Review

Proarrhythmia as a pharmacogenomic entity: A critical review and formulation of a unifying hypothesis

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Abstract

Proarrhythmia represents an extreme example of the phenomenon that drug effects vary widely among individuals. Studies of mechanisms leading to proarrhythmia have had important implications for understanding arrhythmogenesis, rational use of antiarrhythmic therapies, selection of patients for specific therapies, and drug development. In addition, because proarrhythmia often seems to develop in the absence of clear risk predictors, a role for genetics in predisposing to this adverse drug reaction has been postulated. This review presents mechanisms whereby genetic factors may contribute to variable drug responses and describes our current understanding of how these mechanisms play a role in proarrhythmia. A unifying hypothesis is presented: physiologic processes (such as drug elimination or cardiac repolarization) include multiple redundancies, and congenital or acquired absence of such redundancies – due to disease, interacting drugs, or genetic makeup – may confer no baseline phenotype, but nevertheless enhance susceptibility to unusual drug responses.

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Variability in response to treatment is a widely accepted feature of therapy with most drugs. A key challenge to modern therapeutics, therefore, is to identify mechanisms underlying this variability. Studies of these mechanisms can prove informative not only in the more rational use of available drugs, but also can point to new disease mechanisms that ultimately result in development of newer and more effective drugs.

In some settings, adverse responses to drug therapy are readily predictable extensions of a drug’s known pharmacologic effects and are thus anticipated, often in a dose-related fashion, in large numbers of patients exposed. Severe hypotension with antihypertensive agents or bleeding with platelet inhibiting agents is an example. Other adverse drug effects may be less predictable in a population and in an individual subject. These adverse drug reactions are often termed “idiosyncratic,” implying (incorrectly) that there is no known mechanism, and many cases of proarrhythmia appear to fall into this category. It is in such instances that a genetic predisposition seems logical to invoke.

Proarrhythmia can be defined as the generation of new or worsened arrhythmias with drug therapy. It is the goal of this review to survey the state of the art with respect to genetic contributions to proarrhythmia susceptibility and to point to ways in which this very appealing, but to date unvalidated, hypothesis may be tested. This review will first describe the concepts of pharmacogenetics and pharmacogenomics and outline general mechanisms underlying variability in response to drug therapy, focusing on situations in which genetic variants may play an especially prominent role. The recognized and potential role of genetics in mediating risk in individual syndromes of proarrhythmia will then be discussed.

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1. Pharmacogenetics and pharmacogenomics

The concept that the risk of adverse drug reactions, particularly rare and unusual ones, might include a familial or genetic component was first advanced over a century ago [1]. During and after World War II, the first well-documented examples of adverse drug effects that included a very prominent familial or genetic component were described: hemolysis with antimalarial drugs in African–American individuals with G6PD deficiency [2]; variable response to isoniazid and development of lupus during procainamide therapy as a functional of acetylator phenotype [3,4]; prolonged paralysis in individuals with pseudocholinesterase deficiency receiving succinylcholine [5,6]; and malignant hyperthermia as a rare “idiosyncratic” response to anesthetics [7] are examples. Indeed malignant hyperthermia is an especially relevant example for the arrhythmia community, since it is probably the first described example of an ion channel disease (mutations in the skeletal muscle calcium release channel RYR1) predisposing to an abnormal drug response phenotype.

These early examples are pharmacogenetic: variants in one gene appear to underlie aberrant drug responses. The cloning of the human genome has been accompanied by an increasing appreciation of the striking variability, both at the level of disease-associated mutations as well as commoner DNA polymorphisms, among human genomes. This recognition, coupled with frustrations over an inability to accurately identify patients at high risk for adverse drug effects, has led to the very appealing pharmacogenomic notion that single or multiple subclinical DNA variants may only become apparent with drug challenge and may therefore underlie a wide range of adverse drug reactions, including proarrhythmia. As attractive as this concept may seem, it is important to understand that it is only now beginning to be tested. This is hardly surprising given how new the field is and the obstacles that must be overcome to enable pharmacogenomic experiments: these include generating lists of variants, accumulating large numbers of well-phenotyped individuals, implementing technologies to assay polymorphisms accurately in large numbers of individuals, and developing new approaches to analyzing very large phenotype–genotype datasets [8–11].

