Drug-Induced Prolongation of the QT Interval

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I N THE PAST DECADE, THE SINGLE MOST COMMON CAUSE OF THE WITH-drawal or restriction of the use of drugs that have already been marketed has been the prolongation of the QT interval associated with polymorphic ventricular tachy-cardia, or torsade de pointes (Fig. 1), which can be fatal.[1] Nine structurally unrelated drugs that were marketed in the United States or elsewhere for a range of noncardio-vascular indications have been removed from the market or had their availability se-verely restricted because of this rare form of toxicity. These drugs are terfenadine, astemizole, grepafloxicin, terodiline, droperidol, lidoflazine, sertindole, levomethadyl, and cisapride.

A convergence of data obtained from clinicians, basic electrophysiologists, and ge-neticists who have studied the congenital long-QT syndrome (also characterized by torsade de pointes) has resulted in some understanding of the mechanisms whereby drugs may cause this type of arrhythmia. Guidelines,[2,3] which are still evolving, are aimed at predicting whether a new drug carries this risk. Paradoxically, however, in-creased knowledge has also illuminated the fact that the current predictors of this serious side effect are imperfect, both for individual patients and for populations of patients who are exposed to a given drug. Thus, although clinicians, members of regulatory bodies, and drug developers may be able to predict that a given drug may carry some risk, they can neither assess nor quantify it accurately. In this article, I summarize the current knowledge about molecular and clinical predictors of drug-induced prolonga-tion of the QT interval and torsade de pointes, consider how new molecular predictors of a drug's activity might be incorporated into drug-development programs and clinical practice, and suggest a general approach to drugs that are suspected of causing this problem.

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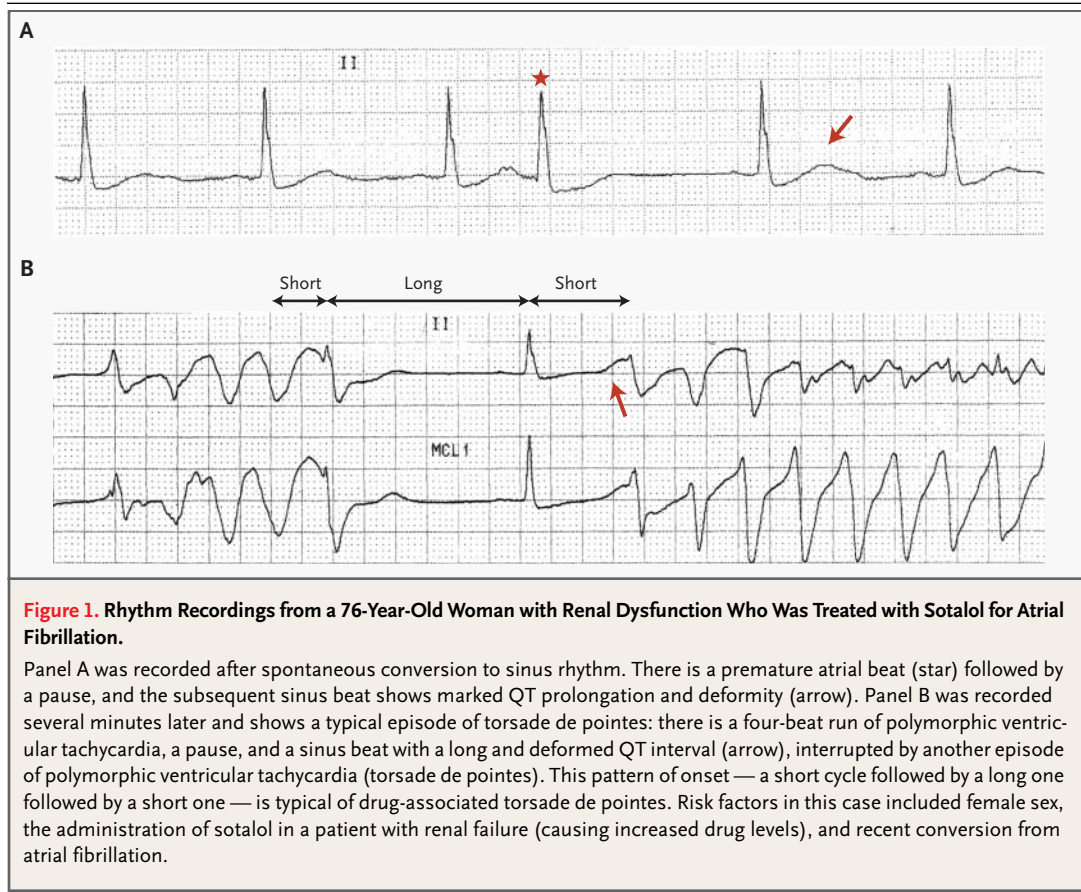
THE CLINICAL BACKGROUND OF LONG-QT SYNDROME

