased QTc intervals from baseline of ≥30 but <60 msec, compared with 11 of 59 (19%) in the placebo group. QTc measurements ≥60 msec from baseline or ≥500 msec overall were not observed in either group.[129,186] One sudden death was reported in phase III studies as a result of cardiac arrest following voriconazole administration.[186] Multiple risk factors were apparent, including mild hypokalaemia and previous history of benign ventricular arrhythmias. Voriconazole exposure data, for example, organ function studies and dosage, were not available for the author to review.

4.3.3 Post-Marketing Data

Post-marketing data for the azole antifungals consists of case reports. No systematic review of the US FDA's AERS database has been presented or published as of yet. Several case reports of TdP have been published in patients receiving fluconazole and are summarised in table III.[113,117-120] In the case of a 59-year-old female who received a 5-week course of parenteral fluconazole 400–800 mg/day followed by 2 days of intraperitoneal administration, the peak plasma concentration reached 216 mg/L compared with normal peak concentrations of 18 and 28 mg/L following 400 and 800 mg/day, respectively.[117,188] During the time period of excessive plasma fluconazole concentrations, the patient developed TdP. Following the discontinuation of fluconazole, paroxysmal ventricular arrhythmias continued over a 3-day period until the plasma concentrations dropped significantly. Because of its long half-life, fluconazole may accumulate over time in patients with impaired renal function, resulting in prolonged pharmacological and toxicological effects. However, in this case, the patient did not have impaired organ function or other reasons for QT prolongation (i.e. no concomitant drugs with QT-prolonging effects, electrolyte disturbances, neurological disease or cardiac disorders), but did receive both parenteral and intraperitoneal fluconazole. The only TdP warning in the fluconazole product labelling is the contraindication of administering concurrent cisapride.[189]

4.3.4 Current Status

Although the newest anti-aspergillus azoles, ravuconazole and posaconazole, are in phase III trials, cardiovascular safety data were not available at the time of this review. It is likely that as more azoles enter the marketplace and their use increases, TdP cases will emerge. It appears that all of the azoles studied impact on the I_{Kr} current to some degree. Because of both pharmacokinetic and pharmacodynamic risk factors, these drugs are likely to be associated with repolarisation abnormalities, including TdP. Patients receiving azoles should be followed carefully for dosage adjustments, potential drug interactions and electrolyte imbalances to minimise the possibility of proarrhythmia. The azoles should be avoided in those with congenital LQTS unless the benefit of therapy outweighs the potential risk.

4.4 Miscellaneous Antimicrobials

4.4.1 Cotrimoxazole

Cotrimoxazole has been extensively prescribed worldwide since its introduction to clinical use some 30 or more years ago. Only four published episodes (occurring in two patients) of cotrimoxazole-associated QT prolongation leading to ventricular arrhythmias were identified in a recent Medline literature search.[130,131] Thus, the available published data do not establish a credible causal relationship between cotrimoxazole, QT prolongation and TdP. However, there may be a unique population of individuals who are susceptible to TdP upon exposure to cotrimoxazole.[39] A recent study identified 98 patients with drug-induced arrhythmias in whom a small number possessed genetic mutations in various cardiac ion channels. One of these patients developed QT prolongation (>600 msec) after receiving cotrimoxazole, despite having a normal QT interval prior to treatment.[39] This patient was identified to have a single-nucleotide polymorphism (SNP) in MiRP1, a peptide subunit of the I_{Kr} channel encoded for by *KCNE2*. When this patient's defective I_{Kr} channels (with this SNP) were expressed in an *in vitro* system, they were exposed to and inhibited by therapeutic concentrations of sulfamethoxazole, whereas wild-type I_{Kr} channels (without the mutation) were unaffected. Trimethoprim inhibited both the wild-type and mutant MiRP1 I_{Kr} channels but only at 75 μg/mL, concentrations far in excess of those achievable in humans. Thus, it appears that the sulfamethoxazole component was the likely culprit in this case of excessive QT prolongation. Some evidence of predisposition to cotrimoxazole-related QT prolongation/TdP existed in both case reports based on the facts that no QT-prolonging drugs were coadministered and later rechallenges with cotrimoxazole resulted in TdP in both patients.[130,131] These findings indicate that a susceptible population of patients may be at risk; an estimated 1–2% of the population possesses this

SNP that potentially places them at risk for drug-induced proarrhythmic events.[39]

4.4.2 Pentamidine

At least 13 reports of TdP associated with pentamidine administration have been published (table III).[132-142] Similar to reports of QT-interval prolongation occurring with other anti-infectives, multiple risk factors existed, particularly electrolyte abnormalities and co-prescription with QT-prolonging drugs. Although published HERG studies were not identified through a Medline literature search, pentamidine is likely to possess intrinsic QT-prolongation properties. Support for this exists in the fact that pentamidine shares a pharmacophore with the antiarrhythmic procainamide.[4]

The effects of intravenous pentamidine on cardiac repolarisation were evaluated in an open-label, non-randomised, prospective study of HIV-infected patients.[142] Fourteen patients were considered evaluable by the investigators. Patients were excluded from enrolment if any of the following criteria were met: history of cardiac disease or arrhythmia, electrolyte abnormality, concomitant use of drugs known at the time to be associated with arrhythmias (e.g. class IA or III antiarrhythmic drugs, tricyclic antidepressants, phenothiazines), ischaemia on baseline ECG, prolonged QTc interval >480 msec, or the presence of other conditions such as congenital LQTS, bradycardia and pacemaker use. Patients were given pentamidine 4 mg/kg/day administered intravenously over 1 hour. Five patients developed significant QTc prolongation (mean [± SD] increase of 120 ± 30 msec), and three of these patients developed TdP. Nine patients were documented to have been concurrently taking drugs now known to contribute to QT prolongation (azole antifungals), and two of these patients developed TdP. Pentamidine is a substrate of CYP2C19; therefore, coadministration of certain azoles (e.g. voriconazole, fluconazole) would be expected to interfere with its metabolism, potentially resulting in elevated pentamidine concentrations. Because pentamidine is used as a second- or third-line treatment for *Pneumocystis jiroveci* (previously *P. carinii*) pneumonia, its necessity for use is likely to outweigh its risks.