2. Mechanisms underlying variability in drug action

Early examples of genetically mediated drug reactions illustrate the two major mechanisms whereby unusual physiology may generate aberrant drug responses: pharmacokinetic and pharmacodynamic. “Pharmacokinetics” is the science describing the processes whereby drug administration results in delivery of drug to plasma and target effector sites and removal from those sites; the four major processes in classical pharmacokinetics are absorption, distribution, metabolism, and excretion, often abbreviated “ADME.” These processes are now well-recognized to result from highly regulated, tissue-specific expression of specific drug metabolizing and drug transport molecules. Variants in the genes encoding these molecules are one well-recognized cause of pharmacogenetically-determined adverse drug reactions, including the early example of procainamide-induced lupus syndrome described above. Other examples are the following:

- The antiarrhythmic propafenone is eliminated by metabolism through the cytochrome P450 CYP2D6, and in individuals with deficient CYP2D6 activity, parent drug accumulates and side effects, including bradycardia (likely due to beta blockade) are common [12,13]. CYP2D6 activity is absent in 7% of Caucasians and African–Americans (“poor metabolizers”) because they are homozygous for loss of function alleles, dozens of which have now been described (http://www.imm.ki.se/CYPalleles/). CYP2D6 activity can also be inhibited in the remaining 93% (extensive metabolizers) by drugs such as tricyclic or other antidepressants. Individuals with functional gene duplications, and thus greatly enhanced catalytic activity in vitro and in vivo, have also been described [14].
- The antihistamine terfenadine is a very potent QT prolonging drug, but undergoes extensive “first-pass” metabolism to a cardio-inactive compound (fexofenadine) in the intestine and liver [15]. This biotransformation is mediated by a group of related cytochromes termed CYP3A, including CYP3A4 and 3A5. While CYP3A activity varies widely, and some of this variability is now recognized as genetically mediated [16,17], individuals with totally deficient activity (who would be at risk for QT prolongation due to high terfenadine concentrations) have not been described. However, CYP3A activity is readily inhibited by coadministration of a wide variety of drugs, notably azole antifungal agents (such as ketoconazole) or macrolide antibiotics (such as erythromycin). It was with coadministration of these inhibitors that terfenadine-induced torsades de pointes was recognized. Although the phenomenon is rare, it is sufficiently alarming as to upset the perception of balance between risk and benefit for this agent and ultimately resulted in its withdrawal; fexofenadine (Allegra) is now marketed as a safer non-sedating antihistamine.
- Digoxin undergoes renal and biliary excretion via a drug-efflux pump, P-glycoprotein. P-glycoprotein function is inhibited by a wide range of drugs, including amiodarone, quinidine, itraconazole, cyclosporine, and verapamil, and each one elevates serum digoxin concentrations) have not been described. However, P-glycoprotein function is readily inhibited by coadministration of a wide variety of drugs, notably azole antifungal agents (such as ketoconazole) or macrolide antibiotics (such as erythromycin). It was with coadministration of these inhibitors that terfenadine-induced torsades de pointes was recognized. Although the phenomenon is rare, it is sufficiently alarming as to upset the perception of balance between risk and benefit for this agent and ultimately resulted in its withdrawal; fexofenadine (Allegra) is now marketed as a safer non-sedating antihistamine.
The key common feature of these examples of pharmacokinetically based aberrant drug responses is that elimination of the culprit drugs is solely or largely dependent on the intact function of a single metabolic or excretory pathway. If a drug can be eliminated by multiple metabolic or excretory pathways, absence of one pathway (through genetic factors or by drug interactions) does not generally result in a major perturbation of plasma drug concentrations and therefore is only rarely a cause of adverse drug effects. Flecainide is eliminated both by metabolism through CYP2D6 and by renal excretion of unchanged drug. Therefore, absent CYP2D6 activity (by genetics or by drug interactions) has little effect on flecainide plasma concentrations or effects, because renal elimination can accommodate the absence of the hepatic metabolism pathway. However, in the rare patient in whom CYP2D6 is functionally absent and in whom renal function is also impaired, plasma flecainide concentrations may reach very high levels and proarrhythmia risk has been suggested [21].

2.1. Pharmacodynamics and variable drug actions

Drugs generate their effects by interacting with specific effector or target molecules in plasma, at the surface of cells, or within cells. The effector sites required to produce beneficial effects may be the same as, or different from, those responsible for generating adverse effects. Even if there is no variability in delivery of drug to effector sites, the clinical effects observed may vary strikingly among individuals. Such variability is termed “pharmacodynamic,” and two fundamental mechanisms can be responsible: there may be variability in the amount or function of the target effector molecule or in the biologic context within which the interaction of drug with its effector(s) occurs. Variability in function or expression of target or other molecules may occur as part of normal biologic variation or may be a manifestation of disease.

