Long QT Syndrome Case Oriented Approach

2005

LQT & TDP

LQTS and TdP

- 48/F
- C/C: Dizziness and chest discomfort for 3 years
- Past Hx: 2003, diagnosed as chronic hepatitis B
- H/X:
 - 2001, 2003, Sudden palpitation and headache, cold sweating, chest pain without LOC
 - Above symptom attack one time in 2 months before
 - 2005, 3, 26. Same symptom developed.
 - 2005, 3, 30 admission: LQT, VPC bigeminy→ CCU
 - 2nd day of admission; 8 am. seizure attack like episode, patient didn't remember



ECG Findings in LQTS

- QT interval should be measured from the onset of Q wave to the end of T wave in an ECG leads, usually lead II.
- QTc=QT/ RR
- QTc prolonged Men > 0.45 s
 Women > 0.46 s



LQTS Diagnostic Criteria

Points

Electrocardiographic Finding

– QTc	
>480 ms	3
460-470 ms	2
450 (male) ms	1
 Torsade de pointes 	2
 T wave alternans 	1
 Notched T wave in 3 leads 	1

Low heart rate for age 0.5

Clinical History	Points
– Syncope	
With stress	2
Without stress	1
 Congenital deafness 	0.5
Family History	
 (+) family Hx of LQTS 	1
 Unexplained sudden death < 30 	0.5

<2 points: low probability</p>
2 to 3 points: intermediate probability
>4 points: high probability of LQTS

Molecular Genetics of LQTS

LQTS Type (Years Discovered)	Chromosomal Locus	Mutant Gene (Alternate Name)	Ion Currents	Frequency
<i>LQT1</i> (1991)	11p15.5	KCNQ1 (KVLQT1)	I _{Ks}	~ 50%
<i>LQT2</i> (1994)	7q35-36	HERG	I _{Kr}	30-40%
LQT3 (1994)	3q21-24	SCN5A	Increased Na ⁺ current (I _{Na})	5-10%
<i>LQT4</i> (1995)	4q25-27	Ankyrin B	Possibly increased late Na⁺ current (I _{Na})	rare
<i>LQT5</i> (1997)	21q22.1-22.2	<i>KCNE1</i> (minK)	I _{Ks}	rare
<i>LQT6</i> (1999)	21q22.1-22.2	KCNE2 (MiRP1)	I _{Kr}	rare
LQT7 (2001)	17q23	KCNJ2	I _{K1}	rare

Moss AJ et al. JAMA; 2003, 289: 2041-2044



Towbin: Am J Med, 2001: 110 0(5)..385-398

Ion Channels Underlie Cardiac Excitability



Marbán E. Nature 2002, 415, 213-218

Day of Admission, 10 PM

Day of admission 11 PM





2nd day of admission, 8 am



2nd day of admission 9 am



2nd day of admission 9 am



2nd day of admission, 10AM



2nd day of admission 11 am



Short Term Management

- IV magnesium sulfate
- Temporary transvenous cardiac pacing,
- Rarely, administration of IV isoproterenol.
- Correction of electrolyte abnormalities and withdrawal of offending agents.

Post temporary pacemaker insertion & Overdrive pacing



Korean ICD indication for LQTS

• Long QT syndrome 기(evaluation)

ICD Indication 가 ullet• • 가(evaluation) • (EPS) 가 가 (1) 30% low EF (2) (3)(EPS)

Propranolol 20 mg tid and temporary pacemaker removed



April. 6. Treatment with Propranolol 20 mg tid



April. 9. 9 am, the day of cardiac arrest



April, 9. 10 am





After Cardiac arrest & CPR



Emergency implantation of dual chamber ICD at April, 9



2 days after ICD implantation

Post ICD



Long Term treatment of LQTS

 Long-term treatment has as its purpose shortening the QTc interval and preventing recurrence of TdPs, treatment that reduces 10-year mortality to 3 to 4%.

