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Review / *Derleme*

Drug-Induced QT Interval Prolongation and Torsade De Pointes: Identification of Risk Factors

İlaca Bağlı QT İnterval Uzaması ve Torsade De Pointes: Risk Faktörlerinin Saptanması

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A progressively increasing number of non-cardiac agents prolong cardiac repolarization predisposing to polymorphic ventricular tachycardia, termed torsade de pointes (TdP), and sudden cardiac death. Drug-induced QT interval prolongation is considered the most frequent cause of withdrawal or relabeling of marketed drugs. Although the exact mechanisms are incompletely understood, the majority of these agents exhibit direct electrophysiological effects on the rapidly activating delayed rectifier potassium current. Additionally, pharmacokinetic interactions with drugs known to inhibit cytochrome P450 isoenzymes may enhance the torsadogenic potential of these agents. Genetic analyses have identified the subclinical congenital form in 5-10% of patients with drug-induced long QT syndrome. The likelihood of drug-induced long QT syndrome is difficult to be predicted in routine clinical practice. However, clinical history may reveal well-established risk factors that act as "effect amplifiers" making an otherwise relatively safe drug dangerous with regard to risk for TdP. The current review describes the underlying mechanisms of drug-induced QT interval prolongation and TdP as well as the risk factors that predispose to this potentially life-threatening conditions.

Key words: Drugs; long QT interval; torsade de pointes; sudden cardiac death.

Kardiyoloji alanı dışında kullanılmakta olan önemli sayıda ilaç, Torsade de pointes (TdP), olarak isimlendirilen, polimorfik ventrikül taşikardisine ve ani kardiyak ölüme zemin hazırlayan kardiyak repolarizasyonu uzatmaktadır Piyasadaki ilaçların toplatılmasının ya da yeniden sürülmesinin en sık nedeninin ilaca bağlı QT interval uzaması olduğu görülmektedir. Tam işleyişleri bütünüyle anlaşılamamasına rağmen, bu ilaçların çoğunluğu gecikmiş düzenleyici potasyum akımını hızlıca etkinleştirerek doğrudan elektrofizyolojik etkiler gösterir. Ek olarak, sitokrom P450 isoenzimlerini baskıladığı bilinen ilaçlar ile farmakokinetik etkileşimleri bu ilaçların proaritmik etkilerini artırabilir. Genetik analizler, ilaca bağlı uzun QT sendromlu hastaların %5-10'unda doğuştan subklinik form ortaya koymuştur. İlaca bağlı uzun QT sendromu ihtimalinin rutin klinik uygulamada tahmin edilmesi zordur. Ancak, klinik öykü, normalde TdP riskiaçısından oldukça güvenli bir ilacı tehlikeli hale sokan "etki yükseltici" olarak rol oynayan iyi belirlenmiş risk faktörlerini açığa çıkarabilir. Bu derlemede ilaca bağlı QT uzaması ve TdP mekanizmaları ve yaşamı tehdit eden durumlara zemin hazırlayan risk faktörleri ele alınmaktadır.

Anahtar sözcükler: İlaçlar; uzun QT aralığı; torsade de pointes; ani kardiyak ölüm.

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A continuously rising number of non-antiarrhythmic agents have been shown to prolong cardiac repolarization predisposing to a certain type of polymorphic ventricular tachycardia termed torsade de pointes (TdP) and sudden cardiac death.[1-5] Drug-induced QT interval prolongation is considered the most frequent cause of withdrawal or relabeling of marketed drugs in the last decade, but this adverse drug reaction is assumed to be rare (less than one in 100 000).[5] Drugs with proven lengthening of the QT interval or a definite association with TdP are common and are estimated to compose approximately 2-3% of all prescriptions written.[6] Antibiotics and psychotropic drugs are the most common non-cardiac drugs involved in drug-induced QT interval prolongation, which in the vast majority of cases are prescribed by non-cardiologists.[1,5,7] Drugs implicated in QT interval prolongation and TdP are listed in Table 1.

