Drug-Induced Torsade de Pointes: From Molecular Biology to Bedside

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ABSTRACT—A progressively increasing number of cardiac and noncardiac drugs prolong the ventricular action potential duration (QT interval of the electrocardiogram) and cause a distinctive polymorphic ventricular tachycardia termed torsades de pointes (Tdp) that can degenerate into ventricular fibrillation and sudden cardiac death. Drugs prolong the QT interval and cause Tdp by blocking cardiac K+ channels in general and selectively blocking the rapidly activating delayed rectifier channel IKr. Coassembly of HERG (human-ether-a-go-go-related gene) α-subunits and MiRP1 (MinK-related peptide 1) β-subunits recapitulate the behavior of native human IKr and mutations of HERG and MiRP1 decrease the repolarizing current, delay ventricular repolarization and prolong the QT. Thus, drug-induced QT prolongation and Tdp might represent an iatrogenic reproduction of the congenital LQTS. In patients with silent forms of the congenital LQTS associated with mutations in IKr, arrhythmic symptoms developed almost exclusively after exposure to QT-prolonging drugs. This review centers on the possible cellular mechanisms underlying drug-induced QT prolongation and Tdp, the description of specific drugs and risk factors facilitating the development of Tdp, and the recommendations for preventing and treating this potentially fatal arrhythmia.

Keywords: Potassium channel, HERG (human-ether-a-go-go-related gene), MiRP1 (MinK-related peptide 1), Long QT syndrome, Cardiac arrhythmia, Torsade de pointes

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1. Introduction

Drugs can potentially cause sudden unexpected death by a variety of mechanisms (e.g., seizures, central nervous system depression or coronary artery spasm), although cardiac arrhythmias are the most frequent cause (1). In the 60's, it was reported that patients treated with quinidine showed the occurrence of marked prolongation of the QT interval of the electrocardiogram (ECG) and recurrent syncope (sudden loss of consciousness) due to a distinctive polymorphic ventricular tachycardia termed torsades de pointes (Tdp). Tdp is characterized by QRS complexes (“pointes”) of changing amplitude and contour that appear to rotate around the isoelectric line and spontaneous termination (Fig. 1). However, Tdp can occasionally degenerate into ventricular fibrillation, leading to sudden cardiac death. Thus, the term Tdp describe a potentially life-threatening ventricular arrhythmia that occurs in the setting of a lengthened QT interval, reflecting delayed ventricular repolarization and prolongation of the action potential duration (APD) (6). The prolongation of the QT
interval (long QT syndrome: LQTS) may be due to any of several congenital disorders or may be an acquired disorder caused by drugs and several clinical conditions (2 - 7).

Table 1 lists a number of drugs widely used in clinical practice and clinical conditions that delay ventricular repolarization, prolong the QT interval and have been shown to cause TdP and even cardiac death. The initial sequence of the acquired drug-induced form of TdP is the so-called “short-long-short” ventricular depolarization (B), which is followed, after a long post-extrasystolic pause (*), by a sinus beat (C) and another short-coupled premature ventricular depolarization (D), which is the first beat of the tachycardia.

2. Mechanisms involved in the prolongation of the cardiac action potential

The cardiac action potential is characterized by a prolonged depolarized state and a plateau phase that can last up to several hundred milliseconds in some cells. Repolarization reflects a delicate balance between inward (depolarizing) and outward (repolarizing) currents and is triggered when the net membrane current becomes outward. Figure 2 shows the relationship between the ventricular action potential, the time course of the ionic cur-

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### Table 1. Drugs and conditions leading to acquired long QT syndromes and tordes de pointes

<table>
<thead>
<tr>
<th>A. Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Antiarrhythmic drugs</td>
</tr>
<tr>
<td>IA: ajmaline, aprindine, disopyramide*, procainamide, quinidine*</td>
</tr>
<tr>
<td>IC: encainide*, flecaïnide*, propafenone*</td>
</tr>
<tr>
<td>III: amiodarone*, almokalant, azimilide, d-sotalol, dofetilide, ibutilide, N-acetyprocainamide, seinatilde, sotalol</td>
</tr>
<tr>
<td>2. Vasodilators: bepridil, fenoxedil, lidoflazine, papaverine, perhexilbine, prenylamine, vincamine</td>
</tr>
<tr>
<td>3. Serotonin agonists/antagonists: cisapride*, ketanserin, zimeldine</td>
</tr>
<tr>
<td>4. Psychotropic drugs</td>
</tr>
<tr>
<td>Antipsychotics: phenothiazines (chlorpromazine, fluphenazine*, mesoridine, perphenazine, thiourazine*, trifluoperazine), droperidol, haloperidol, pimozide, risperidone, sertindole</td>
</tr>
<tr>
<td>Antidepressants: amitryptiline*, clomipramine*, desipramine*, doxepin, imipramine*, maprotiline, trazodone</td>
</tr>
<tr>
<td>Chloral hydrate</td>
</tr>
<tr>
<td>5. Antihistaminics: astemizole*, diphenhydramine, hydroxyzine, terfenadine*</td>
</tr>
<tr>
<td>6. Antimicrobial agents: amantadine, macrolides (clarithromycin, erythromycin, troleandomycin), spiramycin, trimethoprin/sulfamethoxazole</td>
</tr>
<tr>
<td>Antimalarias: chloroquine?, halofantrine, pentamidine</td>
</tr>
<tr>
<td>Imidazole antifungals: itraconazole, ketoconazole, miconazole</td>
</tr>
<tr>
<td>7. Other drugs: anthracyclines, arsenic, cocaine, diuretics, doxorubicin, indoramin, ionic contrast media, organophosphate insecticides, prednisone, probucol, tacrolimus, terodilene, trimetofan, vasopressin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Other conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial ischemia, congestive heart failure, cardiac hypertrophy, myocarditis, mitral valve prolapse</td>
</tr>
<tr>
<td>Nervous-system injury: subarachnoid hemorrhage, stroke, intracranial trauma</td>
</tr>
<tr>
<td>Bradycardias: sinus bradycardia, atioventricular block</td>
</tr>
<tr>
<td>Electrolyte abnormalities: hypokalemia, hypomagnesemia, hypocalcemia</td>
</tr>
<tr>
<td>Metabolic disorders: hypothyroidism, hyperparathyroidism, hyperaldosteronism</td>
</tr>
<tr>
<td>Systemic conditions: liver and renal diseases</td>
</tr>
<tr>
<td>Altered nutritional states: anorexia nervosa, liquid protein diets, starvation, gastroplasty and ileojejunal bypass, coeliac disease</td>
</tr>
<tr>
<td>Female gender</td>
</tr>
</tbody>
</table>

*QT-prolonging drugs metabolized by cytochrome P450 enzyme systems.
rents that generate it and the most probable corresponding clones. Thus, drugs can prolong the ventricular APD and QT interval through entirely different ionic mechanisms (5, 10–14):

1) An increase in depolarizing inward currents that maintained the plateau at a depolarized level due to a delay in Na⁺ current inactivation giving rise to an increase in late Na⁺ current, activation of the L-type Ca²⁺ current (I_L), and an increase in the contribution of the electrogenic current generated by the Na⁺-Ca²⁺ exchanger.

2) Block of outward K⁺ currents that delay repolarization. Under physiological conditions, several voltage-gated K⁺ currents participate in the repolarization process: a) the transient outward current (I_to), responsible for the early rapid repolarization; b) the delayed rectifier K⁺ current (I_k), which in human and guinea pig ventricles can be separated into a rapidly activating (I_k1) and a slowly activating (I_k2) current; and c) the inward rectifier current (I_k1) mainly responsible for the final rapid repolarization and for the maintenance of the resting potential. There are several ligand-gated K⁺ channels, including the acetylcholine-regulated (I_K_ACh), ATP-regulated (I_K_ATP) and the intracellular Na⁺-activated (I_K_Na) channels that can play a role in cardiac repolarization under certain circumstances. However, drugs that prolong the QT interval by blocking voltage-gated cardiac K⁺ channels in general and selectively I_K1 have been often associated with acquired LQTS and TdP ventricular tachycardia. Therefore, the discussion here focuses mainly on I_K1 blockers.

