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Mechanisms of Drug Induced QT Interval Prolongation

Marcelo Luis Ponte*, Guillermo Alberto Keller and Guillermo Di Girolamo

Pharmacovigilance Unit, Second Chair of Pharmacology, School of Medicine, Universidad de Buenos Aires, Argentina; and Department of Physiological, Biochemistry and Pharmacological Sciences, School of Medicine, Universidad Favaloro, Buenos Aires, Argentina

*Address correspondence to this author at the Pharmacovigilance Unit, Second Chair of Pharmacology, School of Medicine, Universidad de Buenos Aires Paraguay 2155 – 16. (C1121ABG), Buenos Aires, Argentina; Tel/Fax: 54 11 4961-0943. E-mail: catedra2@farmaco-vigilancia.com.ar

Abstract: The long QT syndrome (LQTS) is characterized by a prolonged QT interval, as well as a propensity to develop syncope and sudden cardiac death caused by the malignant polymorphic ventricular arrhythmia called torsades de pointes (TdP). The QT interval is measured from the onset of the QRS complex to the end of the T wave and can be affected by both ventricular conduction velocities as well as by the velocity of repolarization. In most cases, QT prolongation is caused by factors that prolong the duration of the action potential, mainly by delaying the repolarization phase 3. The molecular mechanism is partially known. There are two well described mechanisms: blocking of the ion channel cavity of HERG; or causing an abnormal protein trafficking required for the location of HERG subunits in cell membrane. Both of them impair the IKr current. However the blockade of ion channels is not the only condition to generate TdP. Other factors may play an important role, e.g. myocardium heterogeneity, drug-drug interaction, genetic polymorphism, and electrolyte disturbances. Several drugs had been subject of withdrawal because QT-prolongation and arrhythmia. Understanding of processes involved in drug-induced QT prolongation is needed for the study and prevention of life-threatening arrhythmias.

Keywords: HERG channel, IKr current, torsades de pointes, congenital long QT syndrome, QT interval prolongation, physiopathology.

INTRODUCTION

The long QT syndrome (LQTS) is characterized by a prolonged QT interval in the surface ECG, as well as a propensity to develop syncope and sudden cardiac death (SCD). In most documented cases, death was caused by the malignant polymorphic ventricular arrhythmia called torsades de pointes (TdP).

TdP is defined as a polymorphic ventricular tachycardia characterized by a 'twisting of the points' around the isoelectric line on the electrocardiogram (ECG), and is preceded by a long QT interval [1]. TdP is potentially fatal, due to the propensity for it to degenerate into ventricular fibrillation. Although QT prolongation is clearly associated with an increased risk of TdP, there is no reliable criterion to identify the length of QT prolongation that is associated with a clinically significant increased risk of TdP [2].

This makes it difficult for clinicians to decide what QT interval represents significant risk of TdP to require intervention.

Congenital and acquired forms of LQTS are known. Congenital LQTS is an inherited disease in children and adolescents who have a structurally normal heart but presented with sudden death in a high proportion of untreated patients. However the administration of drugs is one of the most frequent causes of acquired LQTS [3-5].

Drug-induced long QT syndrome can, therefore, be defined as an "iatrogenic" form of this potentially lethal condition. Cardiologists are familiar with this adverse drug effect because it has long been a well-known complication of anti-arrhythmic drug treatment [6].

However, since the nineties, it appeared that a large number of non-anti-arrhythmic drugs might prolong the QT interval and consequently predispose exposed patients to TdP and lethal events [7]. Nevertheless, the occurrence of drug-induced TdP is infrequent, and the odds of a given patient on a QT interval-prolonging drug developing TdP are fortunately small [8]. However, in terms of public health and safety, due to the large number of patients receiving such drugs, this issue is becoming increasingly important in daily clinical practice.

ION CURRENTS AND ACTION POTENTIAL IN THE CARDIAC MYOCYTE

The QT interval of the ECG is predominantly determined by the duration of the action potential (AP) of ventricular cells. Indeed, most cases of QT interval prolongation are caused by factors that prolong the duration of the AP, mainly by delaying the repolarization phase 3. Interestingly, the role of specific ion channels in human physiology could only be

ascertained by the finding that alterations (i.e., mutations) of their genes caused congenital LQTS [9].

More than 20 currents subdivided into depolarizing and repolarizing currents are involved in the AP generation of ventricular cells (Fig. 1). The phase 0 (upstroke depolarization) is caused by the very rapid activation of voltage-gated sodium channels Nav1.5. These channels will afterwards inactivate rapidly.

The first repolarization phase 1 is due to the transient outward K+ current for which two components are recognized, ITO1 and ITO2.

The plateau phase 2 is mainly maintained by inward Ca2+ current flowing through Cav1.2 voltage-gated channels that inactivate slowly. Repolarization (phase 3) is obtained through the concerted action of three types of outward currents called IKs (slow), IKr (rapid) and finally IK1. The main pore forming subunit (alpha subunits) of IKs is called KvLQT1 or KCNQ1 (new nomenclature Kv7.1) of IKr HERG (new nomenclature Kv11.1) and for IK1 Kir2.1. These principal alpha subunits are often found in association with so-called ancillary beta-subunits that are not directly involved in the gating machinery of the channels. The currents generated by all other ion transporters (ATPases, exchangers and ion channels) also contribute to shape the AP.

NORMAL VALUES OF QT INTERVAL

The QT interval is measured from the onset of the QRS complex to the end of the T wave. It represents mainly the time of ventricular depolarization, the time to the onset of repolarization and the time required to complete repolarization. That means that this interval can be affected by both ventricular conduction velocities as well as by the velocity of repolarization.

Cardiomyocytes are different from other tissues (neurons and skeletal muscle) in that they possess a long action potential, approximately 300 msec. An ordered pattern of conduction and normal repolarization are essential for the maintenance of normal sinus rhythm.

The QT interval should be measured [10, 11] manually in one of the limb leads (usually DII) from the beginning of the QRS complex to the end of the T wave and averaged over three to five beats. U waves should be included in the measurement if they are large enough to merge with the T wave.

In patients with atrial fibrillation, the measurement of the QT is difficult because of the variation beat-to-beat depending on preceding R-R interval. In case of atrial fibrillation, the QTc intervals after the longest and the shortest R-R should be obtained and averaged.

The normal QT in healthy people without other cardiac conductance altering factors is below 400 msec when measuring this interval in lead DII of ECG (Table 1) [12]. The measure in this lead is suggested because it is the longest interval.

The absolute value of the measured QT interval should be corrected by heart rate. This is because QT interval presents changes with heart rate, i.e. in tachycardia the absolute measure of QT will be shorter as consequence of the shorter action potential, but perhaps, the QT can be relatively longer.

There are several equations to correct the QT interval to the heart rate, however the most frequently used are two described by Bazzet and Fridericia. Bazzet formula is usually to be preferred and was described in 1920 [13]. Bazzet's QT correction is not suitable when heart rate is less than 60 or more than 100 beats per minute.

In these cases the Fridericia formula [14] must be used. Other formulae less used are those described by Framinghan and Hodges (Table 2).

The QTc is considered abnormally prolonged when it is more than 450 msec in women and more than 430 msec in males. Drug induced QTc prolongation considered to be associated with risk for life-threatening arrhythmias is present when the QTc prolongation is 50 msec greater than normal value or then the absolute value of QTc is superior to 500 (Table 1). Other measure that indicates electrical instability is the QTc dispersion, which is calculated as de difference between the longer and shorter QTc in the 12 lead ECG.

