Drug-Proarrhythmic Sudden Cardiac Death

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The possibility of a drug-induced terminal event must always be borne in mind when one is trying to determine the etiology of an actual or aborted sudden cardiac death (SCD). Among the potential mechanisms are acute mechanical or electrical cardiac toxicity from drug overdose, or precipitation of acute myocardial ischemia or infarction by recreational drugs (e.g., cocaine and amphetamines). The present article focuses instead on mechanisms of SCD that result from "drug proarrhythmia," i.e., cardiac arrhythmias triggered by medications administered at therapeutic doses. The terminal rhythm disorder in drug proarrhythmic SCD is most often a ventricular tachyarrhythmia, but can be a bradyarrhythmia.

Causes of drug-proarrhythmic SCD (Table)

Torsade de pointes (TdP) is the paradigm for drug proarrhythmia leading to ventricular tachyarrhythmic SCD. Characterized by polymorphic (PM) ventricular tachycardia (VT) of variable duration that may degenerate into ventricular fibrillation (VF), TdP appears to be initiated by early afterdepolarizations[1] and arises in the setting of prolonged repolarization – manifested on the ECG by QT lengthening, with QTc typically ≥ 0.50 sec.[2,3] Such QT prolongation may occur in response to a whole array of cardiac and non-cardiac drugs [3,4] which have in common the ability to bind to and, thereby, block the *HERG* cardiac ion channel (responsible for the rapid component of the delayed rectifier outward potassium current).[5] Until the present decade, antiarrhythmic agents, such as quinidine,[3] were probably the most common culprit drugs. The potential for TdP to degenerate into VF is attested to by the observation that 25% of patients developing TdP on the QT prolonging antiarrhythmic drug *d,l*-sotalol required defibrillation in order to be resuscitated.[6] Although TdP associated with antiarrhythmic drugs typically occurs within the first few days of drug administration or dosage increase,[6] the development of this potentially lethal ventricular tachyarrhythmia may also occur months or perhaps years later,[4,7] usually upon the introduction of an additional predisposing factor (see below). With contemporary increased awareness of the risk of TdP, VF[8] and SCD[9] associated with QT prolonging antiarrhythmic agents – leading to a decline and much greater caution in their use (for example, requiring in-hospital monitoring during drug initiation[10]) – *non-cardiac* QT-prolonging medications (see www.qtdrugs.org) are emerging as the predominant culprits for drug-related TdP. Such a mechanism for SCD is suggested by community-based studies which have documented a statistically increased risk of SCD in patient populations exposed to erythromycin (especially in association with drugs inhibiting its metabolism)

and certain psychotropic agents.[11-13] It should be noted, however, that the *absolute* incidence of TdP and SCD with non-antiarrhythmic medication capable of prolonging the QT interval is extremely low.[14]

There are host of known risk factors that can promote the occurrence of TdP in patients treated with QT prolonging drugs, under the unifying principle that these predisposing factors may reduce the "repolarization reserve", i.e., the aggregate compensatory outward currents that would tend to oppose action potential prolongation and thereby "defend" against the development of TdP.[15] For virtually all drugs known to prolong the QT interval, there is a female preponderance among the reported cases of TdP.[3,4] Moreover, in a large clinical experience with *d,l*-sotalol, women were found to have a 2- to 3-fold increased risk of TdP upon exposure to the drug, even after correcting for other risk factors.[6] A gonadal hormone mechanism seems underly this sex disparity, with an androgenic "protection" role more in evidence than estrogenic "vulnerability".[6,16] The electrophysiologic remodeling that attends left ventricular hypertrophy and heart failure can result in action potential prolongation[17-19] which, in turn, can predispose to further QT lengthening and TdP upon exposure to QT prolonging drugs.[6,10,20] A similar predisposition to TdP is expected in patients with advanced liver disease, an under-appreciated cause of significant QT prolongation which is not attributable to electrolyte abnormalities and which regresses following liver transplantation.[21-23] The propensity to TdP can also be increased in settings of bradycardia (given the physiologic tendency of QT to lengthen as heart rate slows) and electrolyte abnormalities, particularly hypokalemia and hypomagnesemia.[3,24-26] Excessive QT prolongation, predisposing to TdP, may occur with certain drugs by virtue of inhibition of their metabolism by concomitantly administered medications.[1,4] Some patients who develop drug-induced TdP may have unrecognized congenital overt or low-penetrance ("forme fruste") long QT (LQT) syndrome which can result from a variety of cardiac ion channelopathies, most commonly those involving the slow and rapid components of the delayed rectifier potassium currents;[27] moreover, polymorphisms in some LQT genes that may predispose to exaggerated QT prolongation and TdP in response to culprit drugs are beginning to be identified.[15,27,28]

