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EDITORIAL COMMENT

Pro-Arrhythmic Effects of Noncardiac Medications

Lessons From Macrolide Antibiotics*

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Sudden death resulting from medications prescribed with good intentions is an ever-present threat first recognized nearly a century ago (1,2). As early as 1923, when quinidine was first used as antiarrhythmic therapy, a disturbing phenomenon was noted: some patients treated with quinidine suffered from sudden collapses, sometimes ending in unexpected deaths (2). These events were first attributed to "embolism" (2) or "nervous-system depression" (1). It was only in 1964, when Selzer and Wray (3) first documented polymorphic ventricular tachyarrhythmias (VTA) as the cause for quinidine syncope.

The phenomenon of "drug-induced arrhythmia" became even more puzzling when medications with no cardiac indications, understandably assumed to be free of cardiac effects, were also reported to provoke arrhythmia (4). The first medication was the antipsychotic thioridazine. In 1966, Schoonmaker et al. (4) described a patient with schizophrenia who had normal QT at baseline but developed QT prolongation during thioridazine therapy. This thioridazine-induced QT prolongation "resembled quinidine effect" and was therefore considered benign, so when the patient developed polymorphic VTA, he was treated with no other but quinidine (he eventually survived thanks to cardiac pacing) (4). This twisted course of events emphasizes the lack of understanding of the disease mechanism in those days. It would take an additional 20 years to eventually demonstrate that quinidine prolongs the action potential, thereby prolonging the QT interval, by blocking myocardial cell channels responsible for the potassium outflow current now known as delayed-rectifier potassium current (I_{Kr}) (5). Since then, the list of medications with I_{Kr} channel blocking properties linked to a drug-induced long QT syndrome (LQTS) has steadily grown to include medications as varied as antibiotics and antiallergy remedies (6). For these medications, their potency as I_{Kr} channel blockers in experimental studies correlates with their pro-arrhythmic potential (7). This experimental-to-clinical correlation is not perfect because, in addition to patient-specific characteristics that influence the risk for VTA (see the following text), drugs prolong the QT interval by mechanisms other than "simple" I_{Kr} channel blockade. Drugs may disrupt the trafficking of newly created I_{Kr} protein from the endoplasmic reticulum to the cell membrane, thereby reducing I_{Kr} channel expression (8), or they might increase the highly torsadogenic late-sodium current $I_{Na\text{-}L}$ (9).

Drug-induced LQTS is a nightmare for the pharmaceutical industry; it is among the most common causes of the withdrawal of drugs. Such was the case for terfenadine, the first nonsedating antihistamine, withdrawn from the market when it was 1 of the most frequently prescribed drugs in the world (10). An unkinder fate awaited grepafloxacin, a newly developed quinolone antibiotic predicted to generate $1 billion, which was taken off the market shortly after its first release, following public accusations against the manufacturer and the Food and Drug Administration (11). Drug-induced LQTS is an even worse nightmare for physicians because we are the ones prescribing clinically indicated "noncardiac medications,"

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knowing that our treatment carries a small risk of provoking VTA. Not knowing how small this "small risk" really is has probably made this dilemma easier to cope with. Not anymore….

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HOW SMALL IS "SMALL"?