Syncope associated with the initiation of quinidine therapy has been recognized since the 1920s, and the availability of online electrocardiographic monitoring in the 1960s led to the identification of pause-dependent polymorphic ventricular tachycardia as the underlying mechanism.[4] The term "torsade de pointes," coined in 1966 to describe the peculiar appearance of a ventricular tachycardia occurring in an elderly woman with heart block,[5] is often translated as a "twisting of the points," referring to the beat-to-beat changes in the QRS axis (Fig. 1B). Congenital syndromes involving QT-interval prolongation and syncope or sudden death were first described in the late 1950s and early 1960s.[6-8] The few electrocardiographically documented cases of syncope or sud-den death in patients with a congenital long-QT syndrome have been characterized by torsade de pointes, although the pause dependence that is typical of the drug-related form (Fig. 1) is not always present.[9]

Figure 1. Rhythm Recordings from a 76-Year-Old Woman with Renal Dysfunction Who Was Treated with Sotalol for Atrial Fibrillation.

Panel A was recorded after spontaneous conversion to sinus rhythm. There is a premature atrial beat (star) followed by a pause, and the subsequent sinus beat shows marked QT prolongation and deformity (arrow). Panel B was recorded several minutes later and shows a typical episode of torsade de pointes: there is a four-beat run of polymorphic ventricular tachycardia, a pause, and a sinus beat with a long and deformed QT interval (arrow), interrupted by another episode of polymorphic ventricular tachycardia (torsade de pointes). This pattern of onset — a short cycle followed by a long one followed by a short one — is typical of drug-associated torsade de pointes. Risk factors in this case included female sex, the administration of sotalol in a patient with renal failure (causing increased drug levels), and recent conversion from atrial fibrillation.

Although torsade de pointes can occur in many settings (such as heart block, as originally described), it is usually seen in patients with one of the congenital long-QT syndromes or in association with drug therapy. The drugs that are generally considered to confer a risk of torsade de pointes are listed in Table 1. Multiple clinical risk factors (Table 2 and Fig. 1) are often present in an individual case. These factors are not only helpful in estimating the risk for an individual patient but have also provided a starting point for basic research into underlying mechanisms. One example is the elucidation of mechanisms by which hypokalemia increases risk.[23] Another risk factor is female sex, a powerful predictor of the risk of torsade de pointes in patients with congenital[24] and acquired[10] long-QT syndromes.[25-27] How or whether variability in the expression of genes that determine normal cardiac electrophysiology[28] explain the sex-dependent risk of torsade de pointes is not yet clear.

A unifying concept, "reduced repolarization reserve," has been used to explain the variable risk.[29] This framework suggests that the physiologic mechanisms that maintain normal cardiac repolarization vary among patients but are not apparent in a basal state. However, exposure to a drug that prolongs the QT interval, or the development of a risk factor such as bradycardia or hypokalemia, is more likely to cause exaggerated QT prolongation in a susceptible patient than in a nonsusceptible one.[18] In vitro studies suggest a corollary — that the risk of torsade de pointes varies even among persons with equivalent degrees of QT prolongation.[30,31]

PROBLEMS POSED BY TECHNOLOGICAL AND SCIENTIFIC ADVANCES

Clinical observations have been complemented by two major advances in characterizing drug actions in patients — the ability to acquire and analyze huge quantities of electrocardiographic data and the evolving understanding of the molecular and cellular changes that are induced by drugs that produce torsade de pointes. Both developments, how-

ever, have generated new ambiguities with regard to the arrhythmogenic potential of available and newer drugs.