3. Congenital long QT syndrome
Two forms of congenital LQTS (cLQTS) are known (Table 2): the autosomal dominant Romano-Ward syndrome and the autosomal recessive Jervell and Lange-Nielsen syndrome associated with deafness (5, 7, 15). Six human genetic loci linked to LQTS have been identified so far, and five of these (KVLQT1 or in the new nomenclature KCNQ1, HERG, SCN5A, KCNE1 and KCNE2) encode specific ion channel subunits in the heart (14–17). SCN5A encodes an α subunit of the cardiac Na⁺ channel; KCNE1 encodes β-subunits (hminK or minimal K⁺ channel β-subunit) that coassemble with KCNQ1 α-subunits to form I_Ks and HERG (human-ether-a-go-go-related gene) α-subunits and MiRP1 (MinK-related peptide 1) β-subunits coassemble to recapitulate the behavior of I_K1 (16, 17). Mutations of these genes produce either defective inactivation of Na⁺ channels carrying inward current or defective function of K⁺ channels carrying outward current that delay repolarization, prolong the ventricular APD and the QT interval, and increase the risk of ventricular tachyarrhythmias (5, 15–17). The Jervell and Lange-Nielsen syndrome results from mutations that affect both alleles of an autosomal dominant gene (KCNQ1, KCNE1) for the LQTS (18). KCNQ1 is also expressed in the marginal cells of the stria
vascularis of the inner ear, which could explain the bilateral deafness present in these patients (18).

4. The rapidly activating delayed rectifier K⁺ current

I_{Kr} plays a major role in repolarization of the human cardiac myocytes and termination of individual beats (10–12, 14, 16). It activates very rapidly (τ at 0 mV = 50 ms), shows inward rectification at positive potentials due to a fast C-type inactivation, is specifically inhibited by the methanesulfonanilide E-4031 and is thought to be unaffected by β-adrenergic stimulation. In contrast, I_{Ks} is a slowly activating, nonrectifying, E-4031-insensitive current (10–12, 14, 17). Because of the slow kinetics of gating (it takes seconds to approach a steady-state), a single action potential activates only a small fraction of I_{Ks} channels. However, the contribution of I_{Ks} to repolarization is more important as the heart rate increases. This is because of the incomplete deactivation of I_{Ks} channels between action potentials, leading to an accumulation of I_{Ks} activation and a larger current amplitude. β-Adrenergic stimulation can increase I_{Ks} amplitude and render it more important in action potential repolarization. Blockade of I_{Kr} and I_{Ks} prolongs APD.

Expression of HERG/MiRP1 complexes in Xenopus oocytes results in a current nearly identical to the native I_{Ks} observed in human cardiac myocytes (16). The functional I_{Ks} channels are formed by four HERG α-subunits. The encoded pore-forming protein contains a six-membrane-spanning segments (S1–S6), and the amino- and carboxy-terminal ends are located intracellularly (Fig. 3). The ion conduction pathway is formed by the short hydrophobic segment between S5 and S6, with contributions of S6 and the S4–S5 linker. The S4 segment, which contains at every third position a positively charged residue (lysine or arginine), represents the major component of the voltage sensor that modifies the state of the channel in response to changes of the membrane voltage (11, 14). HERG α-subunits coassemble with four MiRP1 β-subunits, encoded by KCNE1, each containing a single transmembrane segment of 129 amino acids.

Several drugs that bind with high affinity (nanomolar range) to HERG channels expressed in Xenopus oocytes prolong the QT interval and cause TdP (Table 3) (12, 22–27) and mutations decreasing the number of functional HERG channels caused the chromosome 7-linked cLQTS; i.e., LQT2 (Table 2) (5, 7, 19–21). These results indicated that drug-induced LQTS and TdP might represent a iatrogenic reproduction of the LQT2.

Coexpression in Xenopus oocytes of a single mutant subunit with wild-type HERG subunits can lead to loss, alteration or dominant-negative suppression of HERG channel function, indicating that a single mutant subunit may be sufficient to disrupt the normal function of the tetra-
Table 3. Different potencies of I_{Ks} and I_{Kc} blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>I_{Ks}</th>
<th>I_{Kc}</th>
<th>Species/tissues</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almokalant</td>
<td>50 nM</td>
<td>32 μM</td>
<td>RV</td>
<td>61</td>
</tr>
<tr>
<td>Ambosulide</td>
<td>5.6 μM</td>
<td>10 μM</td>
<td>GPV</td>
<td>63</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>48 nM</td>
<td>2 μM</td>
<td>TXO</td>
<td>66</td>
</tr>
<tr>
<td>Azemisole</td>
<td>0.3 μM</td>
<td>1.4 – 5 μM</td>
<td>GPV/TXO</td>
<td>13, 23, 114</td>
</tr>
<tr>
<td>Azimilide</td>
<td>2.93B</td>
<td>1 μM</td>
<td>TXO</td>
<td>71</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>0.1 mM</td>
<td>1 mM</td>
<td>GPV, RV</td>
<td>10, 13</td>
</tr>
<tr>
<td>Cisapride</td>
<td>6.5 mM</td>
<td>10 μM</td>
<td>HEC923</td>
<td>25</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>1.1 μM</td>
<td>21 μM</td>
<td>&gt;10 μM</td>
<td>12, 23, 114</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td>0.75 mM</td>
<td>CHO</td>
<td>16</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>96 μM</td>
<td>17.3 μM</td>
<td>CHO</td>
<td>69</td>
</tr>
<tr>
<td>Clofibrilum</td>
<td>1 μM</td>
<td>150 nM</td>
<td>50 μM</td>
<td>59, 60</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>17.3 μM</td>
<td></td>
<td>HEC</td>
<td>83</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>30 μM</td>
<td>27 μM</td>
<td>130 μM</td>
<td>13, 23, 114</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>31 nM</td>
<td>2.5 – 11 nM</td>
<td>&gt;0.1 mM</td>
<td>12, 22, 28</td>
</tr>
<tr>
<td>E-4031</td>
<td>10 nM</td>
<td></td>
<td>FA</td>
<td>57</td>
</tr>
<tr>
<td>Ebstine</td>
<td>0.14 μM</td>
<td>0.4 μM</td>
<td>0.8 μM</td>
<td>13</td>
</tr>
<tr>
<td>Flecaainde</td>
<td>&lt;10 μM</td>
<td></td>
<td>CV</td>
<td>52</td>
</tr>
<tr>
<td>Granisetron</td>
<td>4.3 μM</td>
<td></td>
<td>CV</td>
<td>93</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1 μM</td>
<td>1 μM</td>
<td>2.6 μM</td>
<td>110</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>16 nM</td>
<td>20 nM</td>
<td>GPV, AT-1</td>
<td>64</td>
</tr>
<tr>
<td>Imipramine</td>
<td>3.4 μM</td>
<td>100 μM</td>
<td>CHO</td>
<td>99, 109</td>
</tr>
<tr>
<td>Indapamide</td>
<td></td>
<td></td>
<td>GPV</td>
<td>70</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>49 μM</td>
<td></td>
<td>TXO</td>
<td>127</td>
</tr>
<tr>
<td>MK-499</td>
<td>123 nM</td>
<td></td>
<td>TXO</td>
<td>24</td>
</tr>
<tr>
<td>Nicardine</td>
<td>1.3 μM</td>
<td></td>
<td>TXO</td>
<td>143</td>
</tr>
<tr>
<td>Onatsbyclon</td>
<td>1.7 μM</td>
<td></td>
<td>CV</td>
<td>93</td>
</tr>
<tr>
<td>Perhexilde</td>
<td>7.8 μM</td>
<td></td>
<td>CHO</td>
<td>90</td>
</tr>
<tr>
<td>Pyrimidine</td>
<td>1.1 μM</td>
<td>0.3 – 1 μM</td>
<td>~50 μM</td>
<td>114</td>
</tr>
<tr>
<td>Quinidine</td>
<td>2 μM</td>
<td>0.2 μM</td>
<td>GPV, AT-1</td>
<td>28, 48</td>
</tr>
<tr>
<td>RP 58866</td>
<td>22 nM</td>
<td></td>
<td>GPV, TXO</td>
<td>58</td>
</tr>
<tr>
<td>Sertindole</td>
<td>2.9 nM</td>
<td>10 μM</td>
<td>Ltk cells</td>
<td>26</td>
</tr>
<tr>
<td>Sotalol</td>
<td>88 μM</td>
<td>&gt;100 μM</td>
<td>GPV</td>
<td>12</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>&lt;3 μM</td>
<td></td>
<td>RV</td>
<td>135</td>
</tr>
<tr>
<td>Tdesamol</td>
<td></td>
<td>2.5 μM</td>
<td>GPV</td>
<td>65</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>50 nM</td>
<td>0.35 μM</td>
<td>10 μM</td>
<td>13, 23, 114</td>
</tr>
<tr>
<td>Terkiallant</td>
<td>31 nM</td>
<td>0.25 μM</td>
<td>GPV, TXO</td>
<td>58</td>
</tr>
<tr>
<td>Terodiline</td>
<td>0.7 μM</td>
<td>14 μM</td>
<td>GPV</td>
<td>111</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>1.2 μM</td>
<td></td>
<td>GPV</td>
<td>128</td>
</tr>
<tr>
<td>Triamterene</td>
<td>100 μM</td>
<td></td>
<td>GPV</td>
<td>69</td>
</tr>
<tr>
<td>Verapamil</td>
<td>143 nM</td>
<td></td>
<td>HEK</td>
<td>83</td>
</tr>
</tbody>
</table>