A different mechanism of drug proarhythmic SCD may arise in <u>patients with structural heart disease who have potential reentrant VT circuits</u> that ordinarily may not be able to support more than one to several successive cycles of reentry before the advancing wavefront encounters refractory tissue, thereby preventing perpetuation of tachycardia (so that just one or a few consecutive premature ventricular complexes [nonsustained VT] are generated). However, in the setting of antiarrhythmic drugs that may have a relative slowing effect on the circulating wavefront

–e.g., Class IC agents such as flecainide and propafenone or Class IA drugs such as quinidine, procainamide and disopyramide – may impose just enough time delay for the refractory "tail" to remain always ahead of the advancing wavefront. The result is drug-induced conversion from non-sustained to sustained VT,[29-31] which may, if rapid enough, directly or indirectly (via degeneration to VF) cause cardiac arrest. Impaired left ventricular systolic function is felt to be a risk factor for Class IC-associated ventricular tachyarrhythmic proarrhythmia.[32,33]

Particularly in patients who have ischemic heart disease with prior myocardial infarction (MI), regardless of whether they have known preexisting non-sustained VT, administration of certain antiarrhythmic agents, especially the Class IC drugs, has been shown in large scale clinical trials to predispose to an increased incidence of SCD compared to placebo.[34,35] This type of drug proarrhythmic mechanism, predicated on an MI-asssociated reentrant substrate, has been experimentally replicated.[36] Whether Class IC-related ventricular proarrhythmia is also more likely to occur in coronary artery disease patients who *lack* prior MI is not clear; however, since such individuals always have the potential to develop an MI, the use of Class IC antiarrhythmic agents should be avoided altogether in patients with ischemic heart disease – regardless of presence or absence of prior MI.[37] Whereas LVH is best identified as a risk factor for proarrhythmia (TdP) in association with QT prolonging drugs, there is also concern that Class IC antiarrhythmic drugs may be proarrhythmic (VT or VF) in individuals with LVH.[37]

In patients with implantable converter defibrillators (ICDs), installed because of either documented or anticipated sustained ventricular tachyarrhythmias, certain antiarrhythmic drugs (particularly Class IC antiarrhythmic agents) may act to raise the defibrillation threshold of the myocardium[38,39] thereby potentially thwarting the life-saving effect of an ICD shock during a VF event. This phenomenon, which can lead to SCD despite device therapy, was more notable during the early ICD era with devices that delivered *monophasic* pulses; in the current era of more efficient *biphasic* ICD waveforms, drug-related elevation of defibrillation threshold may be somewhat less of a clinical concern at least with regard to amiodarone administration.[40]

In the rare setting of known, unrecognized or latent Brugada syndrome, characterized by right precordial ST elevation (typically with associated T wave inversion) and potential susceptibility to PMVT/VF, the latter may be precipitated by administration of certain sodium channel blocking antiarrhythmic drugs (e.g., Class IC agents and procainamide).[41]

Although not so well documented, initiation of PMVT and VF following the administration of sympathomimetic amines (e.g., bronchodilators) is theoretically possible in certain highly susceptible patients. The latter could include individuals who have a genetic predisposition to catecholaminergic PMVT[42] or perhaps certain individuals with severe ischemic heart disease and/or advanced congestive heart failure, who may be very prone to developing ventricular tachyarrhythmias.