MEASUREMENT AND INTERPRETATION OF THE QT INTERVAL

QT-interval–prolonging antiarrhythmic agents such as sotalol, dofetilide, and ibutilide can prolong the QT interval by more than 50 msec at clinically prescribed doses and may cause torsade de pointes. Indeed, the risk is sufficiently high with these drugs (more than 1 percent[15,32,33]) that in-hospital cardiac monitoring is recommended when treatment with these agents is initiated.

It is assumed, but has not been proved, that even a small drug-induced increase in the QT interval in a population indicates some risk of torsade de pointes if large numbers of patients are exposed. Indeed, some noncardiovascular drugs that have been withdrawn from the market because they cause torsade de pointes result in a mean increase in the QT interval as small as 5 to 10 msec in populations of patients.[34,35] Since new drugs have generally been tested in only a few thousand patients at the time of their approval, the fact that no cases of torsade de pointes have been observed before a drug is approved is not very informative; even if no cases are recorded in a data base including 5000 patients, the 95 percent confidence interval for the risk of torsade de pointes would be 0 to 1 in 1600 — with the upper limit reflecting the potential for a very high incidence after marketing. In addition, the arrhythmia itself must be recorded in order to establish the diagnosis firmly, and patients may present not with syncope but with sudden death. If a new drug is being used to treat patients in whom a higher-than-average background incidence of sudden death is anticipated, the diagnosis of drug-induced torsade de pointes may never even be considered. Post-marketing surveillance has helped to identify rare side effects of drugs after they are on the market,[36,37] but the occurrence of such a fatal arrhythmia, which may be ascribed to an underlying disease, is probably underreported.[38]

The QT interval is used during drug development and by clinicians as a surrogate marker for the prediction of a serious adverse drug effect, syncope, or death due to torsade de pointes. However, as with many surrogate markers, its relationship to the event of interest is imperfect — the risk of torsade de pointes is not a linear function of the QT interval, nor of the extent of QT-interval prolongation

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Table 1. Drugs That May Cause Torsade de Pointes.*

Drugs commonly involved
Disopyramide
Dofetilide
Ibutilide
Procainamide
Quinidine
Sotalol
Bepridil

Other drugs†
Amiodarone
Arsenic trioxide
Cisapride
Calcium-channel blockers: lidoflazine (not marketed in the United States)
Antiinfective agents: clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin
Antiemetic agents: domperidone, droperidol
Antipsychotic agents: chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
Methadone

* Further information on the strength of the evidence linking various drugs to torsade de pointes may be found at http://www.torsades.org.
† The level of risk associated with these drugs depends on the dose and the population being treated; in general, the risk is probably less than 1 percent.

Table 2. Risk Factors for Drug-Induced Torsade de Pointes.*

Female sex[10]
Hypokalemia[11,12]
Bradycardia[11,12]
Recent conversion from atrial fibrillation, especially with a QT-prolonging drug[13,14]
Congestive heart failure[15]
Digitalis therapy[16]
High drug concentrations (with the exception of quinidine)
Rapid rate of intravenous infusion with a QT-prolonging drug[17]
Base-line QT prolongation[16]
Subclinical long-QT syndrome[18,19]
Ion-channel polymorphisms[20-22]
Severe hypomagnesemia

* Studies providing evidence of the effects are cited in the table.

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during drug therapy. Prolongation of the absolute QT interval beyond 500 msec is commonly regarded as conferring an increased risk — a belief that is supported by recent data from a study of patients

with the congenital long-QT syndrome.[39] The prolongation of the QT interval to longer than 500 msec during drug therapy should prompt a critical reevaluation of the risks and benefits of that therapy and consideration of therapeutic alternatives, in concert with a search for underlying predisposing factors such as hypokalemia or drug interactions.