One example relevant to the present review comes from our increasing appreciation of variability in the extent to which drugs prolong QT interval [22]. The vast majority of drugs produce this effect by interacting with the Human Ether-a-go-go Related Gene (HERG) product whose expression results in the rapid component of the cardiac delayed rectifier, IKr. Thus variability in the extent to which a drug prolongs the QT interval may arise from variability in (1) delivery of drug to the channel (a pharmacokinetic mechanism; terfenadine is an example), (2) the number or function of HERG channels on the myocyte surface, or (3) factors in the milieu such as serum potassium that affect the drug–IKr interaction. At low serum potassium concentrations, drug block of HERG channels is exaggerated, whereas at higher serum concentrations (within the physiologic range), the effect of drugs on IKr tends to be blunted [23]. Another such factor is variability in the amplitude of the slow component of the cardiac delayed rectifier, IKs, another important component of repolarization. Subclinical reduction of function of IKs may lead to no clinical phenotype at baseline (because of a robust IKr) but result in marked QT prolongation in the presence of an IKr-blocking drug; this phenomenon is discussed further below. Conversely, a robust IKs may limit the extent to which an IKr-blocking drug can prolong the QT interval [24].

3. A unifying hypothesis: physiologic redundancies protect against “idiosyncratic” drug actions

The examples of high-risk pharmacokinetics described above have in common drugs whose elimination depends on a single pathway: propafenone, terfenadine, and digoxin. In each case, risk is conferred by absence of redundancy of drug-elimination pathways for that specific drug. The example of drug-induced torsades de pointes is similar: cardiac repolarization is ordinarily a highly redundant process and can be accomplished by IKs, IKr, and likely other mechanisms. Subjects who exhibit marked QT prolongation with IKr-specific blocking drugs must therefore represent a subset in whom repolarization is highly IKr-dependent and thus have lost redundancy in repolarization mechanisms. This phenomenon has been referred to as “reduced repolarization reserve” [25], but the concept extends to other physiologic processes that include redundancies to prevent extreme physiologic responses. Loss of these redundancies, through disease, concomitant drug therapy, or subclinical genetic variants, may be clinically inapparent until exposed by a drug challenge.

4. Proarrhythmia: a pharmacogenetic phenomenon?

While proarrhythmia is defined here as the generation of new or worsened arrhythmias with drug therapy, it may not be readily apparent in some settings that a drug is, in fact, responsible for an arrhythmia exacerbation; this is a particular problem in patients with advanced heart failure in whom the spontaneous development of frequent, serious arrhythmias may be common in the absence of drugs. The present discussion focuses on three well-described proarrhythmia syndromes: digoxin toxicity, drug-induced torsades de pointes, and toxicity related to sodium channel block. Examples are presented in Table 1.

4.1. Digoxin toxicity

The major recognized mechanism underlying digoxin toxicity is pharmacokinetic, as described above. Variations in MDRI have been reported as a cause of variable digoxin concentrations, but no mutation or polymorphism has been described to date that appears to predict risk [19]. Digoxin’s molecular target is the sodium–potassium ATPase pump, and downstream physiologies that are modulated by pump inhibition include sodium–calcium exchange and other
systems involved in intracellular calcium homeostasis. Therefore, candidate genes in which variants may modulate digoxin effects include those encoding sodium–potassium ATPase, the sodium–calcium exchanger, and those regulating intracellular calcium control. Accordingly, congenital diseases altering intracellular calcium control, including catecholaminergic polymorphic ventricular tachycardia [26,27] and the ankyrin-B-linked form of the long QT syndrome [28], may predispose to digoxin toxicity. To date, no example has been described.

### 4.2. Drug-induced torsades de pointes

Terfenadine provides an example of how pharmacokinetic variability can modulate torsades risk [15]. Another example may be risk with the antipsychotic thioridazine, which is a CYP2D6 substrate, so poor metabolizers may be at increased risk [29,30]; although this has not been formally tested, a warning of this risk now appears in the drug’s US package insert. An interesting twist on pharmacokinetics and torsades de pointes is that risk appears increased when an intravenous bolus is administered very rapidly. This has been reported both preclinical [31] and clinical [32] studies with I_{Kr} blockers such as almokalant and dofetilide; the underlying mechanism is unknown, and factors such as regional myocardial blood flow (with differential delivery of drug to various cell types within the myocardium) may be responsible. A genetic contribution to this phenomenon is unexplored.