In this issue of the *Journal*, Cheng et al. (12) provide robust estimates of the scale of the arrhythmia risk associated with antibiotic treatment with erythromycin and related macrolide antibiotics. Cheng et al. (12) collected data for >20 million patients participating in 33 studies that compared patients treated with macrolide antibiotics to similar patients treated otherwise. Eleven studies (with 6 million patients) provided data for sudden death or VTA (12). The cohort of patients not taking macrolides experienced an average of 80 cases of sudden death or VTA per million treatment courses. Compared with no macrolide use, current macrolide treatment was associated with an additional 118 cases of sudden death or VTA, or 36 additional sudden deaths, per million treatment courses. Simply put, roughly 1:8,500 patients treated with a macrolide antibiotic is expected to develop a serious arrhythmic event, and 1:30,000 could die suddenly, *because of our treatment*. This distressing statement, as opposed to a more palatable announcement that macrolide therapy *is associated with* increased risk of arrhythmic death, is justifiable despite the observational nature of the present study because: 1) the pro-arrhythmic mechanism of macrolides is already well established (13); and 2) a 2-fold increased risk for VTA among patients treated with macrolides also existed in prospective randomized controlled studies (12). Importantly, patients treated with penicillin/amoxicillin had no increased risk of VTA in comparison to patients taking no antibiotic therapy, whereas macrolide therapy increased the arrhythmic risk not only in comparison to no therapy but also in comparison to penicillin/amoxicillin (12), dispersing the confounding effects of infection. Finally, data on total mortality were available for >12 million patients from 23 studies, and overall, macrolide use was not statistically associated with an increased risk of death (12), denoting the small absolute risk of arrhythmic death.

DRUG-INDUCED LONG QT SYNDROME: DON'T ASK, DON'T TELL?

The 1:30,000 iatrogenic arrhythmia death risk reported by Cheng et al. (12) cannot be simply swept under the carpet. The pharmaceutical industry will now be more vulnerable to litigation, and this could persuade them to discontinue the production of macrolides. This would be unfortunate because macrolides are first-line agents for community-acquired pneumonia, legionellosis, sexually transmitted infections, and peptic ulcer caused by *Helicobacter pylori* infection. Alternative antibiotics exist but have their own pitfalls, including increasing worldwide spread of resistance to quinolones (14). Treating infections in young children and pregnant women, for which some macrolides are approved but quinolones and tetracyclines are not, would become challenging, as would treatment of streptococcal pharyngitis in the β-lactam-allergic patient. Although there have been antibiotics removed from use, these have been individual agents (e.g., methicillin), rather than an entire class. One might argue that the drop in use of chloramphenicol because of rare hematologic toxicity represents the stoppage of an entire class, yet the 1950s, when chloramphenicol bone marrow toxicity was reported, was a time of ongoing introduction of new antibiotics. Today, when antimicrobial resistance represents a major threat to global health and new treatment options are frighteningly few (14), losing an entire class of antibiotics would represent a major setback in the fight against infections. Furthermore, it takes years to fully understand the consequences of a drug's disappearance. In 1990, a meta-analysis showed that quinidine prevents atrial fibrillation at the expense of increased mortality (15). The ensuing decline in demand for this product contributed to the decision by its main manufacturer to discontinue the production of quinidine (16). By the time we realized quinidine is practically the *only* effective therapy for preventing VTA related to Brugada syndrome and early repolarization syndromes, patients faced a grim worldwide shortage of this life-saving medication (17).

The 1:30,000 increased risk of sudden death from macrolides must be seen in the context of other iatrogenic complications: drug-induced fulminant hepatitis occurs in 1:8,000 patients and is fatal in 1:50,000 (18), whereas 1:5,000 patients treated with penicillin or with aspirin develop anaphylaxis that is fatal in 1:50,000 (19). The risk for drug-induced LQTS, rare as it is, may be further reduced by screening for well-recognized risk factors (20). A decade ago, we reported that 70% of all published cases of drug-induced LQTS from "noncardiac medications" had ≥2 easily identifiable risk factors: female heart disease, hypokalemia or drug toxicity from excessive dosages or drug interactions (21). Prescription for

≥2 I_{Kr} blockers was common in patients with drug-induced VTA, involving (for example) treatment of "allergic bronchitis" with nonsedating antihistamines and macrolides. It is therefore critical to instruct all patients receiving QT-prolonging medications to meticulously avoid additional I_{Kr} blockers. Avoidance of drug combinations that could lead to toxic levels by competing for the same metabolic pathway is also important now that 20% of all patients receive >5 medications simultaneously (22). Women not only receive polypharmacy more often than men (22), they are also more likely to develop VTA from QT-prolonging medications (21). Computerized prescription support tools, with alerts to potential adverse drug interactions, should integrate data on drug metabolism and pro-arrhythmic potential.