Data are expressed as I_{Ks} values (concentrations producing 50% inhibition of the current). AT-1: mouse atrial tumor cells, CHO: Chinese hamster ovary cells, CV: cat ventricular myocytes, GPV: guinea pig ventricular myocytes, FA: ferret atrial myocytes, HEK293: human embryonic kidney cells, RV: rabbit ventricular myocytes, TXO: HERG channel expressed in oocytes of the toad _Xenopus laevis_.

mionic channel (5, 19 – 21). These mutations are predicted to cause a wide spectrum of diminished I_{Ks} and delayed ventricular repolarization, consistent with the prolonged QT observed in individuals with cLQTS. Missense mutations of KCNE1 are also associated with prolongation of the QT interval and have been found both in patients with cLQTS or drug-induced arrhythmia (16). Thus, a decrease in functional I_{Ks} channels, either by HERG/MiRP mutations or
by drug-induced block, reduces the net repolarizing current and produces prolongation of the APD and propensity to TdP ventricular arrhythmias.

Unlike most other K+ currents, decreasing the extracellular K concentration, [K]o, reduces the amplitude of IKr (19, 28). This would explain why hypokalemia prolongs the APD and the QT interval, effects that in patients receiving IKr blockers resulted in marked QT interval prolongation, and increased the risk of TdP. In contrast, elevation of [K]o increased the number of IKr channels available to open, shortened the APD, and may also induce conformational changes of HERG channels that could affect the access of a drug to its target site on the channel pore (5, 27).

5. Electrophysiological mechanisms underlying TdP

Even when the precise electrophysiological mechanism remains elusive, two principal hypothesis have been proposed to explain drug-induced TdP (2 – 6, 29).

1) One hypothesis proposed that prolongation of the QT interval and TdP are caused by early afterdepolarizations (EADs, Fig 4) defined as single or repetitive depolarizations occurring either during phase 2 and 3 of the action potential that delay repolarization (29 – 34). Upstrokes occurring at the plateau level of the action potential are most likely due to activation of the ICaL, while those occurring at the end of repolarization might be due to inward currents through Na+ channels (5, 31 – 34). EADs that appear on the ECG as pathological U waves can initiate a premature action potential or a train of action potentials when the threshold activation is reached. Monophasic action potential recordings from the endocardium verified the appearance of EADs in hearts with TdP, particularly at slow heart rates, while the suppression of EADs prevented TdP (30, 34).

In in vitro models, drugs prolong repolarization and induce EADs by one of the following mechanisms (29 – 35): a) a reduction in K+ repolarizing currents. Potential channel blockers (cesium, barium, class IA and III antiarrhythmic drugs, terfenadine, astemizol, erythromycin) caused marked QT prolongation, EADs and ventricular tachyarrhythmias and these effects were suppressed by K+ channel openers (e.g., pinacidil, cromakalin, nicorandil). b) An increase of ICaL, since EADs induced by Bay K 8644 and catecholamines were abolished by verapamil, nifedipine and magnesium. c) A delay in Na+ current inactivation giving rise to an increase in late inward Na+ current. In fact, EADs induced by aconitine or anthopleurin-A are sensitive to Na+ channel blockers. EADs are more readily induced in the His-Purkinje system than in ventricular muscle. Recently, it has been proposed that M cells, located in the deep subepicardium, are candidates for the site of origin of drug-induced EADs and TdP arrhythmias (36, 37). M cells display a more marked APD prolongation in response to hypokalemia, slow driving rates or QT prolonging agents (e.g., erythromycin, quinidine) than endocardial or epicardial cells. This distinctive action potential behavior was explained by a reduction in IKr in M cells (as compared to endocardial and epicardial cells), while IKr appears to be similar in all cell layers (38). However, under some experimental conditions, M cells failed to develop EADs, but originated in the Purkinje network and rapidly propagated through the ventricular tissue (34, 35).

2) Increased dispersion of repolarization caused by heterogeneity of APD across the ventricular wall lowered ventricular fibrillation threshold, created the substrate for transient functional block and increased the risk for the development of lethal ventricular arrhythmias (29). Patients with drug-induced TdP presented an increased dispersion of the QT interval, an indirect measure of non-uniform ventricular repolarization, that might be caused by the differential response of the M cells to QT prolonging drugs, hypokalemia and bradyarrhythmia (36, 39). Under these conditions, it is possible that the first beat of TdP results from a premature beat arising from an EAD generated in the M cells or in the Purkinje network, while subsequent activity might be due to repeated EAD-induced activity, reentry triggered by the initial subendocardial focus or a combination of both mechanisms (34, 35, 40). Additionally, premature excitation of myocardial regions with shorter refractory periods creates the conditions for transient functional block with spiral waves meandering across the ventricular wall to maintain the arrhythmia. The polymorphic morphology of the arrhythmia is due to changes in wave
propagation patterns for successive beats initiated by EADs or EADs-induced non-stationary reentrant activity (34). Block of conduction in the reentrant pathway explains the spontaneous termination of TdP.

6. Drug-induced TdP

Drugs that cause TdP (Table 1) also prolong ventricular repolarization, so that marked prolongation of the QT interval (>500 ms) and rate-corrected QT interval (QTc >470 ms) of the ECG are observed in almost all patients with drug-induced TdP (2–6). The propensity of a particular drug to cause TdP is difficult to predict since it may be influenced by differences in local prescribing habits and the frequent presence of risk factors such as bradycardia or hypokalemia. Moreover, no correlation between some critical increase in QT/QTc value and the possible occurrence of TdP has been established (2, 4). The incidence of TdP is also unrelated to either the dose, the plasma drug concentration or the duration of therapy, so that QT prolongation and TdP arrhythmias may occur early after initiation of or months after starting the therapy. For some drugs, the concentrations producing 50% inhibition of IK (IC50) were higher than the therapeutic plasma levels, suggesting that the risk of TdP was associated with conditions resulting from supratherapeutic plasma levels, such as in cases of overdose or suicide attempt (e.g., psychotrophic drugs), as well as conditions associated with an increase in plasma concentrations (e.g., combination with drugs that inhibit the cytochrome P450 systems). On the contrary, some patients developed TdP at subtherapeutic doses of quinidine when the signs of cardiac toxicity were absent (41). Finally, an additional problem is the differential diagnosis of TdP, which is highly subjective and inconsistent even among cardiologists (8). Despite all these difficulties, it is evident that drug-induced TdP is not a trivial problem since the first manifestation of this iatrogenic response may be sudden death.

1) Antiarrhythmic drugs

TdP appeared as a complication of therapy with antiarrhythmic drugs that prolong the QT interval in about 1–8% of treated patients, particularly in those with hypokalemia, bradycardia or when hepatic or renal failure or other drug therapy interferes with drug metabolism (2–4, 6). Moreover, TdP was observed in 20% of all patients with tachyarrhythmia-induced sudden death, and 70% of these patients were indeed on antiarrhythmic therapy (41). However, TdP is far more commonly seen in association with low or therapeutic doses of class IA drugs but is generally associated with high doses of class III drugs, which block outward K+ currents and prolong the ventricular APD, whereas it occurs very rarely with class IB and IC agents (2–6, 34).