4.4.3 Clindamycin

A single case with clindamycin as a possible cause of TdP in a 76-year-old female was identified on Medline.[190] No concurrent risk factors were evident, other than her age and gender. Prior to TdP, the patient had developed bradycardia (a minimum of 40 beats/min) because of a 2 : 1 atrioventricular block. There are no identified nonclinical studies or additional human data that support the role of clindamycin in causing QT prolongation.

5. Summary

Relative to other drug classes, the number of cases of severe cardiac toxicity mediated by changes in the QT interval is uncommon among anti-infective agents. The recent regulatory climate has resulted in a more systematic approach to cardiac safety testing, yielding an enormous amount of discussion centred around the prolongation of the QT interval. Generally, it appears that many of the current antimicrobial agents act as facilitators of QT prolongation when combined with drugs that both prolong the QT interval and are metabolised via important CYP isoforms (e.g. CYP3A4). To a lesser degree, the antimicrobial agents discussed in this article antagonise the I_{Kr} current and, thus, should be prescribed with extreme caution or not at all in patients with reduced repolarisation reserves.

Risk/benefit decisions regarding the use or formulary acceptance of antimicrobials that prolong the QT interval must be made by informed clinicians. As new data emerge regarding this rare form of toxicity, near real-time information sources (e.g. http://www.torsades.org[84]) may be useful to the practising clinician. Once a drug is identified to prolong the QT interval, the clinician must then determine the weight of the data supporting QT prolongation since this list will contain antimicrobial agents ranging from cotrimoxazole (questionable risk) to erythromycin (well documented risk). Nonclinical, clinical and post-marketing safety studies constitute the majority of fundamental cardiac safety data sources. In addition, the prod-

uct's labelling should be read and adhered to by clinicians.

Once the extent of QT prolongation is ascertained, it is important to establish the appropriate patient or population that the antimicrobial agent may be safely used in (risk versus benefit). At this point, attention to pharmacokinetics (dosage, drug interactions) and the patient's individual susceptibility to TdP (inherited LQTS, QT-prolonging co-medications, electrolyte derangements, presence of structural heart disease, age, gender) serve as a guide to clinicians to safely prescribe antimicrobials. An updated reference for CYP-mediated drug interactions is provided by the Indiana School of Medicine's online drug interactions guide (see http://www.drug-interactions.com).[191]

Finally, continued efforts to identify the genetic polymorphisms responsible for drug-induced QT prolongation is critical. The application of this information into the clinic in the form of real-time blood tests may allow clinicians to design safer drug regimens for those at risk for TdP.

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References

1. Yoshikawa TT. Epidemiology and unique aspects of aging and infectious diseases. Clin Infect Dis 2000; 30: 931-3
2. Elming H, Brendorp B, Kober L, et al. QTc interval in the assessment of cardiac risk. Card Electrophysiol Rev 2002; 6 (3): 289-94
3. Roden DM, Lazzara R, Rosen M, et al. Multiple mechanisms in the long-QT syndrome: current knowledge, gaps, and future directions: the SADS Foundation Task Force on LQTS. Circulation 1996 Oct 15; 94 (8): 1996-2012
4. De Ponti F, Poluzzi E, Montanaro N. QT-interval prolongation by non-cardiac drugs: lessons to be learned from recent experience. Eur J Clin Pharmacol 2000 Apr; 56: 1-18
5. Haverkamp W, Breithardt G, Camm AJ, et al. The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications: report on a policy conference of the European Society of Cardiology. Eur Heart J 2000 Aug; 21 (15): 1216-31
6. Committee on Quality of Health Care in America: Institute of Medicine. To err is human: building a safer health system. Washington, DC: National Academy Press, 2000
7. Classen DC, Pestotnik SL, Evans RS, et al. Adverse drug events in hospitalized patients: excess length of stay, extra costs, and attributable mortality. JAMA 1997 Jan 22-29; 277 (4): 301-6
8. Schappert SM. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 1997: National Center for Health Statistics. Vital Health Stat 13 1999 Nov; (143): i-iv, 1-39
9. National Association of Chain Drug Stores. 2000 community pharmacy results. Alexandria (VA): National Association of Chain Drug Stores, 2001
10. Jacubeit T, Drisch D, Weber E. Risk factors as reflected by an intensive drug monitoring system. Agents Actions 1990; 29: 117-25
11. Witchel HJ, Hancox JC, Nutt DK. Psychotropic drugs, cardiac arrhythmia, and sudden death. J Clin Psychopharmacol 2003 Feb; 23 (1): 58-77
12. Owens Jr RC. Risk assessment for antimicrobial agent-induced QTc interval prolongation and Torsades de Pointes. Pharmacotherapy 2001 Mar; 21 (3): 301-19
13. Curtis LH, Ostbye T, Sendersky V, et al. Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. Am J Med 2003 Feb 1; 114: 135-41
14. Bertino JS, Owens Jr RC, Carnes TD, et al. Gatifloxacin-associated corrected QT interval prolongation, torsades de pointes, and ventricular fibrillation in patients with known risk factors. Clin Infect Dis 2002 Mar 15; 34: 861-3
15. Viskin S. Long QT syndromes and torsade de pointes. Lancet 1999 Nov 6; 354: 1625-33
16. European Agency for the Evaluation of Medicinal Products (EMEA): Committee for Proprietary Medicinal Products (CPMP). Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products [online]. Available from URL: http://www.emea.eu.int/pdfs/human/swp/098696en.pdf [Accessed 2003 Mar 10]
17. McCaig LF, Besser RE, Hughes JM. Antimicrobial drug prescriptions in ambulatory care settings, United States, 1992-2000. Emerg Infect Dis 2003 Apr; 9 (4): 432-7
18. Netter FH. Netter collection of medical illustrations. Vol. 5. Teterboro (NJ): Icon Learning Systems, 1979: 49 (plate #2) [online]. Available from URL: http://65.201.6.68/netterart/ [Accessed 2004 Mar 11]
19. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. The 'Sicilian gambit': a new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. Circulation 1991 Oct; 84 (4): 1831-51
20. Swynghedauw B, Baillard C, Milleiz P. The long QT interval is not only inherited but is also linked to cardiac hypertrophy. J Mol Med 2003 Jun; 81 (6): 336-45
21. Woosley RL, Sale M. QT interval: a measure of drug action. Am J Cardiol 1993 Aug 26; 72 (6): 36b-43b
22. Atiga WL, Calkins H, Lawrence JH, et al. Beat-to-beat repolarization lability identifies patients at risk for sudden cardiac death. J Cardiovasc Electrophysiol 1998 Sep; 9 (9): 899-908
23. Molnar J, Zhang F, Weiss J, et al. Diurnal pattern of QTc interval: how long is prolonged?: possible relation to circadian triggers of cardiovascular events. J Am Coll Cardiol 1996 Jan; 27 (1): 76-83
24. Batchvarov V, Malik M. Measurement and interpretation of QT dispersion. Prog Cardiovasc Dis 2000; 42: 325-44
25. Gillis AM. Effects of antiarrhythmic drugs on QT interval dispersion: relationship to antiarrhythmic action and proarrhythmia. Prog Cardiovasc Dis 2000 Mar-Apr; 42 (5): 385-96
26. Hohnloser SH. Effect of coronary ischemia on QT dispersion. Prog Cardiovasc Dis 2000 Mar-Apr; 42 (5): 351-8