LONG QT SYNDROME (LQTS)

From a clinical perspective, the hallmark of LQTS - in both the congenital and acquired forms - is an abnormal cardiac ventricular repolarization that translates, in most cases, into a prolonged QT interval on the surface electrocardiogram (ECG) [3, 15].

The QT interval reflects global ventricular repolarization (i.e., the duration of action potentials of all ventricular cardiomyocytes).

Excessive prolongation of cardiac repolarization may be associated with an increased risk of TdP, a polymorphic ventricular tachycardia that can degenerate into ventricular fibrillation, which may account for cardiac arrest or sudden death [1, 16] (Figs. 2 and 3).

Prolonged repolarization in cardiac ventricular myocytes may be due to an increase in depolarizing inward currents or to a decrease in repolarizing outward currents. The latter

mostly involves potassium channels and, for drug-induced LQTS in particular, the delayed rectifier potassium current, termed IK [17]. In guinea pigs, dogs, and humans, IK comprises both a rapid (IKr rapid component of the delayed rectifier potassium current) and a slow (IKs slow component of the delayed rectifier potassium current) activating component [18-20].

IKr is the primary molecular target for methanesulfonani-lide and most other blocking drugs known to cause TdP, thus linking the congenital and acquired syndromes (LQTS) [15].

CONGENITAL LONG QT SYNDROME

The congenital long QT syndrome (LQTS) was first described in 1957 in a family of several children with bilateral neural hearing defect [21]. Soon thereafter, a milder clinical form of congenital LQTS was described by Romano [22] and Ward [23]. Currently, 10 forms have been identified, and more than 200 mutations have been identified, in several ion channels involved in depolarization or repolarization of cardiac ventricular myocytes have been identified as causal etiology [24]. The knowledge and study of mutations that produce different phenotypes of congenital LQTS syndrome have had great importance for understanding the molecular mechanisms underlying this disease in the acquired forms (Table 3). Women have congenital LQTS more often than men: according to the International LQTS Registry, 70% of patients are female [25-28].

Congenital LQTS increases the risk of ventricular arrhythmia and sudden death in young with a 10-year mortality rate of about 50%. The congenital forms of the LQTS are caused by mutations mostly located in genes encoding cardiac ion channel subunits [29]. This disorder therefore belongs to the genetic cardiac channelopathies (Table 4). In its classic description, the congenital LQTS includes the Romano-Ward [22, 23] and Jervell and Lange-Nielsen syndromes [21]. The latter syndrome is also clinically characterized by neurosensorial deafness.

The phenotypic trademark of LQTS is prolongation of corrected QT interval (QTc) with values above 460 msec, although a subset of patients seems to carry subclinical mutations in cardiac K+ channels manifesting QTc prolongation only after the administration of QTprolonging drugs (“formes frustes” of the congenital LQTS).

Congenital LQTS results from mutations in at least 8 genes, most of them encoding ion channels and causing about 3000 deaths annually in the USA. The most frequently mutations were found in KCNQ1 and HERG. LQT1 is caused by mutations in KCNQ1

(which encodes the alpha-subunit, KvLQT1, of the IKs) located on chromosome 11 where as LQT2 is caused by mutations in HERG (which encodes the -subunit of the IKr) located on chromosome 7.

DRUG INDUCED LONG QT SYNDROME

The long QT syndrome can occur without the existence of genetic mutations. This situation is called acquired long QT-interval syndrome and may have different etiologies, including drugs, and several clinical circumstances such as severe heart failure and cardiomyopathies, in particular left ventricular hypertrophy. For example, left ventricular hypertrophy generates a significant electrical remodeling and its most characteristic feature is an extension of the duration of ventricular action potentials. This remodeling is not homogeneous and therefore also increases the dispersion of repolarization and hence favors the occurrence of polymorphic ventricular tachycardia and sudden death.

In 1964, Seizer and Wray [30] first described what would subsequently be termed drug-induced LQTS with the observation that quinidine could provoke QT prolongation and arrhythmias in otherwise healthy patients. Over the years, this phenomenon has also been noted with several therapeutic agents, and the list of drugs associated with prolongation of the QT interval has become quite long [31-33].

This observation is increasingly intriguing, because [15] the list includes drugs with no apparent cardiac action and from different therapeutic families [5, 15]. With only a few exceptions all different drugs known to prolong the QT interval were shown either to block the HERG channels or to reduce the IKr current recorded in cardiac myocytes [4, 34]. This observation has been quite puzzling since,

unlike other ion channels, the chemical structures of these HERG blocking drugs are very diverse.

The exact molecular mechanism of drug induced QT prolongation is partially known. There are two well described mechanisms: blocking of the ion channel cavity of HERG; or causing an abnormal protein trafficking required for the location of HERG subunits in cell membrane. Drugs can prolong the QT interval by one of the cited mechanisms or through both simultaneously (fluoxetine). All of them cause the IKr current impairment.

HUMAN ETHER-A-GO-GO-RELATED GENE CHANNELS

The human ether-a-go-go related gen (HERG) is homologous other gen found in Drosophila. The original name of ether-a-go-go was appointed in 1960 by William Kaplan

because flies with mutations in this gene when were anesthetized with ether had showed movements and trembles in their legs wich were seen similar to the popular dance a-go-go by Kaplan. The HERG is encoded in chromosome 7 and was first isolated in 1994 by Warmke and Ganetzky by screening a human hippocampal cDNA library with a mouse homologue of ether-a-go-go [35]. The HERG channel is a member of the family of voltage-gated K+ channels and has been shown to form the channel responsible for the IKr [18, 36]. It is composed of 4 identical alpha subunits (1159 amino acids) co-assembling to form the full HERG channel. Each alpha subunit has six transmembrane domains, intracellular N- and C-termini and a pore loop (P loop) linking the S5 and S6 domains

The S4 segment contains positive charges serving as the voltage sensors. In the alpha subunits of the HERG channel, the S6 segment contains two aromatic amino acids (tyrosine-Tyr and phenylalanine-Phe), which participate in the binding site of most of the drugs involved in QT prolongation (Fig. 4).

In most K+ channels the carbonyl atoms of a GYG (Gly-Tyr-Gly) sequence form the selectivity filter; however, in HERG channels the sequence is GFG (Gly-Phe-Gly). Interestingly,

members of the inward rectifier K+ channel family, Kir6.0, also contain a GFG selectivity filter. The central cavity lined by the four S6 segments is especially wide for this channel because these segments lack of a bend found in other K+ channels. This peculiarity may explain why drugs of many different chemical structures can block HERG channels.

HERG channels can be found in three different states: closed, open or inactive (Table 5) [18, 36, 37]. The slow activation and rapid inactivation kinetics causes that HERG channel passes significant current in the inward direction but little current in the outward direction (inward rectifier function). HERG mutations cause a reduction in outward K+ current. However, the mechanisms can be of different types, for example: generation of nonfunctional channels, and mutations affecting intracellular trafficking of channel proteins. The last mechanism seems to be the most frequently [11].

Most HERG blocking drugs are basic compounds that cross the lipid bilayer as neutral molecules, equilibrate in the cytosol as positive charged molecules and bind to the channel only in the open and/or inactivated state. Then, the channel undergoes the process of inactivation increasing the affinity of drug binding.