The prescription of non-cardiac QT-prolonging agents has been recently associated with a significantly increased risk of sudden cardiac death in the general population. The risk of death has been showed to be higher in women and in recent starters.[8] However, the likelihood of drug-induced TdP is difficult to be predicted in routine clinical practice. The present review describes the underlying mechanisms of drug-induced QT interval prolongation and TdP as well as the risk factors that predispose to this potentially life-threatening condition.

ECG MARKERS OF VENTRICULAR REPOLARIZATION

The QT interval is considered as the ECG index of ventricular repolarization. Correct measurement of the QT interval is of paramount importance for the diagnosis of drug-induced QT interval prolongation. Most physicians, including many cardiologists, cannot recognize a long QT interval. Viskin et al.[9] have shown that correct classification of the QT interval as either "long" or "normal" was achieved by 96% of QT experts and 62% of arrhythmia experts, but by less than 25% of cardiologists and non-cardiologists. The QT interval is measured from the beginning of the QRS complex to the end of the T wave on the surface electrocardiogram (ECG). Despite the fact that there are no sufficient data regarding which lead or leads to use for QT interval measurement, lead II is considered the appropriate one because the vectors of repolarization result in a long single wave rather than discrete T and U waves.[10] The QT interval is influenced by the heart rate. Rate acceleration normally leads to QT shortening, whereas bradycardia leads to QT lengthening.[11] The RR interval preceding the QT interval should be measured for rate correction.[11,12] Several formulas may be used to correct the QT interval (QTc). The most commonly used formulas are Fridericia's cube root formula ($QTc = QT/RR^{1/3}$) and Bazett's square root formula ($QTc=QT/RR^{1/2}$). Fridericia's equation is preferred at extremes of physiological heart rate.[11,12] Apart from heart rate, the duration of the QT interval is also influenced by sympathovagal activity, drugs, genetic abnormalities, electrolyte disorders, cardiac or metabolic diseases and changes of cardiac afterload.[12]

Table 1. Drugs implicated in drug-induced QT interval prolongation and TdP

Category	Drugs
Antiarrhythmics	Disopyramide, procainamide, quinidine, mexiletine, propafenone, flecainide, d, l-sotalol, amiodarone, bretylium, dofetilide, ibutilide, azimilide, ajmaline
Antimicrobials	Erythromycin, clarithromycin, azithromycin, levofloxacin, moxifloxacin, sparfloxacin, gatifloxacin, grepafloxacin, trimethoprim-sulfamethoxazole, pentamidine, quinine, itraconazole, ketoconazole, fluconazole, chloroquine, halofantrine, mefloquine, amantadine, spiramycin
Antihistamines	Astemizole, diphenhydramine, ebastine, terfenadine, hydroxyzine
Antidepressants	Doxepin, venlafaxine, fluoxetine, desipramine, imipramine, clomipramine, paroxetine, sertraline, citalopram
Antipsychotics	Chlorpromazine, prochlorperazine, trifluoperazine, haloperidol, fluphenazine, felbamate, thioridazine, droperidol, pimozide, mesoridazine, risperidone, quetiapine, ziprasidone, lithium, chloral hydrate, pericycline, sertindole, sultopride, zimeldine, maprotiline
Diuretics	Indapamide, thiazide, furosemide
Gastrointestinal stimulants	Cisapride, metoclopramide, domperidone
Others	Albuterol, salmeterol, arsenic trioxide, aconitine, veratridine, vincamine, terodiline, tacrolimus budipine, tizanidine tiapride, cocaine, organophosphorus compounds

QTc values greater than 450 msec in men and 470 msec in women are considered abnormal. Values ranging between 430-450 msec in men and 450-470 msec in women are considered borderline.[12] The QTc interval is the best available predictor of TdP episodes.[13] The majority of drug-induced TdP occur with QTc values of more than 500 msec.[14] Data from patients with congenital long QT syndrome (LQTS) have shown that a QTc interval greater than 500 msec is related to an increased risk for arrhythmic events.[15] However, there is no established threshold below which prolongation of the QTc interval is considered free of proarrhythmic events. In terms of QTc change from baseline on treatment, it has been recommended