27. Dessertenne F. Ventricular tachycardia with two variable opposing foci [in French]. Arch Mal Coeur Vaiss 1966 Feb; 59 (2): 263-72
28. Kang J, Wang L, Chen X-L, et al. Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K^+ channel HERG. Mol Pharmacol 2001; 59: 122–6
29. Garson Jr A. How to measure the QT interval: what is normal? Am J Cardiol 1993 Aug 26; 72: 14B-6B
30. Fridericia LS. Die systolendauer im elekrokardiogramm bei normalen menschen und bei herzkranken. Acta Med Scand 1920; 53: 469-86
31. Hnatkova K, Malik M. 'Optimum' formulae for heart rate correction of the QT interval. Pacing Clin Electrophysiol 1999; 22: 1683-7
32. Al-Khatib SM, Allen LaPointe NM, Kramer JM, et al. What clinicians should know about the QT interval. JAMA 2003; 289: 2120-7
33. Malik M, Camm AJ. Evaluation of drug-induced QT interval prolongation: implications for drug approval and labeling. Drug Saf 2001; 24 (5): 323-51
34. De Ponti F, Paluzzi E, Cavalli A, et al. Safety of non-antiarrhythmic drugs that prolong the QT interval or induce torsade de pointes. Drug Saf 2002; 25 (4): 263-86
35. Anderson ME, Al-Khatib SM, Roden DM, et al. Cardiac repolarization: current knowledge, critical gaps, and new approaches to drug development and patient management. Am Heart J 2002; 144: 769-81
36. Moss AJ. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. Am J Cardiol 1993 Aug 26; 72: 23B-5B
37. Chiang CE, Roden DM. The long QT syndromes: genetic basis and clinical implications. J Am Coll Cardiol 2000 Jul; 36 (1): 1-12
38. Kubota T, Shimizu W, Kamakura S, et al. Hypokalemia-induced long QT syndrome with an underlying novel missense mutation in S4-S5 linker of KCNQ1. J Cardiovasc Electrophysiol 2000 Sep; 11 (9): 1048-54
39. Sesti F, Abbott GW, Wei J, et al. A common polymorphism associated with antibiotic-induced cardiac arrhythmia. Proc Natl Acad Sci U S A 2000 Sep 12; 97 (19): 10613-8
40. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. N Engl J Med 2003; 348: 1866-74
41. Vincent GM, Timothy K, Fox J, et al. The inherited long QT syndrome: from ion channel to bedside. Cardiol Rev 1999 Jan-Feb; 7 (1): 44-55
42. Wehrens XTH, Vos MA, Doevendans PA, et al. Novel insights in the congenital long QT syndrome. Ann Intern Med 2002; 137: 981-92
43. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004; 350: 1013-22
44. Moss AJ. The QT interval and torsade de pointes. Drug Saf 1999; 21 Suppl. 1: 69-80
45. Haverkamp W, Monnig G, Schulze-Bahr E, et al. Physician-induced torsade de pointes: therapeutic implications. Cardiovasc Drugs Ther 2002; 16: 101-9
46. Setzer A, Wray HW. Quinidine syncope: paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. Circulation 1964; 30: 17-26
47. Roden DM, Woosley RL, Primm RK. Incidence and clinical features of the quinidine-associated long QT syndrome: implications for patient care. Am Heart J 1986 Jun; 111 (6): 1088-93
48. Kay GN, Plumb VJ, Arciniegas JG, et al. Torsade de pointes: the long-short initiating sequence and other clinical features: observations in 32 patients. J Am Coll Cardiol 1983 Nov; 2 (5): 806-17
49. Bauman JL, Bauernfeind RA, Hoff JV, et al. Torsades de pointes due to quinidine: observations in 31 patients. Am Heart J 1984 Mar; 107 (3): 425-30
50. Haverkamp W, Martinez RA, Hief C, et al. Efficacy and safety of d,l-sotalol in patients with ventricular tachycardia and in survivors of cardiac arrest. J Am Coll Cardiol 1997 Aug; 30 (2): 487-95
51. Lehmann MH, Hardy S, Archibald D, et al. Sex difference in risk of torsade de pointes with d,l-sotalol. Circulation 1996 Nov 15; 94 (10): 2535-41
52. Hohnloser SH. Proarrhythmia with class III antiarrhythmic drugs: types, risks, and management. Am J Cardiol 1997 Oct 23; 80 (8A): 82G-9G
53. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. Pharmacotherapy 2001 Dec; 21 (12): 1468-72
54. Owens RCJ, Ambrose PG. Torsades de pointes associated with fluoroquinolones. Pharmacotherapy 2002 May; 22 (5): 663-72
55. De Ponti F, Poluzzi E, Montanaro N. Organising evidence on QT prolongation and occurrence of Torsades de Pointes with non-antiarrhythmic drugs: a call for consensus. Eur J Clin Pharmacol 2001 Feb 14; 57: 185-209
56. Shaffer D, Singer S, Korvick J. Macrolide and fluoroquinolone associated torsade de pointes: review of the FDA adverse event reporting system [abstract no. A-635]. In: Program and abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2001 Sep 17-20; Toronto, Ontario, Canada. Washington, DC: American Society for Microbiology, 2001: 20
57. ICH S7B Safety Pharmacology studies for assessing the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals. Washington, DC: US Food and Drug Administration, 2002
58. Ambrose PG, Owens Jr RC. New antibiotics in pulmonary and critical care medicine: focus on advanced generation quinolones and cephalosporins. Semin Respir Crit Care Med 2000; 21 (1): 19-32
59. Volberg WA, Koci BJ, Su W, et al. Blockade of human cardiac potassium channel human ether-a-go-go-related gene (HERG) by macrolide antibiotics. J Pharmacol Exp Ther 2002 Jul; 302 (1): 320-7
60. Berlex Laboratories PD. Betapace® (sotalol) tablets: prescribing information. Wayne (NJ): Berlex Laboratories PD, 1998
61. Kyrmizakis DE, Chimona TS, Kanoupakis EM, et al. QT prolongation and torsades de pointes associated with concurrent use of cisapride and erythromycin. Am J Otolaryngol 2002 Sep-Oct; 23 (5): 303-7
62. Katapadi K, Kostandy G, Katapadi M, et al. A review of erythromycin-induced malignant tachyarrhythmia-torsade de pointes: a case report. Angiology 1997 Sep; 48 (9): 821-6
63. Tschida SJ, Guay DR, Straka RJ, et al. QTc-interval prolongation associated with slow intravenous erythromycin lactobionate infusions in critically ill patients: a prospective evaluation and review of the literature. Pharmacotherapy 1996 Apr; 16 (4): 663-74
64. Rubart M, Pressler ML, Pride HP, et al. Electrophysiological mechanisms in a canine model of erythromycin-associated long QT syndrome. Circulation 1993 Oct; 88 (4 Pt1): 1832-44
65. Ambrose PG, Owens Jr RC, Grasela D. Antimicrobial pharmacodynamics. Med Clin North Am 2000 Nov; 84 (6): 1431-45