Class IA drugs: QTc prolongation and TdP has been reported with quinidine, procainamide, disopyramide, aprindine and ajmaline (2–4, 41–46). The overall incidence of quinidine-induced TdP is 1.5%/year, and it may appear at low-subtherapeutic levels when the signs of cardiac toxicity were absent (41). The risk with other class IA drugs is probably in the same range (6). In patients with atrial flutter or fibrillation, the incidence of quinidine-induced TdP ranged from 2.9–8.8% and almost invariably occurred after conversion to sinus rhythm (2, 41). This can be explained because ventricular refractoriness (and probably APD) temporarily increased on cessation of rapid pacing (47) or because in some patients with repolarization abnormalities, tachyarrhythmia may prevent them from showing long QT (6).

QT prolongation and TdP have been observed at subtherapeutic plasma concentrations of quinidine which might be explained because it blocks IK, at concentrations at least one order of magnitude lower than those required to block other K channels (IKs, IK1, IKs) (11, 28, 29, 48). In Purkinje cells, quinidine lengthened the APD and caused EADs that were favored at slow heart rates and by hypokalemia and were suppressed at fast rates and by raising the extracellular K concentration (30, 34). Moreover, a marked increase in QT interval dispersion was observed in patients who develop TdP during quinidine therapy (39, 42). Furthermore, potassium infusion reversed quinidine-induced QT prolongation and QT dispersion, suggesting that blockade of IK was responsible for these changes (49).

At high doses, class IA drugs can inhibit EADs because the prolongation of the ventricular APD due to IK blockade can be nullified by the shortening effect produced by the blockade of Na+ and Ca2+ channels (4).

Patients who developed TdP during therapy with one class IA agent develop the arrhythmia when receiving another class IA agent and possibly other drugs that prolong the QT interval (2, 8, 9). Nattel et al. (50) reported a patient that developed QT prolongation and TdP during quinidine treatment. A few days after discontinuation of the drug, he received erythromycin because of suspected pneumonia that resulted in marked QT prolongation and TdP 3 days later.

Class IB and IC drugs: In Purkinje cells, class IB agents (lidocaine and mexiletine) inhibited the slowly inactivating Na+ current during the plateau more than the Ik during the fast upstroke of the action potential (51). This resulted in a shortening of the APD and suppression of EADs and ventricular tachyarrhythmias induced by K+ channel blockers, Na+ and Ca2+ channel agonists and hypokalemia in experimental models (4, 30, 34). Additionally, they also block the conduction of EADs from the Purkinje network to the myocardium (4), while no effect on outward K+ currents was observed at therapeutic concentrations (10). All
these effects may explain why arrhythmias induced by class IB agents did not show the characteristics of TdP and may be reasonable alternatives for antiarrhythmic therapy in patients with previously documented TdP when exposed to class IA agents (2). However, only 50% of cases of drug-induced TdP responded to the lidocaine (9).  

Class IC drugs (flecainide, propafenone, encaïnide) did not modify the QT interval, and therefore, they are less likely to induce long QT syndrome and TdP (3, 6). Flecainide blocks I_{Na} and I_{K}\(_{\text{f}}\) at the same range of concentrations (52) and propafenone blocks I_{K}\(_{\text{f}}\) and I_{K}\(_{\text{s}}\) (53) as well as I_{Na} and I_{Ca} and exhibits \(\beta\)-adrenoceptor blocking properties (54), which explains the low incidence of TdP reported with these drugs. In fact, class IC drugs produced monomorphic sustained ventricular tachycardia, but not TdP, so that evidence linking these drugs to TdP is lacking. Cases of TdP caused by encaïnide can be attributed to accumulation of its active metabolites that prolong repolarization (55).

**Class III drugs:** They lengthen the APD (QT interval) and refractoriness without delaying intraventricular conduction by blocking several outward K\(^+\) currents and induced arrhythmias resembling TdP (5, 10). Methanesulfonanilide derivatives (E-4031, dolefinitol, d-sotalol, sematilide, MK-499, L-691,121, WAY-123,398, CK3579, clofyllium) and almokalant selectively block I_{K}\(_{\text{f}}\) in the activated-open state (10, 22, 24, 56–61). Azimilide blocks I_{K}\(_{\text{f}}\), I_{K}\(_{\text{s}}\) and I_{Ca} (27, 62); ambisilide and cibenzoline block I_{K}\(_{\text{f}}\) and I_{K}\(_{\text{s}}\) (10, 63); ibutilide enhances a slow component of Na\(^+\) current and blocks I_{K}\(_{\text{f}}\) (10, 64); tedisamil blocks I_{Na} and I_{K}\(_{\text{s}}\) as well as I_{Ca} and I_{Na} at high concentrations (10, 65); and sotalol is both a nonselective \(\beta\)-adrenergic receptor antagonist and blocks I_{K}\(_{\text{s}}\) (12). Amiodarone exhibits a complex mechanism of action since it blocks Na\(^+\), Ca\(^{2+}\) and K\(^+\) channels (I_{K}\(_{\text{f}}\), I_{K}\(_{\text{s}}\), I_{Na}, I_{K}\(_{\text{ATP}}\)) and exhibits noncompetitive \(\alpha\) - and \(\beta\)-adrenergic blocking properties (66, 67). Other QT-prolonging drugs quite selectively block I_{K}\(_{\text{f}}\), including propofol, thiopentane (68), several calmodulin antagonists (trifluoperazine, chlorpromazine) (69), indapamide (70), and chromanol derivatives (e.g., 293B) (71). Table 3 summarizes the blocking potency of different drugs on I_{K}\(_{\text{f}}\) and I_{K}\(_{\text{s}}\).

**Disadvantages of selective I_{K}\(_{\text{f}}\) blockers:** The word “selective” is a relative term and is used here to distinguish compounds that block I_{K}\(_{\text{f}}\) at concentrations at least tenfold less than those required to affect other cardiac currents. Selective I_{K}\(_{\text{f}}\) blockers prolong APD and refractoriness and exhibit antiarrhythmic properties in models of reentrant arrhythmias, but the presence of several disadvantages (10, 56, 57, 72): a) they prolong the APD more in the Purkinje and M cells more than in subepicardial or subendocardial muscle. This effect increases the dispersion of repolarization across the ventricular wall and is associated with reentrant rhythms and the development of TdP. b) They also cause greater prolongation of the APD at slower heart rates, while following \(\beta\)-adrenoceptor stimulation or during sustained tachycardia, this prolongation is much less marked or even absent. This phenomena, termed “reverse use dependence” (73), limits their efficacy in terminating tachyarrhythmias, while maximizing the risk of TdP in patients with bradyarrhythmia-dependent QT prolongation. In guinea pig ventricular myocytes, reverse use-dependence has been attributed to the incomplete deactivation (accumulation) of I_{K}\(_{\text{f}}\), leading to a progressive increase in current amplitude that reverses the APD prolongation produced by the I_{K}\(_{\text{f}}\) blockers at fast heart rates. c) Their effect on APD prolongation might be reduced or even reversed during ischemia, which is frequently accompanied by elevations in [K\(_{\text{e}}]\), and by catecholamine surges that occur during exercise or other activities associated with fast heart rates. Thus, patients whose risk of arrhythmias can be enhanced by transient myocardial ischemia and/or sympathetic stimulation might not benefit from treatment with selective I_{K}\(_{\text{f}}\) blockers. d) I_{K}\(_{\text{f}}\) plays a dominant role in repolarizing the embryonic and neonatal rat and mouse heart (11, 74). Thus, the embryotoxicity produced by specific I_{K}\(_{\text{f}}\) blockers (L691,121, sematilide, d-sotalol, dolefinitol) has been attributed to APD prolongation that triggered EADs and rhythm abnormalities in the fetal rat heart. Whether similar considerations apply to humans remains uncertain (15).