Although abnormal QT-interval morphology (Fig. 1A) might predict an increased risk of torsade de pointes, analytic methods for assessing the relationship remain to be validated.[40] The heart rate is an important variable affecting the QT interval, and a variety of methods have been proposed to derive a "rate-corrected" QT interval that permits the comparison of QT values obtained at different heart rates. Each approach has its deficiencies; no single "correct" method for deriving the QT value has been established.[41] Drugs may independently affect the QT interval and the heart rate, and the successful treatment of a disease (such as infection or psychosis) may itself change the heart rate, further complicating the assessment of the QT interval at varying heart rates.
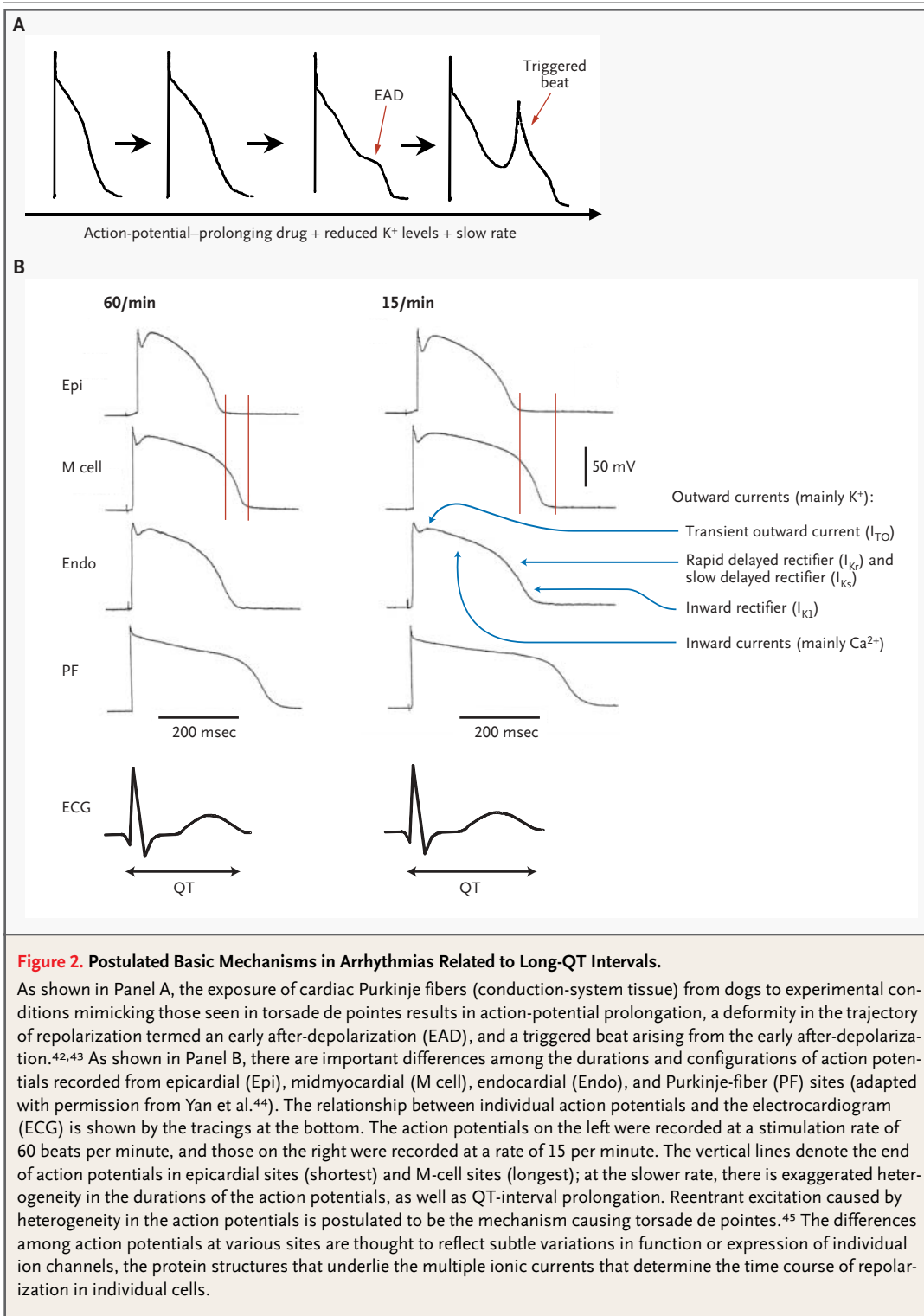
BASIC ELECTROPHYSIOLOGICAL MECHANISMS