Up until now, we have been discussing ventricular tachyarrhythmic drug proarrhythmia. However, it is also possible for drugs to cause SCD through a preterminal atrial tachyarrhythmia mechanism. The primary setting for this phenomenon is the patient with atrial flutter and associated 2:1 ventricular response. When such a patient is given antiarrhythmic agents that slow conduction of the circulating atrial flutter wavefront (typically Class IC drugs, but also potentially Class IA drugs such as quinidine or procainimide), the relatively reduced input frequency to the atrioventricular node, especially when combined with enhanced sympathetic tone (e.g., upon assuming the upright position) or with attendant vagolytic drug action (as may obtain with quinidine), might permit the atrioventricular node to conduct in 1:1 fashion.[43-45] In this way, a situation can arise in which the atrial flutter rate decreases from, say, 300 beats/min, with associated 2:1 conduction, i.e., ventricular rate of 150 beats/min – pre-drug – down to a flutter rate of 250 beats/min but now with 1:1 conduction – post-drug – so that the ventricular rate is thereby *increased* to 250 beats/min. At such rapid rates, especially in individuals with some degree of impaired left ventricular systolic function, hemodynamic collapse and/or degeneration to VT or VF can follow, culminating in SCD.

Bradyarrhythmic SCD, while a much less common drug-proarrhythmia scenario, is certainly a theoretical possibility to be anticipated and, thereby, avoided in potentially susceptible patients. The latter would include individuals with sick sinus syndrome who might develop sinus arrest and asystole upon exposure to drugs that can depress sinus node automaticity (e.g., calcium channel blockers, beta blockers, sympatholytic agents, amiodarone and Class IC drugs[46,47]). Analogously, drugs that can depress His-Purkinje system conduction (e.g., Class IC or Ia antiarrhythmic agents) could precipitate complete heart block, and potentially asystole, in patients with preexisting extensive disease of that conduction system (e.g., bifascicular block or alternating bundle branch block).[48]

Preventing drug-proarrhythmic SCD

Awareness of the phenomenon of drug-proarrhythmic SCD enables the physician to take steps to minimize its occurrence. In the present ICD era, precisely out of concern regarding drug-

proarrhythmic SCD (and in light of the demonstrated survival advantage conferred by device therapy), antiarrhythmic agents are much less likely to be utilized as primary therapy in patients at risk for life-threatening ventricular tachyarrhythmias. If medication is truly necessary for ventricular tachyarrhythmia suppression in such patients, it is safer for the antiarrhythmic drug to be administered *after* placement of an ICD.

The most common setting for use of suppressive antiarrhythmic medication nowadays is the patient with atrial fibrillation or flutter, which may prompt utilization of QT-prolonging or Class IC agents. Preexisting baseline QT prolongation (QTc > 0.45 sec in men, and > 0.46 sec in women, assuming normal QRS duration)[49] should be considered a contraindication to administration of QT-prolonging drugs (except, perhaps, amiodarone in selected cases). Use of such drugs is absolutely contraindicated in patients with known or suspected congenital LQT syndrome (including asymptomatic gene carriers), regardless of QTc duration. Familiarity with risk factors for TdP can help to avert administration of QT-prolonging drugs in other adverse clinical settings. If such antiarrhythmic medications are deemed necessary – especially when being considered in higher risk patients (e.g., women and patients with "TdP-prone" disease states [Table]) – a number of precautions are warranted to help prevent drug-induced TdP/SCD, including: dosage adjustments that take into account drug disposition (e.g., renal function in the case of dofetilide[50]); close observation and electrocardiographic (QTc) monitoring during drug initiation or dosage increase; ascertainment of normal serum potassium and magnesium levels during treatment (particularly in patients on diuretics[51]); and avoidance of any concomitant QT-prolonging drugs (including educating patients about available lists, e.g., *www.qtdrugs.org*) or metabolically adversely-interacting medication that might enhance QT prolongation. Amiodarone and dofetilide (the latter administered only under very stringent conditions[50]) are the preferred agents when QT prolonging drugs are contemplated for suppression of atrial fibrillation or flutter in patients with left ventricular dysfunction, especially those with stigmata of heart failure.[37]