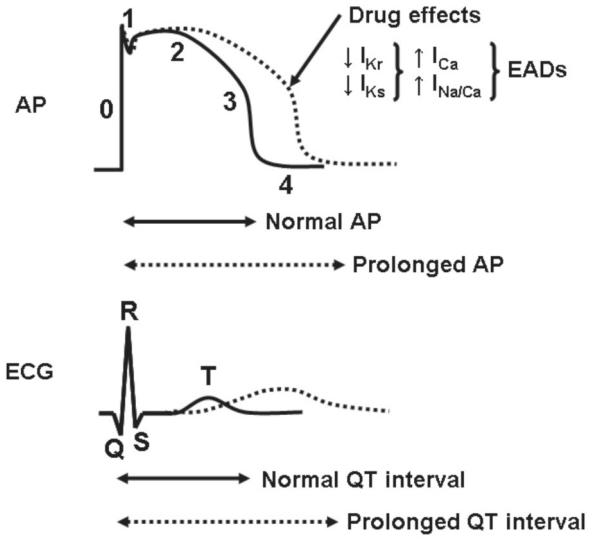

Fig. 1. *Relationship between the phases of ventricular transmembrane action potential (AP) and the surface electrocardiogram (ECG). A reduction of outward currents (I_{Kr}, I_{Ks}) during phase 2 and 3 of the AP leads to QT interval prolongation. Activation of inward depolarizing currents (I_{Ca}, $I_{Na/Ca}$) may then give rise to early afterdepolarizations (EADs).*

that an increase of 30 ms is a potential cause for concern and that a 60 ms increase is a definite cause for concern.[16] Additionally, QT dispersion (defined as the difference between the maximum and minimum QT interval of the 12-leads) greater than 100 ms is considered abnormal.[16]

New ECG markers of ventricular repolarization including the Tpeak-end interval and the Tpeak-end/QT ratio are still under investigation. The Tpeak-end interval in precordial leads is considered as an index of transmural dispersion of repolarization, while the Tp-e interval measured in limb leads is more likely to reflect global dispersion, including apico-basal and inter-ventricular dispersion of repolarization.[17] The Tpeak-end interval has been reported to be prolonged in congenital LQTS and to predict TdP in acquired LQTS.[18] Yamaguchi et al.[19] have demonstrated that the Tpeak-end/QT ratio is a better predictor of TdP as compared to QTc interval and QT dispersion in patients with acquired LQTS. In their study, Tpeak-end/QT ratio greater than 0.28 was strongly associated with risk of developing TdP.[19]

MECHANISMS OF DRUG-INDUCED QT INTERVAL PROLONGATION AND TORSADE DE POINTES

At a cellular level, the repolarisation phase is driven predominantly by the outward movement of potassium ions. Two important potassium currents participating in ventricular repolarisation are the components of the delayed rectifier current, I_{Kr} (rapid) and I_{Ks} (slow). The majority of non-cardiac QT-prolonging agents exhibit direct electrophysiological effects on the rapidly activating delayed rectifier I_{Kr} current encoded by the human ether-a-go-go-related gene (HERG, now termed KCNH2).[1,5] However, many drugs block multiple cardiac ion channels (I_{Kr}, I_{Ks}, I_{Na}) leading to a more complex shift of action potential morphology.[1,5] As showed in Figure 1, I_{Kr} blockade leads to a delay in phase 3 of repolarization of the action potential (reflected as QT interval prolongation on surface ECG). Activation of inward depolarizing currents (most likely L-type calcium channels or sodium-calcium exchange current) may then give rise to early afterdepolarizations that appear as depolarizing oscillations in membrane voltage during phases 2 and 3 of the action potential.[20-22] Early afterdepolarizations that reach the threshold voltage cause ventricular extrasystoles. These phenomena are more readily induced in the His-Purkinje network and also in M cells from the mid ventricular myocardium.[20-22] Compared to subendocardial or subepicardial cells, M cells show much more pronounced action potential prolongation in response to I_{Kr} blockade.[20-22] The resultant heterogeneity in ventricular repolarization creates a zone of functional refractoriness in the mid myocardial layer, which is probably the basis of the re-entry that is sustaining the TdP.[20-22] A "short-long-short" sequence (an extrasystole, followed by a post-extrasystolic pause) precedes the onset of TdP in most cases.[23] An example of a self-terminated episode of TdP preceded by the characteristic "short-long-short" sequence in a patient with drug-induced QT interval prolongation is shown in Figure 2.