Beta blockers

Main stay of long-term treatment. Propranolol, daily dose of 2 to 3 mg/kg, but all beta-blockers should be effective.

- Maximum HR of 130 beats/min on treadmill exercise testing,
- Most effective in the LQT1, in which exercise and physical exertion are the most common triggers for an arrhythmic event.

Disruption of local signaling domains occurs in LQT-1



Cell 2001:104:569

Permanent pacemaker

- Symptomatic despite full dose of betablockers and
- Bradycardia is a prominent feature of the syndrome
- Beta-blockers should be continued.
- Pacing at relatively high rates (more than 80 beats per minute) may be required

- ICD
- Combination of beta-blockers and pacing fails to prevent presyncopal or syncopal episodes
- Initial event is resuscitated cardiac arrest.
- ICD does not prevent TdPs but does prevent SCD
- Beta-blocker should be continued
- Use a device with dual-chamber pacing as a first-line therapy to prevent sudden cardiac death in symptomatic patients with a congenital LQTS

Left thoracic sympathectomy Highly effective method of antiadrenergic therapy.

New mutation specific therapies

- Flecainide and mexiletine for LQT3
- Flecainide therapy (75 to 150 mg twice daily) significantly shortened the QT and QTc intervals in asymptomatic carrier of the mutation.

Effects of Flecainide in Patients With New SCN5A Mutation Mutation-Specific Therapy for Long-QT Syndrome?

J. Benhorin, MD; R. Taub, RN; M. Goldmit, MSc; B. Kerem, PhD; R.S. Kass, PhD; I. Windman, PhD; A. Medina, MD

- **Background**—Mutations in the cardiac sodium channel gene (SCN5A) can cause one variant of the congenital long-QT syndrome. The effects of some of these mutations on the α -subunit channel properties can be blocked by type Ib antiarrhythmic drugs. Recently, we have described a new SCN5A mutation (D1790G) that affects the channel properties in a manner suggesting that sodium blockers of the Ib type will be ineffective in carriers of this mutation. Hence, the ECG effects of flecainide-acetate, a type Ic sodium blocker, were evaluated in carriers of this mutation.
- *Methods and Results*—Eight asymptomatic mutation carriers and 5 control subjects were studied. Intravenous lidocaine was tested first in only 2 mutation carriers and had no significant effect on any ECG parameter. Flecainide significantly shortened all heart rate–corrected repolarization duration parameters only in carriers and not in control subjects: QT_c shortened by 9.5% (from 517±45 to 468±36 ms, *P*=0.011), and the S-offset to T-onset interval shortened by 64.7% (from 187±88 to 66±50 ms, *P*=0.0092). Flecainide also normalized the marked baseline repolarization dispersion in most mutation carriers. These effects among carriers were maintained during long-term (9 to 17 months) outpatient flecainide therapy with no adverse effects.
- Conclusions—This report is the first to describe SCN5A mutation carriers who significantly responded to flecainide therapy yet did not respond to lidocaine. These results have important implications for long-QT allele–specific therapeutic strategies. (Circulation. 2000;101:1698-1706.)

BASELINE









Circulation. 2000;101:1698-1706

• Potassium administration for LQT2.

 Calcium channel blockers, potassium channel activators (nicorandil, pinacidil), and other sodium channel blockers (pentisomide), in investigation Ventricular Tachycardia Induced Cardiomyopathy Related QT prolongation

27 years old male. Palpitation and weakness for 2 months



After DC cardioversion



Jau/21/2005, QTc 532 msec



Jau/18/2005 EF: 35%

Feb/22/2005 EF: 57%



Jau/20/2005

Feb/22/2005

Follow up EKG, 1 month later



Feb/22/2005, QTc 410 msec

Drug related QT prolongation

50 years old female, syncope after 2 month tinea pedis Tx. QTc : 760 msec





0, 68/M C/C: Whole body itching sense and skin eruption P/I:

