Proarrhythmic Effects of Non-Cardiac Drugs

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DISCLOSURE

Relevant Financial Relationship(s)

None
Case: 21 y/o Female with a History of Recurrent Syncope

- History consistent with vasovagal etiology
- F/Hx: -ve for syncope, SCD or arrhythmias
- Medical evaluation unremarkable
- Normal ECG
- Tilt table testing: vasodepressor response
- Treatment: conservative, fluids, salt
21 y/o Female with History of Syncope

ER visit,

Two syncopal events

• Both occurred at rest; preceded by a brief moment of palpitations

• Recent sinusitis; primary MD prescribed a medicine 3 days ago
21 y/o with syncope
21 y/o with syncope

QT 560 ms; QTc 490 ms

On Erythromycin
21 y/o with palpitations and syncope

EES discontinued

QT 440 ms; QTc 450 ms

Now what?
19-year-old female with history of syncope

What will you do next?

1. Start Levaquin, instead of Erythromycin
2. Start Beta-blocker therapy
3. Implant ICD
4. Consider left cardiac sympathetic neural denervation
5. No need for any intervention
6. None of the above
21-y/o Female with Syncope

- Is the episode primarily related to erythromycin effect on cardiac repolarization or she has a LQTS channelopathy?
- Is she at high risk for cardiac arrhythmias and sudden cardiac death?
- Does she need an ICD for prevention of SCD?
- Are other family members at risk of cardiac arrhythmias?
- What advice should be given with regard to exercise, sports activity, pregnancy.
Case: Diagnosis and Therapy

21-year-old female
- Erythromycin discontinued
- Beta blocker therapy started
- Avoidance of QT prolonging drugs (list)

Genetic testing for LQTS Genes? 

1. Yes
2. No
Prolonged QT Syndrome

Congenital / Familial

Autosomal Dominant
Romano-Ward Syndrome
(normal hearing), 1:2,000

Autosomal Recessive
Jervell and Lange-Nielsen Synd
(congenital deafness) Rare (1 in 10^6)

Sporadic
(normal hearing, nonfamilial ?)

Acquired

Drugs
Electrolyte Abn
Bradyarrhythmias
Cardiomyopathy
Myocarditis
Cerebrovascular disease
Hypothyroidism

Concealed Long QT

17 genes:
KCNQ1 (IKs), KCNH2 (IKr), SCN5A (INa)
Medications Related Pro-arrhythmia Risk

“Acquired” Channelopathy

• Cardiac and non-cardiac drugs (antibiotics, antidepressants, antipsychotics) can be proarrhythmic modulating ion channels ($I_{Kr}$, $I_{Na}$) or PK/PD interactions with other drugs

• A major concern in drug safety

• A Modifiable risk factor for lethal arrhythmias and SCD

Medications Related Pro-arrhythmia Risk

“Acquired” Channelopathy

• The incidence of Drug-Induced SCD?
  >15,000 deaths/yr?

• TdP with sotalol, dofetilde 0.5-2%, quinidine 1.5-9%
  Initiated in-hospital with ECG monitoring

• Antibiotics, Antidepressants, antipsychotics
  Nortriptyline x 5-fold ↑ risk of SD (diLQT, diBrS)

  Recommendations for monitoring QT for QT-prolonging “noncardiac” medications in primary care settings, impractical.

  1:8,500 serious arrhythmia on macrolides!
  ~ 1:30,000 can die

OHCA Drug-related vs Cardiac Causes
Ontario 2007-2013

Cardiac Arrest Age Distribution

21,497 OHCA

1.8% drug-related
98.2% presumed cardiac
A Nationwide Cohort Study of Young Patients with SCD: Use of Pharmacotherapy Within 90 Days

1,363 SCD
Median age 38 yrs

58% Pharmacotherapy at least 1 drug
Analgesics, antihypertensive, antibiotics, antidepressants, antipsychotics, anxiolytics

QT prolonging drugs 19%
Brugadogenic drugs 9%

Risgaard: J Am Coll Cardiol EP 2017
QT-Prolonging Drugs Prescription Within 90 Days of TdP/SCD in Young Patients

Drugs prescribed within 30 days before death, >1 QT↑ drug
SADS vs explained SCD OR: 3.48 (95%CI 1.85-6.52)

2- and 3-fold ↑ risk of SADS compared with explained SCD
QT Prolonging Drugs

Antiarrhythmics
- IA: Quinidine, procainamide, disopyramide
- III: Sotalol, NAPA, ibutilde, dofetilide, amiodarone