66. Lacy MK, Owens Jr RC, Xu X, et al. Comparison of bactericidal activity after multidose administration of clarithromycin, azithromycin and cefuroxime axetil against streptococcus pneumoniae. Int J Antimicrob Agents 1998 Nov; 10 (4): 279-83
67. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet 2000 Jan; 38 (1): 41-57
68. Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC, Cantilena LR. Terfenadine-ketoconazole interaction: pharmacokinetic and electrocardiographic consequences. JAMA 1993 Mar 24-31; 269 (12): 1513-8
69. Kivisto KT, Lilja JJ, Backman JT, et al. Repeated consumption of grapefruit juice considerably increases plasma concentrations of cisapride. Clin Pharmacol Ther 1999 Nov; 66 (5): 448-53
70. Desta Z, Zhao X, Shin J-G, et al. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clin Pharmacokinet 2002; 41 (12): 913-58
71. Center for Drug Evaluation and Research. Preventable adverse drug reactions: a focus on drug interactions [online]. Available from URL: http://www.fda.gov/cder/drug/drugReactions/default.htm [Accessed 2003 Mar 10]
72. Goldberg J, Owens Jr RC. Optimizing antimicrobial dosing in the critically ill patient. Curr Opin Crit Care 2002 Oct; 8 (5): 435-40
73. Abbott GW, Sesti F, Splawski I, et al. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. Cell 1999 Apr 16; 97 (2): 175-87
74. Roden DM. Taking the 'idio' out of 'idiosyncratic': predicting torsades de pointes. Pacing Clin Electrophysiol 1998 May; 21 (5): 1029-34
75. Suchard J. Review: wherefore withdrawal? The science behind recent drug withdrawals and warnings [letter]. Int J Med Toxicol 2001; 4 (2): 15
76. Shaffer D, Singer S, Korvick J, et al. 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 Jul 15; 35: 197-200
77. Leone R, Venegoni M, Motola D, et al. Adverse drug reactions related to the use of fluoroquinolone antimicrobials. Drug Saf 2003; 26 (2): 109-20
78. Morgan Jr TK, Sullivan ME. An overview of class III electrophysiological agents: a new generation of antiarrhythmic therapy. Prog Med Chem 1992; 29: 65-108
79. Mitcheson JS, Chen J, Lin M, et al. A structural basis for drug-induced long QT syndrome. Proc Natl Acad Sci U S A 2000 Oct 24; 97 (22): 12329-33
80. Domagala JM. Structure-activity and structure-side-effect relationships for the quinolone antibacterials. J Antimicrob Chemother 1994 Apr; 33 (4): 685-706
81. Owens Jr RC, Russo R, Wikler M, et al. Review of structure-toxicity relationships of fluoroquinolones [abstract]. Clin Infect Dis 1999 Oct; 29 (4): 978
82. Owens Jr RC. Quinolone structure-activity relationships. Antibiotic Clin 1999; 3 Suppl. 1: 5-12
83. Iannini PB. Cardiotoxicity of macrolides, ketolides and fluoroquinolones that prolong the QTc interval. Expert Opin Drug Saf 2002; 1 (2): 121-8
84. Arizona Center for Education and Research on Therapeutics [online]. Available from URL: http://www.torsades.org [Accessed 2004 Jan 13]
85. Arellano-Rodrigo E, Garcia A, Mont L, et al. Torsade de pointes and cardiorespiratory arrest induced by azithromycin in a patient with congenital long QT syndrome. Med Clin (Barc) 2001 Jun; 23: 117 (3): 118-9
86. Samarendra P, Kumari S. QT prolongation associated with azithromycin/amiodarone combination. Pacing Clin Electrophysiol 2001 Oct; 24: 1572-4
87. Lee KL, Jim MH, Tang SC, et al. QT prolongation and Torsades de Pointes associated with clarithromycin. Am J Med 1998 Apr; 104 (4): 395-6
88. Piquette RK. Torsade de pointes induced by cisapride/clarithromycin interaction. Ann Pharmacother 1999 Jan; 33 (1): 22-6
89. Sekkarie MA. Torsades de pointes in two chronic renal failure patients treated with cisapride and clarithromycin. Am J Kidney Dis 1997 Sep; 30 (3): 437-9
90. 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 Jan; 65 (1): 10-20
91. Kundu S, Williams SR, Nordt SP, et al. Clarithromycin-induced ventricular tachycardia. Ann Emerg Med 1997 Oct; 30 (4): 542-4
92. Paar D, Terjung B, Sauerbruch T. Life-threatening interaction between clarithromycin and disopyramide. Lancet 1997 Feb 1; 349 (9048): 326-7
93. Flockhart DA, Drici MD, Kerbusch T, et al. Studies on the mechanism of a fatal clarithromycin-pimozide interaction in a patient with Tourette syndrome. J Clin Psychopharmacol 2000 Jun; 20 (3): 317-24
94. Hayashi Y, Ikeda U, Hashimoto T, et al. Torsades de pointes ventricular tachycardia induced by clarithromycin and disopyramide in the presence of hypokalemia. Pacing Clin Electrophysiol 1999 Apr; 22 (4 Pt 1): 672-4
95. Vallejo CN, Rodriguez PD, Sanchez HA, et al. Ventricular tachycardia and long QT associated with clarithromycin administration in a patient with HIV infection. Rev Esp Cardiol 2002 Aug; 55 (8): 878-81
96. Choudbury L, Grais IM, Passman RS. Torsades de pointes due to drug interaction between disopyramide and clarithromycin. Heart Dis 1999; 1: 206-7
97. Kamochi H, Nii T, Eguchi K, et al. Clarithromycin associated with torsade de pointes. Jpn Circ J 1999 May; 63 (5): 421-2
98. Oberg KC, Bauman JL. QT interval prolongation and torsades de pointes due to erythromycin lactobionate. Pharmacotherapy 1995 Nov-Dec; 15 (6): 687-92
99. Woywodt A, Grommas U, Buth W, et al. QT prolongation due to roxithromycin. Postgrad Med J 2000 Oct; 76 (900): 651-4
100. Promphan W, Khongphatthanayothin A, Horchaiprasit K, et al. Roxithromycin induced torsade de pointes in a patient with complex congenital heart disease and complete atrioventricular block. Pacing Clin Electrophysiol 2002; 26 (6): 1424-6
101. Verdun F, Mansourati J, Jobic Y, et al. Torsades de pointe with spiramycin and metiquazine therapy: apropos of a case. Arch Mal Coeur Vaiss 1997 Jan; 90 (1): 103-6
102. Cooper C. Post-marketing safety data. Ketek (telithromycin) for the FDA Anti-infective Drug Products Advisory Committee Meeting, 2003 Jan 8 [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/03/slides/3919s1.htm [Accessed 2003 Apr 3]