The recently published ACC/AHA/ESC clinical guidelines[37] for treatment of atrial fibrillation and flutter recommend against the use of Class IC antiarrhythmic agents entirely in patients with ischemic heart disease, heart failure or "substantial" LVH (e.g., echocardiographic left ventricular wall thickness ≥1.4 mm). For ICD implantees receiving antiarrhythmic drugs for suppression of atrial flutter/atrial fibrillation or to prevent excessive VT/VF-triggered shocks, there may be a need in selected patients to reassess defibrillation threshold following introduction of amiodarone (and definitely so in the relatively less likely scenario of Class IC antiarrhythmic drug use[38,39]). Class IC and IA antiarrhythmic drugs are best avoided in cases of Brugada syndrome; and

sympathomimetic amines should not be given to individuals with catecholaminergic PMVT. Assurance of adequate spontaneous or drug-facilitated AV nodal blockade (ventricular response of 4:1 or at least 3:1) during atrial flutter, *prior to* initiation of Class IC or Class IA antiarrhythmic drugs,[37] can largely prevent development of a life-threatening 1:1 ventricular response. Finally, mindfulness of preexisting sick sinus syndrome or advanced His-Purkinje system disease will help to prevent administration of antiarrhythmic drugs that have the potential to cause bradyarrhythmic SCD.

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Table. Causes of Drug-Proarrhythmic Sudden Cardiac Death (SCD)

Tachyarrhythmic SCD

- Ventricular tachyarrhythmia mechanism
  - Torsade de pointes
    (associated with a broad group of cardiac and non-cardiac drugs that prolong the QT interval [see www.qtdrugs.org])
    Risk Factors:
    - Female sex
    - LVH; LV systolic dysfunction; heart failure
    - Bradycardia
    - Electrolyte abnormalities (low K^+, low Mg^{++})
    - Adverse drug-interactions*
    - Advanced liver disease
    - Pre-existing LQT-type cardiac ion channelopathy
    - Possible polymorphism in LQT genes
  - Facilitation of existing reentrant VT circuits in patients with structural heart disease (e.g., Class IC or IA antiarrhythmic drugs)
  - Adverse interaction with ischemic substrate (e.g., Class IC antiarrhythmic drugs)
  - Drug-induced failure of ICD defibrillation (e.g., elevated defibrillation threshold from Class IC antiarrhythmic drugs or amiodarone)
  - Precipitation of PMVT/VF in patients with preexisting or "unmasked" Brugada syndrome (e.g., Class IC antiarrhythmic drugs or procainamide)
  - Adrenergically-facilitated PMVT/VF (e.g., sympathomimetic amines)
- Atrial tachyarrhythmia (preterminal) mechanism
  - Conversion from 2:1 to 1:1 ventricular response during atrial flutter (by Class IC or Class IA antiarrhythmic drugs), that can then trigger hemodynamic collapse and/or a terminal VT/VF

Bradyarrhythmic SCD

- Sinus arrest with protracted asystole in patients with sick sinus syndrome (e.g., calcium channel blockers, beta blockers, sympatholytic agents, amiodarone or Class IC antiarrhythmic drugs)
- Complete heart block with asystole in patients with preexisting advanced His-Purkinje system conduction disease (e.g., Class IC or IA antiarrhythmic drugs)

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* Presence of a concomitant medication that either: a) interferes with metabolic breakdown of the administered QT prolonging drug, or b) has its own QT lengthening effect, which becomes superimposed on that of the administered drug.

ICD=implantable cardioverter defibrillator; LQT=Long QT (syndrome); LV=left ventricle; LVH=left ventricular hypertrophy; PMVT=polymorphic ventricular tachycardia; VF=ventricular fibrillation; VT=ventricular tachycardia.