Antimicrobials
- Antibiotics: Macrolides, TMP/SMX, Fluoroquinolones
- Antifungals: itraconazole, ketoconazole
- Antimalarials: chloroquine
- Antiparasitic: pentamidine
- Antivirals: amantadine
- Antihistamine
  - (Terfenadine, asetmizole)
- Antidepressants
  - Tricyclics, tetracyclics, SSRI

Psychotropics
- Haloperidol, droperidol,
- Phenothiazines

Antiemetics
- Ondansetron

Antineoplastics
- Arsenic trioxide, CsCl, Pt, TKI, HDACi, Anthracyclines, Trastuzumab

Opiods
- Methadone, loperamide*

Miscellaneous
- Metamphetamine
- Metoclopramide
  - (Cisapride)
- Organophosphate poisoning

crediblemeds.org
Proarrhythmia with K+ Channel Bockers

Reduction in Repolarization Reserve
LVH, CHF
DM, Age, F
Medications
Genetic Polymorphism/ mutations

Torsade de pointes

Sanguinetti: 1997
**KCNQ1 pathogenic loss of fx mutation (I_{Ks}) – concealed LQT1**

**QT 560 ms; QTc 490 ms**

**On Erythromycin**

**QT 440 ms; QTc 450 ms**

**15% I_{Ks} Block**

**15% I_{Ks} + I_{Kr} Block**

**QTc Normal**

**Concealed LQT1 (G+, P-)**

**KCNQ1 mutation (IKs)**

Incomplete penetrance and variable expressivity of abnormal gene(s) can conceal the distinctive ECG pattern that characterize the inherited arrhythmogenic disorder.

Between 10% (LQT3) and 37% (LQT1) of genotype +ve patients have a QT interval within normal limits.

NEJM 2003  JACC 2011

Concealed Long QT

LQTS Genotyped
Incomplete penetrance and variable expressivity of abnormal gene(s) can conceal the distinctive ECG pattern that characterize the inherited arrhythmogenic disorder.

- ~20% of drug-induced LQT cases shown to have LQTS-associated mutations vs 4% in control population.
Penetrance of LQTS Phenotype According to Genotype

- **LQTS**
  - Concealed ≤460 ms
  - Overt >460 ms

- % of patients

- Mazzanti: JACC 2018;71:1663

- % of individuals with concealed LQTS ↑ from 23% to 50%

- Avoidance of unnecessary prescriptions of QT ↑ drugs

- Awareness - physicians and patients

- Screening ???
The Concept of Repolarization Reserve

LVH, CHF, DM, Age, Gender, Genetic Polymorphism/mutations

Eckardt & Breithardt
Important Pharmacokinetic Considerations

Genetic Variants

Drug interactions

\[ \uparrow \text{Bioavailability (levels)} \]
\[ \uparrow \text{Toxicity} \]

CYP3A4

\[ \text{QT} \uparrow \rightarrow \text{TdP} \]

- Dofetilide*, Quinidine, Amiodarone, Dronedarone, CaChBl
- Erythromycin, Rivoraxaban, Apixaban
- TCA, Methadone

Grapefruit Juice

Inhibitors CYP3A4
- Azole antifungals
- Erythromycin
- Cimetidine
- Diltiazem, Verapamil
- Protease Inhib (HIV)
- Amiodarone, Dronedarone

Inhibitors CYP2D6
- Thioridazine, Methadone
- Flecainide, Propafenone
- Warfarin

CYP2C9*3

\[ \uparrow \text{NaCh-blockade} \]

- Bleeding

Inhibitors CYP2D6
- Fluoxetine, SSRI
Drug-Induced QT Prolongation

Excessive QT Prolongation or Changes in T morphology

\[ \Delta QT_c \ 30 \text{ ms from baseline or } QTc > 470 \text{ ms} \]
\[ \Delta QT_c \ 60 \text{ ms or } QTc > 500 \text{ ms} \]

- Direct effect on repolarization (dose/duration)
- Drug-drug / drug-supplement Interactions
  - Pharmacodynamics
  - Pharmacokinetics
    - metabolic inhibition- metabolites
    - renal clearance
- Drug-substrate Interactions
  - Cardiomyopathy, LVH, low LVEF, SND
  - Liver/ renal disease
  - Underlying Gentic susceptibility
    - Polymorphisms/ mutations
Risk factors for TdP with drug-induced QT Prolongation

Demographic: Female sex, age

Electrolytes: ↓ K⁺, Mg²⁺

Genetic predisposition: Channelopathies, DNA polymorphism

Cardiac - Baseline QT, Concealed LQT, Bradycardia, pauses
- Recent cardioversion, AVJ ablation with sudden HR slowing
- Cardiomyopathy (HF, LVH, MI)