103. Ross D. Aventis Pharma. Ketek (telithromycin) briefing document for the FDA Anti-infective Drug Products Advisory Committee Meeting, 2001 Apr 26 [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3746b_01_aventis.pdf [Accessed 2003 Jan 10]
104. Fournier P, Pacouret G, Charbonnier B. A new cause of torsades de pointes: combination of terfenadine and troleandomycin. Ann Cardiol Angeiol (Paris) 1993 May; 42 (5): 249-52
105. Singh H, Kishore K, Gupta MS, et al. Ciprofloxacin-induced QTc prolongation. J Assoc Physicians India 2002 Mar; 50: 430-1
106. Iannini PB, Circiumanu I. Gatifloxacin-induced QTc prolongation and ventricular tachycardia. Pharmacotherapy 2001 Mar; 21 (3): 361-2
107. Cox E. Factive® (gemifloxacin) briefing NDA 21-158. FDA Anti-infective Drug Products Advisory Committee Meeting, 2003 Mar 5 [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/03/slides/3931s1.htm [Accessed 2003 Mar 10]
108. Paltoo B, O'Donoghue S, Mousavi MS. Levofloxacin induced polymorphic ventricular tachycardia with normal QT interval. Pacing Clin Electrophysiol 2001 May; 21 (5): 895-7
109. Samaha FF. QTc interval prolongation and polymorphic ventricular tachycardia in association with levofloxacin [letter]. Am J Med 1999 Nov; 107 (5): 528-9
110. Fedutes BA, Chan-Tompkins NH, Pannala NR, et al. Assessment of levofloxacin's effects on the QTc interval [abstract no. 611]. In: Program and abstracts of the 40th Annual Meeting of the Infectious Diseases Society of America; 2002 Oct 24-27; Chicago (IL). Alexandria (VA): Infectious Diseases Society of America, 2002: 152
111. Iannini PB, Kramer H, Circiumaru I, et al. QTc prolongation associated with levofloxacin [abstract no. 822]. In: Program and abstracts of the 40th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto, Ontario, Canada. Washington, DC: American Society for Microbiology, 2000: 477
112. Iannini PB, Doddamani S, Byazrova E, et al. Prolongation of QT interval is probably a class effect of fluoroquinolones. BMJ 2001 Jan 6; 322 (7277): 46-7
113. Gandhi PJ, Menezes PA, Vu HT, et al. Fluconazole- and levofloxacin-induced torsades de points in an intensive care unit patient. Am J Health Syst Pharm 2003; 60: 2479-83
114. Amankwa K, Krishnan SC, Tisdale JE. Torsades de pointes associated with fluoroquinolones: importance of concomitant risk factors. Clin Pharmacol Ther 2004; 75: 242-7
115. Ball P. Quinolone-induced QT interval prolongation: a not-so-unexpected class effect. J Antimicrob Chemother 2000 May; 45 (5): 557-9
116. Jaillon P, Morganroth J, Brumpt I, et al. Overview of electrocardiographic and cardiovascular safety data for sparfloxacin. J Antimicrob Chemother 1996 May; 37 Suppl. A: 161-7
117. Wassmann S, Nickenig G, Bohm M. Long QT syndrome and torsade de pointes in a patient receiving fluconazole [letter]. Ann Intern Med 1999 Nov 16; 131 (6): 797
118. Tholakanahalli VN, Potti A, Hanley J, et al. Fluconazole-induced torsade de pointes. Ann Pharmacother 2001 Apr; 35 (4): 432-4
119. Khazan M, Mathis AS. Probable case of torsades de pointes induced by fluconazole. Pharmacotherapy 2002 Dec; 22 (12): 1632-7
120. Dorsey ST, Biblo LA. Prolonged QT interval and torsades de pointes caused by the combination of fluconazole and amitriptyline. Am J Emerg Med 2000 Mar; 18 (2): 227-9
121. Pohjola-Sintonen S, Viitasalo M, Toivonen L, et al. Itraconazole prevents terfenadine metabolism and increases risk of torsades de pointes ventricular tachycardia. Eur J Clin Pharmacol 1993; 45 (2): 191-3
122. Cruccu V, Pedretti D, Confalonieri F. A case of pulmonary aspergillosis effectively treated with itraconazole: possible interaction of the antimycotic agent with hydroquinidine. Clin Ther 1995 May; 146 (5): 383-9
123. Romkes JH, Froger CL, Wever EF, et al. Syncopes during simultaneous use of terfenadine and itraconazole. Ned Tijdschr Geneeskd 1997 May; 141 (19): 950-3
124. Hoover CA, Carmichael JK, Nolan Jr PE, et al. Cardiac arrest associated with combination cisapride and itraconazole therapy. J Cardiovasc Pharmacol Ther 1996 Jul; 1 (3): 255-8
125. Zimmermann M, Duruz H, Guinand O, et al. Torsades de Pointes after treatment with terfenadine and ketoconazole. Eur Heart J 1992 Jul; 13 (7): 1002-3
126. Tsai WC, Tsai LM, Chen JH. Combined use of astemizole and ketoconazole resulting in torsade de pointes. J Formos Med Assoc 1997 Feb; 96 (2): 144-6
127. Monahan BP, Ferguson CL, Killeavy ES, et al. Torsades de pointes occurring in association with terfenadine use. JAMA 1990 Dec 5; 264 (21): 2788-90
128. Dumaine R, Roy M-L, Brown AM. Blockade of HERG and Kv1.5 by ketoconazole. J Pharmacol Exp Ther 1998 Aug; 286 (2): 727-35
129. Baildon R, Patterson T, Boucher HW, et al. (2001) NDA 21-266, Vfend (voriconazole) Tablets, and NDA 21-267, Vfend I.V. (voriconazole) for infusion, Pfizer Global Research and Development. Proposed for the treatment of invasive aspergillosis, serious Candida infections, infections caused by Scedosporium spp. and Fusarium spp., rare and refractory infections and empirical treatment of febrile neutropenia. US FDA [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/01/slides/3792s2.htm [Accessed 2003 Mar 10]
130. Weiner I, Rubin DA, Martinez E, et al. QT prolongation and paroxysmal ventricular tachycardia occurring during fever following trimethoprim-sulfamethoxazole administration. Mt Sinai J Med 1981 Jan-Feb; 48 (1): 53-55
131. Lopez JA, Harold JG, Rosenthal MC, et al. QT prolongation and torsade de pointes after administration of trimethoprim-sulfamethoxazole. Am J Cardiol 1987 Feb 1; 59 (4): 376-7
132. Topol EJ, Lerman BB. Hypomagnesemic torsades de pointes. Am J Cardiol 1983 Dec 1; 52 (10): 1367-8
133. Wharton JM, Demopulos PA, Goldschlager N. Torsade de pointes during administration of pentamidine isethionate. Am J Med 1987 Sep; 83 (3): 571-6
134. Bibler MR, Chou TC, Toltzis RJ, et al. Recurrent ventricular tachycardia due to pentamidine-induced cardiotoxicity. Chest 1988 Dec; 94 (6): 1303-6
135. Pujol M, Carratala J, Mauri J, et al. Ventricular tachycardia due to pentamidine isethionate [letter]. Am J Med 1988 May; 84 (5): 980
136. Mitchell P, Dodek P, Lawson L, et al. Torsades de pointes during intravenous pentamidine isethionate therapy. CMAJ 1989 Jan 15; 140 (2): 173-4
137. Lindsay Jr J, Smith MA, Light JA. Torsades de pointes associated with antimicrobial therapy for pneumonia. Chest 1990 Jul; 98 (1): 222-3