**TdP induced by class III antiarrhythmic drugs:** Because they prolong the APD, class III agents would be expected to induce dose-related TdP (5, 10). However, all class III drugs do not share the same risk to induce TdP. The incidence of TdP for sotalol is 2.4% and increased to 5% at high doses, in elderly patients and in patients with impaired renal function (75), while the real incidence of TdP for newer class III drugs (dolefinitil, d-sotalol, ibutilide, azimilide, almokalant) is unknown (6, 72). The associated rate of TdP during conversion to sinus rhythm with intravenous ibutilide, almokalant and dolefinitol was as low as 2–3% in patients with atrial fibrillation and as high as 8–12% in those with atrial flutter (72, 76–78). However, these figures refer to the incidence observed during the first hours or days of therapy although it is well recognized that TdP can occur during long-term treatment (5, 41).

In contrast, although amiodarone blocked HEGH channels (66) and in long-term therapy produced a marked QT prolongation, it is very rarely associated with onset of TdP (incidence <1%) (79). The precise mechanism for this low incidence of proarrrhythmia remains unclear but may be multifactorial. In contrast to other class III agents, amiodarone (39, 67, 72, 73): a) reduces or suppresses EADs in isolated cardiac preparations, probably because it blocks I_{Ca} and exhibits \(\beta\)-adrenergic receptor blocking properties. b) It produces a shorter prolongation of APD in Purkinje than
in ventricular muscle cells, thus reducing the inhomogeneous recovery of ventricular excitability. As a consequence, chronic amiodarone therapy prolonged the QT interval but did not increase or even decreased QT interval dispersion. In patients with documented TdP due to class IA and III antiarrhythmics, amiodarone and quinidine produced a prolongation of the QT interval of the same magnitude as that observed when TdP developed, but in contrast to quinidine, subsequent long-term amiodarone did not increase the QT dispersion and rarely caused TdP (34, 39, 80). Finally, amiodarone prolongs the APD to a similar extent in different regions of the heart regardless of underlying rates; i.e., it does not display reverse use-dependency (73, 81).

**Class II and IV agents:** Beta-adrenoceptor and L-type Ca\(^{2+}\) channel antagonists do not prolong the QT interval and have not been associated with TdP (3–6). Moreover, \(\beta\)-adrenergic blocking drugs represent the first line of therapy in patients with drug-induced TdP and with cLQTS (LQT1 and LQT2) (5–7, 15, 82). Verapamil and diltiazem block HERG channels, whereas nifedipine did not exert an antagonist effect (83). However, verapamil and diltiazem did not cause TdP, probably because the potential of HERG channel block-induced QT prolongation and EAD generation is counteracted by the blockade of I\(_{Ca}\).

**2) Vasodilators**

TdP has been described with several coronary vasodilators that block the I\(_{Ca}\) and exhibit dose-dependent class IA antiarrhythmic actions, including lidoflazine (84), prenylamine (85), fenoxedil (86) and bepridil (=1% of treated patients presented TdP) (87). The intravenous injection of vincamine produces marked QT prolongation and TdP in patients with intermittent claudication (88). Papaverine can also produce TdP when used by intracoronary injection for measuring coronary flow reserve (89). Perhexiline blocks HERG channels and prolonged the QT duration even when only one case of TdP has been described (90).

**3) Serotonin agonists/antagonists**

Ketanserin, a 5-HT\(_{2A/2C}\) antagonist, blocks I\(_{Kr}\) and lengthened the APD in guinea pig ventricular myocytes (91), prolonged the QT interval and induced TdP in patients with hypertension or coronary artery disease, particularly in those presenting bradycardia or hypokalemia induced by potassium-wasting diuretics (92). In cat ventricular myocytes, the 5-HT\(_{3}\) antagonists ondasetron and ganisteron block I\(_{Kr}\) (93) and in anesthetized dogs, tropisetron and ondasetron prolong the QT interval, particularly at slow driving rates, an effect that may increase the risk of proarrhythmia during bradycardia (94). TdP has also been described after an overdose of zimeldine, a selective serotonin reuptake blocker used as an antidepressant (95). Cisapride, a selective agonist of 5-HT\(_{4}\) receptors that releases acetylcholine, is widely prescribed for the treatment of gastroesophageal reflux disease and gastroparesis. It is a potent blocker of HERG channels (25) that prolongs the QT and produces TdP, particularly when coadministered with cytochrome P450CYP3A4 inhibitors such as macrolides antibiotics and imidazole antifungals (96).

**4) Psychotropic drugs**

QT prolongation, TdP and suspected sudden cardiac deaths have been described with several psychotropic drugs (1, 97, 98). At therapeutic doses, prolongation of the QT interval produced by most of the antipsychotics and tricyclic and tetracyclic antidepressants is partly due to the widening of the QRS complex of the ECG produced as result of their Na\(^+\) channel blocking properties (51, 99) as well as to the blockade of several K\(^+\) channels. Amitriptyline (100), imipramine (99, 100), haloperidol (101), thioridazine (102) and sertraline (28) block I\(_{Kr}\), more potently than other K\(^+\) currents, suggesting that this blockade is involved in their proarrhythmic effects. QT prolongation and TdP have been observed in psychiatric patients as well as after accidental or suicidal overdose with tricyclic and tetracyclic antidepressants [amitriptyline (103), doxepin (104), imipramine (1, 97), maprotiline (105), trazodone (106)], antipsychotics [chlorpromazine (3, 29), droperidol (107), haloperidol (108, 109), sertraline (109), pimozone (110), thioridazine (2, 3)] or chloral hydrate (111).

HERG channels were originally cloned from human brain and three related members of the erg K family have been identified in the nervous system (112). The three erg family members are expressed in peripheral sympathetic ganglia, potentially implicating these transcripts in the mediation of sympathetic outflow to the heart. Therefore, it is tempting to speculate that the effects of some psychotropic drugs could result from the blockade of neuronal HERG-like channels. However, this seems unlikely since patients with HERG mutations (LQT2) did not present neurological abnormalities (5, 15).

**5) H\(_{1}\)-antihistamines**

Several non-sedating H\(_{1}\)-receptor antagonists antihistamines (astemizole, diphenhydramine, hydroxyzine, terfenadine) prolong the QTc interval and induce cardiac arrhythmias, including TdP, particularly in patients with severe hepatic diseases, hypokalemia or pretreated with drugs that inhibit CYP3A4 or prolong the QT interval (13, 113, 114). Terfenadine and astemizole block I\(_{Kr}\) at concentrations at least 100-fold less than that required to block other ion cardiac currents including I\(_{Kr}\) (13, 113). Therefore, this blockade seems to be the major mechanism by which these agents produce QT prolongation. Cetirizine, fexofenadine, loratadine, chlorpheniramine and pyrilamine blocked I\(_{Kr}\).
rather weakly, which could explain why they did not prolong the QT interval at therapeutic plasma levels (10, 13, 113, 114). However, QT prolongation and TdP have been already described with fexofenadine (115), and ventricular arrhythmias and cardiac deaths induced by loratadine have been reported to the WHO and IMS databases (116).

6) Antimicrobials

Several macrolides (erythromycin, clarithromycin, troleandomycin) prolong the QT interval and can produce TdP, particularly at the high drug plasma concentrations found after intravenous administration (117, 118). In cardiac Purkinje cells, erythromycin reduced the maximum upstroke velocity and lengthened the APD, so that it exhibited effects similar to those of class IA antiarrhythmic drugs (50). In isolated ventricular myocytes, erythromycin and clarithromycin block IK (16, 119); and in M and Purkinje cells, erythromycin markedly prolongs the APD and facilitates the occurrence of EADs and TdP (37, 117). QT prolongation, increased QT dispersion and TdP have been observed during toxoplasmosis prophylaxis with spiramycin in newborn infants (120) and following administration of trimethoprim-sulfamethoxazole (121). Marked QT prolongation, but not TdP, has been reported after ampicillin anaphylaxis (3). In patients with acquired immune deficiency states, pentamidine therapy for Pneumocystis carinii pneumonia is accompanied with ECG abnormalities, including QT prolongation, TdP and sudden cardiac death (122). Chloroquine and halofantrine, used in multidrug-resistant strains of P. falciparum, also prolong the QT and produced TdP and even sudden death (123, 124). Amantadine-induced TdP has been attributed to presynaptic inhibition of catecholamine uptake and to its similarity with the cyclic antidepressants (125).