Other risk factors for torsades de pointes appear pharmacodynamic in nature: female gender, advanced heart disease or left ventricular hypertrophy, bradycardias, hypokalemia, and recent conversion from atrial fibrillation [33,34]. Each one of these can be interpreted within the framework of “reduced repolarization reserve,” and in some cases underlying molecular mechanisms have been proposed. Thus, hypokalemia may reduce I_{Kr} by enhancing fast inactivation [35] or by promoting block of I_{Kr} by extracellular sodium [36]. It seems likely that risk conferred by other factors, such as female gender or conversion from atrial fibrillation, may similarly reflect modulation of sensitivity of I_{Kr} or of variable contributions by I_{Ks} or other currents to repolarization. However, the underlying mechanisms have not been well worked out.

Variants in ion channel genes have been reported as risk factors in individual cases and small series of patients with drug-induced torsades de pointes [37–40]. Some of these appear to represent relatively straightforward examples of subclinical long QT syndrome (baseline “reduced repolarization reserve”) that is then exposed by drug administration. The number of cases of torsades that could be explained by this mechanism is not clear. One contemporary estimate is that congenital long QT syndrome mutations occur in ~1/3000 individuals [41]. In the case of culprit antiarrhythmic drugs, the incidence of torsades is 1–5% of patients; thus, the congenital syndrome seems a minor cause. By contrast, torsades de pointes with “non-cardiovascular” drugs seems much more rare. For example, spontaneous reports of torsades with the I_{Kr}-blocking antibiotic moxifloxacin, normalized to the total number of prescriptions, has led to a risk estimate of 1/1,000,000 (http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3956T1.doc; p. 177-178). Therefore, in this case, one must conclude that many patients with the subclinical syndrome may not develop torsades even on exposure to this drug.

Polymorphisms in ion channel genes have also been associated with risk. The largest series to date reported that a sodium channel variant found in African–Americans, S1102Y, was much more common in 23 subjects with arrhythmias (47.8% were SY and 8.7% YY), compared to 100 controls (13.0 and 0%) [42]; interestingly, this variant has been identified as a cause of the congenital long QT syndrome in a Caucasian kindred [43]. In the African–American study, the arrhythmias included both drug-associated torsades de pointes, as well as other phenotypes such as syncope of unknown etiology, or long QT intervals.
This is an example of an association study, and it like many others may suffer from the problem that there are millions of polymorphisms across human genomes, so the chances of a false positive result are very high. Therefore, a key to incorporating polymorphism information such as this into our understanding of biology or ultimately into clinical practice is reproducibility, and most association studies have not been reproducible [44,45]; the S1102Y association has not yet been tested for reproducibility. An added dimension in the case of S1102Y, however, was parallel basic science that lends strong “biologic plausibility” to the association: in vitro, sodium channels with the Y allele generated altered channel function, compatible with altered baseline repolarization reserve [42]. Other studies have asso ciated rarer polymorphisms in the potassium channel β-subunit genes KCNE1 (resulting in D85N) [40,46] and KCNE2 (resulting in T8A and Q9E) [40,47] with torsades risk. Q9E is instructive because it was initially reported as a mutation (and absent in hundreds of controls) in an African–American proband [48], but turns out to be a relatively common polymorphism in African–Americans (with a minor allele frequency of approximately 5%). In our own work, possibly predisposing variants were identified more commonly in KCNE2 than in any other ion channel gene [39]. However, the extent of KCNE2 expression in the heart remains uncertain, so the contribution of these polymorphisms to risk must also remain uncertain.

It has been argued that well-described clinical risk factors listed above are identified in the vast majority of cases of drug-induced torsades de points [49], so a role for genetic variability need not be invoked. This argument is not at variance with a pharmacogenetic view: it seems likely that even among patients judged at “high risk” (e.g., females with recent conversion from atrial fibrillation), there exists a range of risk and that some of this may well reflect genetic factors. Conversely, the risk of torsades de points in patients without other clinical risk markers seems quite low, but not zero. Therefore, an interplay between clinical risk markers (whose mechanisms often remain ill-defined and may include a genetic component) and genetics seems likely.