138. Stein KM, Haronian H, Mensah GA, et al. Ventricular tachycardia and torsades de pointes complicating pentamidine therapy of Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. Am J Cardiol 1990 Oct 1; 66 (10): 888-9
139. Gonzalez A, Sager PT, Akil B, et al. Pentamidine-induced torsade de pointes. Am Heart J 1991 Nov; 122 (5): 1489-92
140. Taylor AJ, Hull RW, Coyne PE, et al. Pentamidine-induced torsades de pointes: safe completion of therapy with inhaled pentamidine. Clin Pharmacol Ther 1991 Jun; 49 (6): 698-700
141. Mani S, Kocheril AG, Andriole VT. Case report: pentamidine and polymorphic ventricular tachycardia revisited. Am J Med Sci 1993 Apr; 305 (4): 236-40
142. Eisenhauer MD, Eliasson AH, Taylor AJ, et al. Incidence of cardiac arrhythmias during intravenous pentamidine therapy in HIV-infected patients. Chest 1994 Feb; 105 (2): 389-95
143. Purkins L, Wood N, Ghahramani P, et al. Pharmacokinetics and safety of voriconazole following intravenous to oral-dose escalation regimens. Antimicrob Agents Chemother 2002 Aug; 46 (8): 2546-53
144. Slaughter RL, Edwards DJ. Recent advances: the cytochrome P450 enzymes. Ann Pharmacother 1995 Jun; 29 (6): 619-24
145. Thompson D, Oster G. Use of terfenadine and contraindicated drugs. JAMA 1996 May; 275 (17): 1339-41
146. Napolitano C, Priori SG, Schwartz PJ. Torsade de pointes: mechanisms and management. Drugs 1994 Jan; 47 (1): 51-65
147. Zhanel GG, Dueck M, Hogan DJ, et al. Review of macrolides and ketolides: focus on respiratory tract infections. Drugs 2001; 61 (4): 443-98
148. van Haarst AD, van't Klooster GA, van Gerven JM, et al. The influence of cisapride and clarithromycin on QT intervals in healthy volunteers. Clin Pharmacol Ther 1998 Nov; 64 (5): 542-6
149. Zehender M, Hohnloser S, Just H. QT interval prolonging drugs: mechanisms and clinical relevance of the arrhythmogenic hazards. Cardiovasc Drugs Ther 1991 Apr; 5 (2): 515-30
150. Harris S, Hilligoss DM, Colangelo PM, et al. Azithromycin and terfenadine: lack of drug interaction. Clin Pharmacol Ther 1995 Sep; 58 (3): 310-5
151. Alvarez-Elcoro S, Enzler MJ. The macrolides: erythromycin, clarithromycin, and azithromycin. Mayo Clin Proc 1999 Jun; 74 (6): 613-34
152. Austin KL, Mather LE, Philpot CR, et al. Intersubject and dose-related variability after intravenous administration of erythromycin. Br J Clin Pharmacol 1980 Sep; 10 (3): 273-9
153. Nattel S, Ranger S, Talajic M, et al. Erythromycin-induced long QT syndrome: concordance with quinidine and underlying cellular electrophysiologic mechanism. Am J Med 1990 Aug; 89 (2): 235-8
154. Ohtani H, Taninaka C, Hanada E, et al. Comparative pharmacodynamic analysis of QT interval prolongation induced by the macrolides clarithromycin, roxithromycin, and azithromycin. Chemotherapy 2000; 44: 2630-7
155. Milberg P, Eckardt L, Hans-Jurgen B, et al. Divergent proarrhythmic potential of macrolide antibiotics despite similar QT prolongation: fast phase 3 repolarization prevents early afterdepolarizations and torsades de pointes. J Pharmacol Exp Ther 2002; 303 (1): 218-25
156. Brinker A. Reporting rates for serious cardiac dysrhythmias among fluoroquinolones, azithromycin, clarithromycin, and cefuroxime: Anti-Infective Drugs Advisory Committee, US Food and Drug Administration [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/99/slides/3558s1e [Accessed 2003 Apr 10]
