Published in final edited form as:
Heart Rhythm. 2009 September ; 6(9): 1342–1344. doi:10.1016/j.hrthm.2009.07.033.

THE ACQUIRED BRUGADA SYNDROME AND THE PARADOX OF CHOICE

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The "paradox of choice" in drug-induced channelopathies

Consider the following two patients: The first is female, asymptomatic, and develops marked QT prolongation while receiving intravenous procainamide for atrial fibrillation. The second is male, also asymptomatic, and develops coved-type ST-segment elevation in the right precordial leads while receiving intravenous flecainide during a diagnostic test. Most physicians would simply recommend discontinuation of procainamide, and avoidance of QT-prolonging medications in the future, as the *only* therapeutic measures needed for the first patient. In contrast, the same physicians would likely perform electrophysiologic studies and, if positive, move on to implant a defibrillator to the second patient.[1] How did we end-up choosing such disparate recommendations for patients with drug-induced long QT syndrome (LQTS) and Brugada syndrome?

Part of the answer is that "timing is everything." The LQTS was first recognized as a *congenital* disorder half a century ago.[2-4] Soon thereafter, description of "quinidine syncope"[5] led to the recognition of *acquired* (drug-induced) LQTS. For many years, congenital and acquired LQTS were viewed as two different entities with intriguing similarities.[6] It would take 40 years to finally realize that loss of function of the same potassium channels -- responsible for the rapidly activating delayed rectifier current (I_{Kr}) -- may be caused by either genetic mutations or medications.[7] The realization that *some* patients with drug-induced LQTS have underlying subclinical genetic mutations that become clinically manifest when treated by QT-prolonging medications, was made only in the year 2000.[8] Finally, the diagnostic use of I_{Kr}-channel blockers to identify patients with underlying LQTS mutations was not formally proposed until recently.[9,10]

The history of the Brugada syndrome unfolded in a different order. Its original description in 1992[11] was soon followed by in-vitro studies describing this disease as a ion-channel disorder[12] and by genetic studies confirming an inborn loss-of-function of the cardiac sodium channel (I_{Na}) as the cause.[13] All this prompted the use of drugs that block I_{Na} to unravel

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Brugada syndrome.[14] It so happened that the use of sodium-channel blockers became a widespread means for identifying patients with underlying Brugada syndrome[15] *before* the idea of acquired (drug-induced) Brugada syndrome was accepted. Ironically, back in 1991, the Cardiac Arrhythmia Suppression Trial (CAST) showed that patients with asymptomatic ventricular arrhythmias after myocardial infarction have increased mortality when treated with sodium-channel blockers.[16] Since CAST was published one year before the description of Brugada syndrome,[11] the possibility that an "acquired Brugada syndrome" was behind this increased mortality was never contemplated.

Beware of drugs dot com

Although the fact that patients with LQTS are at increased risk for developing arrhythmias when treated with QT-prolonging medications is well known, the sheer size of that risk is not appreciated. In a retrospective study, 1 of every 2 patients with congenital LQTS receiving a QT-prolonging medication had cardiac arrest![17] It is therefore imperative that all patients with LQTS, including those with suspected but unconfirmed diagnosis, avoid QT prolonging medications at all times. The internet provides up-to-date information on such drugs. For example, www.QTdrugs.org, a reliable website maintained by the Arizona Center for Education and Research on Therapeutics), had more than one million visits only last year (Woosley R.L., Personal Communication). In this issue of *Heart Rhythm*, Postema[18] reports, on behalf of an outstanding group of experts, the creation of a similar website for Brugada syndrome: www.brugadadrugs.org

Postema et al[18] performed the formidable task of reviewing a vast amount of literature into a concise page with drugs that should be "definitively avoided" or "preferably avoided" by patients at risk for Brugada syndrome. Importantly, www.QTdrugs.org now includes an electronic link to www.brugadadrugs.org. Thus, physicians will soon make recommendations based on a quick look at this new website instead of personally performing a thorough literature search. However, physicians making decisions based on what appears (and does not appear) in www.brugadadrugs.org should remember that behind this website are enthusiastic investigators that will have to cope with an exponentially increasing number of publications. Physicians should also realize that in contrast to the safety evaluation that newly-developed drugs undergo for their "torsadogenic potential," limited data is collected for their "Brugadogenic potential" (see below). Even more limited data are available for medications already on the market. For example, methadone has been used to treat opiate-addiction for almost 50 years,[19] but the fact that methadone is an I_{Kr}-channel blocker that can provoke TdP was discovered only recently.[20] The dictum "if it's not on the website it is not a problem" will not always be correct.