Furthermore, pharmacokinetic interactions with drugs known to inhibit cytochrome P450 isoenzymes (CYP3A4 or CYP2D6) enhance the torsadogenic potential of these agents by decreasing their clearance.[1,5,20] CYP3A4 activity can be inhibited by a wide variety of drugs including some macrolide antibiotics, ketoconazole and related antifungals, cimetidine, fluoxetine, protease inhibitors, and amiodarone. In addition, many non-drug factors, including age, smoking, hepatic disease, genetic polymorphisms and grapefruit juice may lead to CYP3A4 inhibition.[7] Finally,

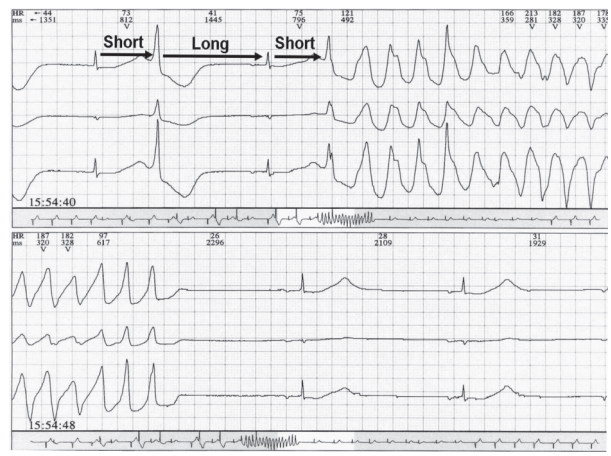

Fig. 2. *Example of a self-terminated episode of TdP preceded by the characteristic "short-long-short" sequence in a patient with drug-induced QT interval prolongation.*

Table 2. Risk factors for drug-induced QT interval prolongation and TdP

Risk factors
Female sex
Advanced age
Electrolyte imbalances (hypokalemia, hypomagnesemia, hypocalcemia)
Bradycardia
Congestive heart failure
Cardiomyopathies
Cardiac hypertrophy
Anorexia nervosa, starvation
Hypothermia
Hypothyroidism
Renal and liver insufficiency
Cytochrome P450 isoenzyme CYP3A4 inhibitors
Baseline QT interval prolongation
Ion channel mutations/polymorphisms
Polypharmacy

cytochrome P450 CYP2D6 is functionally absent in approximately 7% of white and black individuals (poor metabolizer group) because of loss of function gene variants.[24]

RISK FACTORS FOR DRUG-INDUCED QT INTERVAL PROLONGATION AND TDP

The susceptibility of drug-induced QT interval prolongation varies significantly among individuals. The unifying concept of "reduced cardiac repolarization reserve" has been proposed to explain the mechanism by which some patients are rendered more susceptible than others to the QT-prolonging effects of drugs.[5,20,21] Silent mutations and/or polymorphisms in genes encoding cardiac ion channels leading to a reduced cardiac repolarization reserve hold the key to understanding why healthy individuals will be exposed to risk for LQTS when taking medication for unrelated causes.[5,20,21,25,26] Genetic analyses have identified the subclinical congenital form in 5-10% of patients with drug-induced LQTS.[26] Mutations have been reported in KCNQ1, KCNH2, KCNE1, KCNE2 and SCN5A genes.[5,20,21,25,26] Therefore, the administration of an I_{Kr} current blocking agent may significantly prolong the QT interval in these silent carriers predisposing them to TdP and sudden cardiac death.