The high-affinity binding site of most common HERG blocking drugs is located in the central cavity of the channel between the selectivity filter and the activation gate. Tyr652 and Phe656 are the most important drug binding sites. The following drugs have been

shown to interact with these amino acids: MK-499 (Class III antiarrhythmic), terfenadine, cisapride, dofetilide, quinine, quinidine, chloroquine, lidoflazine, prazosin, trazodone, budipine, amsacrine, ajmaline, propafenone, miconazole, halofantrine, vesnarinone, ziprasidone, clemastine, ibutilide, clofilium, bupivacaine, ropivacaine, and mepivacaine [37].

An inactivation-associated reorientation of Tyr652 and Phe656 during closure of the activation gate formed by the crisscrossing of the S6 helical bundles may cause trapping of drugs inside the central cavity after inactivation. This process increases drug sensitivity of HERG channels. Thus, on subsequent depolarization, the channel is not able to conduct K+ ions because the drug remains bound.

HERG is expressed in the heart to a great extent, but the channels are also expressed in a range of other tissues including neurons [35], neuroendocrine glands like pancreatic cells [37] and smooth muscle [38] and contribute to the regulation of cell proliferation and invasiveness of tumor cells [39].

HETEROGENEITY OF REPOLARIZATION

The drug induced blockade of ion channels is necessary but not the only condition to generate TdP. It can be easily confirmed with the example of amiodarone that usually prolongs QTc more than 50 msec but rarely induces TdP. In the other hand, drugs like antihistamines (astemizole) minimally prolong QTc as little as 10 msec with significant risk of TdP induction. This inconsistency may be explained partly because some drugs can increase or decrease the heterogeneity of myocardium repolarization. There is intrinsic transmural heterogeneity in the density of the various ion channels having different effects on action potential duration of the four cell types: subepicardial myocytes, midmyocardial M cells, subendocardial myocytes and Purkinje cells. Drugs that only impair IKr but have no effect on other ionic channels have more propensity to induce TdP because they increase the heterogeneity. That is explaining because midmyocardium and Purkinje fibers have lower density of other channels as IKs and INa comparing to other cells in myocardium. So, the exposure to this kind of drugs will prolong greater the action potential in midmyocardium and Purkinje cells and not in others.

Amiodarone, as described above, may produce marked prolongation of QTc without inducing TdP because it can block other ion channels such as ICa, INa causing homogeneous prolongation of the action potential. More Selective IKr blocking drugs can increase heterogeneity in repolarization between the subepicardium and the endocardium

[40-42]. So, in a certain moment, the action potential in one point (subepicardium, for example) will be ending and action potential can be triggered by a new stimulus, but in another point (subendocardium, for example) the cells will be refractory because they are still in early phase 3. As it can be suspected, this acts as a physiologic reentry (Fig. 5). It has been proposed that the last fragment of the T wave (Tpeak - Tend) is a predictor of heterogeneity of ventricular repolarization [40].

DRUG-DRUG INTERACTIONS

Pharmacokinetics and pharmacodinamics interactions could increase the chances of TdP of torsadogenic drugs. The pharmacodinamics interactions are easier to detect because these occur when two drugs act in the same or a distinct place but induce the same adverse drug effect like QT-prolongation (e.g. antipsychotic and tricyclic antidepressants).

Still, some pharmacodynamic interactions occur through another mechanism. A drug may have potential to prolong the QT interval and a second drug has an effect on other circumstances that increase risk for QT interval prolongation and arrhythmia. Examples of these drugs are those that produce hypokalemia, such as beta 2 agonists, diuretics, amphotericin B and insulin.

Pharmacokinetic interactions occur mainly because inhibition or induction of P450 cytochromes. Some articles can be found in bibliography [17, 43, 44] that expresses TdP as the result of the concomitant use of one torsadogenic drug and another that can inhibit the metabolism of the first one. This leads in increased plasma pick of the torsadogenic drug (Table 6).

Given the quantity of drugs from different chemical classes involved in this adverse effect, the kinetic mechanisms involved may be different. As a general rule, any change that involves increasing the area under the concentration-time curve (increase in exposure to the drug) implies an increased risk of adverse events.

Such changes may be caused by multiple factors that modify the administration, absorption, distribution, metabolism and elimination [44-52].

Within the clinically important changes that alter the absorption, the inhibition of P glycoprotein has been investigated.

This glycoprotein usually behaves as a pump. Extrusion of drugs, is located on enterocytes, and returns part of the drug absorbed to the intestinal lumen, limiting the bioavailable fraction of a drug. Then its inhibition which can be caused by consumption of

grapefruit juice as well as many other substances, leads to an increase in the bioavailable fraction.

The distribution of a drug can be altered by changes in protein binding. Since the therapeutic activity, as well as adverse events, often dependent on the concentration of free drug (not attached to proteins), the displacement of a drug from its protein binding site by the binding of a second drug causes an increase of effects (therapeutic and adverse) of the first drug.

Interactions most often mentioned are those related to the alteration of hepatic metabolism. These are caused when the administration of a drug produces inhibition of enzymes (CYP450) responsible of the transformation into a metabolite with no risk of QT prolongation. This was the mechanism present in most of the detected interaction between macrolide antibiotics and antihistamines that caused the first cases of QT interval prolongation by increasing the concentration of parent antihistamine drugs.

Nevertheless, another mechanism could occur by altering the metabolism, where a drug has no risk of QT prolongation and its metabolite do. In this case, the administration of a second drug with enzymatic activator properties (increase of enzyme activity) will cause an increase on the concentration of the metabolite responsible for the prolongation of the QT interval.

Finally, the elimination of a substance with potential to prolong the QT interval can be reduced when a second drug is administered.

This case can be filed with the administration of a nephrotoxic drug, which lead to renal failure, decrease the elimination of drugs by this route and increased plasma concentrations of the same substance.

Other circumstances that are not drug interactions but constitute specific pathological conditions of a patient can generate the same effects: changes in elimination (renal and hepatic failure) and distribution (edema, heart failure, dehydration, dysproteinemias).

There are few drugs that can prolong QTc and inhibit the cytochromes generating pharmacokinetic/pharmacodinamic interactions and causing a very dangerous situation when are combined with another torsadogenic drug. Examples of these drugs are some macrolides and azoles.

OTHER FACTORS

There are multiple other factors (Table 7) that can prolong QT collaborating to drug-induced QT prolongation. This is now known as "multiple hit hypothesis".

Electrolyte disturbances as hypokalemia and hypomagnesemia, hypothermia, hypothyroidism and obesity are modifiable. Other like advanced age; congestive heart failure and genetic polymorphism are well known unchangeable factors of QT prolongation. Most than two third of the TdP occur in female sex probably because of hormonal influence. Other factors are expressed in Table 7 [27, 45-50].

Drug induced TdP and QT prolongation can be related to a underlying reduced repolarization reserve [51] in some patients. This concept emphasizes that prolonged repolarization could be a patient-specific response. This concept is supported by the fact that some people can experience TdP after being exposed to different drugs, known or not known, to prolong the QTc interval.

This situation may be explained by the presence of nonsymptomatic carriers of mutations involving sodium or potassium channels.

Sympathetic activity, acting in beta adrenergic receptors can increase transmural dispersion of repolarization because an augmentation of IKs in epicardial and endocardial cells but not in midmyocardium cells (where IKs is intrinsically weak).