Imidazole antifungals are potent inhibitors of the cytochrome P450CYP3A4 system, and thus, severe warnings are given against the concomitant administration of imidazoles with QT prolonging drugs that use the CYP3A4 metabolic pathway (Table 1) (1, 126). Ketoconazole blocks IK in cat ventricle and produces a tonic block of HERG channels, indicating a high affinity for the rested-closed states (127). Furthermore, the combination of ketoconazole and terfenadine resulted in additive block of HERG currents, which may explain the development of TdP in patients receiving both drugs (13, 112, 127). These findings confirmed that ketoconazole might potentiate the cardio-toxic effects of IK blockers that are substrates for CYP3A4 not only by a pharmacokinetic mechanism but also by a direct additive effect on HERG currents.

7) Diuretics

The QT prolongation induced by potassium-wasting diuretics in patients with arterial hypertension or congestive heart failure is usually attributed to the hypokalemia that they frequently produce. However, diuretics can also prolong the QT interval independently of changes in plasma potassium concentrations (6), which is consistent with total body K⁺ depletion (not reflected by serum values) as a risk factor (70). In guinea pig ventricular myocytes, indapamide, at clinically relevant concentrations, selectively blocked IKᵣ relative to IKᵢ, whereas chlortalidone was without effect (70). Triamterene also blocked IKᵣ and prolonged the QT interval independently of plasma K⁺ concentrations (128). Diuretic-induced IKᵣ block and hypokalemia predispose to QT prolongation and TdP, particularly when given in combination with drugs or in clinical conditions (congestive heart failure, hypertensive cardiac hypertrophy) that prolong the QT interval (2–6).

8) Autonomic nervous system

Ventricular repolarization is predominantly under sympathetic control and vagal effects are predominantly indirect and secondary to changes in heart rate. Several findings support the association between increased sympathetic tone and drug-induced TdP (30–35, 82, 129): 1) in animal models, catecholamines induced EADs and TdP-like arrhythmias; 2) left stellate ganglion stimulation and right stellate ganglion removal prolonged the QT interval and induced ventricular tachyarrhythmias; and c) in patients with cLQTS, sympathetic stimulation (physical exercise, strong emotions) or adrenaline administration prolonged the APD and increased the amplitude of EADs, the dispersion of ventricular repolarization and the propensity to TdP ventricular arrhythmia.

Sympathetic stimulation can modify ventricular repolarization in a number of ways (2–5, 11, 82, 130, 131). β₁-Adrenergic stimulation increases the magnitude of I₅₋₅, which facilitates the development of EADs and their conduction from Purkinje cells to the surrounding myocardium and enhances the activity of the electrogenic Na⁺-K⁺ pump, which hyperpolarizes the membrane and decreases heart rate. Additionally, β₁-adrenergic activation, increases the cardiac pacemaker current (I₀) and accelerates heart rate and the repolarizing currents IKᵢ, Io and IC₅₋₅ (cAMP-activated chloride current), thus generating a net outward current that shortens the APD and inhibits the development of EADs. The final result of these contradictory effects is an increase in heart rate and a shortening of the APD, but a defect in any of these multiple mechanisms may explain why patients with LQTS fail to shorten their QT interval during sympathetic stimulation (i.e., exercise). α₁-Adrenergic stimulation inhibits several K⁺ currents (IKᵢ, Io and IKᵢᵢᵢ), prolongs the APD, and facilitates the development of EADs and TdP induced by K⁺ channel blockers in animal models (33, 35). However, α₁-adrener-
Drug-induced Torsade de Pointes
gic stimulation does not modify basal $I_{Ca}$, but decreases $I_{Ca}$ stimulated by $\beta$-agonists or forskolin (130). Moreover, $\alpha_{1}$-adrenergic blockade decreases EAD amplitude and the incidence of TdP in animal models (33, 34, 82).

In patients with cLQTs (LQT1 and LQT2), $\beta_{1}$-adrenoceptor blocking drugs and left stellate gangliectomy reduce the dispersion of ventricular repolarization and the incidence of syncope and sudden death, not only by removing the trigger (sympathetic stimulation) but also by modifying the arrhythmogenic substrate (prolongation and dispersion of repolarization) (5, 82). It would be of interest to know whether in patients with congenital or drug-induced LQTS: a) abnormal sympathetic innervation could induce abnormal expression, distribution or function of cardiac $K^{+}$ channels; b) native and mutant HERG/MIRP1 channels are differently modulated when exposed to catecholamines or they respond in an abnormal way, so that patients with LQTS may be particularly vulnerable to sympathetically-induced arrhythmias; and c) mutations in genes regulating the sympathetic-effector apparatus may be responsible for adrenergic sensitivity in some patients.

9) Miscellaneous drugs

QT prolongation and TdP has been reported in cases of arsenic poisoning (132), intoxication with organophosphate insecticides (133), or after intracoronary ionic contrast media injection (134) as well as in patients treated with trimetapham (135), doxorubicin (136), indoramin (137), probucol (138), cocaine (139), vasopressin (140), high concentrations of prednisone, and terodilin, an anticholinergic drug that blocks $I_{Ca}$ and $I_{Kr}$, used for the treatment of urinary incontinence (141, 142). Nicotine inhibits several cardiac $K^{+}$ channels including HERG. This effect is independent of nicotine receptor stimulation or catecholamine release and can contribute to the cardiac effects of nicotine in smokers (143). Sildenafil at concentrations that may be found during coadministration of another CYP3A4 substrate or after drug overdose prolongs ventricular repolarization in guinea pig hearts and blocks HERG channels (IC_{50} = 100 $\mu$M) in human embryonic kidney 293 cells (144). However, there is no evidence that the drug induces QT prolongation or proarrhythmic effects in humans. Very recently, it was reported that ergotoxin, a peptide isolated from the scorpion Centruroides noxius specifically inhibits (IC_{50} = 20 $\mu$M) erg channels of different species and distinct histogenesis (145).

Role of metabolites: The presence of active metabolites can sometimes explain the poor correlation between the occurrence of QT prolongation and TdP and either the dose or the plasma concentrations of the parent compound. TdP induced by encainide, procainamide or imipramine may be due to their active metabolites, 3-methoxy-O-desmethyl encainide, N-acetyprocainamide and desipramine, respectively (2–4, 55, 146, 147). Antihistamines rapidly undergo complete biotransformation to active (desmethyl-astemizole, norastemizole, descabothaxyloratadine) or inactive metabolites (carebastine, fexozenadine). Desmethyl-astemizole blocks $I_{Kr}$ (IC_{50} = 20 nM), prolongs the APD, induces EADs (13, 148) and is cleared very slowly (up to 20 days after chronic dosing), which explains why the risk of ventricular arrhythmias persists for long after discontinuing the treatment with astemizole.

Drug interactions: Table 1 shows that some drugs that prolong the QT interval are metabolized by the cytochrome P450 system, and therefore, inhibition of their metabolism leads to elevated drug plasma concentrations that further prolonged the QT interval (1, 126). For drugs whose systemic clearance is heavily dependent on clearance to an inactive metabolite by an enzyme exhibiting genetic polymorphism, poor metabolizers (8–10% of Caucasians) may be at greater risk of TdP than extensive metabolizers. When the drug is converted to an active metabolite responsible for QT prolongation, inhibition of the P450 system reduces while its stimulation increases the risk of QT prolongation. Thus, intersubject variability in drug metabolism may also account for nonuniform susceptibility of the population to drug-induced TdP. Predictions can be difficult, however, for drugs (antiarrhythmics, astemizole, terfenadine, imipramine) where both the parent compounds and the metabolites are active with potentially different concentration-response relationships in different tissues. Coadministration of terfenadine, astemizole or cisapride with CYP3A4 inhibitors (imidazole antifungals, macrolide antibiotics, cimetidine, haloperidol, grapefruit juice) results in higher drug plasma levels, marked QT prolongation and death due to TdP (1, 6, 14, 112, 126). This type of unwanted drug interactions can be predictable based on the knowledge of which drugs induce and inhibit specific P450 enzymes, and thus, they can be prevented.