Electrocardiographic (ECG) screening and ECG monitoring are recommended for hospitalized patients receiving specific QT-prolonging medications (20) and for out-of-hospital initiation of QT-prolonging antiarrhythmia drugs (23). However, no such recommendations exist for QT-prolonging "noncardiac" medications prescribed in primary-care settings, mainly because it is considered impractical. Exceptions exist: 1) the Center for Substance Abuse Treatment called for ECG surveillance of patients treated with methadone (24), a QT-prolonging drug that is exceptional because it is prescribed for very long-term use (for opioid dependence); 2) the United Kingdom National Health Service instructs physicians to consider ECG surveillance during treatment with QT-prolonging medications of patients with risk factors for drug-induced LQTS. In addition, an increasing number of drug manufacturers now include drug-label warnings recommending ECG recordings before the prescription of "risky" medications. On the other hand, a recent survey of patients beginning out-of-hospital therapy with haloperidol (an antipsychotic agent associated with drug-induced LQTS) found that only 2% of patients had an ECG recorded at the onset of therapy (25).

FOR THE TIMES THEY ARE A-CHANGIN'

Patients' transtelephonic ECG monitoring from home for QT-monitoring, using small dedicated devices (26) or even mobile phones, is feasible and could be offered to high-risk patients. True, most physicians cannot recognize a long QT (27), but that can be changed with proper training (28). Alternatively, dedicated services of home-QT-monitoring could be offered. The technological obstacles, however, are only part of the problem. Although the risk for drug-induced VTA increases as the QT prolongs, there is no absolute cutoff value. For example, among 5,000 patients receiving azimilide, the risk for VTA rose as the QTc increased >500 ms and then increased rapidly with a QTc >520 ms (29); yet, 45% and 60% of patients with VTA had a QTc below these 2 cutoff values (29). Finally, full disclosure of the available information could prove counterproductive by lessening therapeutic compliance (30). In other words, the perception that "this drug could kill you" could lead to premature treatment discontinuation, with serious consequences. No doubt, drug-induced LQTS has no easy solutions. And there is more; long-term use of nortriptyline (an antidepressant that blocks the cardiac sodium channel) is associated with a 5-fold increased risk of sudden death by means of a lesser known form of pro-arrhythmia: drug-induced Brugada syndrome (31). Given the omnipresence of practice guidelines issued by authoritative organizations (i.e., American College of Cardiology/American Heart Association) dealing with just about every topic in cardiology, it is time for a consensus paper on how to deal with these controversies.

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REFERENCES

1. Thomson GW. Quinidine as a cause of sudden death. Circulation 1956;14:757–65.

2. Viko LE. A clinical report on the use of quinidine sulfate. Arch Intern Med 1923;31:341–63.

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

4. Schoonmaker F, Osten R, Greenfield J. Thioridazine (mellaril) induced ventricular tachycardia controlled with an artificial pacemaker. Ann Intern Med 1966;65:1076–8.

5. Roden DM, Bennett PB, Snyders DJ, et al. Quinidine delays IK activation in guinea pig ventricular myocytes. Circ Res 1988;62:1055–8.

6. Viskin S. The long QT syndromes and torsade de pointes. Lancet 1999;354:1625–33.

7. De Bruin ML, Pettersson M, Meyboom RH, et al. Anti-HERG activity and the risk of drug-induced arrhythmias and sudden death. Eur Heart J 2005;26:590–7.

8. Kuryshev YA, Ficker E, Wang L, et al. Pentamidine-induced long QT syndrome and block of hERG trafficking. J Pharmacol Exp Ther 2005;312:316–23.