As we see above, the QTc prolongation is not the only cause of TdP but as longer is the QTc, higher the incidence of TdP. In facts, an equation to estimate the risk of TdP has been used based only in the QTc:

$$Risk = 1.052 \cdot \chi$$

where x is calculted in function of the duration of the corrected QT above 300 msec as follows [52].

$$\chi = \frac{QT_c - 300}{10}$$

DETECTING DRUG-INDUCED EFFECTS ON REPOLARIZATION

There are many models to detect if a drug can potentially prolong the QT [32, 53, 54]. Several examples of in vitro models are described to evaluate the effects on repolarization. Some of them are heterologous expression systems (for studying ion currents), disaggregated cells (for studying ion currents), isolated tissue (for screening large numbers of compounds) and isolated intact heart (for screening large numbers of compounds). In vivo models can be made using multi-lead ECG in conscious or anaesthetized guinea pigs, rabbits, dogs or pigs. The QT should be measured form at least three successive beats. There are several others studies to determine this effect but

there is not a single, standardized and uniform method for pre-clinical screening of the effects of drug effects on cardiac repolarization.

CONCLUSION

AP duration of the ventricular cells is a major determinant of the QT interval. Genetic or acquired factors that alter the delicate balance between inward and outward currents during phase 2 and 3 of the AP significantly prolong its duration, and consequently create a substrate for TdP. The mechanism by which a prolonged AP leads to TdP is still a matter of controversy [44, 55].

QTc prolongation is associated with higher incidence of TdP, however this is not the only cause of TdP. Other factors may play an important role, e.g. myocardium heterogeneity, drug-drug interaction, genetic polymorphism, electrolyte disturbances, reduced repolarization reserve, and sympathe-tic activity. All of them must be considered in clinical pharmacology to understand the real risk of a drug to prolong the QT-interval and produce lifethreatening arrhythmias.

Fig. (1). Representation of the ionic currents and ion transporters involved in the different phases of the cardiac action potential (AP). Therefore, depolarizing currents (phase 0 and 1) are due to an “inward” flux of positive charges (Na+ and Ca2+) into the cells, and consequently they move the negative resting membrane potential toward more positive voltage values. While, repolarization is achieved by a delayed “outward” flux of positive charges (K+) out of the cells. The particularity of the cardiac AP, as compared to neuronal AP, is the “plateau” phase 2 which is mainly due to the inward flux of Ca2+ significantly prolonging the AP duration (about 200–300 ms).

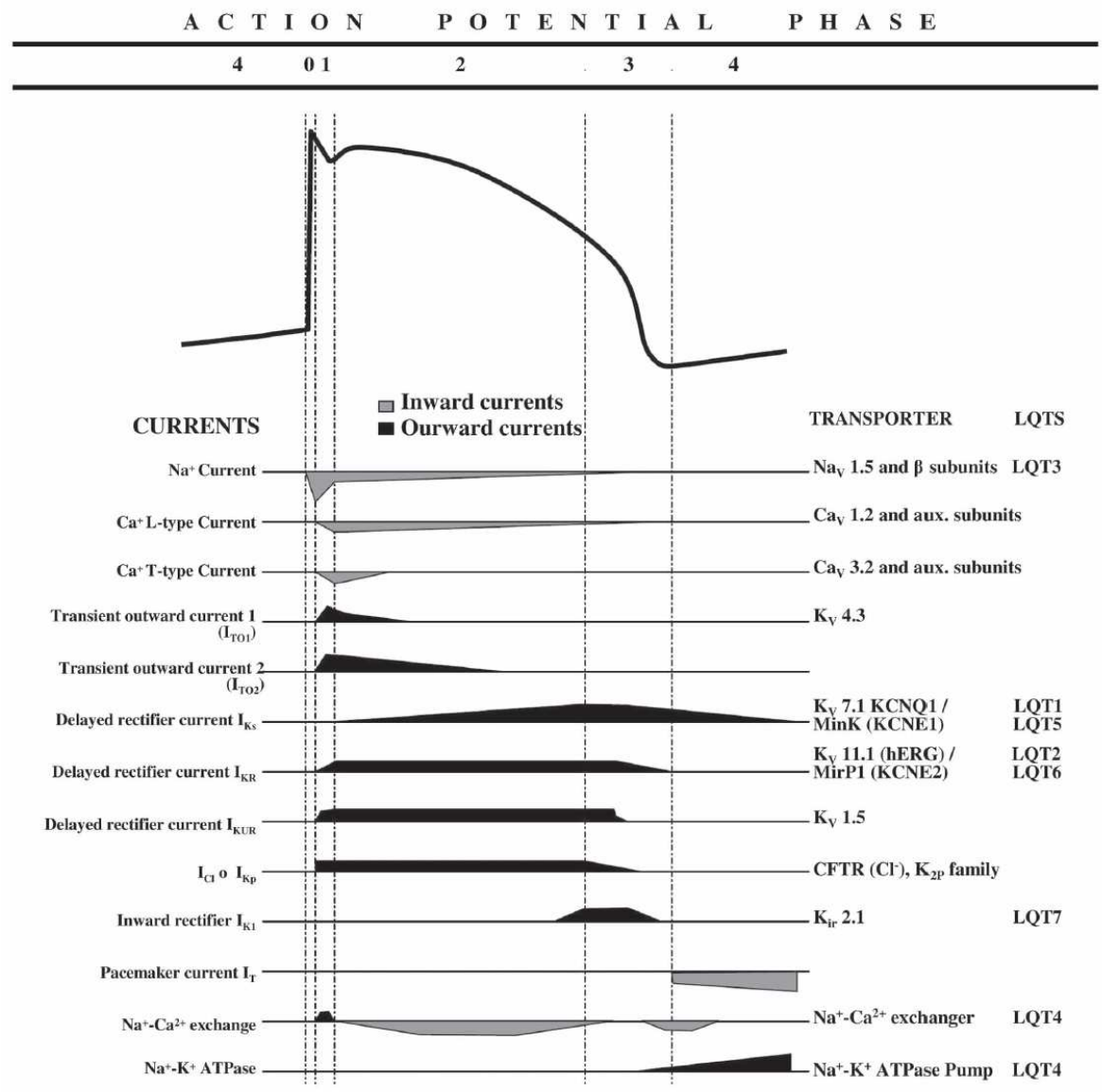

Fig. (2). Main K+ currents contributing to repolarization of the cardiac action potential (upper left, the corresponding genes or proteins are indicated in parentheses) and drug-induced TdP cardiac arrhythmias.