7. Risk factors predisposing to the development of TdP

As already mentioned, there is a discordance between potency in prolonging the QT interval and propensity to induce TdP, since not all drugs that prolong the QT interval culminate in TdP (2, 4). These findings suggest that QT prolongation alone does not explain TdP and that other risk factors, including hypokalemia, slow heart rates, pre-existing cardiac diseases (life-threatening arrhythmias requiring antiarrhythmic therapy, ventricular hypertrophy, heart failure), female gender, baseline QTc interval >0.46 s or coadministration of drugs that prolong the QT interval may predispose to drug-induced TdP (2–6). These observations led to the concept of “repolarization reserve”, which proposed that there is an excess capacity of the myocardium to effect orderly and rapid repolarization via normal mechanisms. The presence of risk factors, particularly
hypokalemia, reduces this reserve and explains why some patients develop TdP after receiving $I_{Kr}$ blocking drugs for long periods of time with no prior evidence of proarrhythmia (9, 149).

Some of these risk factors should be particularly taken into consideration:

a) Gender: Women have a longer average QTc interval than men and are more prone to develop TdP during the administration of QT prolonging drugs (150). Therefore, it was proposed that sex hormone activity can modulate specific ion-channel kinetics and the response to $\beta$-adrenergic receptors to triggering stimuli. Female rabbit ventricular myocytes have lower $I_{Kr}$ and $I_{K1}$ outward current densities than do male cells, which may contribute to the gender difference in QT interval (151). Since $I_{Kr}$ is already reduced, a further reduction produced by $I_{K1}$ blockers may cause an exaggerated QT prolongation in female hearts. Estradiol-induced QT prolongation was associated with a downregulation of $I_{Kr}$ channels in ovariectomized rabbits and a lesser degree of quinidine-induced QT prolongation was observed in dihydrotestosterone- versus estradiol-prefracted ovariectomized rabbits (152). Treatment with progesterone decreases $I_{Ks}$ currents, while no currents can be expressed in Xenopus oocytes from mRNA prepared from uteri of estrogen-deprived rats (153). In this latter condition, rats treated with estrogen for 3 days reexpress $I_{Ks}$ currents. However, the long QT interval in women is independent of age, which suggest that estrogens play only a partial role in the observed sex differences in repolarization (154). The antiestrogen drug tamoxifen used to treat breast cancer blocks $I_{Kr}$ with a potency even greater than quinidine and prolongs the QT interval (155). Thus, caution should be taken when administering tamoxifen to women where other risk factors for TdP exist.

b) Bradyarrhythmias: Slow heart rates, resulting from either sinus bradycardia or atrioventricular block predispose to drug-induced TdP because it markedly prolonged the APD in M and Purkinje cells, increased dispersion of repolarization and induced EADs (2, 8, 34). Moreover, the bradycardia characteristic of drug-induced LQTS suggests that $I_{Kr}$ can play an important role in sinus node function (5, 83). The reverse use-dependence induced by $I_{Ks}$ blockers can also account for the prolongation of the APD with subsequent EAD development observed at slow heart rates (10, 11, 73). Therefore, bradycardia should be corrected with temporary cardiac pacing, isoproterenol infusion or atropine.

c) Electrolyte and metabolic disorders: Hypokalemia reduces the net outward current by decreasing $I_{Kr}$, $I_{K1}$ and electrogenic Na$^+$ pumping and prolongs the ventricular APD, an effect that is more pronounced in Purkinje cells than in ventricular muscle cells (11, 19, 156). Moreover, hypokalemia produces an additional block of the $I_{Kr}$, even in the presence of maximal drug-induced $I_{Kr}$ block (28). These effects explain why hypokalemia produces a marked QT prolongation and facilitates the occurrence of drug-induced TdP even in patients who have been taking QT prolonging drugs for years with no prior evidence of proarrhythmia (2–5, 9). Circumstances that produce hypokalemia, including inadequate intake (chronically ill patients, alcoholics), excessive loss (vomiting, diarrhea, laxative abuse, alkalosis, hyperaldosteronism, magnesium depletion) and drugs (thiazides and loop diuretics, penicillins and aminoglycosides antibiotics, amphotericin B, corticosteroids, carbenoxolone), greatly increased the risk of drug-induced TdP (2–5, 11, 156). Thus, hypokalemia should be corrected before giving a drug known to prolong the QT interval. Prolongation of the QT interval but rare cases of TdP have been reported in patients with hypomagnesemia (157), hypocalcemia (2–4, 29, 158, 159) and severe hypothyroidism (29, 160) as well as in patients with nutritional disorders associated to liquid-protein-modified-fat diets for weight reduction (161), anorexia nervosa (162) and starvation (163). QT prolongation is not entirely explained by the electrolyte imbalance that is common in anorexia (6, 162).

d) Other clinical conditions leading to QT prolongation and increased QT dispersion are summarized in Table 1 (2–6, 29, 164). Under all these circumstances, the concomitant use of drugs that prolong the QT interval may predispose to serious ventricular arrhythmias or sudden cardiac death and therefore, should be avoided.

8. Experimental models of drug-induced TdP

Numerous in vitro and in vivo models have been used to study drug-induced TdP (reviewed in ref. 33). Drugs that prolong the APD easily induced EADs in isolated cardiac tissues that were dependent on the concentration of the drug and favored by low rates and hypokalemia. However, the sustained activity under these conditions rarely exceeds 120 beats per minute (41) and the correlation between the $I_{Kr}$ blockade and APD prolongation is poor (7, 33, 34, 56). This lack of correspondence lies in the complex nature of repolarization, with multiple ionic currents contributing to this process (Fig. 1). The density and contribution of each current is determined by different factors, including cell type (atrial vs ventricle, endocardial vs epicardial, muscle vs Purkinje cells), heart rate, animal species and intrinsic regulation. While both $I_{Kr}$ and $I_{K1}$ coexist in some mammalian species (e.g., human, sheep, guinea pig, dog), other species display $I_{Ks}$ alone or predominantly (rat, cat, rabbit) (10, 11, 56). In in vivo animal models, TdP-like ventricular tachyarrhythmias have been induced by drugs that prolong the QT interval (cesium, anthopleurin-A, class I and III antiarrhythmics) in the presence of bradycardia (achieved by chemically or electrically-induced complete atrioventricular
block) and hypokalemia (induced by high doses of diuretics) (34). Unfortunately, and despite complex experimental procedures, none of these models reproduced the main clinical features of TdP. Therefore, the experimental findings cannot be extrapolated to the human heart.

In native cardiac cells, detailed quantitative study of K⁺ channel function and drug-channel interactions is greatly complicated by the presence of multiple overlapping K⁺ currents (Fig. 1). To study individual K⁺ channels under physiological conditions with minimal interference from other contaminating currents and to perform detailed analysis of the mechanisms and the loci of drug-induced block, channel proteins can be expressed in heterologous expression systems such as mammalian cell lines or oocytes of the toad *Xenopus laevis*. Moreover, channel structure can be modified in these systems, so that it is possible to obtain information about the structural basis of drug action. HERG expression in such systems reproduces the physiological and pharmacological characteristics of I_Kᵢ and allows the rapid screening of blocking drugs (19–21). However, drug potency varies widely with the cell type, ionic conditions and voltage clamp protocols. As is shown in Table 3, the apparent affinity of drugs for HERG channels expressed particularly in X. oocytes was approximately tenfold lower that obtained previously for I_Kᵢ in guinea pig ventricular myocytes (23, 24, 27, 48, 114). This can be explained because the vitelline membrane altered drug diffusion at the surface membrane and the yolk-sac form a sink for lipophilic drugs. Differences in I_Kᵢ deactivation kinetics have also been reported between species, being 4 to 10 times faster in mouse AT-1 cells and guinea pig ventricular myocytes than in HERG channels expressed in oocytes (11, 28, 64). Furthermore, in mammals, there is a surprising degree of heterogeneity of K⁺ channels as a result of multiple genes encoding α-subunits, coassembly of related α-subunits to form heteromultimers and alternative splicing of some channels (11, 14). Other factors that may contribute to the differences between native I_Kᵢ and HERG included post-translational modifications, the presence of auxiliary β-subunits that coassemble with the HERG channel α-subunit or channel modulation by cytoplasmic factors that may alter the sensitivity to I_Kᵢ blockers (14, 16). Thus, minK/KCNQ1 complexes recreate the behaviors of I_Kᵢ channels, while MiRP1/HERG complexes recapitulate those of I_Kᵢ channels (14, 16, 17). Compared to channels formed by HERG subunits alone, those containing MiRP1/HERG were approximately threefold more sensitive to E-4031 and clarithromycin blockade, and inhibition was intensified by hypokalemia (16). The important differences in kinetic and functional properties of human cardiac K⁺ channels and those from other mammalian species, explain why experimental findings cannot simply be extrapolated to the human heart.