The clinical finding of the lengthening of the QT interval represents the prolongation of action potentials in at least some cells in the ventricular myocardium (Fig. 2). When such prolongation of the action potential is recorded in preparations from animals, it may be followed by the development of deformities of the action potential, termed early after-depolarizations, which can, in turn, generate spontaneous, or "triggered," upstrokes (Fig. 2A). When such an upstroke is propagated through the whole heart, a ventricular ectopic beat preceded by a long QT interval is recorded on the surface electrocardiogram. A number of lines of evidence implicate early after-depolarizations and triggered activity in the genesis of torsade de pointes; notably, the conditions that elicit experimental early after-depolarizations (slow stimulation rates, low extracellular potassium levels, and treatment with QT-interval–prolonging drugs) are those associated with torsade de pointes. Certain populations of cells in the conduction system (Purkinje fibers[42]) and midmyocardium (M cells[46]) appear to be especially likely to develop early after-depolarizations on drug challenge. Heterogeneity in the development of prolongation of the action potential and early after-depolarizations results in a myocardium that is vul-

nerable to reentrant excitation, the probable proximate cause of torsade de pointes.[45,47,48]

One promising direction for research into the variability in the risk of torsade de pointes involves defining the molecular mechanisms that control the duration of action potential and the QT interval in the normal heart and in diseases such as the congenital long-QT syndrome or heart failure[49] (which increase the risk of torsade de pointes). Elegant genetic studies have been invaluable in identifying at least six separate genes that, if mutated, can cause the congenital long-QT syndrome.[50-55] Study of one of these genes, the human ether-a-go-go–related gene (*HERG*), which encodes a potassium-channel protein that regulates a major repolarizing potassium current, has been especially informative about drug-associated torsade de pointes. *HERG* controls an important repolarizing current, termed I_{Kr}; mutations in *HERG* reduce I_{Kr} and thus prolong action potentials in individual cells, causing the congenital long-QT syndrome. In addition, virtually all drugs that prolong the QT interval and cause torsade de pointes also block I_{Kr}.[56] Unfortunately, this finding is not specific, since many drugs that do not appear to cause torsade de pointes also block this current.

Another important consequence of clinical studies of congenital long-QT syndrome has been the recognition of incomplete penetrance; that is, family members with near-normal QT intervals may nevertheless carry the same mutations in genes associated with long-QT–syndrome disease[50-55] that cause QT-interval prolongation and an increased risk of sudden death in their relatives.[57]

Current evidence suggests that 5 to 10 percent of persons in whom torsade de pointes develops on exposure to QT-interval–prolonging drugs harbor mutations associated with the long-QT syndrome and can therefore be viewed as having a subclinical form of the congenital syndrome.[18,19,58] This clinical observation is entirely consistent with the concept of reduced repolarization reserve arising from a mutation in an ion-channel gene, which predisposes the carrier to drug-induced torsade de pointes. An extension of this concept is that common polymorphisms may cause subtle variations in the function of any gene that contributes to the generation of normal action potentials and that such variation might become apparent only on exposure to an I_{Kr}-blocking drug or other sources of stress (such as hypokalemia or heart failure). The identi-

A

Triggered beat

EAD

Action-potential–prolonging drug + reduced K⁺ levels + slow rate

B

60/min   15/min

Epi

M cell   50 mV

Outward currents (mainly K⁺):

Transient outward current (I_{TO})

Endo   Rapid delayed rectifier (I_{Kr}) and slow delayed rectifier (I_{Ks})

Inward rectifier (I_{K1})

Inward currents (mainly Ca^{2+})

PF

200 msec   200 msec

ECG

QT   QT

Figure 2. Postulated Basic Mechanisms in Arrhythmias Related to Long-QT Intervals.