4.3. Proarrhythmia due to sodium channel block

Sodium channel block is the common mechanism underlying many well-described proarrhythmia syndromes: slowing of atrial flutter with the potential for 1:1 AV conduction; development of “incessant” slow ventricular tachycardia in patients with myocardial scarring; increased risk of sudden death following myocardial infarction (as in the Cardiac Arrhythmia Suppression Trial, CAST); and patients in whom the Brugada ECG phenotype (and rarely ventricular fibrillation) may be elicited by administration of a sodium channel-blocking drug [50]. The latter example is analogous to the situation of a patient with subclinical long QT syndrome in whom administration of an IKr-blocker exposes the genetic defect. Thus, patients with subclinical Brugada syndrome presumably have sufficient sodium channels (or other mechanisms operating early in the action potential) to prevent the clinical phenotype, and the sodium channel blocker serves to expose the defect. Logically, it seems possible that multiple DNA variants may act together to generate a vulnerable substrate that then exhibits proarrhythmia on exposure to a drug. These variants may be in the same gene; for example, the functional effects of a common polymorphism in the sodium channel gene appear to depend on the specific splice variant (at a distant site) in which the polymorphism is expressed [51]. Variants in multiple genes may act together to create an altered substrate; an example is provided by description of a kindred in which atrial standstill was identified only in subjects with a sodium channel mutation and a polymorphism in the connexin40 promoter [52].

The possibility that subclinical loss of sodium channel function might have contributed to the adverse outcome of drugs in CAST remains an interesting question that will never be settled because the DNA samples from that important clinical trial were not archived. More generally, the diverse clinical settings in which reduced sodium current generates an arrhythmogenic phenotype raises the possibility that DNA variants leading to fewer sodium channels may also contribute to sudden death risk in the susceptible myocardium. Along these lines, studies of the promoter region of the cardiac sodium channel have identified frequent variants [53,54], some of which alter transcriptional activity in vitro. The extent to which such variants modulate arrhythmia phenotypes, such as risk with sodium channel-blocking drugs, or whether Brugada syndrome mutations generate manifest or subclinical ECG findings, is an area of intense investigation.

Whether variants leading to abnormal drug concentrations might contribute to variable sodium channel blocker-related proarrhythmia is unknown. Early experiences with encainide (whose biotransformation to an active metabolite is CYP2D6-dependent [55]) and flecainide did result in incessant ventricular tachycardia that could be fatal [56,57]. This usually occurred at ordinary doses in patients with very advanced heart disease, so a primary pharmacokinetic explanation seems unlikely.

5. Conclusion

Serious proarrhythmia is a rare, but well-recognized, complication of therapy with antiarrhythmic drugs and occasionally “non-cardiovascular” agents. Clinical situations in which this toxicity occurs have been well described, but the reaction appears sufficiently unpredictable in an individual that the idea of a pharmacogenetic contribution, through pharmacokinetic or pharmacodynamic mechanisms, has some appeal. Indeed, important variants in the molecules of drug disposition, in drug targets, and in modulators
of the drug-target interaction, have now been well-described in individual cases of proarrrhythmia. A common mechanism increasing proarrrhythmia risk appears to be elimination of physiologic redundancies that ordinarily “buffer” against such extreme drug reactions. Thus, we propose a unifying framework for analysis of genetically-modulated variable drug responses that includes consideration of such physiologic redundancies and how their absence – due to concomitant drug therapy or genetic variants – predisposes to variant responses.

The field of genomic science, and in particular of pharmacogenomics, is quite young; the term “pharmacogenomics” first appears in PubMed in 1997. Thus, key studies required to test the hypothesis that variability in response to antiarrrhythmic drugs, including the most extreme form of variability (proarrrhythmia), includes a genomic component are only now starting. The key steps in these studies include identification of important variants both in coding and noncoding regions, development of high-throughput technologies to genotype large numbers of subjects at many polymorphic sites, new statistical methods to manage these very large datasets, and, most importantly, accumulation of large numbers of patients in whom drug responses have been well-studied and in whom appropriately consented DNA samples have been obtained. These studies require the participation of scientists with a wide range of talents, including genetics and genomics, basic and clinical pharmacology, genetic statistics and epidemiology, and expert clinicians.

The lay press frequently outlines a vision of diagnosis and therapy based on an individual’s genome. While many clinicians.

References