9. Treatment of drug-induced TdP

Treatment begins with the recognition and immediate withdrawal of any potentially offending drug and the correction of any known risk factors. The goal of therapy is to shorten the APD prolongation, reduce QT dispersion and suppress EADs (2–8). This can be achieved by increasing heart rate (cardiac pacing at about 100 beats/min, infusion of isoproterenol or atropine), by increasing outward repolarizing currents and by intravenous administration of magnesium sulfate (2–8, 165). Cardiac pacing and isoproterenol prevent bradyarrhythmias that facilitate the onset of TdP and offset the prolongation of the APD and the EADs induced by I_Kᵢ blockers because they increase the amplitude of I_Kᵢ, but isoproterenol may also favor the onset of ventricular arrhythmias. Intravenous magnesium is effective and safe to suppress EADs and TdP; and when the diagnosis of TdP is doubtful, it did not aggravate the ventricular arrhythmias, as may occur with isoproterenol (34, 165). These beneficial effects of magnesium have been attributed to the blockade of Ca²⁺ and Na⁺ inward currents (6, 8, 30, 34). EADs can also be suppressed by increasing outward K⁺ repolarizing currents (nicorandil, cromakalin, pinacidil) or by blocking inward depolarizing Na⁺ (class IB drugs that shorten the APD and inhibit the conduction from the Purkinje network to the myocardium) and Ca²⁺ (verapamil, diltiazem) currents (2–8, 15, 33, 34, 166, 167). Unfortunately, none of these drugs have been proved to be consistently effective and many unsuccessful cases have been reported (6).

The integration of molecular genetics with detailed cellular electrophysiological studies allow us to understand the structure, expression, regulation and function of mutant HERG channels and to correlate the underlying genetic defects with clinical phenotypes. The precise identification of genetic defects of ion channels producing cLQTS opens the possibility of developing new therapeutic approaches based on the specific functional properties of the mutant channels encoded by the inherited gene defects (5, 6, 15). In addition, genetic diagnosis identifies patients with specific gene mutations who are at high risk to develop drug-induced TdP (5, 6, 15) and provides information that facilitates the selection of an appropriate therapeutic approach. At the present time, however, genetic testing is not completely sensitive, since not all mutant genes are known; in about 50% of clinically diagnosed LQTS patients who undergo genetic analysis, no gene mutations were found; and in any case, a negative genetic test does not exclude the existence of a cLQTS (6).

Recent evidence demonstrated that raising of serum K⁺ concentration [K]₀ to 4.5 mM in patients given I_Kᵢ blockers or with LQT2 increases I_Kᵢ, shortens the QT interval and may prevent TdP (5, 8, 11, 28, 168). Moreover, potassium infusion reduced QT prolongation and QT dispersion in
normokalemic patients treated with quinidine and in patients with congestive heart failure (49). These patients should also benefit from therapy with K+ channel openers (167). In contrast, class IB drugs (mexiletine, lidocaine), which showed a high affinity for inactivated Na+ channels, markedly shortened the QT interval in LQT3 patients but not in LQT2 patients (5, 7, 11, 15).

10. Is drug-induced TdP an acquired or an inherited disorder?

The scarcity of clinical reports of TdP despite the widespread use of some of these agents in otherwise healthy patients together with the identification of genetic mutations of ion channels involved in cardiac repolarization raises the hypothesis that drug-induced TdP might represent a forme fruste of the cLQTS with an increased susceptibility to drugs that further prolong ventricular repolarization (5–7, 15). In fact, the QT before drug exposure is longer in patients that developed drug-induced TdP than in patients who received the drug safely (2, 6, 149). Moreover, patients with bradycardia-induced TdP exhibit EAD-like activity when given class IA antiarrhythmics (169), and patients with drug-induced TdP are at high risk of arrhythmia when exposed to a second QT prolonging drug (6, 50). Recent studies have identified asymptomatic patients who carry silent mutations on LQTS genes that by themselves produce an alteration in repolarizing currents that is insufficient to prolong the QT at rest (15, 16), so that not all carriers of mutant genes present LQTS (7) and not all those affected have symptoms (15). Moreover, some families may have low penetrance (up to 70% of the LQTS-gene carriers have a normal QT interval) and recessive inheritance of LQTS without deafness (15, 170). Following the concept of “repolarization reserve”, in these patients even a modest degree of Ikr blockage might produce a major prolongation of the QT interval that triggers the onset of TdP; i.e., the drug unmasks a latent form of cLQTS in otherwise healthy patients (7, 15, 149). These patients, particularly those with long baseline QT interval and familial history, are at increased risk of arrhythmias due to QT prolonging drugs.

Another explanation for drug-induced TdP is that some mutations may encode cardiac channels (KCNO1, HERG, SCN5A, KCNE1 and KCNE2) that are not dysfunctional by themselves, but interact with particular drugs in a manner distinct from drug interactions with wild-type channels (13, 169). Thus, multiple forms of drug-induced TdP could possibly exist depending on the mutated channel and the specific drug involved. Furthermore, it is also plausible that these patients may have an increased dispersion of repolarization due to slightly different patterns of expression of normal (i.e., nonmutated) ion channels that contribute to repolarization. This is consistent with the bradycardia dependence of the acquired LQTS, which can further exaggerate the inhomogeneity of repolarization. In these patients, QT prolonging drugs can further exaggerate the inhomogeneity of repolarization, an effect that can be further potentiated in the presence of bradycardia and trigger TdP arrhythmias.

11. Final recommendations

There is evidence that certain drugs that prolong the QT interval can provoke TdP. Moreover, even at clinically recommended doses, apparently harmless drugs that lack the capacity per se to provoke TdP can cause this arrhythmia when used in combination with drugs or conditions that prolong the QT interval or in patients with cLQTS (Table 1). Based on the premise that drugs and conditioning factors create a persistent arrhythmogenic substrate, the ultimate epidemiological question relates to identification of individuals at risk of developing TdP when exposed to QT prolonging drugs. This should allow physicians to anticipate and, therefore, avoid drug-induced TdP.

The prevention of drug-induced TdP begins with the identification and, if possible, the correction of risk factors (e.g., hipokalemia, bradycardia) before giving any drug known to produce TdP. Pre- and post-treatment QT/QTc intervals should be determined and the treatment should be stopped or reduced when QT >0.5 s, bearing in mind that no absolute value of QT interval predicts the development of arrhythmias in all patients. In addition, supratherapeutic drug plasma concentrations and simultaneous co-administration of drugs producing TdP should be avoided (1, 6).

In patients who developed drug-induced TdP, the medications used (prescribed and over-the-counter) should be determined. Drugs known to prolong the QT interval or produce TdP are contraindicated in these patients and the concomitant therapy with drugs that inhibit the cytochrome P450 system should be avoided. In a patient with QTc >470 ms and documented TdP, the diagnosis is straightforward. However, borderline QTc intervals (0.45 –0.47 s) are not sufficient to make or exclude a diagnosis, so that a careful history should be obtained with special attention to symptoms such as palpitations, dizziness and syncope, and a careful monitoring of the ECG to identify the warning signs that precede TdP (QT >500 ms, biphasic T waves or prominent U waves, ventricular bigeminy) should be performed. Because some patients with these symptoms may actually represent asymptomatic cLQTS gene carriers, they should be hospitalized and electrophysiologically monitored for several days. In these patients, the plasma concentrations of the drug and the QT/QTc intervals should be measured before giving a drug known to prolong the QT interval and repeated ECG
should be obtained after at the beginning of therapy, when stable blood levels of the drug are obtained and when the dosage is increased. Any sign of QT prolongation should prompt the physician to exercise great care during the course of treatment and may warrant discontinuation in favor of other therapies with electrophysiologically properties similar to the implicated drug but not associated with development of TdP. If TdP occurred at supratherapeutic plasma levels and in the presence of risk factors (hypokalemia, bradycardia), the drug could be potentially restarted at a lower dose. Under these conditions, a careful monitoring would be required to prevent the development of high plasma levels and/or the QT prolongation.

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