The likelihood of drug-induced LQTS is difficult to be predicted in routine clinical practice. However, clinical history may reveal well-established risk factors that act as "effect amplifiers" making an otherwise relatively safe drug dangerous with regard to risk for TdP (Table 2). These risk factors include female gender, cardiac hypertrophy, chronic heart failure, cardiomyopathies, bradycardia, electrolyte imbalance (hypokalemia, hypomagnesemia, hypocalcemia), digitalis therapy, hypothermia, and hypothyroidism.[1,5,7,11,12,20,21] The vast majority of patients with drug-induced TdP display at least one of these risk factors. In a recent study including 21 patients with drug-induced QT interval prolongation, advanced age (>60 years), female gender, hypertension and paroxysmal atrial tachyarrhytmias were the most common identifiable pre-existing risk factors. In this study, TdP and cardiac arrest events were significantly associated with a QTc interval >510 ms.[27] It has been estimated that approximately 70% of cases of drug-induced TdP occur in females.[28] A reduced cardiac repolarization reserve closely related to sex steroids has been proposed to explain the increased propensity of women to develop drug-induced TdP.[27] Testosterone, by increasing I_{Kr} and I_{Kur} currents, shortens the QT interval and reduces the risk of TdP in males.[29] Polypharmacy should also be considered as a risk factor for drug-induced LQTS. We have recently shown that potential drug-interactions involving inhibition of cytochrome P450 isoenzymes were considered responsible in 24% of cases.[27] An analysis of medication lists from 1.1 million patients have shown that 22.8% were taking at least one medication with potential for QT prolongation, 9.4% were taking two such medications, and 0.7% were taking three or more QT-prolonging drugs. Psychotropic drugs were involved in 50% of cases.[30]

TREATMENT

The management of drug-induced TdP requires the identification and withdrawal of the suspicious medication. Administration of intravenous magnesium sulfate (2 g bolus followed by an infusion of 2-4 mg/minute) is the treatment of choice regardless of serum level.[20,31] Similarly, correction of potassium concentration (4.5-5 mmol/l) is considered important.[20] In cases of hemodynamically unstable polymorphic ventricular tachycardia, immediate non-synchronized defibrillation is indicated.[20] Temporary pacing is indicated in cases refractory to magnesium sulfate or when TdP is precipitated by a pause or bradycardia.[32] Pacing (90-110 beats/min) is highly effective in preventing recurrences.[20,32] Intravenous administration of isoproterenol may be useful if temporary pacing is unavailable.[33]

CONCLUSION

Drug-induced LQTS should always be considered as a predictor of sudden cardiac, and thus should prompt critical revaluation of the risks and benefits of the suspicious medication. In clinical practice, adverse effects of QT-prolonging drugs can be prevented by not exceeding the recommended dose; by restricting the dose in patients with pre-existing risk factors; and by avoiding concomitant administration of agents that inhibit the metabolism of known drugs that prolong the QT interval. Survivors of drug-induced TdP and family members of drug-induced TdP fatalities require careful examination and possibly genetic testing for the presence of congenital LQTS-associated channelopathy.