157. Shaffer D, Singer S. Macrolide antibiotics and torsades de pointes postmarketing analysis, 2001 Apr 26. Anti-Infective Drugs Advisory Committee, US Food and Drug Administration [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_02_shaffer_rev.ppt [Accessed 2003 Jan 10]
158. Smalley W, Shatin D, Wysowski DK, et al. Contraindicated drug use of cisapride: impact of food and drug administration regulatory action. JAMA 2000 Dec 20; 284 (23): 3036-9
159. Iannini P, Stager W, Sharma K, et al. A 24,000 patient trial comparing telithromycin and amoxicillin-clavulanate in the treatment of community acquired respiratory tract infections in a usual care setting [abstract no. LB-240]. In: Abstracts Addendum of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2002 Sep 22-25; San Diego (CA). Washington, DC: American Society for Microbiology, 2002
160. Demolis J-L, Vacheron F, Cardus S, et al. Effect of single and repeated oral doses of telithromycin on cardiac QT interval in healthy subjects. Clin Pharmacol Ther 2003 Mar; 73 (3): 242-52
161. von Keutz E, Schluter G. Preclinical safety evaluation of moxifloxacin, a novel fluoroquinolone. J Antimicrob Chemother 1999 May; 43 Suppl. B: 91-100
162. Fogarty C, Grossman C, Williams J, et al. Efficacy and safety of moxifloxacin vs clarithromycin for community-acquired pneumonia. Infect Med 1999; 16: 748-63
163. Ball P, Mandell L, Niki Y, et al. Comparative tolerability of the newer fluoroquinolone antibacterials. Drug Saf 1999 Nov; 21 (5): 407-21
164. Stahlmann R. Safety profile of the quinolones. J Antimicrob Chemother 1990 Nov; 26 Suppl. D: 31-44
165. Owens Jr RC, Ambrose PG. Clinical use of the fluoroquinolones. Med Clin North Am 2000 Nov; 84 (6): 1447-69
166. Conder ML, Lawrence JH, Levesque PC, et al. Inhibition of the HERG potassium ion channel by fluoroquinolone antibiotics: correlation with the risk for clinically significant QT interval prolongation [abstract no. 810]. In: Program and abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto, Ontario, Canada. Washington, DC: American Society for Microbiology, 2000: 474
167. Bischoff U, Schmidt C, Netzer R, et al. Effects of fluoroquinolones on HERG currents. Eur J Pharmacol 2000; 406: 341-3
168. Stahlmann R, Schwabe R. Safety profile of grepafloxacin compared with other fluoroquinolones. J Antimicrob Chemother 1997; 40 Suppl. A: 83-92
169. Stahlmann R, Lode H. Toxicity of quinolones. Drugs 1999; 58 Suppl. 2: 37-42
170. Adamantidis MM, Dumotier BM, Caron JF, et al. Sparfloxacin but not levofloxacin or ofloxacin prolongs cardiac repolarization in rabbit Purkinje fibers. Fundam Clin Pharmacol 1998; 12 (1): 70-6
171. Anderson ME, Mazur A, Yang T, et al. Potassium current antagonist properties and proarrhythmic consequences of quinolone antibiotics. J Pharmacol Exp Ther 2001; 296 (3): 806-10
172. Morganroth J, Talbot GH, Dorr MB, et al. Effect of single ascending, supratherapeutic doses of sparfloxacin on cardiac repolarization (QTc interval). Clin Ther 1999 May; 21 (5): 818-28
173. Dupont H, Timsit JF, Souweine B, et al. Torsades de pointe probably related to sparfloxacin. Eur J Clin Microbiol Infect Dis 1996 Apr; 15 (4): 350-1