Systemic Conditions - Hepatic impairment, Renal Impairment

Concomitant Drugs - >1 QT prolonging drugs, drugs inhibiting metabolism, diuretics, digoxin
Thank You
Identification of Young Patients at Risk for SCD

• Prodromal Symptoms/signs
  • Aborted CA, Exertional Syncope, VT-palpitations

• Screening Test - Monitoring
  • Cost and inconvenience of untargeted screening
  • Sens of test, Disease prevalence, Cost (test, false +ve), Rx
  • ECG, TMET, Echo - ECG Alerts
  • Targeted screening of family members (phenotype, cascade testing)

• Risk Stratification (known cardiac disease)
  • LQTS, HCM, BrS, CPVT, ARVC, LVDysfx

• Risk Factors for drug-induced adverse effects - Alerts
  • Patient-specific, Drug-specific (dofetilide, sotalol)
    Dynamic factors (repolarization reserve - drug-drug-disease interaction) - ECG Alerts
Minimizing Risk of drug-induced TdP

In Drug Development
- Preclinical screening: invitro and invivo – “thorough QT/QTc test”

Regulation and postmarketing surveillance
- Risk/benefit - RCT
- appropriate warnings, monitoring requirements
- Postmarketing surveillance
  - withdrawal (astemizole, terfenadine, cisapride, grepafloxacin, thioridazine)
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Postmarketing surveillance
16 000 screening ECGs are needed to identify a single case of asymptomatic long QT syndrome (Rodday: Pediatrics 2012129-e999-1010)

Minimizing Risks in Clinical Practice
- Recommendations are lacking
  - Avoidance of QT drugs (https://crediblemeds.org)
  - Patient Education (Sx, concomitant use of drugs)
  - Assessment of Risk factors – cardiac, systemic, external
  - Modifiable risk factors (drugs, electrolytes, OSA)
  - ECG screening ? - High risk monitoring ?
Not all QT prolonging Drugs are Equal
Effect of $I_{Kr}$ vs Multichannel Block on QT interval and Risk for TdP

Vicente: Clin Pharmacol Ther 2018;103:54-66
Effect of $I_{Kr}$ vs Multichannel Block on QT interval – Early vs Late Repolarization


Vicente: *Clin Pharmacol Ther* 2018;103:54-66
$I_{Kr}$ Dofetilde, Sotalol

Erythromycin,

Refractoriness

$\uparrow$ APD, ERP

$\uparrow$ QT Interval

Reverse Use-dependence

Dofetilde ($I_{Kr}$)

Prolongation (%)

<table>
<thead>
<tr>
<th>Stimulation frequency (Hz)</th>
<th>0.2</th>
<th>1.0</th>
<th>4.0</th>
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</thead>
<tbody>
<tr>
<td>EAD/Triggered Activity</td>
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EAD/ Triggered Activity

Each 10 ms $\uparrow$ in QTc associated with 5-7% $\uparrow$ in risk TdP

Drew : Circulation 2010;121:1047-60
The Acquired LQTS: a Genetically Mediated "forme fruste" of Familial LQTS

- "Silent" mutations on LQTS genes
- Mutation Frequency?
- Alteration in repolarization insufficient to prolong QT at rest, but sensitive to $I_{K}$ blockade by drugs prolonging APD or hypokalemia triggering TdP

$I_{Kr}$ .. KCNE2 : Q9E (clarithromycin)  
$I_{Kr}$ .. KCNH2 : R1047L (dofetilide)  
$I_{Ks}$ .. KCNQ1: Y315C (cisapride), MirP1_T8A (sulfa)  
$I_{Na}$ .. SCN5A: S1103Y, S1102Y (Af-Am: Amio, Ischemia)

Acquired form of the LQTS in LVH and DCM:  
Reduction in $I_{to}$, $I_{K1}$, altered $Ca^{2+}$ handling
Drug Interactions Increasing Risk of TdP

- 2 or more QT Prolonging Drugs (additive/synergistic effects)
  
  Sotalol + Erythromycin + Antidepressant + Antihistamine

- QT Prolonging Drug + Drug Inhibiting CYP3A4
  
  Dofetilide or Erythromycin + Verapamil + Grape fruit Juice 
  Diuretic (low K, Mg)
Estimated Annual Incidence of Adverse Drug Events Treated in U.S. Emergency Departments

Estimated annual incidence/1,000 individuals

Patient age (yr)

Budnitz: JAMA 2006;296:1858
Polypharmacy

• older persons take up to 11 different prescribed drugs
  – 2 drugs = 6% risk of interaction
  – 5 drugs = 50% risk of interaction
  – 8 drugs = 100% risk
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