REFERENCES

1. Letsas KP, Efremidis M, Filippatos GS, Sideris AM. Drug-induced long QT syndrome. Hellenic J Cardiol 2007;48:296-9.
2. Letsas KP, Filippatos GS, Kounas SP, Efremidis M, Sideris A, Kardaras F. QT interval prolongation and Torsades de Pointes in a patient receiving zolpidem and amiodarone. Cardiology 2006;105:146-7.
3. Kounas SP, Letsas KP, Sideris A, Efraimidis M, Kardaras F. QT interval prolongation and torsades de pointes due to a coadministration of metronidazole and amiodarone. Pacing Clin Electrophysiol 2005;28:472-3.
4. Letsas K, Korantzopoulos P, Pappas L, Evangelou D, Efremidis M, Kardaras F. QT interval prolongation associated with venlafaxine administration. Int J Cardiol 2006;109:116-7.
5. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004;350:1013-22.
6. De Ponti F, Poluzzi E, Montanaro N, Ferguson J. QTc and psychotropic drugs. Lancet 2000;356:75-6.
7. Heist EK, Ruskin JN. Drug-induced proarrhythmia and use of QTc-prolonging agents: clues for clinicians. Heart Rhythm 2005;2(2 Suppl):S1-8.
8. Straus SM, Sturkenboom MC, Bleumink GS, Dieleman JP, van der Lei J, de Graeff PA, et al. Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death. Eur Heart J 2005;26:2007-12.
9. Viskin S, Rosovski U, Sands AJ, Chen E, Kistler PM, Kalman JM, et al. Inaccurate electrocardiographic interpretation of long QT: the majority of physicians cannot recognize a long QT when they see one. Heart Rhythm 2005;2:569-74.
10. Garson A Jr. How to measure the QT interval--what is normal? Am J Cardiol 1993;72:14B-16B.
11. Viskin S, Justo D, Halkin A, Zeltser D. Long QT syndrome caused by noncardiac drugs. Prog Cardiovasc Dis 2003;45:415-27.
12. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart 2003;89:1363-72.
13. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. Circulation 1991;83:1888-94.
14. Bednar MM, Harrigan EP, Ruskin JN. Torsades de pointes associated with nonantiarrhythmic drugs and observations on gender and QTc. Am J Cardiol 2002;89:1316-9.
15. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, et al. Risk stratification in the long-QT syndrome. N Engl J Med 2003;348:1866-74.
16. Bednar MM, Harrigan EP, Anziano RJ, Camm AJ, Ruskin JN. The QT interval. Prog Cardiovasc Dis 2001;43(5 Suppl 1):1-45.
17. Antzelevitch C, Sicouri S, Di Diego JM, Burashnikov A, Viskin S, Shimizu W, et al. Does Tpeak-Tend provide an index of transmural dispersion of repolarization? Heart Rhythm 2007;4:1114-6.
18. Kanters JK, Haarmark C, Vedel-Larsen E, Andersen MP, Graff C, Struijk JJ, et al. T(peak)T(end) interval in long QT syndrome. J Electrocardiol 2008;41:603-8.
19. Yamaguchi M, Shimizu M, Ino H, Terai H, Uchiyama K, Oe K, et al. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new index for arrhythmogenicity. Clin Sci 2003;105:671-6.
20. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. Am Heart J 2007;153:891-9.
21. Kannankeril PJ, Roden DM. Drug-induced long QT and torsade de pointes: recent advances. Curr Opin Cardiol 2007;22:39-43.
22. Antzelevitch C. Role of transmural dispersion of repolarization in the genesis of drug-induced torsades de pointes. Heart Rhythm 2005;2(2 Suppl):S9-15.
23. Kay GN, Plumb VJ, Arciniegas JG, Henthorn RW, Waldo AL. Torsade de pointes: the long-short initiating sequence and other clinical features: observations in 32 patients. J Am Coll Cardiol 1983;2:806-17.
24. Schulze-Bahr E. Susceptibility genes and modifiers for cardiac arrhythmias. Prog Biophys Mol Biol 2008;98:289-300.
25. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. Circulation 1999;99:529-33.
26. Yang P, Kanki H, Drolet B, Yang T, Wei J, Viswanathan PC, et al. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. Circulation 2002;105:1943-8.
27. Letsas KP, Efremidis M, Kounas SP, Pappas LK, Gavrielatos G, Alexanian IP, et al. Clinical characteristics of patients with drug-induced QT interval prolongation and torsade de pointes: identification of risk factors. Clin Res Cardiol 2009;98:208-12.
28. Zeltser D, Justo D, Halkin A, Prokhorov V, Heller K, Viskin S. Torsade de pointes due to noncardiac drugs: most patients have easily identifiable risk factors. Medicine 2003;82:282-90.
29. Arya A. Gender-related differences in ventricular repolarization: beyond gonadal steroids. J Cardiovasc Electrophysiol 2005;16:525-7.
30. Curtis LH, Østbye T, Sendersky V, Hutchison S, Allen LaPointe NM, Al-Khatib SM, et al. Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. Am J Med 2003;114:135-41.
31. Banai S, Tzivoni D. Drug therapy for torsade de pointes. J Cardiovasc Electrophysiol 1993;4:206-10.
32. Khan IA. Clinical and therapeutic aspects of congenital and acquired long QT syndrome. Am J Med 2002;112:58-66.
33. Viskin S. Torsades de Pointes. Curr Treat Options Cardiovasc Med 1999;1:187-95.