As shown in Panel A, the exposure of cardiac Purkinje fibers (conduction-system tissue) from dogs to experimental conditions mimicking those seen in torsade de pointes results in action-potential prolongation, a deformity in the trajectory of repolarization termed an early after-depolarization (EAD), and a triggered beat arising from the early after-depolarization.[42,43] As shown in Panel B, there are important differences among the durations and configurations of action potentials recorded from epicardial (Epi), midmyocardial (M cell), endocardial (Endo), and Purkinje-fiber (PF) sites (adapted with permission from Yan et al.[44]). The relationship between individual action potentials and the electrocardiogram (ECG) is shown by the tracings at the bottom. The action potentials on the left were recorded at a stimulation rate of 60 beats per minute, and those on the right were recorded at a rate of 15 per minute. The vertical lines denote the end of action potentials in epicardial sites (shortest) and M-cell sites (longest); at the slower rate, there is exaggerated heterogeneity in the durations of the action potentials, as well as QT-interval prolongation. Reentrant excitation caused by heterogeneity in the action potentials is postulated to be the mechanism causing torsade de pointes.[45] The differences among action potentials at various sites are thought to reflect subtle variations in function or expression of individual ion channels, the protein structures that underlie the multiple ionic currents that determine the time course of repolarization in individual cells.

fication and validation of such variants might have important public health consequences, since such polymorphisms may be frequent (the variants reported to date have frequencies of up to 15 percent), and their frequency may vary among ethnic groups.[20-22]

IDENTIFICATION OF DRUGS THAT CAUSE TORSADE DE POINTES

The link between torsade de pointes, a clinical drug effect, and changes in molecular and cellular physiology (the blocking of I_{Kr} and the prolongation of the action potential) (Fig. 3) is imperfect. Some drugs (e.g., verapamil and amiodarone) rarely cause torsade de pointes yet do block I_{Kr}.[59,60] Thus, it is likely that other pharmacologic actions are also involved — actions that prevent torsade de pointes either directly (e.g., by blocking early after-depolar-

izations[61]) or indirectly, by blunting the prolongation of the action potential that precedes an arrhythmia. Indeed, amiodarone routinely prolongs the QT interval to more than 500 msec but rarely causes torsade de pointes.[62] The antihistamine terfenadine, a potent I_{Kr} blocker that can cause torsade de pointes, nevertheless did not prolong action potentials in studies involving cardiac Purkinje fibers in dogs.[63] Thus, it is difficult to predict whether a particular drug will cause torsade de pointes in any single patient or in a population of patients (Fig. 3).

QT-interval–prolonging antiarrhythmic drugs represent one end of a spectrum of risk; torsade de pointes develops in more than 1 percent of patients who receive these agents (with the exception of amiodarone). This outcome can be readily predicted: in large groups of patients, these drugs have been shown to block I_{Kr}, increase the duration of action potentials, and prolong the average QT interval unambiguously (generally by more than 50 msec).

Terfenadine seems to represent the other end of the risk spectrum, given the nature of the evidence that it can induce torsade de pointes and that led to its withdrawal from the market.[64] The average prolongation of the QT interval in normal persons who are exposed to therapeutic doses of terfenadine is minimal — approximately 6 msec.[34] With larger doses, or in patients with heart failure (a setting of reduced repolarization reserve), the terfenadine-induced QT-interval prolongation is greater.[34]

Terfenadine is a very potent I_{Kr} blocker but is nearly completely biotransformed by the CYP3A enzyme system before entering the systemic circulation. Its major metabolite, fexofenadine, is noncardioactive and is now marketed as Allegra. When CYP3A is inhibited (for example, by the simultaneous administration of erythromycin or ketoconazole[65]) or overwhelmed (because of an overdose, for example[66]), or when its activity is reduced by disease (such as cirrhosis[67,68]), the concentration of unmetabolized terfenadine entering the systemic circulation increases markedly, resulting in a greater prolongation of the QT interval (Fig. 3).