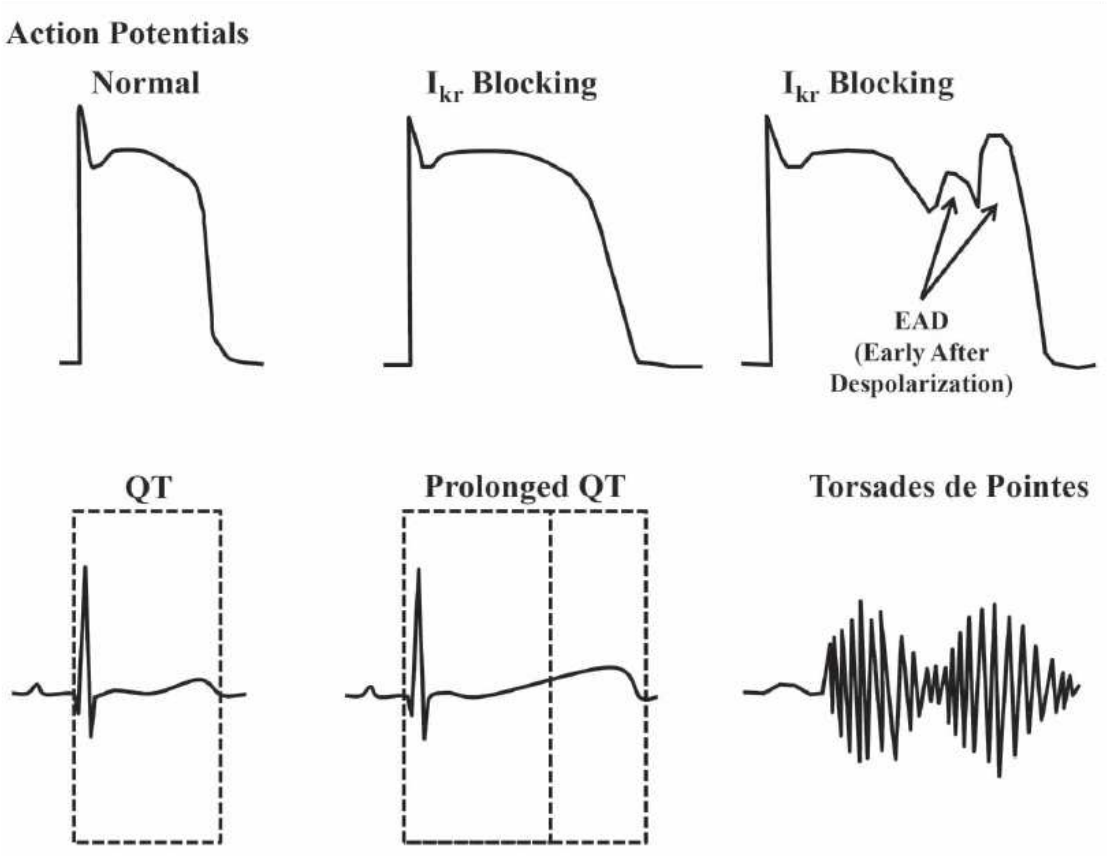

Fig. (3). Action potential of Purkinje fiber. The figure shows the seven LQTS genes and their responsible ionic currents in each phase. EAD, early alter depolarization; DAD, delayed after depolarization.

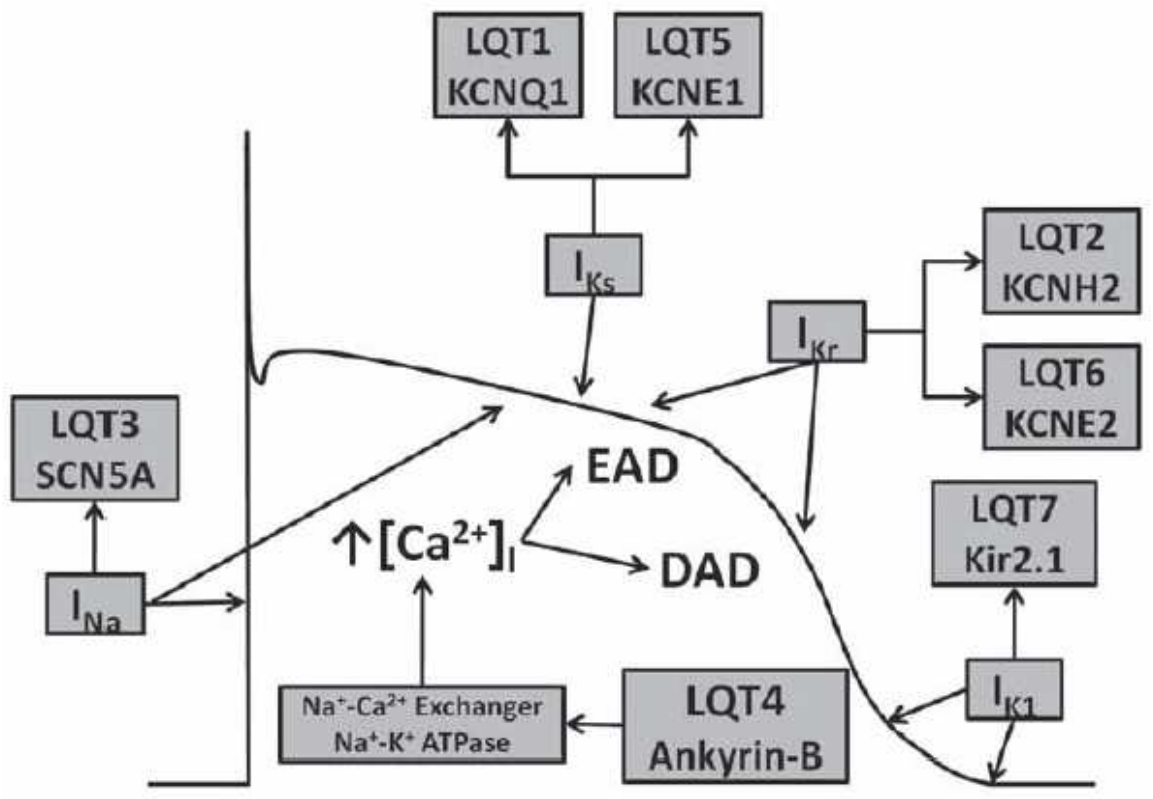

Fig. (4). Schematic representation of the HERG channel. The fourth membrane's panning unit (S4) contains positively charged residues and functions as the voltage sensor. The residues between S5 and S6 form the ion selective pore.