- Jun, 7, 2004: Lt pontine infarction
- Jun, 28, 2004: Chest pain and NSTE-MI Proximal LAD total obstruction, Didn't try PTCA due to long, small and diffuse
- Mar, 3, 2005. Voiding difficulty cystostomy and ozex (toxufloxacin) medication → generalized skin rash
- Mar, 28, 2005: more aggravated skin rash → admission to cardiology department.
- Past H/x: DM, HTN since 1999

3 28



Mar, 31. 2 days after zyrtec (cetirizine) 1t qd and PDS 30 mg qd



April, 1. after this EKG, hold zyrtec



Table 1. Specific mutations reported in acquired long-QT syndrome case studies. Individual case-report studies in which drugs in combination with an underlying mutation in one of the known congenital LQTS genes led to serious ventricular arrhythmia.

Gene	Mutation	Amino-acid change	Drugs	Risk factors	S ymptoms	Reference
KCNQ1	944A > G	Y315C	Cisapride	Hypokalemia, elderly woman (77 yrs)	Sudden loss of consciousness, cardiac arrest	14
	1663 C > T	R555C	Terfenadine or disopyramide or mefloquine	Congenital LQTS	Sudden death, syncopes, TdP	11
	1747 C > T	R583C	Dofetilide		TdP	8
KCNH2	1039 C > T	P347S	Cisapride + clarithromycin + sulfamethoxazole	Elderly woman (77 yrs), congestive heart failure, ventricular pacemaker	TdP, QTc >600 ms (normal 440 ms)	13 + 17
	1048 C > T	R328C	not specified		TdP	9
	2350 C > T	R784W	Amiodarone		TdP	8
KCNE2	22 A > G	T8A	Sulfamethoxazole		QTc >600 ms	7
	25 C > G	Q9E	Clarithromycin	Elderly woman (76 yrs), diabetic, history of stroke, hypokalemia	TdP, VF requiring defibrillation	12
	161 T > C	M54T	Procainamide		TdP	7
	170 T > C	157T	Oxatomide		TdP	7
	347 C > T	A116V	Quinidine + mexiletine	Woman (55 yrs), history of cardiac arrest	Syncope with TdP	7
SCN5A	1844 G > A	G615E	Quinidine		TdP	8
	1852 C > T	L618F	Quinidine		TdP	8
	3305 C > A	S1102Y	Amiodarone	AA* woman (36 yrs) with DCM** and hypokalemia	TdP	10
	3748 T > C	F1250L	Sotalol		TdP	8
	4999 G > A	V1667I	Halofantrine	QTc(baseline) >440 ms, congenital LQTS	Syncopes, TdP, heart block, QTc >600 ms	15
	5474 T > C	L1825P	Cisapride	Elderly woman (70 yrs)	TdP	16

* AA = African-American, ** DCM = dilated cardiomyopathy.

Ann of Med 2004; 36 (Suppl 1): 35-40

Drugs metabolized by cytochrome P450 3A4/5 and its clinically most relevant inhibitors.

CYP3A4/5 substra	CYP3A4/5 inhibitors	
Amiodarone Astemizole Carbamazepine Cisapride Cyclosporin Dapsone Diltiazem	Midazolam Nifedipine Pimozide Propafenone Quinidine Tacrolimus Tamoxifen	Cimetidine Clarithromycin Cyclosporin Diltiazem Erythromycin Fluconazole Fluoxetine
Erythromycin Felodipine Lidocaine Indinavir Lovastatin	Testosterone Valproic acid Verapamil	Grapefruit juice Itraconazole Ketoconazole Miconazole Ritonavir

Adapted from Dresser et al. 2000 (20).