Thus, the small change in the QT interval observed in normal volunteers exposed to usual doses of terfenadine can be interpreted in two ways. First, several million patients were exposed to terfenadine in the late 1980s and early 1990s with no recognized cases of torsade de pointes, so a mean increase of 6 msec might indicate that the drug confers next to no risk of torsade de pointes. On the other hand, this small increase in the QT interval
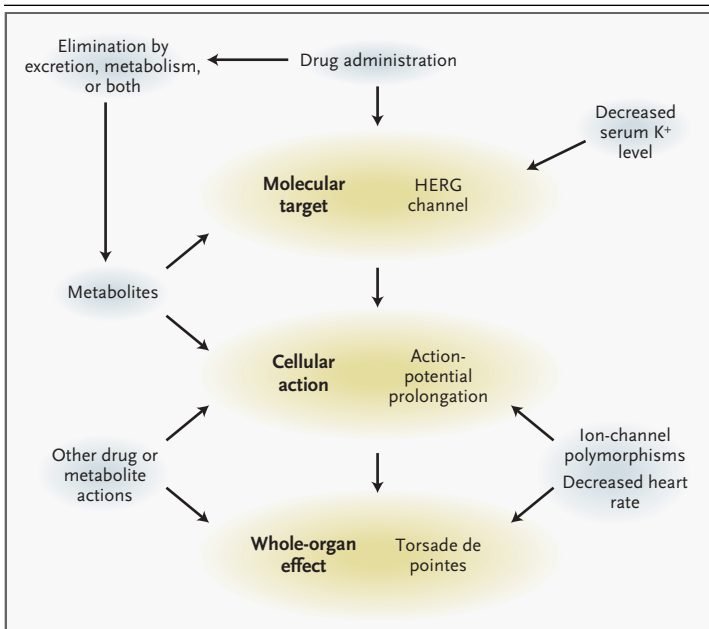

Figure 3. Effects of a Drug on Whole-Organ Function.
The effects of a drug on the function of an organ can be viewed as a cascade. The delivery of the drug to a molecular site of action is the first step. In each yellow area in the center of the figure, subsequent generic levels of action are shown on the left, with the specific example of drug-induced torsade de pointes on the right. Drug metabolites may also contribute to the clinical effects of the drug. At each level, physiological, genomic, or drug-specific or metabolite-specific properties may influence the drug effect that occurs; examples in the case of torsade de pointes associated with HERG blockade are shown on the right. A fundamental difficulty with toxic drug effects that occur at a low frequency is that an action at the level of a molecular target is an imperfect predictor of the effect on the whole organ.

might also suggest that certain patients might be at much higher risk in particular clinical circumstances. The experience with terfenadine suggests that a serious potential for toxic effects can arise with a potent I_{Kr} blocker that is eliminated by a single route of drug disposition, the activity of which depends on genetic factors, the presence or absence of disease, or the simultaneous administration of inhibitor compounds. In addition, patients with already reduced repolarization reserve (such as those with heart failure or subclinical congenital long-QT syndrome), who may not tolerate the insult or even a small increase in the QT interval, may be at increased risk for torsade de pointes.[34]

WEIGHING RISKS AND BENEFITS

The decision by a physician to use a drug (or by a regulatory agency to approve one) is predicated on the assumption that the benefits of therapy, however defined, outweigh the risks. Arsenic trioxide presents an interesting example of this balance. Although this drug is known to provoke torsade de pointes,[69] it is also uniquely effective in an otherwise fatal disease, relapsed acute promyelocytic leukemia.[70] Therefore, until alternative therapy becomes available, arsenic trioxide remains a drug of first choice, despite its potential for causing arrhythmia. Similarly, bepridil may cause torsade de pointes but may provide antianginal activity in some patients whose symptoms are resistant to other drugs,[71] and antiarrhythmic drugs conferring a high risk of torsade de pointes remain on the market because their benefits are believed to outweigh their risks, at least in some settings. On the other hand, a drug that causes even a very low incidence of torsade de pointes would be unacceptable if safer alternative forms of therapy were available or if the indication were not itself serious, however that term was defined.

New drugs present a special problem, because at the time approval by the Food and Drug Administration (FDA) is considered, clinical experience with each drug is limited, and many new agents may weakly antagonize I_{Kr} or produce a small but reproducible degree of QT-interval prolongation in thousands of patients. The decision ultimately rests on an estimate of the perceived risk relative to the expected benefits for patients and society. Estimates of benefit are specific to particular indications, but they may include an assessment of whether the specific disease entity itself is associated with very high morbidity or mortality that the drug may be expected to reduce, as well as consideration of the efficacy and toxicity of other available therapies. These issues have been discussed extensively in FDA deliberations over several recent new drugs (e.g., moxifloxacin[72] and ziprasidone[73]). Both of these agents produce I_{Kr} blockade in vitro and have induced prolongation of the QT interval by 5 to 14 msec in clinical trials. In both cases, there was also a suggestion — unproved by formal clinical studies — of a clinical advantage over existing therapies in some settings.