Patients with Brugada syndrome should avoid all drugs listed as risky in www.brugadadrugs.org even if they have implanted defibrillators. This is because drugs may precipitate arrhythmic-storms with multiple VF episodes.[18] Conversely, every patient presenting with ventricular arrhythmias while receiving such medications should be evaluated for the presence of underlying congenital Brugada syndrome.[18]

Safety evaluation of newly developed drugs: The worst is yet to come

Identification of a new drug's propensity to provoke arrhythmias is a critical issue in drug development. The main focus has been on identifying the drugs' potential for blocking I_{Kr} and prolonging the QT interval.[21] New drugs are tested for these effects at the level of the ion channel, cardiac tissues and whole animals.[22] Guidelines have been developed for both non-clinical and clinical assays (www.ich.org). The International Conference on Harmonization E14 document deals with non-cardiac drugs in development, defining a need for almost all compounds to undergo a thorough QT study in healthy volunteers to test for QT/QTc

prolongation. If the study is positive, extensive further evaluation is required both at the non-clinical and clinical levels. Yet, in the case of drugs, QT prolongation per se may be a poor surrogate of proarrhythmia.[23]

Complicating matters further, it is now clear that, in addition to I_{Kr}-mediated QT prolongation, different drug-induced ion-channel actions may predispose to arrhythmias. These include I_{Ks}-mediated QT prolongation[24] as well as several forms of QT *abbreviation*.[25,26] Drug-induced inhibition of the I_{Na} and I_{Ca}[27] as well as drug-induced augmentation of the transient outward potassium current[28] contribute to the development of the substrate and triggers for ventricular fibrillation (VF) in experimental Brugada syndrome.

Because formulas used for QT correction by heart rate are less than perfect,[29] clinical evaluation of the QT-prolonging effects of medications is difficult. Clinical appraisal of "potentially Brugadogenic" new drugs will be even harder. The degree of ST-segment elevation in Brugada syndrome may be transient or fluctuating and is influenced by multiple factors, including the position of the recording electrodes[30] and ingestion of heavy meals.[31] Thus, to maximize the likelihood of detecting Brugada-like changes during investigation of new drugs, one could argue in favor of Holter recordings using electrodes placed at elevated intercostal spaces.[32] How much of this testing is really necessary is far from clear.

Born to be "wild-type" or born to loose

Identification of patients at risk for proarrhythmia should ideally occur *before* they receive the first dose of the drug. Studies to identify genetic variants that contribute to susceptibility for drug-induced TdP require large numbers of cases and controls. Investigators have used datasets generated by referral centers and, more recently, from networks of such centers (http://allianceagainstscd.org/leducq.php). Larger networks to accumulate cases are being planned (Roden DM: personal communication).

In the meantime, the baseline QT/QTc remains an important – albeit imprecise – tool for predicting risk from QT-prolonging drugs. Even borderline QTc prolongation is an exclusion criterion in clinical trials evaluating new medications with I_{Kr}-blockade properties. However, as explained elsewhere,[33] it is impractical in clinical practice to perform electrocardiographic screening prior to administration of medications with non-cardiac indications except when several risk factors are present (Table 1). Until more is known about the drug-induced Brugada syndrome, it is reasonable to use a similar approach for the drugs listed in www.brugadadrugs.org.

Acknowledgements

Charles Antzelevitch, Ph. D. was supported by grant HL47678 from NHLBI (CA)

References

1. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference. Heart Rhythm 2005;2:429–440. [PubMed: 15898165]
2. Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. Am Heart J 1957;54:59–68. [PubMed: 13435203]
3. Romano C, Gemme G, Pongiglione R. Aritmie cardiache rare dell'eta pediatrica. Clin Pediat 1963;45:656–683.
4. Ward OC. A new familial cardiac syndrome in children. J Irish Med Assoc 1964;54:103–106.
5. Selzer A, Wray HW. Quinidine syncope. Paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. Circulation 1964;30:17–26. [PubMed: 14197832]