Ann of Med 2004; 36 (Suppl 1): 35-40

QTc Prolongation by Grapefruit Juice and Its Potential Pharmacological Basis HERG Channel Blockade by Flavonoids

Edgar Zitron, MD*; Eberhard Scholz, BSc*; Robert W. Owen, PhD; Sonja Lück, BSc; Claudia Kiesecker, MSc; Dierk Thomas, MD; Sven Kathöfer, MD; Feraydoon Niroomand, MD; Johann Kiehn, MD; Volker A.W. Kreye, MD; Hugo A. Katus, MD; Wolfgang Schoels, MD; Christoph A. Karle, MD

- Background—A high intake of dietary flavonoids, which are abundant in fruits, vegetables, tea, and wine, is known to reduce cardiovascular mortality. The effects of flavonoids on cardiac electrophysiology, which theoretically may have both antiarrhythmic and proarrhythmic consequences, have not been studied systematically to date.
- Methods and Results—We screened a broad spectrum of flavonoids for their inhibitory activity on HERG channels by using heterologous expression in Xenopus oocytes. At a concentration of 1 mmol/L, 10 compounds caused a significant inhibition of HERG currents, whereas 11 other flavonoids had no effect. The IC₅₀ value for HERG block by naringenin, the most potent inhibitor, was 102.3 μ mol/L in Xenopus oocytes and 36.5 μ mol/L in HEK cells. To demonstrate the physiological relevance of these findings, we studied the effects of pink grapefruit juice, which contains large amounts of naringenin glycosides (>1000 μ mol/L), in human volunteers. In 10 persons, we observed a peak QTc prolongation of 12.5±4.2 ms 5 hours after oral ingestion of 1 L of grapefruit juice. This effect was significant (P=0.02).
- Conclusions—We found a significant QTc prolongation by grapefruit juice in healthy volunteers, probably caused by block of HERG channels by flavonoids. These findings reveal new perspectives on the potential for dietary modification of cardiac electrophysiology. (Circulation. 2005;111:835-838.)





Oral Erythromycin and the Risk of Sudden Death from Cardiac Causes

Table 1. Characteristics of the Cohort According to Antibiotic Use.*				
Characteristic	Antibiotic Use			
	None	Former Use of Erythromycin	Current Use of Erythromycin	Current Use of Amoxicillin
Person-years (no.)	1,126,013	111,779	5305	6846
Age Mean (yr) ≥65 yr (%)	45.0 26.0	42.2 18.6	41.4 16.5	41.7 17.9
Female sex (%)	68.7	78.6	77.6	76.2
White race (%)	57.5	66.0	69.3	70.7
No outpatient visit in past year (%)	23.6	2.7	2.5	2.1
≤1 prescription in past year (%)	32.0	3.3	1.8	2.0
Encounters involving cardiovascular disease (%)				
Any	33.2	46.1	47.0	46.4
Medication prescribed	31.8	45.2	46.1	45.5
Visit to emergency department or hospital admission	2.9	4.7	4.3	4.2
Visit to emergency department or admission for noncardiovascular condition (%)	11.6	19.2	17.8	16.4

N Engl J Med, 2004, 351. 1086-1096

Oral Erythromycin and the Risk of Sudden Death from Cardiac Causes

Table 2. Incidence-Rate Ratio for Sudden Death from Cardiac Causes, According to Antibiotic Use.*				
Antibiotic Use	Person-Years	Deaths	Incidence-Rate Ratio (95% CI)	
	number			
Current use of erythromycin	5,305	10	2.01 (1.08-3.75)	
Current use of amoxicillin	6,846	8	1.18 (0.59–2.36)	
Former use of erythromycin	111,779	100	0.89 (0.72–1.09)	
None	1,126,013	1358	1.00	



Figure 1. The Incidence-Rate Ratio for Sudden Death from Cardiac Causes According to the Current Use of the Study Antibiotic Medications and CYP3A Inhibitors.

N Engl J Med, 2004, 351. 1086-1096

April, 2, 1 day after zyrtec hold



April. 3, 2 day after zyrtec hold



April. 5, 4 days after zyrtec hold



April. 6, 6 days after zyrtec hold