DECISION MAKING AND DRUGS WITH QT-INTERVAL–PROLONGING POTENTIAL

Clinicians (often noncardiologists) are increasingly faced with both older and newly approved drugs with labeling that mentions the potential to prolong the QT interval and thus to cause torsade de pointes. Performing cardiovascular screening before prescribing such drugs seems unlikely to be cost effective; the package inserts for some, but not all, of the noncardiovascular drugs listed in Table 2 explicitly recommend obtaining a base-line electrocardiogram. However, a few simple aspects of the patient's history should alert a practitioner to a potentially increased risk.

Elderly women, persons with advanced heart disease, patients receiving other drugs that prolong the QT interval directly or indirectly (e.g., diuretics that cause hypokalemia), patients with a family history of sudden death, and patients with a complex medical regimen that includes drugs with the potential to inhibit important drug-elimination mechanisms are all at increased risk. Certain drugs frequently inhibit drug elimination (through a variety of mechanisms) and thus should be a cause for special concern; examples include erythromycin, clarithromycin, ketoconazole, itraconazole, amiodarone, quinidine, and many antidepressants and antiretroviral agents.[74]

If therapy with a drug that has QT-interval–prolonging potential is started, patients should be warned to report promptly any symptoms such as new palpitations and near-syncope or syncope (even without palpitations), as well as intercurrent conditions or therapies that can cause hypokalemia (e.g., gastroenteritis or the addition of a diuretic to the patient's regimen). Routine electrocardiographic examination during treatment to detect asymp-

tomatic prolongation of the QT interval to more than 500 msec or abnormal postectopic QT intervals (Fig. 1) may be considered in such high-risk situations, although whether these precautions can reduce risk is unknown.

If any rare but serious adverse drug reaction occurs often enough, and if alternative therapies are available, the offending drug may be withdrawn from the market, even if the mechanisms underlying the adverse effect are not understood. The current understanding of the mechanisms that cause torsade de pointes changes this situation: a drug may now be implicated as a potential cause of the adverse effect (at some unknown frequency) even in the absence of any cases. The recognition of these mechanisms highlights important issues in the risk–benefit analyses performed daily by the medical community. Clinical pharmacokinetic principles indicate that drugs that interact with a protein that mediates serious toxicity (such as the HERG protein) and that are eliminated by a single route of drug disposition may present an especially serious problem. Genetic variants, disease, or the simultaneous administration of inhibitor compounds are most likely to alter the drug concentrations, and hence the level of risk, in this situation (Fig. 3).

Although it may be difficult, it is important to educate health care providers and to develop pharmacy systems that detect the simultaneous prescribing of drugs with the potential for serious adverse interactions. However, multiple attempts by regulatory agencies and drug companies to limit the administration of dangerous combinations, such as cisapride and erythromycin, have been only transiently successful.[75-77] Prescribers should recognize that most drugs have multiple, and often unanticipated, actions. In addition, even drugs that are designed to interact with a single molecular target act in a complex biologic milieu. Unusual drug reactions may arise as a result of multiple factors, including changes in physiology conferred by the disease being treated, genetics, or environment (e.g., reduced repolarization reserve). Common gene polymorphisms may modulate patients' susceptibility to adverse drug reactions. Finally, evaluation of the risk of toxic drug effects may include the assessment of a drug's effects on physiologically rational surrogate markers (such as the QT interval), but it is rare that there is a one-to-one correspondence between a surrogate for a toxic effect and the effect itself.

BROADER IMPLICATIONS

Rare, poorly understood side effects occur with many highly effective drugs, and the withdrawal of these medications from the market would probably harm more patients than it would help. Our partial understanding of the mechanisms underlying torsade de pointes is a two-edged sword. On the one hand, drug safety has been improved: we are unlikely to see more new drugs that unexpectedly result in a high risk of torsade de pointes after they have reached the market.[78] On the other hand, as the molecular markers of risk for this and other unusual actions of drugs are elucidated, there is a great risk of paralyzing the drug-development process in what is probably a fruitless effort to develop drugs that are entirely devoid of adverse effects. Ultimately, the cost to society of marketing new drugs associated with at most an extremely small incidence of the serious adverse effects that are now crudely predictable on the basis of preclinical experience must be weighed against the overall benefits that such new therapies may confer.

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