9. Yang T, Chun YW, Stroud DM, et al. Screening for acute IKr block is insufficient to detect torsades de pointes liability: role of late sodium current. Circulation 2014;130:224–34.

10. Cimons M. Seldane pulled for a safer allergy drug. Los Angeles Times. 1997. Available at: http://articles.latimes.com/1997/dec/30/news/mn-3495. Accessed August 14 2015.

11. Willman D. RAXAR: warning on label omits deaths. Los Angeles Times. 2000. Available at: http://www.latimes.com/nation/la-122001raxar-story.html. Accessed August 14 2015.

12. Cheng Y-J, Nie X-Y, Chen X-M, et al. The role of macrolide antibiotics in increasing cardiovascular risk. J Am Coll Cardiol 2015;66:2173–84.

13. Antzelevitch C, Sun ZQ, Zhang ZQ, et al. Cellular and ionic mechanisms underlying erythromycin-induced long QT intervals and torsade de pointes. J Am Coll Cardiol 1996;28:1836–48.

14. Report to The President on Combating Antibiotic Resistance. Executive Office of the President, President's Council of Advisors on Science and Technology. September 2014. Available at: https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf. Accessed August 22, 2015.

15. Coplen SE, Antman EM, Berlin JA, et al. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. Circulation 1990;82:1106–16.

16. Viskin S, Antzelevitch C, Marquez MF, Belhassen B. Quinidine: a valuable medication joins the list of 'endangered species'. Europace 2007;9:1105–6.

17. Viskin S, Wilde AA, Guevara-Valdivia ME, et al. Quinidine, a life-saving medication for Brugada syndrome, is inaccessible in many countries. J Am Coll Cardiol 2013;61:2383–7.

18. Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology 2002;36:451–5.

19. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. Arch Intern Med 2001;161:15–21.

20. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. J Am Coll Cardiol 2010;55:934–47.

21. Zeltser D, Justo D, Halkin A, et al. Torsade de pointes due to noncardiac drugs: most patients have easily identifiable risk factors. Medicine 2003;82:282–90.

22. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. BMC Med 2015;13:74–83.

23. Prystowsky EN, Benson W, Fuster V, et al. Management of patients with atrial fibrillation. A statement for healthcare professionals from the Subcommittee on Electrocardiography and Electrophysiology, American Heart Association. Circulation 1996;93:1262–77.

24. Krantz MJ, Martin J, Stimmel B, et al. QTc interval screening in methadone treatment. Ann Intern Med 2009;150:387–95.

25. Warnier MJ, Rutten FH, Souverein PC, et al. Are ECG monitoring recommendations before prescription of QT-prolonging drugs applied in daily practice? The example of haloperidol. Pharmacoepidemiol Drug Saf 2015;24:701–8.

26. Carter EV, Hickey KT, Pickham DM, et al. Feasibility and compliance with daily home electrocardiogram monitoring of the QT interval in heart transplant recipients. Heart Lung 2012;41:368–73.

27. Viskin S, Rosovski U, Sands AJ, 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.

28. Postema PG, De Jong JS, Van der Bilt IA, et al. Accurate electrocardiographic assessment of the QT interval: teach the tangent. Heart Rhythm 2008;5:1015–8.

29. Pratt CM, Al-Khalidi HR, Brum JM, et al. Cumulative experience of azimilide-associated torsades de pointes ventricular tachycardia in the 19 clinical studies comprising the azimilide database. J Am Coll Cardiol 2006;48:471–7.

30. Jin J, Sklar GE, Min Sen Oh V, et al. Factors affecting therapeutic compliance: A review from the patient's perspective. Ther Clin Risk Manag 2008;4:269–86.

31. Bardai A, Amin AS, Blom MT, et al. Sudden cardiac arrest associated with use of a non-cardiac drug that reduces cardiac excitability: evidence from bench, bedside, and community. Eur Heart J 2013;34:1506–16.

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