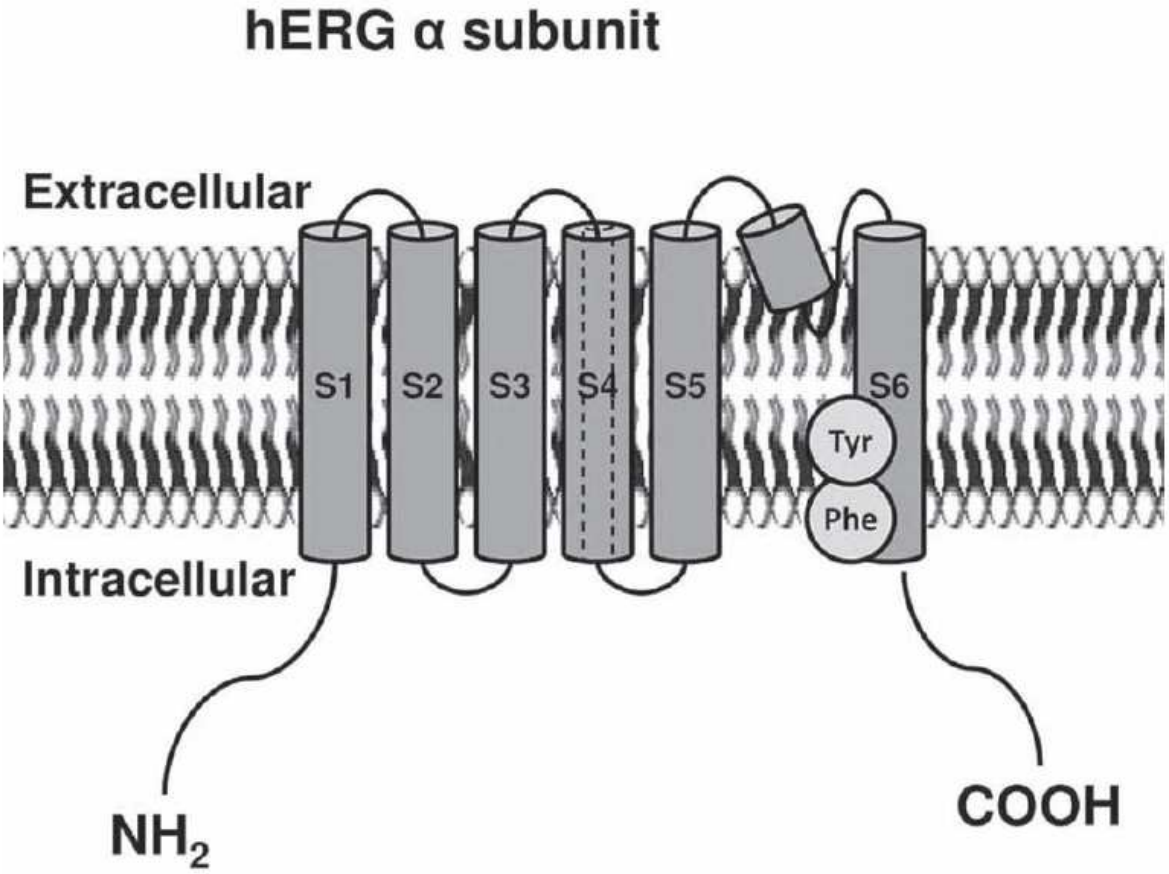

Fig. (5). Heterogeneity induced by drugs. The drugs that increase heterogeneity can induce a functional reentry and generate or maintain tachyarrhythmias.

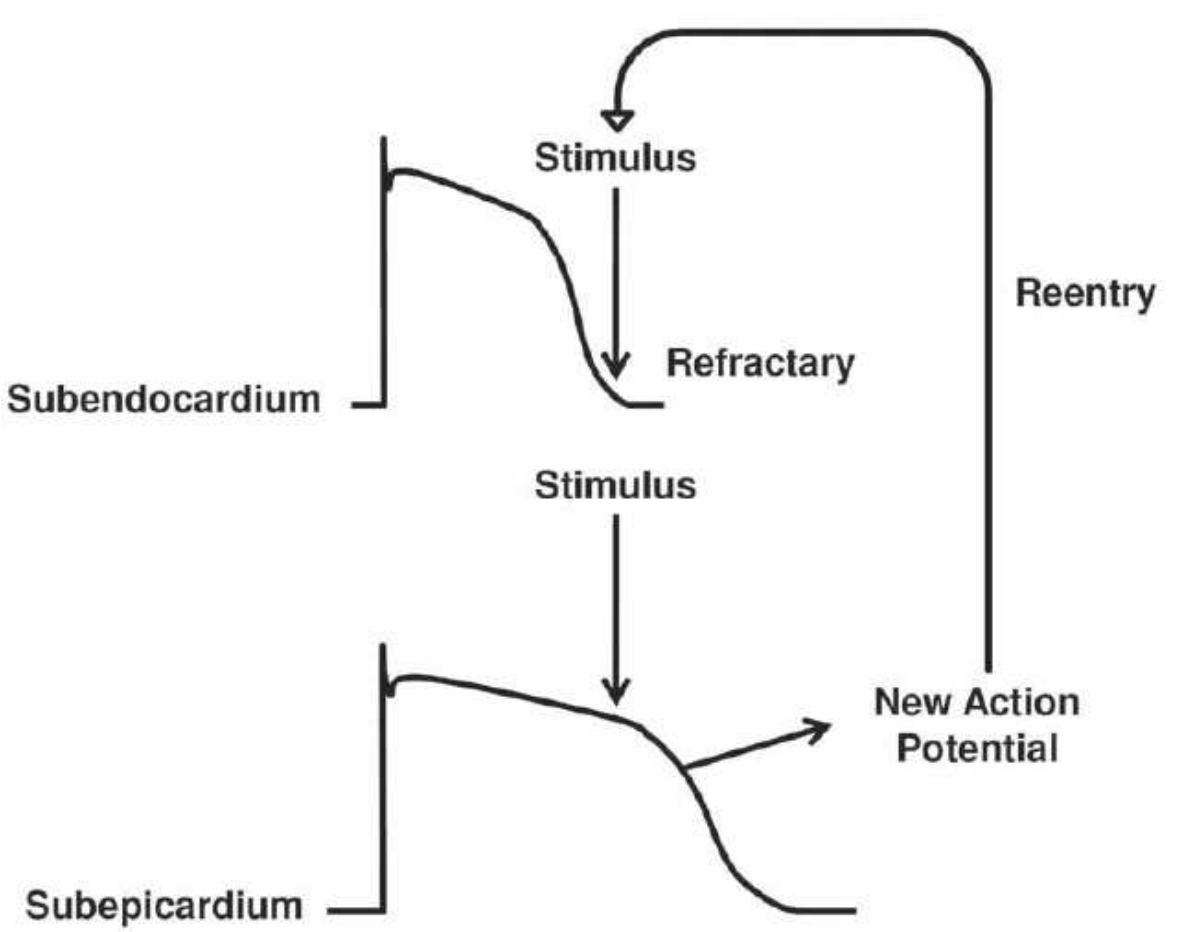

Table 1. Corrected QT Interval Values according to the Committee for Propietary Medicinal Products [12]

	Adult Males	Adult Females
Normal	<430 ms	<450 ms
Borderline	431-450	451-470
Prolonged	>450	>470

Table 2. Formulas for QT-Interval Correction by Heart Rate

Name	Formula
Bazzet	$QT_c = \frac{QT}{\sqrt{RR'}}$
Fridericia	$QT_c = \frac{QT}{RR'^{1/3}}$
Framingham	$QT_c = (QT + 0.156x(1 - RR'))$
Hodges	$QT_c = (QT + 1.75x(HR - 60))$

HR: Heart Rate, RR': Interval between two R waves measured in milliseconds.