174. Thomas SH. Drugs, QT interval abnormalities and ventricular arrhythmias. Adverse Drug React Toxicol Rev 1994; 13 (2): 77-102
175. Von Seggern K, Russo R, Wikler M. A novel approach to postmarketing surveillance: the tequin clinical experience study [abstract no. 2216]. In: Program and abstracts of the 40th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto, Ontario, Canada. Washington, DC: American Society for Microbiology, 2000: 468
176. Iannini PB, von Seggern K, Wikler MA. Safety of gatifloxacin in patients with cardiovascular disease [abstract no. 2218]. In: Program and abstracts of the 40th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20 Toronto, Ontario, Canada. Washington, DC: American Society for Microbiology, 2000: 469
177. Brinker A, Staffa J. Concurrent use of selected agents with moxifloxacin: an examination of labelling compliance within 1 year of marketing. Arch Intern Med 2002 Sep 23; 162: 2011-2
178. Bird N, Lewis A, Montague T, Bygate E, Dixon R. Assessment of the effect of gemifloxacin on QTc interval in healthy volunteers [abstract no. 821]. In: Program and abstracts of the 40th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto, Ontario, Canada. Washington, DC: American Society for Microbiology, 2000: 477
179. Grasela D, Gajjar A, Bello A, et al. Safety and tolerability and pharmacokinetics of BMS-284756 a novel des-F (6) quinolone following a 14 day oral dose in healthy adult subjects [abstract no. 2260]. In: Program and abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto, Ontario, Canada. Washington, DC: American Society for Microbiology, 2000: 36
180. Gajjar D, Geraldes M, Russo R, et al. Lack of an effect of intravenous BMS-284756 on the QTc interval in healthy subjects [abstract no. A-633]. In: Program and abstracts of the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2001 Sep 22-25; Chicago (IL). Washington, DC: American Society for Microbiology, 2001: 19
181. Kahn JB. Quinolone-induced QT interval prolongation: a not-so-unexpected class effect. J Antimicrob Chemother 2000 Nov; 46 (5): 847-8
182. Iannini PB. Quinolone-induced QT interval prolongation: a not-so-unexpected class effect. J Antimicrob Chemother 2001 Jun; 47 (6): 893-4
183. White CM, Grant EM, Quintiliani R. Moxifloxacin does increase the corrected QT interval. Clin Infect Dis 2001 Oct 15; 33 (8): 1441-2
184. Paserchia LA, Hewett J, Woosley RL. Effects of ketoconazole on QTc [abstract]. Clin Pharmacol Ther 1994; 55: 146
185. Albengres E, Le Louet H, Tillement JP. Systemic antifungal agents. Drug interactions of clinical significance. Drug Saf 1998 Feb; 18 (2): 83-97
186. Ghannoum MA, Kuhn DM. Voriconazole-better chances for patients with invasive mycoses. Eur J Med Res 2002 May 31; 7 (5): 242-56
187. Ortho Biotech Inc. Sporanox® (itraconazole) oral solution, Sporanox® (itraconazole) capsules: prescribing information. Raritan (NJ): Ortho Biotech Inc., 2000
188. Owens RCJ. Fluconazole. Antibiot Clin 1997 Nov-Dec; 1 (6): 109-112
189. Pfizer Pharmaceutical Company. Diflucan® (fluconazole) tablets; Diflucan® (fluconazole) injection: prescribing information. New York: Pfizer Pharmaceutical Company, 1998
190. Gabel A, Schymik G, Mehmel HC. Ventricular fibrillation due to long QT syndrome probably caused by clindamycin. Am J Cardiol 1999 Mar 1; 83 (5): 813-5
191. Indiana University School of Medicine. Drug interactions [online]. Available from URL: http://www.drug-interactions.com [Accessed 2004 Jan 13]

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