6. Jackman WM, Friday KJ, Anderson JL, Aliot EM, Clark M, Lazzara R. The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. Prog Cardiovasc Dis 1988;31:115–172. [PubMed: 3047813]
7. Sanguinetti MC, Jiang C, Curran ME, Keating MT. A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the I_{Kr} potassium channel. Cell 1995;81:229–307.
8. Sesti F, Abbott GW, Wei J, et al. A common polymorphism associated with antibiotic-induced cardiac arrhythmia. Proc Natl Acad Sci 2000;97:10613–10618. [PubMed: 10984545]
9. Kaab S, Hinterseer M, Nabauer M, Steinbeck G. Sotalol testing unmasks altered repolarization in patients with suspected acquired long-QT-syndrome--a case-control pilot study using i.v. sotalol. Eur Heart J 2003;24:649–657. [PubMed: 12657223]
10. Jeyaraj D, Abernethy DP, Natarajan RN, et al. I(Kr) channel blockade to unmask occult congenital long QT syndrome. Heart Rhythm 2008;5:2–7. [PubMed: 18273958]
11. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 1992;20:1391–1396. [PubMed: 1309182]
12. Antzelevitch C. The Brugada syndrome. J Cardiovasc Electrophysiol 1998;9:513–516. [PubMed: 9607460]
13. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature 1998;392:293–296. [PubMed: 9521325]
14. Brugada R, Brugada J, Antzelevitch C, et al. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation 2000;101:510–515. [PubMed: 10662748]
15. Wilde AA, Antzelevitch C, Borggrefe M, et al. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation 2002;106:2514–2519. [PubMed: 12417552]
16. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991;324:781–788. [PubMed: 1900101]
17. Vincent GM, Schwartz PJ, Denjoy I, et al. High efficacy of beta-blockers in long-QT syndrome type 1: contribution of noncompliance and QT-prolonging drugs to the occurrence of beta-blocker treatment “failures”. Circulation 2009;119:215–221. [PubMed: 19118258]
18. Postema PG, Wolpert C, Amin AS, et al. Drugs and Brugada syndrome patients: review of the literature, recommendations and an up-to-date website (www.brugadadrugs.org). Heart Rhythm 2009;X:XXX–XXX.www.brugadadrugs.org
19. Dole VP, Nyswander ME, Kreek MJ. Narcotic blockade--a medical technique for stopping heroin use by addicts. Trans Assoc Am Physicians 1966;79:122–136. [PubMed: 4162906]
20. Krantz MJ, Lewkowiez L, Hays H, Woodroffe MA, Robertson AD, Mehler PS. Torsade de pointes associated with very-high-dose methadone. Ann Intern Med 2002;137:501–504. [PubMed: 12230351]
21. Fenichel RR, Malik M, Antzelevitch C, et al. Drug-induced torsades de pointes and implications for drug development. J Cardiovasc Electrophysiol 2004;15:475–495. [PubMed: 15090000]
22. Haverkamp W, Breithardt G, Camm AJ, et al. The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications. Report on a policy conference of the European Society of Cardiology. Eur Heart J 2000;21:1216–1231. [PubMed: 10924311]
23. Antzelevitch C. Arrhythmogenic mechanisms of QT prolonging drugs: is QT prolongation really the problem? J Electrocardiol 2004;37(Suppl):15–24. [PubMed: 15534788]
24. Towart R, Linders JT, Hermans AN, et al. Blockade of the I(Ks) potassium channel: An overlooked cardiovascular liability in drug safety screening? J Pharmacol Toxicol Methods. 2009
25. Extramiana F, Antzelevitch C. Amplified transmural dispersion of repolarization as the basis for arrhythmogenesis in a canine ventricular-wedge model of short-QT syndrome. Circulation 2004;110:3661–3666. [PubMed: 15569843]
26. Patel C, Antzelevitch C. Cellular basis for arrhythmogenesis in an experimental model of the SQT1 form of the short QT syndrome. Heart Rhythm 2008;5:585–590. [PubMed: 18362027]
27. Fish JM, Antzelevitch C. Role of sodium and calcium channel block in unmasking the Brugada syndrome. Heart Rhythm 2004;1:210–217. [PubMed: 15851155]

28. Calloe K, Cordeiro JM, Di Diego JM, et al. A transient outward potassium current activator recapitulates the electrocardiographic manifestations of Brugada syndrome. Cardiovasc Res 2009;81:686–694. [PubMed: 19073629]

29. Malik M. The imprecision in heart rate correction may lead to artificial observations of drug induced QT interval changes. Pacing Clin Electrophysiol 2002;25:209–216. [PubMed: 11915990]

30. Shimizu W, Matsuo K, Takagi M, et al. Body surface distribution and response to drugs of ST segment elevation in Brugada syndrome: clinical implication of eighty-seven-lead body surface potential mapping and its application to twelve-lead electrocardiograms. J Cardiovasc Electrophysiol 2000;11:396–404. [PubMed: 10809492]

31. Nishizaki M, Sakurada H, Mizusawa Y, et al. Influence of meals on variations of ST segment elevation in patients with Brugada syndrome. J Cardiovasc Electrophysiol 2008;19:62–68. [PubMed: 17900254]

32. Shimeno K, Takagi M, Maeda K, Tatsumi H, Doi A, Yoshiyama M. Usefulness of Multichannel Holter ECG Recording in the Third Intercostal Space for Detecting Type 1 Brugada ECG: Comparison with Repeated 12-Lead ECGs. J Cardiovasc Electrophysiol. 2009

33. Viskin S, Justo D, Halkin A, Zeltser D. Long QT syndrome caused by noncardiac drugs. Prog Cardiovasc Dis 2003;45:415–427. [PubMed: 12704598]

34. 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 (Baltimore) 2003;82:282–290. [PubMed: 12861106]

Table 1

Risk factors for proarrhythmic events.

Risk factor	Drug-induced long QT syndrome from I_{Kr}– blockers.[34]	Drug-induced Brugada syndrome from I_{Na} or I_{Ca} blockers.
Gender	Female	Male (?)
Baseline ECG	Long QT Borderline-long QT (?)	Coved-type ST elevation. RBBB (?) rSr' in V1-V2 (?)
Heart disease	Yes	Probably
Excessive drug effects:	1) Combination of more than one I_{Kr}– blocker. 2) Combination with a drug that impairs the metabolism of the I_{Kr}– blocker. 3) Kidney/liver failure.	1) Combined use of I_{Na} and I_{Ca} blockers. 2) Combination with a drug that impairs the metabolism of the I_{Na} or I_{Ca} blockers. 3) Kidney/liver failure.
Electrolyte imbalance	Hypokalemia	Hypokalemia (?) Hyperkalemia (?)