Table 3. Channelopathies associated with Congenital Long QT Syndrome (LQTS)

Syndrome	Mutated Gen	Encode	Results
LQT1	KCNQ1	Alfa subunit of IKs channel: ❖ Channel protein with six transmembrane domains (S1-S6), ❖ Voltage sensor (S4) ❖ Potassium selective pore	"Loss-of-function": Abnormal subunits do not coassembles with normal subunits (50% reduction in the number of functional channels), or coassembles resulting in channel function depression by more than 50%
LQT2	KCNH2	Alfa subunit of IKr channel HERG (the "human ether-a-go-go related" gene): ❖ channel protein (S1-S6), ❖ voltage sensor (S4) ❖ potassium selective pore.	Loss-of-function or dominant negative IKr suppression to decrease the repolarizing currents. This mutation is responsible of 45 % of LQTS.
LQT3	SCN5A	Alpha subunit of the cardiac sodium channel with four homologous domains, each of which contains six transmembrane segments.	"Gain of function" abnormality: channels can also reopen during the plateau phase of the action potential and prolong the action potencial duration. Responsible of 3-4 % of LQTS [25].
LQT4	Ankyrin–B	Essential to recognize certain proteins such as sodium/calcium exchanger, sodium – potassium ATPase and IP3 receptors and to ensure that they are inserted into appropriate domains of cell membranes [26].	Decrease of function of sodium – potassium ATPase and an increase in intracellular calcium. These changes are responsible for the generation of early after depolarizations (EADs) and delayed after depolarizations (DADs).
LQT5	KCNE1 (mimK)	Encodes a membrane protein that consists of 129 amino acids with a single putative transmembrane domain, but not a voltage sensor and potassium selective pore. It forms the beta subunit of IKs [27].	KCNQ1 and KCNE1 coassemble to form the slow component of the delayed rectifier K+ ; named current (IKs) channels.
LQT6	KCNE2	*minK*-related peptide 1 (MiRP1) which is the beta subunit of IKr.	Like with KCNQ1, mutations of the gene cause loss-of-function or dominant negative IKr suppression to decrease the repolarizing currents.
LQT7	KCNJ2	Channel for IKir2.1 (inward rectifier K+ current, IK1). This current is relevant during the late repolarization phase.	Its reduction prolongs the terminal phase of the cardiac action potential.
LQT8	CACNA1C	Codify Cav1.2 protein, involved in L-Type Ca2+current calcium channel.	This mutation increase intracellular calcium.
LQT9	CAV3	Codifies Caveolin 3 protein, involved in sodium channel.	This mutation increase intracellular sodium.
LQT10	SCN4B	Codifies Navb4 protein, involved in sodium channel too.	This mutation increase intracellular sodium.

Table 4. Effect of Blockage of Different Ion Channels in the Four Main Cell Types in Ventricles.

	Purkinje	Endo	Mid-Myocardium	Subepimyocardium
I_{kr} block	+++	+/-	+++	+/-
I_{ks} block	+/-	++	++	++
I_{k1} block	-	+/-	-	-
Activation of late I_{Na}	++++	++	++++	++
Activation of I_{Ca}	+++	+/-	+++	+/-

++++ = maximum action potential prolongation; +++ or ++: intermediate action potential prolongation; +/-: little or no action potential prolongation.

Table 5. Conformational Characteriszation of HERG Channel states

Status	Conformational Changes	Consequences
Closed	• Inner helices (the four S6 domains) are tilted and interweave near the cytoplasmic interface.	• This conformation creates a thin aperture that avoids passage of ions.
Open	• The positively charged S4 which acts as voltage sensor and shows a slow movement outward. • Gly648 amino acid acts as the articulation point for bending of the S6 domain that underlies channel opening and closing.	• The slow movement of S4 causes the slow activation kinetics of the HERG channel. • The outward translation of S4 domain finally causes opening of an activation gate by rotation and kinking of the S6 domain that lines the pore.
Inactive	• The extracellular inactivation gate closes. • The S5/P-loop region is critical for inactivation.	• The channel is not able to conduct K+ currents.

Table 6. Possible Drug-Drug Interactions of Drug that prolong QTc and are metabbolized by Cytochromes

Cytochrome	Substrates that prolong QTc		Cytochrome Inhibitors	
CYP1A2	Amitriptyline Clozapine Desipramine Imipramine Nortriptyline		Cimetidine Ciprofloxacin Diltiazem Erythromycin Fluvoxamine	Grapefruit juice Mexiletine Norfloxacin Ritonavir Tacrine
CYP2C	Amitriptyline Imipramine		Amiodarone Cimetidine Fluconazole Fluoxetine	Fluvastatin Fluvoxamine Omeprazole Ritonavir
CYP2D6	Amitriptyline Clozapine Desipramine Flecainide Fluoxetine Haloperidol Imipramine	Mexiletine Nortriptyline Paroxetine Risperidone Sertindole Tamoxifen Thioridazine	Amiodarone Cimetidine Fluoxetine Haloperidol Paroxetine	Propafenone Quinidine Ritonavir Thioridazine
CYP3A4	Amiodarone Cisapride Disopyramide Erythromycin Imipramine Quinidine	Sertraline Tacrolimus Tamoxifen Terfenadine Pimozide	Amiodarone Cimetidine Clarithromycin Diltiazem Erythromycin Fluconazole Fluoxetine Fluvoxamine Indinavir	Itraconazole Ketoconazole Metronidazole Nefazodone Nelfinavir Omeprazole Quinidine Ritonavir Saquinavir

Table 7. Causes that can induce QTc- Prolongation

- Bradycardia
- Central nervous System disease (intracranial trauma, subarachnoid hemorrhage, stroke)
- Congenital long QT syndrome
- Dysautonomy (Diabetes mellitus, amyloidosis, others)
- Elderly
- Electrolyte disturbance (hypomagnesemia, hypokalemia)
- Heart failure
- Hypoglycaemia
- Hypothermia
- Hypothyroidism
- Ion channel polymorphism
- Ischemic myocardiopathy
- Obesity
- Reduced repolarization reserve (see the text)

REFERENCES

[1] Kannankeril PJ, Roden DM. Drug-induced long QT and torsade de pointes: Recent advances. Curr Opin Cardiol 2007; 22: 3943.

[2] Malik M, Camm AJ. Evaluation of drug-induced QT interval prolongation: implications for drug approval and labelling. Drug Saf 2001; 24: 323-51.

[3] Roden DM. Drug-Induced Prolongation of the QT Interval. N Engl J Med 2004; 350: 1013-22.

[4] Fenichel RR. Drug-Induced Torsades de Pointes and implications for drug development. J Cardiovascular Electrophysiol 2004; 15:475-95.

[5] Arizona CERT. Drugs with a risk of torsades de pointes, Available from: http://www.qtdrugs.org/medical-pros/drug-lists/bycategory.cfm [Accessed April 30, 2008].

[6] Tartini R, Kappenberger L, Steinbrunn W, Meyer UA. Dangerous interaction between amiodarone and quinidine. Lancet 1982; 1: 1327-9.

[7] Woosley RL. Cardiac actions of antihistamines. Ann Rev Pharmacol Toxicol 1996; 36: 233-52.

[8] Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. Pharmacotherapy 2001; 21: 1468-72.

[9] Keating MT, Sanguinetti MC. Molecular and cellular mechanisms of cardiac arrhythmias. Cell 2001; 104: 569-80.

[10] Chern EC. Congenital and acquired long QT syndrome. current concepts and management. Cardiol Rev 2004; 12: 222-34.

[11] Anderson ME, Al Khatib SM, Roden DM et al. Cardiac repolarization: current knowledge, critical gaps, and new approaches to drug development and patient management. Am Heart J 2002; 144: 769-81.

[12] Committee for Proprietary Medicinal Products. Points to consider: The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. The European Agency for the Evaluation of Medicinal Products 1997.

[13] Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920; (7): 353-70.

[14] Fridericia LS. The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease. Acta Medica Scandinavica 1920; (53): 469-86.

[15] Morissette P, Hreiche R, Turgeon J. Drug-induced long QT syndrome and torsade de pointes. Can J Cardiol 2005; 21: 857-64.

[16] Antzelevitch C, Shimizu W. Cellular mechanisms underlying the long QT syndrome. Curr Opin Cardiol 2002; 17: 43-51.

