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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