Precision medicine refers to new treatment and prevention strategies that take individual variability into account. Toward that end, the National Institutes of Health Precision Medicine Initiative envisions supporting a research program to encourage creative approaches to precision medicine, test them rigorously, and ultimately use them to build the evidence base needed to guide clinical practice. A major component of the Precision Medicine Initiative is the National Institutes of Health All of Us Research Program, which will engage ≥1 million volunteers living in the United States to contribute their health data over many years to improve health outcomes, fuel the development of new treatments for disease, and catalyze a new era of evidence-based and more precise preventive care and medical treatment.

The variable clinical response to drug therapy provides an especially compelling case for the promise of the precision medicine paradigm. A significant proportion of individuals treated with drugs display either little benefit, or even more problematic, develop serious and sometimes life-threatening adverse effects. Indeed, in 2014, as many as 253,017 serious outcomes, including 123,927 deaths, were reported through the Federal Drug Administration Adverse Events Reporting System. Among the more devastating adverse drug effects, seen with both antiarrhythmic and noncardiac drugs, are proarrhythmia and sudden cardiac death. The recognition of this problem has significantly impacted the drug development paradigm and led to the withdrawal or disapproval of numerous noncardiac medications from the United States and European markets—including astemizole, cisapride, sertindole, and terodiline.

Azithromycin is a macrolide antibiotic and the most commonly prescribed antibiotic in the United States. Indeed, with over 52 million prescriptions written in 2010, it was the sixth most common medication prescribed in any class. In 2012, based on a retrospective analysis of the Tennessee Medicaid cohort, Ray et al reported that patients who took azithromycin based on a retrospective analysis of the Tennessee Medicaid cohort, Ray et al reported that patients who took azithromycin over a 5-day course of therapy, she developed recurrent episodes of syncope that were attributable to rapid polymorphic runs of ventricular tachycardia. The patient was taking no other medications, the QT interval was normal, and there was no evidence of structural heart disease based on a cardiac magnetic resonance imaging. The episodes of ventricular tachycardia resolved over 3 days. Whole-exome sequencing did not identify any rare nonsynonymous variants in known inherited arrhythmia syndrome genes.

The molecular mechanisms responsible for proarrhythmic drug responses are legion. Most commonly, however, the proarrhythmic behavior is a consequence of drug-dependent block of repolarizing currents, especially binding to and block of hERG, which is responsible for the cardiac $I_{Ks}$ current. Reductions in $I_{Ks}$ lead to QT prolongation and increased propensity for torsade de pointes. From over a decade of genetic studies, we have learned that sequence variants in the genes encoding hERG or its ancillary partners KCNE2 and KCNE1 may increase susceptibility to drug-induced arrhythmias. Viewed in a larger context, variability in one or several genetic determinants of pharmacokinetics and pharmacodynamics, or more globally, variability in the integrated behavior of multicomponent networks of proteins that ultimately influence drug availability and response may play also influence proarrhythmia susceptibility.

However, in this case, given the lack of QT prolongation, the authors of the study used multiple complementary strategies that take individual variability into account. Toward that end, the National Institutes of Health Precision Medicine Initiative envisions supporting a research program to encourage creative approaches to precision medicine, test them rigorously, and ultimately use them to build the evidence base needed to guide clinical practice. A major component of the Precision Medicine Initiative is the National Institutes of Health All of Us Research Program, which will engage ≥1 million volunteers living in the United States to contribute their health data over many years to improve health outcomes, fuel the development of new treatments for disease, and catalyze a new era of evidence-based and more precise preventive care and medical treatment.

See Article by Yang et al

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strategies to identify other potential mechanisms of proarhythmic effects. These included measuring the ECG response in conscious mice challenged with azithromycin, analysis of excitability, and action potential parameters in the cardiac-like HL-1 cell line, patch-clamp studies of Na+ currents (peak and late) and delayed rectifier I_{Kr} K+ currents in transfected human embryonic kidney cells, and patch-clamp studies of L-type and T-type Ca2+ currents in primary rabbit ventricular myocytes. Unexpectedly, they found that chronic exposure of cells to azithromycin potentiated the cardiac Na+ current, which they propose increased intracellular Ca2+ concentration and through Na+/Ca2+ exchange, led to dysregulation of intracellular Ca2+ concentration and the development of a syndrome they suggest most closely resembles catecholaminergic polymorphic ventricular tachycardia. Disappointingly, despite some effort, the authors were unable to identify the precise cause of augmented Na+ currents as their cell biological studies did not reveal an increase in expression or enhanced trafficking of the NaV1.5 sodium channel protein to the cell surface. Although they postulate that the effect may reflect altered post-translational modification or changes in protein–protein interactions, this remains speculative and a topic for further investigation.

Nonetheless, if we are to make significant strides realizing the promise of precision medicine, it is precisely these sorts of initial forays into mechanism that will enlighten and guide us. Precision medicine and big data go hand in hand, as associations between sequence variants or biomarkers and clinical phenotype are typically quite weak, and by necessity require exceedingly large databases to uncover. The translation of these statistical associations into clinically actionable health information is in many ways still dependent on a deliberate and at times tedious pursuit of mechanism. Although the authors’ claim that preclinical screening of new compounds might include an examination of their pharmacological effects on cardiac I_{Kr} amplitude seems premature, their study does take us, albeit incrementally, toward the development of more precise and individualized targeting of drug therapy.

Sources of Funding

Research in the Fishman laboratory is supported by grants from the National Institutes of Health/National Heart, Lung, and Blood Institute and the American Heart Association.

Disclosures

None.

References


Key Words: Editorials • arrhythmias • azithromycin • basic science research • electrophysiology • ion channels/membrane transport • precision medicine
Drug-Induced Arrhythmias, Precision Medicine, and Small Data
Glenn I. Fishman

_Circ Arrhythm Electrophysiol._ 2017;10:
doi: 10.1161/CIRCEP.117.005208

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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