[17] Prosser JM, Mills A, Rhim ES, et al. Torsade de pointes caused by polypharmacy and substance abuse in a patient with human immunodeficiency virus. Int J Emerg Med 2008; 1(3): 217-20.

[18] Sanguinetti MC, Jiang C, Curran ME, Keating MT. A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the IKr potassium channel. Cell 1995; 81: 299-307.

[19] Gintant GA. Two components of delayed rectifier current in canine atrium and ventricle. Does Iks play a role in the reverse rate dependence of class III agents? Circ Res 1996; 78: 26-37.

[20] Li GR, Feng J, Yue L, et al. Evidence for two components of delayed rectifier K+ current in human ventricular myocytes. Circ Res 1996; 78: 689-96.

[21] Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the QT interval, and sudden death. Am Heart J 1957; 54: 59-68.

[22] Romano C, Gemme G, Pongiglione R. Rare cardiac arrythmias of the pediatric age. II. Syncopal attacks due to paroxysmal ventricular fibrillation (Presentation oflst Case in Italian Pediatric Literature). Clin Pediatr (Bologna) 1963; 45: 656-83.

[23] Ward OC. A new familial cardiac syndrome in children. J Ir Med Assoc 1964; 54: 103-6.

[24] Modell SM, Lehmann MH. The long QT syndrome family of cardiac ion channelopathies: a huge review. Genet Med 2006; 8: 143-55.

[25] Locati EH, Zareba W, Moss AJ, et al. Age- and sex-related differences in clinical manifestations in patients with congenital Iong-QT syndrome: findings from the international LQTS registry. Circulation 1998; 97: 2237-44.

[26] Chan AS, Isbister GK, Kirkpatrick CM, et al. Assessing risk of a prolonged QT interval-a survey of emergency physicians. Int J Emerg Med 2008; 1(1): 35-41.

[27] Paran Y, Mashav N, Henis O, et al. Drug-induced torsades de pointes in patients aged 80 years or more. Anadolu Kardiyol Derg 2008; 8(4): 260-5.

[28] Kääb S, Pfeufer A, Hinterseer M, et al. Long QT syndrome. Why does sex matter? Z Kardiol 2004; 93: 641-5.

[29] Splawski I. Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. Circulation 2000; 102: 1178-85.

[30] Selzer A, Wray HW. Quinidine syncope. Paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. Circulation 1964; 30: 17-26.

[31] Roden DM, Balser JR, George AL Jr, Anderson ME. Cardiac ion channels. Annu Rev Physiol 2002; 64: 431-75.

[32] Haverkamp W, Breithardt G, Camm AJ, et al. The potential for QT prolongation and pro-arrhythmia by non-anti-arrhythmic drugs: Clinical and regulatory implications. Report on a Policy Conference of the European Society of Cardiology. Cardiovasc Res 2000; 47: 219-33.

[33] De Ponti F, Poluzzi E, Montanaro N. Organising evidence on QT prolongation and occurrence of torsades de pointes with nonantiarrhythmic drugs: a call for consensus. Eur J Clin Pharmacol 2001; 57: 185-209.

[34] Fenichel RR. Development of drugs that alter ventricular repolarization. Am J Ther 2002; 9: 127-39.

[35] Warmke JW, Ganetzky B. A family of potassium channel genes related to eag in drosophila and mammals. Proc Natl Acad Sci USA 1994; 91: 3438-42.

[36] Trudeau MC, Warmke JW, Ganetzky B, Robertson GA. HERG, a human inward rectifier in the voltage-gated potassium channel family. Science 1995; 269: 92-5.

[37] Zünkler BJ. Human ether-a-go-go-related (HERG) gene and ATPsensitive potassium channels as targets for adverse drug effects. Pharmacol Therapeut 2006; 112: 12-37.

[38] Shoeb F, Malykhina AP, Akbarali HI. Cloning and functional characterization of the smooth muscle ether-a-go-go-related gene K+channel. Potential role of a conserved amino acid substitution in the S4 region. J Biol Chem 2003; 278: 2503-14.

[39] Bianchi L, Wible B, Arcangeli A, et al. HERG encodes a K+ current highly conserved in tumors of different histogenesis: A selective advantage for cancer cells? Cancer Res 1998; 58: 815-22.

[40] Roche B, Kijtawornrat A, Hamlin R, et al. Relationship between prolongation of QTc and prolongation of the peak of T (Tp) to the end of T(Te). J Pharmacol Toxicol Methods 2005; 52: 178-81.

[41] Hii JT, Wyse DG, Gillis AM, et al. Precordial QT interval dispersion as a marker of torsade de pointes. Disparate effects of class Ia antiarrhythmic drugs and amiodarone. Circulation 1992; 86(5): 1376-82.

[42] Antzelevitch C. Drug-induced spatial dispersion of repolarization. Cardiol J 2008; 15(2): 100-21.

[43] Keivanidou A, Arnaoutoglou C, Krommydas A, et al. Moxifloxacin induced acquired long QT syndrome in a patient under class III antiarrhythmic therapy. Cardiol J 2009; 16(2): 172-4.

[44] Stockley. Interacciones Farmacológicas. 2da Ed. Pharma Ed 2007. Barcelona.

[45] Alistair JJ, Wood MD. Drug-induced prolongation of the QT interval. Neng J Med 2004; 350(10): 1013-22.

[46] Sicouri S, Antzelevithc C. Sudden cardiac death secondary to antidepressant and antipsychotic drugs. Expert Opin Drug Saf 2008; 7(2): 181-94.

[47] Badshah A, Mirza B, Janjua M, et al. Amiodarone-induced torsade de pointes in a patient with wolff-Parkinson-white syndrome. Hellenic J Cardiol 2009; 50(3): 224-6.

[48] Raschi E, Poluzzi E, Zuliani C, et al. Exposure to antibacterial agents with QT liability in 14 European countries: trends over an 8-year period. Br J Clin Pharmacol 2009; 67(1): 88-98.

[49] Sakaguchi T, Itoh H, Ding WG, et al. Hydroxyzine, a first generation H(1)-receptor antagonist, inhibits human ether-a-go-gorelated gene (HERG) current and causes syncope in a patient with the HERG mutation. J Pharmacol Sci 2008; 108(4): 462-71.

[50] Shojaie M, Eshraghian A. Primary hypothyroidism presenting with Torsades de pointes type tachycardia: a case report. Cases J 2008; 1(1): 298.

[51] Roden DM. Taking the ¨idio¨ out of ¨idiosyncratic¨:Predicting torsades de pointes. PACE 1998; 21: 1029-34.

[52] Webster R, Leishman D, Walker D, et al. Towards a drug concentration effect relationship for QT prolongation and torsades de pointes. Curr Opin Drug Discov Dev 2002; 5: 116-26.

[53] Anyukhovsky EP, Sosunov EA, Rosen MR. Regional differences in electrophysiological properties of epicardium, midmyocardium, and endocardium. In vitro and in vivo correlations. Circulation 1996; 94: 1981-8.

[54] Ye L, Feng J, Li GR, Nattel S. Transient outward and delayed rectifier currents in canine atrium: properties and role of isolation methods. Am J Physiol 1996; 272: H1292-301.

[55] Sims C, Reisenweber S, Viswanathan PC, et al. Sex, age, and regional differences in L-type calcium current are important determinants of arrhythmia phenotype in rabbit hearts with druginduced long QT type 2. Circ Res 2008; 102(9): e86-100.